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# Asymmetric Aldol Reaction with Diisopinocampheyl Enolborinates of Propionates

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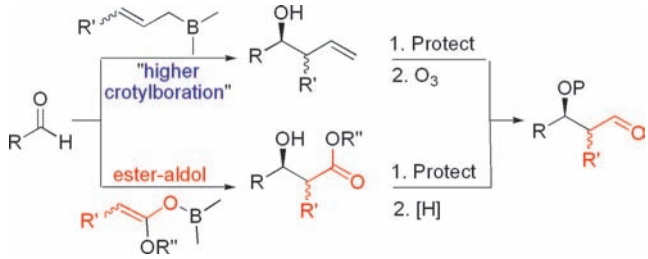
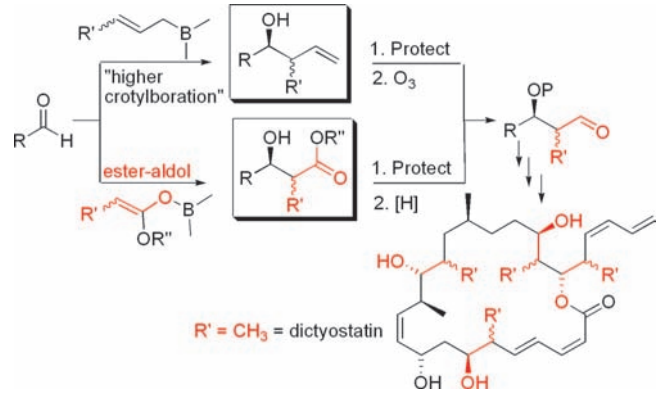
## ABSTRACT




**A convenient and general, *reagent-controlled*, diastereo- and enantioselective aldol reaction of diisopinocampheylboron enolates of esters, followed by reduction, has been developed as an alternative to crotylboration-ozonolysis. This protocol was then exploited for the double diastereoselective synthesis of the C11−C17 subunit of (−)-dictyostatin.**

Pinane-mediated asymmetric crotylboration[1] and enolboration-aldolization[2] are highly diastereo- and enantioselective carbon−carbon bond-forming reactions routinely employed for the syntheses of complex molecules bearing $\beta$-methyl hydroxyl units. Although repetitive crotylboration[3] and enolboration-aldolization of ketones[2] and amides[4] have been exploited for polyketide syntheses, the potential application of the enolboration-aldolization of esters remains relatively unexplored. In continuation of our project on the total synthesis of potent tubulin polymerizing anticancer agent (−)-dictyostatin (Scheme 1),[5] we were confronted with the need for sufficient quantities of the subunits for a practical synthesis of its analogs and homologues. Our initial approach using Brown's "higher crotylboration"[6] was inadequate because of the cumbersome preparation of the expensive starting allenes. Our ensuing investigations were channelled

**Scheme 1**




(1) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
(2) (a) Cowden, C. J.; Paterson, I. *Organic Reactions*; John Wiley & Sons: New York, 1997; Vol. 51, pp 1−209. (b) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (c) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (d) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.
(3) For a review on crotylboration for synthesis, see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *34*, 23.
(4) (a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartoli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767.

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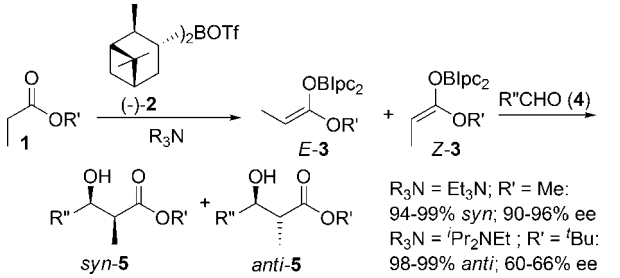
toward a more efficient diisopinocampheylboron triflate ($Ipc_2BOTf$, **2**)-mediated aldol reaction of esters.

