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Stereoselective Acylation of the *E,E*-Vinylketene Silyl *N,O*-Acetal and Its Application to the Synthesis of Khafrefungin

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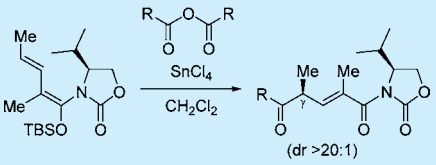
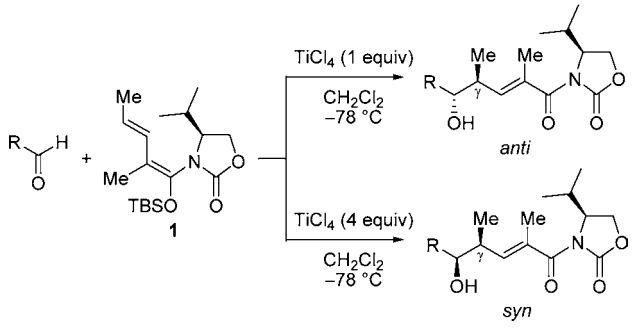
Supporting Information

ABSTRACT: Stereoselective acylation of the *E,E*-vinylketene silyl *N,O*-acetal possessing a chiral auxiliary has been achieved by using acid anhydrides and $SnCl_4$. Acid anhydrides having alkyl chains gave the adducts in excellent stereoselectivity. The formal synthesis of khafrefungin has been accomplished by the methodology.



Many polypropionates have attractive structures and bioactivities, and methods to synthesize them in short steps have been studied and developed. One of the most useful methods is the vinylogous Mukaiyama aldol reaction (VMAR),[1] of which asymmetric versions have been reported recently and applied to natural product syntheses.[2] We have developed VMARs using the *E,E*-vinylketene silyl *N,O*-acetal possessing a chiral auxiliary (Scheme 1)[3−5] and indicated that the

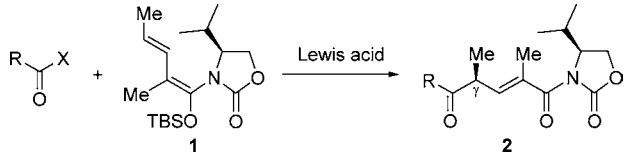
Scheme 1. Remote Asymmetric Induction by the Vinylogous Mukaiyama Aldol Reaction Using the *E,E*-Vinylketene Silyl *N,O*-Acetal 1



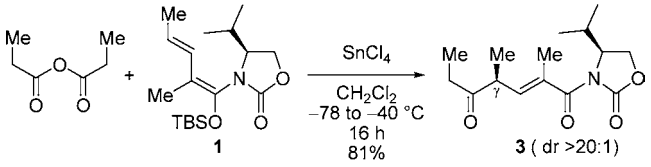
stereochemistry of the product was controlled by the amount of $TiCl_4$.[3b] Although the stereochemistry of the δ position was affected by the amount of $TiCl_4$, that of the γ position was not changed under the reaction conditions. These results led us to the consideration that the acylation reaction of the *E,E*-vinylketene silyl *N,O*-acetal **1** would proceed in high stereoselectivity (Scheme 2). Herein, we present the stereoselective acylation of the *E,E*-vinylketene silyl *N,O*-acetal.

After examination with various acylating reagents and Lewis acids, we found that acid anhydride with $SnCl_4$ gave the best results to produce the adduct **3** in high yield as a single isomer (Scheme 3). The configuration of the adduct **3** was determined by identification with the compound that was synthesized by the Kobayashi reaction with propionaldehyde to give **4**[4f] and the subsequent oxidation (Scheme 4).

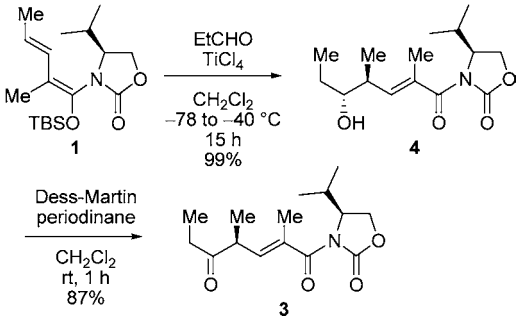
Scheme 2. Acylation of the Vinylketene Silyl *N,O*-Acetal 1



Scheme 3. Acylation of 1 with Carboxylic Acid Derivatives



Scheme 4. Structural Determination of Ketone 3



Various acid anhydrides were subjected to the optimized conditions (Table 1). Under these conditions, saturated acid anhydrides except sterically hindered pivalic anhydride gave the corresponding adducts in good yields (Table 1, entries 1−4). Unsaturated acid anhydride provided the adduct in moderate yield, while benzoic anhydride did not work to react with the *E,E*-vinylketene silyl *N,O*-acetal **1** (Table 1, entries 5 and 6).

