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Rapid Access to Polyketide Scaffolds via Vinylogous Mukaiyama Aldol Reactions

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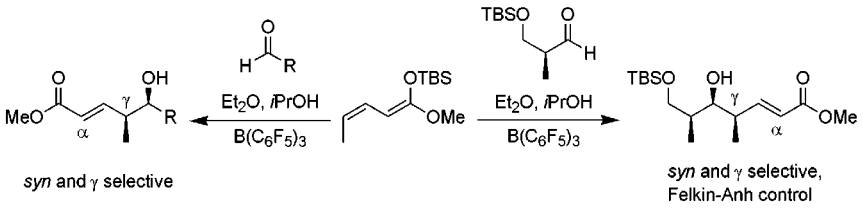
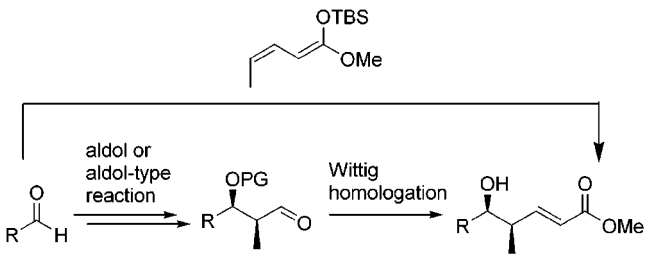
ABSTRACT



The use of the *Z*-configured vinylogous silyl ketene acetals in Mukaiyama aldol reactions is described. Isopropyl alcohol as scavanger and the use of tris(pentafluorophenyl)borane as the Lewis acid are required for obtaining the γ-alkylated *syn*-product selectively. In cases of α-chiral aldehydes, Felkin–Anh selectivity was observed.

Polyketides have become one of the most extensively investigated groups of natural products. The alternating incorporation of acetate or propionate in their biosynthesis is paralleled by aldol or aldol-type reactions in syntheses of these compounds. For the linear extension of ketide fragments, Evans' [1] and Paterson's aldol[2] methodology, Braun's Hytra reagent,[3] and allylations[4] are just four prominent examples from a set of reactions that can be applied with very good predictability in their stereochemical outcome. Herein we report the first direct stereoselective access to δ-hydroxy-γ-methyl-α,β-unsaturated esters, which represents the addition of a joint acetate−propionate subunit. The established approach for such fragments consists of an aldol addition followed by Wittig homologation and requires additional functional group manipulations (Scheme 1). One drawback of the established polyketide chemistry is the fact that, as in the biosynthesis, only one acetate or propionate building block is added at a time. Despite the potential strategic advantage of those advanced building blocks, examples describing the entrance to these fragments are limited. Similar strategies developed by Panek[5a] and Marshall[5b,c] employ chiral allylsilanes and chiral allenylmetal reagents, respectively. Very recently, an allylboration/cross metathesis sequence[6] was shown to be an interesting alternative for the synthesis of similar structures. Since a one-step solution to this problem would have major impact on the efficiency of polyketide syntheses, we initiated a study of the vinylogous Mukaiyama aldol reaction (VMAR) with dif-

Scheme 1. Sequence of Aldol Reaction Followed by Wittig Homologation Compared to Vinylogous Mukaiyama Aldol Reaction



(1) For an application to total synthesis in which *all-syn* stereotriades are generated, see: Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.

(2) (a) For recent examples, see: Paterson, I.; Collet, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem.* **2000**, *112*, 385; *Angew. Chem., Int. Ed.* **2000**, *39*, 377.

(3) Braun, M.; Waldmüller, D. *Synthesis* **1989**, 856.

(4) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

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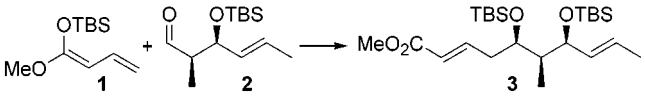
ferent diketide equivalents as their silyl ketene acetals.[7] The significant advantage of using ketene acetals is the ease in which they can be generated.[8] Even though the VMAR could be used to generate two asymmetric centers and one double bond, its full potential has yet to be exploited (Scheme 1).

