Stereoselectivity in the Synthesis of *cis*- and *trans*-4,4a-Dimethyl-2-octalone Derivatives

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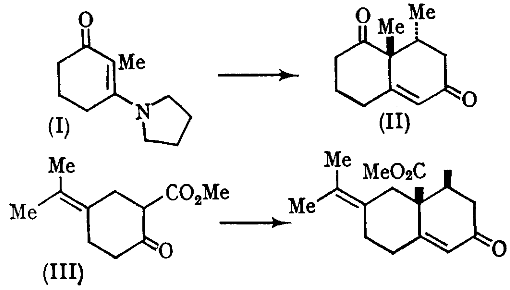
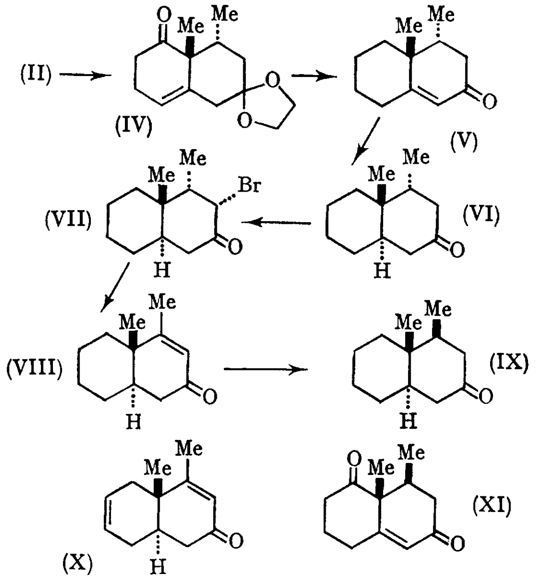
The Robinson annelation reaction of substituted cyclohexanones with pent-3-en-2-one offers an apparently simple synthetic entry into the sesquiterpene group related to eremophilone. Since a *cis*-relationship between the two annular methyl groups is an established fact in this family of natural products, the stereochemical course of the condensation reaction assumes a critical role in this synthetic scheme. Marshall, Faubl, and Warne have recently reported the formation of the *cis*-geometry from the β-keto-ester (III).[1] On the other hand, we now find that the pyrrolidine enamine of 2-methylcyclohexane-1,3-dione reacts with pent-3-en-2-one to give either predominantly the *trans*-stereochemistry or a mixture of both isomers, depending upon the exact conditions.



The *trans*-bicyclic diketone (II) [m.p. 82·5—83·5°; ν_{max} 1715, 1675, 1625 cm.$^{-1}$; τ 4·25 (s, vinyl H), 8·55 (s, Me), and 9·12 p.p.m. (d, J = 7·0 c./sec., Me)] is isolated in 59% yield from (I) and pent-3-en-2-one[2] in a mixture of benzene, acetic acid, and aqueous sodium acetate at reflux temperature [the crude product has (II) : (XI) ratio of *ca.* 10]. The *trans*-orientation of the two methyl groups in (II) follows from the conversions described below.

