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Asymmetric Two-Fold Michael Reaction.
Synthesis of Optically Active 4-Substituted 1-Decalones from Trimethylsilyl Enol Ether of 1-Acetylcyclohexene

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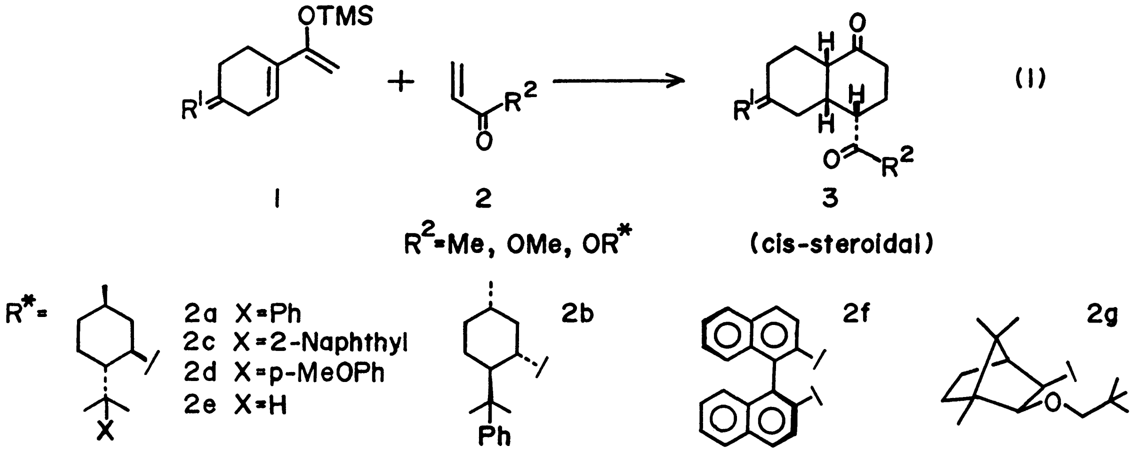
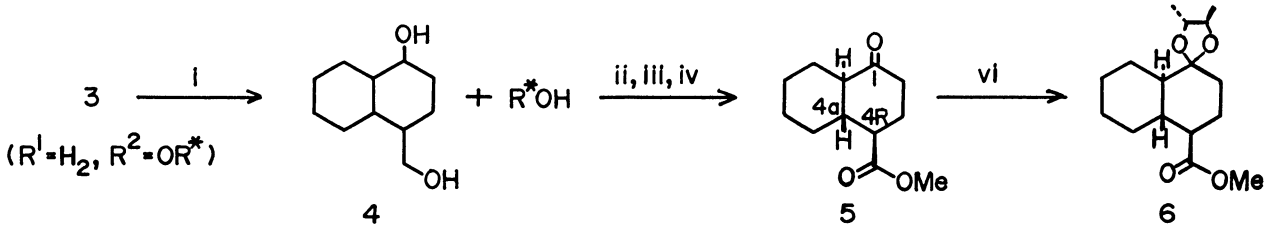
Acrylates having a chiral auxiliary react with the trimethylsilyl enol ether of 1-acetylcyclohexene in the presence of Et_2AlCl to give 4-substituted 1-decalones with 0—70% diastereoselectivity. The absolute stereostructure of the decalones have been determined by applying the exciton chirality method to the dibenzoate derivative.

Our current interests on multiple C-C bond forming reactions in a one-pot process1) have reported the double Michael reaction of the trimethylsilyl enol ether of 1-acetylcyclohexenes (**1**) ($R^1=H_2$, or $-OCH_2CH_2O-$) and α,β-unsaturated carbonyl compounds **2** under Lewis acid catalysis to produce 4-substituted 1-decalones **3** (Eq. 1).1b) The reaction proceeds via two-fold Michael pathway not a Diels-Alder reaction, since the single Michael product was obtained on quenching the reaction at low temperature and the reaction with methyl vinyl ketone (MVK) in the presence of an equimolar amount of dimethyl fumarate, which is a good dienophile in the Diels-Alder reaction, gave only **3** derived from MVK. The decalones **3** thus obtained have a cis-steroidal conformation. This result could be explained that the reaction proceeded via chelation of a metal [Al(III) or Ti(IV)] with two carbonyls of the reactants followed by axial protonation to the metal enolate with an equatorial carbonyl group.1b) Such an arrangement of reactants controlled by chelation suggests us that a chiral auxiliary in an unsaturated carbonyl component would be expected to affect bond formations in a diastereoselective manner, where the chirality would be induced at the stage of the more congested second Michael addition. Within this context, we delineate attempts on the asymmetric double Michael reaction leading to chiral 4-substituted 1-decalones **3**.



(1)

The reaction conditions of the double Michael reaction were the same as reported previously,[1b)] the equimolar amounts of the trimethylsilyl enol ether **1** ($R^1=H_2$) and the chiral acrylate **2** ($R^2=OR^*$), 3 equiv. of Et_2AlCl, CH_2Cl_2, -80 °C to room temperature (Eq. 1). Two chiral auxiliaries, (-)-8-(p-Methoxyphenyl)-menthol and (-)-8-(2-naphtyl)menthol, were prepared according to the procedure of the synthesis of (-)-8-phenylmenthol.[2)] Diastereomeric excess of the product 3 thus obtained was determined as follows (Scheme 1). Since **3** ($R^1=H_2$, $R^2=OR^*$) resisted to alkaline hydrolysis, the diastereomeric mixture was reduced to the diol **4** by lithium aluminum hydride in 70—90% yield in order to remove the chiral auxiliary which was recovered almost quantitatively. The keto ester, obtained by Jones oxidation of **4** followed by esterification with diazomethane, was treated with sodium methoxide in methanol to settle in the thermodynamically stable trans isomer **5** in 70% yield, because, in the original cis-steroidal conformation, the α-positions of the carbonyl groups were liable to epimerize. Then, the keto-ester **5** was quantitatively transformed into a diastereomeric mixture of the acetal **6** with 2R,3R-2,3-butanediol. The acetal **6** was analyzed by MPLC (Silica-gel, AcOEt/hexane= 1/7), and the results were listed in Table 1. When (-)- or (+)-phenylmenthol was used as a chiral auxiliary (entries 1 and 2), asymmetric induction of about 70% was observed. Increased steric shielding (entry 3) and increased site of chelation (entry 4) in a chiral auxiliary did not improve diastereomeric selection. Diastereomeric enrichment was achieved by isolation of the cis-steroidal diastereoisomer **3a** at the initial stage by MPLC in entry 1. In this case, the d.e. value of **6** increased to 97% but the chemical yield of **3a** decreased to 45%.



