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Editor's Choice

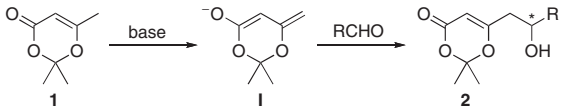
anti-Selective Vinylogous Aldol Reaction by Silylated Alkyldioxinone Dienolate

Tomohiro Yoshinari, Ken Ohmori, and Keisuke Suzuki*
Department of Chemistry, Tokyo Institute of Technology, SORST-JST Agency, O-okayama, Meguro-ku, Tokyo 152-8551

(Received July 8, 2010; CL-100615; E-mail: ksuzuki@chem.titech.ac.jp)

Diastereoselective vinylogous aldol reaction is reported by exploiting a silylated dioxinone to give *anti*-adducts in high selectivity.

Vinylogous aldol reactions of acetoacetate derivatives allow the synthesis of δ-hydroxy-β-keto acids and derivatives, which are useful building blocks for biologically active natural products.[1] Cyclic dienolate **I** derived from dioxinone **1** is particularly useful[2] to give adduct **2**, which serves as versatile intermediate to allow various elaborations (eq 1).



(1)

Another feature of dioxinone is its ability to serve as the precursor to ketene species.[3] We exploited this feature in our recent total synthesis of macrocidin A (**3**), a cyclic tetramic acid natural product: the dioxinone in **III** was used for generating the key ketene species **II** for macrocyclization (Figure 1).[4] As for control of the C(12)-stereogenic center next to the dioxinone moiety, the Pfaltz asymmetric hydrogenation[5] worked in excellent selectivity for trisubstituted olefin **V**.

In addressing the synthesis of the congener with an extra hydroxy group at C(13), macrocidin B (**4**: R = OH), we envisioned that a unified strategy would be realized, given that *the vinylogous aldol reaction proceeded in anti-selective manner to establish C(12) and C(13) stereogenic centers* (**VI** → **IV**).

However, we noted an uneasy situation, because in contrast to the impressive advances in enantioselective reactions for simple dienolate **I** (vide supra),[2] no enantio- or even diastereoselective reactions have been developed for γ-methyl dienolate **VII** (Scheme 1): the *syn*/*anti* stereoselectivity is low,[2b,6] suggesting the difficulty in controlling its *E*/*Z* geometry. At this

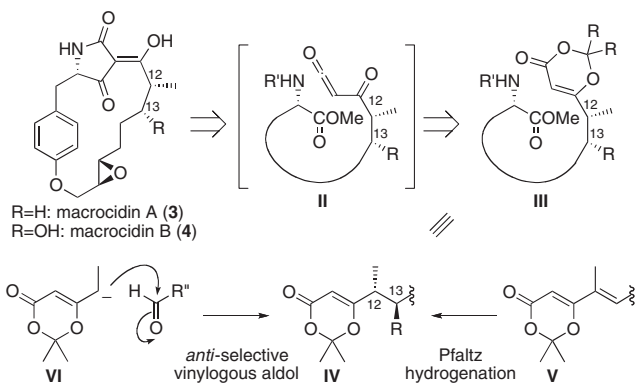
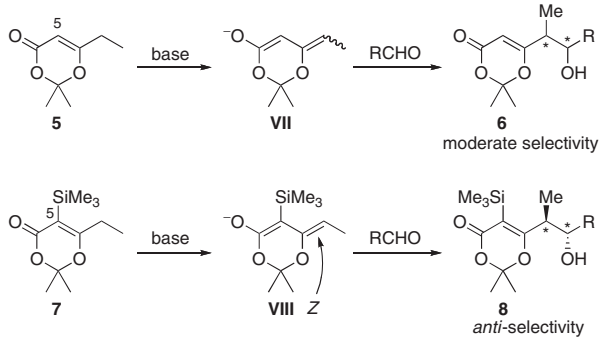


Figure 1. Retrosynthesis of the macrocidins.



