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MODEL STUDIES ON NARCISSUS ALKALOIDS.
SYNTHETIC METHODOLOGY FOR THE SYNTHESIS OF LYCORICIDINE ANALOGUES.

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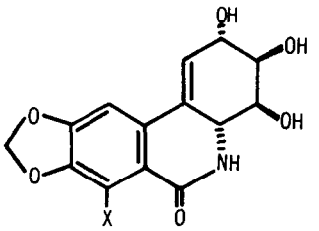
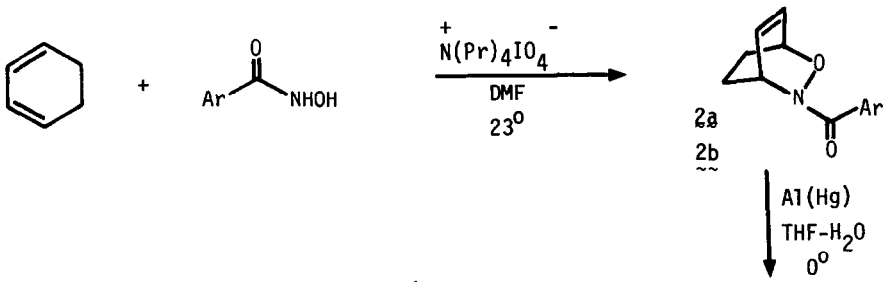
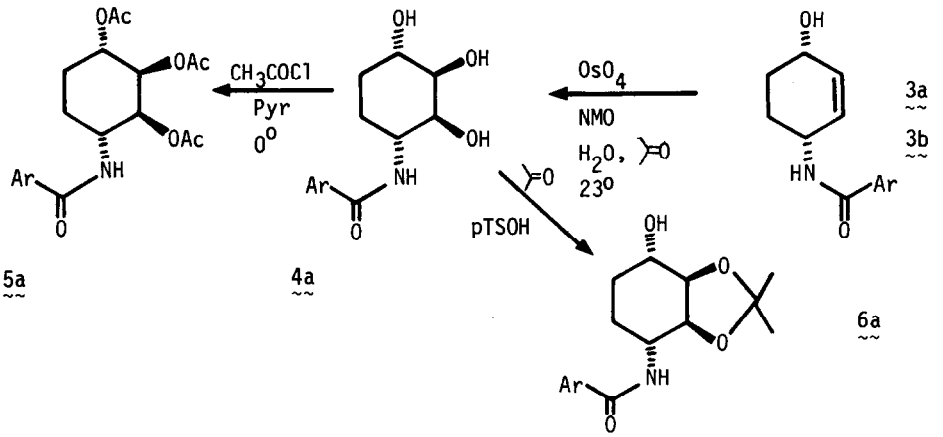
Lycoricidine[1] (1a) and narciclasine[2] (1b) are narcissus alkaloids which have shown a number of interesting biological effects, including potent antitumor activity against larynx carcinoma and cervix carcinoma.[2] In addition, both cis and trans dihydronarciclasine showed activity against these carcinomas.[2] In view of the promising antitumor activity and interesting biological properties associated with these alkaloids, it seems remarkable that little activity directed towards their synthesis has been recorded. We now report model studies leading to the synthesis of a pair of simple analogues of dihydrolycoricidine, using newly developed synthetic methodology which should also prove of utility for the construction of the naturally occurring materials themselves.



1a X = H
1b X = OH

Slow addition[3] of a DMF solution of benzhydroxamic acid[4] (1 mmol/mL) to a stirred solution of cyclohexadiene (1.2 eq) and tetra-N-propyl ammonium periodate[5] (1.05 eq) in DMF (1 mL per mmol of oxidant) at 23° under argon, gave, after normal extractive workup, Diels-Alder adduct 2a[6,7] mp 105-108° (from hexane-$CHCl_3$), in 65-70% yield. Reductive cleavage of the N-O bond in 2a with preservation of both the carbon-carbon double bond and the amide carbonyl was readily accomplished in quantitative yield by treatment of adduct 2a with excess (7 eq) aluminum amalgam in 10:1 THF-H_2O at 0° for several hours. Conversion of olefin 3a to trihydroxy amide 4a in quantitative yield proved possible by reaction of olefin 3a with OsO_4 (0.05 eq) and N-methyl-morpholine-N-oxide[8] (1.2 eq) in acetone-water (2:1) at 23° for 24 hours, affording exclusively the trihydroxy





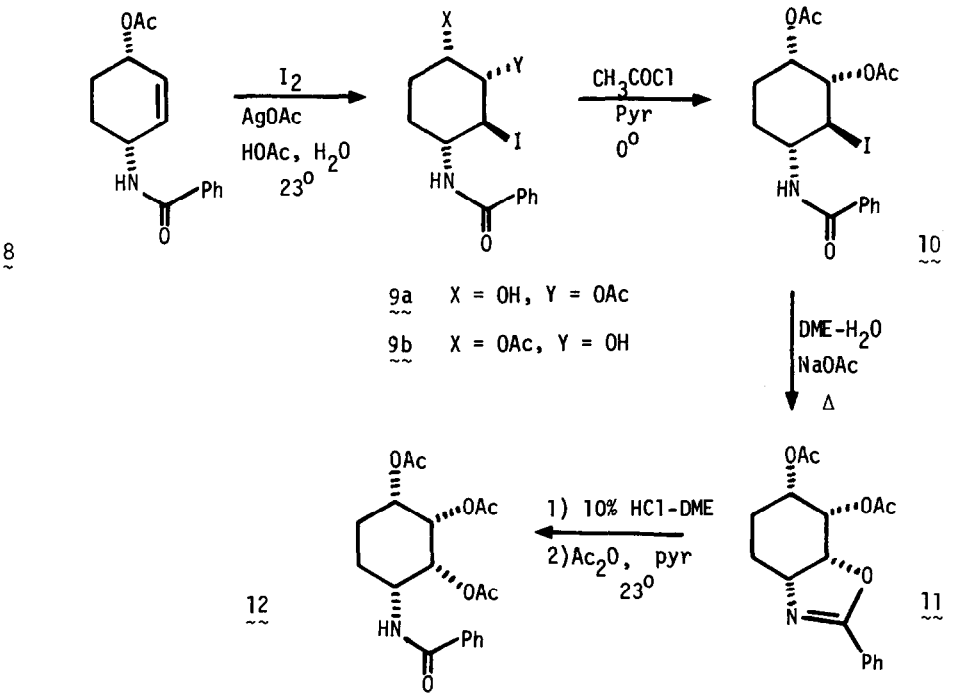
amide isomer 4a with the stereochemistry shown (vida supra).

