

New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride

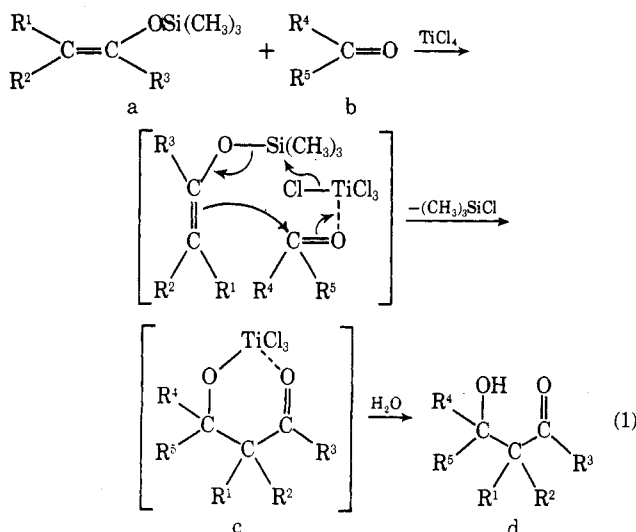
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Abstract: It was found that silyl enol ethers, prepared from various carbonyl compounds, react with aldehydes and ketones in the presence of titanium tetrachloride under mild conditions to give cross-aldol addition products in good yields. A mono-methylol product, 4-hydroxy-3-phenyl-2-butanone, was prepared in good yield from 1-phenyl-2-trimethylsilyloxy-1-propene and trioxane. Further, regiospecific addition of carbonyl compounds was observed with silyl enol ethers, derived from unsymmetrical ketones, such as phenylacetone or 2-methylcyclohexanone.

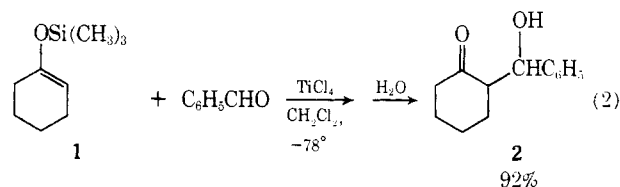
The aldol condensation has long been recognized to be one of the most versatile synthetic tools in organic chemistry. However, that the aldol product always contains di-, poly-, or self-condensation products frequently limits the utilization of this otherwise efficient reaction. This is due to ordinarily difficult separation of a desired product from the product mixture. In order to alleviate this difficulty, a useful synthetic procedure has been developed by Wittig and Hesse¹ using lithio derivatives of imines. In addition, House and coworkers² recently reported the use of lithium enolates and metal salts in the aldol condensation reaction. Prior to House, *et al.*, we published the method of preparing various aldols from silyl enol ethers and carbonyl compounds in the presence of titanium tetrachloride.^{3,4} We now wish to describe the scope and limitations of this method.

On preparing thiovinyl ethers⁵ from thiols and ketones or aldehydes in the presence of titanium tetrachloride, it was found in our laboratory that titanium tetrachloride powerfully activates the carbonyl carbon for nucleophilic reactions. This finding led us to the assumption that a silyl enol ether (compound a) could readily attack a carbonyl compound (b) activated by titanium tetrachloride in a nucleophilic fashion to form trimethylsilyl chloride and an intermediate chelate (c). Here the dissociation of the intermediate c would be inhibited because of the formation of a plausibly stable titanium chelate. Hydrolysis of the intermediate c should then afford aldol d as shown in eq 1.

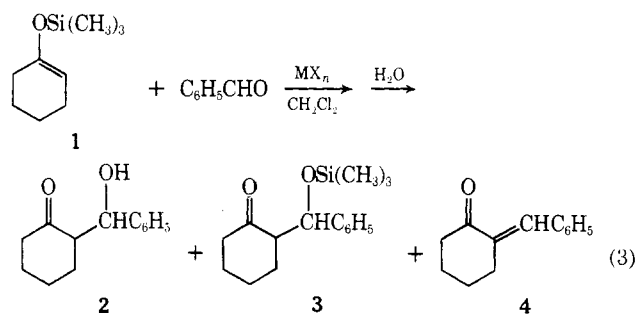


The reaction of 1-trimethylsilyloxy-1-cyclohexene (1), prepared from cyclohexanone and trimethylsilyl chloride,

with benzaldehyde was tried first. To a methylene chloride solution of equimolar amounts of benzaldehyde and titanium tetrachloride was added an equimolar amount of 1 under an argon atmosphere at -78° , and the reaction mixture was stirred for 1 hr. After hydrolysis, the resulting organic layer was extracted with ether, and the extract was concentrated. The aldol product, 2-(1'-hydroxybenzyl)-1-cyclohexanone (2), was obtained in 92% yield after purification by column chromatography (silica gel).



In order to probe the specific activity of titanium tetrachloride, the reaction of 1 with benzaldehyde in the presence of various other metal salts was examined according to the procedure mentioned above (see eq 3).



The results described in Table I demonstrate that among metal salts examined the effect of titanium tetrachloride (at -78°) notably outdoes those of boron trifluoride etherate and stannic chloride in terms of the product yields.

The relative effect of the amount of titanium tetrachloride upon the yield of the aldol was then investigated using the reaction between silyl enol ether 5 and β -phenylpropionaldehyde as a model reaction. It was found that the aldol 6 was obtained in the highest yield when an equimolar amount of titanium tetrachloride was applied (Table II).

Furthermore, the solvent effects on this reaction were studied by treating the silyl enol ether 1 with equimolar amounts of dibenzyl ketone and titanium tetrachloride in various solvents at room temperature (Table III). The results shown herein give immediate recognition of the fact that methylene chloride is significantly favored in this reaction to give the best yield, while, in contrast, aldol product 9

Table I. Reaction of the Silyl Enol Ether **2** with Benzaldehyde in the Presence of Various Metal Salts

Metal salts	Conditions		Yield of products, %		
	Temp, °C	Time, hr	2 (threo:erythro)	3^a	4
TiCl ₄	RT ^b	2	82 (63:19)	Trace ^c	2
TiCl ₄	-78	1	92 (69:23)	0	0
SnCl ₄	RT	1	33 (25:8)	Trace	28
SnCl ₄	-78	1	83 (63:20)	Trace	Trace
FeCl ₃	RT	1	0	0	12
AlCl ₃	RT	1	55 (41:14)	Trace	Trace
BCl ₃	RT	1	26 (18:8)	0	24
Et ₂ O · BF ₃	-78	1	80 (59:21)	12	0
ZnCl ₂	RT	10	69 (51:18)	8	3
ZnCl ₂	-78	12	Trace	0	0
(<i>n</i> -C ₄ H ₉) ₃ SnCl	RT	24	0	0	0
MgCl ₂	RT	24	0	0	0
CdCl ₂	RT	24	0	0	0
LiCl	RT	24	0	0	0

