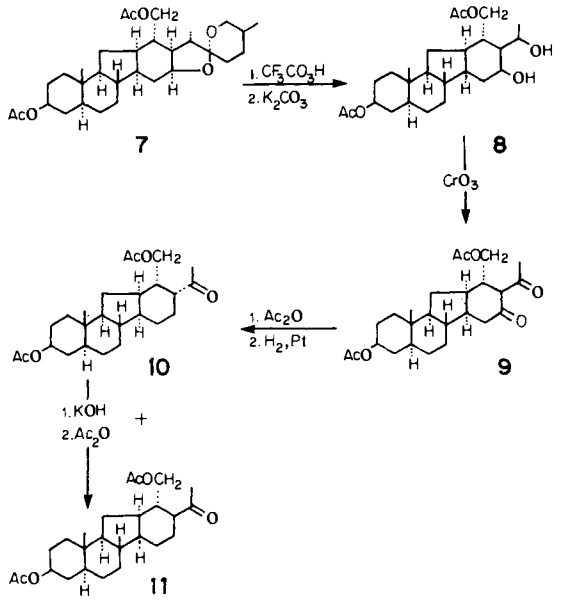
Scheme II



J = 6 Hz, C_{27}-CH_3), 8.90 (d, J = 6.5 Hz, C_{21}-CH_3), 6.4 (m, 1 H, C_3-H), 6.25 (d, J = 4.5 Hz, 2 H, CH_2OH); MS *m/e* 432 (M^+), 402, 373, 363, 360, 345, 318, 300, 288, 145, 139, 126, 115 (base peak), 105. The diacetate **7**, mp 112.5–114 °C, was prepared in the conventional manner and in high yield. The first important phase of the synthetic program was now complete.

The second phase of the program concerned the degradation of the spiroketal system in **7** to an appropriate side chain which could be utilized in the subsequent synthesis of the Ceveratrum alkaloids. An attractive solution to this problem is summarized in Scheme II.

Peroxytrifluoroacetic acid catalyzed (4.5 h, room temperature) ring opening of the spiroketal side chain in **7** and immediate treatment of the resultant mixture with potassium carbonate provided, after purification, the 16,20-diol **8:** mp 211–212 °C (70% yield); NMR τ 9.22 (s, 3 H, C_{19}-CH_3), 8.71 (d, J = 6.5 Hz, 3 H, C_{21}-CH_3), 8.03 and 7.99 (2s, 6 H, 2 × $OCOCH_3$), 5.90 (m, 1 H, C_{20}-H), 5.52 (bs, 1H, C_{16}-H); MS *m/e* 436 (M^+), 400, 358, 340, 314, 273, 260, 254, 187, 147, 145, 107 (base peak), 105. Oxidation of **8** (chromium trioxide–acetone, 5 °C) provides a quantitative yield of diketone **9,** mp 130–134 °C. The latter on reaction with acetic anhydride affords a mixture of enol acetates, which upon reduction, and chromatographic separation of the resultant mixture provides the pure ketones **10** and **11.** Ketone **10,** mp 145–147 °C, was obtained as a minor component (NMR τ 9.18 (s, 3 H, C_{19}-CH_3), 8.08 (s, 6 H, 2 × $OCOCH_3$), 7.94 (s, 3 H, C_{21}-CH_3), 7.15 (t, J = 5 Hz, 1 H, C_{13}-H), 5.92 (d, J = 7 Hz, 2 H, CH_2OAc), 5.40 (m, 1 H, C_3-H); MS *m/e* 418 (M^+), 374, 358, 300, 298, 255, 149, 135, 107) while the 17β-ketone **11,** mp 109–111 °C, was the major component (NMR τ 9.19 (s, 3 H, C_{19}-CH_3), 8.01 and 7.99 (2s, 6 H, 2 × $OCOCH_3$), 7.84 (s, 3 H, C_{21}-CH_3), 5.85 (m, 2 H, CH_2OAc), 5.28 (m, 1 H, C_3-H); MS *m/e* 418 (M^+), 374, 358, 300, 298, 255, 149, 141, 135, 107). As Scheme II indicates, ketone **10** is readily converted to **11** so that the overall yield of the latter is 62%.

