

## Chelation-Controlled Aldol Reaction of Silyl Dienolate Derived from Ethyl Crotonate with a Chiral Aldehyde

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The Lewis acid promoted asymmetric aldol reaction of ketene silyl acetal with aldehydes is one of the most straightforward methods for generating C-C bonds with the well-established stereochemical framework of 1,3 oxygen functionality.<sup>1</sup> The importance of this synthetic methodology has increased further interest in exploring synthetic methods for the synthesis of unsaturated carbonyl compounds with appropriately controlled stereochemistry by the addition of silyl ester polyenolates to carbon electrophiles.<sup>2</sup> Especially, the reaction of carbon electrophiles with silyl dienolates derived from  $\alpha,\beta$ -unsaturated esters would be highly attractive to produce regioselectively and stereoselectively controlled  $\alpha$ - or  $\gamma$ -substituted products which could serve as a useful synthetic precursor for natural product synthesis, but the reaction has been investigated less extensively probably due to difficulties in controlling stereochemistry.

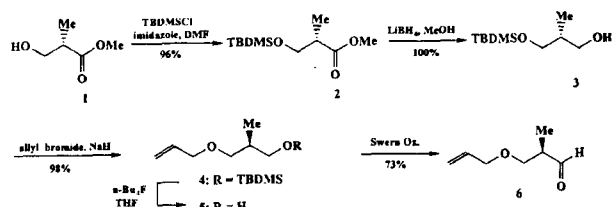
As part of a synthetic program directed toward potent anti-tumor agents, cryptophycins,<sup>3</sup> isolated from the terrestrial blue-green algae *Nostoc* sp. GSV 224, we attempted to develop the more efficient method to synthesize a key intermediate of (2E,5S,6R)-5-hydroxy-6-methyl-2-heptenoic acid derivative, which was synthesized by several synthetic steps for the establishment of the required stereochemical framework. We have examined in detail the chelation-controlled aldol reaction<sup>4</sup> of silyl ester dienolate derived from methyl crotonate with a chiral aldehyde to obtain the key intermediate with the established stereochemistry (2E,5S,6R) in a single step (Scheme 1). Since vitamin A was successfully synthesized by the regioselective Reformatsky reaction of  $\gamma$ -bromocrotonate with  $\beta$ -ionone,<sup>5</sup> a few research in this field suggested that the aldol or the Reformatsky reaction of dienolate of crotonic acid esters or  $\gamma$ -bromocrotonate with aldehydes generally produced the regioselective  $\gamma$ -adduct in excellent to good yield under thermodynamic control; kinetic control mainly produced  $\alpha$ -adduct.<sup>2,6</sup> Especially, exclusive  $\gamma$ -addition products were elaborated through the  $\alpha$ -silyl protection of  $\beta,\gamma$ -unsaturated carbonyl ester with  $\text{TiCl}_4$  in good yield.<sup>2,7</sup> To our knowledge, any result of asymmetric induction using  $\alpha$ - or  $\beta$ -alkoxyaldehyde with silyl polyenolates has not been reported yet despite of a wide variety of

the successful asymmetric aldol reactions with  $\alpha$ - or  $\beta$ -alkoxyaldehydes with ketene silyl acetal. We report the unprecedented results of the chelation-controlled asymmetric induction using methyl crotonate with a chiral aldehyde.

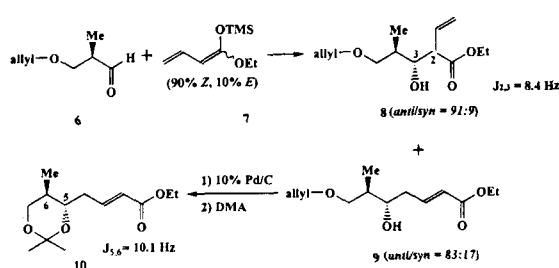
$\beta$ -Alkoxy- $\alpha$ -methylpropanal, a chiral building block, was widely used in natural product synthesis and their preparation has been well established.<sup>8</sup> In most cases of asymmetric induction with  $\beta$ -alkoxyaldehyde, benzyloxy and allyloxy group were primarily chosen for the protection of  $\beta$ -hydroxy aldehyde and the higher asymmetric induction. In our research,  $\beta$ -hydroxy aldehyde **1** was converted to the corresponding allyl ether **2** which was designed for easy manipulation of protecting group for further synthetic purpose (Scheme 2).

