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An Unprecedented Silver Salt Effect Switches the Facial Selectivity in the Vinylogous Mukaiyama Aldol Reaction

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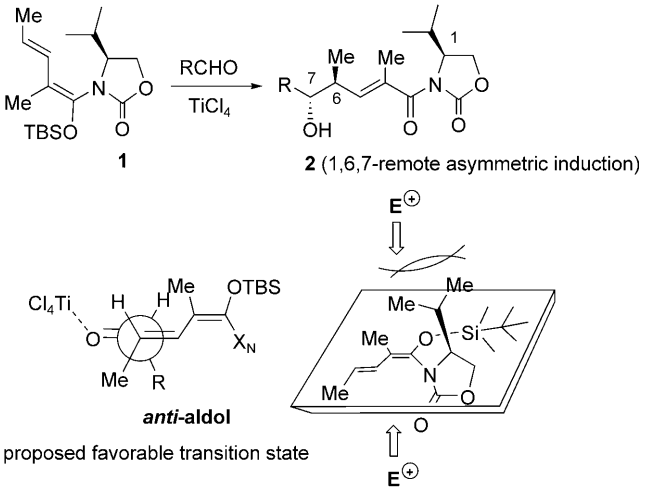
Abstract: Silver hexafluroantimonate was identified as a highly efficient agent to reverse the facial selectivity of the titanium chloride-mediated vinylogous Mukaiyama aldol reaction (VMAR), and this unprecedented reaction provides a concise, diastereoselective synthesis of δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl units from readily available chiral vinylketene silyl *N*,*O*-acetal **6** and ethyl glyoxylate **8**.

Keywords: chiral vinylketene silyl *N*,*O*-acetals; ethyl glyoxylate; silver hexafluroantimonate; titanium chloride-mediated reaction; vinylogous Mukaiyama aldol reaction

Asymmetric aldol reactions have been the subject of intensive synthetic and mechanistic studies because of their importance in the asymmetric construction of carbon-carbon bonds.[1] The vinylogous Mukaiyama aldol reaction (VMAR)[2] developed by Kobayashi and co-workers[3] has emerged as an efficient method for the rapid syntheses of δ-hydroxy-α,γ-dimethyl-α,β-unsaturated unit **2** from chiral vinylketene silyl *N*,*O*-acetal **1** *via* remote asymmetric induction[4] (Scheme 1).

In the context of our recent studies aimed at syntheses of structurally diverse of maytansinoids, we have demonstrated a concise strategy for the formal synthesis of *N*-methylmaysenine, featuring VMAR and RCM reactions as key steps (Figure 1).[5] In this synthesis, the key intermediate **5** with an adjacent methyl-hydroxy *syn*-stereochemical motif was made *via* VMAR by using vinylketene silyl *N*,*O*-acetal **6** and β-dithiane-substituted aldehyde **7** as substratres.

As a potent antimitotic agent, maytansine was extensively evaluated in human clinical trials, but its clinical advancement was hampered by its poor therapeutic index *in vivo*.[6] Stimulated by our interest in the unusual biological properties of maytansinoids, together with their structurally intriguing architectures, we therefore initiated a program for a combinatorial synthesis of maytansinoids, and hoped that such a library would find its utilization in the improvement of the therapeutic index of maytansinoids through profiling their SAR. However, the early study in this program has been impeded by lack of simple and stereo-



Scheme 1. Kobayashi's remote asymmetric induction.

