17 as a foam which was nearly homogenous on TLC (system F). A sample obtained by preparative TLC (system F) showed the following: EI MS m/e 385 (M^+), 384 ($M^+ - 1$), 248 ($M^+ - C_8H_9O_2$, base[22]); IR ($CHCl_3$) 3546 (OH), 1686 (C=O) cm^{-1}; $[\alpha]^{23}_D$ -57.3° (c 0.15, $CHCl_3$); NMR ($CDCl_3$; for the mixture of rotomers) δ 1.28 (t, 3 H, CH_2CH_3, J = 8 Hz), 2.64-2.91 (m, 2 H), 3.24-3.50 (m, 2 H), 3.77, 3.83, and 3.86 (3 s, 6 H, 2 OCH_3), 4.09-4.32 (m, 2 H, CH_2CH_3), 5.32-5.55 (m, 2 H), 5.60 (br s, 2 H, OH, exchanges with D_2O), 6.41 and 6.44 (2 s, 1 H, ArH), 6.51 and 6.53 (2 s, 1 H, ArH), 6.65 (s, 1 H, ArH), 6.73 (s, 1 H, ArH). The ratio of rotomers in this sample was ~1:1.

(-)-Bisnorargemonine (11a). A solution of 750 mg (1.95 mmol) of 17 in 25 mL of dry THF was added dropwise to a stirred, refluxing solution of 500 mg (13.2 mmol) of LAH in 200 mL of dry THF. The mixture was refluxed 18 h, cooled, and cautiously treated dropwise with 40 mL of concentrated aqueous NH_3. When the addition was completed, the mixture was allowed to stand 10 min, and then the clear THF (which contained only traces of **11a**) was decanted and discarded. To the gellike precipitate which adhered to the sides of the flask were added 50 mL of H_2O and sufficient 37% aqueous HCl to dissolve the inorganic material and acidify the aqueous phase to pH <1 (Hydrion paper). The aqueous was removed, and the small amount of brown tarry material remaining in the flask was triturated with boiling H_2O (2 × 25 mL). The combined, stirred aqueous phase was treated with 100 mL of $CHCl_3$ and rendered alkaline to pH 9-9.5 with concentrated aqueous NH_3, and the resulting emulsion was filtered through Celite. The filter was washed with $CHCl_3$ (2 × 50 mL), and the aqueous was separated and extracted with $CHCl_3$ (5 × 50 mL). The Celite and inorganic material was slurried with boiling methanol (2 × 50 mL) and filtered, and the methanol was evaporated. The residue was triturated with 50 mL of boiling $CHCl_3$ and filtered. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to afford 526 mg of a foam which was crystallized from 2.0 mL of cold methanol to afford 206 mg (32%) of off-white **11a**, mp 248.5-249.5 °C dec. Preparative TLC of a portion of this material (system B) followed by recrystallization from MeOH provided pure **11a**: mp 252-253 °C dec; $[\alpha]^{23}_D$ -222.7° (c 0.3, $CHCl_3$) [lit.[17] mp 243-246 °C, $[\alpha]^{27}_D$ -222° (c 0.3, $CHCl_3$)]. The chromatographic (TLC systems A and B) and spectral properties (IR, EI MS) of **11a** were identical with those of the racemate **11**.

(-)-Argemonine (12a). Methylation of 100 mg of **11a** as described above for **7** gave a foam that crystallized from aqueous 2-propanol to afford 45 mg (41%) of hydrated **12a**: mp 129-134 °C (lit.[17] mp 125-135 °C). Drying this material overnight at 100 °C afforded anhydrous **12a**, mp 152.5-153.5 °C (lit.[13] mp 151-151.5 °C). The chromatographic (TLC systems A and B) and spectral properties (IR, EI MS) of **12a** were identical with those of the racemate **12**.

Acknowledgment. The authors thank Ms. Paula Parisius and Alice Wong for combustion analyses, Mr. William Landis and Mr. Noel Whittaker for mass spectra, and Dr. Arthur Jacobson for helpful discussions.

Registry No. 1, 72258-92-5; 3, 72258-98-1; 4, 72258-99-2; 5, 72259-00-8; 6, 72259-01-9; 7, 63162-85-6; 7·HCl, 72300-71-1; 7a, 63110-83-8; 8, 33579-95-2; 8a, 18944-92-8; 9, 72259-02-0; 10, 72259-03-1; 11, 29944-24-9; 11a, 6808-63-5; 12, 18831-00-0; 12a, 6901-16-2; 13, 24192-18-5; 14, 72264-53-0; 15, 72259-04-2; 16, 72259-05-3; 17, 72259-06-4; (-)-N-norreticuline·HCl, 6451-82-7.

Synthetic Study of (+)-Nootkatone from (-)-β-Pinene

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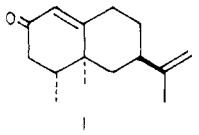
A facile stereoselective synthesis of (+)-nootkatone (1) has been achieved starting with (+)-nopinone (**2b**). The key step was the conjugate addition of methallyltrimethylsilane (**20b**) to *trans*-3-ethylidenenopinone (**16**), which was obtainable from **2b** on the cross condensation with acetaldehyde followed by acid treatment, giving an adduct with the desired stereochemistry, **24a**, as the predominant product. Dione **23**, obtained from the adduct on methylation followed by ozonization, afforded nootkatone hydrochloride (**26**) on treatment with hydrogen chloride. Regioselective dehydrochlorination of the hydrochloride yielded 1. An alternative route in which allyltrimethylsilane was used is also described.

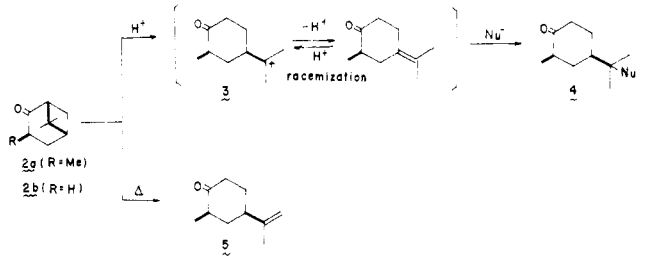
(+)-Nootkatone (1) is an eremophilanoid isolated first from the heartwood of Alaska yellow cedar (*Chamaecyparis nootkatensis*).[1] MacLeod found this ketone in the peel oil of grapefruit (*Citrus paradisi*), revised the structure proposed,[2] and recognized it as the constituent that most powerfully contributed to grapefruit flavor.[3] His results undoubtedly stimulated synthetic efforts toward nootkatone.



