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STEREOCONTROLLED SYNTHESIS OF α,β-UNSATURATED CARBOXYLIC ESTERS FROM O-METHYL-C,O-BIS(TRIMETHYLSILYL)KETENE ACETAL AND ALIPHATIC ALDEHYDES

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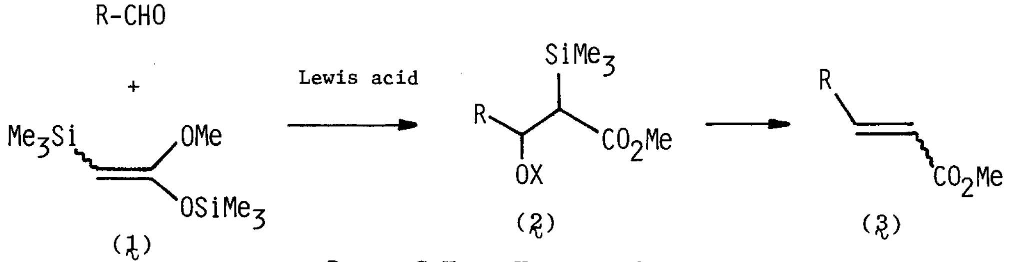
Summary: (*R**,*S**) Selective aldol type reaction of O-methyl-C,O-bis(trimethylsilyl)ketene acetal (**1**) with aldehydes and stereoselective formation of α,β-unsaturated carboxylic esters are attained by the combination of *Z*-**1** and Lewis acids.

One of the most versatile methods to *E* selective synthesis of α,β-unsaturated carboxylic esters is the Wadsworth-Wittig-Horner type reaction[1] which is controlled thermodynamically. Alkyl trimethylsilylacetate carbanion is also used as a highly reactive condensation reagent with carbonyl compounds.[2, 3] But the stereocontrol of the reactions is almost impossible. From the viewpoint of synthetic utility, it is desirable to obtain each isomer selectively from an identical starting material by stereocontrolled reaction.

It is reported that O-(trimethylsilyl)ketene acetals react readily with carbonyl compounds to give aldol type products in the presence of $TiCl_4$.[4] We recently reported the smooth Michael type addition of ketene acetal **1** to α,β-unsaturated ketones by the assist of $TiCl_4$.[5, 6] If ketene acetal **1** could react with carbonyl compounds to give aldol products, it would be utilized for the



a, R = n-C_8H_{17}; X = H
b, R = n-C_6H_{13}; X = H
c, R = iso-C_3H_7; X = H
d, R = Ph; X = H
e, R = n-C_8H_{17}; X = MCl_n or Me_3Si

stereoselective synthesis of **3** because of the possibility to control the stereochemistry in the reaction sequence, aldol type addition and elimination steps. We report herein a stereocontrolled synthesis of methyl dodec-2-enoate **3a** in the one pot reaction of **1** with nonanal by the selection of Lewis acid as an activating agent.

To an equimolar mixture of nonanal and $TiCl_4$ in CH_2Cl_2 was added dropwisely a CH_2Cl_2 solution of ketene acetal **1** (E:Z = 3:1) at -78°C. After the similar procedure reported by Mukaiyama,[4] aldol type product **2a** was isolated in 91% yield as the mixture of two diastereomers [($2R^*$,$3S$):($2R^*$,$3R^*$) = 3:1].[7, 8] The relative configuration of isolated each isomer of **2a** was deduced from the geometry of **3a** which was formed by the *anti* elimination of Me_3SiOH in the interaction of each isomer with $BF_3\cdot Et_2O$.[9] The analogous aldol products **2b**[8] [98%, ($2R^*$,$3S^*$):($2R^*$,$3R^*$) = 3:1], **2c**[8] [75%, ($2R^*$,$3S^*$):($2R^*$,$3R^*$) = 4:1], and **2d**[8] [96%, ($2R^*$,$3S^*$):($2R^*$,$3R^*$) = >95:<5] were obtained by the reaction of **1** with the corresponding aldehydes.

Although stereoselective synthesis of **3** is accomplished by the elimination reaction from each isolated pure diastereomer of **2**, it is desirable to obtain **3** directly from **1** and aldehydes. α,β-Unsaturated esters **3** were isolated directly in the reaction of **1** with aldehydes by the assist of an equivalent of Lewis acid under the appropriate condition. The results obtained in the case of nonanal are summarized in Table 1 as a typical example. The drastic variation of the E/Z ratio in **3a** from 14/86 ($TiCl_4$) to 93/7 ($AlCl_3$) is observed by the selection of Lewis acid.

Table 1. Effect of Lewis acid in the direct synthesis of **3a** from **1** and nonanal.