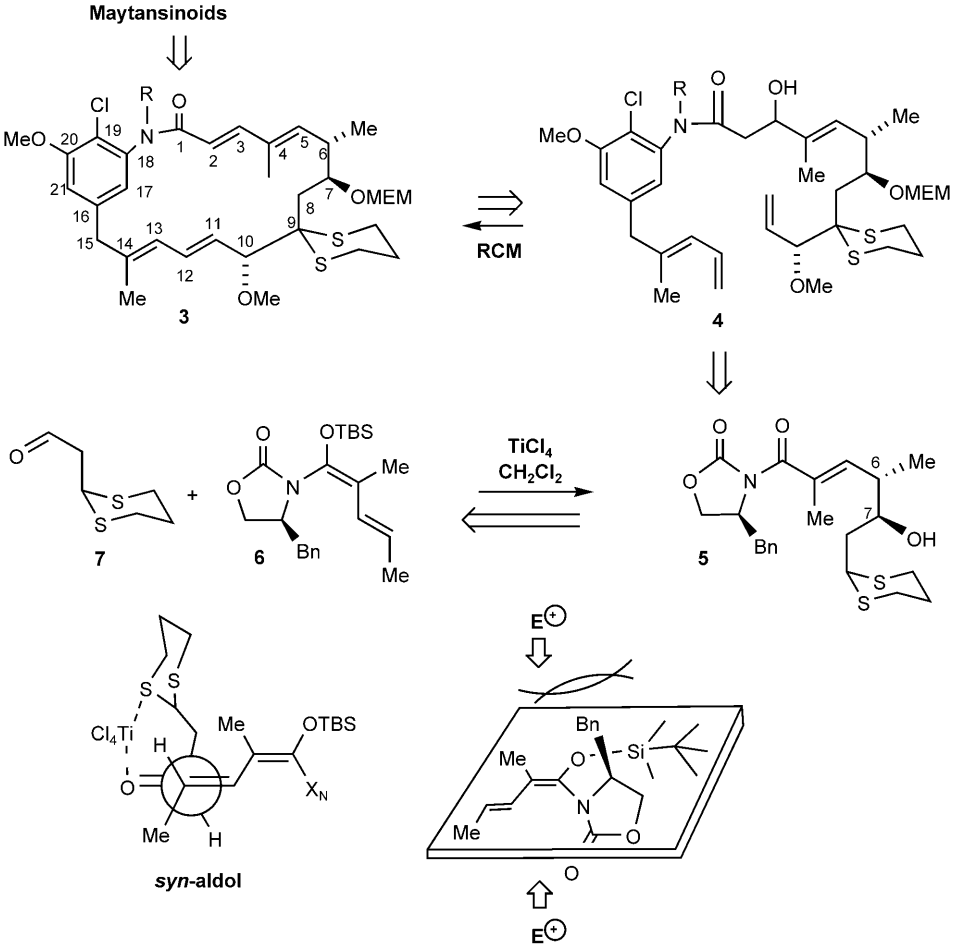


Figure 1. Rationale for the synthesis of maytansinoids.

selective methods for the synthesis of the δ-hydroxy-α,γ-dimethyl-α,β-unsaturated units.

The use of chlorotitanium enolates of thiazolidinethione as chiral auxiliaries to synthesize either "Evans" or "non-Evans" *syn*-aldol products with high diastereoselectivity by changing the stoichiometry and nature of the amine base has been described by Crimmins and his co-workers.[7] However, a method for the highly stereoselective synthesis of "Kobayashi" or "non-Kobayashi" *anti*-aldol products *via* VMAR has not been reported yet. In this communication, we wish to report that $AgSbF_6$ can completely switch the facial selectivity of Kobayashi's VMAR adducts **9** and **10** (Table 1) when vinylketene silyl *N,O*-acetal **6** and ethyl glyoxylate **8**[8] were utilized as the starting materials. This versatile approach to the assemblage of δ-hydroxy-α,γ-dimethyl-α,β-unsaturated units **9** and **10** may find application in the combinatorial synthesis of maytansinoid libraries, as well as other natural products and biological active molecules.[9]

