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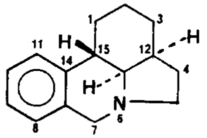
AN INTRAMOLECULAR DIELS-ALDER APPROACH TO THE GALANTHAN RING SYSTEM

D.J. Morgans, Jr.[14] and Gilbert Stork
Department of Chemistry
Columbia University
N.Y., N.Y. 10027

ABSTRACT: A novel "phenylbutadiene + Δ^2-pyrroline" intramolecular cycloaddition has been used to construct a functionalized galanthan.

Construction of the galanthan ring system (1), common to many Amaryllidacaea alkaloids[1] (lycorine, 2, for example) has been the focus of many studies since the early sixties.[2] Most natural substances of this structural type exhibit a highly functionalized and sensitive C-ring. A novel intramolecular Diels-Alder[3] approach (Scheme I) to a galanthan (4a) suitably functionalized for further elaboration to naturally occurring C-ring functional arrays is the subject of this report.



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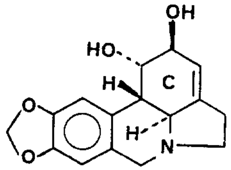

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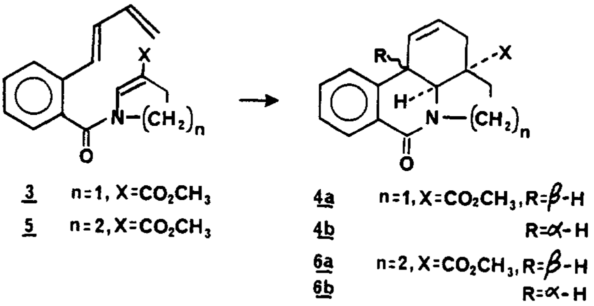
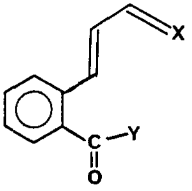
The preparation of amide 3 was accomplished as follows. Slow addition of any HMPA solution of 2-carboxybenzaldehyde and diethyl 2-(cyclohexylamino)vinyl phosphonate[4] (1.1 equiv.) to an HMPA slurry of NaH (2.2 equiv.) at 30-40° followed by stirring at room temperature overnight, quenching with MeI (5 equiv.) and acidic workup afforded 7a[6a,c](m.p.=45-46) in 50% yield. Treatment of 7a with Me_3SiCH_2MgCl[5](1.1 equiv.) in THF (0°, inverse addition) and elimination of the crude silyl carbinol (pentane-50% acetic acid, two phase) yielded 7b[6a](75%). Saponification afforded the diene acid 7c[6a,c](m.p.=100-105). Phosphine mediated[7] condensation of 7c with 3-carbomethoxypyrrolidine[6a,8](1 equiv. 7c, 1.3 equiv.

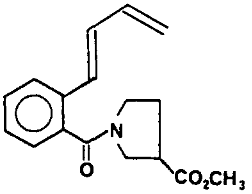
SCHEME I



ϕ_3P, 3 equiv. $BrCCl_3$ in THF followed by addition of 4 equiv. of the pyrrolidine then 75° for 1 hr; 80%) yielded 8[6a] which was converted to pyrroline 3[6a-c] by sequential treatment with lithium tetramethylpiperidide (1.3 equiv., THF, -78°, 15 min), I_2(1.1 equiv., THF, -78°, 15 min) and DBU (2 equiv., THF, -78°→-10°, 10 hr) in 35-40% overall yield from 8. None of the undesired Δ^3 isomer was obtained.

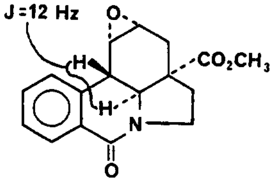


7a X=O, Y=OCH₃
7b X=CH₂, Y=OCH₃
7c X=CH₂, Y=OH



8

Cyclization of 3 (degassed o-dichlorobenzene, 0.01M, reflux, 2.5 hr; 84%) proceeded to a mixture of amides 4a[6a,b] and b[6a,b]. In the PMR spectrum, the olefinic signals of each amide (not readily separable by chromatography) in the mixture were well separated. Integration revealed a 0.84:1 ratio of 4a:4b. Epoxidation (m-chloroperbenzoic acid, CH_2Cl_2; 92%) of this mixture and chromatography allowed separation of two major epoxides 9[6a,b] and 10[6a,b] (9:10 is 1:1.67; 70% of epoxide mixture). Further confirmation of the structure of 9 was obtained by conversion to diacetate 11[6a,b] (catalytic $HClO_4$, THF, H_2O, 60° then Ac_2O, pyridine; 65%). The essential features of the PMR spectrum of 11 agree with the published[9] data for related naturally derived substances (i.e. 12).