In summary, the investigations summarized in Schemes I and II provide an efficient pathway for the synthesis of the important C_{18}-functionalized *C*-nor-*D*-homo steroid intermediate **11** from the readily available hecogenin acetate. The utilization of this intermediate in the synthesis of verticine forms the subject of the accompanying communication.[14]

Acknowledgments. Financial aid from the National Research Council of Canada is gratefully acknowledged. We would also like to thank Syntex Laboratories, G. D. Searle and Company, and Ayerst Laboratories for generous gifts of hecogenin acetate.

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Synthetic Studies in the Veratrum Alkaloid Series. The Total Synthesis of Verticine

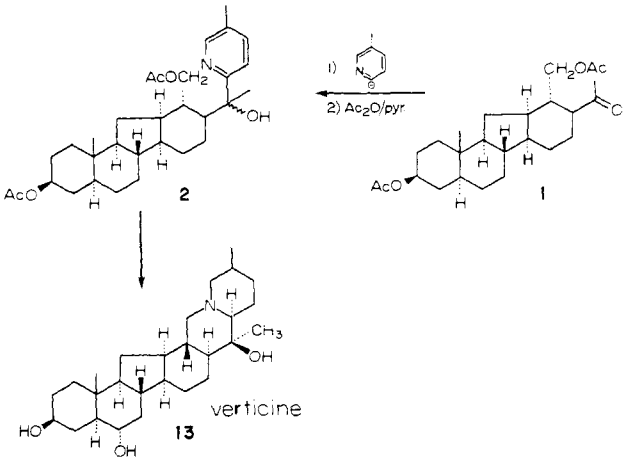
Sir:

In the accompanying communication[1] we described our investigations on the synthesis of appropriate C_{18}-functionalized *C*-nor-*D*-homo steroid derivatives and indicated that these substances were important intermediates in our synthetic program concerned with the synthesis of Ceveratrum alkaloids. We would now like to present our studies in which such intermediates are employed in the first synthesis of the alkaloid verticine (**13**).

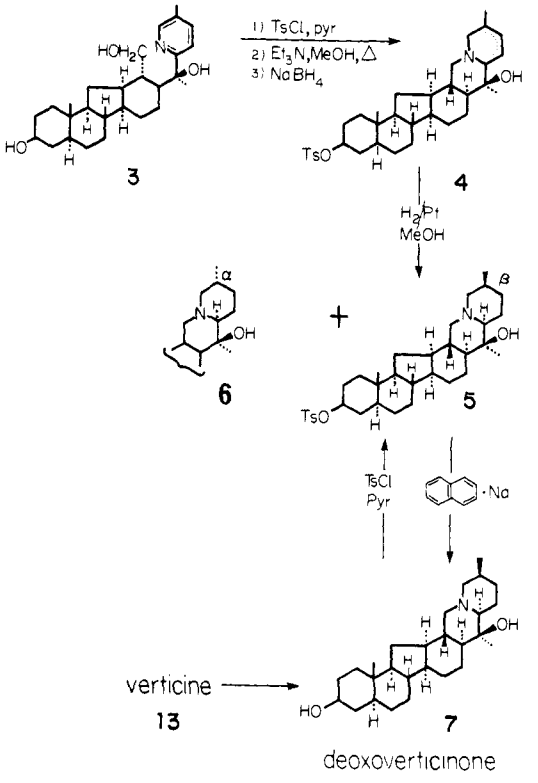
Verticine is one of the simpler members of the hexacyclic Ceveratrum group[2] and its structure and absolute configuration have been established by x-ray analysis of verticinone methobromide.[3] For this reason it was selected as the first synthetic objective in this series.