Very few reports on the boron-mediated aldol reaction of esters have appeared in the literature since the description of (*E*)-enolborinates of thioesters by Masamune three decades ago.[7] This could be attributed to the report of a failed attempt to enolize methyl propionate using dibutylboron triflate.[8] Successful *B*-bromodiazaborolidine and *B*-iododicyclohexylborane-mediated aldol reaction of esters were later reported by Corey[9] and Brown,[10] respectively.[11] A decade ago Masamune and Abiko amended the literature[12] with the dialkylboron triflate-mediated enolization of esters, followed by aldolization of aldehydes, which led to a substrate-controlled asymmetric aldol reaction of norephedrine-derived ester enolates.[12b−d] They obtained either *syn*- or *anti*-α-methyl-*β*-hydroxy esters, depending on the alkyl group on boron.[12d] Herein, we report a convenient and general, *reagent-controlled*, diastereo- and enantioselective aldol reaction of diisopinocampheylboron enolates of esters (Scheme 2) and its application to the double diastereoselective synthesis of the C11−C17 subunit of (−)-dictyostatin.

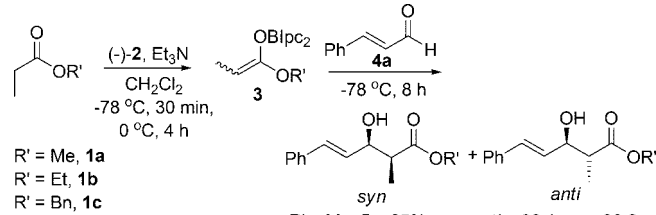
**Scheme 2**




With prior knowledge that the stereochemical course of the ester-aldol reaction can be controlled by choosing appropriate reagents and amines,[13] the enolization of methyl propionate (**1a**) with diisopinocampheylboron triflate (**2**), prepared from diisopinocampheylborane and triflic acid,[2a] and subsequent aldolization of cinnamaldehyde (**4a**)[14] was optimized to achieve maximum diastereo- and enantioselectivity. The enolization of **1a** with (−)-**2** in the presence of $^{i}Pr_2NEt$ at −78 °C for 4 h and aldolization of **4a** at −78 °C for 4 h achieved only a 3:2 mixture of *syn*- (major) and *anti*-products (entry 1, Table 1). The ratio of the *syn*-product could be increased to 6:1 by replacing $^{i}Pr_2NEt$ with $Et_3N$, under similar conditions. Subsequently, a change in the enolization temperature to 0 °C for 5 h dramatically increased the *syn*-diastereomer ratio to 97:3.

The optimal conditions were finally established by commencing the enolate formation at −78 °C for 30 min and then warming to 0 °C for 4 h, followed by aldolization at −78 °C, when the hydroxy ester was obtained in 85% yields with a 99:1 diastereoselectivity and 98:2 enantioselectivity. Notably, the enolization temperature influences the diastereoselectivity, whereas the aldolization conditions have little or no effect.

**Scheme 3.** Effect of Ester Group on Stereo- and Enantioselectivity




R' = Me, **1a**
R' = Et, **1b**
R' = Bn, **1c**
R' = $^{i}$Pr, **1d**
R' = $^{t}$Bu, **1e**

R' = Me, **5a**, 85%, *syn*:*anti* = 99:1, er = 98:2
R' = Et, **6a**, 72%, *syn*:*anti* = 90:10, er = 96:4
R' = Bn, **7a**, 70%, *syn*:*anti* = 85:15, er = 94:6
R' = $^{i}$Pr, **8a**, 68%, *syn*:*anti* = 80:20, er = 94:6
R' = $^{t}$Bu, **9a**, 50%, *syn*:*anti* = 1:99, er = 20:80

Under these standardized conditions, we examined the stereoselection by varying the alkyl group of the propionates (**1b**−**e**) and identified methyl propionate (**1a**) as the ester of choice for the preparation of *syn*-aldols. Although the enantioselectivity remained high, a gradual decrease of *syn*-diastereoselectivity was observed for ethyl, benzyl, and isopropyl esters (**1b**−**d**). The enolization was very slow for *tert*-butyl propionate (**1e**) (Scheme 3), and aldolization provided the *anti*-aldol (**9a**) essentially exclusively in 50% yields with 60% ee, much higher than typically observed for the *anti*-aldols obtained with diisopinocampheyl boron enolates of ketones.[2a] The reversal of diastereoselection is similar to what has been noted earlier by Corey, Brown, and Masamune.[9−10,12] Remarkably, when $Et_3N$ was replaced with $^{i}Pr_2NEt$, the *anti*-selectivity increased from 1:4 to 95:5 for **1d** and the exclusive *anti*-aldol product was achieved with **1e** (Scheme 4).