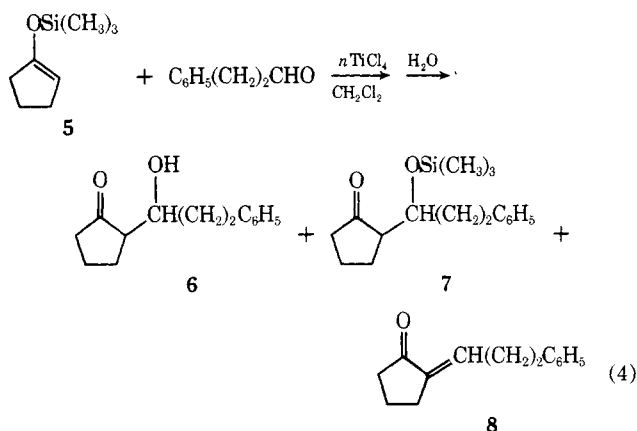
^a Threo and erythro mixture. ^b Room temperature. ^c By tlc analysis.

Table II. The Effect of the Amount of TiCl₄ on the Yield

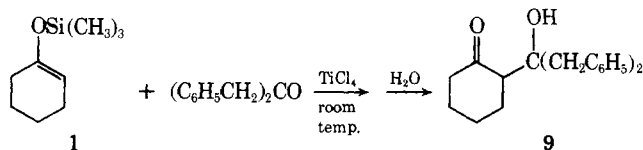
Molar ratio of TiCl ₄	Yield of products, %		
	6 (threo, erythro)	7	8
0	0	0	0
0.13	80 (28, 52)	8	0
0.25	81 (42, 39)	12	Trace
0.5	81 (41, 40)	7	3
1	94 (49, 45)	Trace	3
2	71 (34, 37)	Trace	12

Table III. Solvent Effects on This Reaction

Solvent	Isolated yield of 9 , %
Methylene chloride	64
Benzene	24
<i>n</i> -Hexane	24
Tetrahydrofuran	0
Diethyl ether	0



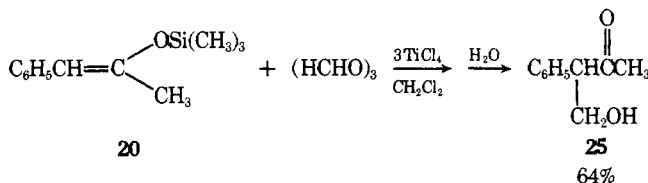
was not obtained at all in diethyl ether or tetrahydrofuran.⁶



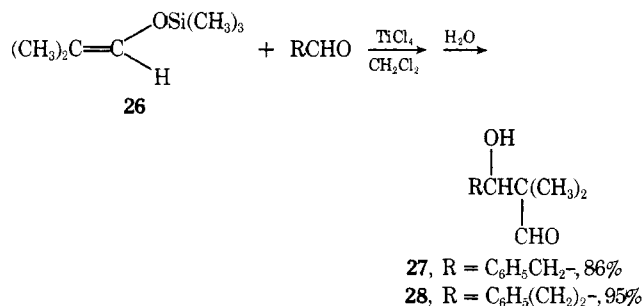
The reaction of various silyl enol ethers with a variety of carbonyl compounds was tried in the presence of an equimolar amount of titanium tetrachloride, and the corresponding aldols were obtained in high yields (Table IV).

Careful scrutinizing of the result listed in Table IV leads to the fact that, in the case of aldehydes, the aldols were obtained in excellent yields when the reaction was carried out at -78°, whereas, in the case of ketones, the reaction proceeded very sluggishly at -78°, and a reaction temperature of 0° or room temperature was required.

In general, a condensation reaction of a ketone with formaldehyde results in the formation of mono-, unsymmetrical bis-, and polymethylol products,⁹ and hence it is difficult to prepare a monomethylol exclusively. By the new method, however, monomethylol compounds could be easily and unmixedly prepared from silyl enol ethers and trioxane as formaldehyde. For example, 1-hydroxy-2-phenyl-3-butanone (**25**) was obtained in 64% yield when 1-phenyl-2-trimethylsilyloxy-1-propene (**20**) was treated with trioxane in methylene chloride in the presence of titanium tetrachloride at -78° for 2 hr.



The silyl enol ethers used in the reaction described so far were those derived from only ketones. Consequently, to furnish the added versatility of the new method, it remained to examine synthetic behavior of silyl enol ethers derived from aldehydes. At first, the reaction of 2-methyl-1-trimethylsilyloxy-1-propene (**26**) having no hydrogen atom at the β position with aldehydes was attempted. When silyl enol ether **26** was allowed to react with equimolar amounts of phenylacetaldehyde and titanium tetrachloride at -78° for 1 hr, the aldol product, 2,2-dimethyl-3-hydroxy-4-phenylbutyraldehyde (**27**), was obtained in 86% isolated yield. Following essentially the same procedure, silyl enol ether **26** and β-phenylpropionaldehyde gave 2,2-dimethyl-3-hydroxy-5-phenylvaleraldehyde (**28**) in 95% isolated yield.



When treated with *n*-butyraldehyde in the presence of titanium tetrachloride at -78° for 1 hr, 3-phenyl-1-trimethylsilyloxy-1-propene (**29**) having a hydrogen atom at the β position, in contrast, did not give aldol **30** but 2-benzyl-2-hexenal (**31**) in 78% yield by column chromatography (silica gel deactivated by water). This result was interpreted to indicate that aldol **30**, even under conditions as weakly acid

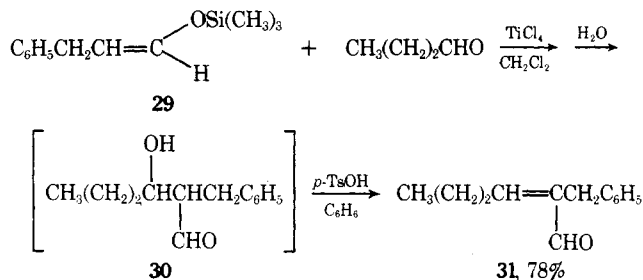
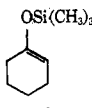
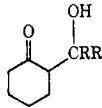
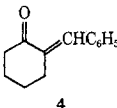
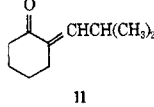
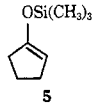
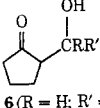
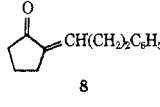
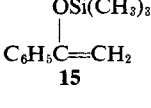
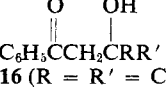
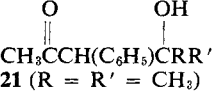
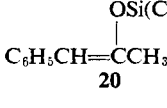