As already noted[1] our synthetic program in this area considered, as one of the important synthetic steps in the pathway, the coupling of a heterocyclic nitrogen system onto the C_{17} position of a *C*-nor-*D*-homo steroid derivative and finally bond formation between the basic nitrogen atom and the C_{18} position to complete the hexacyclic skeleton. The coupling reaction which was utilized for this purpose involved an adaptation of a procedure employed by Schreiber[4] in the synthesis of Solanum alkaloids. Thus the *C*-nor-*D*-homo steroid intermediate **1**[1] was treated with 2-lithio-5-methylpyridine, available from 2-bromo-5-methylpyridine and *n*-butyllithium, at −40 °C (helium atmosphere), and the resultant mixture acetylated directly to provide a mixture of two products. Chromatographic separation into the two pure components and subsequent analysis of the elemental and spectral data allowed the assignment of the gross structure **2** to these products (Scheme

Scheme I



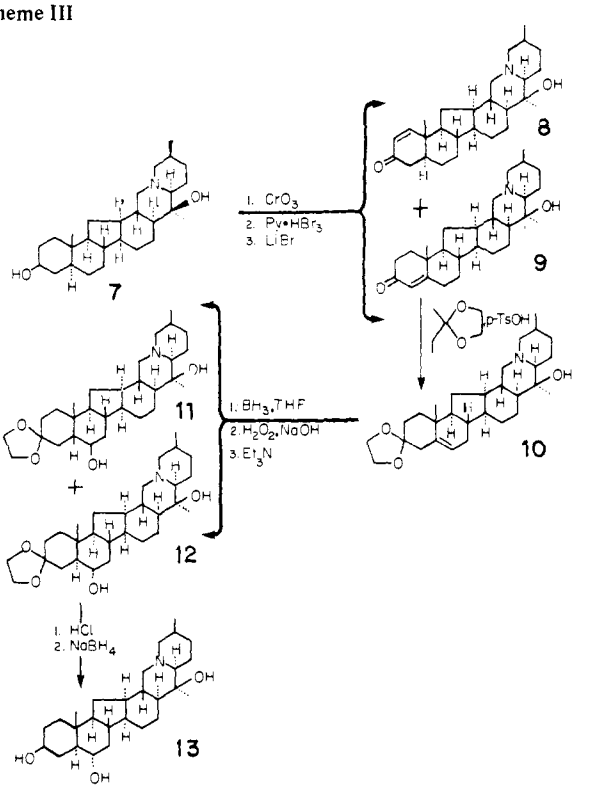
Scheme II



I). The major component possessed the desired C_{20} stereochemistry for the verticine synthesis (see later) so its spectral characteristics and chemistry will be discussed presently while discussion of the other C_{20} isomer is deferred to our detailed publication: NMR τ 9.21 (s, 3 H, C_{19}-CH_3), 8.55 (s, 3 H, C_{20}-CH_3), 8.11 and 8.01 (2s, 6 H, 2 × $OCOCH_3$), 7.68 (s, 3 H, C_{27}-CH_3), 6.33 (m, 2 H, CH_2OAc), 5.28 (m, 1 H, C_3-H), 2.96 (d, J = 8 Hz, 1 H, C_{23}-H), 2.50 (dd, J = 2.5 and 8 Hz, 1 H, C_{24}-H), 1.65 (bs, 1 H, C_{26}-H); MS *m/e* 511 (M^+), 496, 493, 451, 358, 255, 136 (base peak), 107; λ_{max} 267 nm (ϵ 3700). The remaining steps in the synthetic pathway to verticine (**13**) are summarized in Schemes II and III.

The crystalline alcohol **3**, mp 222–223.5 °C (Scheme II), obtained either by hydrolysis of **2** or by direct reaction of **1** with 2-lithio-5-methylpyridine and isolation prior to any acetylation, was reacted with tosyl chloride in pyridine (0 °C, 24 h), the resulting mixture first treated with triethylamine (reflux, 1.5 h) and finally with sodium borohydride to provide a mixture of two olefins generally represented by structure **4**. These olefins could be separated and characterized: structure **4**

Scheme III



(23–24 double bond): NMR τ 9.23 (s, 3 H, C_{19}-CH_3), 9.09 (d, J = 7 Hz, 3 H, C_{27}-CH_3), 8.84 (s, 3 H, C_{21}-CH_3), 7.54 (s, 3 H, Tos-CH_3), 5.54 (m, 1 H, C_3-H), 4.26 (m, 2 H, C_{23} and C_{24}-H); MS *m/e* 395 (M^+), 110 (base peak), 96; IR 2760 (*trans*-quinolizidine). Structure **4** (24–25 double bond); NMR 9.26 (s, 3 H, C_{19}-CH_3), 8.92 (s, 3 H, C_{27}-CH_3), 8.74 (s, 3 H, C_{21}-CH_3), 4.41 (m, 1 H, C_{24}-H); IR 2760 (*trans*-quinolizidine). For preparative purposes, the olefin mixture was reduced immediately (H_2, Pt) to provide the desired deoxoverticinone 3-tosylate (**5**) and its C_{25}-epimer **6** (overall yield from **3** is 50%).

