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SYNTHESIS OF THE 2-AZA-7-OXATRICYCLO[4.3.2.$0^{4,8}$]UNDECANE NUCLEUS OF SOME GELSEMIUM ALKALOIDS

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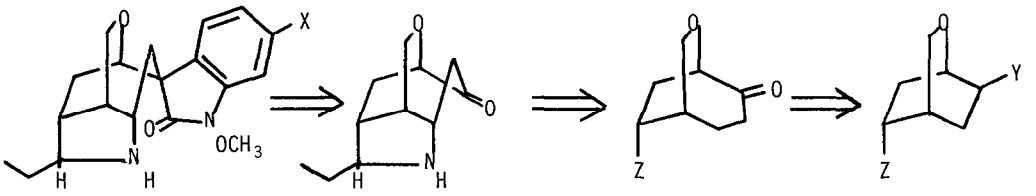
The preparation of a key tricyclic intermediate for the eventual total synthesis of the alkaloids gelsemicine and gelsedine is described.

The alkaloids gelsemicine (A)[2] and gelsedine(B),[3] isolated from extracts of Carolina jasmine (G. sempirvirens),[4] possess marked physiological activity and unique molecular architecture. Several years ago these features attracted our attention and led to the initiation of a program aimed at the eventual total syntheses of gelsemicine and gelsedine. This note describes highlights of the preparation of an important intermediate which contains the major structural features of the tricyclic non-aromatic portion of the target molecules.

One attractive mental dissection of gelsemicine and gelsedine suggests a four stage synthesis beginning with the preparation of a [2.2.2]oxabicyclooctane ring systems such as E and culminating with the incorporation of the spirooxindole-hydroxamic acid group into a tricyclic intermediate (eg., C). An outline of the synthesis of a close analog of C is presented here.



A; X=OCH_3 C D E

B; X=H

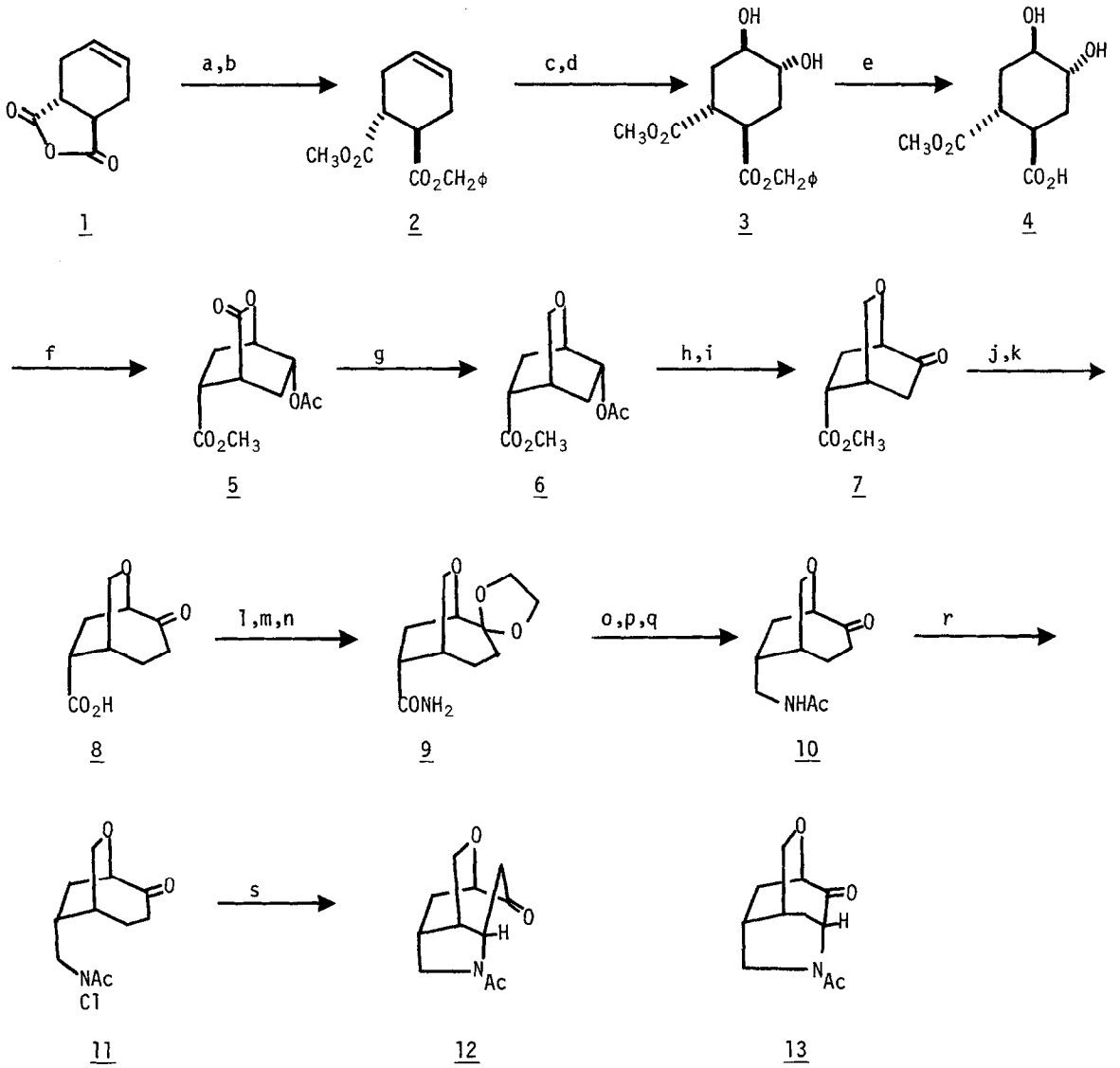
Anhydride 1[5] was readily converted to the functionally differentiated diester 2 which on epoxidation and careful acidic hydrolysis yielded, stereospecifically, the dihydroxy diester 3. Removal of the benzylic ester by catalytic hydrogenolysis afforded acid 4 (mp. 169-169.5°) in 74% yield from 1. Lactonization, with simultaneous acetylation of the remaining hydroxyl group, was then effected by heating 4 with acetic anhydride to give triester 5 (mp. 65.5-66°; δ 4.9 and 4.6).