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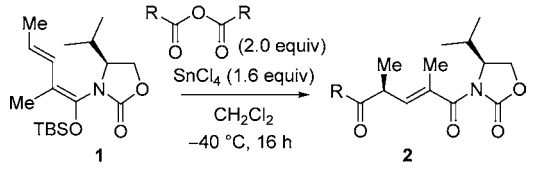
Table 1. Acylation of 1 with Acid Anhydrides



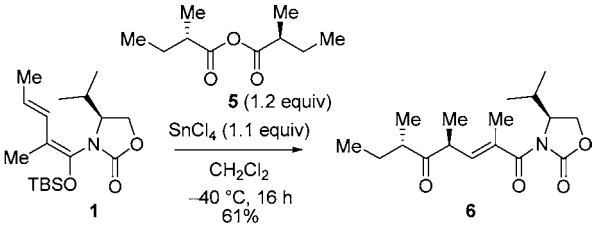
entry	R	yield (%)	dr[a]
1	Me	quant	>20:1
2	Et	89	>20:1
3	*i*-Pr	84	>20:1
4	*t*-Bu	0	
5	(*E*)-MeCH=CH	39	>20:1
6	Ph	0	
7	$(CH_2)_3$	0	

[a]Determined by ^{1}H NMR.

Glutaric anhydride, a cyclic acid anhydride, also afforded no adducts (Table 1, entry 6), which suggested that the chelation of acid anhydride to $SnCl_4$ was necessary to proceed the reaction.

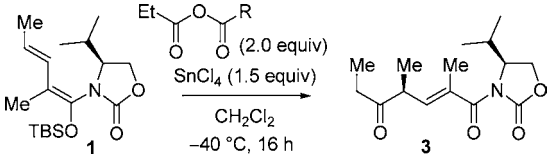
Additionally, acid anhydride **5** possessing a stereogenic center at the α position was also subjected to the reaction (Scheme 5). The reaction gave adduct **6** as a single isomer, which proved that the reaction did not include the ketene intermediate.

Scheme 5. Acylation of 1 with Anhydride 5



Next, mixed anhydrides were examined to react under the optimized conditions (Table 2). Mixed anhydrides including

Table 2. Acylation of 1 with Mixed Anhydride



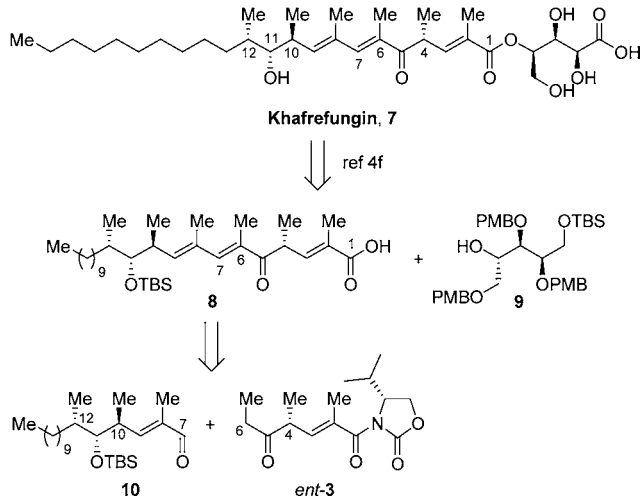
entry	R	yield (%)	dr[a]
1	*t*-Bu	75	>20:1
2	OEt	81	>20:1
3	Ph	84	>20:1
4	2-MeOC$_6$H$_4$	62	>20:1

[a]Determined by ^{1}H NMR.

pivalate (Table 2, entry 1), carbonate (Table 2, entry 2), benzoate (Table 2, entry 3), and *o*-methoxybenzoate (Table 2, entry 4) worked well to give adduct **3** in good to high yields.

On the basis of the acylation reaction, we planned a short step synthesis of a polypropionate. Khafrefungin, **7** (Scheme 6), is a potent antifungal agent isolated from the fermentation culture MF6020 by a Merck group in 1997.[6] It has been shown

Scheme 6. Synthetic Plan for Khafrefungin, 7



to inhibit inositol phosphorylceramide (IPC) synthase, which catalyzes the fungal specific step in *Saccharomyces cerevisiae* and pathogenic fungi such as *Cryptococcus neoformans* and *Candida albicans*, in picomolar and nanomolar concentrations.[6] Total synthesis of khafrefungin has been achieved by Kobayashi's group in 2001 and our group in 2007.[7,4f] Our precedent synthesis started from methyl (*R*)-*β*-hydroxyisobutyrate to secure the stereochemistry of the C12 position and took 14 steps to obtain the polypropionate segment **8** (Scheme 6).[4f] Herein, we present the alternative route to carboxylic acid **8**, in which all stereogenic centers were constructed by using the reactions with *E*,*E*-vinylketene silyl *N*,*O*-acetals and the following transformation. The carboxylic acid **8** would be constructed by coupling of *ent*-**3** and aldehyde **10**, both of which would be derived from *E*,*E*-vinylketene silyl *N*,*O*-acetals (Scheme 6).

