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THE TOTAL SYNTHESIS OF (+)-NOOTKATONE AND (−)-7-EPI-NOOTKATONE

YOSHIKAZU TAKAGI,* YOSHIAKI NAKAHARA and MASANAO MATSUI
Institute of the Physical and Chemical Research, Wakoshi, Saitama, Japan

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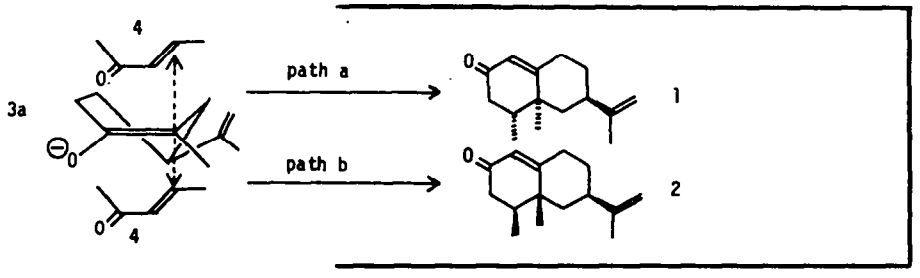
Abstract—Both (+)-nootkatone and (−)-7-epi-nootkatone have been synthesized from (+)-2-mithyl-4-isopropenyl-cyclohexanone.

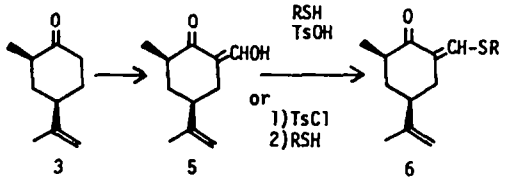
The eremophilane sesquiterpene (+)-nootkatone (1), first isolated from the heartwood of Alaska yellow cedar (*Chamaecyparis nootkatensis*)[1] and later found in grape fruit peel oil (*Citrus paradisi*)[2] and other citrus oils,[3] is extensively utilized in the perfumery field as a key flavor of grapefruit. The chemical structure of (+)-nootkatone (1) was determined by Mac Leod[4] in 1965, and partial syntheses of this ketone from the parent hydrocarbon valencene[5,6] and from nootkatene[7] as well as five total syntheses[8–12] of (±)-nootkatone (1) have been reported; however, the total synthesis of (+)-isomer (1) has not been achieved.

In this paper, we wish to describe the total synthesis of (+)-nootkatone (1) and (−)-7-epi-nootkatone (2) from (+)-2-methyl-4-isopropenylcyclohexanone (3).

Van Der Gen[10] and Pinder[11] reported that the Robinson annelation of (±) - *cis* - 2 - methyl - 4 - isopropenylcyclohexanone (3) with *trans* - 3 - penten - 2 - one (4) yielded mostly (±)-2, accompanied by (±)-1 as a minor product in *ca.* 90:10 ratio. This result means that approach of pentanone (4) from the α-side of the enolate anion (3a), i.e. path b, was preferred to β-side attack (path a), and it therefore seemed necessary to change the shape (and/or conformation) of the cyclohexane ring to make the product ratio more favorable to the desired isomer. After some preliminary experiments, we found that the introduction of an alkylthiomethylene group at the C_6-position gave the best result in the annelation reaction. We describe th synthetic scheme below.



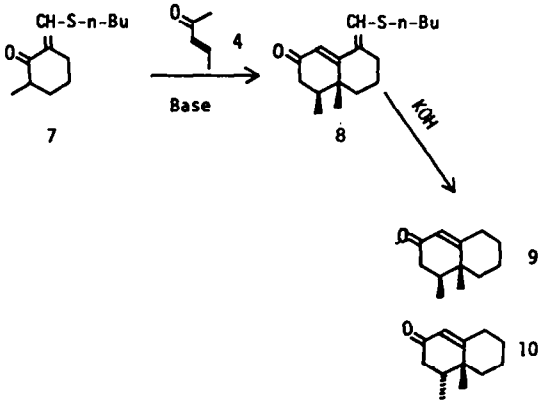
The starting material, (+) - 2 - methyl - 4 - isopropenylcyclohexanone (3),† was prepared from (−) - β - pinene‡ in five steps by patented procedures[13,14] in 24% overall yield. This 3 was transformed to its thiomethylene derivatives (6a–c), the key intermediates of our synthesis, by Marshall's procedure[15] in 70 ~ 93% yield.



