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A GENERAL SYNTHETIC APPROACH TO AMARYLLIDACEAE ALKALOIDS

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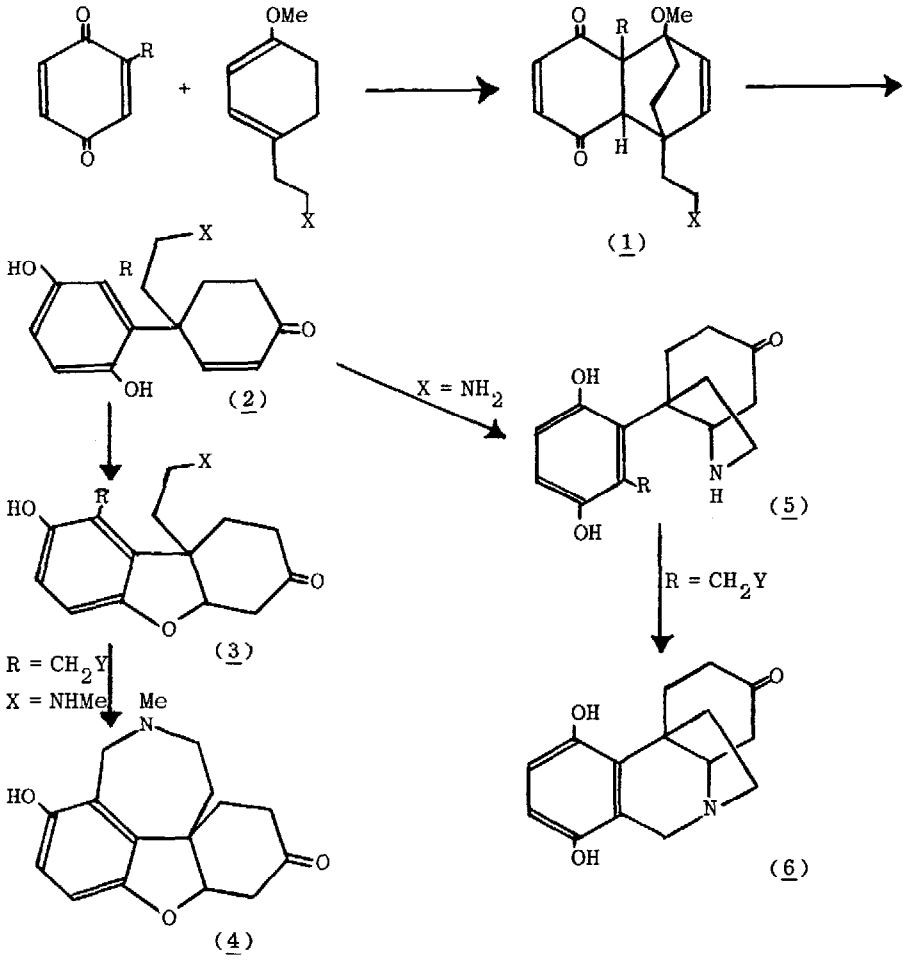
Abstract: A general strategy is outlined for the obtention of the various skeletons of the Amaryllidaceae alkaloids based upon the Diels-Alder addition of a benzoquinone to an alkoxycyclohexa-1,3-diene and subsequent acid catalysed rearrangement of the adduct. The approach is exemplified by the synthesis of the lycoramine system.

Various pharmacological activities are displayed by alkaloids of the Amaryllidaceae group. For the most part synthetic activity[1] in this area has been directed towards the production of specific alkaloids and is not readily adapted to the production of the variety of structurally modified compounds required for probing structure-activity relationships. Most of these alkaloids are derived biosynthetically by combination of (C_6-C_1) and (C_6-C_2) units and this suggested that a general synthesis might be possible based on a comparable combination of such fragments.

Our general plan is outlined in Figure I and is based upon the Diels-Alder addition of a benzoquinone to an alkoxycyclohexa-1,3-diene followed by acid catalysed rearrangement[2] of the resulting adduct (1), *via* the cyclohexenone (2), to the tetrahydrodibenzofuranone (3). Subsequent cyclisation of (3) would then provide access to the lycoramine skeleton as in (4). The reversibility[3] of the cyclisation of (2) to (3) opens up the possibility of capture of the cyclohexenone by other nucleophilic centres leading *inter alia* through (5) to (6) representing the crinine group. Similar transformations are in principle capable of yielding most of the other skeletons found inthis group of alkaloids. In this paper we report the successful implementation of the first phase of this approach as illustrated by the obtention of the lycoramine derivative (19).