Table IV. Synthesis of Aldols^a from Silyl Enol Ethers and Carbonyl Compounds

Reagent		Conditions		Products			
Silyl enol ether	Aldehyde or ketone	Time, hr	Temp, °C	β -Hydroxy ketone	Isolated yield, %	α,β -Unsaturated ketone	Isolated yield, %
 1	$\text{C}_6\text{H}_5\text{CHO}$	2	RT	 2 ($\text{R} = \text{H}; \text{R}' = \text{C}_6\text{H}_5$)	82 (t, 63; e, 19) ^b	 4	6
		1	0		81 (t, 58; e, 23)		8
		1	-78		92 (t, 69; e, 23)		
	$(\text{C}_6\text{H}_5\text{CH}_2)_2\text{CO}$	1	RT	9 ($\text{R} = \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$)	64		
		1	0		25		
		10	-78		5		
	$(\text{CH}_3)_2\text{CHCHO}$	5	RT	10 ($\text{R} = \text{H}; \text{R}' = \text{CH}(\text{CH}_3)_2$)	50 (t and e mixt)	 11	31
		1	-78		92 (t and e mixt)		
 5	$\text{C}_6\text{H}_5(\text{CH}_2)_2\text{CHO}$	1	RT	 6 ($\text{R} = \text{H}; \text{R}' = (\text{CH}_2)_2\text{C}_6\text{H}_5$)	70 (t, 35; e, 35)	 8	
		1	-78		94 (t, 49; e, 45)		
	$(\text{C}_6\text{H}_5\text{CH}_2)_2\text{CO}$	18	RT	12 ($\text{R} = \text{R}' = (\text{CH}_2\text{C}_6\text{H}_5)$)	61		
	$\text{C}_6\text{H}_5\text{CHO}$	1	0	13 ($\text{R} = \text{H}; \text{R}' = \text{C}_6\text{H}_5$)	74		
		1	-78		86 (t, 37; e, 37)		
	$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	1	-78	14 ($\text{R} = \text{H}; \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$)	95 (t, 42; e, 44)		
					39 (t, 47; e, 48)		
 15	$(\text{C}_6\text{H}_5\text{CH}_2)_2\text{CO}$	3	RT	 16 ($\text{R} = \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$)	37		
		1	reflux		73		
	$(\text{CH}_3)_2\text{CO}$	5	RT	17 ($\text{R} = \text{R}' = \text{CH}_3$)	64		
		1	-78		78		
	$(\text{CH}_3)_2\text{CHCHO}$	2	RT	18 ($\text{R} = \text{H}; \text{R}' = \text{CH}(\text{CH}_3)_2$)	94		
		1	-78		78		
	$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	2	RT	19 ($\text{R} = \text{H}; \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$)	40		
	$(\text{CH}_3)_2\text{CO}$	5	RT	 21 ($\text{R} = \text{R}' = \text{CH}_3$)	60		
 20		1	0		68 (t, 25; e, 43)		
	$1/3(\text{CH}_3\text{CHO})_3$	5	RT	22 ($\text{R} = \text{H}; \text{R}' = \text{CH}_3$)	92 (t, 30; e, 62)		
		1	-78		52 (t and e mixt)		
	$(\text{CH}_3)_2\text{CHCHO}$	1	RT	23 ($\text{R} = \text{H}; \text{R}' = \text{CH}(\text{CH}_3)_2$)	93 (t and e mixt)		
		1	-78		77 (t, 53; e, 24)		
	$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	5	RT	24 ($\text{R} = \text{H}; \text{R}' = \text{CH}_2\text{C}_6\text{H}_5$)			

^a The stereoisomer (threo or erythro) of the aldols was determined by nmr examination,^{7,8} and the details are described in the Experimental Section. ^b t is threo, and e is erythro.

as silica gel, is unstable and susceptible to dehydration. Consequently, the crude aldol **30** from silyl enol ether **29** and *n*-butyraldehyde was obtained by quenching the product with water at -78° and dehydrated with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene. Chromatography on silica gel of the benzene extract afforded 2-benzyl-2-hexenal (**31**) in 78% yield.

The regiospecificity of the reaction of this paper was investigated by analyzing the stereochemical outcome of the

reactions of two structural isomers of silyl enol ether prepared from 2-methylcyclohexanone, such as 2-methyl-1-trimethylsilyloxy-1-cyclohexene (**32**) and 6-methyl-1-trimethylsilyloxy-1-cyclohexene (**34**) with benzaldehyde. Silyl enol ether **32** and an equimolar amount of benzaldehyde in methylene chloride at room temperature afforded by the agency of titanium tetrachloride two stereoisomers, *threo*- and *erythro*-2-(1'-hydroxybenzyl)-2-methyl-1-cyclohexanone (**33a** and **33b**). On the other hand, silyl enol ether **34**

