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Synthetic Studies in the *Veratrum* Alkaloid Series

The Total Synthesis of Verarine, Veratramine, Jervine, Veratrobasine, and Verticine[1]

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A review summarizing our results in a research program directed at the syntheses of alkaloids within the *Jerveratrum* and *Ceveratrum* groups of *Veratrum* alkaloids is provided. The overall synthetic strategy involves the syntheses of appropriate C-nor-D-homo steroid intermediates and, then, reaction of the latter with the required heterocyclic units to afford the important synthetic intermediates for final elaboration to the natural systems. The discussion illustrates the application of this strategy to the synthesis of verarine, 5α,6-dihydroveratramine, and the hexacyclic base verticine.

The *Veratrum* alkaloid family occupies a position of importance among the large group of natural products generally known as steroidal alkaloids. Due to the unique C-nor-D-homo steroid skeleton inherent in this family, its members have provided a considerable challenge to structural and synthetic chemists for a long time. Detailed studies by various groups (*1*, *2*) have allowed the complete structural assignments to many members within this class, while biological evaluation has shown possible application to the control of hypertension (*3*) and the insecticidal area (*4*). More recently (*5*), some teratogenic activity has been noted in some members. All of these investigations have provided considerable stimulation among various research groups (*6–10*) to develop laboratory syntheses of these natural products. This article provides a summary of our investigations in this area.

It is convenient, in presenting the overall synthetic strategy which we have employed in our studies, to consider the division of the *Veratrum* alkaloids into the *Jerveratrum* and *Ceveratrum* groups as originally proposed by Fieser and Fieser (*11*). Examples of the former group which were considered initially in our synthetic program are verarine (**1**), veratramine (**2**), and jervine (**3**), while verticine (**4**) is representative of the latter group.

We consider the *Veratrum* alkaloids to possess two main structural units: (i) the C-nor-D-homo steroid skeleton and (ii) an appropriately functionalized heterocyclic system which is attached in various ways to this steroidal unit, as shown schematically in **5**. According to this plan, the synthesis of verarine (**1**) and veratramine (**2**) would require attachment of the heterocyclic unit at position a in **5**, while the jervine system

[1] This article is written in memory of S. M. Kupchan, an outstanding scientist and close friend. Among the numerous elegant contributions which Kupchan made to the scientific community, his investigations of the structures of the veratrum alkaloids are of fundamental importance.

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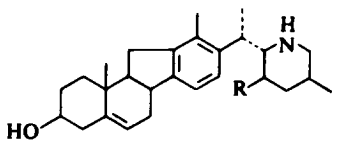
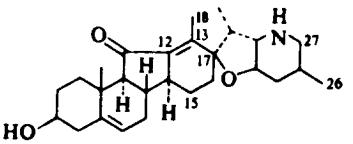


1 R = H
2 R = OH



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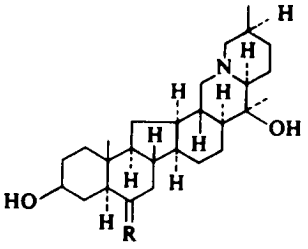
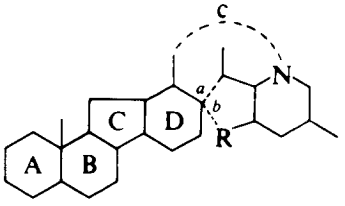


4 R = 

necessitates bond formation at both a and b. Syntheses of the cevanine bases would require attachment at a and c in **5**. Indeed, utilization of this overall plan has resulted in the completion of laboratory syntheses of members within these various families, and this manuscript provides a discussion of these experiments.



5

a veratranine bases
a + *b* jervanine bases
a + *c* cevanine bases

On the basis of the above considerations, it was clear that efficient laboratory syntheses of appropriate C-nor-D-homo steroid intermediates must be developed, and such studies constituted the initial phases of our synthetic program. In our previous studies (*12–14*), we reported stereospecific syntheses of various hydrochrysene analogs, via multistep sequences starting from naphthalene intermediates. One of these intermediates, the *trans*–anti-*trans*-acetate (**6**), appeared well suited for further elaboration to the required C-nor-D-homo steroid units, and considerable effort was expended in this direction.

Somewhat surprisingly, the conversion of **6** to the desired steroid system met with considerable difficulty. In particular, the transformation of the six-membered ring-C structure in **6** to the five-membered ring-C structure necessary for the *Veratrum* system provided more problems than were anticipated. It was envisaged that the most direct

approach for this synthetic objective would employ introduction of appropriate substituents at the benzylic C_{12} site in **6** and then subsequent manipulation to provide the desired ring contraction. In the synthetic experiments which followed, the introduction of such substituents was not a straightforward process. The other benzylic center, C_{4b}, by virtue of its *para* relationship to the methoxyl function in **6**, provided complications due to its apparent higher reactivity. Thus, attempts to introduce substituents at C_{12} by the usual reagents (chromium trioxide, *N*-bromosuccinimide, lead tetraacetate, etc.) did not provide the desired 12-substituted intermediate, but, rather, the ring-C aromatic hydrochrysene derivatives **8**, **9**, and **10** (Fig. 1). Success was achieved by the use of the sterically hindered oxidant *t*-butyl chromate, whereupon the major product obtained

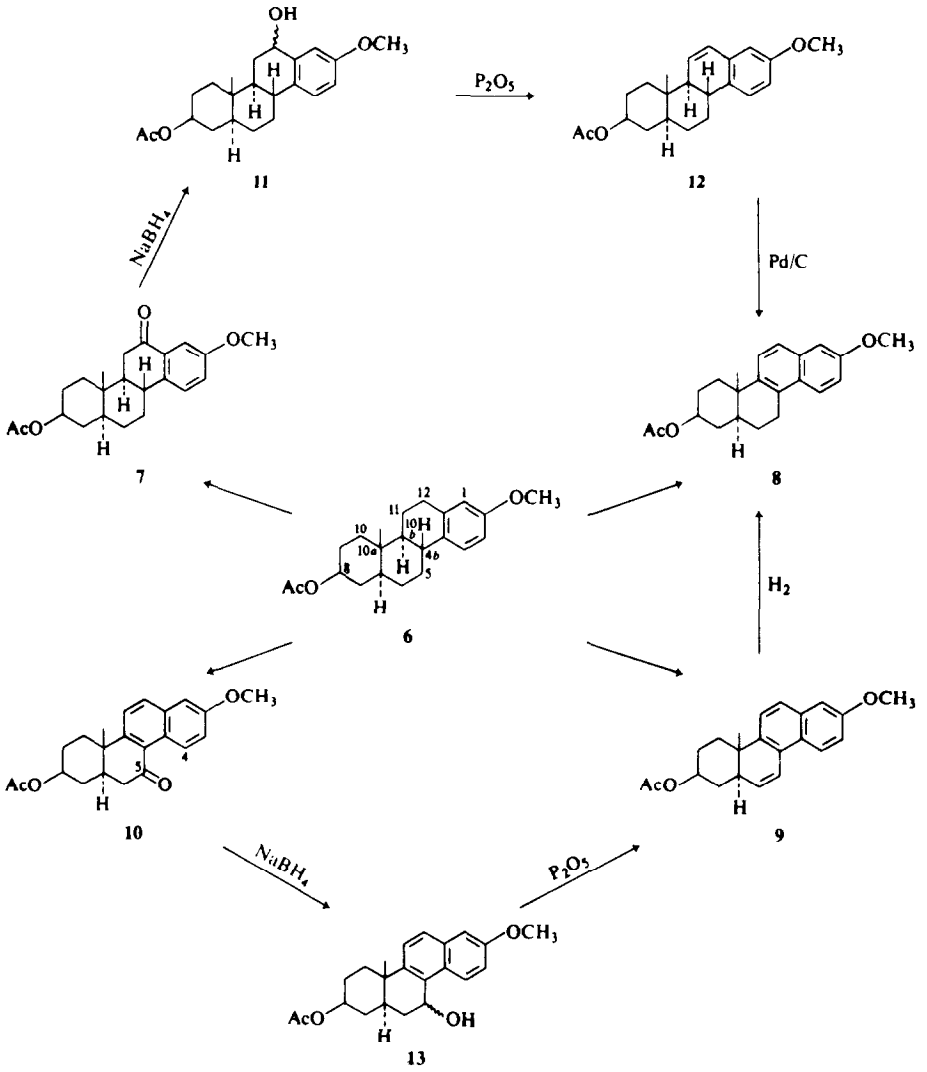


FIG. 1. Oxidation studies on *trans*–anti-*trans*-acetate (**6**) and the various interrelationships between the products formed.

was the desired 12-keto derivative **7**. Detailed discussions of these experiments are already provided in several publications (*9*, *13*). Figure 1 provides an overall summary of the experiments which were performed in this area.

