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STEREOSPECIFIC TOTAL SYNTHESIS OF (+)-ε-CADINENE
ENOLIC EPIMERIZATION IN THE WITTIG AND METHYLLITHIUM REACTIONS

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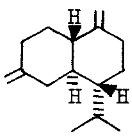
(-)-ε-Cadinene was initially obtained in 1964 (1) as the major product of a partially directed dehydrohalogenation of (-)-cadinene dihydrochloride, and since that time both (-)-ε-cadinene (2) and (+)-ε-cadinene (I) (3,4), without rigorous identification, have been reported to occur in different botanical species. For several years previous to Westfelt's definitive work (1), the name ε-cadinene and its formula I were incorrectly applied to ε-muurolene (II) (1,5).

In synthetic investigations directed toward the above sesquiterpenes we have recently found that the Wittig and methyllithium reactions with the <u>cis</u>-octalone enol ether III (6) proceed, even under the mildest conditions required for these reactions, with inversion of configuration at the C_9 bridgehead position. In Wittig reactions reported previously, as well as in addition reactions of alkyllithiums with ketones, the evidence for enolization has been provided by either the isolation of an enolate, inert to the nucleophilic reagent, or the recovery of unreacted carbonyl compound (7,8). In these cases the addition reactions do not take the normal course. The reactions of III with methylenetriphenylphosphorane and with methyllithium in the present work, involving presumably a fast reversible enolization followed by normal addition to give products IV and V in high yield, are to the best of our knowledge the first cases in the literature where both enolization and the usual nucleophilic attack upon the carbonyl group take place in the same synthetic step. The new reactions eliminate the need for a separate isomerization step in the syntheses of <u>trans</u>-decalins by these methods.

In the case of the reaction of III with methylenetriphenylphosphorane (9),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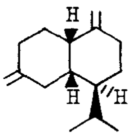
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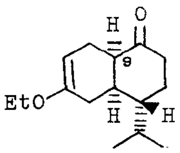
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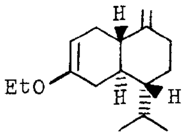
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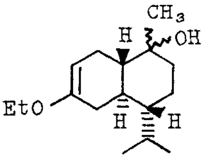
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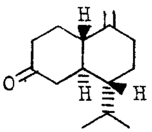
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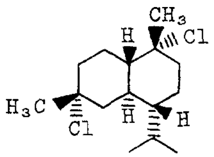
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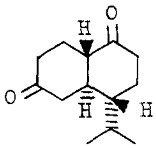
VIII

mild hydrolysis of the resulting olefinic enol ether IV (10) at room temperature for twenty-five minutes with 0.5N hydrogen chloride in 95% ethanol produced in 60% overall yield (homogeneous by gc analysis), the methylene ketone VI (11), which was shown by its relatively strong positive Cotton effect ($[\alpha]_{308(\max)}+865°$) to belong to the trans-decalone series. The corresponding cis isomer in its stable ring inversion conformation, with the isopropyl group in the equatorial alignment, should show a rather strong negative Cotton effect (12). Conversely, the starting cis-octalone enol ether III showed a relatively weak but clear negative effect ($[\alpha]_{311(\max)}-376°$; homogeneous by gc analysis), which is compatible only with the cis stereochemistry required on other grounds (6).

Further Wittig treatment (9) of the methylene ketone VI converted it in 70% yield, after purification, to (+)-ε-cadinene (I) (13), whose structure was evident from its nmr data which indicated four vinyl protons. The ir spectrum, showing intense absorption for the exocyclic methylene groups and for no other unsaturation, is in good agreement with that reported for (-)-ε-cadinene (1), but is markedly different from that of ε-muurolene (1,14). The structure was confirmed by an unambiguous conversion at low temperature (1) to (+)-cadinene dihydrochloride VIII, which was identical with an authentic sample (6) on the basis of its ir spectrum, optical rotation ($[\alpha]_D^{27}+37.5°$), m.p. and mixed m.p. (117-117.5°). The same (+)-ε-cadinene was obtained in 79% yield after distillation and preparative gc, by direct treatment (9) of the (+)-trans-diketone VIII (6) with excess Wittig reagent. The product, on admixture with that from the previous synthesis, showed a single peak on the gas chromatogram and was converted, as before, to (+)-cadinene dihydrochloride.

