Pergamon

*Tetrahedron: Asymmetry*, Vol. 8, No. 20, pp. 3371–3374, 1997

Printed in Great Britain
PII: S0957-4166(97)00461-8
0957-4166/97 $17.00 + 0.00

# Enantioselective acyclic stereoselection under catalyst control — III. A very short asymmetric synthesis of the bryostatin $C_1$–$C_9$ segment using the chiral oxazaborolidinone-promoted aldol reaction †

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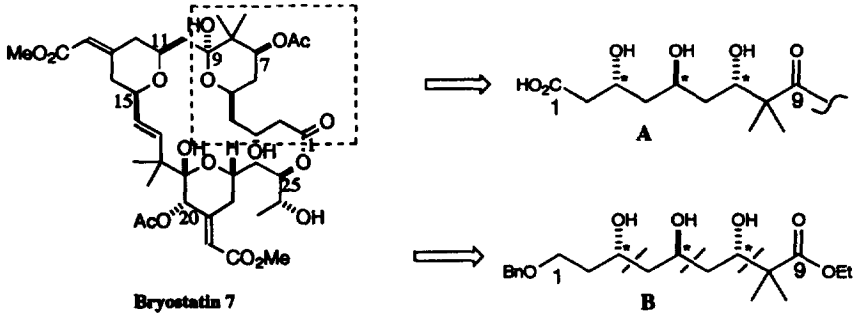
***Abstract:*** A very short asymmetric synthesis of the bryostatin $C_1$–$C_9$ segment was achieved by three sequential chiral oxazaborolidinone-promoted aldol reactions under 'catalyst control'. This synthetic methodology is based on a direct asymmetric incorporation of two acetate and one isobutyrate synthones into the framework. © 1997 Elsevier Science Ltd

The bryostatins including **bryostatin 7** exhibit high levels of antineoplastic activity and their unique macrolide skeleton has attracted synthetic interest.[2] The bryostatin backbone was retrosynthetically reduced to an acetate-derived oxygenation pattern.[3] The retrosynthesis allows us to construct the $C_1$–$C_9$ segment by three sequential excellent aldol reactions, as depicted by slant lines in Scheme 1. A straightforward synthetic strategy might provide a simple, general way toward the stereoselective synthesis of compounds containing such 1,3-polyol units. The superior chiral oxazaborolidinone (**1** and **2**) promoted aldol reaction is susceptible to the facile synthesis of enantiomerically homogeneous acetate aldols using silyl nucleophile **3** having an eliminable sulfur substituent.[4] An example is shown in Scheme 2 where the aldol reaction time was revised to be 8 h for improving yields because of the inherent low reactivity of **3**; in our preceding paper, reaction with **3**, which is a viable method for constructing contiguous acetate aldol frameworks under 'catalyst control', was reported under catalytic conditions, but stoichiometric conditions are strongly recommended for the same reason.[1] We disclose herein a very short asymmetric synthesis of the bryostatin $C_1$–$C_9$ segment (the partially protected **B**) under catalyst-based stereocontrol using the chiral oxazaborolidinone-promoted aldol reaction.




**Scheme 1.**

Reaction of 3-benzyloxypropanal **5** with **3** quite easily gave the aldol having a dithiolane moiety at the α position in the presence of a stoichiometric amount of chiral oxazaborolidinone promoter **2**, derived from D-valine, followed by desulfurization with nickel boride under a hydrogen atmosphere

† See reference 1.

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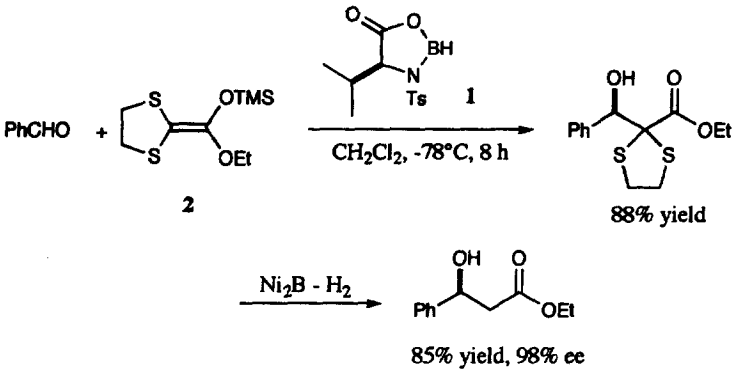


Scheme 2.