The structural and stereochemical assignments portrayed in **5** were established when authentic deoxoverticinone **7**[6] was treated with tosyl chloride in pyridine to provide the 3-tosylate derivative and this compound was shown to be identical (IR, NMR, MS, TLC) with **5** prepared above. Further confirmation was available when **5** was treated with sodium naphthalene[7] and the resultant product was identical in every respect with deoxoverticinone (**7**).

To complete the synthesis of verticine it was necessary to introduce the 5,6-double bond in deoxoverticinone and a summary of the successful reactions is provided in Scheme III.

Deoxoverticinone (**7**) was converted to the known dehydrodeoxoverticinone[6] by means of chromium trioxide and the latter was treated with pyridine hydrobromide perbromide (50 °C, 15 min). The resulting mixture of bromoketones was reacted directly with lithium bromide (DMF, reflux) to provide the two expected conjugated ketones **8** and **9**. Compound **8** which was not directly useful in the synthesis was reduced (H_2, Pt) back to the saturated ketone and recycled while **9** (NMR τ 8.96 (s, 3 H, C_{21}-CH_3), 8.89 (d, J = 7 Hz, 3 H, C_{27}-CH_3), 8.82 (s, 3 H, C_{19}-CH_3), 4.22 (s, 1 H, C_4-H); MS *m/e* 411 (M^+), 368, 366, 113, 112 (base peak), 111, 98; IR 2781 (*trans*-quinolizidine) 1661 cm^{-1}; UV λ_{max} 236.5 nm (ϵ 11 900)) could be utilized to complete the synthesis.

The unsaturated ketone **9** was reacted with 2-ethyl-2-methyl-1,3-dioxolane and *p*-toluenesulfonic acid (80 °C, 3 h) to provide the unsaturated ketal **10.** Hydroboration of **10** in

the normal manner occurred with attack of the reagent from both the β (compound **11**, 50% yield) and α (compound **12**, 25% yield) sides of the molecule. The major component **11**, with the undesired stereochemistry at positions 5 and 6, is convertible to the desired **12** by oxidation and equilibration. The desired alcohol **12**, after removal of the ethylene ketal and reduction of the 3-ketone, provides verticine (**13**) identical in all respects with a sample of the natural alkaloid.

Acknowledgments. Financial aid from the National Research Council of Canada is gratefully acknowledged. We also wish to express our thanks to Professor Sho Ito, Tohoku University, Sendai, Japan, for generous gifts of verticine, deoxoverticinone, and related samples.

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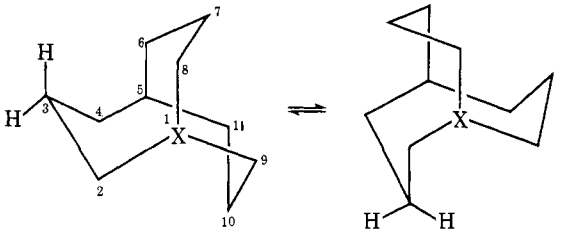
The Bridgehead Bicyclo[3.3.3]undecyl (Manxyl) Mono- and Dications[1]

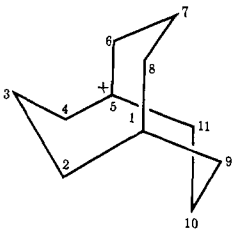
Sir:

The intriguing bridge flipping process which interverts "in" and "out" hydrogens in bicyclo[3.3.3]undecane (**1**) (manxane) has recently been shown to require about 11 kcal/mol of free energy of activation.[2,3] Similar observations also have been extended to 1-azabicyclo[3.3.3]undecane (**2**) (manxine) and its salt **3**.[4] The enhanced rate of 1-chloromanxane (**4**) (10^4



