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A NEW STEREOSELECTIVE SYNTHESIS OF (±)NOOTKATONE BY MEANS OF CYCLOPENTENONE ANNULATION

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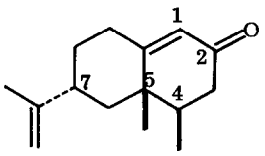
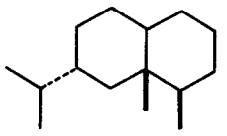
The title sesquiterpene is synthesized by means of the new cyclopentenone annulation which involves acid-treatment of IIIb. The ester group of the resulting V is transformed selectively into isopropenyl appendage of the trans configuration to the two methyl groups. Successive ring-enlargement via a dibromomethyllithium adduct X has yielded (±)nootkatone.

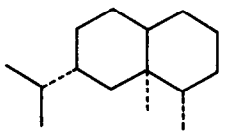
Nootkatone (I) is a constituent of the flavor of grapefruit (citrus paradisi Macfayden)[1] and its structure is characteristic of valencane skeleton. Synthesis of this carbon skeleton as well as its 7-epimer, eremophilane, should involve an annulation process which produces 4,5-cis dimethyl system with high degree of selectivity. Thus far, the Robinson annulation has been applied in general, but the selectivity is not always acceptable.[2] In order to produce this cis-vic dimethyl unit several approaches have been explored such as intermolecular[3a] and intramolecular Diels-Alder reaction.[3b] Herewith we wish to report a new stereocontrolled synthesis of (±)nootkatone based on the recently established cyclopentenone annulation procedure.[4]



nootkatone (I)



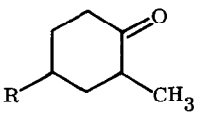
valencane



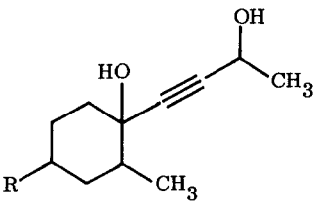
eremophilane

Starting with 4-isopropenyl-2-methylcyclohexanone (IIa), we first attempted to prepare a key intermediate VIIa. Addition of 1-butyn-3-ol was effected as described earlier (71% yield),[4] and the resulting adduct IIIa was exposed to sulphuric acid-methanol (1:1, 0°) conditions. The isolated product was proved to be IV (55% yield)[5a] instead of VIIa. Thus migration of the terminal double bond occurred to give the conjugated dienone. Therefore we had to choose the cyclohexanone derivative having a functional group which should tolerate the acidic conditions.

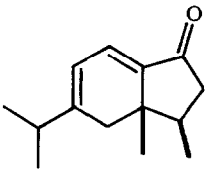
The Diels-Alder reaction of 2-methyl-3-trimethylsilyloxybutadiene[6] with methyl acrylate followed by acidic hydrolysis gave 4-methoxycarbonyl-2-methylcyclohexanone (IIb)[5a,7] in 77% yield as a 2:1 mixture of stereoisomers. Subsequent addition of 1-butyn-3-ol was effected smoothly with concomitant hydrolysis of the ester group to give IIIb[5b] in 83% yield as a stereoisomeric mixture. The mixture was directly used for the next annulation. Treatment of IIIb with sulphuric acid-methanol (1:1) at 50° for 30 min afforded V[5a,8] (49-60% yield). GLC and ^{13}C NMR indicated V was a 3:2 mixture of two stereoisomers, the major one being presumably all cis and the minor one its 5-epimer.[4]



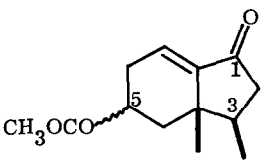
IIa, R = CH_2=C(CH_3)
b, R = CH_3OCO



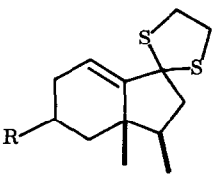
IIIa, R = CH_2=C(CH_3)
b, R = HOCO



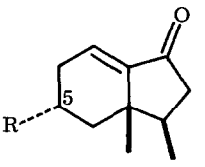
IV



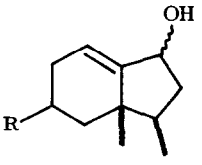
V



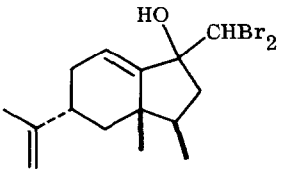
VIa, R = CH_3OCO
b, R = CH_3CO
c, R = CH_2=C(CH_3)



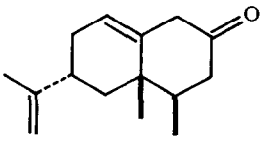
VIIa, R = CH_2=C(CH_3)
b, R = $(CH_3)_2CH$



VIIIa, R = CH_3OCO
b, R = CH_3CO
c, R = CH_2=C(CH_3)



