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Remote Asymmetric Induction with Vinylketene Silyl *N,O*-Acetal

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In contrast to the well-established methods of controlling acyclic stereochemistry at sites in close proximity to one another (i.e., 1,2- or 1,3-relationships),[1] there are only a limited number of effective methodologies to control stereoselectivity at more remote sites.[2,3] Furthermore, these asymmetric induction procedures often utilize intramolecular chelation with metal species, and development of an effective and general methodology of remote asymmetric induction is a challenging reaction in organic synthesis.[4] In this communication, we describe the highly stereoselective vinylogous Mukaiyama aldol reaction[5,6] using the vinylketene silyl *N,O*-acetals, which provides a efficient and hitherto unprecedented high degree of remote (1,7- and 1,6,7-) asymmetric induction.

During the course of our total synthesis of madindoline A,[7] we developed a efficient method for the stereoselective construction of a chiral quaternary carbon by regio- and stereoselective alkylation of an α,β-unsaturated chiral imide **1**[8] (Scheme 1). A relatively high degree of stereocontrol (∼10:1) can be achieved by both the initial stereoselective formation of *E*-*O*-enolate **2** and the diastereoselective alkylation of **2**. The stereochemistry of an intermediary dienolate anion **2** was established by treatment with TBSCl to obtain **4** in 90% yield. The fact that **4** was isolated as a single isomer prompted us to examine vinylogous Mukaiyama aldol reaction using **4** with remote asymmetric induction in mind. Furthermore, the vinylketene silyl *N,O*-acetal was unknown, and the reactivity and stereochemical behavior of **4** was of interest.

First, we examined the reaction of **4** and hexanal, as a model aldehyde, in the presence of a Lewis acid. We found $TiCl_4$ to be most effective in terms of both yield and stereoselectivity.[9] The reaction took place only at the γ-position, affording δ-hydroxy-α-methyl-α,β-unsaturated imide **5a** in 97% yield with 42:1 diastereoselectivity. The stereochemistry at the newly formed chiral center was determined by comparison to the known compound.[10]

There are a few precedents for C−C bond formation with such a high degree of remote 1,7-asymmetric induction in an acyclic system.[2] Table 1 summarizes the results with other typical aldehydes. Excellent diastereoselectivity was achieved using aliphatic aldehydes (entries 1−3), whereas the reaction with conjugated aldehydes, such as crotonaldehyde and 2-methyl-2-pentenal, gave moderate yield and high selectivity (entries 4 and 5). Stereochemistry of major isomers was determined by the modified Mosher's method[11] except for the case of benzaldehyde.[12]

The α,β-unsaturated imide **6**, derived from crotonic acid, was transformed into the vinylketene silyl *N,O*-acetal **7** using a method similar to that for **1**. (Scheme 2) The stereochemistry of **7** was established as *Z*-*O*-enolate by NOE experiments (Figure 1). The $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction of silyl acetal **7** and hexanal was then carried out to obtain the aldol adduct **8** in 38% yield with 4:1 diastereoselectivity. The low yield was probably due to the relative instability of **7** under acidic conditions. The stereochemistry of **8**, determined by the modified Mosher's method,

Scheme 1. Stereoselective Formation of Vinylketene Silyl *N,O*-Acetal **4**

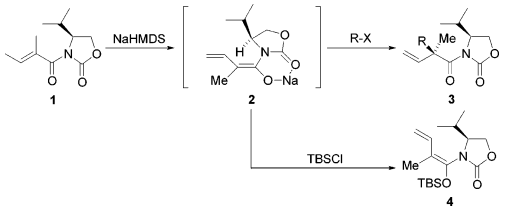
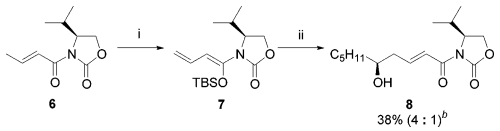


Table 1. Vinylogous Mukaiyama Aldol Reaction with Vinylketene Silyl *N,O*-Acetal **4**

entry	R	product	yield (%)	d.s.[c]
1	$CH_3(CH_2)_4$	**5a**	97	42:1
2	$CH_3(CH_2)_{10}$	**5b**	92	94:1
3	$(CH_3)_2CH$	**5c**	95	40:1
4	(*E*)-CH_3CH═CH	**5d**	54 (87[b])	20:1
5	(*E*)-CH_3CH_2CH═$C(CH_3)$	**5e**	55 (65[b])	86:1
6	Ph	**5f**	94	30:1

[a] 1.0 equiv of $TiCl_4$, 2.0 equiv of aldehyde, 1.0 equiv of **4**, 0.1 M in CH_2Cl_2, −78 °C. [b] Conversion yield. [c] Determined by HPLC analysis.

Scheme 2. Vinylogous Mukaiyama Aldol Reaction with Vinylketene Silyl *N,O*-Acetal **7**[a]



[a] Reagents: (i) NaHMDS, TBSCl, THF, −78 °C (63%). (ii) Hexanal, $TiCl_4$, CH_2Cl_2, −78 °C (38%). [b]Determined by ^1H NMR spectroscopy.