Scheme 1. Vinylogous aldol reaction.

juncture, an idea occurred to us: if a bulky substituent, such as a trimethylsilyl group, were introduced to dioxinone as in **7**, allylic strain[7] would allow stereocontrolled enolization.

This communication describes an affirmative answer to this scenario, and introduction of a silyl group to the 5-position of dioxinone indeed realizes the vinylogous aldol reaction in highly *anti*-selective manner.

For the required installation of a silyl group, several sets of conditions were applied to model dioxinone **1**, which turned out to be not straightforward. Direct silylation (Me_3SiOTf and NEt_3)[8] only gave the wrong regioisomer **9**, while vinylmagnesium species,[9] generated from iodide **11**, failed to react with silylating agent (Figure 2).

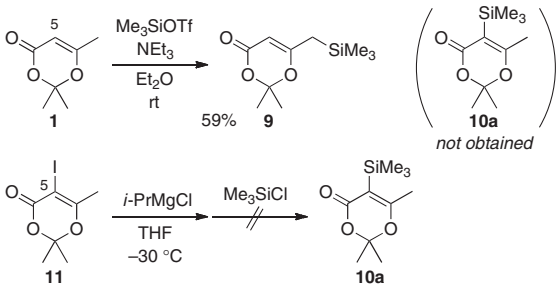
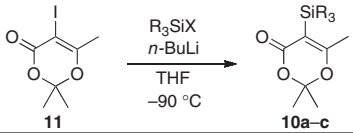


Figure 2. Attempts for the introduction of silyl group.

As for the latter process, we expected that the corresponding vinyllithium species may be more reactive, which indeed proved to react with silylating agents (Table 1). A high-yielding protocol was established, including the addition of *n*-butyllithium to the premixed solution of iodide **11** and silyl triflates in THF at −90 °C, by which several trialkylsilyl groups proved to be installed (Runs 1–3).[10]

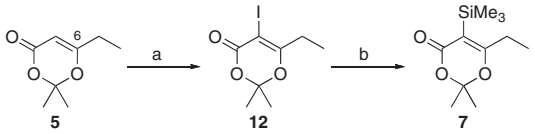
This protocol allowed the silylation of homologous dioxinone **5** [note that ethyl group is at C(6)], and iodination–silylation by the above-mentioned conditions gave **7** as colorless oil (Scheme 2).

Table 1. Synthesis of 5-silylated dioxinones



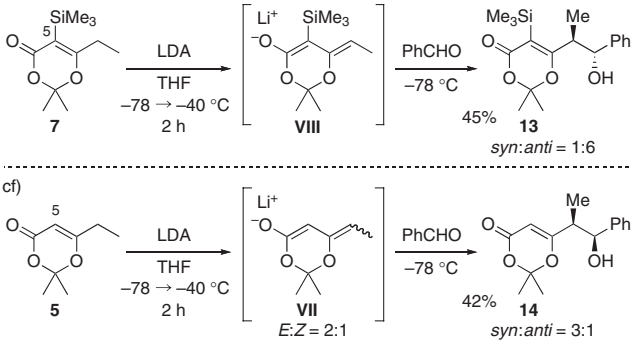
11 10a–c

Run	Electrophile	Product: Yield/%
1	Me_3SiOTf	**10a**: 94
2	*t*-$BuMe_2SiOTf$	**10b**: 94
3	*i*-Pr_3SiOTf	**10c**: 92



Scheme 2. (a) *N*-Iodosuccinimide, AcOH, room temp., 18 h, 87%; (b) Me_3SiOTf, *n*-BuLi, THF, −90 °C, 10 min, 89%.