These processes were then extended to a diverse set of aldehydes. Under the optimized conditions for *syn*-aldols

(5) (a) Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157. For other total syntheses of dictyostatin, see: (b) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629. (c) Shin, Y.; Fournier, J.; Fukui, Y.; Bruckner, A. M.; Curran, D. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4633. (d) O'Neil, G. W.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340.

(6) Brown, H. C.; Narla, G. *Tetrahedron Lett.* **1997**, *38*, 219.

(7) (a) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225.

(8) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(9) (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

(10) (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (b) Brown, H. C.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 2716. (c) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336.

(11) Boron-mediated aldol reactions of glycolates have been reported. (a) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035. (b) Lang, F.; Zewge, D.; Song, Z. J.; Biba, M.; Dormer, P.; Tschaen, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2003**, *44*, 5285.

(12) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590. (b) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (c) Abiko, A.; Liu, J.-F.; Buske, D. C.; Moriyama, S.; Masamune, S. *J. Am. Chem. Soc.* **1999**, *121*, 7168. (d) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.

(13) Abiko, A.; Liu, J.-F. *Acc. Chem. Res.* **2004**, *37*, 387.

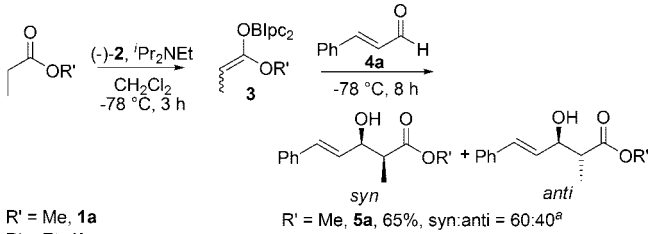
(14) Cinnamaldehyde (**4a**) was chosen because of the ease in the chromatographic separation of the product aldol.

**Table 1.** Optimization of Conditions for *syn*-Aldol Reaction

| | enolization condition | | | | | |
|---|---|---|---|---|---|---|
| entry | amine | temp | aldolization condition | yield (%) | *syn*:*anti*[a] | er[b] |
| 1 | $^{i}Pr_2NEt$ | −78 °C, 4 h | −78 °C, 4 h | 55 | 60:40 | *c* |
| 2 | $Et_3N$ | −78 °C, 4 h | −78 °C, 4 h | 72 | 85:15 | 96:4 |
| 3 | $Et_3N$ | −78 °C, 2 h; 0 °C, 3 h | −78 °C, 5 h | 65 | 87:13 | 96.5:3.5 |
| 4 | $Et_3N$ | −78 °C, 2 h; 0 °C, 3 h | −78 °C, 5 h | 69 | 89:11 | 96.5:3.5 |
| 5 | $Et_3N$ | −78 °C, 1 h; 0 °C, 1 h | −78 °C, 2 h; rt, 8 h | 57 | 90:10 | 96.5:3.5 |
| 6 | $^{i}Pr_2NEt$ | −78 °C, 0.5 h; 0 °C, 4 h | −78 °C, 8 h | 65 | 95:5 | 97:3 |
| 7 | $^{i}Pr_2NEt$ | 0 °C, 5 h | −78 °C, 2 h; rt, 8 h | 70 | 97:3 | 96.5:3.5 |
| **8** | **$Et_3N$** | **−78 °C, 0.5 h; 0 °C, 4 h** | **−78 °C, 8 h** | **85** | **99:1** | **98:2** |

[a] Determined from $^1$H NMR analysis of the crude reaction mixture. [b] Enantiomeric ratio determined by $^{19}$F NMR analysis of the Mosher ester derivative of the product. [c] Not determined.

