Lewis Acid Assisted Annelation of Trimethylsilyl Enol Ethers of 1-Acetylcyclohexenes with α,β-Unsaturated Carbonyl Compounds to give Substituted 2-Decalones; Synthesis of (±)-ε-Cadinene

Hisahiro Hagiwara,* Akihiro Okano, Tsutomu Akama, and Hisashi Uda*

Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira, Sendai 980, Japan

The trimethylsilyl enol ethers of 1-acetylcyclohexenes undergo a Lewis-acid-assisted one-pot annelation reaction with α,β-unsaturated carbonyl compounds to produce 5-substituted 2-decalones; the application of this reaction has enabled a synthesis of (±)-ε-cadinene (**12**).

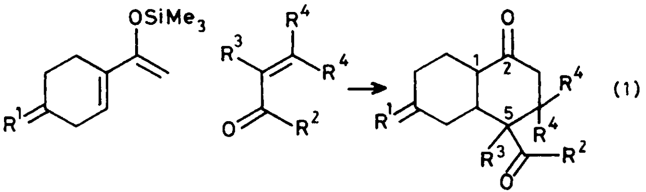
A reaction which forms multiple C–C bonds in one step would provide an efficient method of transformation of simple molecules into synthetically useful functionalised intermediates.[1] Our interest in the development of a one-pot annelation reaction with multiple C–C bond formation,[2] coupled with recent reports of reactions of 1-acetylcyclohexene and derivatives,[3] prompts us to disclose here our work on the Lewis-acid-assisted two-fold Michael reactions of trimethylsilyl enol ethers of 1-acetylcyclohexenes (**1**) with α,β-unsaturated carbonyl compounds (**2**) to give 5-substituted 2-decalones (**3**) [equation (1)], and the application of this reaction to the synthesis of (±)-ε-cadinene (**12**) (Scheme 1).

In a typical procedure, to a stirred solution of Lewis acid in CH_2Cl_2 were added successively at −85 °C solutions of an α,β-unsaturated carbonyl compounds (**2**) and the silyl enol ether (**1**) in CH_2Cl_2. The reaction temperature was raised gradually and stirring was continued at room temperature overnight. After the addition of aqueous potassium carbonate, the resulting suspension was filtered. The filtrate was extracted with ether, and the extracts were concentrated to

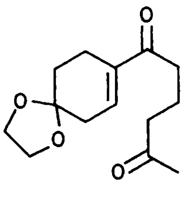
Table 1. Lewis-acid-assisted annelation of the trimethylsilyl enol ethers of 1-acetylcyclohexenes (**1**) with α,β-unsaturated carbonyl compounds (**2**).

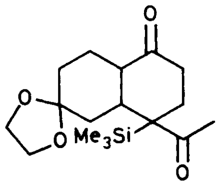
Entry	Trimethylsilyl enol ether (**1**)	α,β-Unsaturated carbonyl compound (**2**)	Lewis acid[a]	Product yield (%)[b]	
1	(**1a**) ($R^1 = H_2$)	(**2a**) (R^2 = Me, $R^3 = R^4$ = H)	$TrClO_4$[c]	(**3a**)	21
2	(**1a**)	(**2a**)	$TiCl_2(OPr^i)_2$	(**3a**)	22
3	(**1a**)	(**2a**)	$EtAlCl_2$	(**3a**)	24
4	(**1a**)	(**2a**)	Et_2AlCl	(**3a**)	56
5	(**1a**)	(**2a**) + Dimethyl fumarate	Et_2AlCl	(**3a**)	34
6	(**1a**)	(**2b**) (R^2 = Me, $R^3 = Me_3Si$, R^4 = H)	Et_2AlCl	(**3a**)	64
7	(**1a**)	(**2c**) ($R^2 = R^4$ = Me, R^3 = H)	Et_2AlCl	(**3b**)	51[d]
8	(**1a**)	(**2d**) (R^2 = OMe, $R^3 = R^4$ = H)	Et_2AlCl	(**3c**)	64
9	(**1b**) ($R^1 = OCH_2CH_2O$)	(**2a**)	$TiCl_2(OPr^i)_2$[e]	(**3d**)	34[d]
10	(**1b**)	(**2b**)	$TiCl_2(OPr^i)_2$	(**4**) +(**5**)	19 +12

[a] 3 equiv. [b] A single isomer was obtained. [c] A catalytic amount (10 mol %). [d] A mixture of two isomers was obtained. [e] Reaction was quenched at −50 °C in 1.5 h.

