ORGANIC LETTERS

2012
Vol. 14, No. 11
2734–2737

Highly Enantio- and Diastereoselective Vinylogous Aldol Reaction by LiCl-Assisted BINOL–Titanium Species

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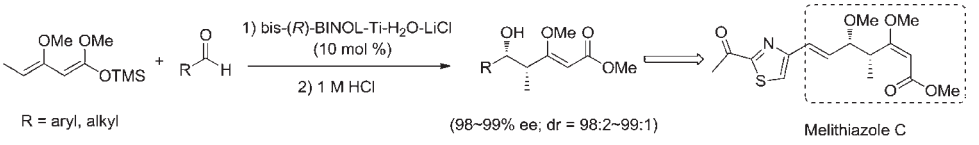
Received April 12, 2012

ABSTRACT



The first highly enantio- and diastereoselective vinylogous aldol reaction between propionyl acetate-derived Brassard's diene and aldehydes was accomplished by titanium–lithium combined Lewis acid, affording δ-hydroxy-γ-methyl-β-methoxy acrylates. This methodology was utilized in convenient and concise construction of the polypropionate moiety in cystothiazole A and melithiazole C.

The asymmetric vinylogous Mukaiyama aldol (AVMA) reaction has emerged as one of the most applied C–C bond-forming transformations in the total synthesis of complex structures.[1] Among all the *O*-silyl dienolates that have been developed, the synthetic equivalents of acetoacetate represent a group of promising reagents as their addition to aldehydes provides easy access to optically pure δ-hydroxy-β-ketoesters, versatile key intermediates in the synthesis of biologically active natural products and commercial drugs.[2,3] Meanwhile, scarce attention has been devoted to the homologous propionyl acetate derived dienolate,[4] and no effective catalytic methodology has been exploited for the AVMA reaction with propionyl acetate derivatives in terms of both high enantio- and diastereoselectivity. The vinylogous aldol addition of propionyl acetate dienolate to aldehyde would deliver δ-hydroxyl carbonyl compounds with vicinal hydroxymethyl stereogenic centers which occur frequently in natural products and pose a great challenge to the organic chemists.

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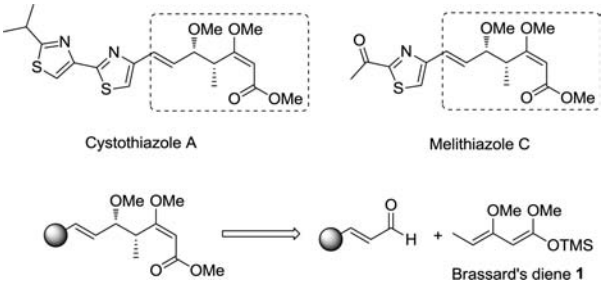
10.1021/ol300946j
Published on Web 05/23/2012

Cystothiazole A and melithiazole C represent a group of fungicidal β-methoxy acrylate antibiotics which have been isolated from different strains of myxobacteria.[5] As shown in Scheme 1, they share a common pharmacophoric polypropionate moiety linked to a bisthiazole, a thiazole–thiazoline, or a single thiazole ring system via a double bond. Several total synthesis attempts have been accomplished toward compounds of this group, and the *syn*-methylmethoxy(hydroxy) vicinal stereogenic centers could be concisely constructed by asymmetric Evans aldol reaction (catalytic or chiral auxiliary assisted), ring-opening of methyl oxirane, or crotylation of dimethyl acetal.[6] However, in all of these reports, additional multisteps were needed to extend the carbon chain for construction of the β-methoxy acrylate moiety. Consequently, with the goal of a more convenient and faster synthetic strategy, we considered the AVMA reaction between aldehyde and the propionyl acetate derived Brassard's diene **1**[7] as a potentially powerful tool for simultaneous formation of the vicinal stereogenic centers and the β-methoxy acrylate moiety. Based on the two points mentioned above, we started our research to investigate the AVMA reaction between aldehydes and Brassard-type diene **1**, and in this paper we describe our efforts toward this goal.

