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A DIRECT METHOD FOR α-METHYLENEBUTYROLACTONE SYNTHESIS USING HOMOALLYL ALCOHOLS

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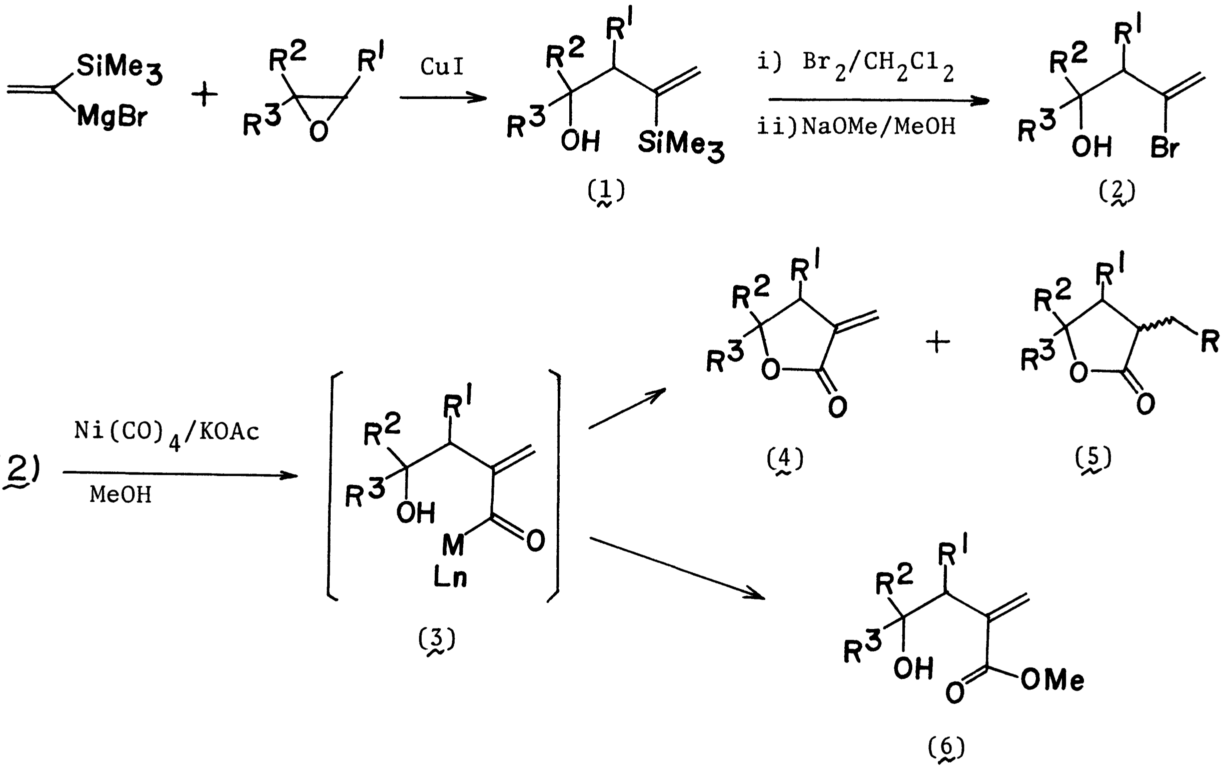
3-Trimethylsilyl-3-buten-1-ols (**1**) are prepared by a ring opening of epoxides with α-trimethylsilylvinylmagnesium bromide in the presence of catalytic amounts of CuI. 3-Bromo-3-buten-1-ols (**2**) derived from (**1**) react with $Ni(CO)_4$ to give directly α-methylenebutyrolactones (**4**) with the assistance of potassium acetate in good yields except the case of a cyclopentanol derivative (**2e**).

α-Methylenebutyrolactones have recently attracted much synthetic effort,1∿4) because some sesquiterpenes possess cytotoxic and/or antitumore property caused mainly by this characteristic system.5∿7) Although several procedures have been developed for the synthesis of α-methylenelactones, the current methodology bases primarily upon manners for the introduction and subsequent elimination of a heteroatom attached to the β-carbon. Few examples 8∿11) are known, which allow to omit such a procedure. It is reported here to synthesize directly some α-methylenebutyrolactones (**4**) by using the insertion of carbon monoxide to vinyl bromide in homoallyl alcohols (**2**).

α-Trimethylsilylvinylmagnesium bromide reacted with epoxides to give homoallyl alcohols (**1**) in the presence of catalytic amounts of cuprous iodide as shown in Table 1. When the catalyst was absent, the formation of bromohydrin or the rearrangement of epoxides was predominant as reported previously,12,13) and expected **1** was not obtained at all. The structure of **1** is favorable as the precursor of α-methylenelactones (**4**) if **1** could be transformed to acyl complex **3** by the interaction of transition metals and carbon monoxide, which would decay spontaneously by means of intramolecular attack of the hydroxy group to form **4**. However, the direct substitution of the trimethylsilyl group with carbon monoxide did not succeed in the presence of catalytic or stoichiometric amounts of palladium chloride.14,15)

Therefore, homoallyl alcohols (**2**) were selected as relay intermediates in order to realize the lactonization, since it is well-known that vinyl and aryl halides form esters by the interaction of nickel tetracarbonyl16,17) or carbon monoxide catalyzed with zerovalent palladium complex.18,19) The trimethylsilyl



group of 1 was substituted with bromide by the two step reactions, bromination of the vinyl group and the subsequent elimination of bromotrimethylsilane with sodium methoxide in methanol.[20] The results are summarized in Table 1.