1

The stereoselective synthesis of (±)-1 has been accomplished by annulation reactions of substituted cyclohexanones[4] or by acid cleavage-cyclization of a bicyclo-

Scheme I

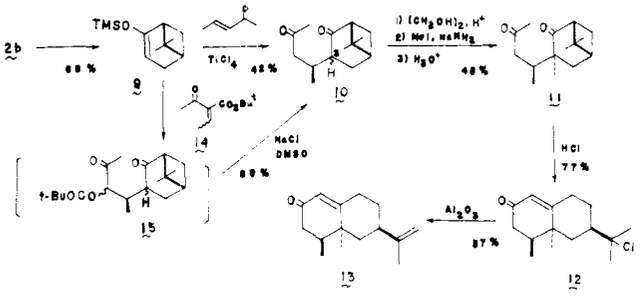


[2.2.2]octyl derivative.[5] Only the (+)-enantiomer of this ketone, however, possesses the intrinsic scent of grapefruit peel oil.[6] This fact has prompted the synthesis of the

(1) Erdtman, H.; Hirose, Y. *Acta Chem. Scand.* **1962**, *16*, 1311.
(2) MacLeod, W. D., Jr. *Tetrahedron Lett.* **1965**, 4779.
(3) MacLeod, W. D., Jr.; Buigues, N. M. *J. Food Sci.* **1964**, *29*, 565.
(4) (a) Pesaro, M.; Bozzato, G.; Schudel, P. *J. Chem. Soc., Chem. Commun.* **1968**, 1152. (b) Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1971**, *36*, 594. (c) McGuire, H. M.; Odem, H. C., Jr.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1879. (d) Hiyama, T.; Shinoda, M.; Nozaki, H. *Tetrahedron Lett.* **1979**, 3529.
(5) Dastur, K. P. *J. Am. Chem. Soc.* **1974**, *96*, 2605.

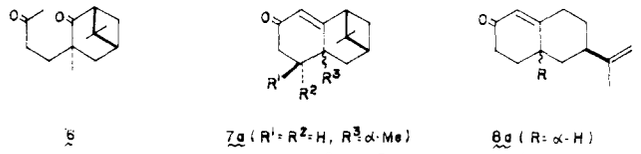
0022-3263/80/1945-0607$01.00/0

Scheme II



(+)-enantiomer[7] from readily available natural monoterpenes, in particular from β-pinene, because nopinone derived by oxidation therefrom gives (upon acid[8a] or thermal cleavage[8b]) cyclohexanones substituted with an isopropyl unit at C(4) with the proper configuration to serve as useful intermediates for the nootkatone synthesis. The first approach to (+)-1 in this conception was reported by van der Gen et al.,[9] who examined acid cleavage of (+)-*cis*-methylnopinone (**2a**). They unfortunately obtained the racemized cyclobutane-ring-cleavage product **4** as a result of a deprotonation–protonation process of the resulting carbonium ion along with epimerization of the α-methyl, and (±)-1 was synthesized from the product. On the other hand, pyrolytic cleavage of (+)-**2a** was found to give an optically active cyclohexanone, (+)-**5**,[10] and an attempt to synthesize (+)-1 employing **5** was reported.[11] In this synthesis, however, the subsequent Robinson annulation with 3-penten-2-one showed poor stereoselectivity, and for this reason a very low overall yield of (+)-1 was obtained in this sequence (Scheme I). Thomas et al.[12] have most recently addressed this problem. They encountered the following difficulties in model experiments: (1) failure to effect the aldol cyclization of **6** (obtained from (+)-nopinone (**2b**)) to enone **7a** for steric reasons, (2) preponderant formation of the undesired epimer **7b** in the annulation of **2b** with 3-penten-2-one (enamine method) followed by alkaline cyclization, and (3) minor distribution of the desired compound **8a** (or **8b**) in the thermolysis product of **7c** (or **7d**). They therefore concluded that the preparation of (+)-1 by this route was hopeless.

We have circumvented the difficulties mentioned above and describe here the stereocontrolled synthesis of (+)-1 from (−)-β-pinene in high overall yield.[13]



6

7a ($R^1 = R^2 = H$, R^3 α-Me)
7b (R^1 = Me, $R^2 = H$, R^3 β-H)
7c ($R^1 = R^2 = H$, R^3 α-H)
7d ($R^1 = R^2 = H$, R^3 β-Me)

8a (R = α-H)
8b (R = β-Me)

(6) For a review of this problem, see: Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 477–8.

(7) The (−)-enantiomer has been synthesized from (+)-sabinene: van der Gen, A.; van der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pay-Bas* **1971**, *90*, 1045.

(8) (a) Lewis, K. G.; Williams, G. J. *Aust. J. Chem.* **1968**, *21*, 2468. (b) Mayer, C. F.; Crandall, J. K. *J. Org. Chem.* **1970**, *35*, 2688.

(9) van der Gen, A.; van der Linde, L. M.; Witteveen, J. G.; Boelens, H. *Recl. Trav. Chim. Pay-Bas* **1971**, *90*, 1034.

(10) Yoshikoshi, A.; Takagi, Y.; Nishimura, T.; Iwamoto, M.; Kogami, K. Japanese patent pending and ref 12.

(11) Takagi, Y.; Nakahara, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 517.

(12) Bessière, Y.; Parthélémy, M.; Thomas, A. F.; Pickenhagen, W.; Starkmann, C. *Nouv. J. Chim.* **1978**, *2*, 365.

(13) Part of this work was published in: *J. Chem. Soc., Chem. Commun.* **1979**, 525.

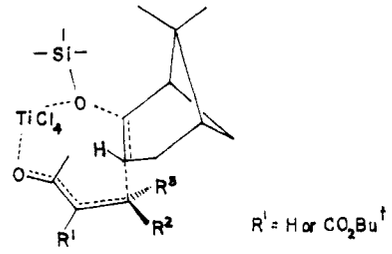


Figure 1.

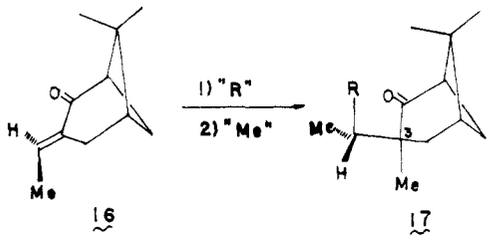


Figure 2.

