Total Synthesis of (±)-Nootkatone

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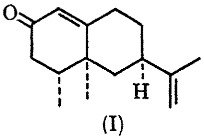
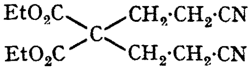
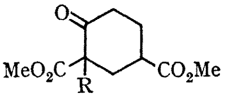
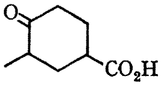
THE recent disclosure[1] of a total synthesis of racemic nootkatone (I), the (+)-form of which is a constituent of the heartwood of Alaska yellow cedar,[2] and also of grapefruit[3] and other citrus species, prompts us to report our synthetic studies, which have also culminated in a total synthesis of the racemic sesquiterpene ketone.


(I)


$$(EtO_2C)_2C(CH_2{\cdot}CH_2{\cdot}CN)_2$$
(II)

$MeO_2C{\cdot}CH{\cdot}(CH_2{\cdot}CH_2{\cdot}CO_2Me)_2$ (III)


(IV)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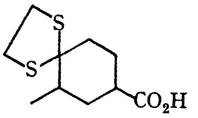
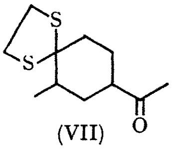
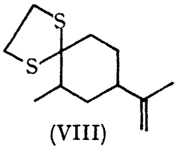
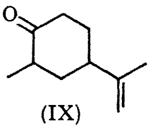
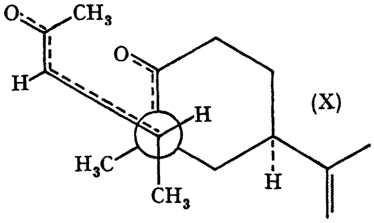

(VI)


(VII)


(VIII)


(IX)

Michael addition of diethyl malonate to acrylonitrile furnished the dinitrile (II),[4] which on hydrolysis, decarboxylation, and re-esterification afforded the triester (III).[5] Dieckmann cyclisation of the latter yielded the β-keto-ester (IV; R=H), which was methylated to (IV; R=Me). Hydrolysis and decarboxylation led to the *cis*-keto-acid (V).[4] Attempts to protect the keto-group in this acid by acetal formation with ethylene glycol were only partially successful, owing to some ester formation *via* the carboxyl group. However, condensation with ethanedithiol was satisfactory, and led to the dithioacetal (VI). Reaction of (VI) with methyl-lithium transformed it into the ketone (VII),[6] converted by a Wittig reaction with methylenetriphenylphosphorane[7] into the alkene (VIII). Hydrolysis of (VIII) with mercuric ions in methanol[8] gave *cis*-4-isopropenyl-2-methylcyclohexanone (IX).


(X)

Annelation of (IX) with *trans*-pent-3-en-2-one in the presence of sodium hydride afforded, after careful fractional distillation, and column and preparative t.l.c., crystalline (±)-nootkatone (I), m.p. 45—46°, identical in chromatographic and spectral properties with a sample of natural (−)-nootkatone, m.p. 36°.†

The stereochemistry of the final step requires comment. Compound (IX) is assigned the *cis*-configuration, both isopropenyl and methyl groups presumably being equatorial.[9] We feel that steric and electronic factors would favour a transition state for the Michael addition (the first

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† Kindly provided by Dr. G. L. K. Hunter, of the Coca-Cola Co., Atlanta, Georgia (G. L. K. Hunter and W. B. Brogden, jun., *J. Food Sci.*, 1965, **30**, 876).

step of the annelation) as depicted in (X),[10] the new ring to be established eventually on the same face of the existing ring as the isopropenyl group.[11] This would lead to structure (I), with the methyl groups at positions 4 and 5 *cis* and α, as was observed. We have made a careful g.l.c. and t.l.c. analysis of our annelation product, and find it to be stereochemically homogeneous and crystalline. This result is in harmony with that of a similar annelation (using sodium methoxide in methanol as base) described by Marshall *et al.*,[11] but at variance with others[12,13] using less basic conditions, in which mixtures of *cis*- and *trans*-isomers were formed. It has been shown[12] that an alteration in annelation reaction conditions can result in a marked change of *cis*:*trans*-ratio in the product, and it would seem that very strongly basic conditions lead exclusively to the *cis*-epimeride in this case.

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

[11] For discussion of the stereochemistry of the Robinson–Mannich and related annelations, see, *inter al.*, F. J. McQuillin, *J. Chem. Soc.*, 1955, 528; T. A. Spencer, K. K. Schmiegel, and K. L. Williamson, *J. Amer. Chem. Soc.*, 1963, **85**, 3785; J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, 1964, **29**, 2501.

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