1, X = CH
2, X = N
3, X = N^{+}—H
4, X = CCl
5, X = C^{+}

greater than that of the *tert*-butyl chloride)[5] in solvolytic reactions reflects the great stability of carbocation **5**. According to empirical force field calculations,[3b,6] the rate enhancement of **4** is due largely to the relief of angle strain during ionization. The flattening at the bridgehead, at which a trigonal, planar atom is readily accommodated,[7] reduces the repulsive nonbonded interactions involving the C(3), C(7), and C(10) methylene groups. The calculations also show that in going from the hydrocarbon **1** to the monocation **5**, the C(1)···C(5) nonbonded separation diminishes from 3.322 to 2.990 Å. On this basis C(1)···C(5) distance in dication **6** would be expected to be even shorter. Having prepared previously the pseudoaromatic 1,4-bicyclo[2.2.2]octyl dication (**7**),[8] we



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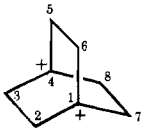

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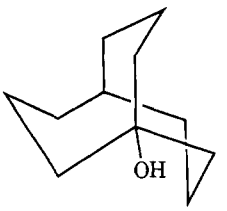
wish to report now the preparation of the stable 1-bicyclo[3.3.3]undecyl cation (**5**) and 1,5-bicyclo[3.3.3]undecyl dication (**6**) and their spectroscopic study.

Addition of solutions of 1-chloro- (**4**) and 1-hydroxybicyclo[3.3.3]undecane (**8**) in sulfuryl chloride fluoride to a solution of SbF_5 in the same solvent at −78 °C resulted in the formation of the same carbocationic species whose ^1H NMR spectrum (Figure 1A) shows three deshielded absorptions at δ 4.15 (t, 6 H), 3.20 (br, 7 H), and 2.19 (b, 6 H) corresponding



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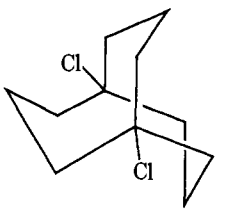

9

to the expected manxyl monocation **5**. The structure of **5** is further confirmed by its FT ^{13}C NMR spectrum (Figure 1B) which consists of *five* carbon resonances[9] at $\delta_{^{13}C}$ 356.3 (s), 57.9 (t, J_{CH} = 134.3 Hz), 37.0 (t, J_{CH} = 126.1 Hz), 32.7 (t, J_{CH} = 123.2 Hz), and 35.7 (d, J_{CH} = 120 Hz), which are assigned to C(1), C(2), C(3), C(4), and C(5), respectively. The solution of **5** does not show appreciable change between −135 and −30 °C, and it slowly decomposes at high temperatures.

The temperature-independent behavior of the manxyl monocation **5** seems to suggest either a rapid ring flipping process with a lower energy barrier than that of the parent hydrocarbon **1**[2,4] (faster than can be detected on the NMR time scale) or a very slow inversion of conformation due to the introduction of sp^2 hybridized carbon at C(1) causing additional strain to raise the energy barrier so that the ring flipping process is not detectable at the highest attainable temperature (−30 °C) before the ion starts to decompose. Either behavior is surprising in comparison with that exhibited by **1** and by **6**.

The bridgehead manxyl dication **6** was prepared from 1,5-dichloromanxane (**9**)[10] in SbF_5–SO_2ClF solution at −78 °C. **6** was found stable below −50 °C. It is found to be in conformation equilibrium at −60° as indicated by the ^1H NMR spectrum, which consists of two broad absorptions at δ 4.50 and 3.50 in a ratio of 2:1. The process, however, is *frozen* out at −80 °C, as shown in the 100-MHz spectrum observed at this temperature (Figure 1C), indicating the non-equivalency of the six β-methylene protons, being resolved into two sets of broad absorptions centered at δ 3.70 and 3.30 in a ratio of 1:1. The 12-proton α-methylene absorption apparently is not affected. The natural abundance FT ^{13}C NMR (proton noise decoupled, Figure 1D) spectrum of **6** is in accordance with the proton NMR study. At −85 °C, there are three carbon resonances at $\delta_{^{13}C}$ 346.2 (s), 58.7 (t, J_{CH} = 137.2 Hz), and