Scheme 1.

Reagents and conditions; i, $LiAlH_4$, Et_2O, reflux; ii, Jones reagent, acetone, 0 °C; iii, CH_2N_2, Et_2O; iv, MeONa, MeOH, 30 °C, overnight; v, (2R,3R)-2,3-butanediol, benzene, PTSA, reflux.

Table 1. Asymmetric two fold Michael reaction of the trimethylsilyl enol ether of acetylcyclohexene (**1**) with chiral acrylate **2**

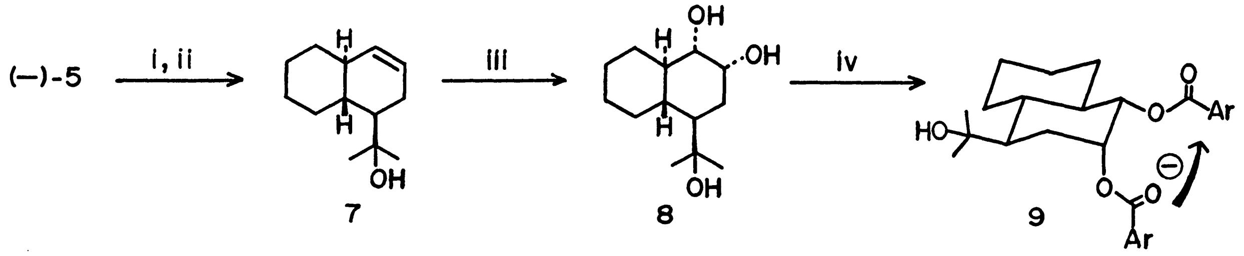
Entry	R^*=Chiral auxiliary in **2**	Yield of **3** %	$[\alpha]_D$/°[a] of **5**	d.e. %[b]
1	a:(-)-8-Phenylmenthyl-	64	-23.4	70
2	b:(+)-8-Phenylmenthyl-	62	+24.9	73
3	c:(-)-8-(2-Naphthyl)menthyl-	64	-22.9	64
4	d:(-)-8-(p-Methoxyphenyl)menthyl-	44	-21.5	62
5	e:(-)-Menthyl-	54	0	0
6	f:(-)-2,2'-bis-1,1'-Binaphthyl-	80	-1.4	2.3
7	g:(-)-cis-3-Neopentyloxyisobornyl-[c]	63	+2.0	17

a) Measured in chloroform solutions at 22 °C.

b) Determined by MPLC analysis of the acetal esters **6**.

c) See Ref. 3.

The absolute stereochemistry of **5** was determined by applying the exciton chirality method,[4] owing to the lack of **5** with the known absolute configuration or it's derivatives. Thus the (-)-keto ester **5** (>97% e.e.), derived from the product **3a** using (-)-phenylmenthyl acrylate (**2a**), was transformed into the dibenzoate **9** (Scheme 2). The Shapiro reaction of **5** using methyllithium gave regioselectively the single olefinic alcohol **7** in 55% yield. Subsequent cis hydroxylation with osmium tetroxide proceeded fairly stereoselectively from the α-face (α/β=7/2) of **7** to give the triol **8** in 90% yield. Benzoylation of the secondery glycols of **8** with p-methoxybenzoyl chloride gave the di-p-methoxybenzoate **9** in 71% yield, whose relative stereochemistry (cis-α) was determined from the NMR coupling patterns [δ 4.87 (1H, dd, J=10,3 Hz) and δ 5.57 (1H, m, $W_{1/2}$=7 Hz)] of the protons at C-1



Scheme 2.

Reagents and conditions; i, TsNHNH$_2$, EtOH, reflux; ii, MeLi, THF, room temp; iii, OsO$_4$, *N*-methylmorpholine-*N*-oxide, t-BuOH, H$_2$O; iv, *p*-methoxybenzoyl chloride, pyridine, DMAP, 60 °C, 1 h.

and C-2. The CD spectrum of **9** exhibited the typical exciton type, the first negative ($\Delta\varepsilon$ -16.0 at 266 nm) and the second positive ($\Delta\varepsilon$ +7.8 at 246 nm) Cotton effects. This clearly indicates that the chirality between the two long axes of the transition moments of benzoate chromophores is negative as depicted in the structure **9** (Scheme 2). Thus, the absolute configuration of the (-)-ketoester **5** was determined to be *4R*, *4aR*, *8aR* as shown in the structure 5 (Scheme 1), representing that the second Michael addition occured from *Re* face of the cyclohexene moiety.

In summary, the asymmetric two-fold Michael reaction has been accomplished leading to either enantiomer of 4-substituted 1-decalone derivatives in about 70% diastereoselective and 60% chemical yields. This procedure would provide a useful access to synthesize some natural products in optically active form.

References

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