Our first approach started with the Lewis acid-catalyzed reaction of trimethylsilyl enol ether **9**,[14] prepared from (+)-**2b**, with 3-penten-2-one which provided dione **10**,[15,16] although the configuration of its secondary methyl was not assigned at this stage (Scheme II). After selective ketalization of the carbonyl of the side chain in **10**, the product was methylated and then deketalized to yield dione **11**.[17] Treatment of **11** with acetic acid saturated with hydrogen chloride produced chloro enone **12** in good yield as a result of concurrent cyclobutane cleavage–aldol cyclization. The chemical shift of the angular methyl in the product **12** (δ 1.33) was suggestive of the presence of a trans-disposed vicinal dimethyl grouping,[18] and this stereochemical assignment was further verified by dehydrochlorination of **12** with active alumina[19] to (+)-4-epinootkatone (**13**), $[\alpha]_D$ +86°, as confirmed by comparison with an authentic sample of (±)-**13**.[4a] We thus found a facile route leading to the 4-epieremophilane framework from **2b**. The remaining problem to be solved was the stereoselective introduction of the secondary methyl on the cyclohexenone ring in **1** in the desired direction.

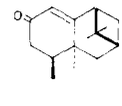
3-Penten-2-one is usually a mixture of *E* and *Z* isomers in which the former isomer is predominant,[20] while *tert*-butyl 2-ethylideneacetoacetate[21] (**14**) was observed to be

(14) Cf.: Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.

(15) The annulation of **2b** with 3-penten-2-one via an enamine of the former was reported in ref 12.

(16) The stereochemistry of nopinone derivatives monoalkylated at C(3) was assigned by ^{1}H NMR throughout this paper. For details, cf.: Bessière-Chrêstien, Y.; Meklati, B. *Bull. Soc. Chim. Fr.* **1971**, 2591 and ref 12.

(17) Attempted alkaline aldol cyclization of this dione leading to i was unsuccessful as described for **6** (vide ante).



(i)

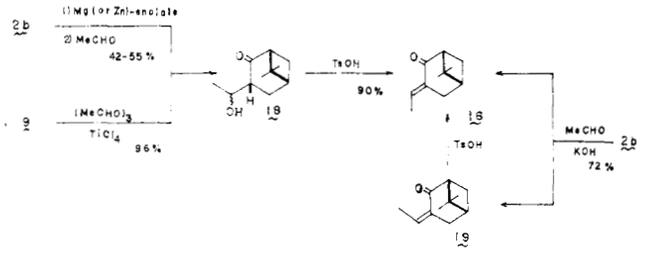
(18) Scanio, C. J. V.; Starett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539 and ref 4a.

(19) The regioselective dehydrochlorination of the α-chloroisopropyl group in nootkatone hydrochloride (**26**) on solid catalysts will be mentioned in detail later.

(20) Baldwin, J. E. *J. Org. Chem.* **1965**, *30*, 2423. The pentenone used by us was prepared from **14** according to Lawesson et al.,[21] and the content of the *E* isomer was estimated as over 90% (GLC).

(21) Lawesson, S.-O.; Larsen, E. H.; Sundstrom, G.; Jakobsen, H. J. *Acta Chem. Scand.* **1963**, *17*, 2216.

Scheme III



a nearly 1:1 mixture of the geometrical isomers (^{1}H NMR). Therefore, we used **14** as an electrophile in the alkylation of **2b**, expecting that a product possessing a secondary methyl with the desired configuration would be at least partly produced.[22] The reaction of **9** and **14** yielded diketo ester **15**, and the crude product was treated with sodium chloride in Me_2SO[23] to effect dealkylative decarboxylation. Unexpectedly, the dione **10** was obtained as a mixture of C(3) diastereomers. These results can be rationalized by postulating that the specifically oriented enones in the transition state (Figure 1), i.e., the *E* enones (R^1 = H or CO_2-*t*-Bu, R^2 = Me, R^3 = H), may approach via the less hindered face of the pinane substrate whereas the *Z* enones (R^1 = H or CO_2-*t*-Bu, R^2 = H, R^3 = Me) may be sterically repulsed by the cyclobutane methylene bridge. Since the *E* and *Z* isomers of these enones may equilibrate under the reaction conditions,[24] the reaction of **9** would have proceeded only with the *E* isomers through the equilibration. This disappointing outcome turned our attention to a second approach.

Our second approach to (+)-**1** was aimed at using *trans*-3-ethylidenenopinone (**16**) as the key intermediate. Provided acetonyl (or its equivalent), R, undergoes a 1,4-addition, one can prepare on subsequent methylation of the product a compound **17** that has the desired configuration with respect to the tertiary methyl at C(3) and the secondary methyl in the side chain, although presumably the introduction of R would be less stereoselective than the following methylation (Figure 2). If **17** is formed, a cyclobutane cleavage reaction of **17** (R = $MeCOCH_2$) with hydrogen chloride should afford nootkatone hydrochloride (**26**) by analogy with the reaction **11** → **12**.

We thus set about the synthesis of **16** from **2b**. The magnesium[25] or zinc[26] enolate of **2b** reacted with acetaldehyde to give ketol **18** as a homogeneous product in moderate yield, while the trimethylsilyl enol ether **9** also afforded **18** quantitatively as a mixture of epimeric alcohols in the reaction with paraldehyde in the presence of titanium tetrachloride[27] (Scheme III). It was found that the major ketol in the latter reaction was an epimer of the ketol obtained from the metal enolates, although their configurations have not been assigned. Acid dehydration of **18** produced the desired trans enone **16** in excellent yield, and its stereochemistry was assigned by the chemical shift of the olefinic proton (δ 6.96). On the other hand, the direct cross condensation of **2b** and acetaldehyde was also examined to seek a more practical procedure. The condensation was performed by treatment of **2b** with excess acetaldehyde in an alcoholic potassium hydroxide solution, resulting in the formation of a mixture of **16** and its cis isomer **19** (δ 6.28) in a ratio of 4:1 (^{1}H NMR). The mixture was then treated, in one pot, with acid at room temperature to effect the complete isomerization of **19** to **16**, and the pure trans enone **16** was also obtained by this route in good yield.

After unsatisfactory results in some attempts[28] for the introduction of acetonyl or its equivalent to **16**, we found that the titanium tetrachloride catalyzed conjugate addition of allyltrimethylsilane[29] (**20a**) to **16** took place smoothly to give an inseparable diastereomeric mixture of **21a** and **21b**, whose composition (80:20) was determined by capillary column GLC (Scheme IV). As expected, the major diastereomer **21a** had the desired configuration with respect to the secondary methyl as will be described later. Methylation of the mixture with methyl iodide proceeded stereoselectively to yield a mixture of **22a** and **22b**. The methylation product was submitted to oxidative oxymercuration–demercuration[30] to convert the allyl group to acetonyl affording a mixture of diones (81:19), which was separated by column chromatography. The minor dione was identical with **11** obtained from **10**, and the major one was presumed to be the desired compound **23**. To find a more convenient route, we also examined the conjugate addition of methallyltrimethylsilane[31] (**20b**) to **16**, which similarly gave a mixture of adducts **24a** and **24b** (76:24) in good yield. After methylation, the product, a mixture of **25a** and **25b** (74:26), was ozonized to afford the diones **23** and **11**.