Lewis acid	Solvent	Condition	**3a**	
			Yield (%)[a]	E:Z[b]
$TiCl_4$	CH_2Cl_2	-95°C 3h → rt 2h	91	14:86
$TiCl_4$	CH_2Cl_2	rt 3h	82	27:73
$TiCl_4$	CH_2Cl_2	-78°C 3h → rt 2h	90	5:95[c]
$BF_3\cdot Et_2O$	CH_2Cl_2	-95°C 3h → rt 2h	90	23:77
$AlCl_3$	C_6H_6	reflux 8h	70	89:11
$AlCl_3$	CCl_4	reflux 8h	89[d]	93:7
$AlCl_3$	CCl_4	reflux 8h	75[d]	96:4[c]
$ZnCl_2$	C_6H_6/THF	reflux 6h	56[e]	96:4
$ZnCl_2$	Toluene/THF	reflux 22h	92	69:31

[a] Isolated yield. [b] Determined by GLC (SE-30). [c] Z rich (E:Z = 5:95) **1** was used, otherwise E rich (E:Z = 3:1) **1** was used. [d] Two moles of **1** was used.
[e] 20% of ($2R^*$,$3R^*$) **2a** was isolated.

Table 2. Stereoselectivity of Me_3SiOH elimination from **2a**.

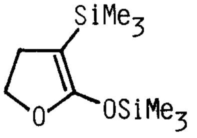
Diastereomer of **2a**	Lewis acid	Condition	**3a**	
			Yield (%)^a	E:Z^b
$(2R^*,3S^*)$	$TiCl_4$	CH_2Cl_2/rt/1h	93	2:98
$(2R^*,3R^*)$	$TiCl_4$	CH_2Cl_2/rt/1h	97	99:1
$(2R^*,3S^*)$	$AlCl_3$	CCl_4/reflux/6h	78	89:11
$(2R^*,3R^*)$	$AlCl_3$	CCl_4/reflux/6h	73	80:20

^{a}Isolated yield. ^{b}Determined by GLC (SE-30).

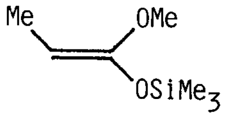
The elimination of Me_3SiOX is highly regulated to *anti* manner in the case of $TiCl_4$. On the other hand, the result with $AlCl_3$ seems to be controlled by the opposite manner of elimination in each isomer of **2e**, *syn* manner for $(2R^*,3S^*)$ **2e** and *anti* manner for $(2R^*,3R^*)$ **2e**. These deduction are based on the other elimination reactions from the isolated respective diastereomers of **2a** by the interaction of $TiCl_4$ or $AlCl_3$. The results are summarized in Table 2.

The results in Table 2 show that the geometrical ratio of **3a** reflects the diastereomerical ratio of **2e** in the case of $TiCl_4$. Thus, the higher $(2R^*,3S^*)$ selectivity in aldol reaction secures the higher Z selectivity of **3a**. Since the stereochemistry of aldol reactions is affected by the geometry of enolate anion,[10] Z selective **1** (E:Z = 5:95) was prepared by the addition of 18% HMPTA to THF,[11, 12] and served to the reaction with nonanal. Remarkable $(2R^*,3S^*)$ selectivity $[(2R^*,3S^*):(2R^*,3R^*) = 95:5]$ was observed in $TiCl_4$ assisted aldol reaction at -78°C. This result is consistent with the (R^*,S^*) preference of γ-lactone enolate **4**, in which the relationship between trimethylsiloxy and trimethylsilyl groups is fixed to *cis*.[13] It is interesting that the preferred geometry of **1** (Z) for stereoselective aldol reaction contrast with the result of ketene acetal **5**.[14] Although the cyclic transition state is posturated in $TiCl_4$ assisted aldol reactions,[13, 14] the (R^*,S^*) selective result which is observed regardless of the geometry of **1** would be explained by the participation of the acyclic transition state.[15, 16]

Thus, stereoselective synthesis of **3a** was accomplished in one pot reaction of Z-**1** with nonanal by the selection of Lewis acid, $TiCl_4$ (Z) and $AlCl_3$ (E).



(**4**)



(**5**)

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5. The mixture of stereoisomers (E:Z = 3:1) was obtained in THF solution.
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7. The ratio of $(2R^*,3S^*)$ and $(2R^*,3R^*)$ was determined by the comparison of O-methyl signals in the p.m.r. spectrum of the mixture.
8. All these compounds were isolated by column chromatography (C_6H_6/hexane/AcOEt = 49/49/2) and showed correct values of analyses and corresponding i.r. and p.m.r. spectra, except $(2R^*,3R^*)$ **2d** and **2e**. Spectral data in CCl_4 of **2a** are shown.
   $(2R^*,3S^*)$ **2a**; $\nu_{C=O}$ 1714 cm^{-1}; δ 0.12 (9H, s), 0.89 (3H, t, J=5.5 Hz), 1.3 (14H, m), 2.14 (1H, d, J=7.0 Hz), 2.16 (1H, br.s), 3.61 (3H, s), 4.1 (1H, m).
   $(2R^*,3R^*)$ **2a**; $\nu_{C=O}$ 1702 cm^{-1}; δ 0.12 (9H, s), 0.90 (3H, t, J=5.5 Hz), 1.3 (14H, m), 2.11 (1H, d, J=3.3 Hz), 3.1 (1H, br.s), 3.5 (1H, m), 3.68 (3H, s).
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