The synthesis of the C-nor-D-homo intermediates from the keto acetate **7** became the next important phase of the synthetic program, and a summary of the most relevant experiments is provided in Fig. 2.

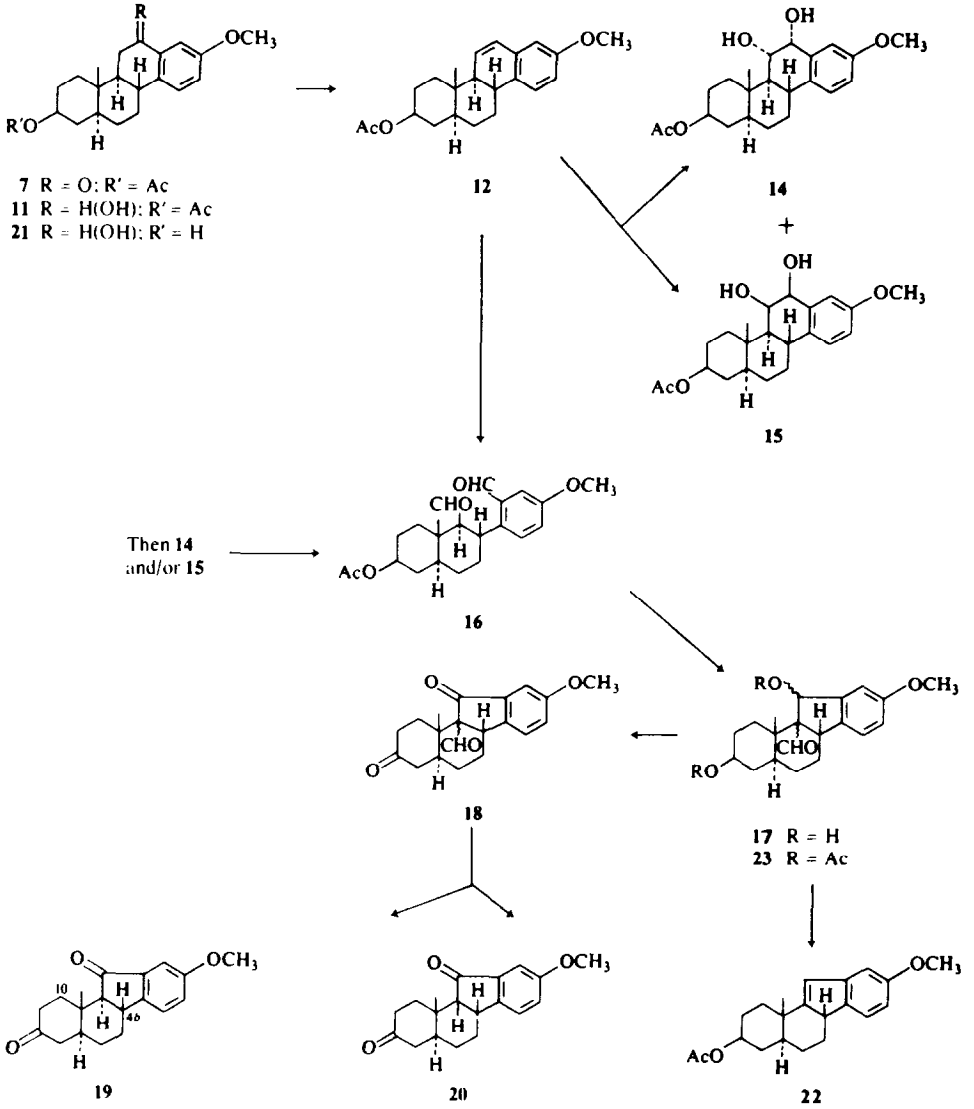


FIG. 2. The synthesis of various C-nor-D-homo steroid intermediates from the hydrochrysene analog **7**.

Borohydride reduction of **7** at room temperature provided a high yield of the expected C_{12}-hydroxy compounds with the 12β configuration of the alcohol function present in the major product (**11**; $C_{12}\beta$-OH). At refluxing methanol temperature, reduction and hydrolysis of the C_8 acetate function are achieved, so that the diol, **21** ($C_{12}\beta$-OH), is isolated in high yield.

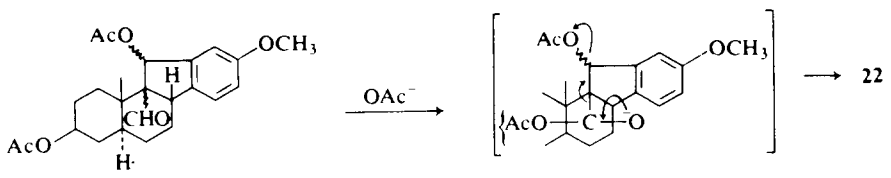
The olefin **12** obtained by phosphorus pentoxide dehydration of either of the two pure alcohols (**11**) or, preferably, of a mixture obtained directly from the borohydride reduction of **7**, was then employed in a normal hydroxylation procedure (osmium tetroxide) to provide the two diols **14** (minor) and **15** (major) in good overall yield. Periodate cleavage of the latter substances allows the synthesis of the important dialdehyde intermediate **16**.

The synthesis of the desired C-nor-D-homo system as seen in **17** was accomplished by an internal aldol condensation of **16**, employing alcoholic sodium hydroxide as reagent. Removal of the tertiary aldehyde function in **17** and generation of the required *trans*–anti-*trans* stereochemistry as shown in **19** were achieved via several different routes.

The well known deformylation of β-keto aldehydes suggested the sequence **17** → **18** → **19** or **20** (Fig. 2), and some success was achieved in this direction. Oxidation of diol aldehyde **17** with Jones reagent provided the unstable diketo aldehyde **18**, and the latter undergoes deformylation in a basic medium (alumina or potassium hydroxide) to provide a 1:1 mixture of the expected C-nor-D-homo ketones **19** and **20**. Separation of these ketones proved extremely difficult and, in fact, could only be accomplished by separation of the different crystalline forms of these isomers with the aid of a microscope.

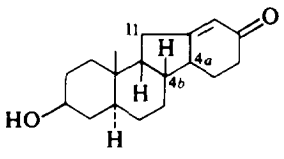
Thermodynamic stability of hydrindanone systems is an interesting area of conformational analysis and is by no means as simple as the decalone systems where, in general, *trans* fusion of the rings provides for more stability. Depending on the nature of the substitution, either *cis*- (*15–22*) or *trans*-hydrindanones (*23–27*) can be considered as thermodynamically more stable. In our studies, the 1:1 ratio of the desired *trans*–anti-*trans* ketone **19** and the undesired *trans*–syn-*cis* intermediate **20** could not be altered, and the deformylation procedure via **18** was abandoned.