The dione **23** thus obtained was treated with hydrogen chloride saturated in acetic acid at room temperature, yielding a crystalline product in good yield. The crystals were identified as (+)-nootkatone hydrochloride (**26**) by comparison with an authentic sample prepared by the reported hydrochlorination of (+)-**1**.[7] Furthermore, in the preparation of **26** we were able to eliminate the chromatographic separation step at the stage of the dione (**23** and **11**) by the following procedure. A petroleum ether solution of the crude ozonolysis product obtained from a mixture of **25a** and **25b** was chilled, precipitating most of the undesired dione **11** as crystals. The enriched dione mixture (91:9) in the filtrate was similarly treated with hydrogen chloride, and **26** was isolated on simple recrystallization of the crude hydrochlorination product in a somewhat higher overall yield (34% from **25**) than that in the foregoing procedure (31% overall yield from **25**).

As the final step, a highly regioselective dehydrochlorination of **26** to (+)-**1** was required.[32] Recently Kato et al. reported a highly selective dehydrochlorination of α-

(22) In the annulation of 2-methylcyclohexane-1,3-dione with 3-penten-2-one (enamine method), it was reported that the diastereomeric distribution of products was not affected by the geometry of the latter: Coates, R. M.; Shaw, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5657.

(23) Krapcho, A. P.; Jahngen, E. G., Jr.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091.

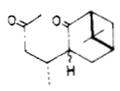
(24) The equilibration was confirmed by treatment of **14** (5:4) under comparable conditions, distinctly altering the isomer ratio (3:1).

(25) Cf.: Ayyar, K. S.; Cookson, R. C.; Kagi, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1727.

(26) For example, see: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(27) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

(28) For example, **16** and 2-[(trimethylsilyl)oxy]propene gave, in the presence of $TiCl_4$, a dione, to which the tentative structure ii has been assigned, in 8% yield along with other unidentified ketones (8%).



(ii)

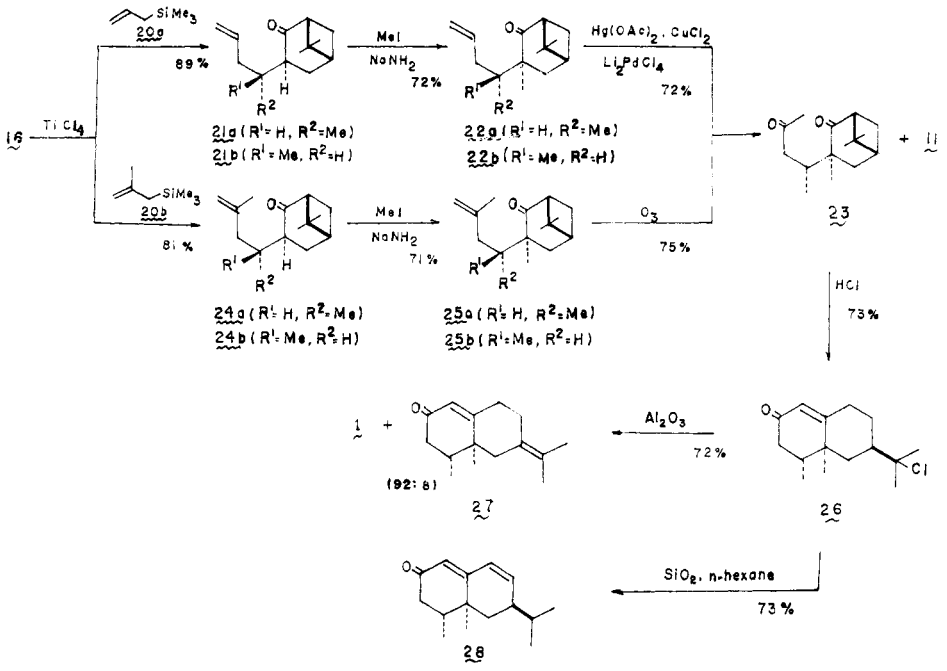
(29) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. For the preparation of the reagent, see ref 38.

(30) Rodeheaver, G. T.; Hunt, D. F. *J. Chem. Soc., Chem. Commun.* **1971**, 818.

(31) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, 4041. We are grateful to Professor H. Sakurai for helpful advice on the preparation of this reagent prior to publication.

(32) van der Gen et al. reported an 85% regioselectivity in dehydrochlorination of **26** with sodium acetate in acetic acid.[7]

Scheme IV



chloroisopropyl to isopropenyl on silica gel TLC,[33] and we also examined the reaction on solid catalysts. The reaction of **26** on a silica gel TLC plate proceeded very slowly to give (+)-**1** containing (+)-isonootkatone (**27**) in a minor ratio (95:5), showing good selectivity as they described. When a warm $CHCl_3$ solution of **26** was stirred with silica gel in order to accelerate the reaction and to handle more material, the exclusive formation of **27** was observed, while the replacement of the solvent by *n*-hexane resulted in the double-bond migration of the initial product to give conjugate dienone **28** in good yield. Under similar conditions, however, the predominant formation of **1** was realized by pyridine-impregnated silica gel (85:15) or active alumina (92:8). Pure (+)-nootkatone, $[\alpha]_D$ +188°, identical with the natural compound, was isolated by simple recrystallization from the crude crystalline product obtained with alumina. The overall yield of (+)-nootkatone (**1**) from (+)-nopinone (**2b**) was ca. 11–13% by way of **24**.

Experimental Section

IR spectra were taken on a Hitachi EPI-S32 or a JASCO A-3 spectrometer. ^1H NMR spectra were recorded on a JEOL C-60HL (60 MHz) spectrometer in $CDCl_3$ solutions unless otherwise stated. Coupling constants are given in hertz. GLC was carried out on a JEOL 750 gas chromatograph (10% SE30 or OV17, 2 m) using He as a carrier gas: capillary column GLC was performed on a Hitachi 103 FID gas chromatograph equipped with a 30-m glass capillary column (OV101) and using N_2 as a carrier gas.[34] Solvent systems that developed the major reaction products in a moderate R_f range (0.4–0.6) are described for preparative-layer chromatography.