R= n-Butyl 6a
sec-Butyl 6b
Benzyl 6c

In order to find the best reaction conditions, 2 - methyl - 6 - n - butylthiomethylene cyclohexanone (7), prepared from 2-methylcyclohexanone as described above[15] in 82% yield, was employed for the model annelation with *trans* - 3 - penten - 2 - one (4), the key step of our synthesis. The results obtained in different media are summarized in Table 1.

As shown in Table 1, the t-BuOK/t-BuOH method gave the desired *cis*-octalone[16]§ (9) in better yield, while in the NaH/DMSO procedure *trans*-isomer[16]¶ (10) was



†$[\alpha]_D^{20}$ +5.9° (c = 5.0 in EtOH).
‡$[\alpha]_D^{20}$ −18.2° (c = 5.0 in EtOH).
§The chemical shift of the angular methyl group in *cis*-octalone (9) is δ^{CCl_4} 1.08.
¶The chemical shift of the angular methyl group in *trans*-octalone (10) is δ^{CCl_4} 1.27.

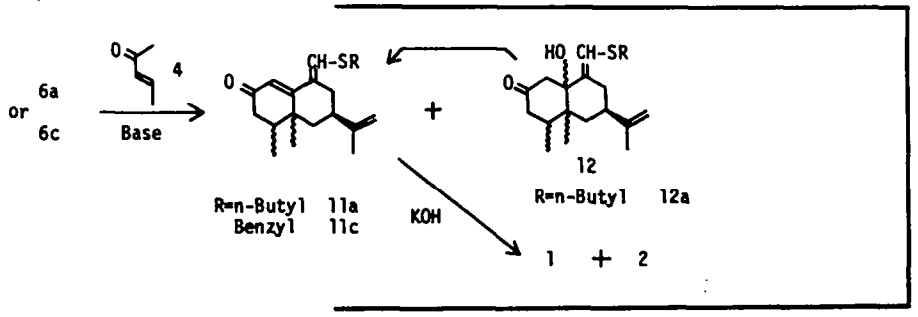
Table 1. The Robinson annelation of 7 with 4

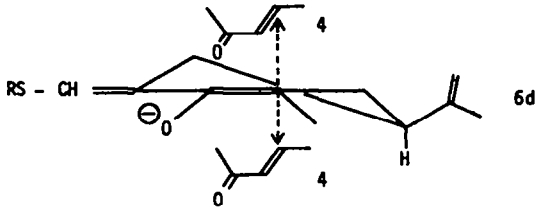
Base (Meq.)	Solvent	Temp.	Hour (hr)	Yield (%)	9 : 10
t-BuOK (0.1)	t-BuOH	rt	24	55	100 : 0
NaH (1.0)	Dioxane	rt	24	41	100 : 0
NaH (1.0)	DMSO	rt	24	39	33 : 67

predominantly produced. That *cis*-vicinal-dimethyl derivative (9) was obtained under less polar or protic solvent system is probably for the reasons described in the literature.[16,17] Thus we carried out our key step annelation in t-BuOK/t-BuOH. Ketone (**6a**) and pentenone (**4**) were treated with t-BuOK (0.1 Meq.) to give octalone (**11a**) and ketol (**12a**) in 69% yield (3:2 ratio), the latter of which was converted to the former enone (**11a**) by treating with 0.5 N KOH. Alternatively the reaction of benzyl derivative (**6c**) with enone (**4**) in t-AmOK/t-AmOH afforded only octalone (**11c**) in 71% yield. Thiomethylene protective groups of **11a** and **11c** were removed[15] with aqueous KOH to give mixtures of nootkatone (**1**) and 7-epi-nootkatone (**2**) in 74 and 76% yield respectively. The ratio of the two products varied according to the conditions and was determined by NMR† and GLC‡ analyses. Table 2 shows the results of Robinson annelation under various conditions.

From these experimental data, it is clear that under milder conditions the mixture of **1** and **2** is obtained in higher yield, but with a ratio favoring the C_7-epimer (**2**); whereas more drastic conditions give a lower total yield of mixture but a higher proportion of the desired compound (**1**). Bulkiness of the substituent R on the thiomethylene group does not have any significant influence on the stereochemistry of product, probably because it is located far away from the reaction site at the C_2-position. The introduction of a thiomethylene group causes the C_6-position to bear a new sp_2 bonding in the enolate (**6d**) which makes the 6-membered ring more planar, thus it seems rational that the β-face of the enolate (**6d**) is sterically more accessible than that of the enolate (**3a**).