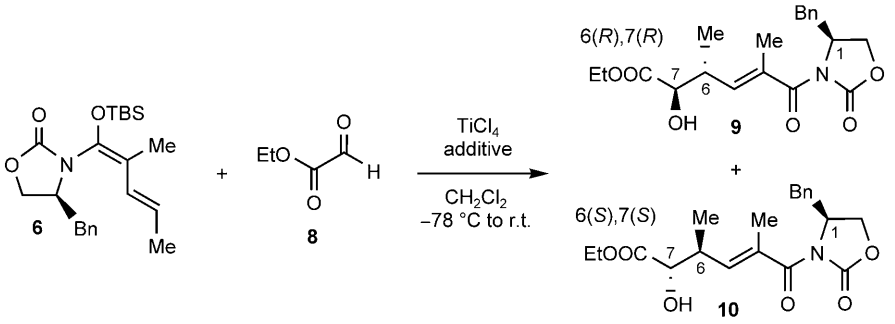
Our research started with the study of VMAR with **6** and **8** as substrates. After preliminary screening of the VMAR conditions, we found that the aldol adducts **9** and **10** could be obtained in 82% yield and with moderate diastereoselectivity (Table 1, **9**/**10** = 3.6:1). It is worth noting that the chiralities at C-6 and C-7 in **9** are opposite to the corresponding chiralities in **2** (Scheme 1) generated in Kobayashi's VMAR.

The absolute stereochemistries of **9** and **10** were established by converting them to their corresponding acetonides **13** and **14** by literature methods.[3b] Accordingly, an efficient reduction-silylation sequence elaborated imide **9** into alcohol **11** in overall 66% yield in two steps.

Alcohol **11** underwent ozonolysis and reduction to give diol **12**, which was then subjected to the treatment with 2,2-dimethoxypropane in the presence of PPTS to give acetonide **13** in 67% in three steps (Scheme 2). Following the same synthetic sequence, compound **10** was transferred to **14**, which shares the same spectroscopic data with acetonide **13**, except for its opposite optical rotation.

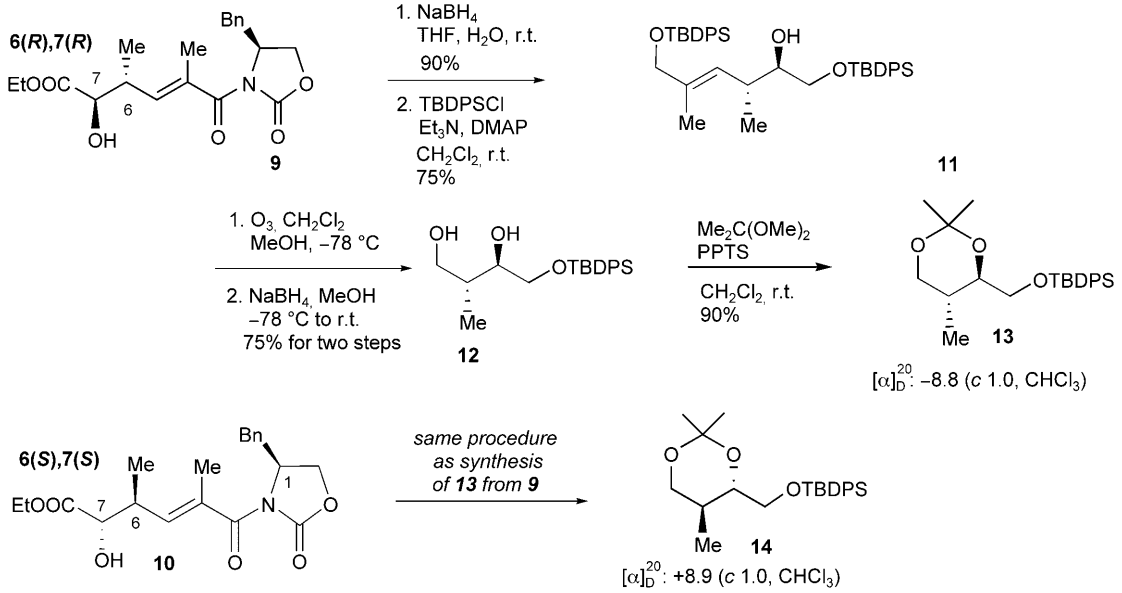
To further comfirm the stereochemical assignment of **9**, acetonide **13** was independently made *via* the Evans aldol method[10] as illustrated in Scheme 3.