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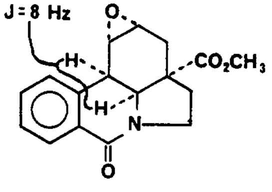

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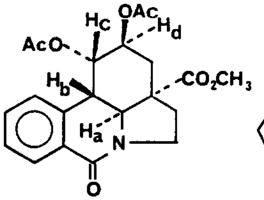
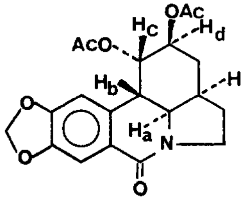




	11^a	12^b
H_a	4.42(d,13)	3.93(dd,13,9.2)
H_b	3.35(dd,13,3)	3.21(dq,13,3.2,1.0)
H_c	5.75(t,3)	5.61(t,3.2)
H_d	5 08(ddd,9,4,3)	5.03(dq,7.8,4 8,3.2)

ppm (mult., J,...)

a- 80 MHz, $CDCl_3$
b-100 MHz, $CDCl_3$

The novel use of a Δ^2-pyrroline dienophile[10] in an intramolecular cycloaddition establishes this method for the construction of complex heterocyclic systems. The disappointing stereochemical outcome of the cyclization is somewhat perplexing since in a related tetrahydropyridine system, 5, opposite stereospecificity is observed[11] (3.5 hr in refluxing o-dichlorobenzene; 74%, 6a.6b=2:1). The very subtle differences observed in the internal cyclizations of 3 and 5 serve to illustrate the delicate nature of the interactions controlling the stereochemistry of intramolecular Diels-Alder reactions.[12,13]

REFERENCES AND NOTES

1) C.Fuganti, Ch. III, Vol. XV, in The Alkaloids, R.H.F. Manske, ed., Academic Press, Inc., New York, N.Y.

2) See Ref.1, B. Umezawa, O. Hoshino, S. Sawaki, S. Sato, and N. Numao, J.Org. Chem., 42, 4272 (1977); O. Moller, E. Steinberg and K. Torsell, Acta. Chem. Scand., B32, 98 (1978) and references cited therein. Lycorine has recently been synthesized: Y. Tsuda, T. Sano, J. Taga,K. Isobe, J. Toda, H. Irie, H. Tanaka, S.Takagi, M. Yamaki, and M. Murota, Chem. Commun., 933 (1975).

3) For a recent review see: W. Oppolzer, Angew. Chem. Int. Ed. Eng., 16, 10(1977)

4) W. Nagata, T. Wakabayashi and Y. Hayase, Org. Syn., 53, 44 (1973).

5) D.J. Peterson, J. Org. Chem., 33, 780 (1968); T.H. Chan and E. Chang, J. Org. Chem., 39, 3264 (1974).

6a) All yields refer to purified material. Satisfactory IR and NMR data were obtained for this substance.

b) Satisfactory mass spectral data was obtained for this substance.

c) Satisfactory carbon and hydrogen analysis was obtained for this substance.

7) L.E. Borstow and V.J. Hruby, J. Org. Chem., 36, 1305 (1971).

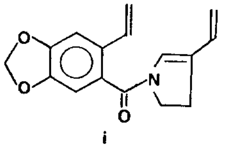
8) Prepared from 1-benzyl-3-carbomethoxypyrrolidine (M.J. Kornett, P. Thiu, and S. Tan, J. Org. Chem., 33, 3637 (1968)) by hydrogenolysis (CF_3CO_2H, H_2, Pd-C, MeOH; 73% b.p.(0.5 mm)=65°). For the ethyl ester b.p.(17 mm)=92-94°; Y. Wu and R. Feldkamp, J. Org. Chem., 26, 1519 (1961).

9) K. Kotera, Y. Hamada, K. Tori, K. Aono, and K. Kuriyama, Tet. Lett., 2009 (1966).

10) Intermolecular Diels-Alder reactions of 3-aryl-Δ^2-pyrroline-4,5-diones have been reported. Y. Tsuda, K. Isobe and A. Ukai, Chem. Commun., 1554 (1971); Y. Tsuda and K. Isobe, Chem. Commun., 1555 (1971).

11) D.J. Morgans, Jr., Ph.D. Thesis, Columbia University (1979).

12) We have recently observed a stereospecific cyclization of i to the 3,12-didehydrogalanthan ring system. A report on this work will appear in due course.



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14) Present address: Department of Chemistry, Stanford University, Stanford, California.

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