**Scheme 4.** Optimization of Conditions for *anti*-Aldol Reaction




R' = Me, **1a**
R' = Et, **1b**
R' = Bn, **1c**
R' = $^{i}$Pr, **1d**
R' = $^{t}$Bu, **1e**

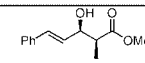
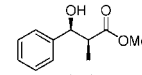
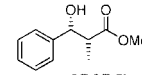
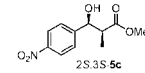
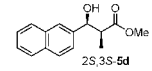
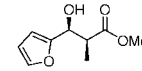
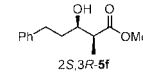
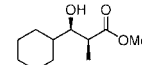
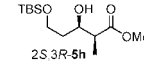
R' = Me, **5a**, 65%, syn:anti = 60:40[a]
R' = Et, **6a**, 68%, syn:anti = 60:40[a]
R' = Bn, **7a**, 70%, syn:anti = 56:44[a]
R' = $^{i}$Pr, **8a**, 60%, syn:anti = 5:95, er = 79:21
R' = $^{t}$Bu, **9a**, 75%, syn:anti = 1:99, er = 82:18
[a]er not determined

(Table 1, entry 8), the reactions of representative aromatic (**4a**−**d**), aliphatic (**4f**−**g**), and heterocyclic (**4e**) aldehydes proceeded with excellent diastereoselectivity (94−99%) and enantioselectivity (90−97%) for **5a**−**g**. An aldehyde bearing an acid-sensitive *tert*-butylsilyloxy group (**4h**, entry 9) was also included, which provided 63% of the corresponding *syn*-aldol (2*S*,3*R*)-**5h** in 94:6 diastereo- and 95:5 enantioselectivity. The results are summarized in Table 2. A select series of aldehydes were converted to the *anti*-aldols, as summarized in Table 3.

Taking advantage of the natural availability of both antipodes of α-pinene, the ester enolate *E*-**3a**, derived with the antipode of the reagent, (+)-**2**, was treated with benzaldehyde to provide the hydroxy ester 2*R*,3*R*-**5b** (Table 2, entry 3) in similar de and ee. Comparison of the optical rotations[15] of the enantiomers of **5b** with those reported confirmed the ee and the configurations. The stereochemistry of all other product aldols **5a**−**h** were assigned on the basis of analogy.

Pinene-derived reagents typically override the chirality of substrates in double diastereoselections.[16] A similar effect was observed in the case of the ester-aldol reaction of chiral aldehyde **11**, derived from the Roche ester (**10**), with the antipodes of *E*-**3a**. The aldol products **12** were obtained in

**Table 2.** *syn*-Aldol Reaction of Ester Enolborinate[a]

| entry | RCHO | product | yield, %[b] | dr[c] | er[d] |
|---|---|---|---|---|---|
| 1 | **4a** |  2*S*,3*R*-**5a** | 85 | 99:1 | 98:2 |
| 2 | **4b** |  2*S*,3*S*-**5b** | 82 | 97:3 | 98:2 |
| 3[e] | **4b** |  2*R*,3*R*-**5b** | 79 | 95:5 | 2:98 |
| 4 | **4c** |  2*S*,3*S*-**5c** | 70 | 96:4 | 97:3 |
| 5 | **4d** |  2*S*,3*S*-**5d** | 72 | 95:5 | 96:4 |
| 6 | **4e** |  2*S*,3*S*-**5e** | 68 | 95:5 | 95:5 |
| 7 | **4f** |  2*S*,3*R*-**5f** | 75 | 98:2 | 99:1 |
| 8 | **4g** |  2*S*,3*R*-**5g** | 73 | 98:2 | 98:2 |
| 9 | **4h** |  2*S*,3*R*-**5h** | 63 | 94:6 | 95:5 |

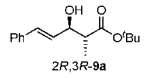
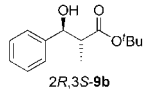
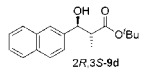
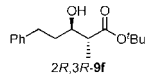
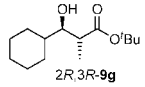
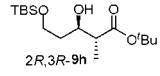
[a] Reaction conditions: (−)-**2** (1.3 mmol), prepared from (−)-$Ipc_2BH$ (from (+)-α-pinene) and trifluoromethanesulfonic acid, $Et_3N$ (2.2 mmol), and methyl propionate (1 mmol) were stirred at −78 °C for 30 min and at 0 °C for 4 h; aldehyde (0.94 mmol) was added at −78 °C, and the mixture was stirred for 8 h. Entry 4, stirred at rt for 5 h. [b] Isolated yield after column chromatography. [c] Determined from $^1$H NMR analysis of the crude reaction mixture. [d] Determined via $^1$H and $^{19}$F NMR spectroscopy of the MTPA ester. [e] (+)-**2** was used for the aldol reaction.