When the resultant homoallyl alcohol (2b) was heated at 50° with an excess of nickel tetracarbonyl in the presence of sodium methoxide as a base, the expected lactone 4b was obtained in only 4% yield. The remaining main product was saturated lactone 5 (R = OMe, 40%) which would be formed by the conjugate addition of MeO^- toward the desired lactone. It is expected that the usage of a weaker nucleophilic base would prevent the saturation of the methylene group. In fact the addition of potassium acetate instead of sodium methoxide improved drastically the yield of 4b as shown in Table 2. On the other hand, neither disodium tetracarbonylferrate nor carbon monoxide catalyzed with $(Ph_3P)_2PdCl_2$ did react with 2b. Some other homoallyl alcohols 2 except 2e gave lactones 4 under analogous conditions in good yields as shown in Table 1. Since the ring opening of cycloalkene oxide with α-trimethylsilylvinylmagnesium bromide occurs in the trans manner, 4b and 4c obtained would be trans-fused bicyclic lactones. The coupling pattern in the H^1 nmr spectrum of 4b shows clearly the trans-fused cyclization. An intermolecular ester formation is preferred to a trans-fused cyclization in the case of 2e, because the trans-fused bicyclic system with both five membered rings is difficult.

This method is widely applicable to α-methylenelactone synthesis because it can be achieved from epoxides in shorter steps than the reported one.[21]

A typical example is described in the following. *trans*-2-(α-trimethylsilyl)-

vinylcyclohexan-1-ol (1b); to a solution of α-trimethylsilylvinylmagnesium bromide (10.7 mmol) in THF (8 ml) and Et_2O (40 ml) was added CuI (0.56 mmol) and the mixture was stirred for 30 min at -30°. Cyclohexene oxide (11.3 mmol) was added to the solution at -30°. The mixture was stirred for 4 hr at -10° and 12 hr at 15° and then hydrolyzed with 1N HCl (25 ml). The residual liquid obtained after extraction with CH_2Cl_2 and evaporation of the solvent was stirred for 10 hr in MeOH (30 ml) solution of NaOMe (7 mmol) to exclude small amounts of bromohydrin. The mixture was concentrated under reduced pressure and neutralized with aq. $NaHCO_3$. The organic product was extracted four times with CH_2Cl_2. After drying and evaporation of the solvent the residue was distilled to give 1.64g (77%, bp 70-73°/6 mmHg) of pure 1b. *trans*-9-Methylene-7-oxa-bicyclo[4.3.0]nonan-8-one (4b); to

Table 1. Homoallyl alcohols and lactones

	R^1	R^2	R^3	1[i]		2[ii]		4 or 6[ii]	
				Yield (%)	δ_{Si-CH_3}[iii] (ppm)	Yield (%)	$\nu_{C=C}$[iii] (cm^{-1})	Yield (%)	$\nu_{C=O}$[iii] (cm^{-1})
a	H	Et	H	72	0.10	57	1632	63 (4)	1774
b	$-(CH_2)_4-$		H	77	0.10	65[iv]	1630	66 (4)	1782
c	$-(CH_2)_5-$		H	71	0.12	49	1623	75 (4)	1778
d	H	$-(CH_2)_5-$		82[ii]	0.09	41	1624	50 (4)[v]	1772
e	$-(CH_2)_3-$		H	85	0.11	53	1626	62 (6)[vi]	1709

i Bp (°C/mmHg); a 83-92/28, b 70-73/6, c 77-80/1, e 86-89/10. ii Isolated as oily liquid by column chromatography (silica gel) eluted with benzene (1d), benzene/chloroform = 2/1 (2 and 4), or chloroform (6e). iii In carbon tetrachloride. iv Mp 83.5-84.5°. v Mp 29-30°. vi $\delta(OCH_3)$ 3.75 ppm (s).

Table 2. Lactone formations from 2b

Reagent	Condition (°C/h)	Yield (%)	
		4b	5b[i]
$Ni(CO)_4$/KOAc/MeOH	50/4	66	0
$Ni(CO)_4$/NaOMe/MeOH	50/5	4	40 (R = OMe)[ii]
$Ni(CO)_4$/n-BuLi/THF	25/5	9	0
$Ni(CO)_4$/NaH/DMF	50/3	0	15 (R = H)[iii]
$Na_2Fe(CO)_4$/THF	25/3	no reaction	
$(Ph_3P)_2PdCl_2$/CO/Et_2NH/MeOH	50/6	no reaction	

i Isolated as oily liquid by column chromatography (silica gel) eluted with benzene/chloroform = 1/2. ii ν(C=O) 1786 cm^{-1}, $\delta(OCH_3)$ 3.30 ppm (s). iii ν(C=O) 1787 cm^{-1}, $\delta(CH_3)$ 1.17 ppm (d).

a MeOH (10 ml) solution of KOAc (2.88 mmol) and Ni(CO)$_4$ (1.5 ml) was added **2b** (1.92 mmol) in MeOH (3 ml). The mixture was stirred for 4 hr at 50° and the color changed to wine red. After cooling it to room temperature, CO gas was bubbled through the reaction mixture for 30 min. It was poured into 20 ml of 0.2N HCl and extracted three times with Et$_2$O. The extracts were washed twice with H$_2$O and dried over MgSO$_4$. Pure **4b** (0.192g, 66%, mp 39.5-40.5°) was obtained after evaporation of the solvent and column chromatography (SiO$_2$) eluted with C$_6$H$_6$/CHCl$_3$ = 2/1.

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