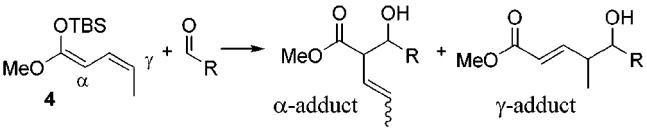
Our first experiments were carried out on aldehyde **2**, an intermediate in our synthesis of ratjadone. The VMAR was used to establish a stereotriade (**3**) adjacent to an α,β-unsaturated ester. In this context we reported that the VMAR with a diacetate equivalent (**1**) derived from crotonic acid methyl ester provides the γ-aldol adduct in good Felkin−Anh selectivity (Scheme 2).[7] These encouraging results set

Scheme 2. VMAR in the Synthesis of Ratjadone



the foundation for our continuing efforts toward the VMAR utilizing substituted dienolates. At the outset of our investigations with the γ-methyl-substituted diene **4**, two major problems had to be addressed: (a) the regioselection (γ vs α attack)[8] and (b) diastereoselection (*syn* vs *anti* configuration of the newly formed stereocenters) (Scheme 3). In

Scheme 3. Products Derived through Different Regio and Stereoselectivities Using BF_3·Et_2O as the Lewis Acid



our preliminary studies it became clear that tris(pentafluorophenyl)borane (TPPB) as Lewis acid gives significantly higher selectivities compared to BF_3·Et_2O.[7] We rationalized these results with the proposal that the sterically more congested transition state in the case of TPPB leads to better discrimination between the possible pathways. When we started our investigation we prepared the 3,4-*Z*[9] (**4**) and the 3,4-*E*[10] ketene acetals (**7**) and subjected them to the VMAR conditions with TPPB and isobutyraldehyde. Interestingly, the *E*-configured ketene acetal gave low yields and poor regioselection, with the undesired α-alkylated produced in substantial amounts (Scheme 4). In contrast, the *Z*-ketene acetal **4** gave high yields and exclusively γ-alkylation.

In the open transition state it can be seen that for the *E*-ketene acetal (**7**) always one substitutent is on the same side as the R group of the aldehyde and that the α-position

(5) For recent examples of these strategies in total syntheses, see: (a) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229. (b) Marshall, J. A.; Fitzgerald, R. N. *J. Org. Chem.* **1999**, *64*, 4477. (c) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

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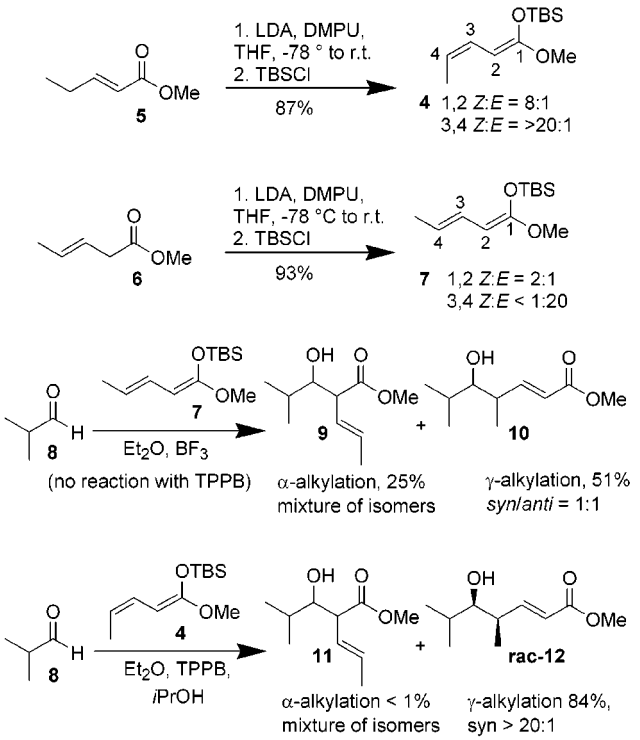
Scheme 4. Synthesis of the Ketene Acetals and TPPB-Catalyzed Reaction with Isobutyraldehyde



is accessible to alkylation (Figure 1). In the transition state involving the *Z*-configured ketene acetal (**4**), both substituents on the double bond are directed away from the R group of the aldehyde. At the same time, the *Z*-configuration prevents α-alkylation by increasing steric hindrance through the adjacent methyl group. These experiments identified the *Z*-ketene acetal as the more selective nucleophile for the vinylogous Mukaiyama aldol reaction.