Table 1. Silver salts effects on the VMAR.



Entry	Additive	Yield[a]	**9/10** Ratio[b]
1	no	82%	3.6:1
2	$AgClO_4$	80%	0.9:1
3	AgF	85%	4:1
4	AgOTf	83%	4.3:1
5	$AgBF_4$	55%	1:1
6	$AgPF_6$	70%	0.7:1
7	$AgSbF_6$	89%	1:120

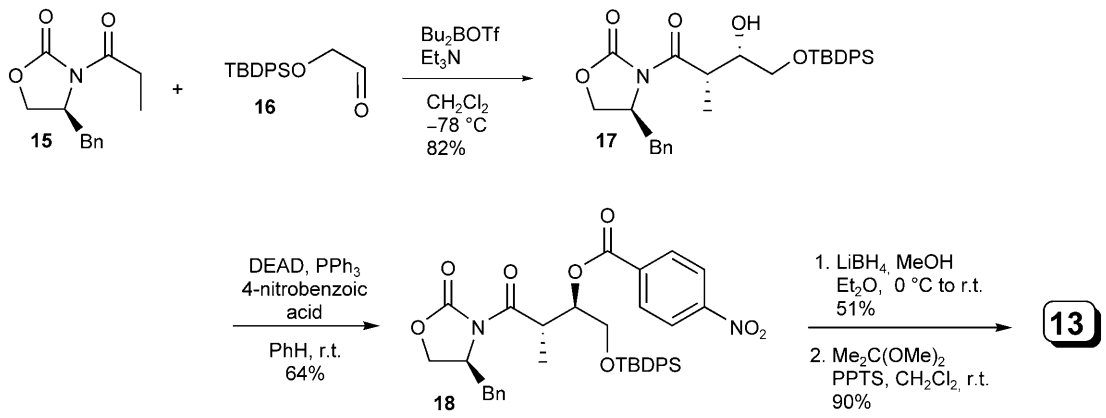
[a] Isolated yield.
[b] Determined by HPLC analysis.



Scheme 2. Stereochemistry of compounds **9** and **10**.

In the event, substrate **15** was reacted with aldehyde **16** in the presence of Bu_2BOTf and Et_3N to give aldol adduct **17** in 82% yield. Alcohol **17** was subjected to a Mitsunobu reaction to afford its ester **18** in 64% yield. Ester **18** underwent a sequential reduction-acetonification to give the acetonide **13** with the expected spectroscopic data. The absolute stereochemistry of **10** was also verified by the modified Mosher method (see Supporting Information for details).[11]

This unusual observation led us to consider whether the cationic Ti complex would improve the stereoselectivity of the VMAR, considering its high rigidity and reactivity.[12] To this end, $AgSbF_6$[7a,c] was utilized



Scheme 3. Synthesis of **13** *via* the Evans aldol reaction.

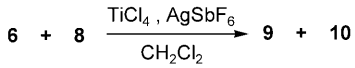
as an agent to generate the cationic $TiCl_3^+$-chelated complex. Thus, the aldol reaction was carried out in the presence of $AgSbF_6$ under the conditions listed in Table 1. To our surprise, the facial selectivity of the VMAR was reversed and, as a result, **10** became the major product in 89% yield with the ratio of **9**/**10** being 1:120.

To examine the effect of other silver salts on the outcome of the VMAR, we employed $AgClO_4$, AgF, AgOTf, $AgBF_4$ and $AgPF_6$ as additives under the conditions listed above, however, no stereochemical reversal was observed with any of these salts (see Supporting Information for details). Clearly, there is a strong dependence of the reaction pathway on the nature of the counterion.

To find the optimal reaction conditions to synthesize product **10**, we studied the effect of various reaction parameters on the outcome of the reaction, and the results are listed in Table 2.