65% and 60% yields and in 98:2 and 95:5 diastereomeric ratios, respectively. The absolute stereochemistry of **12** was confirmed by converting the 2*R*,3*S*,4*S*-diastereomer to **15**, the C11−C17 subunit of (−)-dictyostatin (Scheme 5), as follows.

The secondary alcohol 2*R*,3*S*,4*S*-**12** was protected as the TBS ether to 2*S*,3*R*,4*S*-**13**, followed by a borane reduction of the ester to the primary alcohol, 2*S*,3*R*,4*S*-**14**. Conversion

(15) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296.
(16) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1.

**Table 3.** *anti*-Aldol Reaction of Ester Enolborinate[a]

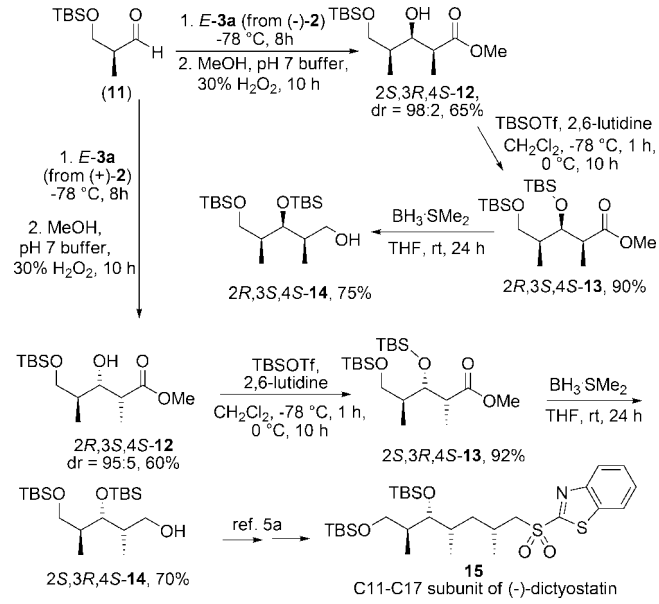
| entry | RCHO | product | yield, %[b] | dr[c] | er[d] |
|---|---|---|---|---|---|
| 1 | **4a** |  2*R*,3*R*-**9a** | 75 | 1:99 | 82:18 |
| 2 | **4b** |  2*R*,3*S*-**9b** | 80 | 1:99 | 81:19 |
| 3 | **4d** |  2*R*,3*S*-**9d** | 72 | 1:99 | 80:20 |
| 4 | **4f** |  2*R*,3*R*-**9f** | 61 | 1:99 | 80:20 |
| 5 | **4g** |  2*R*,3*R*-**9g** | 70 | 2:98 | 83:17 |
| 6 | **4h** |  2*R*,3*R*-**9h** | 70 | 1:99 | 75:25 |

[a] Reaction Conditions: (−)-**2** (1.3 mmol), $^{i}Pr_2NEt$ (2.2 mmol), and *tert*-butyl propionate (1 mmol) were stirred at −78 °C for 3 h; aldehyde (0.94 mmol) was added at −78 °C, and the mixture was stirred for 8 h. [b] Isolated yield after column chromatography. [c] Determined from $^1H$ NMR of the crude reaction mixture. [d] Determined via $^1H$ and $^{19}F$ NMR spectroscopy of MTPA ester.

to the sulfone **15** was achieved via a Myers' alkylation, lithium amidoborohydride (LAB) reduction, Mitsunobu reaction, followed by MCPBA oxidation.[5a] The $^1H$ NMRs of both **14** and **15** were identical to those reported earlier by us.

In summary, we have described the first general asymmetric aldol reaction of diisopinocampheylboron-mediated enolates of esters. We have also shown the utility of this protocol with the preparation of the C11−C17 subunit of (−)-dictyostatin. We believe that this sequential asymmetric

**Scheme 5.** Synthesis of C11−C17 Subunit of (−)-Dictyostatin




ester enolate aldol reaction-ester reduction will become a versatile and excellent approach, if not a superior alternative, to sequential crotylboration-ozonolysis. A second generation synthesis of (−)-dictyostatin and its trifluoromethyl analogs are underway and will be reported in due course.

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**Supporting Information Available:** Experimental details and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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