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(18) Aldol adducts showed characteristic IR bands at ~1790 cm^{-1}. Monosubstituted cyclopentanediones showed IR bands characteristic of an enolic diketone, and NMR signals (TFA) of ring methylenes at δ ~3.00 (s). 2,2-Disubstituted ones commonly showed an IR band at ~1720 cm^{-1}, and NMR signals (CCl_4) at δ ~2.65 (s), indicating symmetrical structure. The diketone **8**, however, showed IR bands at 1760 (w) and 1717 cm^{-1} and NMR signals at δ 2.50–2.83 (m), and **10** exhibited IR absorption at 1750 (w) and 1717 cm^{-1} (s).

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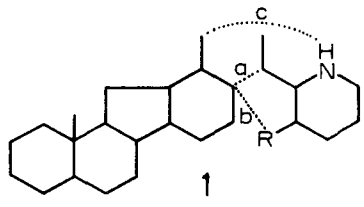
Synthetic Studies in the Veratrum Alkaloid Series. The Total Synthesis of C_{18}-Functionalized *C*-Nor-*D*-homo Steroid Derivatives—Valuable Intermediates in the Total Synthesis of Veratrum Alkaloids

Sir:

The Veratrum alkaloid family is unique among the steroidal alkaloids in that many of its members possess the interesting *C*-nor-*D*-homo steroid skeleton.[1,2] Synthetic endeavors by several groups have now provided the laboratory syntheses of several members of the Jerveratrum group.[3] Thus elegant investigations by Johnson[4] and Masamune[5] and their co-workers have culminated in the syntheses of veratramine and jervine. Our own studies[6-8] have allowed the completion of the syntheses of verarine and 5α,6-dihydroveratramine. On the other hand, the more complex hexacyclic Ceveratrum group[3] which also exhibits interesting pharmacological activities[9] has not yet been synthesized. We would now like to present our studies in this direction. This communication describes the synthesis of C_{18}-functionalized *C*-nor-*D*-homo steroid derivatives, which are important intermediates in our synthetic program, while the accompanying publication illustrates the utilization of these intermediates in the first total synthesis of the Ceveratrum alkaloid verticine.

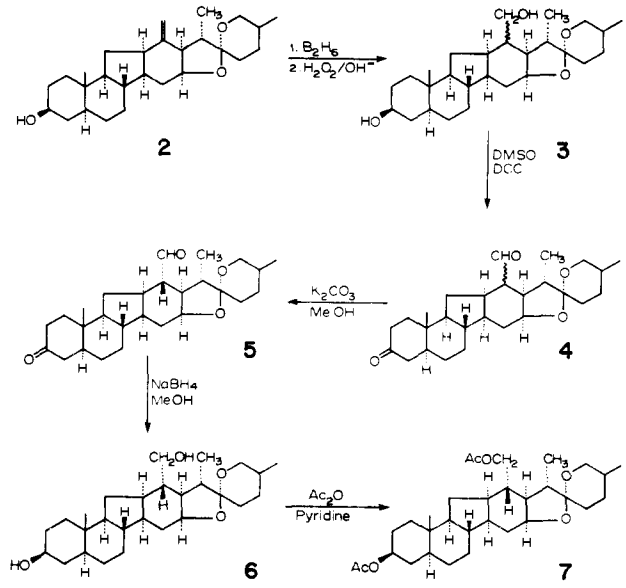
In outlining our synthetic strategy, we considered that the Veratrum bases are made up of two structural units: (i) the *C*-nor-*D*-homo steroid skeleton and (ii) an appropriate heterocyclic nitrogen system as shown schematically in **1**. The coupling of the steroid unit with the heterocyclic system at position a was employed in the synthesis of verarine and veratramine while bond formation at a and b allows the synthesis of jervine.[6-8] In expanding this strategy toward the synthesis of the hexacyclic Ceveratrum bases the attachments of the two units must occur at a and c. Such bond formation between the basic nitrogen atom and C_{18} of the steroid unit clearly requires the preparation of the requisite C_{18}-functionalized *C*-nor-*D*-homo steroid intermediates.