Fortunately, the Z-configured ketene acetal can easily be derived from the corresponding *E*-configured α,β-unsaturated ester (**5**) in good selectivity by deprotonation and trapping the anion with TBSCl (Scheme 4). Employed in the VMAR, two *syn* aldol products were obtained. One that had the newly formed hydroxyl group unprotected and a second one that showed TBS protection on the alcohol. Surprisingly, the TBS-protected product gave always a *syn*/*anti* ratio of about

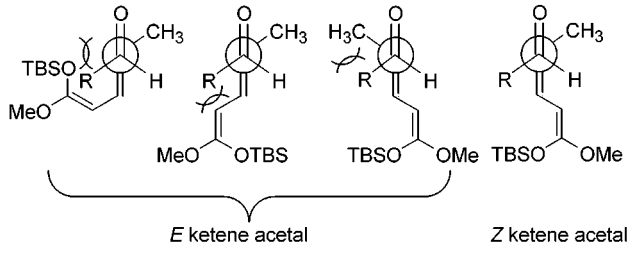
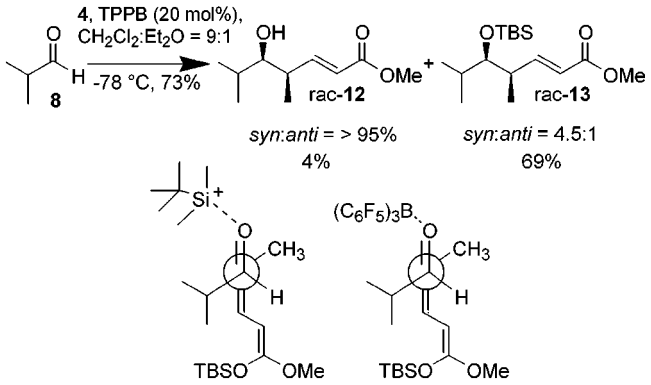


Figure 1. Proposed transition states for the nucleophilic attack of both ketene acetals.

4.5:1 irrespective of reaction conditions such as temperature, solvent, or amount of catalyst. On the other hand, we observed that the product with the free hydroxyl group gave exclusively one isomer which we identified to be the *syn* diastereoisomer. We envisioned that two competing carbonyl activations take place (Scheme 5). One involves activation

Scheme 5. Two Different Catalytic Activations



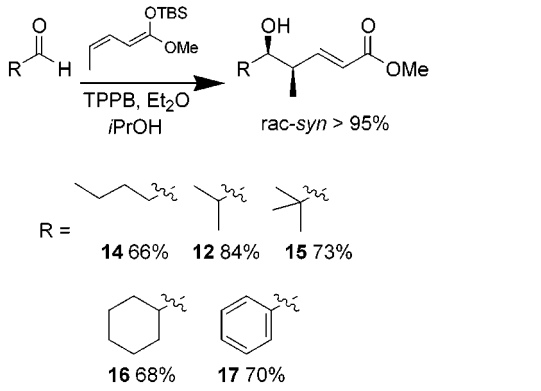
with the boron Lewis acid which results in diastereoselective formation of compound **12**, and a second one is catalyzed by "R_3Si^+" which is liberated from the ketene acetal during the reaction and leads to the 4.5:1 mixture of diastereoisomers (**13**). A rationale for the loss in diastereoselectivity can be given considering the differences in length between the silicon−oxygen and the boron−oxygen bonds. Our initial reason for choosing TPPB as the Lewis acid was the increased steric hindrance due to the bulky Lewis acid that leads to higher selectivities. With a longer bond between the Lewis acid and the carbonyl oxygen as in the case with "R_3Si^+", steric interactions became less significant and the selectivities decreased. To overcome the undesired activation by "R_3Si^+", isopropyl alcohol was added to the reaction mixture to trap the reactive silicon species which suppressed the undesired catalytic pathway. Other reagents, such as 2,6-diisopropylphenol,[11] were also used as scavangers but gave no improvement in yield or selectivity. Isopropyl alcohol was therefore chosen since it proved to simplify workup and purification of the product. Consequently, we could perform the vinylogous aldol reaction in yields ranging between 66 and 84% with complete *syn*-selectivity and γ-regioselection.

We applied these conditions to a variety of different aldehydes. As shown in Scheme 6, aldehydes ranging from pentanal to pivalaldehyde gave exclusively the *syn*-isomer in good yields.

Since at the outset of our investigation we observed that the vinylogous Muakiyama aldol reaction is a very efficient method in total synthesis, we employed our conditions to chiral aldehydes in order to evaluate the stereoinduction by neighboring asymmetric centers. In our previous studies both, the TBS-protected product and the one without gave excellent Felkin−Anh selectivity.

Using aldehyde **18** we were able to generate the *all-syn* stereoisomers in **19** stereoselectively (Felkin−Anh control).