(1*R*,5*R*)-6,6-Dimethyl-2-[(trimethylsilyl)oxy]bicyclo-[3.1.1]hept-2-ene (9). The silyl enol ether **9** was prepared by the procedure described by House et al.[35] A mixture of nopinone[36] (**2b**) (5.0 g, 36.2 mmol), $[\alpha]^{25}_D$ +17.9°, trimethylchlorosilane (7.85 g, 72 mmol), triethylamine (11.0 g, 109 mmol), and dry DMF (20 mL) was stirred at 95 °C for 1 day under Ar. After addition of aqueous $NaHCO_3$, the mixture was extracted with pentane, and the extract was successively washed with cold dilute HCl and aqueous Na_2CO_3. The extract was evaporated to leave an oil, which was distilled through a short Vigreux column. A fraction of **9**, bp 83–85 °C (8 mmHg), was obtained as a colorless oil (6.70 g, 88%): IR (liquid) 2970, 1622, 900, 854, 822 cm^{-1}; ^1H NMR 0.18 (s, 9 H), 0.92 (s, 3 H), 1.27 (s, 3 H), 4.50 (br s, 1 H). Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.53. Found: C, 68.56; H, 10.70.

(1*R*,3*R*,5*S*)-3-[(1*S*)-1-Methyl-3-oxobutyl]-6,6-dimethylbicyclo[3.1.1]heptan-2-one (10). (a) From the Silyl Enol Ether 9 and 3-Penten-2-one. 3-Penten-2-one[20] (0.7 g, 8.3 mmol) was added dropwise to a stirred solution of $TiCl_4$ (1.58 g, 8.3 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C under Ar, and then **9** (1.75 g, 8.3 mmol) was slowly added. After an additional 10 min of stirring at the same temperature, the reaction was quenched with a solution of K_2CO_3 (3 g) in water (50 mL). The mixture was then filtered and extracted with ether. A colorless oil obtained from the extract on evaporation was purified through a silica gel column. A mixture of petroleum ether and ether (9:1) eluted **2b** and then **10** (0.78 g, 42%): bp 130–135 °C (bath temperature) (1 mmHg); IR ($CHCl_3$) 1704 (br) cm^{-1}; ^1H NMR 0.88 (s, 3 H), 0.93 (d, 3 H), 1.33 (s, 3 H), 2.15 (s, 3 H). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.41; H, 9.79.

(b) From 9 and *tert*-Butyl α-Ethylideneacetoacetate (14). The ester **14**[21] (a mixture of geometrical isomers in a ratio of 5:4 as analyzed by ^1H NMR) (4.6 g, 25 mmol) was added dropwise to a stirred solution of $TiCl_4$ (4.75 g, 25 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C under Ar, and then **9** (5.25 g, 25 mmol) was added in a similar manner. The mixture was further stirred at the same temperature for 30 min and then worked up as described in a, affording the crude **15** (8.66 g) as an oil. A solution of the crude **15** (3.0 g) and NaCl (503 mg) in dry Me_2SO (45 mL) was stirred at 160 °C for 20 h and then cooled to room temperature. The mixture was poured into ice water and extracted with ether–petroleum ether, and the extract was washed with water. After evaporation of the solvent, the crude product was passed through a short silica gel column with the aid of ether, giving an oil. The oil was distilled through a short column, affording **10** as a colorless oil (1.69 g, 88%), bp 120–125 °C (bath temperature) (1 mmHg). As judged from the ^1H NMR spectrum [0.77 and 0.88 (s each, 3 H in total), 0.93 and 1.05 (d each, 3 H in total, J = 6 each), 1.33 (s, 3 H), 2.12 and 2.15 (s each, 3 H in total)], the product was a mixture of the dione in a and its C(3) epimer (40:60 in GLC). This was further verified by transformation of the mixture into **11** on a series of reactions, i.e., partial ketalization, methylation, and hydrolysis (vide post).

(1*R*,3*S*,5*R*)-3-[(1*S*)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (11). A solution of **10** (550

(33) Takayanagi, H.; Uyehara, T.; Kato, T. *J. Chem. Soc., Chem. Commun.* **1978**, 359.

(34) We are indebted to Professors K. Yamashita and A. Kobayashi for capillary column GLC.

(35) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(36) Reference 8a and references cited therein.

mg, 2.5 mmol), ethylene glycol (770 mg), and a catalytic quantity of *p*-toluenesulfonic acid in benzene (25 mL) was refluxed for 25 min, and the water formed was continuously removed with a Dean–Stark trap. The mixture was neutralized with $NaHCO_3$ and diluted with ether. An oil (658 mg) obtained from the organic layer by workup was refluxed with $NaNH_2$ (320 mg) in dry benzene (10 mL) for 7 h with stirring. The reaction mixure was cooled to 45 °C and then methyl iodide (944 mg) was added. After 18 h of stirring at 45 °C, aqueous NH_4Cl was added, and the benzene layer was separated by the aid of ether. Workup gave an oil, which was stirred with 70% aqueous acetic acid (9 mL) at 90 °C for 1 h. After neutralization with aqueous K_2CO_3, the product was extracted with ether. Workup afforded an oil, which was purified by preparative silica gel thick-layer chromatography (TLC) (ether–petroleum ether (1:3) as solvent), giving crystals (261 mg, 45% from **10**). An analytical sample, mp 106–108 °C, was obtained by recrystallization from ether–petroleum ether: IR ($CHCl_3$) 1694 (br) cm^{-1}; ^1H NMR 0.92 (s, 3 H), 1.16 (d, 3 H, J = 6.5), 1.30 (s, 3 H), 1.33 (s, 3 H), 2.16 (s, 3 H). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.97; H, 10.67.

(4*S*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-6-(1-chloro-1-methylethyl)-4,4a-dimethyl-2(3*H*)-naphthalenone (12). A solution of **11** (516 mg, 2.2 mmol) in dry acetic acid (30 mL) was saturated with dry HCl at room temperature, stirred for 77 h at the same temperature under Ar, and then poured into ice water. The product was extracted with CH_2Cl_2, and the extract was washed with water and then dried. Evaporation of the solvent left an oil, which was purified by TLC (ether–petroleum ether (1:2) as solvent), affording a thick oil (430 mg, 77%). An analytical sample was obtained by short-path distillation: bp 135–145 °C (bath temperature) (0.2 mmHg); IR (liquid) 1676, 1624, 900, 870, 800, 630 cm^{-1}; ^1H NMR 1.02 (d, 3 H, J = 6), 1.33 (s, 3 H), 1.60 (s, 6 H), 5.75 (br s, 1 H). Anal. Calcd for $C_{15}H_{23}ClO$: C, 70.83; H, 9.11; Cl, 13.76. Found: C, 70.73; H, 9.29; Cl, 14.14.