An alternative and highly successful sequence for removal of the aldehyde group in **17** was devised. It seemed reasonable to expect that the acetate derivative **23**, available as a derivative from the aldol condensation studies, might undergo elimination in the manner indicated, **23** → **29** → **22**, to provide a suitable C-nor-D-homo steroid system for eventual elaboration to the *Veratrum* alkaloid unit. Schiess et al. (*28*) had utilized a similar reaction in their studies. Indeed, when **23** was subjected to reaction with sodium acetate–acetic acid, an 80% yield of the olefin **22** was isolated.

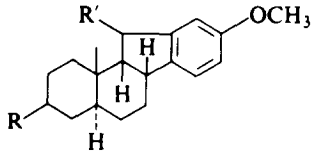


23 **29**

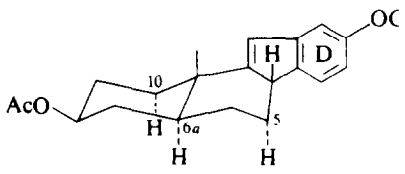
Saturation of the olefinic linkage in **22** was studied in considerable detail. It was found that Birch conditions provided reduction of both the double bond and the aromatic ring to afford **30**, catalytic hydrogenation provided **31**, while hydroboration converts **22** to **32**. It is to be noted that, in all instances, the reaction products contain the undesired *cis* fusion of rings B and C, and, clearly, a solution of this stereochemical problem was mandatory.



30



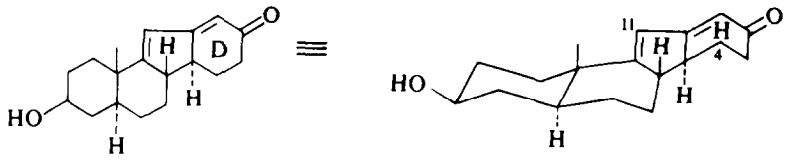
31 R = OAc; R′ = H
32 R = R′ = OH



33

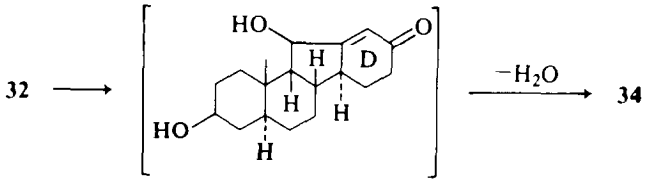
Consideration of the conformational structure (**33**) for this olefin reveals some preference for attack of reagents to the β face of the molecule. The rather "bent" backbone of this system provides interference for approach from the α side particularly from the axial hydrogen atoms at C_5, C_{6a}, and C_{10}, as shown. Consequently, any alteration in the molecular shape, particularly with respect to rings C and D, might be expected to alter the steric course of reaction at the olefinic linkage in **22**. Evaluation of such considerations did provide a successful solution to this important problem.

The unsaturated ketone **34**, possessing a nonplanar ring D (see **34a**) and, thereby, increasing steric hindrance to β attack at C_{10b}–C_{11}, was selected as a possible intermediate for the preparation of the desired B/C *trans*-fused systems.



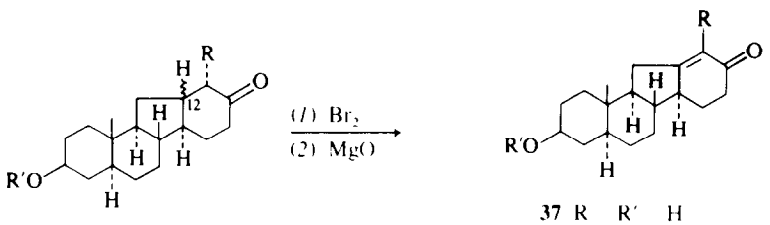
34 34*a*

The synthesis of **34** was accomplished as shown by the sequence, **32** → **35** → **34**. Birch reduction (lithium, ammonia, dioxane, isopropanol) of **32** provided the desired reduction of the aromatic ring, and the resultant intermediate **35** is not isolated but, as expected, undergoes spontaneous dehydration to **34**.



35

Catalytic reduction of the unsaturated ketone **34** provided a product mixture of the saturated ketone **36** and the conjugated ketone **37**. These compounds proved difficult to separate, and, since **37** was the desired product for the future objectives, it was convenient to react the hydrogenation mixture initially with bromine and then with magnesium oxide, thereby allowing facile isolation of **37**. A comparison of **30** and **37** clearly established their differences, and the stereochemical assignments as shown were proven in subsequent studies.



36 R R′ H
38 R CH_3; R′ Ac

37 R R′ H
39 R CH_3; R′ Ac

Analysis of the structures of the veratramine and jervine series of alkaloids reveals that they possess a methyl substituent at C_{13} in the C-nor-D-homo steroid portion, and it was now essential to study methods for the introduction of this substituent. Of the several procedures evaluated, the enolate-trapping technique developed by Stork et al. (*29*) proved most satisfactory. The C-nor-D-homo ketone **37**, upon reaction with lithium in a mixture of ammonia and dioxane, followed by addition of methyl iodide, provided, after acetylation, the desired intermediate **38**. Subsequent comparison of the latter with 3β-acetoxy-5α-etiojervan-17-one (**38**; αH at C_{12}), prepared according to a known procedure from hecogenin (see later), established the correctness of its structure and stereochemistry as shown.

The conversion of **38** to **39** was accomplished by the route indicated, and, again, this intermediate proved identical with an authentic sample of 3β-acetoxy-5α-etiojerv-12(13)-en-17-one (**39**) as prepared below. An important phase of the synthetic program had now been completed.

Although a synthetic route to the required C-nor-D-homo units was available, it was felt desirable to substantiate the structural and stereochemical assignments in the above-mentioned C-nor-D-homo intermediates since, in all instances, such assignments were made from analyses of spectroscopic data. Fortunately, it was possible to provide an unambiguous correlation with compounds derived from the degradation of the readily available steroid sapogenin, hecogenin acetate (**40**). Johns and Laos (*30*) had developed an appropriate degradation of **40**, and, with minor modifications to their scheme (**40** → **41** → **42** → **39**) as outlined in Fig. 3, the syntheses of optically active **38** and **39** were accomplished. Comparison of these compounds with the above synthetic intermediates established their identity.

Resolution of the racemic synthetic intermediate **39** by microbiological methods involving the steroid dehydrogenase of *Arthrobacter simplex* to provide optically active **39** was also carried out (*31*) to substantiate the previous comparisons.

Continuing our synthetic program according to the original plan, we considered the utilization of the above C-nor-D-homo steroid intermediates in the synthesis of verarine (**1**). A summary of the successful sequence leading to 5α,6-dihydroverarine (**49**; R = R^1 = H) is presented in Fig. 4.

The desired heterocyclic unit for the verarine system is the known (*32*) 2-ethyl-5-methylpyridine prepared in our laboratories by the methylation of 2,5-lutidine (phenyl lithium and methyl iodide). The lithium salt (**46**; R^1 = H) of this pyridine derivative was condensed with the etiojervene unit (**39**; R = Ac; Fig. 4) to provide a mixture of compounds possessing the gross structure **47** (R = Ac; R^1 = H). Since the coupling reaction generates two new chiral centers (C_{17} and C_{20}), four products were expected