IX



X

Next problem was to convert the methoxycarbonyl group to isopropenyl moiety with correct stereochemistry. In order to protect the ketonic carbonyl we first transformed V to its ethylene acetal,[5b] which later turned out ineffective, as alkaline hydrolysis of the ester group followed by liberation of the carboxylic acid regenerated the ketone instantaneously. Thus, enone V was treated with ethanedithiol to give VIa (57% yield),[5b] whose methoxycarbonyl group was hydrolyzed (2 equiv of KOH, MeOH-H_2O 1:1, reflux, 1 hr) to carboxyl which was successively transformed to the acetyl group of VIb (66%)[5b] with 3 equivalents of methyllithium (ether, 0°, 4.5 hr) and further to isopropenyl group (VIc,[5b] 96% yield) by means of triphenylphosphonium methylid in dimethyl sulphoxide (DMSO) at room temperature. PMR spectra showed VIb was a ca 7:3 mixture of stereoisomers, while VIc was at least 97% pure stereochemically. Probably epimerization took place before the Wittig olefination to yield a thermodynamically favorable product and/or the thermodynamically favorable isomer reacted more rapidly. Deprotection of the dithioacetal group by cupric oxide-cupric chloride[10] or mercuric chloride[11] turned out futile and the yield of VIIa was variable. However, the recently established method by Fujita et al.[12] gave reproducible results. Thus, VIc was treated with excess isoamyl nitrite (dichloromethane, room temperature) to give the desired intermediate VIIa[5a] in 48% yield. The configuration at C(5) turned out to be the correct one (>97% pure) as revealed by hydrogenation of VIIa to VIIb with chlorotris(triphenylphosphine)rhodium(I) as a catalyst and by comparison of the chromatographic and spectrometric data with those of the authentic specimen. Although the stereochemical purity of VIIa prepared by this route is acceptable, both protection and deprotection of the carbonyl group are relatively inefficient, and hence we had to take an alternative route.

The enone V was reduced with sodium borohydride-cerium(III) chloride[13] in methanol to give an allyl alcohol VIIIa which was converted to the methyl ketone VIIIb[5b] as above by successive hydrolysis (2 equiv KOH in methanol, 80°, 30 min) and methyllithium treatment (4.5 equiv MeLi, ether, 0°, 2 hr). The Wittig reaction (4 equiv $Ph_3P{=}CH_2$ in DMSO, 10°, 1 hr) of VIIIb followed by oxidation of the resulting VIIIc with pyridinium chlorochromate[14] gave VIIa[5a,15] of >88% stereochemical purity at C(5) in 78% overall yield.

Final ring-enlargement was effected by the β-oxido carbenoid procedure.[16] The hydrindanone VIIa was allowed to react with 2 equivalents of dibromomethyllithium at -78° to afford an adduct IX[5b] in 84% yield which in turn was treated with 3 equivalents of butyllithium at -95° for 1.6 hr to give an octalone X[5b,17] in 83% yield. The IR spectrum of X showed the presence of a cyclohexanone moiety without contamination of an conjugated enone. Thus it is remarkable that one methylene carbon is selectively inserted between the olefinic and carbonyl carbons of VIIa. Subsequently X was isomerized to (±)nootkatone in 5% sulphuric acid-THF (1:1) at room temperature.[18] Synthetic sample (>93% pure) was chromatographically and spectrometrically identical with the authentic specimen.[2e,19,20]

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5. (a) The compound was characterized spectrometrically and analytically. (b) The compound was characterized spectrometrically.

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8. Bp 139-145° (bath temp)/0.05 Torr; PMR (CCl_4): δ 0.84* (major one), 0.98** (minor one) (s each, 3H), 1.07*, 1.09** (d each, J = 6.0 Hz, 3H), 3.83 (s, 3H), 6.3-6.6 (m, 1H); IR (neat): 1735, 1719, 1654 cm^{-1}.

9. The major isomer gave a peak at δ (from TMS in $CDCl_3$) 128.73 (OMe) and the minor at δ 129.09.

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14. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).

15. Bp 128-135° (bath temp)/0.3 Torr; PMR (CCl_4): δ 1.00 (s, 3H), 1.07* (VIIa), 1.10** (C(5)-epimer of VIIa) (d each, J = 6 Hz, 3H), 1.76 (s, 3H), 4.72 (br s, 2H), 6.39* (t, J = 3.6 Hz, >0.88H), 6.53** (m, <0.12H); IR (neat): 3086, 1718, 1654, 886 cm^{-1}.

16. H. Taguchi, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., 50, 1588, 1592 (1977).

17. PMR (CCl_4): 0.97 (d, J = 6.5 Hz, 3H), 1.17 (s, 3H), 4.70 (s, 2H), 5.3-5.5 (m, 1H); IR (neat): 3090, 1721, 1644, 887 cm^{-1}.

18. Isolated yield was 58%; 74% yield based on the consumed X.

19. Following the same sequence (+)nootkatone of >97% purity was obtained using the sample of VIIa derived from the dithioacetal VIc.

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