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THE STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC FUKINONE

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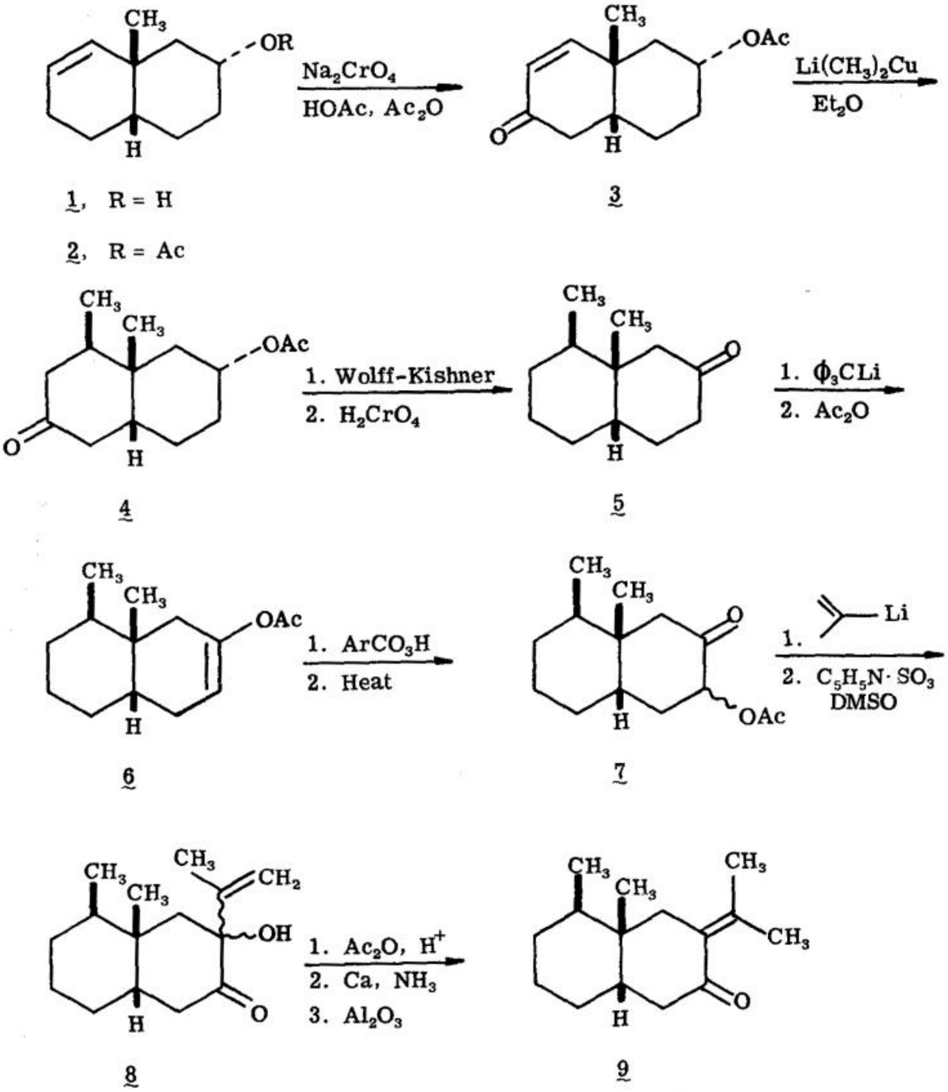
Considerable effort has been devoted in recent years to the development of rational schemes for the synthesis of sesquiterpenes of the eremophilane-nootkatone family.[1] Most approaches to date have failed to provide a stereoselective method for introducing the cis related vicinal methyl groupings which distinguish this unusual nonisoprenoid group of sesquiterpenes from the vast numbers of related isoprenoid hydronaphthalene sesquiterpenes.[2] In this report we present one solution to this stereochemical problem as applied to a total synthesis of racemic fukinone (9).[3]

The known unsaturated alcohol 1[4] upon acetylation and allylic oxidation with sodium chromate in acetic acid-acetic anhydride[5] afforded the enone 3. Conformational and mechanistic considerations[6] lead to the prediction that the product derived from 1,4-addition of lithium dimethylcopper[7] to this enone should have the stereochemistry indicated in 4. Wolff-Kishner reduction of this ketone followed by Jones oxidation[8] of the resulting alcohol gave the decalone 5 [λ_{max}^{film} 5.84 μ; $\delta_{TMS}^{CCl_4}$ 0.95 and 0.85 ppm (doublet, J = 6 Hz); 36% overall yield based on alcohol 1].

Treatment of decalone 5 with triphenylmethyllithium in DME followed by acetic anhydride to trap the resulting enolate[9] yielded the enol acetate 6 in 68% yield [$\delta_{TMS}^{CCl_4}$ 5.10


CH₃
OR
Na₂CrO₄
HOAc, Ac₂O
H
1, R = H
2, R = Ac
CH₃
OAc
Li(CH₃)₂Cu
Et₂O
O
H
3
CH₃
CH₃
OAc
1. Wolff-Kishner
2. H₂CrO₄
O
H
4
CH₃
CH₃
O
1. Φ₃CLi
2. Ac₂O
H
5
CH₃
CH₃
OAc
1. ArCO₃H
2. Heat
H
6
CH₃
CH₃
O
1. Li
2. C₅H₅N·SO₃ DMSO
H
OAc
7
CH₃
CH₃
CH₃
CH₂
OH
1. Ac₂O, H⁺
2. Ca, NH₃
3. Al₂O₃
H
O
8
CH₃
CH₃
CH₃
CH₃
H
O
9

(unresolved triplet), 2.00 (CH_3CO), 0.92, and 0.90 ppm (doublet, J = 6 Hz)]. Acidic enol acetylation reactions led to a mixture of both possible double bond isomers. Epoxidation of the enol acetate 6 followed by thermal rearrangement[10] afforded the keto acetate 7 (48% yield), a mixture of epimers. Addition of isopropenyllithium followed by oxidation of the resulting secondary, tertiary diol by the DMSO-pyridine-sulfur trioxide method[11] yielded the keto alcohol 8 (44% yield). Numerous alternative oxidation methods either caused extensive degradation of the foregoing diol or were ineffective.

Acetylation of the tertiary alcohol grouping of ketol 8 followed by reduction with calcium in ammonia led to a mixture of α, β and β, γ-unsaturated ketones *via* the related enolate. Chromatography of this mixture on alumina afforded racemic fukinone (40% yield). The infrared and nmr spectra of this material exactly matched the published spectra of natural fukinone.[3]

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