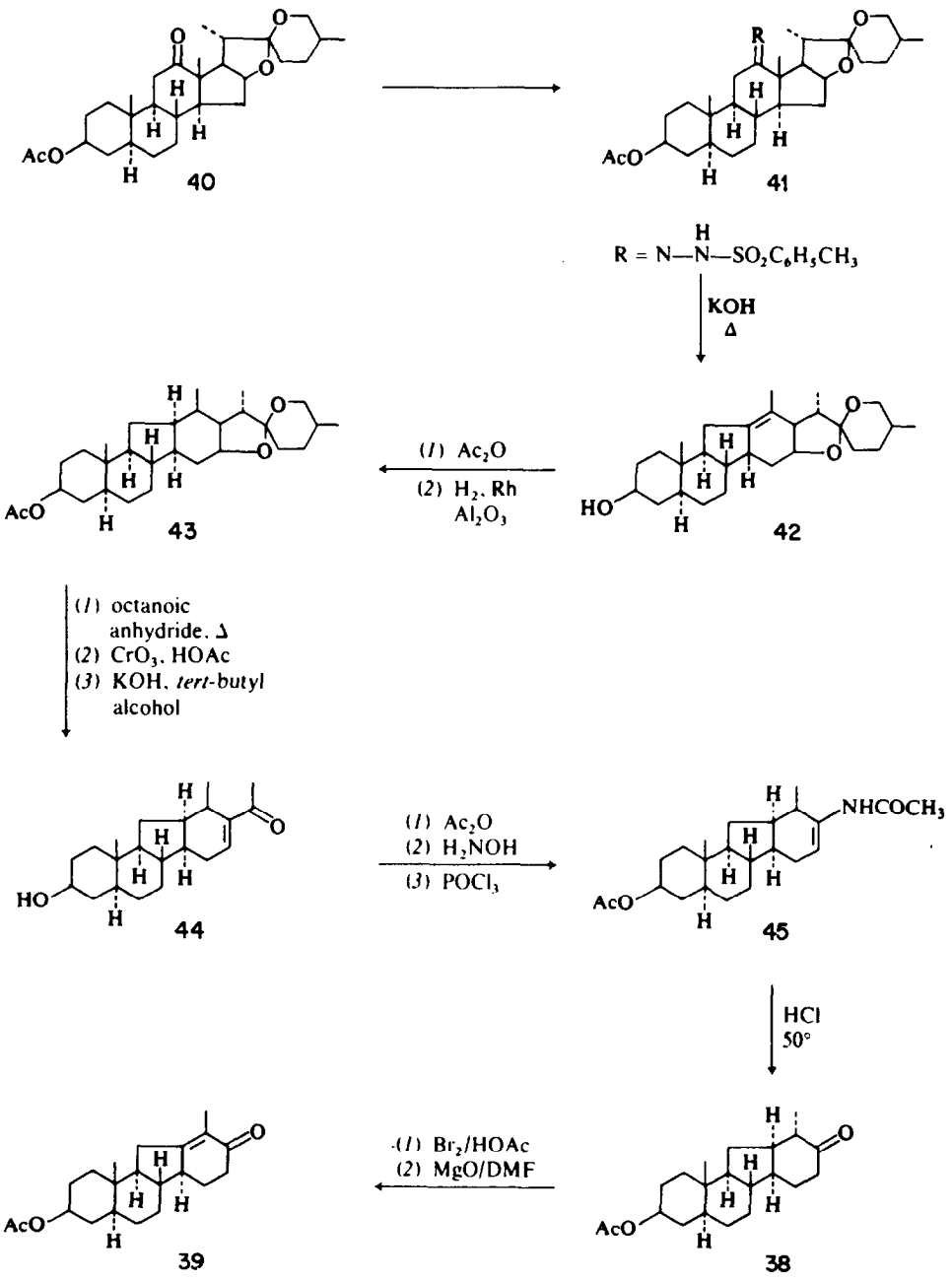


FIG. 3. The degradation of hecogenin acetate (**40**) to 3β-acetoxy-5α-etiojerv-12(13)-en-27-one (**39**).

and were indeed isolated and characterized. A detailed discussion of the chemistry of these various products is provided elsewhere (*10*), so only the most salient features will be presented here.

Two of the major products possessing the gross structure **47** (R = Ac; R^1 = H) were each subjected to an aromatization reaction (10% palladized charcoal, 200°C) and the

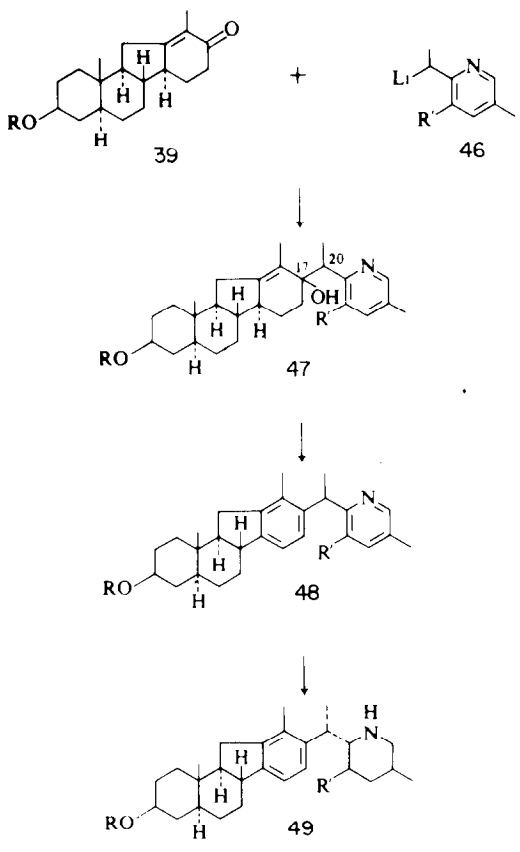
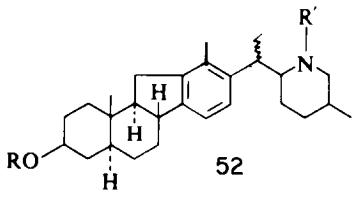


FIG. 4. An outline of the sequence leading to the synthesis of 5α,6-dihydroverarine (**49**; R = R^1 = H).

products isolated could be readily assigned structures **50** and **51** (R = Ac; R^1 = H), differing only in the stereochemical orientation of the methyl group at C_{20}. The absolute configuration at C_{20} could not be ascertained at this time, but the subsequent conversion of **51** (R = Ac; R^1 = H) to the natural series settled this question.

Catalytic reduction of the aromatic compound **51** (R = Ac; R^1 = H) afforded four compounds possessing the gross structure **52** (R = Ac; R^1 = H). Here again these compounds could be separated by careful preparative layer chromatography and converted to the *N*-acetyl derivatives [gross structure **52** (R = H; R^1 = Ac)], via the 3-*O*,*N*-diacetates (**52**; R = R^1 = Ac) and the selective hydrolysis of the 3-acetoxyl group (0.1 *M* potassium hydroxide in methanol). Comparison of these compounds with authentic samples of dihydroverarine derivatives (see later) established that the *major*

product from the reduction of **51** (R = Ac; R^1 = H) possesses the desired stereochemistry at the various chiral centers, as shown in **53**.



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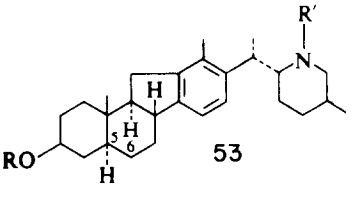
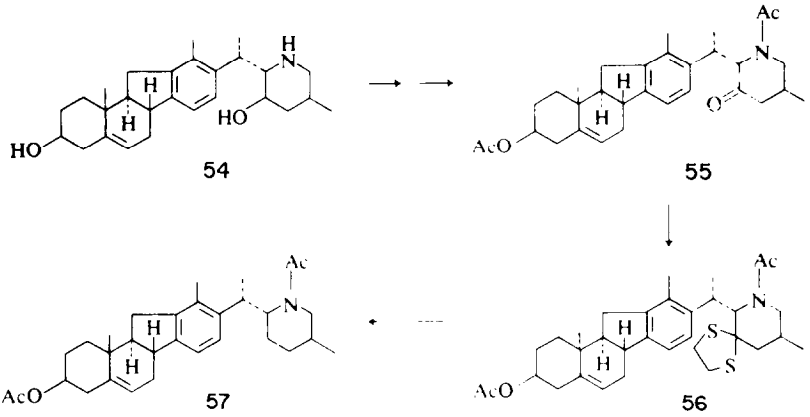


53

Unambiguous assignment of stereochemistry in the various synthetic products discussed above required a degradation of a natural alkaloid to appropriate verarine derivatives, since the stereochemistry in the natural series had been settled by X-ray analysis. Veratramine (**54**) was selected for this purpose, and its degradation was performed essentially according to the scheme developed by Masamune et al (*33*) (**54** → **55** → **56** → **57**). Hydrogenation of 3-*O*,*N*-diacetyl verarine (**57**), employing Adams' catalyst in acetic acid, provided authentic 3-*O*,*N*-diacetyl-5α,6-dihydroverarine (**53**; R = R^1 = Ac) which, on selective hydrolysis in the previously described manner, afforded *N*-acetyl-5α,6-dihydroverarine (**53**; R = H; R^1 = Ac). These latter substances were compared with the synthetic compounds obtained earlier to establish their identities.