1

a: veratranine bases
a+b: jervanine "
a+c: cevanine "

Scheme I



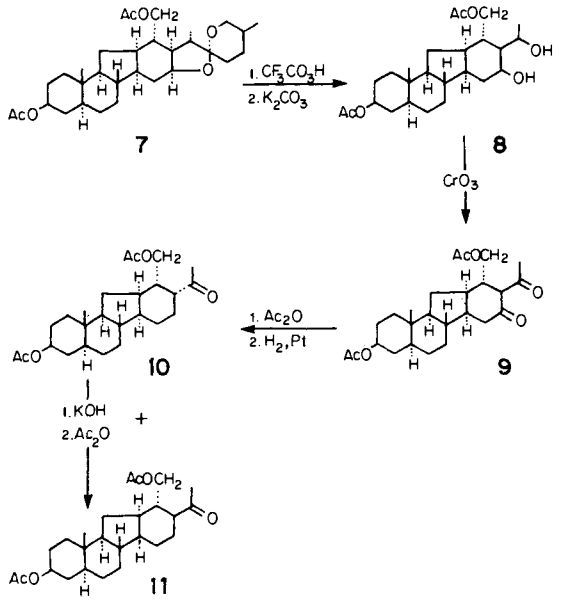
Our first objective was to obtain a *C*-nor-*D*-homo spirostan derivative with an appropriate functionality at C_{18} and possessing the desired α stereochemistry at C_{13}. For this purpose the exocyclic olefin **2** (Scheme I) became the initial target compound. Rockogenin 12-methanesulfonate 3-pivalate[10] after rearrangement in refluxing anhydrous pyridine[11] (82% yield) and normal hydride reduction of the C_3 protecting group provides an excellent route to this intermediate (overall 75% yield from hecogenin acetate).

Hydroboration (diborane, THF) of **2** (or its C_3-acetate) provided the expected 13β-hydroxymethyl derivative **3** (Scheme I, β-CH_2OH) as a major component (82% yield):[12] mp 182–184 °C, NMR τ 9.22 (s, 3 H, C_{19}-CH_3), 9.2 (d, J = 6 Hz, 3 H, C_{27}-CH_3), 8.98 (d, J = 6 Hz, C_{21}-CH_3), 6.4 (m, 1 H, C_3-H), 6.35 (d, J = 5.5 Hz, 2 H, CH_2OH); MS *m/e* 432 (M^+), 402, 373, 363, 360, 345, 318, 300, 288, 145, 139, 126, 115 (base peak), 107. The isomeric 13α-hydroxymethyl derivative **6** was present as a minor component and could also be utilized as indicated below.

Oxidation of **3** (β-CH_2OH) via the Moffatt technique[13] (benzene, dimethyl sulfoxide, dicyclohexylcarbodiimide, pyridine, trifluoroacetic acid, 40 h, room temperature) provided the expected keto-aldehyde **4** (β-CHO): NMR τ 9.21 (d, J = 6 Hz, 3 H, C_{27}-CH_3), 9.08 (s, 3 H, C_{19}-CH_3), 9.03 (d, J = 6 Hz, C_{21}-CH_3), 7.33 (m, J = 5.5 and 7 Hz, 1 H, C_{13}H), 0.22 (d, J = 5.5 Hz, 1 H, CHO); MS *m/e* 428 (M^+), 369, 359, 356, 341, 314, 285, 256, 206, 149 (base peak), 135, 126, 115. This latter product could be smoothly converted, in essentially quantitative yield, to the thermodynamically more stable desired isomeric aldehyde **5**, mp 174–176 °C, by reaction with potassium carbonate at room temperature: NMR τ 9.22 (d, J = 6 Hz, 3 H, C_{27}-CH_3), 9.10 (d, J = 5 Hz, 3 H, C_{21}-CH_3), 9.08 (s, 3 H, C_{19}-CH_3), 0.57 (d, J = 4 Hz, 1 H, CHO); MS *m/e* 428 (M^+), 369, 359, 356, 341, 314, 285, 257, 206, 149, 135, 126, 115 (base peak).

Conversion of **5** to the required 13α-hydroxymethyl derivative **6**, mp 243.5–245 °C, could be achieved directly with sodium borohydride: NMR τ 9.25 (s, 3 H, C_{19}-CH_3), 9.21 (d,

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]

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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