Other protective groups were also introduced to the





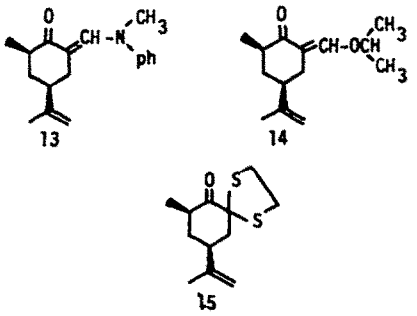
†The chemical shifts of angular methyl group and enone olefin in nootkatone (**1**) are δ^{CCl_4} 1.12 and 5.62, and those of 7-epimer (**2**) are δ^{CCl_4} 1.07 and 5.68 respectively.

‡An authentic sample of 7-epimer (**2**) was prepared from direct annelation of 3 with 4 by Pinder's procedure.[11]

Table 2. The Robinson annelation of 6 with 4

R	Base (Meq.)	Solvent	Temp(°C)	Hour(hr)	Yield(%)	1 : 2
n-Butyl	t-BuOK (0.1)	t-BuOH	rt	20	55	30 : 70
n-Butyl	t-BuOK (1.0)	t-BuOH	rt	5	42	35 : 65
n-Butyl	t-BuOK (1.0)	t-BuOH	50~55	0.5	35	45 : 55
n-Butyl	t-AmOK (0.1)	t-AmOH	-5~-10	20	63	25 : 75
n-Butyl	t-AmOK (0.1)	t-AmOH	rt	20	53	30 : 70
n-Butyl	t-AmOK (0.1)	t-AmOH	50~55	5	38	35 : 65
n-Butyl	t-AmOK (1.0)	t-AmOH	50~55	0.5	32	45 : 55
n-butyl	NaH (1.0)	Dioxane	rt	5	49	30 : 70
n-Butyl	NaH (1.0)	Dioxane	50~55	0.5	42	40 : 60
sec-Butyl	t-AmOK (1.0)	t-AmOH	50~55	0.5	33	40 : 60
Benzyl	t-AmOK (0.1)	t-AmOH	rt	20	54	30 : 70
Benzyl	t-AmOK (1.0)	t-AmOH	50~55	0.5	35	45 : 55
Benzyl	t-AmOK (1.0)	t-AmOH	95~100	0.25	30	50 : 50
Benzyl	NaH (1.0)	Dioxane	rt	5	31	30 : 70

ketone (3), but the annelation reaction under various conditions completely failed with these derivatives, (13),[18] (14)[19] and (15).[20]



13 14 15

In order to isolate pure (+)-nootkatone (1), the reaction should be carried out at high temperature (50–55°) for a short period (~30 min) in the presence of t-BuOK (1 Meq) in t-BuOH. Under these conditions a yield of about 35% with a ratio of 1 to 2 of about 45:55 was obtained.

Finally, the separation of (+)-nootkatone (1) from epimer (2) was achieved by repeated fractional recrystallization of their semicarbazone[21] mixture to give pure (+)-nootkatone semicarbazone (m.p. 195–6°, $[\alpha]_D^{20}$ +328°). This semicarbazone was hydrolyzed with 10% H_2SO_4 aq. or 10% oxalic acid[21] to give (+)-nootkatone (1) (m.p. 28–30°, $[\alpha]_D^{20}$ +170°), the purity of which was shown to be more than 95% by NMR and GLC analyses. Physical data for synthetic (+)-nootkatone (1) were entirely identical with those of an authentic sample from natural sources. (−) - 7 - epi - Nootkatone (2) was similarly isolated from the mother liquor of the semicarbazone mixture solution.

Thus the synthesis of (+)-nootkatone (1) from (+) - 2 - methyl - 4 - isotpropenyl-cyclohexanone (3) was accomplished in six steps.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. NMR spectra were recorded on Varian HA-100 and Varian EM-360 spectrometers with TMS as an internal standard. IR spectra were determined on a Hitachi Grating IR spectrophotometer. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. GLC was carried out on a Shimazu GC-6AM Pr. (glass capillary; SF-96 column 20 m × 0.28 mm).