To complete the synthesis of verarine it was necessary to introduce the 5,6 double bond and to remove the amide function in **53** (R = H; R^1 = Ac). The steps involved in completing this objective are outlined in Fig. 5. A similar sequence has been employed by Johnson et al. (*6*) for the introduction of the 5,6 double bond in the veratramine series.

The extension of the synthetic strategy portrayed in the verarine series was now considered for the veratramine (**2**) family. A sequence outlining the most important steps in the successful synthesis of 5α,6-dihydroveratramine (**65**) is presented in Fig. 6.

As Fig. 6 indicates, the heterocyclic unit necessary for coupling with **39** is a pyridine derivative possessing an oxygen function. The unknown pyridine derivative, 2-ethyl-3-hydroxy-5-methylpyridine, was selected for this purpose, and an efficient synthesis of this compound was first required. Gruber (*34*) had studied the reaction of furyl ketones

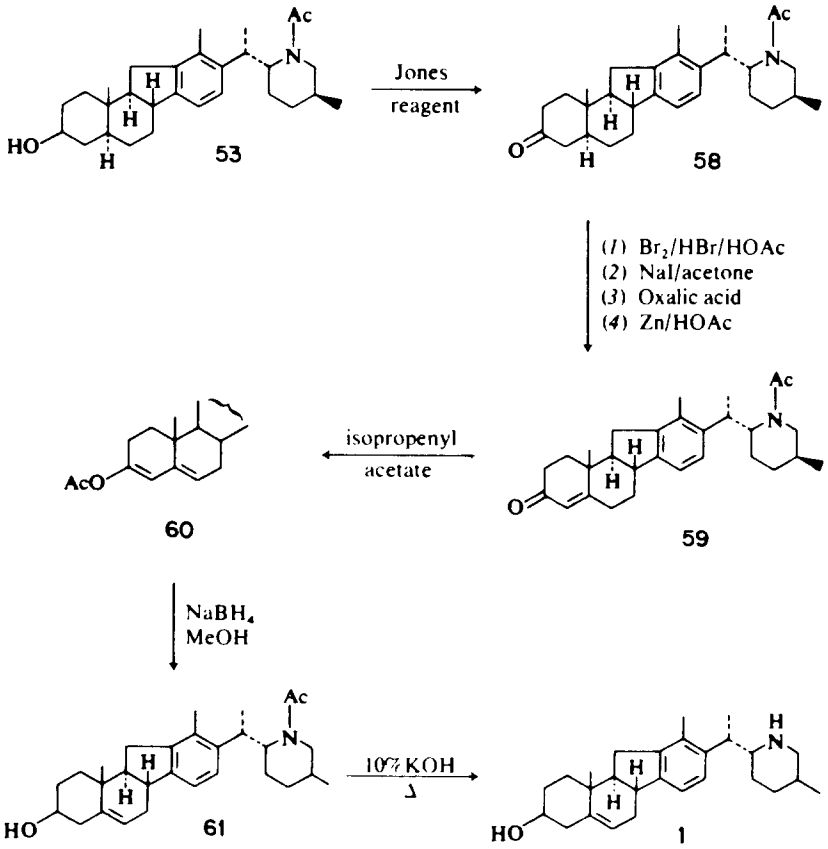


FIG. 5. Conversion of *N*-acetyl-5α,6-dihydroverarine (**53**) to verarine (**1**).

with ammonia and had shown that 3-hydroxypyridines were the products isolated. The evaluation of this approach for our purpose required the availability of 2-propionyl-4-methyl furan (**67**), and, therefore, its synthesis was considered. Two routes (Figs. 7 and 8) were developed, but since all experimental details concerning these studies are published (*10*), no further discussion is provided here. It is sufficient to indicate that the route outlined in Fig. 8 is much preferable and was employed for most of the studies associated with this phase of the synthetic program.

Conversion of **67** to 2-ethyl-3-hydroxy-5-methylpyridine according to the known procedure (*34*) proceeded normally, and conversion of the latter to the required *O*-methyl ether was achieved by reaction with diazomethane. The stage was now set for the coupling of this heterocyclic unit with the C-nor-D-homo steroid intermediate **39**.

Condensation of the lithium salt derivative **62** (Fig. 6) with **39** in the manner already developed earlier provided a reaction product mixture of two compounds possessing the expected gross structure **63** (R = H). In order to achieve separation of these components, conversion to the corresponding acetate derivatives (acetic anhydride, pyridine) was attempted. Some interesting results were obtained after isolation and characterization of the two products resulting from the acetylation reaction. It was clear that *one* of these possessed the gross structure **63** (R = Ac) while the other was a ring-D

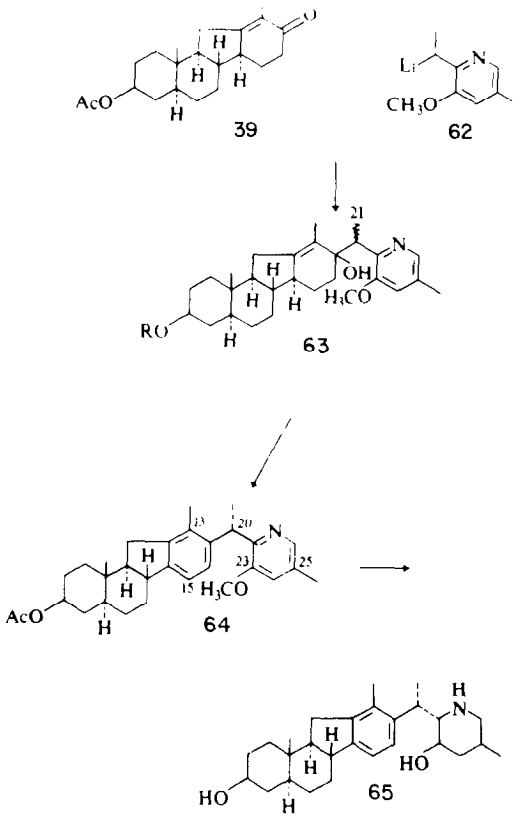


FIG. 6. The synthesis of 5α,6-dihydroveratramine (**65**).

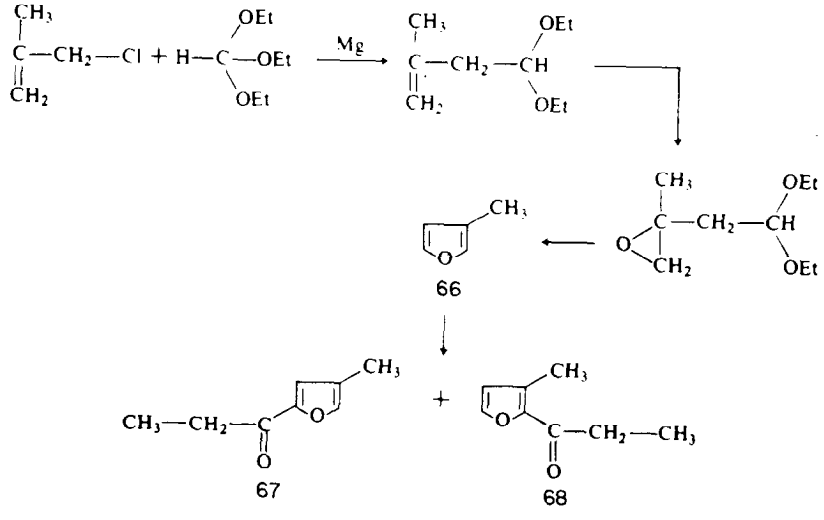


FIG. 7. Synthesis of 2-propionyl-4-methylfuran (**67**) in propionylation of 3-methylfuran (**66**).

