CHEMISTRY LETTERS, pp. 1793-1796, 1988.

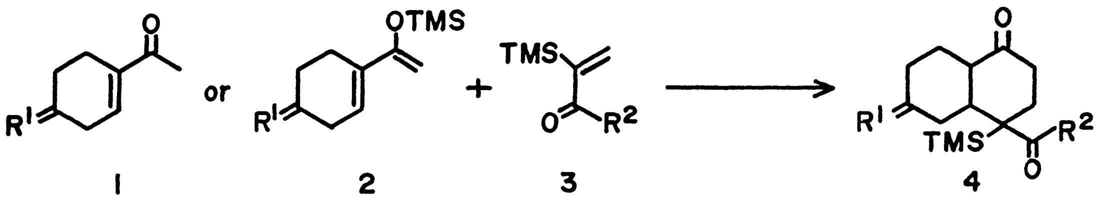
Synthesis of Substituted 2-Decalones from 1-Acetylcyclohexenes and α-Trimethylsilyl α,β-Unsaturated Carbonyl Compounds by Two-Fold Michael Reactions. Synthesis of (±)-Khusitone

Hisahiro HAGIWARA,* Tsutomu AKAMA, Akihiro OKANO, and Hisashi UDA
Chemical Research Institute of Non-aqueous Solutions,
Tohoku University, Katahira, Sendai 980

The kinetic enolates of 1-acetyl cyclohexenes undergo two-fold Michael reaction with α-trimethylsilyl α,β-unsaturated carbonyl compounds to produce 5-substituted 2-decalones. The application of this reaction has enabled a synthesis of (±)-khusitone.

A one-pot annelation with multiple C-C bond formation is an efficient method for approach to synthetically useful functionalised intermediates.[1,2,3] In a course of our programme in the development of sequential multi-fold Michael reactions,[2] we disclose herein the two-fold Michael reactions of the kinetic enolates of 1-acetylcyclohexenes (**1**)[3a] with α-trimethylsilyl α,β-unsaturated carbonyl compounds (**3**) to give 5-substituted 2-decalones (**4**) (Eq. 1), and the application of this reaction to the synthesis of (±)-khusitone (**11**) (Scheme 1). The reaction condition of the present reaction is alternative and complementary to that of the previously reported Lewis acid assisted reaction of the trimethylsilyl enol ethers of 1-acetylcyclohexenes with α,β-unsaturated carbonyl compounds.[2a,3b) The trimethylsilyl group in the product would be useful leaving group for further transformation.

The kinetic enolates of 1-acetylcyclohexenes generated from **1** by treatment with LDA or by MeLi cleavage of the corresponding trimethylsilyl enol ethers (**2**) reacted with α-trimethylsilyl α,β-unsaturated carbonyl compounds at -80 °C in THF. The reaction temperature was gradually raised to room temperature and progress of the reaction was monitored by TLC. Isolation by preparative MPLC gave the pure 2-decalone **4**.[4,5]



(1)

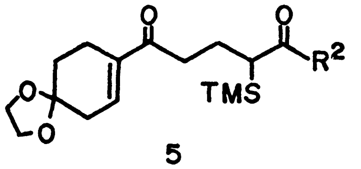
Table 1. Two-fold Michael reaction of kinetic enolates of 1-acetylcyclohexenes (**1**) with α-trimethylsilyl α,β-unsaturated carbonyl compounds (**3**)

Entry	1-Acetylcyclohexene (**1**)	α,β-Unsaturated carbonyl compound(**3**)	Reaction conditions	Product yield %
1	**1a**(R^1=H_2)	**3a**(R^2=OMe)	a)	**4a** (62) + **6a** (8)
2	**2a**(R^1=H_2)	**3a**	b)	**4a** (39)
3	**1b**(R^1=OCH_2CH_2O)	**3a**	a)	**4b** (71) + **6b** (5)
4	**2b**(R^1=OCH_2CH_2O)	**3a**	b)	**4b** (18) + **6b** (9)
5	**1b**	**3a**	a,c)	**4b** (24) + **5a** (5)
6	**1a**	**3b**(R^2=Me)	a)	**4c** (26)
7	**2a**	**3b**	b)	**4c** (9)
8	**1b**	**3b**	a)	**4d** (30)
9	**1b**	**3b**	a,d)	**5b** (9)
10	**2b**	**3b**	b)	**4d** (trace)

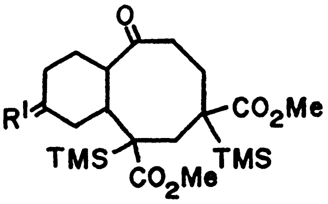
a) Acetylcyclohexene **1** was treated with LDA. b) Silyl enol ether **2** was cleaved by MeLi. c) Reaction was quenched at -45 °C in 1 h. d) Reaction was quenched at -10 °C in 3.6 h.

Some of the results are listed in Table 1. The reaction of the kinetic enolates generated by LDA or of methyl α-trimethylsilyl acrylate (**3a**) gave higher yields.

When the reaction was quenched at low temperature (entries 5 and 9), single Michael products (**5a** and **5b**) were obtained in 5 and 9% yield, respectively. These results, together with the co-occurence of bicyclo[6.4.0]dodecanes (**6a** and **6b**) (entries 1, 3, and 4), clearly indicate that the present reaction proceeds via a sequential two-fold Michael addition. It should be noted that the presence of α-trimethylsilyl group in α,β-unsaturated carbonyl compounds is essential for the reaction; parent methyl acrylate and methyl vinyl ketone did not give any desired product.