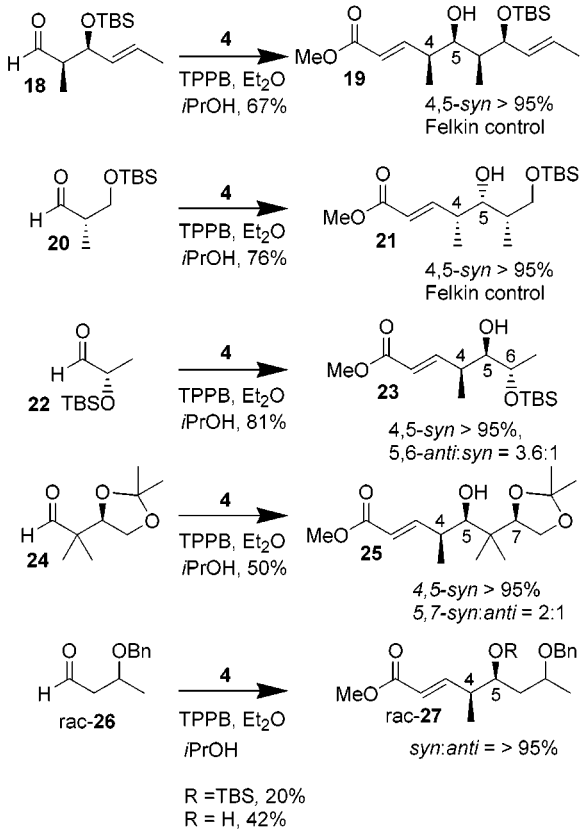
Scheme 6. VMAR with Achiral Aldehydes



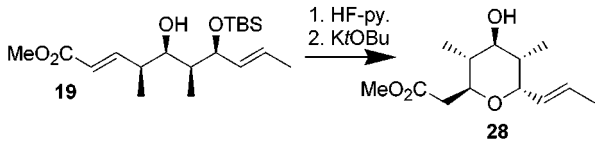
The stereochemistry of **19** was confirmed by transformation into tetrahydropyran **28** and analysis of the coupling constants (Scheme 8). The same Felkin−Anh and *syn*-selectivity was observed for the frequently used aldehyde **20**. The so-generated compound **21** can be easily converted to key intermediates in various syntheses of complex natural products.[1,5,12]

The stereochemistry was assigned by comparison of the ^{13}C NMR data to known compounds.[5c,13] The VMAR with aldehyde **22**, another frequently employed aldehyde, gave a 3.6:1 selectivity for the Felkin−Anh product.[14] Scheme 7 summarizes the results for five chiral aldehydes.[15] It became

Scheme 7. VMAR with Chiral Aldehydes in the Presence of *i*PrOH



Scheme 8. Configuration of **19** Determined via Transformation into Tetrahydropyrane **28** and Subsequent X-ray Analysis



clear that activation with TPPB provides very good Felkin−Anh selectivity but only poor 1,3-stereo induction (Scheme 7). First attempts with bidentate Lewis acids such as $MgBr_2$ or $TiCl_4$[16] did not improve selectivities.

Nevertheless, the full potential of 1,3-induction is currently under investigation in our laboratories. Additionally, the use of chiral Lewis acids in vinylogous Mukaiyama aldol reactions[17] with substituted ketene acetals will be reported in due course.

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support.

Supporting Information Available: Spectroscopic data and experimental procedures for compounds **4**, **12**, **14**, **15**, **16**, **17**, **19**, **21** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Typical procedure for the synthesis of 21:** Aldehyde **20** (44 mg, 0.217 mmol) dissolved in ethyl ether (2 mL) was cooled to −78 °C under argon. Tris(pentafluorophenyl)borane (111 mg, 0.217 mmol) was added, and a mixture of ketene acetal **4** (100 mg, 0.438 mmol) and isopropyl alcohol (17 μL, 0.24 mmol) dissolved in diethyl ether (1 mL) was added over 6 h. After completion, the cold reaction mixture was directly poured on a silica gel column. Flash chromatography using ethyl acetate/hexanes (1:4) as eluant afforded 52 mg (0.164 mmol, 76%) of product **21** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, J = 15.7, 9.3 Hz, 1H), 5.83 (dd, J = 15.7, 0.9 Hz, 1H), 3.76 (dd, J = 9.8, 3.1 Hz, 1H), 3.69 (s, 3H), 3.64 (dd-like, J = 8.7, 1.3 Hz 1H), 3.62 (dd, J = 9.8, 3.9 Hz, 1H), 3.38 (broad s, 1H), 2.43 (dtq-like, J = 9.3, 6.6, 0.9 Hz, 1H), 1.57−1.66 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.1, 120.8, 77.8, 69.2, 51.4, 40.9, 26.6, 25.8, 18.1, 16.7, 9.3, −5.6, −5.7.

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