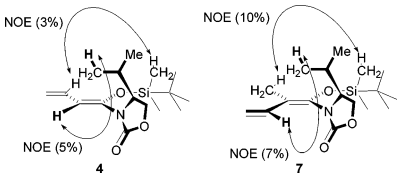


Figure 1. NOE experiments of vinylketene silyl *N,O*-acetal **4** and **7**.

was found to be 5*S*. Interestingly, this stereochemistry is the opposite of that of **5a**.

The methyl group at the α-position is important in achieving a high level of stereoselectivity in the present vinylogous Mukaiyama aldol reaction. We propose the transition states depicted in Figure 2. It is assumed that the oxazolidin-2-one ring is almost perpendicular to the dienol ether plane and that the isopropyl group overhangs the upper face of the dienol ether.[13] The aldehyde presumably approaches from the less hindered side to give the observed stereochemistry (A). The opposite stereochemical behav-

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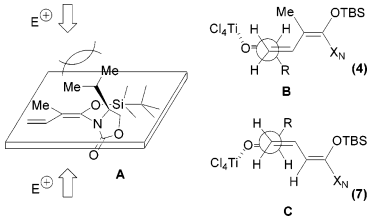
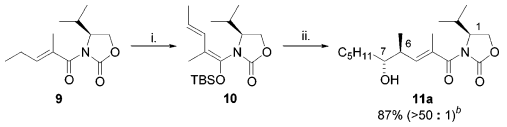


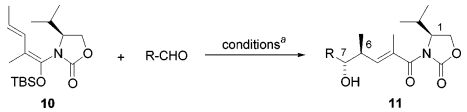
Figure 2. Proposed transition states for the nucleophilic attack of vinylketene silyl *N*,*O*-acetal **4** and **7**.

Scheme 3. Remote 1,6,7-Asymmetric Induction by Vinylogous Mukaiyama Aldol Reaction Using **10**[a]



[a] Reagents: (i) NaHMDS, TBSCl, THF, −78 °C (90%). (ii) Hexanal, $TiCl_4$, CH_2Cl_2, −78 °C (87%). [b] Determined by ^1H NMR spectroscopy.

Table 2. Vinylogous Mukaiyama Aldol Reaction with Vinylketene Silyl *N*,*O*-Acetal **10**



entry	R	temp (°C)	product	yield (%)	d.s.[c]
1	$CH_3(CH_2)_4$	−78	**11a**	87	>50:1
2	$(CH_3)_2CH$	−78	**11b**	99	>50:1
3	(*E*)-$CH_3CH_2CH{=}C(CH_3)$	−78 to −40	**11c**	67 (81[b])	>50:1
4	Ph	−78 to −55	**11d**	90	20:1

[a] 1.0 equiv of $TiCl_4$, 2.0 equiv of aldehyde, 1.0 equiv of **10**, 0.1 M in CH_2Cl_2. [b] Conversion yield. [c] Determined by 400 MHz ^1H NMR spectroscopy.

ior, as well as the difference in the degree of stereoselectivity in the cases of **4** and **7**, can be rationalized by the Newman projection models shown in Figure 2 (B for **4** and C for **7**). In the case of **7**, approach of hexanal from the upper face is not effectively blocked by chiral oxazolidin-2-one because the alkyl group of the aldehyde is located at the opposite site of chiral auxiliary X_N. Consequently, the diastereoselectivity of **7** was lower than that for **4**.

We examined the enol silylation of chiral imide **9**, derived from 2-methyl-2-pentenoic acid, with NaHMDS and TBSCl. The vinylketene silyl *N*,*O*-acetal **10** was isolated in 90% yield as a single isomer. The *E*,*E*-stereochemistry of **10** was established by NOE experiments. The $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction of **10** with hexanal gave the aldol adduct **11a** ($R{=}C_5H_{11}$) in 87% yield as an almost single isomer. The relative as well as absolute stereochemistry of **11a** was established by correlation to the known compound.[14] Results with other aldehydes are summarized in Table 2. In all cases (entries 2−4), we tentatively assumed that the major isomer has anti-stereochemistry. This was confirmed by separate experiments.[15] The excellent stereoselectivity in this strategy with **10** is noteworthy. We assume that the major anti-isomer was formed from transition state D (Figure 3) by analogy to the reaction of **4** (transition state B). Transition state E, which would lead to the syn-isomer, is unfavorable because of interaction between the α-methyl and the R group, as well as the δ-methyl and $TiCl_4$.

In conclusion, we found that the chiral vinylketene silyl *N*,*O*-acetal **4** and **10** underwent a highly regio- and diastereoselective vinylogous Mukaiyama aldol reaction which provides a unique and effective means of controlling remote asymmetric induction. From

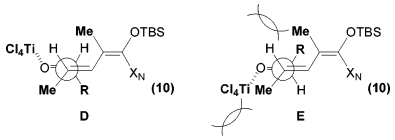


Figure 3. Proposed transition states for the nucleophilic attack of vinylketene silyl *N*,*O*-acetal **10**.

a synthetic point of view, our method using **10** can directly afford the δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl unit that is seen in many polyketide natural products.[16] Further optimization and application of the methodology to the synthesis of biologically interesting natural products are currently under investigation.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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