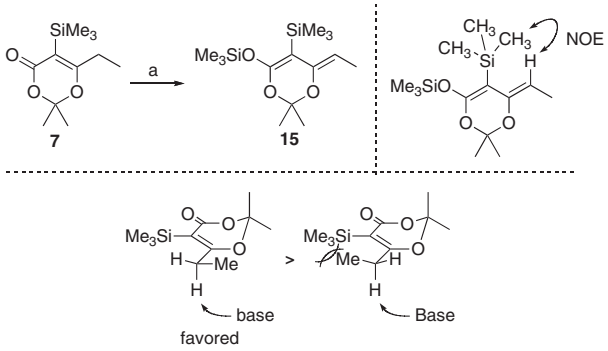
Upon attempts at the vinylogous aldol reaction of **7**, via its lithium dienolate, with benzaldehyde, we were pleased to find the desired product **13** was obtained in high *anti*-selectivity (*syn*/*anti* = 1:6) (Scheme 3).[11] By contrast, the corresponding reaction of the nonsilylated dioxinone **5** gave *syn*-adduct **14** in moderate stereoselectivity, clearly showing the role of the trimethylsilyl group for stereocontrol.[12]



Scheme 3. Vinylogous aldol reaction with Li^+–dienolate.

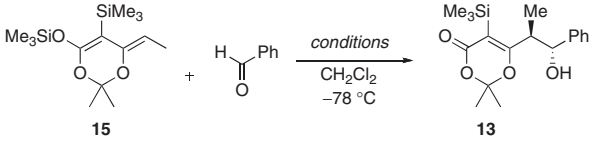
The (*Z*) geometry of the enolate **VIII** was confirmed by trapping experiment by treatment of **7** with LDA followed by Me_3SiCl followed by NOE study ($CDCl_3$, 400 MHz). This geometric selectivity could be explained by an allylic interaction between the trimethylsilyl group and the methyl group. This trapping was also possible in a preparative scale to give dienol silyl ether **15** as colorless liquid; 63% yield (70–71 °C/0.3 mmHg) (Scheme 4).

We turned our attention to the Mukaiyama conditions by using dienol silyl ether **15**.[13] Several Lewis acids were screened in the reactions by adding them to a preformed mixture of benzaldehyde and dienol silyl ether **15** (Table 2). While Me_3SiOTf or $BF_3{\cdot}OEt_2$ gave low stereoselectivity (Runs 1 and 2), high *anti*-selectivities were observed by bulky Lewis acids, such as $SiCl_4$ and $TiCl_2(Oi\text{-}Pr)_2$ (Runs 4 and 5). An optimal set of conditions was established: the suitable reaction temperature was starting with −78 °C and was raised to −50 °C.



Scheme 4. (a) $LiN(i\text{-}Pr)_2$, THF, −78 → −40 °C, 2 h; Me_3SiCl, −78 °C, 1 h, 63%.

Table 2. Mukaiyama conditions



15 (1.2–1.5 equiv) 13

Run	Lewis acid[a]	Time/h	Yield/%	*syn*:*anti*
1	Me_3SiOTf	3	82[b]	1:1.2
2	$BF_3{\cdot}OEt_2$	4	75	1:3
3	$TiCl_4$	3	24 (59)[b]	1:2.4 (1:1.2)
4	$SiCl_4$[c]	3	52	1:15
5	$TiCl_2(Oi\text{-}Pr)_2$	5	22	1:10
6	$TiCl_2(Oi\text{-}Pr)_2$, MS4A	3[d]	72	1:22

[a]0.1 equiv. [b]Yield of trimethylsilyl ether of **13**. [c]$EtN(i\text{-}Pr)_2$ was added as base. [d]The reaction temperature was gradually raised to −50 °C.

By employing MS4A as an additive, fair improvement of the yield and stereoselectivity was observed (Run 6).[14]

The stereochemical outcome, i.e., *anti*-selectivity, could be explained by an open transition state (TS) model. The decisive factors are severe steric interactions between the phenyl and the trimethylsilyl groups as well as the methyl group and the coordinated Lewis acid in the disfavored TS **A**,[15] which are not present in the favored TS **B** (Figure 3).