TBDMS-protected methylpropionate **2**, obtained by treatment of TBDMSCl with methyl (2S)-3-hydroxy-2-methylpropionate (**1**), was reduced with  $\text{LiBH}_4$  in methanolic ether to give 2-methylpropanol **3** (in 96% from **1**). Protection of hydroxyl group of **3** with allyl bromide (NaH, 25 °C, 24 h) followed by deprotection of TBDMS group ( $n\text{-Bu}_4\text{NF}$ , THF, 25 °C, 45 min) and subsequent Swern oxidation gave aldehyde **6** in 72% overall yield from **3**.

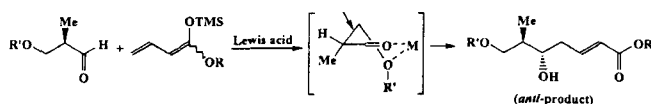
The Reformatsky reaction of aldehyde **6** with methyl  $\beta$ -bromocrotonate was first examined under reflux condition in THF with activated or dried zinc dust (1-5 equiv); the isolated yield of  $\gamma$ -substitution product (*anti/syn* = 55 : 45) ranged from 10-20% accompanying polymerized products without any trace of  $\alpha$ -adduct. The chelation controlled aldol



Scheme 2



Scheme 3



Scheme 1

**Table 1.** Aldol addition of 1-ethoxy-1-(trimethylsilyloxy)-1,3-butadiene (**7**) under various conditions

| catalyst/equiv              | solvent                         | reaction temp/time | yield (%)        | ratio of $\alpha$ - and $\gamma$ -adducts |                            |
|-----------------------------|---------------------------------|--------------------|------------------|---|----------------------------|
|                             |                                 |                    |                  | (anti/syn)                                | (anti/syn)                 |
| TiCl <sub>4</sub> /1        | CH <sub>2</sub> Cl <sub>2</sub> | -94 °C/3 h         | 70 <sup>a</sup>  | 53 (91/9)                                 | : 47 (83/17) <sup>b</sup>  |
| TiCl <sub>4</sub> /1        | CH <sub>2</sub> Cl <sub>2</sub> | -78 °C/3 h         | 75 <sup>a</sup>  | 35  | : 65 (78:22) <sup>b</sup>  |
| 1M ZnCl <sub>2</sub> THF/1  | CH <sub>2</sub> Cl <sub>2</sub> | 0-25 °C/18 h       | 85 <sup>a</sup>  | 5   | : 95 (60:40) <sup>b</sup>  |
| anhydrous ZnCl <sub>2</sub> | CH <sub>2</sub> Cl <sub>2</sub> | -78 °C/1 h         | ~20 <sup>b</sup> | 35  | : 65 (65:35) <sup>b</sup>  |
| Et <sub>2</sub> AlCl/1      | CH <sub>2</sub> Cl <sub>2</sub> | -78 °C/1 h         | ~                | polymerized                               |                            |
| LiClO <sub>4</sub> /1       | CH <sub>2</sub> Cl <sub>2</sub> | 0 °C/5 h           | ~                | sluggish reaction                         |                            |
| Zn/excess <sup>c</sup>      | THF                             | 78 °C/1 h          | 20 <sup>a</sup>  | 0   | : 100 (55:45) <sup>b</sup> |

<sup>a</sup>isolated yield. <sup>b</sup>the ratio of *anti*:*syn* based on 300 and 500 MHz NMR analysis. <sup>c</sup>Reformasky reaction with ethyl bromocrotonate.

addition to  $\beta$ -alkoxyaldehyde in the presence of various Lewis acid catalyst was then examined by using 1-ethoxy-1-(trimethylsilyloxy)-1,3-butadiene (**7**,  $Z/E = 90/10$ ), which was prepared by the literature procedure.<sup>2b</sup> The reaction of aldehyde **6** with 1.5 equiv of **7** in the presence of 1 equivalent of 1 M TiCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C afforded 75% of the mixture of  $\alpha$ - and  $\gamma$ -adduct in the ratio of 35 : 65 (Scheme 3). The diastereoselectivity of *anti* and *syn*-products of  $\gamma$ -adduct was observed to be 78 : 22 in which the olefinic geometry of two diastereomers proved to be *trans*, based on the vicinal coupling constant of 16 Hz, characteristic for the *trans* olefinic coupling. It is interesting that this reaction system produced  $\gamma$ -adduct as major product even at low temperature (-78 °C) although the reported examples showed only  $\alpha$ -adduct below the temperature of -78.<sup>2b</sup> In order to increase the diastereoselectivity, the reaction carried out at -94 °C gave the *anti*- $\gamma$ -adduct **9** with 83 : 17 diastereoselectivity and  $\alpha$ -vinyl adduct **8** (91 : 9 diastereoselectivity) in 33 and 37% yields respectively. Hence, a high degree of diastereoselection of the *anti*-products **8** and **9** was observed, which could be explained in terms of a chelated intermediate (Scheme 1). The use of anhydrous ZnCl<sub>2</sub> at -78 °C showed sluggish reaction resulting in 20% overall yield of  $\alpha$ - and  $\gamma$ -adducts in the ratio of 35 : 65; the diastereoselectivity of *anti*/*syn* of  $\gamma$ -adduct was somewhat decreased to 65 : 35 (Table 1). The reaction with 1 M ZnCl<sub>2</sub> in THF at 0-25 °C improved the yield (85%) with mainly 95% of the regioselective  $\gamma$ -adduct as expected from the favorable formation of thermodynamically-controlled product at higher temperature.<sup>2b</sup> The *anti*/*syn* diastereomeric ratio of the  $\gamma$ -adduct was still observed to be 60 : 40, which could suggest that ZnCl<sub>2</sub> works moderately in a wide range of temperature for the chelation-controlled reaction. Other acid catalysts such as Et<sub>2</sub>AlCl and LiClO<sub>4</sub> gave low yield or caused sluggish reaction.

