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A SIMPLE SYNTHESIS OF (±)-CEDRENE AND (±)-CEDROL USING A SYNCHRONOUS DOUBLE ANNULATION PROCESS

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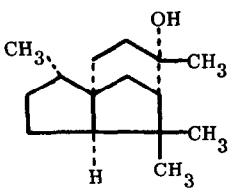
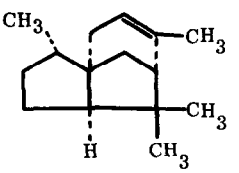
The tricyclic sesquiterpenoids cedrol (I) and cedrene (II) have long been focal points for chemical

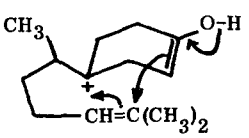


I

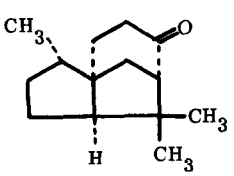


II

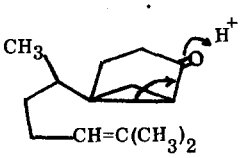
investigation.[1-5] In continuation of previous research in this Laboratory,[5a] we projected a synthesis involving as a key step the direct conversion of the cation III (or equivalent) to cedrone IV. Our earlier



III



IV

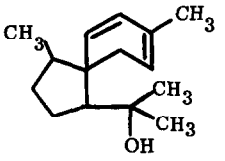


V

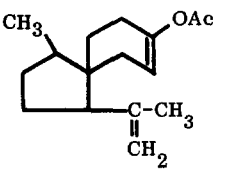
experience with a bicyclic precursor of IV[5a] provided a clear indication that the transformation III → IV might be very efficient. The cyclopropyl ketone V seemed the logical precursor of the cation III, especially in view of the results of Stork's school on cation-olefin cyclizations which are initiated by protonation of cyclopropyl ketones.[6] The attractiveness of this synthetic approach was further enhanced by the availability of very simple routes to V. Accordingly a synthesis of V was developed, and a study was made of the

crucial cyclization step.

We were nettled to find that the reaction of V in formic acid solution at temperatures between 0 and 25° yielded little if any cedrone (IV), as contrasted to the earlier observation[5a] that the cyclization of various bicyclic substrates, e.g., VI, to form cedrene derivatives occurs smoothly under these conditions. The

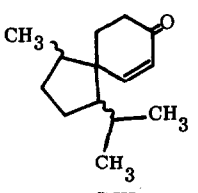


VI

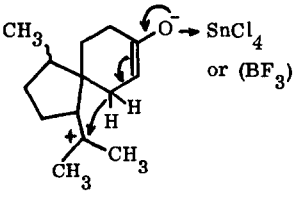


VII

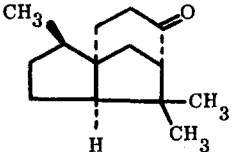
use of boron trifluroide--methylene chloride (which converts VII to cedrone with high efficiency[5a]) also led to disappointingly low yields of cedrone. Further, cedrone was only a minor product when V was treated with stannic chloride--benzene following the procedure of Stork et al.[6] The major product obtained from V under the influence of Lewis acids in aprotic media was a cyclohexenone derivative for which structure VIII appears reasonable on the basis of spectral data.[7,8] The conversion of V to VIII, which can be rationalized



VIII



IX



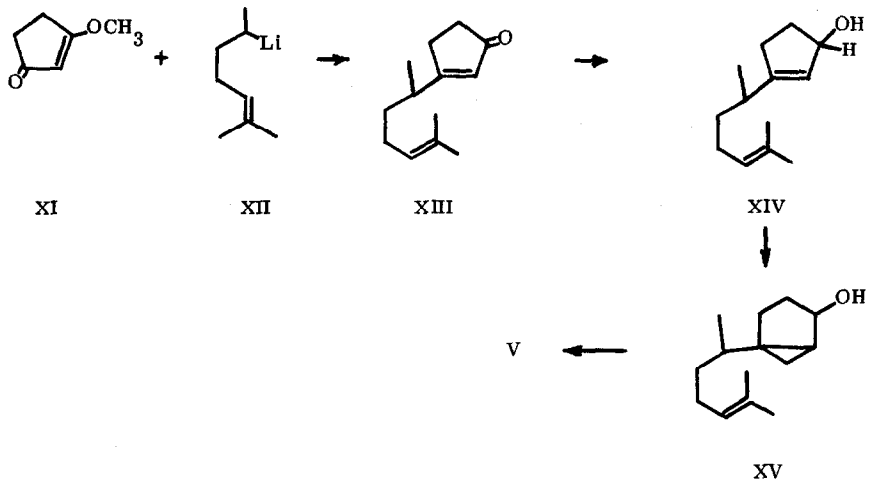
X

along lines depicted by expression IX, involves a rather uncommon 1,4-hydride shift. Starting from the view that the 1,4-hydride shift might owe its existence to a driving force associated with the high electron density at oxygen, another approach to the cyclization of V was pursued involving carbon electrophiles which would convert V to a cationic enol ester rather than a cation-enolate dipolar ion structure. An especially gratifying result was achieved in this way.