Selective ketalization (toluene-*p*-sulphonic acid, ethylene glycol, benzene under reflux for 4 hr.) transforms the conjugated carbonyl group into its ethylene dioxy-derivative with double bond migration to give (IV) [49%, m.p. 87—88°; ν_{max} 1715 cm.$^{-1}$; τ 4·34 p.p.m. (multiplet, vinyl H)].† Wolff–Kishner reduction of the unmasked ketone followed by ketal hydrolysis affords the $\alpha\beta$-unsaturated ketone (V) [91%; ν_{max} 1668, 1618 cm.$^{-1}$; τ 4·41 (s, vinyl H), 8·72 (s, Me), and 9·02 p.p.m. (d, J = 7·0 c./sec., Me); the 2,4-dinitrophenylhydrazone, m.p. 134—136°]. The double bond in (V) is smoothly reduced (72%) with lithium–ammonia–tetrahydrofuran and the resulting saturated bicyclic ketone (VI) [b.p. 133—137°/9 mm.; ν_{max} 1713 cm^{-1}; τ 8·84 (s, Me) and 9·08 p.p.m. (d, J = 7·0 c./sec., Me); the 2,4-dinitrophenylhydrazone, m.p. 164—166°] is assigned the *trans* ring fusion.[3],‡ The bromo-ketone (VII) [m.p. 107·5—108·5°; ν_{max} 1733 cm.$^{-1}$ (equatorial bromine); τ 4·84 p.p.m. (d, J = 5·1 c./sec., =CHBr)] is obtained (75%) after treatment with bromine–acetic acid at 10° for 30 min. The location of the bromine substituent at position 3 in (VII) is confirmed by dehydrobromination ($CaCO_3$–DMA, reflux 17 min.) to a different $\alpha\beta$-unsaturated ketone (VIII) [58%; ν_{max} 1668, 1617 cm.$^{-1}$; τ 4·45 (quartet, J = 1·5 c./sec., vinyl H), 8·18 (d, J = 1·5 c./sec., Me), and 8·97 p.p.m. (s, Me)].



The low coupling constant for =CHBr in (VII) indicates that the neighbouring methyl group must be axial, and, hence, *trans* to the quaternary methyl group.[4],‡ This assignment is further supported by hydrogenation (5% Pd–C, absolute methanol, atmospheric pressure) of (VIII) to a different, saturated bicyclic ketone (IX) {64% after prep. v.p.c.; ν_{max} 1714 cm.$^{-1}$; τ 9·09 (s, Me) and 9·12 p.p.m. (d, J = 6·2 c./sec., Me); the 2,4-dinitrophenylhydrazone, m.p. 141—142° [lit.,[5] m.p. 136—138° for the enantiomer (IX)]}. These hydrogenation conditions[5] have been previously shown to reduce the optically active dienone (X) to the enantiomer (IX), the stereochemistry of which was established by o.r.d. measurements.

If benzene is replaced by formamide in the reaction of (I) with pent-3-en-2-one, a mixture of approximately equal amounts of two stereoisomers, (II) and (XI) [m.p. 58—60°; ν_{max} 1717, 1674, and 1628 cm.$^{-1}$; τ 4·23 (s, vinyl H), 8·69 (s, Me), and 8·98 p.p.m. (d, J = 6·2 c./sec., Me)], is formed in somewhat reduced yield. It is clear, therefore, that the stereochemical outcome of the condensation reaction can be subject to the exact conditions of the reaction as well as the structure of the cyclohexanone reactant.

In addition to having the proper stereochemistry, the *cis*-bicyclic ketone (XI) has structural features well-suited for the construction of certain sesquiterpenes in the eremophilone group. Although (XI) is bifunctional, the non-conjugated carbonyl group resides in a sterically hindered environment, thus permitting selective operation at the other carbonyl function [*e.g.*, (II)→(IV)]. Investigations along these lines are in progress.

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† All new compounds have been satisfactorily characterized by microanalytical and spectral data, either as such or in the form of a 2,4-dinitrophenylhydrazone derivative in the case of the liquid ketones. The n.m.r. and i.r. spectral data quoted refer to carbon tetrachloride solutions.

‡ This assignment is considered tentative but none the less does not affect the conclusion regarding the stereochemistry of (II). Had the methyl groups been *cis*, the lithium–ammonia reduction would surely have produced the *trans*-fused product (IX) in which the secondary methyl group must be equatorial (G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, 1964, **86**, 1761).

[1] J. A. Marshall, H. Faubl, and T. M. Warne, jun., *Chem. Comm.*, 1967, 753.

[2] S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, 1963, **28**, 928.

[3] For numerous examples, *cf.* "Steroid Reactions", ed. C. Djerassi, Holden-Day, San Francisco, 1963, ch. 7, and references cited therein.

[4] W. D. MacLeod, jun., *Tetrahedron Letters*, 1965, 4779; J. A. Marshall and N. H. Anderson, *J. Org. Chem.*, 1966, **31**, 667; J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, 1967, **89**, 2748.

[5] L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 6354.