Reduction of the lactone carbonyl of 5 initially posed serious problems, but after considering numerous possibilities, a solution was found in the elegant work of Tsurugi.[6,7] Thus exposure of 5 to $HSiCl_3$ (2.5 eq.) in the presence of $(t\text{-BuO})_2$ (catalytic, uv initiation) led to the production of ether 6 in 50% yield, a highly selective reaction. Conversion of 6 to ketone 7 was then accomplished in a routine fashion. After considerable investigation the ring expansion step (E → D) was achieved by the BF_3 OEt_2 catalyzed reaction between ketone 7 and ethyl diazoacetate.[8] Basic hydrolysis of the resulting regioisomeric β-ketoesters followed by acidic workup gave a product from which ring expanded ketone 8 was isolated by fractional crystallization (25%; mp. 137-137.5°; δ 4.1 and 2.8).[9]

The final stage in the construction of the non-aromatic tricyclic nucleus of gelsemicine and gelsedine (D → C) involved closure of the pyrrolidine ring. This was effectively accomplished by employing a modification of the Hofmann-Loffler reaction.[10] Acid 8 was first converted to protected amide 9 (mp. 152-153°) which was then reduced, acetylated, and hydrolyzed to give ketone 10 (mp. 126-127°; ir 1670 cm^{-1}). N-Chlorination of acetamide 10 with tert-butylhypochlorite[11] gave the unstable N-chloro compound 11 which on irradiation followed by workup and chromotographic purification afforded the pyrrolidine 12 as a waxy solid (43%) plus a small amount of recovered starting amide 10. That cyclization had occurred was evident from the amide carbonyl absorption of 1631 cm^{-1}, a value in agreement with absorptions of 1626 cm^{-1} and 1621 cm^{-1} for N-acetylpyrrolidine[12a] and N-acetylpiperidine respectively.[12b] More important, it is in agreement with the value of 1626 cm^{-1} obtained for N-acetyldemethoxygelsedine.[3]

That the product was the pyrrolidine 12 and not the alternative piperidine 13 was clear from a close examination of the pmr spectrum. Particularly diagnostic was the absorption for the C-5 bridgehead methine proton adjacent to the nitrogen at δ 4.65, a value in accord with literature reports for several bridged bicyclic N-acetylamines[13] and inconsistent with the additional deshielding which would be present in structure 13. Furthermore the multiplicity of this absorption (quintet, J = 4Hz) is only consistent with structure 12.

Thus a synthesis of the tricyclic nucleus of gelsemicine and gelsedine has been accomplished. The remaining tasks of stereospecific incorporation of the C-20 ethyl group and the spirooxindole-hydroxamic acid group, as well as improving the efficiency of some of the reactions reported herein, are under active investigation.



[a] ϕCH_2OH (90%); [b] CH_2N_2 (91%), [c] mcpba (95%); [d] H_3O^+ (95%); [e] H_2, Pd/C (100%); [f] Ac_2O, 90° (66%); [g] $HSiCl_3/h\nu$ (50%); [h] K_2CO_3/CH_3OH (67%); [i] H_2CrO_4 (83%); [j] $N_2CHCO_2C_2H_5$, $BF_3 \cdot OEt_2$; [k] $NaOH/C_2H_5OH$ (25%), two steps); [l] NaH/C_6H_6, $(COCl)_2$ (88%); [m] NH_3 (86%); [n] $HOCH_2CH_2OH/C_6H_6$/p-TsOH (78%); [o] $LiAlH_4$/THF (95%); [p] Ac_2O/pyr (94%); [q] H_3O^+ (90%); [r] t-BuOCl/CCl_4/HOAc (78-100%); [s] $h\nu/C_6H_6$ (43%).

References and Notes

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14. All new compounds reported herein gave satisfactory elemental analyses (± 0.3%) or consistent high resolution mass spectral molecular ions for homogenous materials. In addition all spectral data were fully consistent with the assigned structures.

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