Table V. Physical Properties and Analytical Data of the Aldols

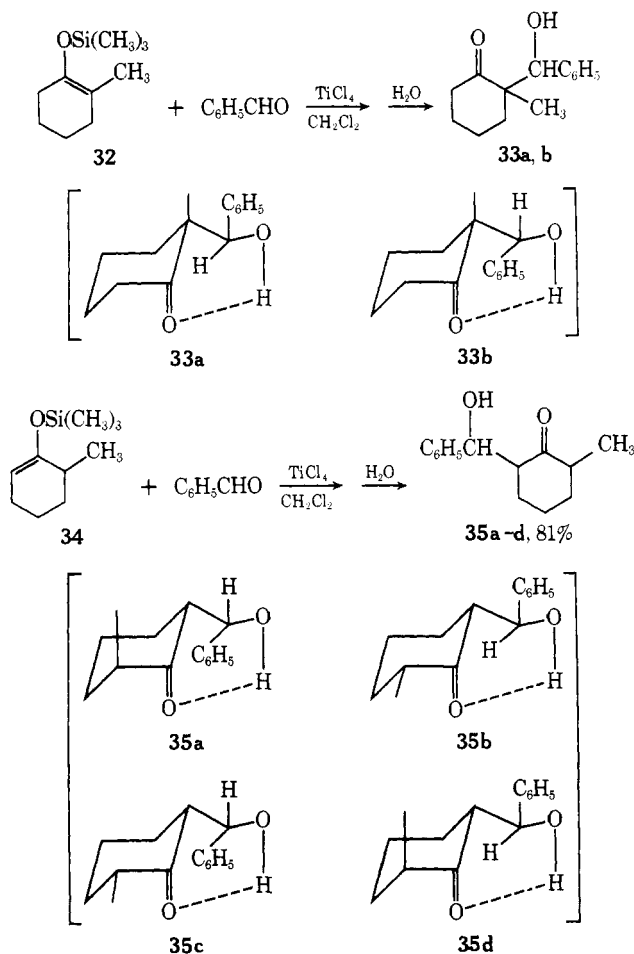
Product	Physical property	Ir, cm ⁻¹	Nmr, δ	Anal. Found, % (calcd)
3, threo		1696 (C=O)	7.52 (5 H, s, aryl CH), 5.31 (1 H, d, J = 8.5 Hz, O-CH), 1.4-2.9 (9 H, broad, aliphatic CH), 0.18 (9 H, s, Si(CH ₃) ₃)	
erythro		1695 (C=O)	7.51 (5 H, s, aryl CH), 5.63 (1 H, d, J = 3.0 Hz, O-CH), 1.4-2.8 (9 H, broad, aliphatic CH), 0.19 (9 H, s, Si(CH ₃) ₃)	
4		1695 (C=O) 1630 (C=C)	7.38 (5 H, s, aryl CH), 7.30 (1 H, s, vinyl CH), 1.4-3.0 (8 H, m, aliphatic CH)	C, 84.07; H, 7.46 (83.83) (7.58)
6, threo		3440 (OH) 1736 (C=O)	7.12 (5 H, s, aryl CH), 4.00 (1 H, t, J = 6.5 Hz, O-CH), 3.56 (1 H, s, OH), ^a 1.30-2.87 (11 H, broad, aliphatic CH)	C, 77.42; H, 8.34 (77.03) (8.31)
erythro		3496 (OH) 1722 (C=O)	7.18 (5 H, s, aryl CH), 3.72 (1 H, s, OH), ^a 3.51 (1 H, q, J = 6.0 Hz, O-CH), 1.2-2.8 (11 H, m, aliphatic CH)	C, 77.05; H, 8.32 (77.03) (8.31)
7		1730 (C=O)	7.15 (5 H, s, aryl CH), 3.98 (0.5 H, t, J = 6.5 Hz, O-CH), 3.70 (1 H, broad OH), ^a 3.50 (0.5 H, q J = 6.0 Hz, O-CH), 1.2-2.9 (11 H, broad, aliphatic CH)	
8		1720 (C=O) 1648 (C=C)	7.16 (5 H, s, aryl CH), 6.32 (1 H, broad, vinyl CH), 1.5-2.9 (10 H, broad, aliphatic CH)	C, 84.21; H, 8.36 (83.96) (8.05)
9	Mp 136°	3510 (OH) 1695 (C=O)	7.22 (10 H, s, aryl CH), 3.53 (1 H, broad, OH), ^a 2.85 (2 H, s, CH ₂), 2.77 (2 H, d, J = 3.0 Hz, CH ₂), 1.2-2.5 (9 H, broad, aliphatic CH)	C, 81.99; H, 7.84 (81.78) (7.84)
10		3510 (OH) 1700 (C=O)	3.50 (1 H, m, O-CH), 2081 (1 H, s, OH), ^a 1.1-3.0 (10 H, broad, aliphatic CH), 0.92 (6 H, d, J = 7.0 Hz, CH ₃)	C, 70.45; H, 10.23 (70.54) (10.66)
11		1690 (C=O) 1620 (C=C)	6.35 (1 H, d, t, J = 9.5, J = 2.0 Hz, vinyl CH), 1.5-2.7 (9 H, broad, aliphatic CH), 1.02 (6 H, d, J = 6.0 Hz, CH ₃)	C, 79.25; H, 11.01 (78.89) (10.59)
12	Mp 88-90°	3460 (OH) 1727 (C=O)	7.28 (5 H, s, aryl CH), 4.30 (1 H, broad, OH), ^a 2.87 (2 H, d, J = 1.5 Hz, CH ₂), 2.70 (2 H, d, J = 4.5 Hz, CH ₂), 1.30-2.40 (7 H, broad, aliphatic CH)	C, 81.35; H, 7.56 (81.60) (7.53)
13, threo		3460 (OH) 1725 (C=O) 1740 (C=O)	7.20 (5 H, s, aryl CH), 4.68 (1 H, d, J = 9.0 Hz, O-CH), 4.47 (1 H, s, OH), ^a 1.28-2.54 (7 H, broad aliphatic CH)	C, 76.06; H, 7.52 (75.76) (7.42)
erythro		3440 (OH)	7.20 (5 H, s, aryl CH), 5.16 (1 H, d, J = 2.0 Hz, O-CH), 3.90 (1 H, s, OH), ^a 1.14-2.44 (7 H, broad aliphatic CH)	C, 75.55; H, 7.68 (75.76) (7.42)
14, threo	Mp 82°	3420 3390 (OH) 1720 (C=O)	7.30 (5 H, s, aryl CH), 4.36 (1 H, t, J = 8.0 Hz, O-CH), 2.78 (2 H, d, J = 8.0 Hz, CH ₂), 2.71 (1 H, s, OH), ^a 1.70-2.80 (7 H, broad, aliphatic CH)	C, 76.38; H, 7.65 (76.44) (7.90)
erythro		3460 (OH) 1730 (C=O)	7.31 (5 H, s, aryl CH), 3.85 (1 H, q, J = 6.0 Hz, O-CH), 3.64 (1 H, s, OH), ^a 1.3-2.89 (9 H, broad, aliphatic CH)	C, 76.52; H, 7.82 (76.44) (7.90)
16	Mp 162°	3500 (OH) 1680 (C=O)	7.9-8.74 (5 H, m, aryl CH), 7.23 (10 H, s, aryl CH), 4.00 (1 H, broad, OH), ^a 3.03 (4 H, s, CH ₂), 2.93 (2 H, s, CH ₂)	C, 83.63; H, 6.64 (83.60) (6.71)
17		3440 (OH) 1666 (C=O)	7.20-8.12 (5 H, broad, aryl CH), 3.98 (1 H, s, OH), ^a 3.07 (2 H, s, CH ₂), 1.30 (6 H, s, CH ₃)	C, 74.62; H, 7.63 (74.13) (7.92)
18		3400 (OH) 1677 (C=O)	6.90-7.90 (5 H, broad, aryl CH), 3.81 (1 H, q, J = 6.0 Hz, O-CH), 3.20 (1 H, s, OH), ^a 2.90 (2 H, d, J = 6.0 Hz, CH ₂), 1.55 (1 H, m, CH), 0.92 (6 H, d, J = 6.0 Hz, CH ₃)	C, 74.86; H, 8.56 (74.97) (8.39)
19	Mp 86°	3490 (OH) 1666 (C=O)	7.20-8.10 (5 H, broad, aryl CH), 7.27 (5 H, s, aryl CH), 4.40 (1 H, qu, J = 9.0 Hz, O-CH), 2.95 (1 H, s, OH), ^a 2.70-3.12 (4 H, m, aliphatic CH)	C, 79.84; H, 6.69 (79.97) (6.71)
21		3455 (OH) 1720 (C=O)	7.32 (5 H, s, aryl CH), 3.70-4.00 (2 H, m, aliphatic CH), 2.67 (1 H, s, OH), ^a 1.97 (3 H, s, COCH ₃), 1.43 (1 H, m, aliphatic CH), 0.86 (6 H, d, J = 5.0 Hz, CH ₃)	C, 75.90; H, 8.83 (75.69) (8.80)
22, threo		3430 (OH) 1725 1718 (C=O) 1708	7.21 (5 H, s, aryl CH), 4.10-4.65 (1 H, m, O-CH), 3.94 (1 H, s, OH), ^a 3.65 (1 H, d, J = 9.5 Hz, CH), 2.06 (3 H, s, COCH ₃), 0.95 (3 H, d, J = 6.0 Hz, CH ₃)	C, 74.49; H, 7.92 (74.13) (7.92)
erythro		3450 (OH) 1714 (C=O)	7.19 (5 H, aryl CH), 4.25 (1 H, qu, J = 6.10 Hz, O-CH), 3.50 (1 H, d, J = 6.10 Hz, CH), 1.94 (3 H, s, COCH ₃), 1.04 (3 H, d, J = 6.0 Hz, CH ₃)	C, 74.49; H, 7.91 (74.13) (7.92)
23		3500 (OH) 1718 (C=O) 1700	7.30 (5 H, s, aryl CH), 4.14 (1 H, s, OH), ^a 3.75 (1 H, s, CH), 2.03 (3 H, s, COCH ₃), 1.27 (3 H, s, CH ₃), 1.03 (3 H, s, CH ₃)	

