CHEMISTRY LETTERS, pp. 2067-2068, 1989.

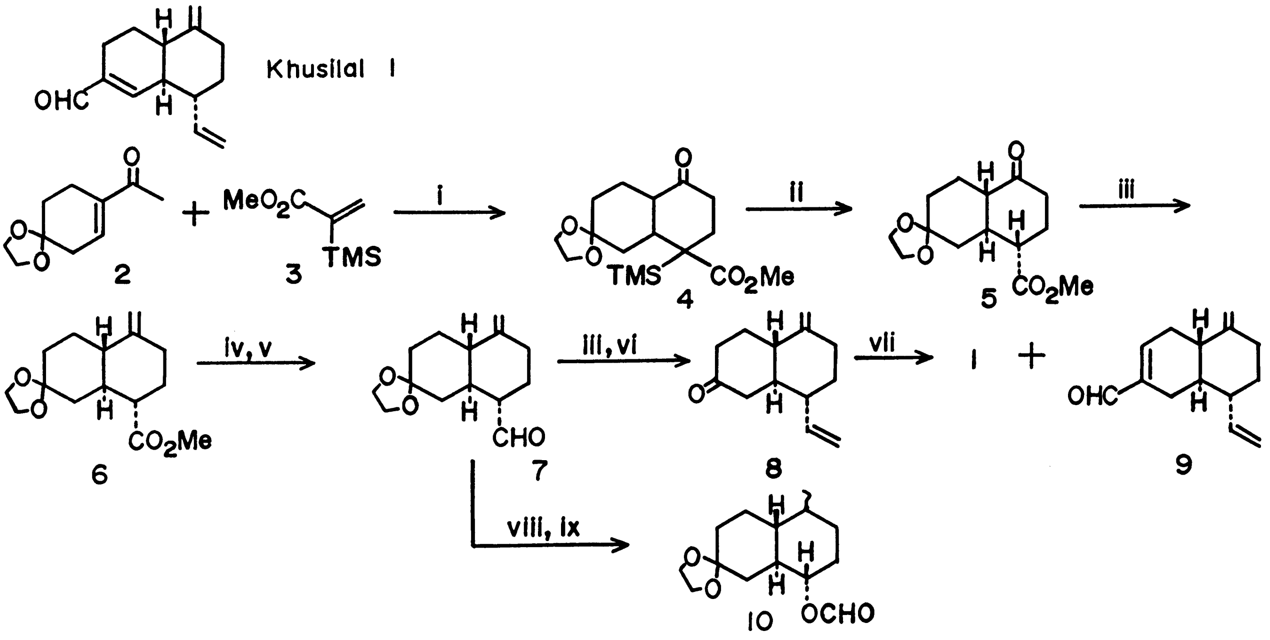
A Synthesis of (±)-Khusilal

Hisahiro HAGIWARA,* Tsutomu AKAMA, and Hisashi UDA
Chemical Research Institute of Non-Aqueous Solutions, Tohoku University,
Katahira, Aoba-ku, Sendai 980

(±)-Khusilal, a C_{14}-terpenoid isolated from North Indian vetiver oil, has been synthesized from the decalone derivative prepared by a double Michael reaction.

(-)-Khusilal (**1**) isolated from North Indian vetiver oil (Vetiveria zizanioides, Linn.), is a rare C-nor-sesquiterpenoid having a trans decaline framework with an unsaturated aldehyde group.$^{1)}$ The relative stereochemistry of the ring fusion and absolute stereostructure were established to be trans and antipodal to cadinene terpenoids as depicted in structure **1** on the basis of the optical rotational dispersion study,$^{2)}$ though the relative configuration of the vinyl group has not yet been established. Our continuing interest towards successive double Michael reaction and its application to terpenoid synthesis$^{3)}$ report here a total synthesis of (±)-khusilal (**1**) thereby establishing the relative stereochemistry of the vinyl group to be α-equatorial (Scheme 1).

The double Michael reaction of the kinetic enolate of acetylcyclohexene derivative (**2**) with methyl α-trimethylsilylacrylate (**3**) gave decalone (**4**) in 71% yield.$^{3c)}$ On the other hand, the reaction with methyl acrylate led directly to decalone (**5**) in 25% yield. Treatment of **4** with sodium methoxide in methanol at 40 °C for 4.4 h removed the trimethylsilyl group smoothly and afforded the thermodynamically more stable decalone (**5**) in 53% yield.$^{3c)}$ It was assigned that the ring fusion of **5** was trans and the orientation of methoxycarbonyl group was equatorial, since two protons at δ 2.40 (1H, td, J=12, 5.8 Hz) and δ 2.58 (1H, ddd, J=12, 10, 3.5 Hz) have two axial-axial coupling patterns. Wittig condensation of **5** gave the exo-methylene ester **6** in 94% yield. Lithium aluminumhydride reduction of **6** followed by Swern oxidation afforded the aldehyde (**7**). The orientation of the formyl group of **7** was checked again and was established to be more stable equatorial one by the following reasons: 1) Treatment of **7** with methanolic potassium carbonate at room temperature overnight recovered the starting aldehyde (**7**). 2) In the nmr spectrum of the formate (**10**) which was obtained by catalytic hydrogenation of the exocyclic olefin of **7** followed by Baeyer-Villiger oxidation, the proton on the carbon bearing the formyloxy group showed the axial coupling pattern (δ 4.3—4.7, 1H, $W_{1/2}$ =22 Hz). Wittig condensation of **7** and hydrolysis of the acetal furnished the keto olefin (**8**) in 80% overall yield from **6**. Although the aldehyde **7** and the intermediary diene acetal were used without purification because of instability of the former and volatility of the latter, the overall yield was quite satisfactory. Finally, requisite α,β-unsaturated aldehyde moiety was introduced to **8** by a one-pot procedure of Nozaki-Yamamoto4) using dichloromethyllithium to furnish (±)-khusilal (**1**) (21%) along with positional isomer of double bond (**9**) (25%). The synthetic khusilal (**1**) isolated by MPLC has the spectral data identical with reported ones in Ref.1. Thus the first synthesis of (±)-khusilal has been accomplished and the relative stereochemistry of the vinyl group was assigned to be α-equatorial.



Scheme 1.

Reagents and conditions; i, LDA, THF, -80 °C-room temp ; ii, MeONa, MeOH, 40 °C, 4.4 h; iii, $Ph_3P=CH_2$, THF, 0 °C; iv, $LiAlH_4$, Et_2O, 0 °C; v, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; vi, PPTS, aq. Acetone, reflux; vii, CH_2Cl_2, n-BuLi, -95 °C-room temp, then $LiClO_4$, $CaCO_3$, HMPA, 130 °C; viii, H_2, Pd/C, AcOEt; ix, MCPBA, CH_2Cl_2, room temp.

References

1) P. S. Kalsi, K. K. Chakravarti, and S. C. Bhattacharyya, Tetrahedron, 20, 2617 (1964).
2) K. K. Chakravarti, Indian J. Chem., 3, 324 (1965).
3) a) H. Hagiwara and H. Uda, J. Chem. Soc., Perkin Trans. 1, 1986, 629; b) H. Hagiwara, A. Okano, T. Akama, and H. Uda, J. Chem. Soc., Chem. Commun., 1987, 1333; c) H. Hagiwara, T. Akama, and H. Uda, Chem. Lett., 1988, 1793.
4) H. Taguchi, S. Tanaka, H. Yamamoto, and H. Nozaki, Tetrahedron Lett., 27, 2465 (1973).

(Received August 30, 1989)