to give the first aldol **6** in 64% yield (from **5**) with >98% ee (determined using HPLC with Daicel Chiralcel OD).[5] For the effective desulfurization, nickel boride should be prepared *in situ* in ethanol from large excesses of anhydrous nickel chloride (20 mol equiv.), which was finely ground to a powder, and sodium borohydride (10 mol equiv.) under a hydrogen atmosphere. Enantiomerically pure β-silyloxy aldehyde **7** could be furnished *via* the successful silyl protection and DIBAL reduction in 85% yield (from **6**). Exposure of **7** to the second aldol reaction with promoter **1**, derived from L-valine, (under similar conditions to the first reaction) resulted in the formation of an *anti*-1,3-diol system in almost complete diastereoselectivity. After desulfurization, the enantiomerically pure second aldol **8** was obtained in 58% yield (from **7**).[5] By the usual method of subsequent TBS protection and DIBAL reduction, aldehyde **9** was prepared in 71% yield (from **8**). The third aldol reaction of **9** was examined on introducing a stereogenic center adjacent to a quarternary carbon unit using popular silyl nucleophile **4** in the presence of promoter **2** (the reaction time, 3 h, is adequate in this case). Then the highly enantioselective aldol reaction enabled the almost completely diastereoselective formation of the desired 1,3,5-*anti*,*anti*-triol ester **10** in enantiomerically pure state in 82% yield (from **9**).[5]

Scheme 3 demonstrates the useful strategy of the asymmetric aldol reactions repeated three times under 'catalyst control' toward a novel and excellent short asymmetric synthesis of the bryostatin $C_1$–$C_9$ segment. Thus our synthetic strategy has the fruitful prospect of developing a new field of application. In addition, the facial selectivity can be simply explained by using the crucial idea, introduced by Corey, of hydrogen bonding between an aldehyde hydrogen and a heteroatom involved in the applied Lewis acid, as depicted in **A** (on the first aldol reaction) and **B** (on the second aldol reaction) of Figure 1.[6]

Further applications of this work are in progress.

## Acknowledgements

This work was supported by Grant-in-Aid Scientific Research (Nos. 9231236 and 9554046) from the Ministry of Education. We thank Ms Mai Uchida, a undergraduate student, for the technical assistance of the synthetic work.

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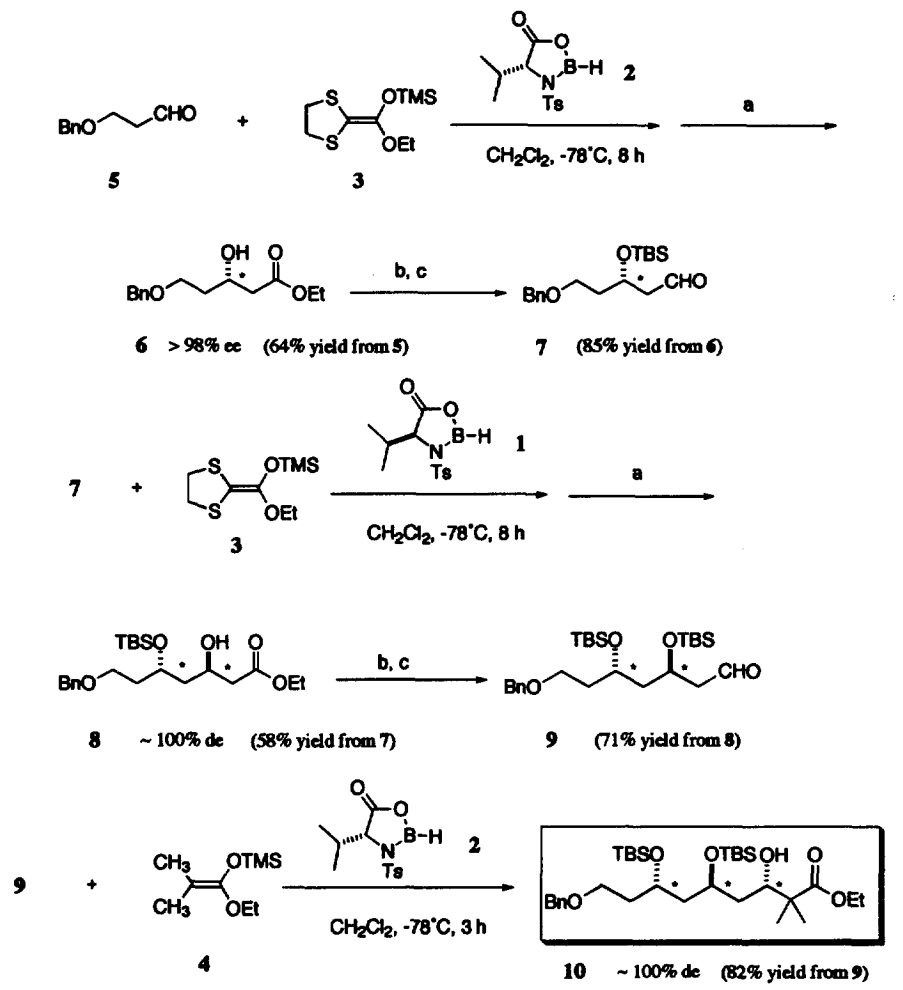


