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

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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 (<u>+</u>)-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})

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

	1-Acetylcyclohexene (1)	α , β -Unsaturated	Reaction	Product	yield
		carbonyl compound(3)	conditions	8	
Entry					
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	$2\mathbf{b}(\mathbb{R}^1 = OCH_2CH_2O)$	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 (trad	ce)

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 <u>via</u> 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.



We next attempted the synthesis of (\pm) -khusitone (11), a member of the rare class of C_{14} -terpenoids, isolated from north indian vetiver oil⁶) (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 <u>trans</u>-isomer 7^{2a} in 72% yield. A Wittig methylenation with 1 equiv. of methylene triphenylphosphorane proceeded selectively on the ring carbonyl to give the <u>exo</u>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 POCl₃ in pyridine afforded (<u>+</u>)-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)



<u>Reagents and conditions</u>; i, MeONa, MeOH, room temp; ii, $Ph_3P=CH_2$, THF room temp.; iii, LiAlH₄, Et₂O, room temp; iv, p-MeC₆H₄SO₃H, <u>aq</u> acetone, reflux; v, MeLi, Et₂O, 0 C; vi, Jones oxidation; vii, POCl₃, 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.

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