(4*S*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-2(3*H*)-naphthalenone (13). A solution of **12** (130 mg, 0.5 mmol) in *n*-hexane (4 mL) was stirred with active alumina (Wako Chemicals, for chromatographic use, 0.7 g) at 60 °C for 24 h. After filtration, the solution was evaporated, and the oil obtained was purified by TLC (ether–petroleum ether (1:2) as solvent) to yield **13** (62 mg, 57%), $[\alpha]^{25}_D$ +85° (*c* 0.37 in $CHCl_3$), which was identified by spectral comparison with racemic 4-epinootkatone:[4a,37] IR (liquid) 3080, 1680, 1624, 896 cm^{-1}; ^1H NMR 1.01 (d, 3 H, J = 6), 1.33 (s, 3 H), 1.72 (br s, 3 H), 4.37 (br s, 2 H), 5.75 (br s, 1 H).

(1*R*,3*R*,5*R*)-6,6-Dimethyl-3-(1-hydroxyethyl)bicyclo[3.1.1]heptan-2-one (18). (a) From the Magnesium Enolate of 2b and Acetaldehyde. A solution of *N*-methylaniline (10.8 mL, ca. 0.1 mol) in dry benzene (10 mL) was added dropwise to an ethylmagnesium bromide solution, prepared from Mg (2.42 g, 0.1 mol) and ethyl bromide (7.52 mL, ca. 0.1 mol) in dry ether (10 mL), in an ice bath. To this solution, a solution of **2b** (11.45 g, 83 mmol) in dry benzene (10 mL) was added dropwise at the same temperature. After 40 min of stirring at room temperature, a solution of acetaldehyde (6.0 mL, ca. 0.11 mol) in dry benzene (20 mL) was added dropwise at 0 °C. After 1 h of stirring at the same temperature, the mixture was poured into cold dilute HCl. The product was extracted with petroleum ether, and the extract was washed with dilute HCl and then water. The oil (17.1 g) obtained was distilled through a Vigreux column giving recovered **2b** (2.4 g), bp 80–90 °C (9 mmHg), and oily **18** (8.29 g, 55%), bp 118 °C (4 mmHg), which was homogeneous by thin-layer chromatography and GLC: IR (liquid) 3430, 1690, 1120 cm^{-1}; ^1H NMR 0.95 (s, 3 H), 1.25 (d, 3 H, J = 6), 1.35 (s, 3 H), 1.4–2.8 (m, 7 H), 3.91 (dq, 1 H, J = 6 and 9). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.57; H, 9.73.

(b) From the Zinc Enolate of 2b and Acetaldehyde. A mixture of **2b** (138 mg, 1 mmol), $NaNH_2$ (52 mg, 1.2 mmol), and dry THF (3 mL) was stirred at reflux for 3 h under Ar. A solution of $ZnCl_2$ (163 mg, 1.2 mmol) in dry THF (3 mL) and then acetaldehyde (0.2 mL) were added to the above mixture at 0 °C. After 1 h of stirring at 0 °C, aqueous acetic acid was added. The product was extracted with ether and purified by TLC (ether–petroleum ether (1:2) as solvent), giving **18** (76 mg, 42%) which showed the same spectra as described in a.

(c) From the Silyl Enol Ether 9 and Paraldehyde. Paraldehyde (470 mg, 3.5 mmol) was added to a stirred solution of $TiCl_4$ (1.69 g, 8.9 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C under Ar. The silyl enol ether **9** (1.87 g, 8.9 mmol) was slowly added to the above solution, and after an additional 1.5 h of stirring at the same temperature, water was added and the product was extracted with ether. The usual workup gave an oil, which was distilled to afford an epimeric mixture of **18** (1.55 g, 96%): bp 110–120 °C (bath temperature) (2 mmHg); IR, almost identical with that of the product in a; ^1H NMR 0.94 (slightly broadened singlet, 3 H), 1.24 (slightly broadened doublet, 3 H, J = 7), 1.35 (s, 3 H), 3.9 and 4.4 (each m, 1 H total). Integrated areas of signals at 3.9 and 4.4 in the ^1H NMR spectrum indicated that the product was a mixture of the ketol obtained in a and its epimer in a ratio of roughly 1:3. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.66; H, 9.87.

(1*R*,5*R*)-6,6-Dimethyl-3-(*E*)-ethylidenebicyclo[3.1.1]heptan-2-one (16). (a) Dehydration of the Ketol 18. The ketol **18** (7.0 g, 38.5 mmol) obtained in a and *p*-toluenesulfonic acid (0.4 g) in dry benzene (150 mL) were refluxed for 2 h, the water formed being continuously removed with a Dean–Stark trap. The mixture was neutralized with aqueous $NaHCO_3$. Workup of the organic layer gave an oil which was purified by distillation, bp 108 °C (9 mmHg), yielding **16** (5.68 g, 90%), $[\alpha]^{25}_D$ +21.6° (neat liquid), as a colorless oil. GLC and thin-layer chromatography showed the product to be homogeneous: IR (liquid) 1700, 1630 cm^{-1}; ^1H NMR 0.87 (s, 3 H), 1.36 (s, 3 H), 1.78 (dt, 3 H, J = 7 and 1), 1.3–2.7 (m, 6 H), 6.96 (qt, 1 H, J = 7 and 2). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.75; H, 9.54.

(b) Cross Condensation of 2b and Acetaldehyde. A solution of acetaldehyde (assay 80%, 4.2 mL) in ethanol (30 mL) was added to a stirred solution of **2b** (6.9 g, 50 mmol) and KOH (3.3 g) in ethanol (120 mL) at 5 °C over 30 min under Ar, and stirring was continued at the same temperature. After four additional portions of acetaldehyde (4.2 mL each) had been added to the solution at intervals of 15 h, stirring was continued for an additional 6 h. The ^1H NMR spectrum of an aliquot showed the product to be a mixture consisting of **16** and its *Z*-isomer **19** in a ratio of 4:1. The following signals were assignable to **19**: 0.87 (s), 1.36 (s), 1.88 (dt), 6.28 (m). *p*-Toluenesulfonic acid monohydrate (13.3 g) was added to the mixture, and the resulting solution was stirred for 3 h at room temperature. The solvent was removed in vacuo, and the brown residue was dissolved in ether. The ethereal solution was passed through a short silica gel column and the eluate was evaporated to leave an oil, which was purified by distillation to give **16** (5.93 g, 72%) as identified spectroscopically.