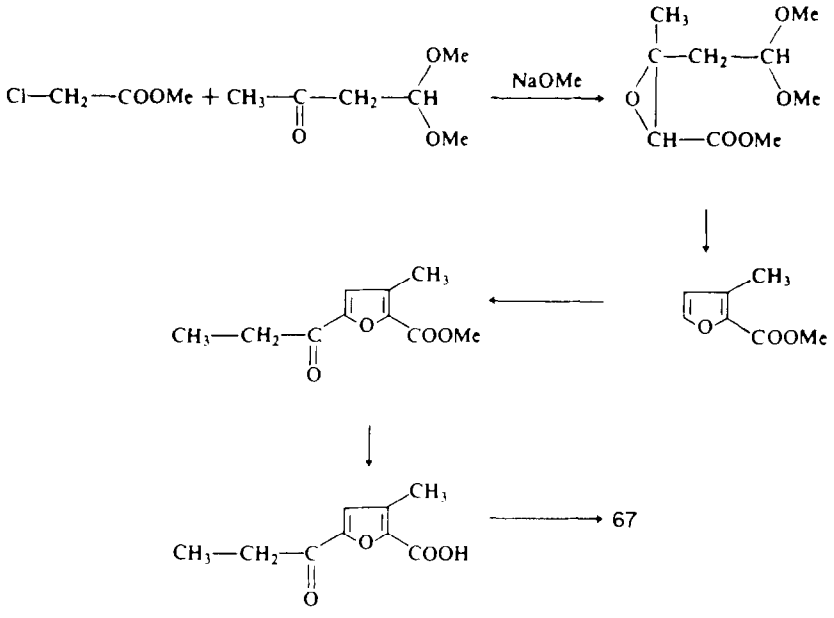
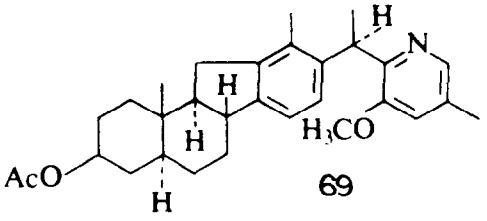


FIG. 8. Synthesis of 2-propionyl-4-methylfuran (**67**) via propionylation of a 2,3-disubstituted furan derivative.

aromatic compound arising from facile dehydration of the C_{17} hydroxyl function and subsequent aromatization of the resulting diene. Since, in subsequent experiments, this aromatic compound gave rise to the natural series, its complete structure and stereochemistry at C_{20} is as portrayed in **64**. The other component resulting from the acetylation (**63**; R = Ac) was exposed to more drastic aromatization conditions (palladized charcoal, 200°C), and it *then* provided an isomeric ring-D aromatic compound possessing the structure **69**. In summary, these results indicated that the coupling reaction had provided a mixture of two isomeric alcohols of gross structure **63** (R = H), and that one of them undergoes facile conversion to the desired aromatic derivative **64**, while the other provides **69**, but only after more severe reaction conditions are applied. A rationale to explain these results is provided elsewhere (*10*).



69

Catalytic reduction (PtO_2, ethanol, hydrochloric acid) of **64** provided the required conversion to 5α,6-dihydroveratramine (**65**), the latter being isolated as a major component along with two other minor products. These studies completed the synthesis of veratramine since the conversion of **65** to the natural product had already been successfully accomplished elsewhere (*6*). Since **65** has also been converted to jervine, **3**,

(*7*, *35*), veratrobasine (*35*, *36*), and 11-deoxojervine (*37*), a synthesis of this intermediate represents, in a formal sense, the total synthesis of these natural systems.

In our most recent investigations in this area we have considered the synthesis of the more complex hexacyclic *Ceveratrum* alkaloids. Since the structure and absolute configuration of verticine (**4**) had been established by X-ray analysis of verticinone methobromide (*38*), it was selected as the first synthetic objective in this series.

The synthetic strategy, as outlined schematically in **5**, requires the coupling of an appropriate heterocyclic system at the C_{17} and C_{18} positions of the C-nor-D-homo steroid intermediate to complete formation of the hexacyclic ring system. For this reason the preparation of the required C_{18}-functionalized C-nor-D-homo steroid intermediates became the first objective in this phase of the program, and the exocyclic olefin **72** was selected as the target compound (Fig. 9). Rockogenin 12-methanesulfonate 3-pivalate (**70**), prepared from hecogenin acetate according to a published procedure (*39*),

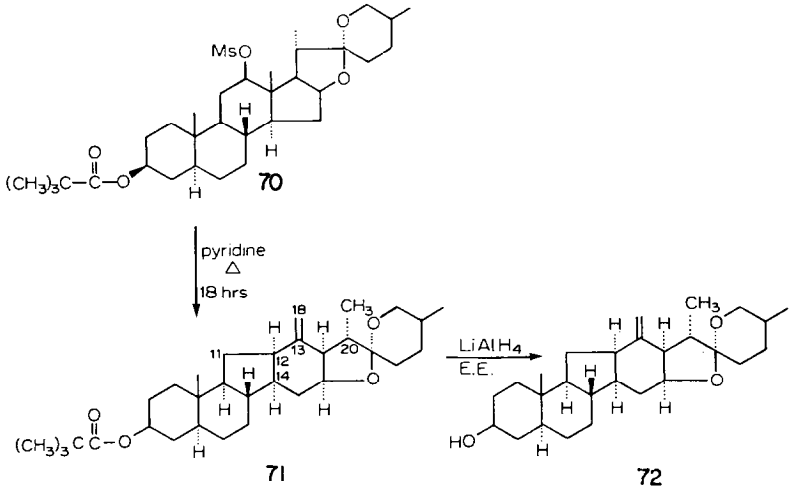


FIG. 9. The synthesis of exocyclic olefin **72** from rockogenin 12-methane sulfonate 3-pivalate (**70**).

was converted in refluxing anhydrous pyridine (*40*) to the C-nor-D-homo exocyclic olefin **71** in 82% yield. Normal reduction with lithium aluminum hydride removes the C_3 protecting group, and the desired olefin **72** is obtained (overall yield from hecogenin acetate is 75%).

It was felt that the C_{13}–C_{18} double bond in **72** would allow the desired functionalization at C_{18}, and the successful sequence is summarized in Fig. 10. Diborane addition converted **72** to a mixture of primary alcohols, with the expected 13β-hydroxymethyl derivative **73** (β-CH_2OH) as the major component. Oxidation of **73** (β-CH_2OH), or the hydroboration mixture directly, via the Moffatt procedure afforded the keto aldehyde **74** which, after equilibration with potassium carbonate, was smoothly converted to the desired thermodynamically more stable aldehyde **75**. Normal borohydride reduction of the latter and acetylation furnished the C_{18}-functionalized C-nor-D-homo steroid derivative **77**.

