Stereocontrolled Synthesis of (+)-Nootkatone from (−)-β-Pinene

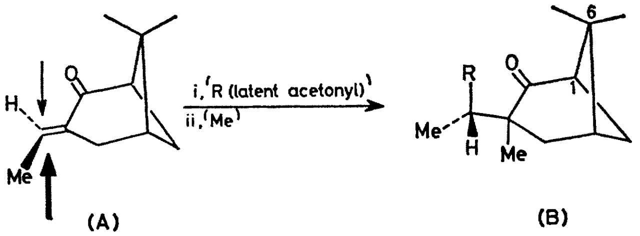
By Tetsuji Yanami, Masaaki Miyashita, and Akira Yoshikoshi*

(*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai* 980, *Japan*)

Summary (+)-Nootkatone (**8a**) has been synthesised stereoselectively from (+)-nopinone (**1**) *via* six steps.

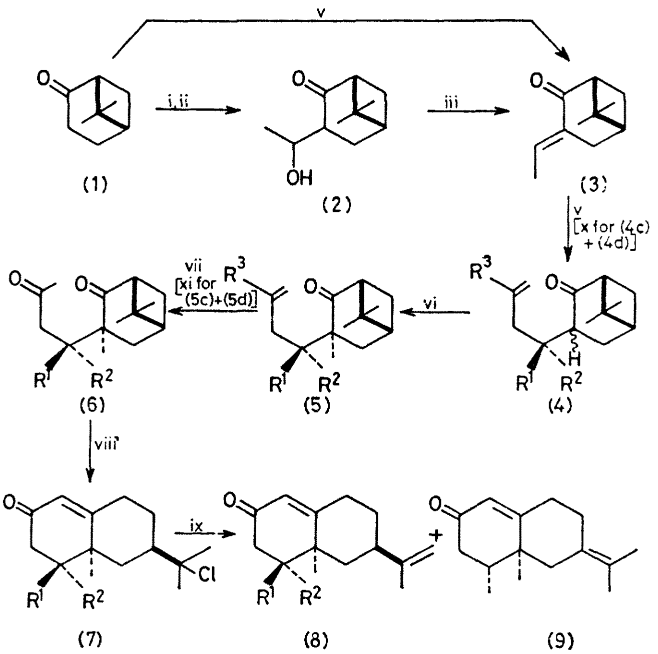
In the past decade, much effort has been devoted to the synthesis of the *cis*-1,8a-dimethylperhydronaphthalene framework which is a characteristic structural feature of eremophilane sesquiterpenes; much of this has involved stereocontrolled Robinson annulation or related reactions.[1] Of the eremophilanoids, nootkatone (**8a**) is an interesting flavour compound, and its total synthesis has been achieved in the racemic[2] and enantiomeric forms.[3] However, it has been suggested that only (+)-(**8a**), the natural enantiomer, has the intrinsic scent of grapefruit peel oil, while the other optical isomers are less useful as flavour materials.[4]

We here report a stereocontrolled synthesis of (+)-(**8a**) from the readily available (−)-β-pinene.[5]



(A) (B)

We planned to introduce stereoselectively a latent acetonyl group into 3-*trans*-ethylidene-nopinone (**3**) by conjugate addition, anticipating the well known difference in stereochemical environment between both faces of the pinane molecule (see A). One would also expect that subsequent methylation of the resulting saturated ketone would proceed with higher stereoselectivity to give (B) by the same reasoning. This stereocontrol, if it is operative, would ensure that the *cis* vicinal dimethyl grouping assumed the correct configuration as the isopropenyl group in (**8a**) after ring opening, because regioselective cleavage of the C(1)–C(6) bond of the cyclobutane ring in B is easily effected.



a, $R^1 = H, R^2 = R^3 = Me$
b, $R^1 = R^3 = Me, R^2 = H$
c, $R^1 = R^3 = H, R^2 = Me$
d, $R^1 = Me, R^2 = R^3 = H$