The relative and absolute stereochemistry of the major product **9** was proved by spectral analysis of acetone **10**; decoupling experiments at 500 MHz revealed 10.1 Hz of the vicinal coupling constant between 5-H and 6-H, which was assignable to diaxial coupling.<sup>9</sup> Direct measurement of vicinal coupling ( $J_{2,3}$ ) of  $\alpha$ -adduct **8** showed 8.4 Hz which was assignable to *anti* configuration based on the behavior of  $\beta$ -hydroxy carbonyl compounds where  $J_{anti} > J_{syn}$  ( $J_{anti}$  typical 7-10 Hz).<sup>10</sup> Interestingly, only two diastereomer of **8** was detected after chromatographic separation on silica gel of any expected products; this could give the evidence that the

aldol reaction with TiCl<sub>4</sub> was carried out without a loss of chiral integrity. Especially, product analysis (*vide supra*) of the reaction with silyl dienolate (90% *Z*) showed the *anti* configuration of C2-C3 of **8** which was unexpected, compared to the formation of *syn*-aldol products as major with (*Z*)-enolates *via* associative 6-membered transition state.

Thus, asymmetric aldol reaction of a chiral alkoxyaldehyde with silyl dienolate derived from methyl crotonate was accomplished with moderate to high diastereoselection *via* chelation control under the presence of TiCl<sub>4</sub> or ZnCl<sub>2</sub> at 25 to -94 °C. The regioselectivity of  $\gamma$ -adduct was enhanced with increase of temperature at the expense of diastereoselectivity. Hence the method using aldol addition for one-step homologation of a crotonic acid unit with aldehydes might be proved to be a potential synthetic methodology to give regioselectively and stereoselectively-controlled  $\alpha$ - or  $\gamma$ -substituted products which could serve as a useful synthetic precursor for natural product synthesis.

## Experimental Section

**Synthesis of ethyl (2E, 5S, 6R)-7-allyloxy-5-hydroxy-6-methyl-2-heptenoate (9) and ethyl (1R, 2R, 3R)-5-allyloxy-3-hydroxy-4-methyl-2-vinylpentanoate (8).** To a cooled (-78 °C), stirred solution of aldehyde **6** (1.0 g, 7.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added 1 M TiCl<sub>4</sub> (7.8 mL) and vinylsilyl ketene acetal **7<sup>2b</sup>** (2.18 g, 11.7 mmol). The mixture was stirred at -78 °C for 3 h and quenched with 5% NaHCO<sub>3</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL $\times$ 3). The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 9% EtOAc/hexane) afforded 0.91 g (49%) of **9** as a diastereomeric mixture (78 : 22); major diastereomer: IR (CH<sub>2</sub>Cl<sub>2</sub>) 3454, 2965, 1730, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.05 (m, 1H, C3-H), 5.89 (d, 1H,  $J=15.1$  Hz, C2-H), 5.88 (m, 1H, allyl), 5.25 (dd, 1H,  $J=17.3, 1.6$  Hz, allyl), 5.18 (dd, 1H,  $J=10.5, 1.6$  Hz), 4.17 (q, 2H,  $J=7.0$  Hz, OEt), 3.97 (m, 2H, allyl), 3.67 (m, 1H, C5-H), 3.59 (d, 1H,  $J=4$  Hz), 3.57 (dd, 1H,  $J=9.5, 3.9$  Hz, C7-H), 3.43 (dd, 1H,  $J=9.5, 7.8$  Hz, C7-H), 2.45 (m, 1H, C4-H), 2.35 (m, 1H, C4-H), 1.86 (m, 1H, C6-H), 1.27 (t, 3H,  $J=7.0$  Hz), 0.89 (d, 3H,  $J=7.0$  Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  166.3 (C1), 145.6 (C3), 134.0 (allyl), 123.4 (C2), 117.4 (allyl), 75.2 (C5), 75.0 (C7), 72.3 (allyl), 60.1 (OEt), 37.8 (C4), 37.6 (C6), 14.1 (OEt), 13.7 (C6-Me); EIMS  $m/z$  (rela-

