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AN ALTERNATIVE SYNTHESIS OF 17-ACETYL-5α-ETIOJERVA-12, 14, 16-TRIEN-3β-OL

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The total synthesis of the title substance (formula 1), which is the key relay compound in the synthesis of veratramine[1] and jervine,[2] has recently been described.[3] Now we are disclosing a completely different approach to the hydroxy ketone 1 which is based on a ring contraction scheme that was also developed in our laboratory.[4]*

Starting with the readily accessible racemic tetracyclic acetate 2,[5] we applied the same sequence of transformations that was performed[4] on the 5β epimer of 2. Thus lead tetraacetate treatment followed by dehydroacetoxylation afforded the known[6] dl-11, 12-dehydro-2 which, on ozonolysis, was cleaved to the dl-dialdehyde 3, mp 159-162°. The crude semicrystalline dialdehyde, on treatment with methanolic sodium hydroxide, underwent aldol cyclization to give a crystalline mixture of stereoisomeric forms of the dl-dihydroxy aldehyde 4, mp about 187-220°, from which a specimen, mp 220-228°, was isolated by repeated recrystallization. Oxidation of the crude dihydroxy aldehyde with Jones reagent afforded the corresponding dl-diketo aldehyde (mp 154-165° after recrystallization), which, without purification, was induced to undergo deformylation, by treatment for 4 hr at room temperature with potassium hydroxide in aqueous dioxane, to give a 9:1 mixture of the dl-diketones 5 and 6, respectively. The former isomer, mp 220-223°, could be readily separated by crystallization. Thus from 13.5 g of 11, 12-dehydro-2 there was obtained 4.6 g (38% over-all yield) of the diketone 5, mp 218.5-222°, which was satisfactory for continuing the synthesis.

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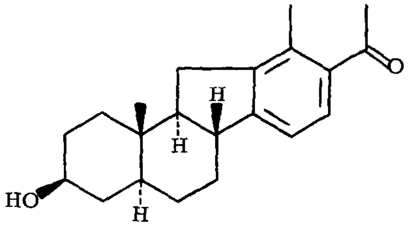
* It is to be noted that this ring contraction approach has been applied successfully to an isomeric series, J. P. Kutney, A. By, T. Inaba and S. Y. Leong, Tetrahedron Letters, 2911 (1965).



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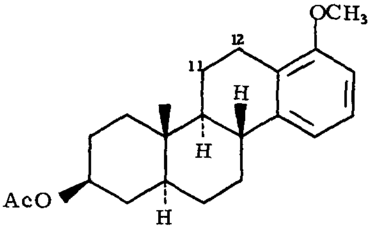

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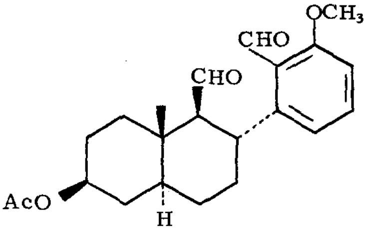

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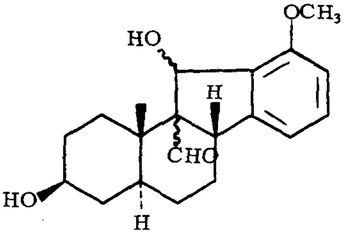

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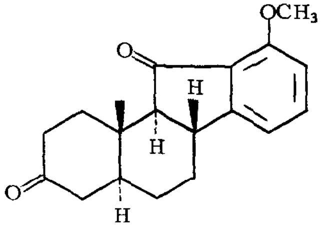

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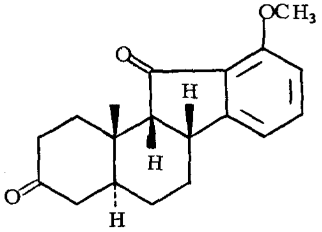

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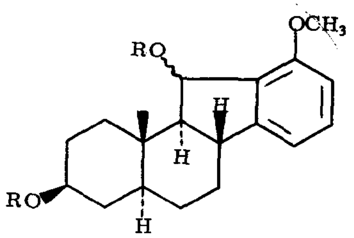
The configurations of the epimeric diketones 5 and 6 were assigned on the basis of the positions of the signals for the angular methyl groups in the nmr spectra which appeared at δ = 1.18 and 1.24 ppm, respectively. The former value is to be compared with that (1.19) for the 5β epimer of known configuration.[7] Confirmation of the configuration of the 222° diketone followed from its conversion (see below) into the known alcohol 12 of established *trans-anti-trans* configuration.[8] When the 222° diketone was submitted to the heterogeneous basic conditions of the aforementioned deformylation reaction for an extended period (20 hr), the ratio of the epimeric diketones 5 and 6, as ascertained by the relative intensities of the nmr spectral signals at 1.18 and 1.24 ppm, was about 7:3. Therefore the 9:1 ratio of products obtained in the deformylation reaction must have been the result of kinetic control. Isomerization of the 222° diketone under homogeneous equilibrating (as ascertained by deuterium exchange) conditions gave a 3:2 mixture of the epimers **5** and **6**. Thus in the 5α series the equilibrium is somewhat in favor of the B/C *trans* isomer; while in the 5β series the situation is reversed, the *trans*:*cis* ratio being 3:7.[7]