From Table 2, we can make the following observations. (i) Considering the temperature effect on the outcome of VMAR of **6** with **8**, reactions carried out at room temperature gave the best diastereoselectivity (entries 1 and 4). (ii) In the presence of 2.0 equivalents of aldehyde, the reaction conducted at room temperature gave the highest yield and excellent diastereoselectivity (entry 4). (iii) With catalytic amounts of $TiCl_4$ and $AgSbF_6$, VMARs could proceed at room temperature, but the yield and diastereoselectivity decreased (entries 7 and 8).

Table 2. Cationic $TiCl_3^+$-catalyzed VMAR.



Entry	Aldehyde [equiv.]	$TiCl_4$ [equiv.]	$AgSbF_6$ [equiv.]	Temperature	Yield[a]	**9/10** Ratio[b]
1	1	1	1	–78 °C to r.t.	70%	1:135
2	1	1	1	–78 °C to –40 °C	79%	1:62
3	1	1	1	–78 °C	82%	1:73
4	2	1	1	–78 °C to r.t.	89%	1:120
5	2	1	1	–78 °C to –40 °C	78%	1:106
6	2	1	1	–78 °C	83%	1:107
7	2	0.5	0.5	–78 °C to r.t.	71%	1:58
8	2	0.1	0.1	–78 °C to r.t.	71%	1:43

[a] Isolated yield.
[b] Determined by HPLC analysis.

To account for the observed facial selectivity of the *anti* VMAR products, we proposed the following mechanistic interpretations. As shown in Figure 2, in the absence of silver salt, aldehyde **8** could be attacked by the C-6 carbon of vinylketene silyl *N*,*O*-acetal **6** from either the *re*-face (**TS-1**) or *si*-face (**TS-2**). However, due to the dipole repulsion between the ester carbonyl group and the carbonyl group of the oxazolidinone in the *si*-face (**TS-2**), the **TS-1** is more favorable than **TS-2**, thus, product **9** turned out to be the major product.

On the other hand, in the presence of silver salt, we assumed that the resultitng bidentate cationic intermediate **A** may have tendency to form hexacoordinated complex (**TS-3**) with substrate **3**. As a result, the product **10** would be derived dominantly, realizing the reverse of the facial selectivity through chelation control.[13]

To investigate the substrate effect on the outcome of the coupling reactions, we selected five additional substrates **19**–**23** to test their performance in this VMAR, and the primary results are listed in Table 3.

From the results in Table 3, we can make the following observations. (i) In comparison to aldehydes (entries 1–6) as substrates in the VMARs, ketones gave lower yields of coupling products (entries 7–10), a result presumably due to the favorable steric and electronic effects of aldehyde. (ii) Considering the effects for the formation of bidentate cationic $TiCl_3^+$ complexes on the outcome of the stereochemistry, it is interesting to note that the five-membered ring based bidentate cationic $TiCl_3^+$ complexes give the

