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THE STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC NOOTKATONE

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The sesquiterpene nootkatone (9), a citrus constituent whose characteristic flavor and odor properties hold some commercial interest, has been the subject of recent synthetic investigations in several laboratories. At least one successful total synthesis of the racemate can be cited to date.[1] We now describe an efficient alternative stereoselective route to this interesting and useful natural product.

Dimethyl γ-ketopimelate (1)[2] afforded the ethylidenecyclohexanonecarboxylic ester 2, a 1:1 mixture of Z and E isomers, directly upon treatment with ethylenetriphenylphosphorane in dimethyl sulfoxide.[3] Condensation with trans-3-penten-2-one in dilute potassium t-amylate solution, and subsequent cyclization of the resulting diketo ester with methanolic sodium methoxide led to the bicyclic keto ester 3 (λ_{max} 5.80, 6.01 μ), a 3:1 mixture of CH_3/CO_2CH_3 cis-trans isomers in 75% yield.[4] The major isomer, m.p. 93-102, whose separation from the mixture could be readily effected by crystallization, was selectively epoxidized by m-chloroperoxybenzoic acid in aqueous 1,2-dimethoxyethane. The derived epoxide 4 yielded the diketo ester 5 (λ_{max} 5.78, 5.85, 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic H), 3.73

(CH_3O-), 2.17 (CH_3CO), and 0.98 ppm (CH_3 doublet, J = 6.0 Hz.)] after BF_3 etherate catalyzed rearrangement[5] followed by basic equilibration. The overall yield of diketo ester 5 based upon the crystalline keto ester 3 exceeded 75%.

The requisite $CO_2CH_3 \rightarrow CH_3$ transformation leading ultimately to dione 8 proved surprisingly difficult to effect, and a satisfactory sequence was developed only after extensive studies of numerous *a priori* reasonable schemes. Accordingly, the *bis*-ketal aldehyde secured from the *bis*-ketal ester 6 *via* reduction ($LiAlH_4$) and oxidation (DMSO-DCC[6]) was subjected to Wolff-Kischner reduction[7] followed by ketal hydrolysis. The desired dione 8 [λ_{max} 5.88, 6.01μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic H), 2.07 (CH_3CO), 1.04 (angular CH_3), and 0.93 ppm (CH_3 doublet, J = 6.0 Hz.)] was thereby obtained in 50% yield based upon the diketo ester 5.

Treatment of dione 8 with a slight excess of methylenetriphenylphosphorane in DMSO[3] afforded racemic nootkatone (9, m.p. 44-45°) identified by spectral and gas chromatographic comparison with the natural material.[8] This final step appears to be highly selective as only a trace of the other possible dienone and triene related to dione 8 could be detected in the crude product.

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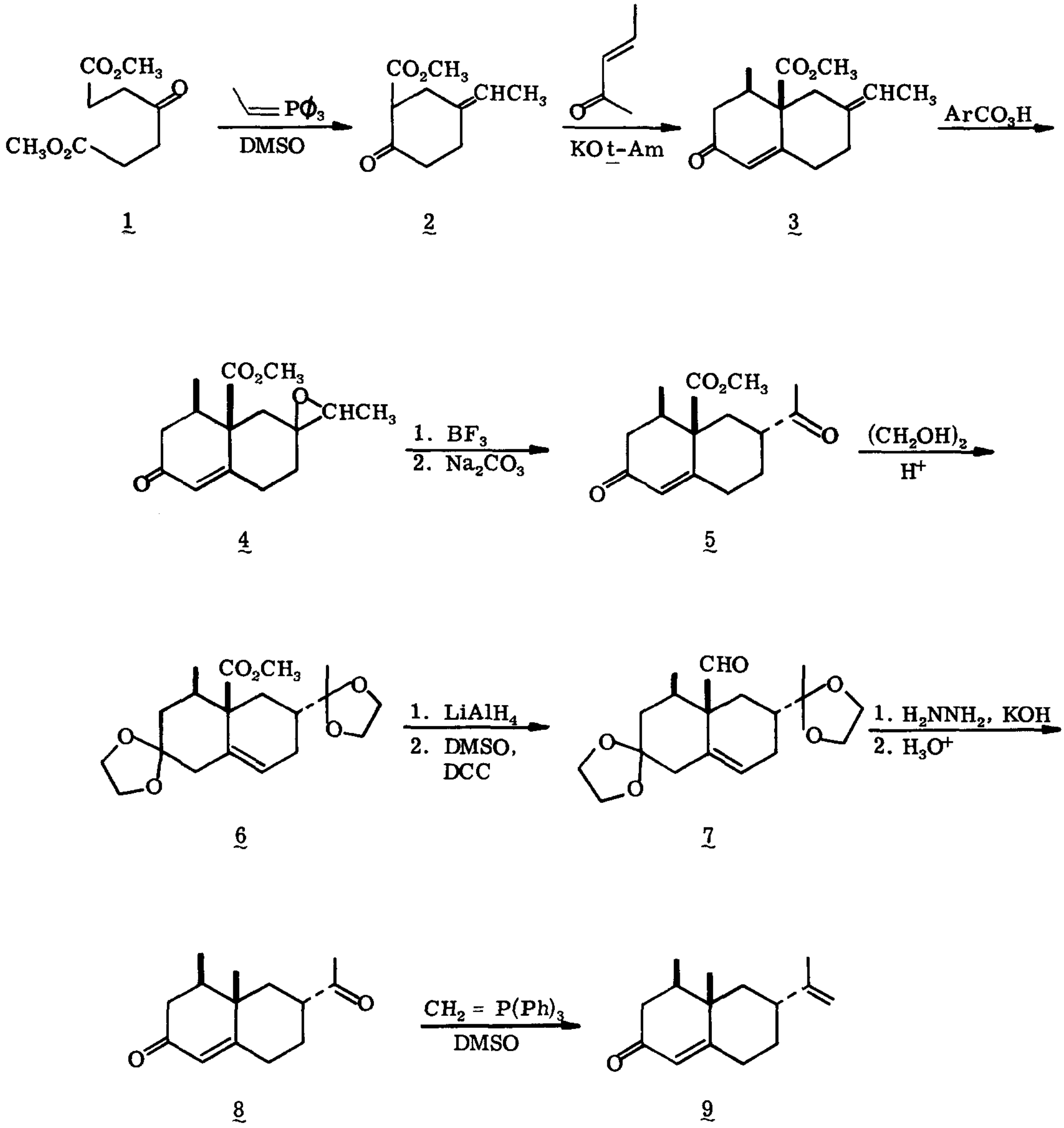
CO2CH3
CH3O2C
1
P𝜙3
DMSO
CO2CH3
CHCH3
2
KOt-Am
CO2CH3
CHCH3
3
ArCO3H
CO2CH3
CHCH3
4
1. BF3
2. Na2CO3
CO2CH3
5
(CH2OH)2
H+
CO2CH3
6
1. LiAlH4
2. DMSO, DCC
CHO
7
1. H2NNH2, KOH
2. H3O+
8
CH2 = P(Ph)3
DMSO
9

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8. We are indebted to Dr. R. E. Erickson, Givaudan Corporation, Clifton, New Jersey, for a sample of natural nootkatone.