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"SYNTHETIC STUDIES ON LYCORICIDINE. II. AN EFFICIENT ROUTE TO CIS DIHYDROLYCORICIDINE."

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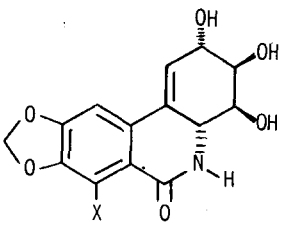
Summary: The tricyclic skeleton of lycoricidine has been prepared by a route involving an intramolecular [4 + 2] cycloaddition of a trimethylsilyloxydienamide.

The substances lycoricidine (1a) and narciclasine (1b) have attracted considerable interest due to their range and potency of biological effects, including inhibition of protein synthesis and potent *in vitro* antitumor activity.[1] Moreover, the *cis* and *trans* dihydro narciclasines also exhibit antitumor activity. In view of the relative scarcity of lycoricidine and the absence of biological assay of its dihydro derivatives, we have been

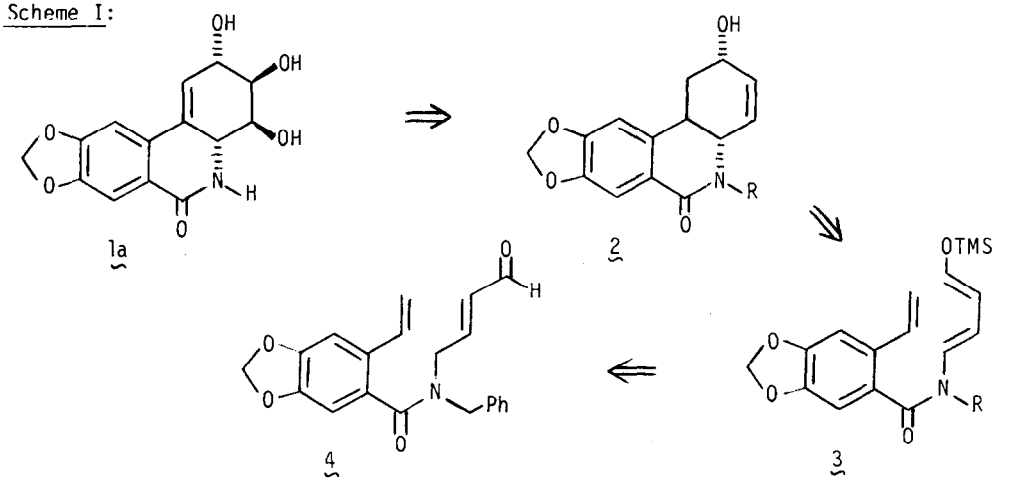


1a X=H
1b X=OH

engaged for some time[2] in studying synthetic approaches to these materials. Presently, we report an especially direct method for stereocontrolled construction of the tricyclic nucleus of 1a, which makes the *cis* dihydro derivative of lycoricidine available in multigram quantities. The approach (as detailed below) involves, as its key feature, the first example of Diels-Alder reaction utilizing a trimethylsilyloxydienamide. The efficacy of this process suggests that such moieties may find further use as Diels-Alder diene components.

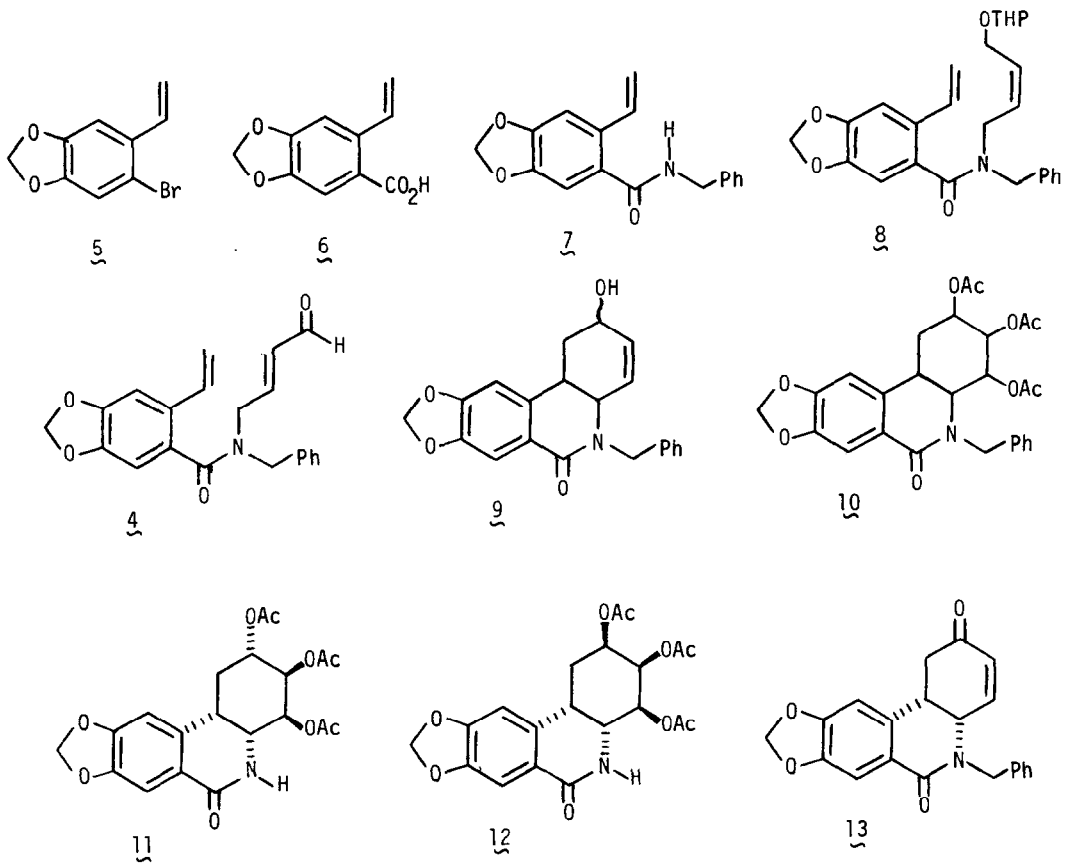
Our analysis of the structural problem posed by lycoricidine suggested that an especially direct approach could proceed via the strategy outlined in Scheme I.