2 - Methyl - 4 - isopropenyl - 6 - hydroxymethylene cyclohexanone (5)

To a stirred suspension of powdered NaOMe, freshly prepared from Na (13.8 g, 0.60 g atom) and MeOH (600 ml), in dry benzene (600 ml) was added a mixture of (+)-3 (45.6 g, 0.30 mole) and ethyl formate (44.4 g, 0.60 mole) dropwise over 1 hr under N_2 with ice-cooling, and the stirring was continued for 20 hr at room temp. Ice water (500 ml) was added and the aqueous layer was separated, washed once with ether (100 ml), and acidified with cold 6 N HCl aq. The resulting oil was extracted with ether (100 ml × 2) and the combined ethereal extract was washed twice with brine, and dried over Na_2SO_4. After removal of ether, the residue was distilled to give 5 (47.6 g, 88%): b.p. 72 ~ 4°/0.7 mm; IR (film) 3060, 1640, 1630, 1595 and 895 cm^{-1}; NMR (CCl_4) δ 1.22 (3H, d, J = 7 Hz), 1.75 (3H, broad s), 4.70 (2H, broad s) and 8.55 (1H, m).

2 - Methyl - 4 - isopropenyl - 6 - n - butylthiomethylene cyclohexanone (6a)

A soln of 5 (20.0 g, 0.11 mole) in benzene (100 ml) containing n-BuSH (12.0 g, 0.13 mole) in the presence of TsOH (200 mg) was refluxed for 2 hr with continuous azeotropic removal of water (2 ml). The mixture was cooled, washed with water, $NaHCO_3$ aq, and brine, and dried over Na_2SO_4. After removal of benzene, the residue was distilled to give 6a (25.8 g, 93%): b.p. 142–5°/0.5 mm; IR (film) 3060, 1660, 1640, 1545 and 890 cm^{-1}; NMR (CCl_4) δ 0.95 (3H, t, J = 7 Hz), 1.12 (3H, d, J = 7 Hz), 1.78 (3H, broad s), 2.86 (2H, t, J = 7 Hz), 4.78 (2H, m) and 7.35 (1H, m); $[\alpha]_D^{20}$ +30.9° (C = 5.0 in EtOH).

2 - Methyl - 4 - isopropenyl - 6 - benzilthiomethylene cyclohexanone (6c)

To a soln of 5 (5.4 g, 0.03 mole) in pyridine (50 ml) at 0° was added TsCl (6.0 g, 0.032 mole). The mixture was stirred at 0–5° for 3 hr and then benzyl mercaptan (4.0 g, 0.032 mole) was added. The mixture was stirred at 0–5° for 20 hr, then poured into water (300 ml) and extracted with ether (100 ml × 3). The combined ethereal extract was washed with water, 5% NaOH aq and brine (three times), and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel (300 g) with n-hexane–ethyl acetate (8:1) as eluent to give oily 6c (7.0 g, 82%): IR (film) 3060, 3040, 3020, 1660, 1640, 1600, 1545, 1495 and 890 cm^{-1}; NMR (CCl_4) δ 1.10 (3H, d, J = 7 Hz), 1.74 (3H, broad s), 4.00 (2H, s), 4.74 (2H, m), 7.24 (5H, s) and 7.41 (1H, m); $[\alpha]_D^{20}$ +32.7° (c = 5.0 in EtOH).

2 - Methyl - 4 - isopropenyl - 6 - sec-butylthiomethylene cyclohexanone (6b)

In the same fashion, 5 (2.7 g, 0.015 mole) was converted to 6b in 70% yield with TsCl (3.0 g, 0.016 mole) and sec-BuSH (1.5 g, 0.017 mole). IR (film): 3060, 1660, 1640, 1540 and 890 cm^{-1}. NMR (CCl_4): δ 1.05 (3H, t, J = 7 Hz), 1.15 (3H, d, J = 7 Hz), 1.44 (3H, d, J = 7 Hz), 1.82 (3H, broad s), 4.72 (2H, m) and 7.40 (1H, m).