Along the synthetic plan, we achieved the formal synthesis of khafrefungin (Scheme 7). The synthesis started from the selective cross aldol condensation reaction with decanal **11** and propanal **12**. Treatment of the mixture of aldehydes and piperidine in the presence of AcOH gave 2-methyl-2-dodecenal **13** in 89% yield.[8] The resulting unsaturated aldehyde **13** was submitted to the vinylogous Mukaiyama aldol reaction to give *anti* adduct **14** as a single isomer. Allylic alcohol of **14** was converted to the silyl ether **15**, which was hydrogenated using Adam's catalyst to give 12*S* isomer **16** as the major compound of a separable mixture (dr = 6:1, isolated yield of **16**: 60%).[9] DIBAL-H reduction gave aldehyde **10** directly. On the other hand, *ent*-**3** was prepared under the optimized conditions affording **3** by using vinylketene silyl *N*,*O*-acetal *ent*-**1**. The adduct *ent*-**3** was coupled with aldehyde **10** by aldol condensation using $SnCl_4$ and triethylamine to yield *α*,*β*,*γ*,*δ*-unsaturated ketone **17** directly. Hydrolysis of imide **18** gave the carboxylic acid **8**, spectral data of which were consistent with those of **8** previously synthesized by our group.[4f]

Additionally, we synthesized the C4-epimer of **8** (**18**) to prove stability of the stereochemistry at the C4 position (Scheme 8). The Kobayashi group reported that epimerization of the C4 position did not occur through their total synthesis and concluded that khafrefungin was under strict conformational constraints to prevent the epimerization process.[7b] We also verified the stability of the C4 stereochemistry in our route. Acylation adduct **3** was coupled with aldehyde **10** under the

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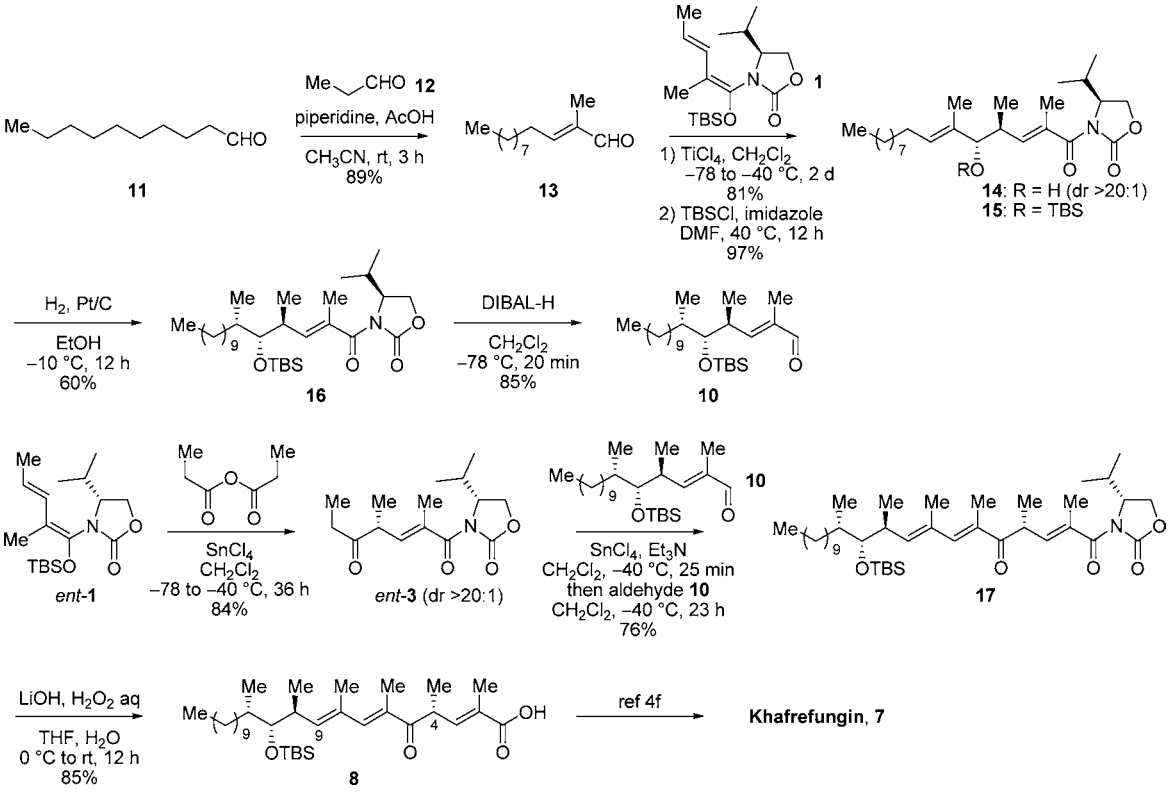
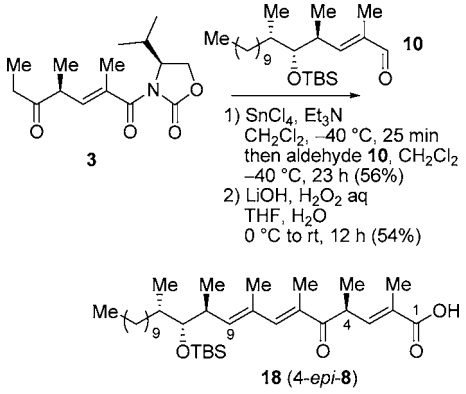
Scheme 7. Formal Synthesis of Khafrefungin