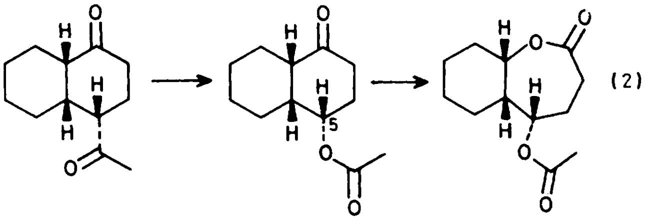


(1) **(2)** **(3)**


(4)



(5)

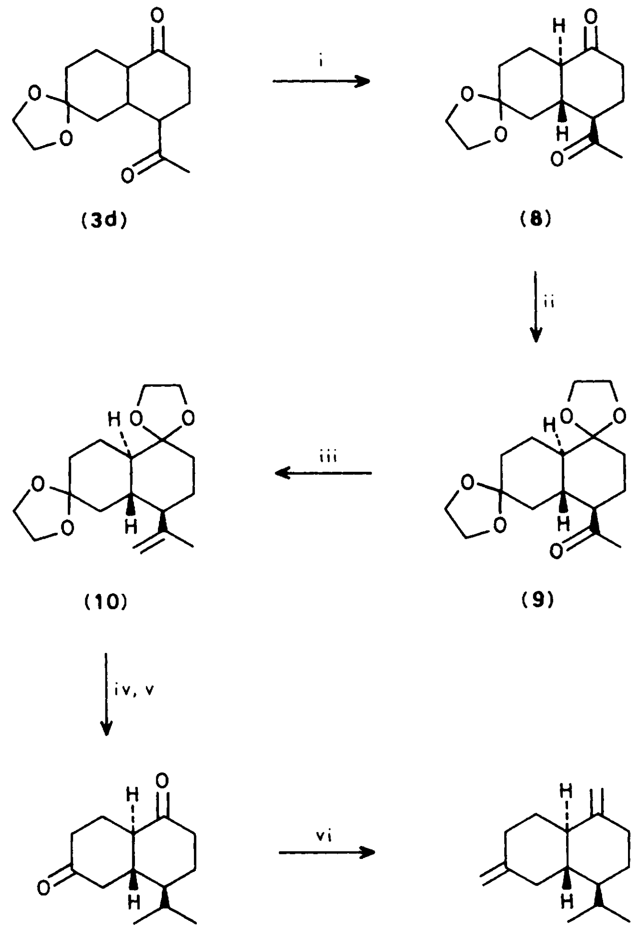


(3a) **(6)** **(7)**

give an oil, which was subjected to preparative h.p.l.c. to afford the pure 2-decalone (**3**). Among the Lewis acids investigated, particularly satisfactory results were obtained with Et_2AlCl (3 equiv.). Some of the results are summarized in Table 1.

When the reaction was run in the presence of methyl vinyl ketone (**2a**) and an equivalent amount of dimethyl fumarate (a good dienophile for a Diels–Alder reaction), only the decalone (**3a**) was obtained, in 34% yield (entry 5). Moreover, the 1,5-dicarbonyl compound (**4**) derived from a single Michael adduct was isolated in 18% yield along with the 2-decalone (**5**) (12%) in the $TiCl_2(OPr^i)_2$-catalysed reaction between the silyl enol ether (**1b**) and 3-trimethylsilylbut-3-en-1-one (**2b**) (entry 10). These results indicate that the present reaction proceeds *via* a sequential two-fold Michael addition.