Scheme I:



Thus, our earlier studies[2] and literature precedent[3] suggested that vicinal hydroxylation of 2 could be expected to produce cis-dihydrolycoricidine stereospecifically. Amongst possible approaches to 2, the intramolecular cycloaddition of 3 was particularly attractive, particularly since generation of the E, E diene system of 3 could be expected from exposure of aldehyde 4 (or, in fact, any isomer of 4) to the now classic House conditions for conversion of carbonyl compounds to trimethylsilylenol ethers.[4] The possibility that 3 could cyclize under the conditions of its formation, thus obviating the need for manipulation of such a labile intermediate, provided further impetus for subjecting such a route to experimental scrutiny.

Wittig methenylation of 5-bromopiperonal[5] (THF, 0°) afforded bromostyrene 5, which was converted to the known[6] acid 6 (mp 163-164°, 60% overall) by metal-halogen exchange (nBuLi in ether, -65°) followed by introduction of gaseous CO_2 (-40°). Conversion to amide 7 (mp 129-130°, from methanol) was cleanly effected by exposure of 6 to excess (3 eq.) triethylamine and methanesulfonylchloride (1.5 eq.) in dry methylene chloride (-20°, 40 min.) followed by addition of excess (5 eq.) of benzylamine, warming to 23°, and further reaction (23°) for 12 h. Alkylation of the sodium salt of 7 (NaH, DMF) with cis-1-chloro-2-butene-4-tetrahydropyranyl ether[7] (23°, 18h.) gave 8 in essentially quantitative yield. Removal of the tetrahydropyranyl ether (PPTS[8], methanol, reflux) and Corey-Suggs oxidation[9] then furnished the key aldehyde 4. Exposure of 4 to excess (6 eq.) of triethylamine and 3 eq. of trimethylchlorosilane in dry dimethylformamide (DMF, 25ml per g of 4) at reflux (160° oil bath) for 12 h. gave, after normal extractive workup and exposure of the organic (ethyl



5 6 7 8 4 9 10 11 12 13

acetate) extract to 2% aqueous hydrochloric acid, alcohol 9 in 60-65% yield after purification by column chromatography. This simple in situ process for generation of the requisite dienamide (3) with concomitant [4 + 2] cycloaddition proved superior to alternative procedures involving low temperature generation of 3, isolation, and thermolysis to effect cyclization. Alcohol 9 was obtained as an inseparable mixture of two isomers, both separation and determination of isomer ratio (and structures) were conveniently effected at a later stage.

Acetylation of 9 (excess acetic anhydride in pyridine) and catalytic osmium tetroxide oxidation[10] gave a diol which was again exposed to excess acetic anhydride in pyridine to give triacetate 10 in 76% yield from 9. Removal of the N-benzyl group proved extremely difficult, but was eventually accomplished in 95% yield by hydrogenolysis over palladium chloride in 4:1 ethyl acetate - acetic acid at 23°. The resulting isomeric triacetates (Rf 0.51 and 0.41, respectively, with chloroform-methanol, 92:8) were easily separated by column chromatography to provide cis dihydrolycoricidine triacetate (11, mp. 268-271°) and its C_2

epimer (12, mp. 224-225°) in a ratio of ca. 3:1. The assignments of structure to the purified triacetates were made by comparison of their richly detailed 300 MHz NMR spectra to those of the known cis and trans dihydronarciclasine tetraacetates,[1] which clearly revealed, quite unexpectedly, that both products isolated possessed a cis ring fusion. The assignment was corroborated by subjecting the mixture of isomers obtained from the intramolecular cycloaddition to MnO_2 oxidation, which very smoothly (23°, 3 h) yielded a single enone 13. Although the origin of 12 is not known with certainty, it most probably results from acid (triethylamine hydrochloride) catalyzed isomerization of the trimethylsilyl ether of 12 under the conditions utilized for intramolecular Diels-Alder reaction.[11]

The approach outlined above clearly demonstrates the utility of 4-trimethylsiloxydienamides as diene components for Diels-Alder cycloaddition. Moreover, modifications of the above route to permit a facile introduction of the unsaturation present in 1a may allow a very direct synthesis of the natural material itself. Further studies are in progress.[12]

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7) This material was very conveniently prepared from the mono-THP of cis-2-butene-1,4-diol via the procedure of Meyers: E.W. Collington and A.I. Meyers, J. Org. Chem., 36, 3044 (1971).

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11) We are at present unable to exclude the formation of a Z,E isomer of 3 as the precursor of isomer 12.

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