The methoxycyclohexadiene (7) was generated by Birch reduction of *p*-methoxyphenylethanol to the corresponding 1,4-cyclohexadiene[4] followed by acetylation and acid catalysed conjugation to give the equilibrium mixture of 1,3- and 1,4-dienes in *ca*. 2:1 ratio. The initial plan to add to this a benzoquinone bearing an electron withdrawing group, representing the (C_6-C_1) unit, had perforce to be modified as such dieneophiles were

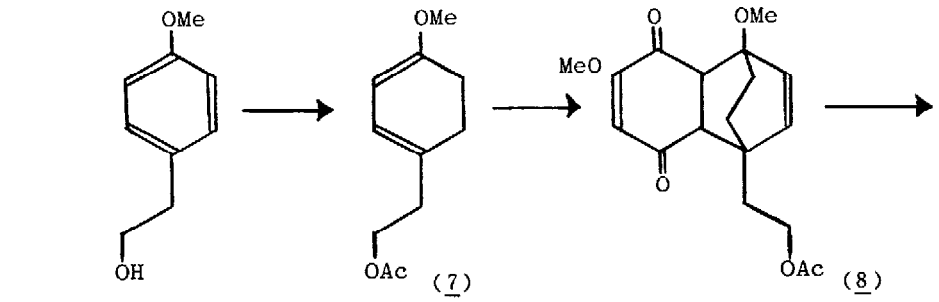
FIGURE I

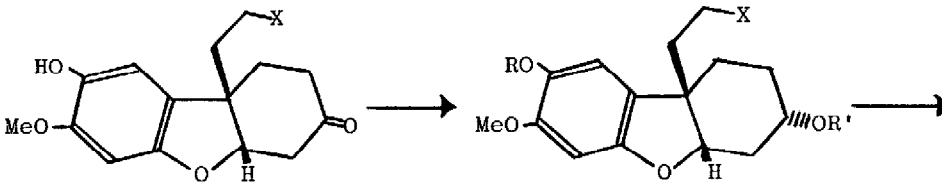


found to react predominantly by hydrogen abstraction rather than cycloaddition[5]. Consequently the introduction of the C_1 fragment was deferred to a later stage. Reaction of the diene mixture with 2-methoxybenzoquinone at 80° in benzene gave a 45% yield of the adduct (8). This was rearranged with 2M HCl in ethanol at room temperature to the tetrahydrodibenzofuranone (9), plus a small amount of the deacetylated compound (10) in 80% overall yield.

Attempts at this stage to introduce a functionalised carbon adjacent to the phenolic hydroxyl using, amongst other methods, the Reimer-Tiemann reaction were thwarted[6] by steric hindrance. Treatment of (9) with trimethylsilyl chloride and sodium iodide in acetonitrile provided the

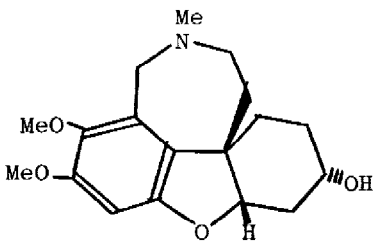
FIGURE II





(9) X = OAc
(10) X = OH
(11) X = I

(12) R = R' = H, X = I
(13) R = R' = OAc, X = I
(14) R = R' = OAc, X = N_3
(15) R = R' = OAc, X = NH_2
(16) R = R' = OAc, X = NHCHO
(17) R = Me, R' = H, X = NHCHO
(18) R = Me, R' = H, X = NHMe



(19)

iodo compound (11), whose carbonyl group was reduced with sodium borohydride in ethanol to give (12). It proved desirable to convert (12) to its diacetyl derivative (13) in order to ensure a satisfactory displacement of the iodine with sodium azide in acetonitrile leading to (14). The azido group of (14) was then reduced with hydrogen and a palladium on charcoal catalyst to provide the amine (15), which was formylated with acetic formic anhydride in pyridine to yield (16). Treatment of this compound with methyl iodide and potassium carbonate in ethanol removed the acetyl groups and selectively O-methylated the phenolic hydroxyl group thereby providing (17). Reduction of the N-formyl group with diborane at -70°C in tetrahydrofuran gave the N-methyl compound (18).

The conversion of the N-formyl derivative of (18) to (19) was first attempted using Vilsmeier-Haack methodology but without success. However, the desired transformation was achieved by reacting (18) with bis(dimethylamino)methane in refluxing dioxan. While such Mannich type reactions are more usually associated with phenols we attribute the successful outcome of the reaction in the present case to a combination of the activation of the aromatic ring towards electrophilic substitution by the three alkoxy substituents and also to the intramolecular nature of the reaction.

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References

1. S.F. Martin, Alkaloids, 1987, 30, 251; K. Hayakawa, T. Yasukouchi and K. Kanematsu, Tetrahedron Lett., 1987, 28, 5895; D.J. Ackland and J.T. Pinhey, J. Chem. Soc., Perkin Trans. 1,1987, 2695; O. Hoshino, S. Sawaki, N. Shimamura, A. Onodera and B. Umezawa, Chem. Pharm. Bull., 1987, 35, 2734; R.A. Holton, M.P. Sibi and W.S. Murphy, J. Amer. Chem. Soc., 1988, 110, 314; S.F. Martin and C.L. Campbell, J. Org. Chem., 1988, 53, 3148; L.E. Overman and H. Wild, Tetrahedron Lett., 1989, 30, 647.
2. A.J. Birch, D.N. Butler and J.B. Sidall, J. Chem. Soc., 1964, 2932.
3. C.W. Bird, Y.-P.S. Chauhan and D.R. Turton, Tetrahedron, 1981, 37, 1277.
4. All new compounds were fully characterised by microanalysis and displayed appropriate NMR, infrared and mass spectra.
5. C.W. Bird and M. Kapili, unpublished observations.
6. C.W. Bird, A.L. Brown and C.C. Chan, Tetrahedron, 1985, 41, 4685.

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