Scheme 1. Examples of Antibiotics Isolated from Myxobacteria and Our Retrosynthetic Analaysis



For the AVMA reaction of Brassard's diene **1** with aldehyde, the challenge would mainly lie in the triple selectivities: not only the inherent enantio- and diastereoselectivity but also the chemoselectivity that a competitive hetero-Diels–Alder reaction could also happen under the catalytic conditions.[7] Previously, our group reported a novel combined Lewis acid[8] catalyst BINOL–Ti–H_2O–LiCl (BTHL) that was generated in situ by equal molar combination of hydrolyzed BINOL–Ti species and weak Lewis acid LiCl (Figure 1) to effectively promote the AVMA reaction between aldehydes and acetoacetate-derived Brassard's diene.[3p] We reasoned that the terminal methyl substituent at C4 position of the diene **1** may facilitate its facial discrimination toward the attacked aldehyde in aldol reaction compared with its acetoacetate analogue.

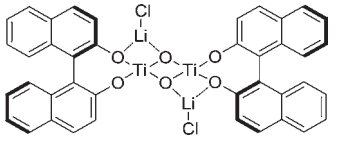
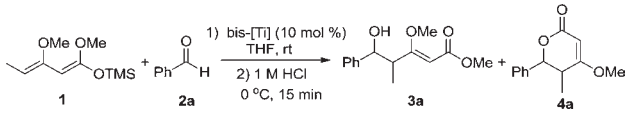


Figure 1. Proposed structure for (*R*)-BTHL: weak Lewis acid (LiCl) assisted BINOL–Ti species.

We initiated our research employing 5 mol % of the catalytic (*R*)-BTHL in the addition of Brassard's diene **1** to benzaldehyde at 25 °C in THF. To our delight, this reaction delivered the linear aldol product **3a** in 80% yield with perfect enantio- and diasteroselectivity (99.4% ee and dr = 98:2), while only 19% of cycloadduct **4a** was yielded (Table 1, entry 1). The configuration of the double bond in **3a** was identified as *Z* via the NOE difference spectroscopy by measurement of the alkene hydrogen and the γ-methyl hydrogen. To the best of our knowledge, this is the first example of highly both enantio- and diastereoselective AVMA reaction of propionyl acetate derived Brassard's diene with aldehydes.

Table 1. Various (*R*)-BINOL-Ti Species Catalyzed AVMA Reaction of Brassard's Diene **1** with Benzaldehyde **2a**[a]



entry	BINOL/Ti(O-*i*-Pr)$_4$/H_2O/LiCl	**3a**[b] (%)	dr[c]	ee[c] (%)	**4a**[b] (%)
1[d]	1:1:1:1	80	98:2	99.4	19
2	1:1:1:1	94	99:1	99.6	6
3	1:1:0:0	55	64:36	79.4	44
4	1:1:1:0	96	52:48	29.6	4
5	1:1:0:1	58	92:8	92.7	41

[a] Unless specially noted, all reactions were performed with 0.5 mmol of benzaldehyde and 1 mmol of Brassard's diene **1** in 2 mL of THF at 25 °C over 16 h. [b] Isolated yield. [c] Determined by HPLC analysis using chiral OJ-H column. [d] The catalyst loading is 5 mol % and reaction time is 40 h.

An increase of the (*R*)-BTHL loading to 10 mol % greatly depressed the HDA pathway and afforded the aldol product **3a** almost exclusively (yield 94%, dr = 99:1,

(6) For selected examples of total synthesis, see: (a) Williams, D. R.; Patnaik, S.; Clark, M. P. *J. Org. Chem.* **2001**, *66*, 8463. (b) Bach, T.; Heuser, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3184. (c) Bach, T.; Heuser, S. *Chem.—Eur. J.* **2002**, *8*, 5585. (d) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetradron Lett.* **2002**, *43*, 643. (e) Deroy, P. L.; Charette, A. B. *Org. Lett.* **2003**, *5*, 4163. (f) Shao, J.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3083. (g) Clough, J. M.; Dube, H.; Martin, B. J.; Pattenden, G.; Reddy, K. S.; Waldron, I. R. *Org. Biomol. Chem.* **2006**, *4*, 2906. (h) Takayama, H.; Kato, K.; Kimura, M.; Akita, H. *Heterocycles* **2007**, *71*, 75. (i) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425. (j) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Eur. J. Org. Chem.* **2008**, 2701.