In the ^1H n.m.r. spectrum (300 MHz) of the decalone (**3a**), the coupling pattern (dt, J 11.8 and 4.0 Hz) of the one-proton signal at δ 2.97, assigned to 5-H, indicates that compound (**3a**) has the *cis*-steroidal coformation with an equatorial acetyl group. This stereochemistry was confirmed by the ^1H n.m.r. spectra of the acetoxy derivative (**6**) and the acetoxy-lactone derivative (**7**), prepared by heating compound (**3a**) with *m*-chloroperbenzoic acid in CH_2Cl_2 for 24 and 62 h, respectively [equation (2)]. The signal due to 5-H in compound (**6**) appeared as a broad peak at δ 5.26 with a half-height width ($W_{1/2}$) of 31 Hz, and compound (**7**) revealed two one-proton signals at δ 4.61 (1-H, $W_{1/2}$ 8.8 Hz, equatorial) and 4.98 (5-H, $W_{1/2}$ 30 Hz, axial). Furthermore, exposure of compound (**3a**) to sodium methoxide (MeONa) in methanol (MeOH) produced the more stable *trans*-isomer. The conformation of the methoxycarbonyldecalone (**3c**) was established in analogous manner.



(3d) **(8)** **(10)** **(9)** **(11)** **(12)**

Scheme 1. *Reagents*: i, MeONa, MeOH, room temp., 2 h; ii, $HOCH_2CH_2OH$ (1.2 equiv.), p-$MeC_6H_4SO_3H$ (PTSA), benzene, reflux, 1 h; iii, $Ph_3P{=}CH_2$ (30 equiv.), tetrahydrofuran (THF), reflux, 31 h; iv, H_2 Pd–C (10%), EtOH, 23 h; v, THF–H_2O (3 : 1), PTSA, reflux, 4 h; vi, $Ph_3P{=}CH_2$, THF, room temp., 0.5 h.

The decalones (**3**) thus obtained, especially compound (**3d**), would be expected to be suitable intermediates for the synthesis of cadinane-type sesquiterpenoids. Therefore, we next attempted the synthesis of (±)-ε-cadinene (**12**) isolated from ylang-ylang oil[4,5] (Scheme 1).

Treatment of the decalone (**3d**) with MeONa at room temperature catalysed its isomerisation to the *trans*-isomer (**8**) with equatorial acetyl group in 93% yield. After selective protection of the ring carbonyl group of compound (**8**) (73% yield), a Wittig methylenation of the acetyl group of the resulting bis-ketal (**9**) furnished the isopropenyl decalin (**10**) (81% yield). Catalytic hydrogenation followed by hydrolysis of the ketals afforded the known diketone (**11**)[5a,c] in 66% yield. Finally, a double Wittig reaction of (**11**) gave (±)-ε-cadinene (**12**) (75% yield), which shows spectral data (n.m.r., i.r., and mass) identical with those reported.[5c]

Thus the present one-pot annelation offers a useful method for the preparation of substituted 2-decalones of defined stereochemistry in acceptable yields.

We thank Professor M. Niwa for providing the i.r. spectrum of authentic (±)-ε-cadinene (**12**). 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.

Received, 24th April 1987; Com. 555

References

1 G. H. Posner, *Chem. Rev.*, 1986, **86**, 831; M. Ihara and K. Fukumoto, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 96.

2 H. Hagiwara and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1986, 629, and references cited therein.

3 F. Richter and H.-H. Otto, *Tetrahedron Lett.*, 1985, **26**, 4351; T. Mukaiyama, Y. Sagawa, and S. Kobayashi, *Chem. Lett.*, 1986, 1821.

4 E. von Rudloff and K. W. Hefendehl, *Can. J. Chem.*, 1966, **44**, 2015; E. von Rudloff and V. K. Sood, *Can. J. Chem.*, 1969, **47**, 2081.

5 Syntheses: (*a*) L. A. Burk and M. D. Soffer, *Tetrahedron*, 1976, **32**, 2083; *Tetrahedron Lett.*, 1970, 211; (*b*) M. Niwa, M. Iguchi, and S. Yamamura, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3148; (*c*) F.-H. Koster, H. Wolf, and H. Kluge, *Liebigs Ann. Chem.*, 1986, 78.