Treatment of a mixture of the two diastereomeric forms of V in methylene chloride solution (0.01 M) at -40° with 10 equiv. of the reactive acetylating agent acetyl methanesulfonate (Willowbrook Chem. Co.) for 12 hr. and subsequent aqueous work-up produced cedrone IV and epi-cedrone X in 85% combined yield. The cyclization was also studied using the individual diastereomeric forms of V which could be separated from one another by preparative gas chromatography (30 ft., 12.5% diethylene glycol succinate column at 140° with a flow rate of 50 ml./min.; R_t 93 min., diastereomer A, and R_t 89 min., diastereomer B).[9] In each

case the cyclization was stereospecific. Diastereomer VA was converted cleanly to (±)-cedrone (IV)[10] and diastereomer VB was transformed into (±)-epi-cedrone (X). The observed stereospecificity of the cyclization process agrees with the proposal by Stork et al.[6] that such cyclizations occur synchronously with cleavage of the cyclopropane ring. (±)-Cedrone has previously been converted to (±)-cedrol and (±)-cedrene.

The cyclopropyl ketone V was obtained as follows. Treatment of a 0.01 M solution of cyclopentane-1,3-dione in 1:3 ether--methanol at 0° with excess diazomethane (2.0 equiv.) for 10 min., followed by removal of solvent and sublimation (25°, 0.5 mm.) gave 90% of the methyl enol ether XI.[11] The dropwise



XI XII XIII XIV

V

XV

addition (30 min.) of a 0.51 M solution of XI in THF to a 0.7 M solution (2.5 equiv.) of 2-(6-methyl-5-heptenyl)-lithium (XII) in hexane at -78° (available by treatment of a 1.4 M solution of 6-chloro-2-methyl-2-heptene with lithium--1% sodium wire at 50° in hexane[5a]), followed by additional stirring for 4 hr. at -78°, gave, after acidic work-up and preparative t.l.c. (R_f 0.15 on silica gel using chloroform), 60% of the enone XIII[7] as a clear oil showing infrared maxima at 1710 and 1598 cm.$^{-1}$. Selective reduction of XIII was carried out in ca. 90% yield by treatment of a 0.5 M solution of the enone in benzene with excess diisobutylaluminum hydride[12] (1.50 equiv.) at 5° for 2 hr. Quenching with methanol, filtration, and removal of solvent in vacuo gave the pure allylic alcohol XIV[7] in 85% yield. Treatment of a 0.05 M solution of XIV in ether with several equiv. of Conia's silver-modified Simmon-Smith reagent[13] at reflux for 1.5 hr. gave the cyclopropyl alcohol XV[7] in 70% yield. The cyclopropyl protons appeared in the n.m.r. spectrum ($CDCl_3$) at 0.4 (q., 1 H, J = 5 Hz) and 0.75 (t., 1 H, J = 5 Hz) δ (the third proton was obscured under alkyl protons). Finally, oxidation of alcohol XV with 6 equiv. of a 0.3 M solution of Collins reagent in methylene chloride at 25° for 15 min. afforded the desired cyclopropyl ketone as a 1:1 mixture of diastereomers VA and VB in 89% yield.[14,15]

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5. Syntheses by cation-olefin cyclization along proposed biosynthetic lines: (a) E. J. Corey, N. N. Girotra, C. T. Mathew, ibid., 91, 1557 (1969); (b) T. G. Crandall and R. G. Lawton, ibid., 91, 2127 (1969); (c) N. H. Andersen and D. D. Syrdal, Tetrahedron Lett., 2455 (1972).
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7. Mass spectral data including molecular ion value were consistent with the assigned structure.
8. In agreement with VIII, the ultraviolet spectrum showed $\lambda_{max.}$ 211 nm, ϵ 15,000 (in EtOH), and the infrared spectrum exhibited enone absorption bands at 1685 and 1610 $cm.^{-1}$ (thin film). The n.m.r. spectrum showed peaks at (p.p.m. downfield from internal tetramethylsilane) 6.75 (d.d., J = 10, 2 Hz, 1 H, O=C-C=C<u>H</u>), 5.90 (d., J = 10 Hz, 1 H, O=C-C<u>H</u>=C); in addition peaks due to methyls of type $CH-CH_3$ and $CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$ appeared at 0.9 and 0.80 p.p.m. which were further identified by decoupling experiments.
9. The infrared (1727, s., C=O) and mass spectra of the two diastereomers of V were identical; the n.m.r spectra differed only by the position of the secondary methyl protons (diastereomer VA 1.00 p.p.m., diastereomer VB 1.02 p.p.m.).
10. Synthetic (±)-cedrone was characterized by comparison of the n.m.r., infrared, and mass spectra, and also v.p.c. and t.l.c. behavior with those for an authentic sample.
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14. Satisfactory C-H analytical data obtained for this intermediate.
15. This work was assisted financially by the National Institutes of Health and the National Science Foundation. We thank Barbara Manuck for help in obtaining n.m.r. spectra using a Varian XL-100 instrument.