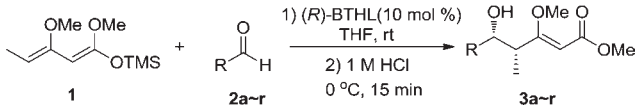
(7) For HDA reaction of Brassard's diene with aldehydes, see: (a) Togni, A. *Organometallics* **1990**, *9*, 3106. (b) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185. (c) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X. *Eur. J. Org. Chem.* **2005**, 3542. (d) Du, H.; Zhao, D.; Ding, K. *Chem.—Eur. J.* **2004**, *10*, 5964. (e) Lin, L.; Fan, Q.; Qin, B.; Feng, X. *J. Org. Chem.* **2006**, *71*, 4141. (f) Lin, L.; Chen, Z.; Yang, X.; Liu, X.; Feng, X. *Org. Lett.* **2008**, *10*, 1311. (g) Lin, L.; Kuang, Y.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3868.

ee = 99.6%, entry 2). Some comparison experiments were then carried out to highlight the indispensability of both H_2O and LiCl in the high performance of BTHL (entries 3–5, Table 1). At first, the simple equal molar combination of (*R*)-BINOL and Ti(O-*i*-Pr)$_4$ was tested under identical conditions, and the desired aldol product **3a** was obtained in only 55% yield with disappointing selectivities (dr = 64:36, 79% ee, entry 3), while 44% yield of the HDA product **4a** was produced. When the (*R*)-BINOL–Ti complex was hydrolyzed with 1 equiv of water and used as catalyst,[9] the aldol product **3a** was dominantly obtained with only a trace of **4a**, whereas the enantio- and diastereoselectivity dropped dramatically (dr = 52:48, 29.6% ee, entry 4). When LiCl was added to the (*R*)-BINOL–Ti complex in the absence of H_2O, both the enantio- and diastereoselectivity were increased significantly (dr = 92:8, 93% ee, entry 5), while the poor selectivity of aldol/HDA product sustained compared with entry 2. All these experiments demonstrated that the presence of both LiCl and H_2O was essential for the high performance of BHTL.

The substrate generality of this methodology was then investigated utilizing 10 mol % of (*R*)-BTHL, and the results are summarized in Table 2. Various substituted benzaldehydes **2a**–**k**, bearing an electron-donating and -withdrawing group on the benzene ring, smoothly proceeded through the aldol reaction with Brassard's diene **1** to afford the target compounds with excellent yields and enantio- and diastereoselectivities (82–94% yields, dr = 98:2–99:1, 98–99% ee, entries 1–11, Table 2). The furaldehyde and cinnamaldehyde were also tolerated with excellent results (entries 12 and 13). Moreover, aliphatic aldehydes were also suitable substrates, although an extended time to 40 h was needed for acceptable yields. Linear aliphatic aldehyde **2n**–**p** underwent the aldol reaction smoothly in good yields with excellent stereoselectivities (yield 67–75%, dr = 99:1, 99% ee, entries 14–16). The crotonaldehyde **2q** and phenylpropanal **2r** were also well tolerated (entries 17 and 18).