The *dl*-*trans*-*anti*-*trans*-diketone (**5**) was reduced with lithium aluminum hydride to a mixture of diols, mainly **7** (R = H), which was acetylated with acetic anhydride and pyridine. The resulting mixture of diacetates **7** (R = Ac), on mild treatment with potassium in liquid ammonia, underwent hydrogenolysis to give, after saponification, the *dl*-methoxy alcohol **8**, mp 138-141°. This alcohol, on treatment with potassium and alcohol in liquid ammonia under forcing conditions,[9] followed by acid-catalyzed hydrolysis, was converted into a mixture, chromatography of which gave, in 44% yield, an oily fraction which was rich in the unsaturated ketone **9** as shown by the ultraviolet spectrum, λ_{max}^{EtOH} 253 mμ (ε 8770). This product appeared to be air-sensitive and so was treated directly with excess methyllithium. The resulting crude adduct was then heated over 30% palladium-on-carbon in xylene containing a trace of *p*-toluenesulfonic acid, which effected dehydration and dehydrogenation of ring D. Since this treatment also caused partial dehydrogenation of the 3-hydroxyl group, the mixture was oxidized with Jones reagent to give a crystalline product containing the desired *dl*-ketone **10**, mp 159.5-160.5°, and the dehydro ketone **11**, mp 135-136°, which were separated by preparative thin layer chromatography. The solution infrared spectrum of the racemic 160° ketone was identical with that of the ketone, mp 121.5-122.5°, $[\alpha]_D$ +75° in dioxane by ORD, obtained by oxidation of the authentic *d*-alcohol **12**[8] derived from dihydroveratramine. Reduction of the racemic 160° ketone with sodium borohydride in isopropyl alcohol[9] afforded the *dl*-alcohol **12**, which was separated from a trace of its C-3 epimer by preparative thin layer chromatography. The solution infrared spectrum of this material, which melted at 78-103° (polymorphic mixture), was identical with that of the naturally derived *d*-alcohol, mp 125-127°,[8] $[\alpha]_D$ +31.5° in $CHCl_3$, $[\alpha]_D$ +51° in dioxane by ORD. The *dl*-alcohol **12**



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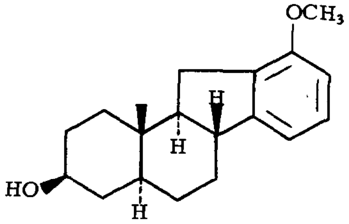

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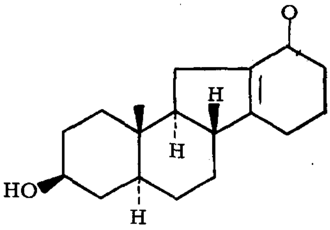

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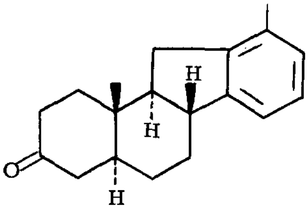

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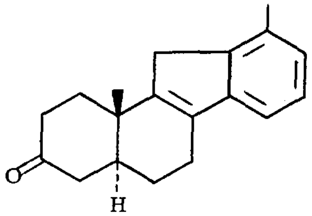

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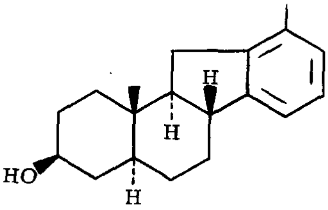

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was condensed with (-)-α-phenylethyl isocyanate to obtain a diastereoisomeric mixture of urethanes, which were separated by chromatography. Only one of the two diastereoisomers crystallized, mp 160-161°, undepressed on admixture with the urethane, mp 161-162°, from naturally derived d-alcohol. The ORD curves of the two samples were qualitatively identical.* Reconversion to the alcohol, by lithium aluminum hydride reduction, yielded material mp 125-127°. A mixture of the totally synthetic sample with the naturally derived specimen melted at 125-127°.

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* The amount of the resolved product in hand was insufficient for accurate quantitative measurements.

All that remained was the conversion of the d-alcohol 12 into the hydroxy ketone 1. This transformation was accomplished by the reaction of the acetate of the d-alcohol 12 with acetic anhydride and aluminum chloride in methylene chloride at 0°. Chromatography followed by crystallization gave material, mp 171.5-175°, undepressed on admixture with authentic hydroxy ketone 1, mp 173-174.5°, obtained by degradation of dihydroveratramine. The infrared spectra of these two substances were identical.

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