SCHEME. *Reagents:* i, Me_3SiCl, Et_3N, dimethylformamide, 50 °C (88%); ii, $(C_2H_4O)_3$, $TiCl_4$, CH_2Cl_2 −78 °C (96%); iii, *p*-$MeC_6H_4SO_3H$, C_6H_6, reflux (94%): iv, MeCHO, KOH, EtOH, 5 °C (72%); v, $CH_2{=}CMeCH_2SiMe_3$ $TiCl_4$, CH_2Cl_2, −78 °C (81%); vi, $NaNH_2$, MeI, C_6H_6, 45—50 °C, [71 and 72% from (**4a**) + (**4b**) and (**4c**) + (**4d**), respectively]; vii, O_3, MeOH, −78 °C, then Me_2S (79%); viii, HCl, HOAc, room temp., [73 and 77% for (**7a**) and (**7b**), respectively]; ix, Al_2O_3 or C_5H_5N-impregnated SiO_2, C_6H_{14}, 60 °C, [72 and 57% from (**7a**) and (**7b**), respectively]; x, $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −78 °C (89%); xi, $Hg(OAc)_2$, room temp. then Li_2PdCl_4, $CuCl_2$, MeOH, 55 °C (72%).

An excellent yield of (**3**) was obtained in the reaction of the trimethylsilyl enol ether of (+)-nopinone (**1**), obtained from (−)-*β*-pinene on ozonolysis,[6] with paraldehyde,[7] followed by acidic dehydration of the resulting mixture of epimeric hydroxy-ketones (**2**) (Scheme). The *trans* geometry of the ethylidene group in (**3**) was shown by the chemical shift of its olefinic proton (δ 6·96). The KOH-catalysed condensation of (**1**) and excess of acetaldehyde was also examined;[†] the mixture [(**3**) and its *cis* isomer] obtained was treated with a slight excess of toluene-*p*-sulphonic acid in a one-pot procedure to yield (**3**) in comparable yield

The reaction of (**3**) with methallyltrimethylsilane[8] in the presence of titanium tetrachloride afforded (**4a**) and its epimer (**4b**) (76:24[‡]) as an inseparable mixture in good yield. The adduct mixture was then methylated to give a mixture of (**5a**) and (**5b**) (74:26[‡]). These ratios may be regarded as showing the measure of the stereoselectivity in the conjugate addition (**3**) → (**4**). The latter mixture was oxidised to a mixture of diones (75:25), which, after silica gel chromatography, gave (**6a**) as an oil and crystalline (**6b**), m.p. 106—108 °C, in 60 and 19% yields, respectively. When the dione (**6a**) was treated with acetic acid saturated with hydrogen chloride, cyclobutane ring cleavage and cyclohexenone ring formation occurred consecutively to yield a homogeneous product, m.p. 84—85·5 °C, $[\alpha]_D^{25}$ +160° (*c*, 0·5 in $CHCl_3$), in high yield. The product was identified as nootkatone hydrochloride (**7a**) by comparison with an authentic sample prepared from (+)-(**8a**).[3]

A more convenient procedure for (**7a**) was as follows; on cooling a light petroleum solution of the crude ozonolysis product of (**5**), most of the undesired product (**6b**) crystallised. The enriched dione mixture (91:9) obtained from the filtrate was similarly treated with hydrogen chloride, and pure (**7a**) was isolated after recrystallisation of the crude product [overall yield from (**5**), 34%].

Regioselective dehydrochlorination of (**7a**) with active alumina or pyridine-impregnated silica gel in warm hexane yielded a mixture of (+)-nootkatone (**8a**) and (+)-isonootkatone (**9**) (92:8 and 85:15, respectively). The pure (**8a**), m.p. 29 °C, $[\alpha]_D^{30}$ +188° (*c*, 0·5 in $CHCl_3$),[9] was readily separated on recrystallisation and identified by comparison with an authentic sample. However, treatment of (**7a**) with silica gel[§] (without pyridine) under similar conditions afforded, as the major product, (+)-isonootkatone (**9**), $[\alpha]_D^{20}$ +217° (*c*, 0·5 in $CHCl_3$), as identified by spectral comparison.[10] Thus, (+)-(**8a**) was obtained from (**1**) in *ca.* 14% overall yield.