(a) $Ni_2B$-$H_2$, EtOH, r.t., 16 h; (b) TBSCl, Imidazole, DMF, r.t., 16 h; (c) DIBAL, $CH_2Cl_2$, -78 °C, 2 h.

Scheme 3.

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5. Selected data. **6**: $^1$H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (t, 3H, J=7.07), 1.75–1.87 (m, 2H), 2.49 (d, 2H, J=6.34), 3.37 (d, 1H, J=3.42), 3.62–3.73 (m, 2H), 4.16 (q, 2H, J=7.07), 4.52 (s, 2H), 7.27–7.37 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.0, 25.7, 29.9, 35.9, 41.5, 60.4, 66.7, 67.7, 73.0, 127.5, 127.5, 128.3, 137.9, 172.3. $[\alpha]_D^{25}$ 13 (c 1.00, $CHCl_3$). **8**: $^1$H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.00 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 1.18 (t, 3H, J=7.1), 1.50 (ddd, 1H, J=2.68, 5.88, 14.16), 1.61 (ddd, 1H, J=3.88, 9.76, 13.92), 1.74–1.87 (m, 2H), 2.32 (ABX dd, 1H, J=4.9, 16.8), 2.39 (AB dd, 1H, J=7.8, 16.8), 3.45 (t, 2H, J=6.3), 3.52 (brs, 1H), 4.09–4.17 (m, 1H), 4.20–4.28 (m, 1H), 4.07 (q, 2H, J=7.1), 4.38 (AB d, 1H, J=11.9), 4.43 (AB d, 1H, J=11.9), 7.18–7.28 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.8, −4.7, 14.1, 17.9, 25.8, 36.6, 42.1, 42.2, 60.4, 65.0, 66.6, 67.9, 77.9, 127.4, 127.5, 128.3, 138.3, 172.1, $[\alpha]_D^{24}$ 5.2 (c 1.01, $CHCl_3$).

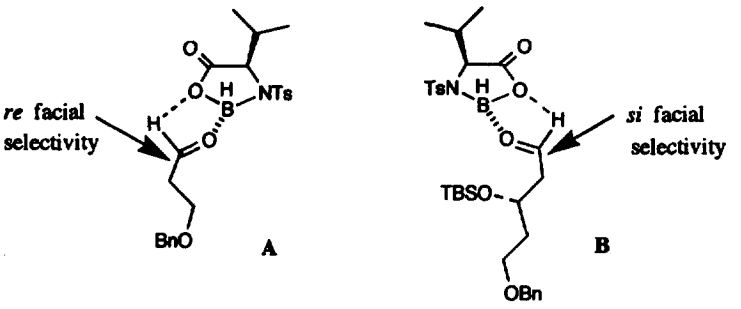


**Figure 1.**

**10**: $^1$H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.06 (s, 3H), 0.07 (s, 3H), 0.09 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.13 (s, 3H), 1.17 (s, 3H), 1.23 (t, 3H, J=7.02), 1.45 (ddd, 1H, J=1.5, 5.5, 14.0), 1.59 (ddd, 1H, J=3.0, 11.0, 14.0), 1.65–1.72 (m, 1H), 1.75–1.86 (m, 3H), 3.33 (d, 2H, J=3.36), 3.55 t, 2H, J=6.71), 3.86 (ddd, 1H, J=3.4, 7.0, 12.5),4.06 (m, 2H), 4.12 (q, 2H, J=7.02), 4.46 (AB d, 1H, J=11.9), 4.49 (AB d, 1H, J=11.9), 7.32 (s, 5H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ (ppm) −4.7, −4.4, −4.1, 14.2, 17.9, 18.0, 20.4, 21.3, 25.8, 25.9, 36.9, 37.2, 44.9, 46.9, 60.4, 66.8, 67.3, 68.9, 72.7, 73.0, 127.5, 127.6, 128.3, 138.5, 177.1. $[\alpha]_D^{19}$ −21 (c 1.45, $CHCl_3$).

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*(Received in Japan 15 August 1997)*