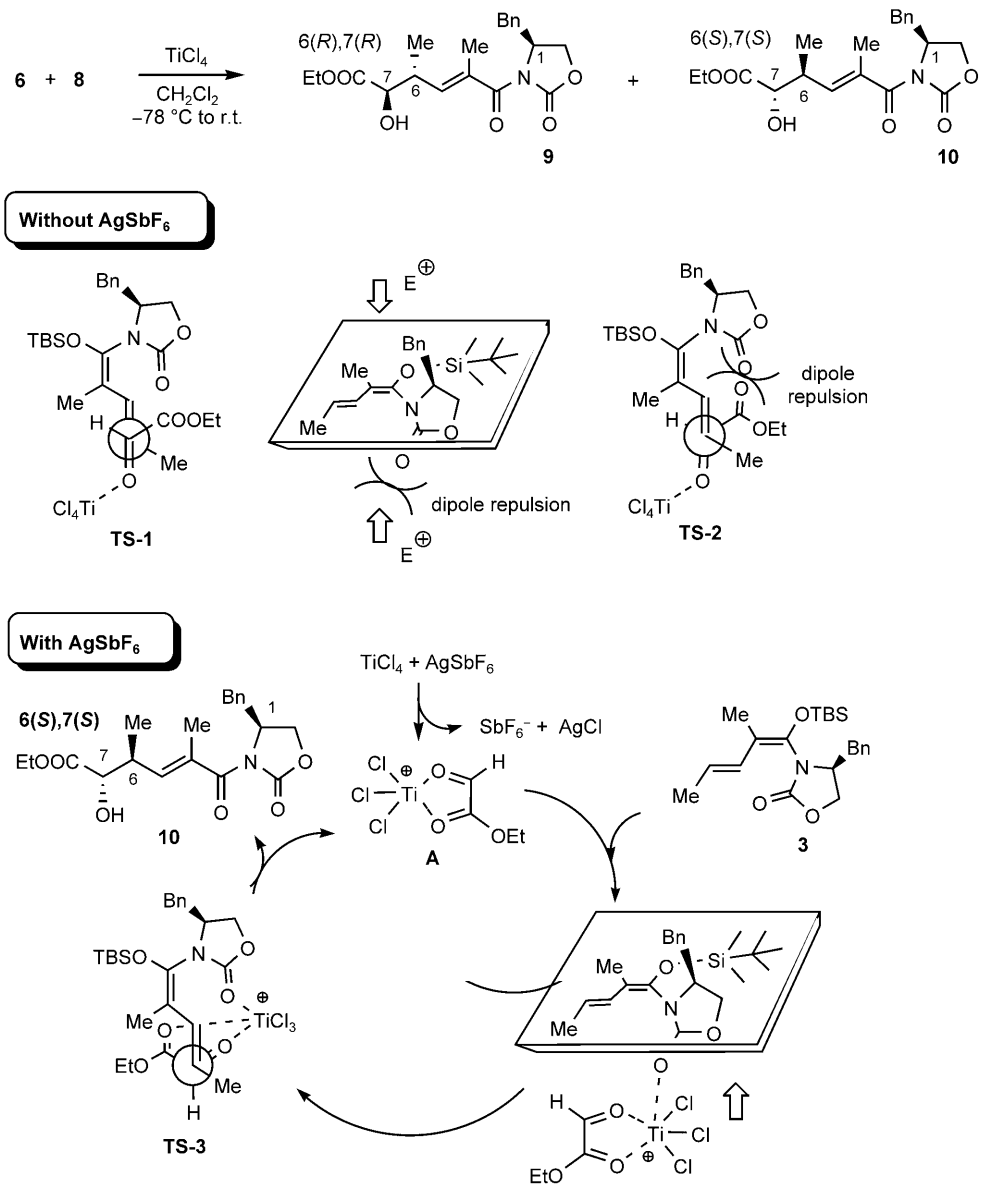


Figure 2. Mechanistic interpretation.

expected inversed stereochemical outcomes (entries 2, 4, 8 and 10), however, the ratios of their selectivity are less satisfied. On the other hand, substrate **21**, with a potential to form a six-membered ring based bidentate cationic $TiCl_3^+$ complex (entry 6), did not give any inversion effect. (iii) In the presence of the silver effect, the tested VMARs generally gave higher yields (entries 2, 4, 6 and 8) than the ones without the silver effect (entries 1, 3, 5 and 7), except for the last case (entries 9 and 10). The structural information for the synthesized compounds (**24a**, **24b** to **28a**, **28b**) is provided in the Supporting Information.