We have previously revealed that the Brassard-type diene derived *Z* aldol product would transform to a thermodynamically more stable *E* isomer under acidic conditions.[3p] However, when the aldol product **3h** was treated with TFA in THF at 0 °C, the isomerization was rather slow (Scheme 2). We reasoned that the γ-methyl group posed a steric hindrance which decreased the energy difference of the *E*/*Z* isomers. After being stirred over 24 h, without purification, the residue was treated with 1 M NaOH in methanol to afford the cycloproduct **4h** in 25% yield for two steps with maintained stereoselectivity (dr = 98:2, 98% ee). Solvent screening revealed that in $CHCl_3$ the quick isomerization was accomplished in 30 min, and followed by annulation, 60% yield of the lactone **4h** was obtained albeit with epimerization (dr = 89:11, 92% ee). The lactone **4h** shares the same subunit with many biologically active natural products, such as prelactones, leiodermatolide, and disdodermatolide,[10] which greatly expands the scope of this methodology. The absolute configuration of **4h** was unambiguously determined to be (5*R*,6*R*) by X-ray crystal analysis,[11] and the aldol product **3h** was assigned to be (4*R*,5*R*) accordingly.[12] The absolute configuration of the hydroxyl carbon center parallels that which we observed in the previous report.[3p]

Table 2. (*R*)-BTHL-Catalyzed AVMA Reaction of Brassard's Diene **1** with Various Aldehydes[a]



entry	R	yield[b] (%)	*syn*/*anti*[c]	ee[c] (%)
1	C_6H_5 (**2a**)	94	99:1	99
2	*p*-$CH_3C_6H_4$ (**2b**)	92	99:1	99
3	*o*-$CH_3OC_6H_4$ (**2c**)	92	99:1	99
4	*p*-$CH_3OC_6H_4$ (**2d**)	88	99:1	99
5	3,4,5-$(CH_3O)_3C_6H_2$ (**2e**)	93	99:1	99
6	*o*-ClC_6H_4 (**2f**)	90	99:1	99
7	*p*-ClC_6H_4 (**2g**)	94	98:2	98
8	*p*-BrC_6H_4 (**2h**)	91	99:1	99 (*R*,*R*)[e]
9	*o*-FC_6H_4 (**2i**)	93	99:1	99
10	*p*-FC_6H_4 (**2j**)	93	99:1	99
11	*p*-$NO_2C_6H_4$ (**2k**)	82	98:2	98
12	2-furyl (**2l**)	95	99:1	99
13	$C_6H_5CH{=}CH$ (**2m**)	96	99:1	99
14[d]	*n*-C_3H_7 (**3n**)	75	99:1	99
15[d]	*n*-C_4H_9 (**2o**)	71	99:1	99
16[d]	*n*-C_5H_{11} (**2p**)	67	99:1	99
17[d]	$CH_3CH{=}CH$ (**2q**)	48	99:1	99
18	$C_6H_5CH_2CH_2$ (**2r**)	86	99:1	99

[a] Unless specially noted, all reactions were performed with 0.5 mmol of aldehyde **2a**–**r** and 1 mmol of Brassard's diene **1** in 2 mL of THF at 25 °C over 16 h. [b] Isolated yield. [c] Determined by HPLC analysis using indicated chiral columns. [d] Over 40 h. [e] The absolute configuration was determined unambigously by X-ray crystal analysis; see below.

(8) For review of combined acid in asymmetric catalyst design, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. For selected examples, see: (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (c) Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 8271. (d) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, 393. (e) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186. (f) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (g) Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628. (h) Cheon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 13248.

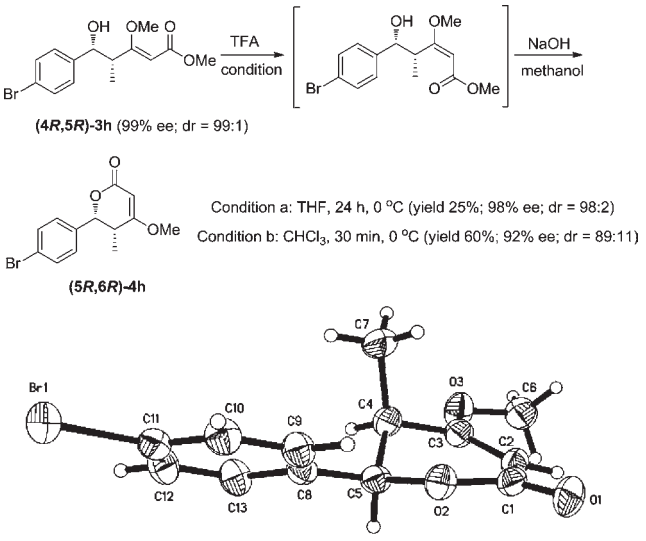
(9) (a) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861. (b) Takizawa, S.; Somei, H.; Jayaprakash, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5711.