2 - Methyl - 6 - n - butylthiomethylene cyclohexanone (7)

2 - Methyl - 6 - hydroxymethylene cyclohexanone[19] (28.0 g, 0.20 mole), prepared from 2-methylcyclohexanone in 85% yield, was converted to 7 in 96% yield with n-BuSH (22.0 g, 0.24 mole) by the benzene azeotropic procedure described by Ireland and Marshall,[15] b.p.: 108–111°/0.3 mm (lit.[15] b.p. 93–5°/0.05 mm); IR (film): 1660 and 1545 cm^{-1}. NMR (CNl_4): δ 0.94 (3H, t, J = 7 Hz), 1.08 (3H, d, J = 7 Hz), 2.84 (2H, t, J = 7 Hz) and 7.31 (1H, t, J = 2 Hz).

cis - 4,5 - Dimethyl - 9 - n - butylthiomethylene - 1(10) - octalin - 2 - one (8)

To a soln of t-BuOK, prepared from K (80 mg, 0.002 g atom) and t-BuOH (30 ml), was added 7 (4.2 g, 0.02 mole) and the mixture was stirred under N_2 for 10 min at room temp. and then cooled to 0–5°. To this was added a soln of *trans*-4 (2.5 g, 0.03 mole) in t-BuOH (10 ml) dropwise over 30 min, and the mixture was stirred for 24 hr. The mixture was diluted with water (200 ml), and extracted with ether (100 ml × 2). The ethereal extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (200 g) with n-hexane–ethyl acetate (8:1) as eluent to give crystalline 8 (4.2 g, 76%) which was recrystallized from n-pentane: m.p. 70.5–71.0°; IR (KBr) 1655, 1635 and 1530 cm^{-1}; NMR (CCl_4) δ 0.96 (3H, t, J = 7 Hz), 0.97 (3H, d, J = 7 Hz), 1.01 (3H, s), 2.74 (2H, t, J = 7 Hz), 5.74 (1H, broad s) and 6.28 (1H, m). (Found: C, 73.27; H, 9.13; S, 11.42. Calc. for $C_{17}H_{26}OS$: C, 73.33; H, 9.41; S, 11.51%).

cis - 4,5 - Dimethyl - 1(10) - octalin - 2 - one (9)

(a) A mixture of 8 (2.8 g, 0.01 mole) and 25% KOH aq (10 ml) in diethylene glycol (10 ml) was refluxed under N_2 for 15 hr. The cooled mixture was diluted with water (100 ml) and extracted with ether (50 ml × 2). The combined ethereal extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (100 g) with n-hexane–ethyl acetate (8:1) as eluent to give crystalline octalone 9 (1.3 g, 72%) which was recrystallized from n-pentane: m.p. 61–62°; IR (KBr) 1660 and 1610 cm^{-1}; NMR (CCl_4) δ 0.95 (3H, d, J = 6 Hz), 1.08 (3H, s) and 5.60 (1H, broad s).

(b) In the same manner, crude annelation product, obtained by

treatment of a mixture of 7 (4.2 g, 0.02 mole) and 65% NaH (740 mg, 0.02 mole) in DMSO (40 ml) with *trans*-4 (2.5 g, 0.03 mole), was dethiomethylenated to give a mixture (1.4 g, 39%) of *cis*- and *trans*-isomers (9 and 10) in *ca.* 1:2 ratio: NMR (CCl_4) δ 1.08 (3H × $\frac{1}{3}$, s) and 1.27 (3H × $\frac{2}{3}$, s).

4,5 - Dimethyl - 7 - isopropenyl - 9 - n - butylthiomethylene - 1(10) - octalin - 2 - one (11a) *and 4,5 - dimethyl - 7 - isopropenyl - 9 - n - butylthiomethylene - 10 - hydroxydecalin - 2 - one* (12a)

To a soln of t-BuOK prepared from K (80 mg, 0.002 g atom) and t-BuOH (30 ml) was added 6a (5.0 g, 0.02 mole) and the mixture was stirred for 15 min under N_2 at room temp. To this was added a soln of 4 (2.5 g, 0.03 mole) in t-BuOH (10 ml) dropwise over 30 min, and the stirring was continued at room temp. for an additional 20 hr. The mixture was diluted with water (200 ml), and extracted with ether (100 ml × 2). The combined ethereal extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (200 g) with n-hexane–ethyl acetate (6:1) as eluent to give 11a (2.4 g, 41%) and 12a (1.6 g, 24%).

Octalone 11a: IR (film) 3060, 1655, 1550 and 890 cm^{-1}; NMR (CCl_4) δ 0.89 (3H, t, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 1.01 (3H, s), 1.75 (3H, broad s), 2.76 (2H, t, J = 7 Hz), 4.74 (2H, broad s), 5.75 (1H, m) and 6.36 (1H, m).