Scheme 8. Synthesis of Polypropionate 18, the C4-Epimer of 8



same conditions used in the coupling of *ent*-**3** and **10**. The adduct (the C4-epimer of **17**) was exposed to hydrolysis conditions mentioned in Scheme 7 to afford carboxylic acid **18** (C4-epimer of **8**).

Comparison of ^{1}H NMR spectra of carboxylic acids **8** and **18** is shown in Figure 1. These epimers are distinguished with the chemical shift of the H9 and C4-Me protons, which place at 5.77 and 0.99 ppm in **8**, while those of **18** are at 5.76 and 0.98 ppm, respectively (Figure 1). Even when these compounds are mixed in equal amounts, their own peaks are easily distinguished (Figure 1, **A**). Therefore, we confirmed that epimerization of C4 position did not occur through our synthetic route.

In conclusion, the stereoselective acylation of the *E,E*-vinylketene silyl *N,O*-acetal **1** with saturated acid anhydrides has been accomplished. The reaction afforded the adduct as a single isomer, which is able to undergo the aldol reaction at the α position of the ketone. Additionally, we have established a concise synthesis of khafrefungin by using our developed methodologies including the acylation method. The synthesis is straightforward so that the longest linear sequence to polypropionate **8** is seven steps from commercially available

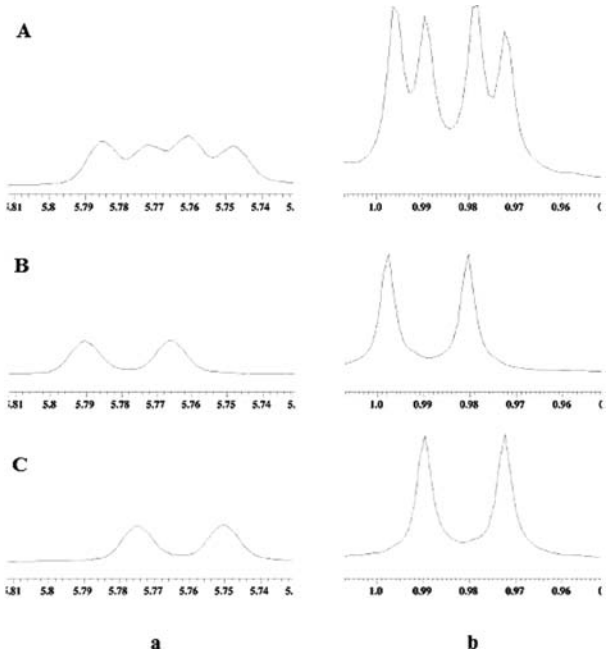


Figure 1. Comparison of ^{1}H NMR spectra of **8** and **18** (C4-epimer of **8**). (A) Mixture (~1:1) of **8** and **18**. (B) Compound **8**. (C) Compound **18**: (a) H9 proton (δ 5.81–5.73 ppm); (b) C4-Me proton (δ 1.01–0.95 ppm).

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aldehyde **11**. We also synthesized 4-*epi*-**8** (**18**) and confirmed that epimerization at the C4 position did not occur through our synthetic route. The present acylation method should be a powerful tool to accomplish short step syntheses of polypropionates. Further application of this methodology to natural product synthesis is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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