Treatment of (**6b**) with hydrogen chloride gave 4-epinootkatone hydrochloride (**7b**) as a thick oil, which was similarly dehydrochlorinated by active alumina to afford 4-epinootkatone (**8b**), $[\alpha]_D^{25}$ +86° (*c*, 0·4 in $CHCl_3$), identified by spectral comparison with the racemic compound.[2a]

An alternative approach, in which allyltrimethylsilane[11] was employed in place of its methallyl analogue, was also examined. Conjugate addition of (**3**) and allyltrimethylsilane gave a diastereoisomeric mixture of (**4c**) and (**4d**) (80:20[‡]), which was then methylated. On oxidative oxymercuration–demercuration,[12] the resulting mixture of

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[†] We have also examined cross aldol condensation of other metal (sodium, magnesium, and zinc) enolates of (**1**) and acetaldehyde, which gave lower yields of (**2**).

[‡] Determined by capillary column g.l.c.

[§] It was reported that regioselective dehydrochlorination of an α-chloroisopropyl group in an acyclic system to an isopropenyl group took place slowly on silica gel at room temperature; H. Takayanagi, T. Uyehara, and T. Kato, *J.C.S. Chem. Comm.*, 1978, 359.

allylic ketones (**5c**) and (**5d**)¶ was converted into a dione mixture, from which (**6a**) and (**6b**) were separated by silica gel chromatography in 58 and 14% yields, respectively.

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¶ Inseparable even in capillary column g.l.c.

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[2] (a) M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Comm.*, 1968, 1152; (b) J. A. Marshall and R. A. Ruden, *J. Org. Chem.*, 1971, **36**, 594; (c) A. van der Gen, L. M. van der Linde, J. G. Witteveen, and H. Boelens, *Rec. Trav. chim.*, 1971, **90**, 1034; (d) K. P. Dastur, *J. Amer. Chem. Soc.*, 1974, **96**, 2605.

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[5] The synthesis of (**8a**) from (−)-β-pinene, resulting in the racemic product, has been reported (ref. 2c). Recently (+)-(**8a**) was prepared from (−)-β-pinene with poor stereoselectivity in low overall yield; Y. Takagi, Y. Nakahara, and M. Matsui, *Tetrahedron*, 1978, **34**, 517. An attempted synthesis of (+)-(**8a**) using the annulation of (+)-(**1**) with pent-3-en-2-one was recently reported; Y. Bessière, M. Barthélémy, A. F. Thomas, W. Pickenhagen, and C. Starkemann, *Nouveau J. Chim.*, 1978, **2**, 365.

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[7] *Cf.* T. Mukaiyama, K. Banno, and K. Narasaka, *J. Amer. Chem. Soc.*, 1974, **96**, 7503.

[8] A. Hosomi and H. Sakurai, *Tetrahedron Letters*, 1977, 4041. We thank Professor H. Sakurai for helpful advice on the preparation of this reagent prior to publication.

[9] H. Erdtman and Y. Hirose, *Acta Chem. Scand.*, 1962, **16**, 1311. *Cf.* W. D. MacLeod, Jr., *Tetrahedron Letters*, 1965, 4779.

[10] J. A. Marshall and N. H. Andersen, *Tetrahedron Letters*, 1967, 1611.

[11] For the reaction of conjugated enones with the reagent, see A. Hosomi and H. Sakurai, *J. Amer. Chem. Soc.*, 1977, **99**, 1673.

[12] G. T. Rodeheaver and D. F. Hunt, *Chem. Comm.*, 1971, **818**.