Ketol 12a: IR (film) 3450, 3060, 1710, 1600, 1640 and 890 cm^{-1}; NMR (CCl_4) δ 0.90 (3H, t, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 1.06 (3H, s), 1.74 (3H, broad s), 2.64 (2H, t, J = 7 Hz), 4.72 (2H, m) and 5.80 (1H, s).

4,5 - Dimethyl - 7 - isopropenyl - 9 - benzylthiomethylene - 1(10) - octalin - 2 - one(11c)

In the same fashion, 6c (1.43 g, 0.005 mole) was treated with t-AmOK prepared from K (20 mg, 0.0005 atom) and t-AmOH (20 ml) and 4 (0.63 g, 0.0075 mole) at room temp. for 20 hr. After the usual work-up, the residue was chromatographed on silica gel (50 g) with n-hexane–ethyl acetate (6:1) as eluent to give only 11c (1.26 g, 71%): IR (film) 3060, 3010, 1650, 1600, 1540, 1490 and 890 cm^{-1}; NMR (CCl_4) δ 0.91 (3H, s), 0.94 (3H, d, J = 7 Hz), 1.69 (3H, broad s), 3.95 (2H, s), 4.70 (2H, broad s), 5.73 (1H, s), 6.44 (1H, broad s) and 7.24 (5H, s).

Conversion of ketol 12a *to octalone* 11a

A soln of 12a (1.0 g, 0.003 mole) in 0.5 N KOH–MeOH (20 ml) was refluxed for 10 hr. The cooled mixture was diluted with water (200 ml) and ectracted with ether (100 ml × 2). The combined ethereal extract was washed with water and brine and dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on silica gel (30 g) with n-hexane–ethyl acetate (6:1) as eluent to give 11a (0.83 g, 87%).

(+)-Nootkatone (1) *and (−)-7-epi-nootkatone* (2)

(a) A mixture of 11a (2.0 g, 0.0063 mole), prepared by the t-BuOK (0.1 Meq)/t-BuOH procedure at room temp. for 20 hr, and 25% KOH aq (10 ml) in diethylene glycol (10 ml) was refluxed under N_2 for 15 hr. The cooled mixture was diluted with water (100 ml) and extracted with ether (50 ml × 2). The combined ethereal extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (50 g) and n-hexane–ethylacetate (6:1) as eluent to give a mixture (1.01 g, 74%) of 1 and 2 in *ca.* 3:7 ratio: NMR (CCl_4) δ 1.07 (3H × 7/10, s), 1.12 (3H × 3/10, s), 5.62 (1H × 3/10, broad s) and 5.68 (1H × $\frac{7}{10}$, broad s); $[\alpha]_D^{20}$ −64.0° (*c* = 1.5 in $CHCl_3$). (+)-Nootkatone (1) and 7-epimer (2) were identical with authentic samples on GLC (glass capillary column: SF-96, 20 m × 0.28 mm).

(b) In the same fashion, the treatment of 11c (1.1 g, 0.0031 mole), prepared by the t-AmOK (0.1 Meq)/t-AmOH procedure at room temp. for 20 hr, with 25% KOH aq (5 ml) in diethylene glycol (5 ml) gave a mixture (0.53 g, 76%) of 1 and 2 in *ca.* 3:7 ratio.

(c) To a soln of t-BuOK prepared from K (3.9 g, 0.1 g atom) and t-BuOH (200 ml) was added dropwise a mixture of 6a (25.2 g, 0.1 mole) and 4 (12.6 g, 0.15 mole) over 10 min at 50° under N_2 and the mixture was stirred at 50–55° for an additional 20 min. The mixture was diluted with water (1 l.), and extracted with ether (300 ml × 2). The combined ethereal extract was washed with water and brine. After removal of solvent, the crude annelation product was added to a soln of 25% KOH aq (200 ml) in diethylene glycol (200 ml), and the mixture was refluxed for 15 hr under N_2. The cooled mixture was diluted with water (1 l.) and extracted with ether (200 ml × 2). The combined ethereal extract was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (800 g) with n-hexane–ethyl acetate (6:1) as eluent to give a mixture (7.6 g, 35%) of 1 and 2 in *ca.* 45:55 ratio: $[\alpha]_D^{20}$ −18.8° (*c* = 1.5 in $CHCl_3$).