The next phase of this program concerned the degradation of the spiroketal system present in **77** to suitable side chain for the future synthetic objectives. Although a great deal of literature precedent is available for this type of conversion, the classical

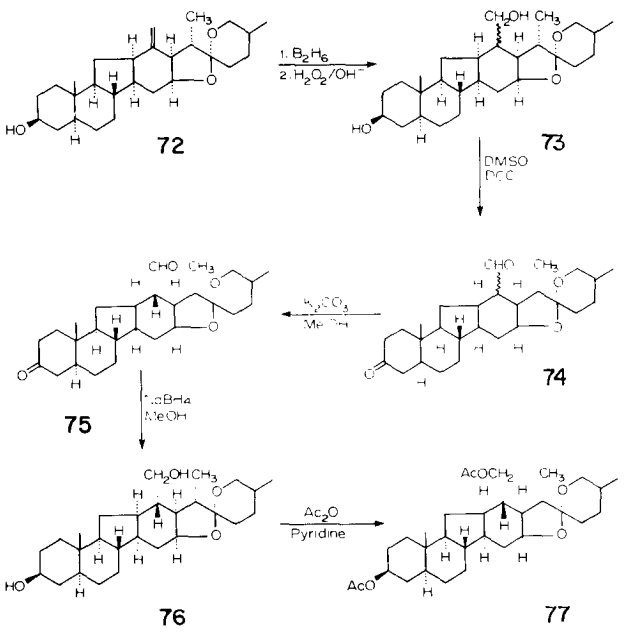


FIG. 10. The synthesis of C-nor-D-homo steroid derivative **77** from the exocyclic olefin **72**.

approach involving an acid anhydride followed by chromic acid oxidation proved unsuccessful in some C_{18}-substituted C-nor-D-homo steroids studied by Johns (*41*), so its application was not seriously considered. An alternative method involving the reaction of sapogenins under Baeyer–Villiger conditions (*41*) was studied in considerable detail, and the results of these experiments are summarized in Fig. 11. The

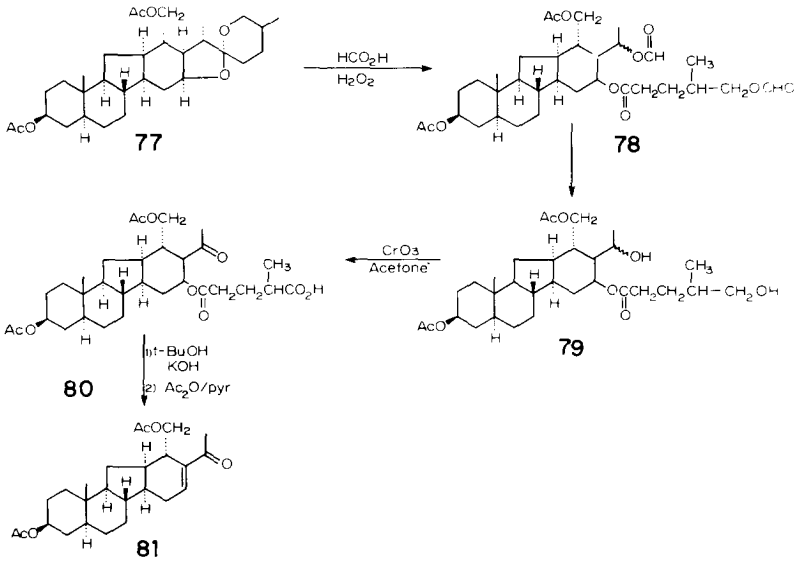


FIG. 11. The synthesis of C-nor-D-homo steroid derivative **81** from performic acid degradation of diacetate **77**.

diacetate **77** was subjected to treatment with performic acid under varying conditions of temperature (0–45°C) so as to obtain optimum conditions for the ring opening of the spiroketal system and provide the desired intermediate **78**. In fact, the resulting reaction mixture was very complex and generally was subjected directly to mild alkaline hydrolysis. The hydrolysis mixture containing **78** as one of the components was reacted with chromium trioxide, followed by base-catalyzed elimination, and finally by acetylation to afford the desired α,β-unsaturated ketone **81**. Unfortunately the overall yield of **81** from the diacetate **77** was low (15–20%), and a more satisfactory route was required. Figure 12 provides an attractive solution to this problem.

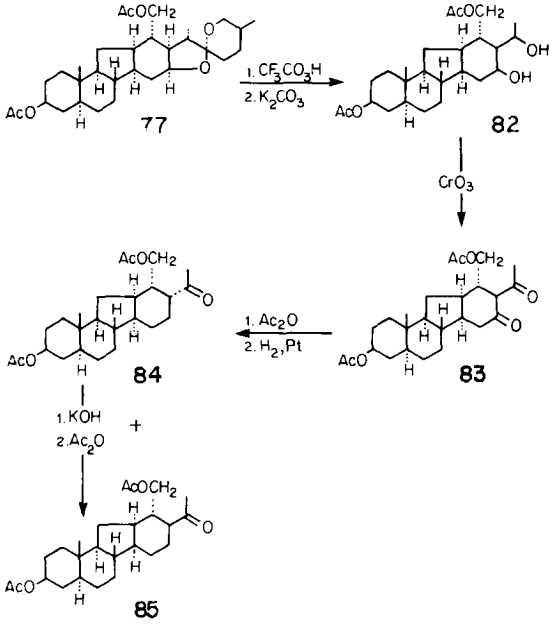


FIG. 12. The synthesis of C-nor-D-homo steroid intermediate **85** from peroxytrifluoroacetic acid degradation of diacetate **77**.

Reaction of diacetate **77** with peroxytrifluoroacetic acid at room temperature and immediate treatment of the resultant mixture with potassium carbonate provided the diol **82** in 70% yield. Jones oxidation of the latter allows isolation of diketone **83** in an essentially quantitative yield. Elaboration of the diketone **83** to the C-nor-D-homo steroid ketone **84** and its isomer **85** was accomplished by conversion of **83** to a mixture of enols and acetates and direct catalytic reduction of the latter. The reduction mixture can be purified to afford the pure ketones **84** and **85**, but, for preparative purposes, it is equilibrated with base and then acetylated to provide the desired intermediate **85**. In this way, **85** is obtained in an overall yield of 62%. The sequence summarized in Fig. 12 provides an efficient synthesis of the required C-nor-D-homo steroid intermediates from the diacetate **77** and has been employed in all of our most recent studies.

The attachment of the heterocyclic unit to the ketonic side chain present in **85** required the consideration of a method which was rather different from the one employed in the above-mentioned syntheses of *Jerveratrum* alkaloids. The particular approach

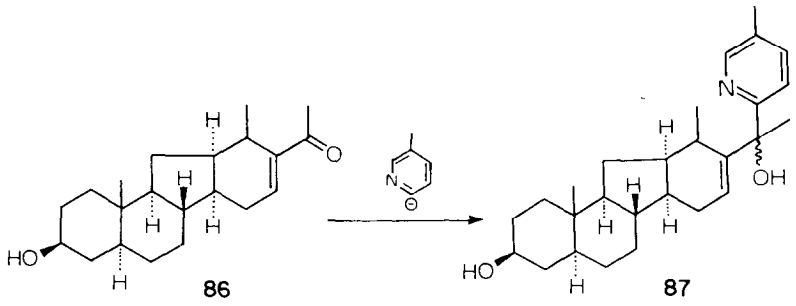


FIG. 13. The reaction of 2-lithio-5-methylpyridine with the C-nor-D-homo steroid intermediate **86**.

selected involves the reaction of pyridine anions with steroid ketones, a method employed by Schreiber and Adam (*42*) in the synthesis of *Solanum* alkaloids. To evaluate the feasibility of this procedure for our purpose, a model compound (**86**) available from an earlier study (*9*) was employed (Fig. 13).

The C-nor-D-homo steroid ketone **86** was condensed with 2-lithio-5-methylpyridine, available from 2-bromo-3-methylpyridine and *n*-butyllithium, at low temperature and inert (helium) atmosphere (Fig. 14). The resulting two products, isomeric at C_{20} and possessing the gross structure **87**, indicated that the desired coupling had been achieved. Extension of this reaction to the C-nor-D-homo steroid diacetate **85** provided a product mixture which, after acetylation, could by purified to furnish the two products of gross structure **88** and epimeric at C_{20}. Subsequent experiments revealed that the major component from this reaction possessed the desired stereochemistry at C_{20}, and it was utilized in our future investigations. The remaining steps in the pathway to verticine (**4**) are summarized in Figs. 15 and 16.