Table V (continued)

Product	Physical property	Ir, cm ⁻¹	Nmr, δ	Anal. Found, % (calcd)
24, threo	Mp 101–102°	3470 (OH) 1692 (C=O)	7.32 (5 H, s, aryl CH), 7.23 (5 H, s, aryl CH), 4.43 (1 H, m, O-CH), 3.75 (1 H, d, $J = 9.0$ Hz, COCH), 3.49 (1 H, broad, OH), ^a 2.53 (2 H, t, $J = 4.4$ Hz), 2.07 (3 H, s, CH ₃)	C, 80.11; H, 7.19 (80.28) (7.13)
erythro		3455 (OH) 1710 (C=O) 1703	7.20 (5 H, s, aryl CH), 7.15 (5 H, s, aryl CH), 4.41 (1 H, q, $J = 6.0$ Hz, O-CH), 3.58 (1 H, d, $J = 6.0$ Hz, CH), 2.76 (1 H, s, OH), ^a 2.56 (2 H, d, $J = 6.0$ Hz, CH ₂), 1.85 (3 H, s, CH ₃)	C, 80.30; H, 7.22 (80.28) (7.13)

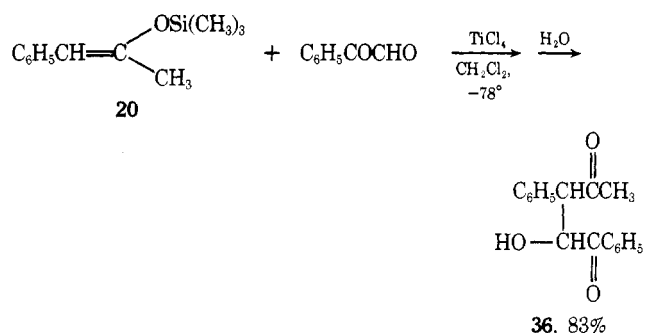
^a Exchanged with D₂O.

reacted with benzaldehyde in the presence of titanium tetrachloride at -78° to give four stereoisomers. Axial erythro, equatorial threo, equatorial erythro, and axial threo 2-(1'-hydroxybenzyl)-6-methyl-1-cyclohexanone (**35a-d**) were obtained in a total yield of 81%. In all cases, the addition reactions of silyl enol ethers of unsymmetrical ketones, such as phenylacetone and 2-methyl-1-cyclohexanone, take place regiospecifically at the olefinic position derived from the silyl enol ether.

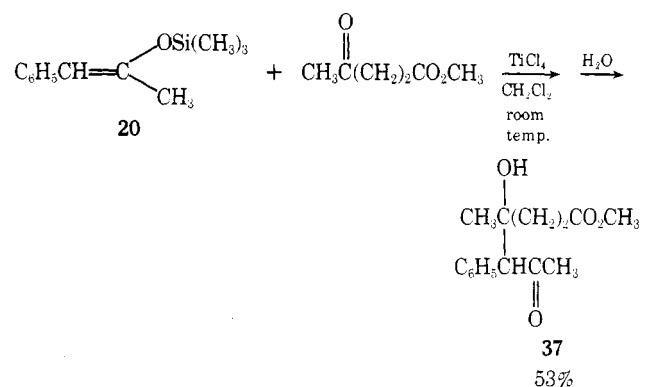


Furthermore, the selectivity of the reaction with respect to functional groups was examined by the use of carbonyl compounds with two different carbonyl groups, such as aldehyde, ketone, or ester,¹⁰ in the same molecule. When 1-phenyl-2-trimethylsilyloxy-1-propene (**20**) was allowed to react with an equimolar amount of phenylglyoxal at -78° for 2 hr, 1,3-diphenyl-1,4-dioxo-2-hydroxypentane (**36**) was obtained exclusively in 83% yield, and none of the addition product to the ketone function was detected.

In similar fashion, a mixture of 1 equiv of methyl levulinate and 1 equiv of titanium tetrachloride was treated with



1 equiv of 1-phenyl-2-trimethylsilyloxy-1-propene (**20**) at room temperature, and methyl 3-hydroxy-3-methyl-4-phenylheptanoate (**37**) was obtained in 53% yield and 23% of the methyl levulinate was recovered unreacted.