(10) For recent examples of total synthesis, see: (a) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1221. (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133. (c) Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 3219. (d) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, J. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (e) Lemos, E. D.; Porée, F. H.; Commerçon, A.; Betzer, J. F.; Pancrazi, A.; Ardisson, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1917.

(11) CCDC 867439 (**4h**) is available free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) For the assumed transition state for the *syn*-diastereoselectivity, see the Supproting Information.

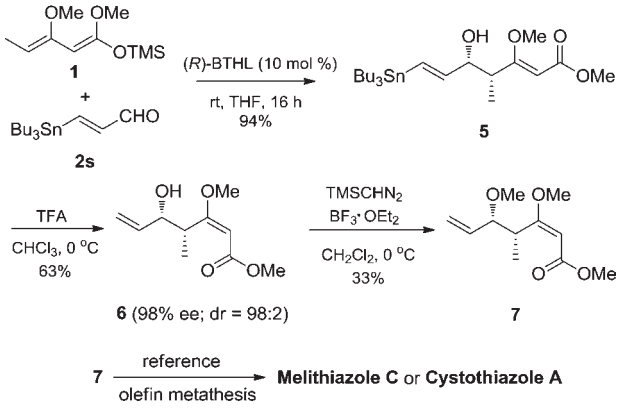
Scheme 2. Lactonization of **3h** and the Structure of **4h** Determined by X-ray Crystal Analysis[a]



[a] Ellipsoids set at 30% probability.

With elucidation of the *syn* stereochemistry of the vicinal stereogenic centers which is consistent with the above-mentioned β-methoxy acrylate fungicides, we set out to examine the versatility of this methodology in the synthesis of these structures. We chose the tributylstannyl acrolein **2s** as the starting aldehyde because we reasoned that the tributylstannyl group was a good synthetic handle for further Stille coupling. Using (*R*)-BTHL as catalyst, the aldehyde **2s** reacted smoothly with Brassard's diene **1** to afford the desired compound **5** in perfect yield up to 94%. The aldol product **5** was then treated with TFA in $CHCl_3$ to undergo the *Z*/*E* isomerization. However, the tributylstannyl group was detached unexpectedly, and product **6** was obtained in 63% yield with simultaneously thorough *Z*/*E* isomerization of the double bond in the acrylate moiety, and the epimerization could be avoided with well-controlled reaction time and conditions (*syn*/*anti* = 98:2, ee = 98%). The hydroxyl group of compound **6** was then methylated using $TMSCHN_2$ in the presence of $BF_3 \cdot OEt_2$ affording the known building block **7** in 33% yield. Both cystothiazole A[6i] and melithiazole C[6j] could be easily synthesized from compound **7** according to the reported procedure via olefin cross-metathesis (Scheme 3). We believe that this methodology provides a common strategy for convenient and concise construction of the polypropionate moiety in all the related antibiotics.

Scheme 3. Formal Synthesis of Melithiazole C and Cystothiazole A



In conclusion, we have described the first highly enantio- and diastereoselective AVMA reaction of propionyl acetate derived Brassard's diene with aldehydes catalyzed by LiCl assisted BINOL–Ti species. The methodology features high stereoselectivity and a wide aldehydes tolerance under mild conditions. In addition, the utility of this protocol was demonstrated in the convenient and formal synthesis of cystothiazole A and melithiazole C.

Acknowledgment. We acknowledge financial support from the National Natural Science Foundation of China (Nos. 20972022, 21076035) and the "111" project of Ministry of Education of China.

Supporting Information Available. Experimental procedures, spectral and analytical data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.