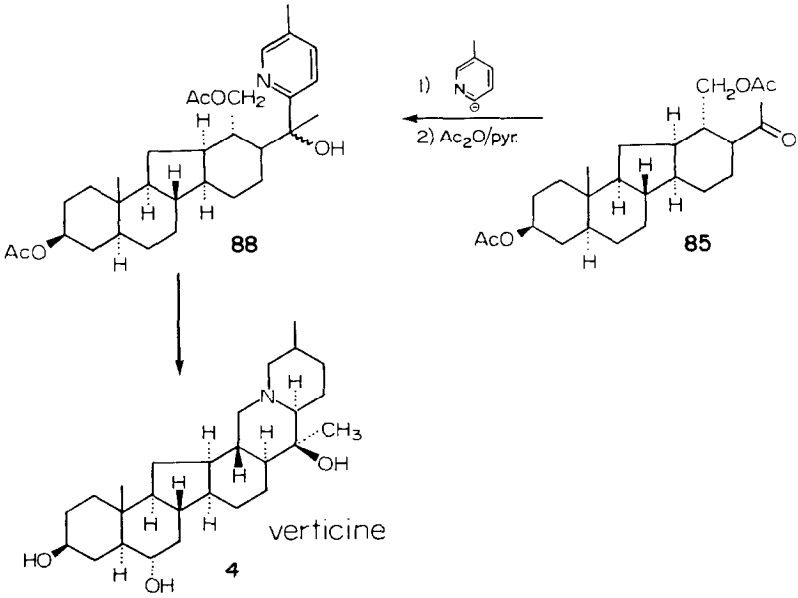


FIG. 14. The reaction of 2-lithio-5-methylpyridine with the C-nor-D-homo steroid diacetate **85**.

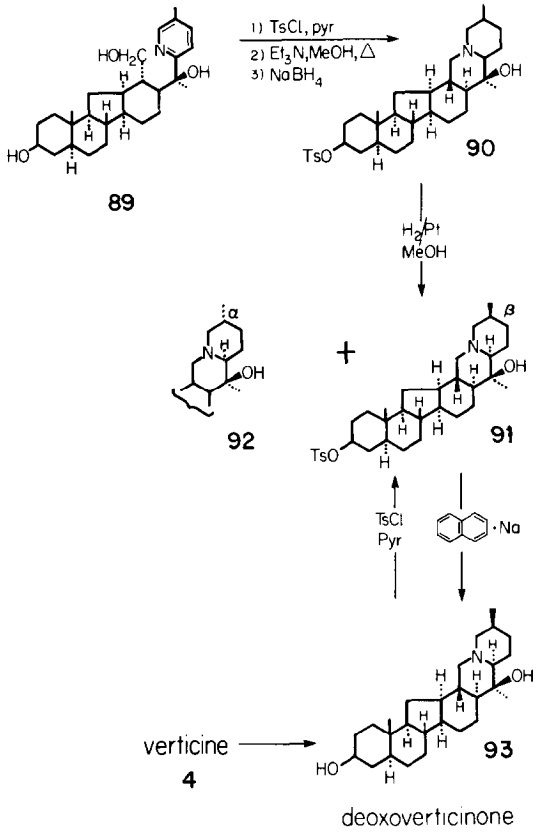


FIG. 15. The conversion of intermediate **89** to deoxoverticinone (**93**).

The alcohol **89** (Fig. 15), obtained by reaction of **85** with 2-lithio-5-methyl pyridine or by hydrolysis of **88**, was converted to its tosylate derivative, and the latter was treated directly in refluxing triethylamine and finally with sodium borohydride to provide a mixture of two olefins generally represented by structure **90**. One of these olefins possesses the double bond at C_{23}–C_{24}, while the other isomer has the olefinic linkage at C_{24}–C_{25}. Each of these compounds, or preferably the olefin mixture, was reduced by catalytic methods to afford the desired hexacyclic intermediate **91** and its C_{25} isomer **92**. At this stage in the program it was not possible to assign with certainty the chiral centers generated in the conversion of **89** to **91** and **92**. However, an appropriate interrelationship with the natural series provided the solution to this problem.

When verticine (**4**) was transformed to deoxoverticinone (**93**) by a published procedure (*43*), and the latter was converted to its tosylate derivative (**91**), complete identity of the authentic natural and synthetic series was established. On this basis it was now possible to assign complete structures and absolute stereochemistry to the synthetic intermediates **90**–**92**. Removal of the tosyl-protecting group in **91** furnishes deoxoverticinone (**93**) where comparisons between the synthetic and natural compounds were made again.

To complete the synthesis of verticine (**4**), the introduction of the 5,6 double bond

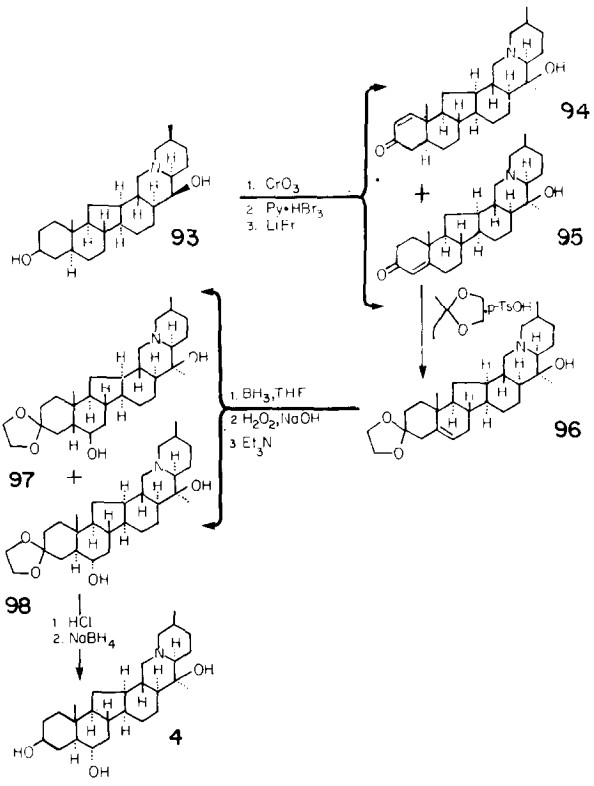


FIG. 16. The conversion of deoxoverticinone (**93**) to verticine (**4**).

into the deoxoverticinone system was necessary, and these experiments are summarized in Fig. 16.

Chromium trioxide oxidation (*43*) of **93** to the known dehydrodeoxoverticinone, bromination of this ketone, and finally lithium bromide dehydrobromination afforded the two unsaturated ketones **94** and **95**. The Δ1,2-ketone **94** was not directly useful but was reduced back to the saturated ketone and was recycled, while **95** can be readily converted to the unsaturated ketal **96** by reaction with 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulfonic acid.

Hydroboration of the ketal **96** provided a mixture of the 6β (50%) and 6α (25%) alcohols, **97** and **98**, respectively. Fortunately, the major component (**97**) is readily converted to the desired **98** by oxidation, equilibration, and reduction, thereby providing an efficient conversion of ketal **96** to 6α alcohol **98**, Finally, removal of the C_3-protecting group and borohydride reduction of the resulting ketone completed the first synthesis of the *Ceveratrum* alkaloid verticine (**4**). A brief discussion of these synthetic experiments is provided in two recent communications (*44*, *45*).

In conclusion, this discussion provides an overall summary of our recent investigations directed at the syntheses of various members within the *Jerveratrum* and *Ceveratrum* families of alkaloids. The synthetic strategy in which appropriate heterocyclic units are linked to various C-nor-D-homo steroid intermediates provides an effective and versatile synthetic entry into these natural systems.

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