It was apparent that the reaction of silyl enol ethers with aldehyde proceeds more rapidly than with ketone or ester. Therefore, when aldehyde and ketone functions coexist in a molecule, the silyl enol ether selectively reacts with the aldehyde function in preference to the ketone in the presence of titanium tetrachloride at -78° . When ketone and ester functions coexist, the silyl enol ether reacts only with the ketone function at room temperature.

In conclusion, it is noted that all the common aldehydes or ketones are strongly activated by titanium tetrachloride, and the cross-aldol addition products are obtained in excellent yields by the reaction with various silyl enol ethers. Further, the regiospecific additions take place at the olefinic position of silyl enol ethers.

Experimental Section

Materials. Commercially available TiCl_4 , SnCl_4 , BCl_3 , ($n\text{-C}_4\text{H}_9$)₃ SnCl , and $\text{Et}_2\text{O} \cdot \text{BF}_3$ were distilled under an argon atmosphere before use. Anhydrous AlCl_3 was used without purification, and FeCl_3 , ZnCl_2 , MgCl_2 , CdCl_2 , and LiCl were dried over phosphorus pentoxide *in vacuo* at $110\text{--}220^\circ$.

Trimethylsilyl enol ethers of carbonyl compounds, 1-trimethylsilyloxy-1-cyclohexene (**1**), 1-trimethylsilyloxy-1-cyclopentene (**5**), 1-phenyl-1-trimethylsilyloxyethylene (**15**), 1-phenyl-2-trimethylsilyloxy-1-propene (**20**), 1-methyl-2-trimethylsilyloxy-1-cyclohex-

ene (**32**), and 3-methyl-2-trimethylsilyloxy-1-cyclohexene (**34**), were prepared according to the procedures in the literature⁶ and purified by distillation: **1**, bp 73–74° (20 mm) [lit. bp 74–75° (20 mm)]; **5**, bp 158–159° (760 mm) [lit. bp 158–159° (760 mm)]; **15**, bp 89–91° (12 mm) [lit. bp 89–91° (12 mm)]; **20**, bp 105–106° (10 mm) [lit. bp 106° (10 mm)]; **32**, bp 105–106° (45.5 mm) [lit. bp 101–102° (45 mm)]; **34**, bp 101–102° (44 mm) [lit. bp 59–61° (7 mm)]. In a similar manner, 2-methyl-1-trimethylsilyloxy-1-propene (**26**) and 3-phenyl-1-trimethylsilyloxy-1-propene (**29**) were prepared from the corresponding aldehydes, trimethylsilyl chloride, and triethylamine, and the physical data are as follows. **26**: bp 118–119° (760 mm); ir 1654 (C=C) cm^{-1} ; nmr (CCl_4) δ 5.97 (1 H, m, vinyl CH), 1.55 (6 H, s, CH_3), 0.16 (9 H, s, $\text{Si}(\text{CH}_3)_3$). **29** (cis and trans mixture): bp 119–121° (20 mm); ir 1655 (C=C) cm^{-1} ; nmr (CCl_4) δ 7.14 (5 H, s, aryl CH), 6.31 (0.6 H, m, vinyl CH), 5.01 (0.4 H, m, vinyl CH), 3.50 (1.2 H, d, $J = 7.0$ Hz, CH_2), 3.18 (0.8 H, d, $J = 7.0$ Hz, CH_2), 0.20 (9 H, s, $\text{Si}(\text{CH}_3)_3$).

Reaction of 1-Trimethylsilyloxy-1-cyclohexene (1) with Benzaldehyde. A methylene chloride (10 ml) solution of 0.426 g (2.5 mmol) of **1** was added dropwise into a mixture of 0.292 g (2.75 mmol) of benzaldehyde and 0.55 g (2.75 mmol) of TiCl_4 in dry methylene chloride (20 ml) under an argon atmosphere at -78° , and the reaction mixture was stirred for 1 hr. After hydrolysis at that temperature, the resulting organic layer was extracted with ether, and the extract was washed with water and dried over anhydrous Na_2SO_4 . The mixture was condensed under reduced pressure, and the residue was purified by column chromatography (silica gel). Elution with methylene chloride afforded 115 mg (23%) of *erythro*-2-(1'-hydroxybenzyl)-1-cyclohexanone (**2**): mp 103° (recrystallized from 2-propanol: mp 103.5–104.5° [lit. 102°, 102–103°]³); ir 3530 (OH), 1700 (C=O) cm^{-1} ; nmr (CDCl_3) δ 7.27 (5 H, s, aryl CH), 5.40 (1 H, d, $J = 2.5$ Hz, O-CH), 3.05 (1 H, s, OH, exchanged with D_2O), 1.1–2.7 (9 H, broad, aliphatic CH).

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C, 76.44; H, 7.90. Found: C, 76.42; H, 7.58.

From the last fraction, 346 mg (69%) of *threo*-2 was obtained: mp 74° (recrystallized from *n*-hexane-ether: mp 75° [lit.³ 71–74°]); ir 3495 (OH), 1695 (C=O) cm^{-1} ; nmr (CCl_4) δ 7.29 (5 H, s, aryl CH), 4.83 (1 H, d, $J = 9.0$ Hz, O-CH), 3.77 (1 H, s, OH, exchanged with D_2O), 1.1–2.9 (9 H, broad, aliphatic CH).

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: C, 76.44; H, 7.90. Found: C, 76.46; H, 7.85.

The reactions of silyl enol ethers, such as 1-trimethylsilyloxy-1-cyclohexene (**1**), 1-trimethylsilyloxy-1-cyclopentene (**5**), 1-phenyl-1-trimethylsilyloxyethylene (**15**), and 1-phenyl-2-trimethylsilyloxy-1-propene (**20**), with various carbonyl compounds were carried out according to the same procedure, and the reaction conditions and the yields of the corresponding aldols are listed in Table IV. The physical properties and analytical data of the products are shown in Table V.