In separate experiments, epimerization at C_8 took place when the *cis*-octalone III was treated with excess methyllithium. In this case the resulting crude enol ether methyl carbinol (V) (15) obtained in quantitative yield, was directly hydrolized by repeated extraction from ether with aqueous sodium bisulfite. When the regenerated hydroxyketone (16) was again allowed to react with excess methyllithium and the resulting crude diol (17) was treated with hydrogen chloride under specific conditions (-23°) for the retention of the bridgehead stereochemistry (1), the only crystalline product obtained was (+)-cadinene dihydrochloride. No muurolene dihydrochloride could be detected, even with the sensitive techniques of Westfelt (1) which are specifically effective in the presence of cadinene dihydrochloride.

The above reactions, taken together with the stereospecific syntheses of the starting ketones III and VIII, provide new variations in the total stereospecific synthesis of (+)-cadinene dihydrochloride (6,18), and the first total synthesis of (+)-ε-cadinene. The synthesis of the latter provides additional support for the revised structure I (1) of this sesquiterpene.

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9. R. Greenwald, M. Chaykovski and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963). The reagent was prepared with a slight excess of methyltriphenylphosphonium bromide over the sodium hydride used to insure the absence of any carbanion base during the reaction with the ketone.
10. Found for the methylene enol ether IV: $\nu_{max}^{CCl_4}$ (cm^{-1}) 3080 (m), 1660 (m), 1189 (s, enol ether), 890 (s), 1715 (vw, trace of unreacted ketone).
11. Found for the methylene ketone VI: C, 81.51; H, 10.86. $\nu_{max}^{CCl_4}$ (cm^{-1}) 3080 (m) 1715 (s), 1650 (m), 895 (s); nmr (Varian A-60-A, δ, downfield from internal TMS) 4.62 (2H, doublet, terminal methylene), 0.92 (3H) and 0.68 (3H) [both doublets (J = 6.5 Hz) isopropyl group].
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13. Found for (+)-ε-cadinene from III: n_D^{22} 1.5039; $[\alpha]_D^{20}$+6° ($CHCl_3$); $\nu_{max}^{CCl_4}$ (cm^{-1}) 3075 (m), 1790 (w), 1648 (s), 1188 (m), 1140 (m), 1085, 1075 (m, doublet), 893 (vs); $\nu_{max}^{CS_2}$ 3075 (m), 1785 (w), 1648 (s), 1188 (m), 1138 (m), 1080, 1072 (m, doublet), 890 (vs), 817 (m), 652 (m), 638 (s); nmr ($CDCl_3$, δ) 4.58 (4H multiplet, terminal methylene), 0.91 (3H) and 0.70 (3H)[both doublets (J = 6.5 Hz) isopropyl group]; homogeneous by gc analysis, retention time 19 min. at 155°, 10 ft. x 0.125 in. 25% Carbowax 20M/firebrick, He 0.17 ml./sec. For (+)-ε-cadinene from VIII: n_D^{22} 1.5033; $[\alpha]_D^{20}$ +10° ($CHCl_3$); ir, nmr and gc as above. Reported: $[\alpha]_D^{25}$ +5.6° (9). Reported for (-)-ε-cadinene n_D^{22} 1.5032; $[\alpha]_D^{22}$ -15.9° (1). Reported for (+)-ε-muurolene: n_D^{22} 1.5049; $[\alpha]_D^{22}$ +50.7° (1).
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15. Found for the enol ether methyl carbinol V: $\nu_{max}^{CCl_4}$ (cm^{-1}) 3615 (m, sharp), 1660 (m), 1188 (s, enol ether), 1718 (vw, trace of unreacted ketone).
16. Found for the hydroxyketone: $\nu_{max}^{CCl_4}$ (cm^{-1}) 3615 (m, sharp), 1715 (vs).
17. Found for the diol: $\nu_{max}^{CCl_4}$ (cm^{-1}) 3610 (m∼s), 1714 (vw, trace of unreacted ketone).
18. For a synthesis of the racemic dihydrochloride, see M. V. R. K. Rao, G. S. K. Rao and S. Dev, *Tetrahedron* **22**, 1977 (1966).