The very polar trihydroxy amide 4a (Rf. 0.05 with 20:10:1 benzene-dioxane-acetic acid as solvent, vs. 0.34 for 3a) could be converted (3.3 eq of acetylchloride in pyridine, 0^{o}, 5 hrs) to a crystalline triacetate (5a, mp 187-189°, from hexane-chloroform) which exhibited only 3 methyl singlets in its 90 MHz NMR spectrum, and which was homogeneous by tlc analysis in four different solvent systems. Similarly triol 4a gave a single acetonide (6a) upon treatment with a catalytic amount of para-toluenesulphonic acid in refluxing acetone. These observations require that only one trihydroxyamide be produced by the sequence outlined above.

Chemical evidence that 4a was in fact the desired trans, cis, trans isomer rather than the alternative all cis isomer 7 was obtained through independent synthesis of 7 (as its triacetate) by subjection of acetate 8 (from acetylation of alcohol 3 with 1.2 eq of CH_3COCl in pyridine, 0^{o}, mp 130-132°, from hexane-chloroform) to a modified Woodward-Prevost reaction - a reaction well known to result in cis hydroxylation from the more hindered face of the olefin.[9]

Thus, exposure of 8 to 1.05 eq each of iodine and silver acetate in acetic acid containing 20 eq of water at 23^{o} for 20 hrs gave, after acetylation of the resulting crude hydroxy acetate product, iodo-diacetate 10 in 63% isolated yield from 3 after purification by column chromatography. The stereochemistry of 10 follows unambiguously from the observation of a mixture of isomeric hydroxy acetates as the initial reaction product, formed via neighboring group participation by the proximate acetyl function. The proposed stereochemistry is readily confirmed by the nmr spectrum of 10, which shows the proton α to iodine coupled equally ($J_{ax,ax}$ = 6 Hz) to two adjacent axial protons. Solvolysis of iododiacetate 10 in DME-H_2O (1:1, 40 ml per g of 10) buffered with sodium acetate (5.5 eq) at reflux for 30 hours afforded, after purification by column chromatography, oxazoline 11 in 61% isolated yield. Hydrolysis of oxazoline 11 with 10% HCl (0.1 ml per mg of 11) in DME (0.2 ml per mg of 11) at reflux for 15 hours, followed by acetylation of the resulting crude product (excess acetic anhydride in pyridine, 23^{o}, 24 hrs) gave the desired all cis triacetoxy amide 12. The stereochemistry assigned to 12 follows uniquely from the observation of neighboring

group participation during the formation of 9 and 11.



A similar oxidative cycloaddition of 3,4-methylenedioxybenzhydroxamic acid with cyclohexadiene furnished adduct 2b in 69% yield. Reduction and hydroxylation as above afforded dihydrolycoricidine analogue 4a, possessing all functional groups of the authentic material, and the correct stereochemical disposition of the four asymmetric centers generated by the presence of four contiguous heteroatom substituents. It is of interest to note that the dienophilic nature of nitroso-carbonyl benzene appears (for synthetic purposes) little effected by the electron donating para oxygen substituent present in the 3,4-methylenedioxy derivative which was an a priori concern with the present approach.

In summary, we note that the synthetic methodology described herein should not only simplify the challenge posed by narciclasine and lycoricidine, but should prove a generally useful addition to available methodology for the synthesis of alkaloids and other nitrogen containing compounds. These and other applications are being actively investigated in our laboratory.[11]

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3. A Sage syringe drive was utilized with settings such that a 20-25 sec interval between drops was obtained.

4. L. W. Jones and C. D. Hurd, J. Am. Chem. Soc., 43, 2422 (1921).

5. This reagent was prepared by simply mixing equimolar amounts of tetra-N-propyl ammonium hydroxide (10% in water) and aqueous periodic acid. The resulting thick precipitate was filtered, dried, and recrystallized from ethanol to afford needles, mp 180-182°, in 91% yield.

6. Satisfactory spectral data were obtained on chromatographically homogeneous material for all new compounds reported herein. Full experimental detail will be given in our full paper.

7. For a previous example of Diels-Alder reactivity of acyl nitroso compounds note G. W. Kirby, J.C.S. Chem. Comm., 704 (1972).

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10. Triacetates 6a and 14 are readily distinguished by their NMR spectra. Additionally, the observed relative R_F^Ts of 6a and 14 (0.58 vrs. 0.33 in PhH-dioxane-HOAC 20:10:1) are in accord with the expectation that the isomer in which all heteroatom substituents are on the same molecular face should be more polar.

11. This paper is dedicated to Professor E. J. Corey on the occasion of his 50th birthday.

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