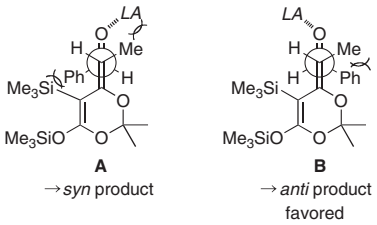
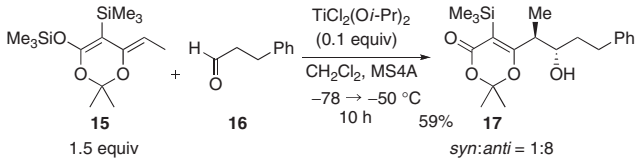


Figure 3. Transition-state model.

The high *anti*-selectivity was also valid for the reaction with aliphatic aldehyde **16**, giving smoothly **17** (*syn*/*anti* = 1:8) under the conditions stated above (Scheme 5).[16]

Upon attempted removal of the silyl group in adduct **13** with *n*-Bu_4NF, sizable epimerization was observed (Run 1, Table 3),



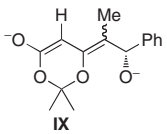
Scheme 5. Reaction with aliphatic aldehyde.

as rationalized by generation of the dienolate **IX** under the basic conditions followed by nonselective protonation. Fortunately, the stereochemistry was completely retained in the product **18** when the desilylation as attempted under acidic conditions (CF_3CO_2H). This *anti*-product **18** is stereoisomeric to the main product in **14** (Scheme 3), which was obtained from **5** without a silyl group at the C-5 position.

Table 3. Removal of silyl group

13 *syn*:*anti* = 1:15 **18**

Run	Reagent	Temp/°C	Time/h	Yield/% (*syn*:*anti*)
1	*n*-Bu_4NF, THF	0	0.5	51 (1:1)
2	CF_3CO_2H, CH_2Cl_2	25	0.5	96 (1:15)



IX

In summary, a highly *anti*-selective vinylogous aldol reaction was developed.[17] Further work is now in progress to develop an asymmetric version of the reaction.

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10 For trapping with other electrophiles, see the following. PhCHO 95%; CH_2=C(Me)CHO, 90% (1,2-adduct); cyclo-C_6H_{11}CHO, 82%; PhCOMe, 81%; PhCH=NSO_2Ph, 75%; MeOTf, 59%; PhCON(Me)OMe, 74%; PhSSPh, 72%.

11 The *syn*/*anti* ratio was estimated by ^{1}H NMR. *anti*-**13** was isolated by recrystallization (hexane), and the stereochemistry assigned by comparison of the NMR data,[2b] after removal of the silyl group.

12 The *syn*/*anti* ratio was estimated by ^{1}H NMR. Stereochemistry of *syn*-**14** was determined by X-ray crystallographic analysis. The data has been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-773065.

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14 Similar transition state model was proposed, see: S. Shirokawa, M. Kamiyama, T. Nakamura, M. Okada, A. Nakazaki, S. Hosokawa, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 13604.

15 The *syn*/*anti* ratio was estimated by ^{1}H NMR. *anti*-**17** was isolated by recrystallization (hexane), and the stereochemistry assigned by comparison of the NMR data of ref. 6a, after removal of the silyl group.

16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

17 General procedure: To a mixture of benzaldehyde (20.4 µL, 0.200 mmol) and **15** (90.1 mg, 0.300 mmol) and activated MS 4A (100 mg) in CH_2Cl_2 (2.0 mL) was added $TiCl_2$(O*i*-Pr)$_2$ (1.0 M toluene solution, 20 µL, 20 µmol) at −78 °C. After stirring for 3 h at −50 °C, the reaction mixture was poured into sat. aq. $NaHCO_3$. The mixture was filtered through a Celite® pad, and the products extracted (EtOAc, ×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by preparative TLC (hexane/EtOAc = 4/1) gave adduct **13** (47.9 mg, 72%, *syn*/*anti* = 1:22).