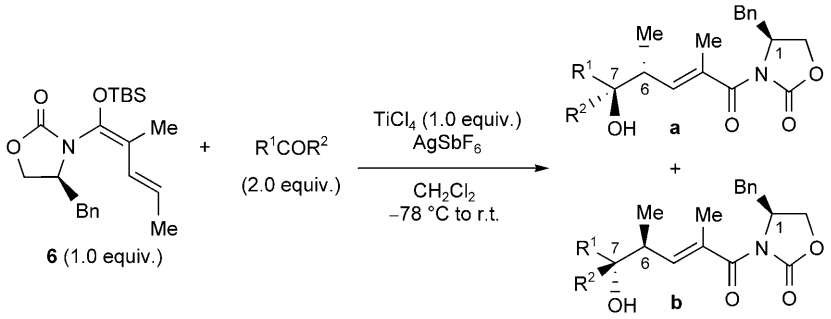
In conclusion, $AgSbF_6$ was identified as an efficient agent to reverse the facial selectivity of titanium chloride-mediated Kobayashi's VMAR, and this unprecedented reaction provides a concise, highly diastereoselective synthesis of δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl units from readily available chiral vinylketene silyl *N*,*O*-acetal **6** and ethyl glyoxylate **8** simply by using $AgSbF_6$ as a switch. A further rational analysis of this unprecedented VMAR by a combination of experimental and computational studies is currently underway in our laboratories and will be reported in due course.

Experimental Section

Procedure A

To a solution of ethyl glyoxylate **8** (53.1 mg, 106 μL, 50% w/w in toluene, 0.52 mmol) in dry CH_2Cl_2 (2 mL) was slowly

Table 3. VMARs with different electrophiles.



Entry	Electrophile	$AgSbF_6$	Products	Yield[a]	**a**/**b** Ratio[b]
1	BnO CHO (**19**)	0 mol%	**24a** + **24b**	88%	2.2:1
2		100 mol%		96%	1:7.5
3	PivO CHO (**20**)	0 mol%	**25a** + **25b**	76%	4.2:1
4		100 mol%		95%	1:1.5
5	BnO CHO (**21**)	0 mol%	**26a** + **26b**	56%	20:1
6		100 mol%		85%	20:1
7	EtO Me (**22**)	0 mol%	**27a** + **27b**	61%	10:1
8		100 mol%		66%	1:2.0
9	Me (**23**)	0 mol%	**28a** + **28b**	69%	4:1
10		100 mol%		57%	1:2.0

[a] Isolated yield.
[b] Determined by HPLC analysis.

added $TiCl_4$ (260 μL, 1 M in CH_2Cl_2, 0.26 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To this solution was added a solution of vinylketene silyl *N*,*O*-acetal **6** (100.8 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was warmed up to room temperature and stirred for 2 h. The reaction mixture was quenched by addition of a saturated aqueous Rochelle's salt (10 mL), and the mixture was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2×5 mL) and brine (5 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give products **9** and **10**. The ratio was determined by HPLC with Chiralcel OJ-H column (90:10 hexanes:*i*-PrOH), 1.0 mL min^{-1}, 254 nm; for isomer **10**, t_r = 70.4 min, and for isomer **9**, t_r = 90.2 min.

Procedure B

To a solution of silver salt (0.26 mmol) in dry CH_2Cl_2 (2 mL) was added $TiCl_4$ (260 μL, 1 M in CH_2Cl_2, 0.26 mmol) slowly at −78 °C, and the formed mixture was warmed up to room temperature and stirred vigorously for 15 min until a precipitation was observed. To this solution was added a solution of ethyl glyoxylate **8** (53.1 mg, 106 μL, 50% w/w in toluene, 0.52 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. After addition of a solution of vinylketene silyl *N*,*O*-acetal **6** (100.8 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) to the above solution at −78 °C, the formed mixture was warmed up to room temperature and stirred for 2 h. The reaction mixture was quenched by addition of a saturated aqueous Rochelle's salt (10 mL), and the mixture was extracted with ethyl acetate (3×5 mL). The combined organic layers were sequentially washed with a saturated aqueous solution of $NaHCO_3$ (2× 5 mL) and brine (5 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give products **9** and **10**, and their ratio was determined by HPLC with Chiralcel OJ-H column (90:10 hexanes:*i*-PrOH), 1.0 mL min^{-1}, 254 nm; for isomer **10**, t_r = 70.4 min, and for isomer **9**, t_r = 90.2 min.

Acknowledgements

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