[1*R*,3*S*,5*S*]-6,6-Dimethyl-3-[(1*R*)-1-methyl-3-butenyl]bicyclo[3.1.1]heptan-2-one (21a) and Its Epimer (21b). *trans*-Ethylidenenopinone **16** (328 mg, 2 mmol) was added to a stirred solution of $TiCl_4$ (380 mg, 2 mmol) in dry CH_2Cl_2 (6 mg) at −78 °C under Ar, and allyltrimethylsilane[29,38] (274 mg, 2.4 mmol) was then added to the above solution. The resulting deep purple solution was stirred for an additional 2 h at the same temperature. The reaction was quenched by addition of water, and the product was extracted with ether. Workup gave a colorless oil. Purification was made by TLC (ether–petroleum ether (1:5)) followed by short-path distillation [90–95 °C (bath temperature) (0.2 mmHg)], yielding a mixture of **21a** and **21b** (365 mg, 89%) as an oil: IR (liquid) 3100, 1702, 1642, 910 cm^{-1}; ^1H NMR 0.79 (s, 3 H), 0.95 and 1.05 (each d, 3 H total, J = 6 each), 1.33 (s, 3 H), 1.5–3.0 (m, 10 H), 4.8–6.1 (m, 3 H, ABM pattern).

Capillary column GLC showed the ratio of these epimers to be 80:20. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.28; H, 10.47.

(1*R*,3*S*,5*R*)-3-[(1*R*)-1-Methyl-3-butenyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (22a) and Its Epimer (22b). After a mixture of the above ketones **21a** and **21b** (300 mg, 1.5 mmol), $NaNH_2$ (assay 90%, 189 mg, 4.4 mmol), and dry benzene (6 mL) was refluxed for 5 h with stirring under N_2, the mixture was cooled to 45 °C and methyl iodide (511 mg, 3.6 mmol) was added. After

(37) We are greatful to Dr. P. Schudel, who provided us with an authentic sample of this compound.

(38) Sommer, L. H.; Whitemore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 2872; **1946**, *68*, 475.

2.5 h of additional stirring, a further portion of methyl iodide (334 mg) was added and the mixture was stirred for 15 h at the same temperature. Saturated aqueous NH_4Cl was added to the cooled solution and the product was extracted with ether. Workup gave an oil, which was purified by TLC (ether–petroleum ether (1:10) as solvent), giving an inseparable mixture of **22a** and **22b** (232 mg, 72%). An analytical sample was obtained by short-path distillation, bp 95–100 °C (bath temperature) (0.1 mmHg): IR (liquid) 3080, 1698, 1640, 906 cm^{-1}; ^1H NMR 0.90 (s, 3 H), 0.93 and 1.14 (each d, 3 H total, J = 6 each), 1.30 (s, 3 H), 1.33 (s, 3 H), 4.8–6.1 (m, 3 H, ABM pattern).

This mixture was inseparable even by capillary column GLC; an exact mass determination gave m/e 220.1853 (calcd for $C_{15}H_{24}O$, 220.1827).

[1*R*,3*S*,5*S*]-6,6-Dimethyl-3-[(1*R*)-1-methyl-3-methyl-3-butenyl]bicyclo[3.1.1]heptan-2-one (24a) and Its Epimer (24b). In a manner similar to that described for **21**, a crude reaction product was obtained from **16** (9.84 g, 60 mmol) and methallyltrimethylsilane[31] (14.7 mL, ca. 72 mmol). Purification was made by distillation to give a mixture of **24a** and **24b** (10.69 g, 81%): bp 104–105 °C (2 mmHg); IR (liquid) 3080, 1708, 1650, 890 cm^{-1}; ^1H NMR 0.80 (s, 3 H), 0.92 and 0.98 (each d, 3 H total, J = 6 each), 1.33 (s, 3 H), 1.70 (br s, 3 H), 4.74 (br s, 2 H).

Capillary column GLC showed a 76:24 ratio of epimers. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.48; H, 10.93.

(1*R*,3*S*,5*R*)-3-[(1*R*)-1-Methyl-3-methyl-3-butenyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (25a) and Its Epimer (25b). In a manner similar to that described for **22**, a crude product was obtained from the above unsaturated ketone mixture, **24a** and **24b** (8.8 g, 40 mmol), and excess methyl iodide. Distillation of the crude product afforded an inseparable mixture of **25a** and **25b** (6.68 g, 71%) as an oil: bp 110–125 °C (1–2 mmHg); IR (liquid) 3075, 1702, 1645, 890 cm^{-1}; ^1H NMR 0.88 and 1.10 (each d, 3 H total, J = 6 each), 0.90 (s, 3 H), 1.32 (s, 6 H), 1.70 (br s, 3 H), 4.70 (br s, 2 H).

Capillary column GLC showed the product to be an epimeric mixture in a ratio of 74:26. Exact mass determination gave m/e 234.1974 (calcd for $C_{16}H_{26}O$, 234.1980).

(1*R*,3*S*,5*R*)-3-[(1*R*)-1-Methyl-3-oxobutyl]-3,6,6-trimethylbicyclo[3.1.1]heptan-2-one (23). (a) From a Mixture of 22a and 22b. A mixture of the unsaturated ketones **22a** and **22b** (220 mg, 1.0 mmol), mercuric acetate (319 mg, 1.0 mmol), and methanol (2 mL) was stirred at room temperature for 15 min. The mixture was then added to a solution of LiCl (9 mg), $PdCl_2$ (18 mg), and $CuCl_2$ (402 mg) in methanol (1 mL), and the mixture was stirred at 55 °C for 1 h. Aqueous $NaHCO_3$ was added and the product was extracted with ether. Workup afforded an oil, which was purified by TLC (ether–petroleum ether (1:3) as solvent). The dione **23** (137 mg, 58%) was isolated as an oil from the less polar fraction: bp 100 °C (bath temperature) (0.1 mmHg); $[\alpha]^{25}_D$ +120° (*c* 0.51 in $CHCl_3$); IR (liquid) 1710 (sh), 1698 cm^{-1}; ^1H NMR 0.92 (d, 3 H, J = 7), 0.94 (s, 3 H), 1.26 (s, 3 H), 1.33 (s, 3 H), 2.16 (s, 3 H), 3.72 (dd, 1 H, J = 17 and 4). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.07; H, 10.42.

From the polar fraction of the TLC, the dione **11** (32 mg, 14%) was obtained and identified with a sample obtained from **10**.