tive intensity) 179 (3), 143 (11), 114 (100), 86 (62); HRMS (EI) 197.1182 (M-C<sub>2</sub>H<sub>5</sub>O).

Flash chromatography (silica gel, 9% EtOAc/hexane) also afforded 0.49 g (26%) of  $\alpha$ -adduct **8** as a diastereomeric mixture; major diastereomer: IR (CH<sub>2</sub>Cl<sub>2</sub>) 3450, 2872, 1729, 1262 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.87 (m, 2H), 5.24 (m, 3H), 4.18 (dq, 2H, *J*=7.0, 2.8 Hz, OEt), 3.96 (dd, 2H, *J*=5.6, 1.5 Hz, allyl), 3.78 (ddd 1H, *J*=8.4, 7.7, 5.2 Hz, C3-H), 3.56 (dd, 1H, *J*=9.2, 4.5 Hz, C5-H), 3.49 (dd, 1H, *J*=11.94, 4.5 Hz, C5-H), 3.36 (d, 1H, *J*=7.7 Hz, OH), 3.31 (t, 1H, *J*=8.4 Hz, C2-H), 1.92 (m, 1H, C4-H), 1.27 (t, 3H, *J*=7.0 Hz, OEt), 1.08 (d, 3H, *J*=7.1 Hz, C4-Me); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  172.9 (C1), 134.4 (allyl), 133.6 (vinyl), 118.8 (vinyl), 117.1 (vinyl), 76.4 (C3), 72.4 (allyl), 72.3 (C5), 60.8 (OEt), 55.3 (C2), 35.5 (C4), 15.3 (C4-Me), 14.12 (OEt); EIMS *m/z* (relative intensity) 187 (3), 183 (2), 114 (100), 86 (83); HRMS (EI) 197.1183 (M-C<sub>2</sub>H<sub>5</sub>O).

**Ethyl (2E,5S,6R)-5,7-dihydroxy-6-methyl-5,7-O-(1-methylethylidene)-2-heptenoate (10).** To a stirred solution of the diastereomeric mixture **9** (20 mg) in EtOH (5 mL) was added TsOH (2 mg) and 10% pd/C (*ca.* 1 mg). The mixture was refluxed for 4 h and filtered through Celite. The filtrate was washed with brine, dried over MgSO<sub>4</sub>, filtered, and evaporated *in vacuo* to give a yellowish residue (15 mg). The residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was mixed with dimethoxy propane (0.2 mL) and TsOH (2 mg). The mixture was stirred at 25 °C for 12 h, and the solvent was evaporated *in vacuo*. Preparative thin-layer chromatography on silica gel (9% EtOAc/hexane) gave 10 mg of the title compound as a diastereomeric mixture.

Major diastereomer (*anti*): IR (CH<sub>2</sub>Cl<sub>2</sub>) 1713, 1269 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.01 (m, 1H), 5.88 (d, 1H, *J*=16 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.68 (dd, 1H, *J*=11.5, 5.5 Hz), 3.61 (m, 1H), 3.51 (t, 1H, 11.5 Hz), 2.49 (m, 1H), 2.34 (m, 1H), 1.69 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.29 (t, 3H, *J*=7.0 Hz), 0.75 (d, 3H, *J*=7.0 Hz). Decoupling experiments showed *J*<sub>5,6</sub>=10.1 Hz.

Minor diastereomer (*syn*): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  6.90 (m, 1H), 5.90 (d, 1H, *J*=16 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 4.10 (dd,

1H, *J*=11.5, 3.0 Hz), 4.07 (m, 1H), 3.59 (dd, 1H, *J*=11.5, 2.0 Hz), 2.41 (m, 2H), 1.45 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.28 (t, 3H), 1.08 (d, 3H, *J*=7.0 Hz). Decoupling experiments showed *J*<sub>5,6</sub>=2.3 Hz. EIMS *m/z* (relative intensity) 227 (97), 129 (100), 97 (50), 93 (82); HRMS (EI) 242.1484 (M).

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