Isolation of (+)-nootkatone (1)

To a soln of crude product (1 and 2 in *ca.* 45:55 ratio; 5.0 g, 0.022 mole), obtained by the preceding procedure (c), in 60% EtOH aq (50 ml) were added AcONa (3.0 g, 0.037 mole) and semicarbazide–HCl (3.0 g, 0.027 mole), and the mixture was heated on a steam bath for 20 min this allowed to stand overnight at room temp. to give yellow crystals, which were filtered off, washed well with water, and dried: m.p. 176–9°; $[\alpha]_D^{20}$ +9.4° (*c* = 0.5 in $CHCl_3$). This crystalline product was recrystallized four times from 95% EtOH aq to give colorless crystals of (+)-nootkatone semicarbazone (0.47 g): m.p. 196–7° [lit.[1] m.p. 195–7°]; $[\alpha]_D^{20}$ +328° (*c* = 0.5 in $CHCl_3$) [lit.[1] $[\alpha]_D$ +384° (*c* = 0.51 in $CHCl_3$)]. A mixture of (+)-nootkatone semicarbazone (200 mg, 0.73 m mole), and 10% H_2SO_4 aq (2 ml) in benzene (2 ml) was stirred at room temp. for 72 hr. The mixture was diluted with water (50 ml), and extracted with ether (50 ml). The ethereal extract was washed with water, $NaHCO_3$ aq and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (20 g) with n-hexane–ethyl acetate (6:1) as eluent to give 1 (144 mg, 91%): m.p. 28–30° [lit.[1] m.p. 36–7°]; $[\alpha]_D^{20}$ +170° (*c* = 0.5 in $CHCl_3$) [lit.[1] $[\alpha]_D$ +195.5° (*c* = 1.5 in $CHCl_3$)]; purity 95% by GLC (glass capillary column; SF-96, 20 m × 0.28 mm) analysis. Physical data of synthetic (+)-1 were identical with those of authentic (+)-nootkatone.

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REFERENCES

[1]H. Erdtman and Y. Hirose, *Acta. Chem. Scand.* **16**, 1311 (1962).
[2]W. D. MacLeod and N. M. Buignes, *J. Food Sci.* **29**, 565 (1964).
[3]J. W. Kesterson, R. Hendrickson, R. R. Seiler, C. E. Huffman, J. A. Brent and J. T. Griffiths, *Am. Perfum. Cosmet.* **80**, 29 (1965).
[4]W. D. MacLeod, *Tetrahedron Letters* 4779 (1965).
[5]G. L. Hunter and W. B. Brogden, *J. Food Sci.* **30**, 876 (1965).
[6]W. G. Dauben, M. Lorber and D. S. Fullertan, *J. Org. Chem.* **34**, 3587 (1969).
[7]Firmenich & Cie, *Netherlands Pat. Appl.* 6914545 (1965).
[8]M. Pesaro, G. Bozzato and P. Schudel, *Chem. Commun.* 1152 (1968).
[9]J. A. Marshall and R. A. Ruden, *Tetrahedron Letters* 1239 (1970).
[10]A. Van Der Gen, L. N. Van Der Linde, J. G. Witeveen and H. Boelens, *Recl. Trav. Chim.* **90**, 1034 (1971).
[11]H. C. Odom and A. R. Pinder, *J. Chem. Soc.* Perkin I, 2193 (1972).
[12]K. P. Dastur, *J. Am. Chem. Soc.* **96**, 2605 (1974).
[13]T. Hasegawa Co., Ltd., *Japan Pat.* 91046 (1973).
[14]T. Hasegawa Co., Ltd., *Pending Pat*; *cf.* C. F. Mayer and J. K. Crandall, *J. Org. Chem.* **35**, 2688 (1970).

[15]R. E. Ireland and J. A. Marshall, *Ibid.* **27**, 1615 (1970).
[16]C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.* **93**, 1539 (1971).
[17]J. A. Marshall and T. M. Warne, Jr., *J. Org. Chem.* **36**, 178 (1971).
[18]A. J. Birch and R. Robinson, *J. Chem. Soc.* 501 (1944).
19. W. S. Johnson and H. Posvić, *J. Am. Chem. Soc.* **69**, 1361 (1947).
[20]R. B. Woodward, I. J. Pachter and M. L. Scheinbaum, *J. Org. Chem.* **36**, 1137 (1971).
[21]H. L. Haller and F. B. LaForge, *Ibid.* **1**, 38 (1936).