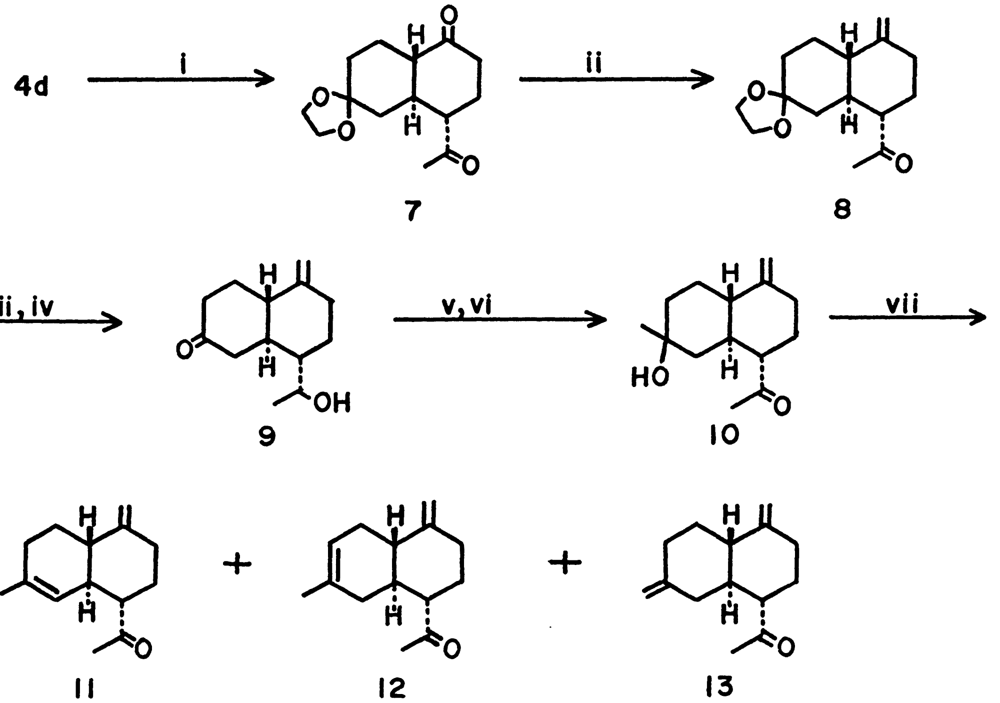
5



6

We next attempted the synthesis of (±)-khusitone (**11**), a member of the rare class of C_{14}-terpenoids, isolated from north indian vetiver oil[6] (Scheme 1.).

Treatment of the decalone **4d** with MeONa at room temperature resulted in smooth removal of the trimethylsilyl group and catalysed isomerisation to the known *trans*-isomer 7[2a] in 72% yield. A Wittig methylenation with 1 equiv. of methylene triphenylphosphorane proceeded selectively on the ring carbonyl to give the *exo*-methylene compound **8** in 53% yield. Reduction of the acetyl group followed by hydrolysis of the ketal furnished the diastereomeric mixture of keto-alcohol **9** in 87% yield. Methylation of **9** and then oxidation of the secondary alcohol gave the acetyl-alcohol **10** in 39% yield. Finally, dehydration with $POCl_3$ in pyridine afforded (±)-khusitone **11** along with the inseparable mixture of olefinic isomers **12** and **13** [**11**:**12**:**13**=2:3:1] (a combined yield 51%). The spectral properties of synthetic **11** (NMR, IR) are identical with those reported.[6]



Scheme 1.

Reagents and conditions; i, MeONa, MeOH, room temp; ii, $Ph_3P=CH_2$, THF room temp.; iii, $LiAlH_4$, Et_2O, room temp; iv, p-$MeC_6H_4SO_3H$, *aq* acetone, reflux; v, MeLi, Et_2O, 0 C; vi, Jones oxidation; vii, $POCl_3$, pyridine, room temp.

Thus, the present one-pot annelation provides synthetically useful substituted 2-decalones **4**, applicable to the substrates having acid sensitive functional groups.

This work was supported partially by a Grant-in-Aid for Scientific Research (No. 61540390) from the Ministry of Education, Science, and Culture of Japan.

References

1) G. H. Posner, Chem. Rev., 86, 831 (1986); M. Ihara and K. Fukumoto, Yuki Gosei Kagaku Kyokai Shi, 44, 96 (1986).

2) a) H. Hagiwara, A. Okano, T. Akama, and H. Uda, J. Chem. Soc., Chem. Commun., 1987, 1333; b) H. Hagiwara and H. Uda, J. Chem. Soc., Perkin Trans. 1, 1986, 629, and references cited therein.

3) a) F. Richter and H.-H. Otto, Tetrahedron Lett., 26, 4351 (1985); 28, 2945 (1987); b) T. Mukaiyama, Y. Sagawa, and S. Kobayashi, Chem. Lett., 1986, 1821.

4) The relative stereochemistry of 2-decalones **4** have not yet been determined.

5) All new compounds exhibited satisfactory ^{1}H NMR, IR, and high resolution mass and/or elemental analyses.

6) G. K. Trivedi, P. S. Kalsi, and K.K. Chakravarti, Tetrahedron, 20, 2631 (1964).

(Received August 6, 1988)