(b) From a Mixture of 25a and 26b. Excess ozone was passed through a solution of an unsaturated ketone mixture (**25a** + **25b**) (1.29 g, 5.5 mmol) in methanol (20 mL) at −78 °C for 30 min. The resulting reaction mixture was then stirred with excess Zn powder and acetic acid at room temperature overnight. After addition of water, the product was extracted with ether and workup gave an oil which showed two peaks on GLC analysis (72:28). Petroleum ether was added and the resulting crystals of **11** (204 mg) were filtered. An oil obtained from the filtrate gave additional crystals of **11** (46 mg; total yield of **11**, 19%) and oily **23** (726 mg, 56%) by TLC in a manner similar to that described in a.

(4*R*,4a*S*,6*R*)-4,4a,5,6,7,8-Hexahydro-4,4a-dimethyl-6-(1-chloro-1-methylethyl)-2(3*H*)-naphthalenone (26). Dry gaseous HCl was saturated in a solution of **23** (0.3 g, 1.3 mmol) in dry acetic acid (14 mL) at room temperature under Ar. After 21 h of stirring, the mixture was poured onto ice and the product was extracted with CH_2Cl_2. Workup gave an oil which crystallized in a refrigerator. Recrystallization from *n*-hexane yielded **26** (235 mg, 73%): mp 84–85.5 °C; $[\alpha]^{25}_D$ +160° (*c* 0.47 in $CHCl_3$); IR ($CHCl_3$) 1658, 1620, 906, 870 cm^{-1}; ^1H NMR 0.98 (d, 3 H, J = 6), 1.11 (s, 3 H), 1.59 (s, 6 H), 5.75 (br s, 1 H).

The product was identical with an authentic sample of nootkatone hydrochloride prepared from natural nootkatone according to the literature.[7]

Preparation of Nootkatone Hydrochloride 26 from a Mixture of 25a and 25b without Chromatographic Separation. A solution of the ketone mixture (**25a** + **25b**) (450 mg, 1.9 mmol) in methanol (7 mL) was ozonized as described above, and dimethyl sulfide (1 mL) was added. The mixture was stirred while the temperature was allowed to gradually rise to room temperature over a period of 1.5 h. After the mixture was allowed to stand overnight, the solvent was removed and the oil obtained by workup was dissolved in a small quantity of petroleum ether and cooled in an ice bath. The mixture was filtered to separate crystals of **11** (81 mg), and the oil (372 mg) obtained from the filtrate was dissolved in acetic acid (15 mL). The solution was saturated with gaseous HCl and left at room temperature for 17 h. Workup gave an oil, which was dissolved in a small quantity of *n*-hexane. Nootkatone hydrochloride **26** (165 mg, 34% from **25**) was obtained as crystals on cooling.

Dehydrochlorination of Nootkatone Hydrochloride 26. (a) By a TLC Plate. The hydrochloride **26** (66 mg) was applied to a preparative silica gel TLC plate. After standing for five days at room temperature, the product was eluted with ether to give a mixture of **1** and **27** (43 mg, 76%), GLC analysis of which showed the ratio of both ketones to be 95:5.

(b) Formation of (4*R*,4a*S*,6*R*)-4,4a,5,6-Tetrahydro-4,4a-dimethyl-6-(1-methylethyl)-2(3*H*)-naphthalenone (28) by Silica Gel in *n*-Hexane. A mixture of **26** (127 mg), silica gel (Merck Kieselgel 60, 0.5 g), and *n*-hexane (4 mL) was stirred at 60 °C for 15 h under N_2. After filtration and removal of the solvent, the residue was purified by TLC (ether–petroleum ether (1:1) as solvent) to give the conjugated dienone **28** (80 mg, 73%): IR (liquid) 3040, 1664, 1623, 1592, 910, 881, 780 cm^{-1}; ^1H NMR (CCl_4) 0.90–1.06 (4 methyls), 5.55 (s, 1 H), 6.05 (br s, 2 H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.78; H, 10.14.

(c) Formation of Isonootkatone (27) by Silica Gel in $CHCl_3$. The hydrochloride **26** (127 mg) was similarly treated with silica gel (0.5 g) in $CHCl_3$ (4 mL) at 60 °C for 18 h. Silica gel (0.5 g) was added anew and the mixture was further stirred at the same temperature for 9 h. After workup, the product was purified by TLC (ether–petroleum ether (1:1) as solvent), yielding **27** (88 mg, 81%), $[\alpha]^{20}_D$ +217° (*c* 0.54 in $CHCl_3$), as identified by spectral comparison.[39]

(d) By Pyridine-Impregnated Silica Gel. A similar treatment of **26** (100 mg) with silica gel (0.5 g) impregnated with pyridine (5 drops) in *n*-hexane (4 mL) at 60 °C for 43 h and TLC purification of the product afforded an oil (55 mg), which was shown to be a mixture of **1** and **27** (85:15) by GLC.

(e) By Alumina. A mixture of **26** (400 mg), active alumina (Wako, for chromatographic use, 2.0 g), and *n*-hexane (10 mL) was stirred at 60 °C for 24 h under Ar. Workup followed by TLC purification gave an oil (246 mg), which was a mixture of **1** and **27** (92:8) as shown by GLC. The oil crystallized on standing in a refrigerator and pure **1**, mp 27–29 °C, $[\alpha]^{30}_D$ +188° (*c* 0.5 in $CHCl_3$), identical with authentic (+)-nootkatone in all respects, was obtained by recrystallization from protroleum ether.

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Registry No. **1**, 4674-50-4; **2b**, 38651-65-9; **9**, 72453-33-9; **10**, isomer 1, 72453-34-0; **10**, isomer 2, 72541-04-9; **11**, 72521-65-4; **12**, 72453-35-1; **13**, 27621-99-4; (*E*)-**14**, 64507-86-4; (*Z*)-**14**, 64507-87-5; **15**, 72453-36-2; **16**, 72453-37-3; **18**, isomer 1, 72453-38-4; **18**, isomer 2, 72541-05-0; **19**, 72453-37-3; **20a**, 762-72-1; **20b**, 18292-38-1; **21a**, 72453-39-5; **21b**, 72541-06-1; **22a**, 72521-66-5; **22b**, 72453-40-8; **23**, 72453-41-9; **24a**, 72453-42-0; **24b**, 72541-07-2; **25a**, 72453-43-1; **25b**, 72541-08-3; **26**, 72453-44-2; **27**, 15764-04-2; **28**, 15401-59-9; 3-penten-2-one, 625-33-2.

(39) Marshall, J. A.; Andersen, N. H. *Tetrahedron Lett.* **1967**, 1611.