Stereochemistry of Aldol Products. The *threo* and *erythro* isomers of aldols could be separated by column chromatography (silica gel), and the stereochemistry of the isomers was assigned on the basis of nmr spectra (shown in Table VI). Each of the isomers of **2**,

Table VI. Nmr Signals of Methylene Protons in Aldols

Compd	H_a	H_b	J_{ab} , Hz	Solvent
2 , <i>threo</i>	4.83		9.0	CDCl_3
<i>erythro</i>	5.40		2.5	CDCl_3
6 , <i>threo</i>	4.00		6.5	CCl_4
<i>erythro</i>	3.51		6.0	CCl_4
13 , <i>threo</i>	4.68		9.0	CCl_4
<i>erythro</i>	5.16		2.0	CCl_4
14 , <i>threo</i>	4.36	2.78	8.0	CCl_4
<i>erythro</i>	3.85		6.0	CCl_4
22 , <i>threo</i>	4.38	3.65	9.5	CCl_4
<i>erythro</i>	4.25	3.50	6.1	CCl_4
24 , <i>threo</i>	4.43	3.70	9.0	CCl_4
<i>erythro</i>	4.40	3.43	6.0	CCl_4

6, **13**, **14**, **22**, and **24** has an absorption due to the proton (H_a) of the O-CH group or the other tertiary hydrogen (H_b), and the comparison of the coupling constant (J_{ab}) of the isomers suggests the assigned stereochemistry.^{6,7}

Reaction of 1-Trimethylsilyloxy-1-cyclohexene (1) with Benzaldehyde in the Presence of Various Metal Salts. Into a mixture of a metal salt (2.75 mmol) and 0.292 g (2.75 mmol) of benzaldehyde in methylene chloride (20 ml) was added a methylene chloride (10 ml) solution of 0.426 g (2.5 mmol) of **1**. The reaction mixture was worked up as described above and purified by preparative tlc (silica gel) using methylene chloride as a developing solvent. The ratio of the *threo*- and *erythro*-**2** was determined by nmr, and the results are listed in Table I.

Reaction of 1-Phenyl-2-trimethylsilyloxy-1-propene (20) with Trioxane. To a methylene chloride (20 ml) solution trioxane (0.225 g, 2.5 mmol) and TiCl_4 (1.4 g, 7.5 mmol) was added dropwise a methylene chloride (10 ml) solution of **20** (0.515 g, 2.5 mmol) at -78° , and the reaction mixture was stirred for 2 hr at that temperature. According to the similar procedure as the above 260 mg (62%) of 4-hydroxy-3-phenyl-2-butanone (**25**) was obtained by column chromatography (silica gel) using methylene chloride as eluent: ir 3400 (OH), 1720 (C=O) cm^{-1} ; nmr (CCl_4) δ 7.21 (5 H, s, aryl CH), 4.93 (1 H, s, OH), 3.4–4.3 (4 H, m, CH_2), 2.02 (3 H, s, COCH_3).

Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 73.14; H, 7.37. Found: C, 72.96; H, 7.23.

Reactions of 2-Methyl-1-trimethylsilyloxy-1-propene (26) with Aldehydes. To a methylene chloride (20 ml) solution of phenylacetaldehyde (0.33 g, 2.75 mmol) and TiCl_4 (0.55 g, 2.75 mmol) was added a methylene chloride (10 ml) solution of **26** (0.36 g, 2.5 mmol) at -78° , and the reaction mixture was stirred for 1 hr at that temperature. After the usual work-up, the resulting mixture was chromatographed on silica gel (deactivated by water). Elution with methylene chloride afforded a trace amount of an unidentified product and 434 mg (86%) of 2,2-dimethyl-3-hydroxy-4-phenylbutyraldehyde (**27**): ir 3410 (OH), 1718 (C=O) cm^{-1} ; nmr (CCl_4) δ 9.50 (1 H, s, CHO), 7.21 (5 H, s, aryl CH), 3.86 (1 H, d, $J = 10.0$ Hz, $J = 4.0$ Hz, O-CH), 2.67 (2 H, d, $J = 4.0$ Hz, CH_2), 2.60 (1 H, broad, OH), 1.10 (6 H, d, $J = 2.0$ Hz, $(\text{CH}_3)_2$).

Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$: C, 74.97; H, 8.39. Found: C, 75.18; H, 8.61.

Similarly, the reaction of β -phenylpropionaldehyde (0.37 g, 2.75 mmol) and **26** (0.361 g, 2.5 mmol) in the presence of TiCl_4 (0.55 g, 2.75 mmol) gave 490 mg (95%) of 2,2-dimethyl-3-hydroxy-5-phenylvaleraldehyde (**28**): ir 3400 (OH), 1720 (C=O) cm^{-1} ; nmr (CCl_4) δ 9.42 (1 H, s, CHO), 7.13 (5 H, s, aryl CH), 3.61 (1 H, s, OH), 3.53 (1 H, q, $J = 5.0$ Hz, O-CH), 2.4–3.0 (2 H, broad, CH_2), 1.67 (2 H, t, $J = 8.0$ Hz, CH_2), 0.7–1.0 (6 H, m, $(\text{CH}_3)_2$).

Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.69; H, 8.80. Found: C, 76.06; H, 8.65.

Reaction of 3-Phenyl-1-trimethylsilyloxy-1-propene (29) with *n*-Butyraldehyde. According to the same procedure as the above, *n*-butyraldehyde (0.20 g, 2.75 mmol) reacted with **29** (0.515 g, 2.5 mmol) in methylene chloride (30 ml) in the presence of TiCl_4 (0.55 g, 2.75 mmol) at -78° for 1 hr. After hydrolysis, the resulting organic layer was extracted with ether-benzene mixture, washed with water, and dried over anhydrous Na_2SO_4 . The extract was condensed, and the residue was heated to reflux with *p*-toluenesulfonic acid (0.2 g) in dry benzene (30 ml) with a conventional Dean Stark apparatus. The resulting crude product was chromatographed on silica gel (deactivated with water). Elution with benzene gave 358 mg (76%) of 2-benzyl-2-hexenal (**31**): ir 1683 (C=O), 1635 (C=C) cm^{-1} ; nmr (CCl_4) δ 9.39 (1 H, s, CHO), 7.10 (5 H, s, aryl CH), 6.43 (1 H, t, $J = 8.0$ Hz, vinyl CH), 3.56 (2 H, s, CH_2), 2.36 (2 H, q, $J = 8.0$ Hz, CH_2), 1.46 (2 H, m, CH_2), 0.92 (3 H, t, $J = 6.0$ Hz, CH_3).

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: C, 82.93; H, 8.57. Found: C, 82.52; H, 9.01.

Reaction of 1-Methyl-2-trimethylsilyloxy-1-cyclohexene (32) or 3-Methyl-2-trimethylsilyloxy-1-cyclohexene (34) with Benzaldehyde. Into a methylene chloride (20 ml) solution of 0.291 g (2.75 mmol) of benzaldehyde and 0.48 g (2.5 mmol) of TiCl_4 was added a methylene chloride (10 ml) solution of 0.45 g (2.5 mmol) of **32** at -78° . The reaction mixture was stirred at room temperature for 30 min and then quenched with water. The resulting substance was chromatographed on silica gel. From the benzene eluent, 49 mg of benzaldehyde was recovered. The rest was eluted with *n*-hexane-ether (5:1) mixture. The first fraction was 80 mg (15%) of 2-(1'-hydroxybenzyl)-2-methyl-1-cyclohexanone (**33a**): nmr (CDCl_3) δ 7.19 (5 H, s, aryl CH), 4.96 (1 H, s, O-CH), 3.00 (1 H, s, OH),

1.0–2.5 (8 H, broad, aliphatic CH), 0.98 (3 H, s, CH₃). The second fraction was 102 mg (19%) of the mixture of **33a** and **33b** [**33a**:**33b** = 3:1 on the basis of the relative intensities of the benzylic proton absorptions at δ 4.96 (**33a**) and 4.85 (**33b**)]. The last fraction was 131 mg (24%) of 2-(1'-hydroxybenzyl)-2-methyl-1-cyclohexanone (**33b**): nmr (CCl₄) δ 7.20 (5 H, s, aryl CH), 4.85 (1 H, s, O-CH), 3.75 (1 H, s, OH), 1.0–2.6 (8 H, broad, aliphatic CH), 1.05 (3 H, s, CH₃).

A methylene chloride (10 ml) solution of 0.45 g (2.5 mmol) of **34** was added to a mixture of 0.29 g (2.75 mmol) of benzaldehyde and 0.55 g (2.75 mmol) of TiCl₄ in methylene chloride (20 ml), and the reaction mixture was stirred at -78° for 15 min. After usual work-up, purification by column chromatography (silica gel) using petroleum ether–ether (5:2) mixture as a developer gave four aldol isomers. The fraction eluted first was 13 mg (2%) of axial *erythro*-2-(1'-hydroxybenzyl)-6-methyl-1-cyclohexanone (**35a**): nmr (CCl₄) δ 7.12 (5 H, s, aryl CH), 5.26 (1 H, d, J = 2.0 Hz, O-CH), 2.92 (1 H, broad, OH), 1.2–2.7 (8 H, broad, aliphatic CH), 1.01 (3 H, d, J = 6.0 Hz, CH₃). The second fraction was 107 mg (20%) of the mixture of equatorial *threo*- and equatorial *erythro*-**35** (**35b** and **c**): nmr (CCl₄) δ 7.20 (5 H, s, aryl CH), 5.12 (0.6 H, d, J = 5.0 Hz, O-CH), 4.65 (0.4 H, d, J = 8.0 Hz, O-CH), 1.05 (1.8 H, d, J = 5.5 Hz, CH₃), 0.94 (1.2 H, d, J = 4.0 Hz, CH₃). The last fraction was 301 mg (55%) of axial *threo*-**35** (**35d**): mp 88.5–90.0° (recrystallized from ethanol); nmr (CCl₄) δ 7.23 (5 H, s, aryl CH), 3.60 (1 H, broad, OH), 1.2–2.8 (8 H, broad, aliphatic CH), 1.07 (3 H, d, J = 7.0 Hz, CH₃).

Anal. Calcd for C₁₄H₁₈O₂: C, 77.03; H, 8.31. Found: C, 77.03; H, 8.15.

Reaction of 1-Phenyl-2-trimethylsilyloxy-1-propene (20) with Phenylglyoxal. To a mixture of phenylglyoxal (0.37 g, 2.75 mmol) and TiCl₄ (0.55 g, 2.75 mmol) in methylene chloride (20 ml), a methylene chloride (10 ml) solution of **20** (0.502 g, 2.5 mmol) was added dropwise at -78° . After stirring for 1 hr at that temperature, the reaction mixture was quenched with water and extracted with ether. The ether layer was washed with water and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the crude oil was purified by column chromatography (silica gel). Elution with methylene chloride gave 583 mg (85%) of 3,5-diphenyl-4-hydroxypentane-2,5-dione (*threo* and *erythro* mixture) (**36**) as an oil: ir 3430 (OH), 1720, 1685 (C=O) cm⁻¹; nmr (CCl₄) δ 7.10–8.10 (10 H, broad, aryl CH), 5.61 (0.5 H, d, J = 7.0 Hz, O-CH), 5.23 (0.5 H, d, J = 6.0 Hz, O-CH), 4.17 (0.5 H, d, 0.6 Hz, COCH), 4.10 (0.5 H, d, J = 7.0 Hz, COCH), 2.08 (1.5 H, s, CH₃), 2.03 (1.5 H, s, CH₃). A mixture of 2-propanol (5 ml) and *n*-hexane (1 ml) was added to 583 mg of oil **36**, and a white

precipitate was deposited. The precipitate was isolated by filtration to afford 231 mg of only *erythro*-**36**: mp 98° (recrystallized from 2-propanol and *n*-hexane); ir 3430 (OH), 1720, 1687 (C=O) cm⁻¹; nmr (CDCl₃) δ 7.1–8.1 (10 H, broad, aryl CH), 5.23 (1 H, d, J = 6.0 Hz, O-CH), 4.39 (1 H, s, OH), 4.17 (1 H, d, J = 6.0 Hz, COCH), 2.03 (3 H, s, COCH₃).

Anal. Calcd for C₁₇H₁₆O₃: C, 76.10; H, 6.01. Found: C, 75.78; H, 6.43.

Reaction of 1-Phenyl-2-trimethylsilyloxy-1-propene (20) with Methyl Levulinate. To a mixture of methyl levulinate (0.35 g, 2.75 mmol) and TiCl₄ (0.55 g, 2.75 mmol) in methylene chloride (20 ml), a methylene chloride (10 ml) solution of **20** (0.502 g, 2.5 mmol) was added at room temperature, and the reaction mixture was stirred at room temperature for 2 hr. After hydrolysis, the resulting mixture was purified by column chromatography (silica gel). From methylene chloride eluent, 77 mg of methyl levulinate was recovered, and then 384 mg (58%) of methyl 4-hydroxy-4-methyl-5-phenyl-6-oxoheptanoate (**37**) was obtained: ir 3550 (OH), 1740, 1720 (C=O) cm⁻¹; nmr (CCl₄) δ 3.73 (1 H, s, OH), 3.55 (1 H, s, CH), 2.05 (3 H, s, COCH₃), 1.4–2.7 (4 H, m, (CH₂)₂), 0.90 (3 H, s, CH₃).

Anal. Calcd for C₁₅H₂₀O₄: C, 68.16; H, 7.63. Found: C, 68.64; H, 7.88.

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