Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2343–2349

TETRAHEDRON: *ASYMMETRY*

Superior substrate control on diastereoselection in boric Lewis acid-promoted aldol reactions. Asymmetric synthesis of a 3,4-*syn* homologous series of ethyl 3,5-dihydroxy-2,4-dimethyl-5-phenylpentanoates

Syun-ichi Kiyooka,[a,*] Kazi A. Shahid,[b] Kazunori Murai,[a] Yong-Nan Li,[a] Momotoshi Okazaki[b] and Yoshihiro Shuto[b]

[a]*Department of Chemistry, Faculty of Science, Kochi University, 2-5-1 Akebono-cho, Kochi 780-8520, Japan*
[b]*The United Graduate School of Agricultural Sciences, Ehime University, 3-5-7 Tarumi, Matsuyama 790-8566, Japan*

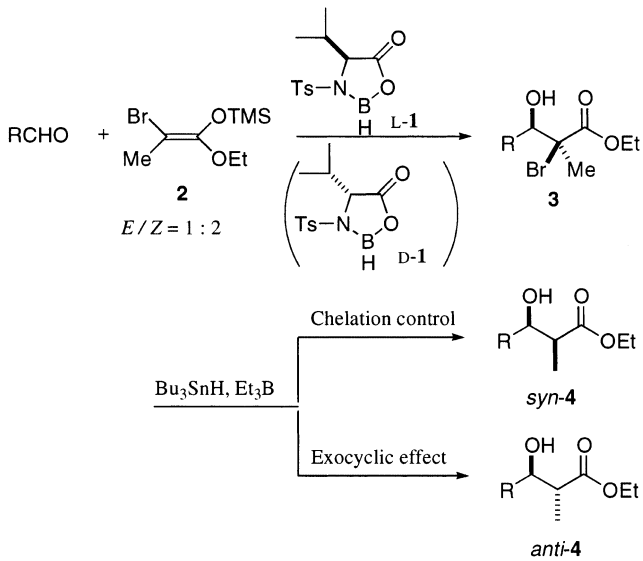
Received 14 August 2001; accepted 11 September 2001

Abstract—The $BF_3{\cdot}OEt_2$-promoted aldol reaction of chiral *syn*- and *anti*-α-methyl-β-siloxy aldehydes with a silyl ketene acetal resulted in essentially complete *syn* Felkin selection. Even in the asymmetric aldol reaction using chiral oxazaborolidinones, the substrate control with respect to diastereoselection was found to overcome the promoter (catalyst) control which would normally occur depending on the stereocenter of the chiral boranes.

1. Introduction

In previous reports, we described that essentially enantiopure *syn*- and *anti*-propionate aldol adducts can be divergently prepared by using a reaction sequence which is comprises the highly enantioselective oxazaborolidinone (L-**1** or D-**1**)-promoted aldol reaction with a silyl ketene acetal **2**, derived from ethyl 2-bromopropionate, and followed by a highly diastereoselective radical debromination reaction (Scheme 1).[1,2] These findings led us to extend the divergent aldol strategy to the diastereoselective construction of polypropionate units, which are building blocks for the synthesis of a variety of macrolides.

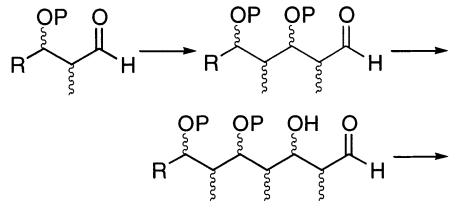
If the reaction sequence is repeatedly applicable to polypropionate synthesis, the iterative aldol strategy might provide an ideal approach to the synthesis of polypropionate units involving various combinations of stereogenic centers (Scheme 2). However, the aldol reaction of α-methyl-β-siloxy aldehydes with silyl nucleophile **2** failed to proceed in the presence of the chiral oxazaborolidinones because of excessive steric hindrance caused by the aldehyde, the nucleophile and the promoter (Scheme 3). Consequently, we attempted to employ the silyl ketene acetal **5**, instead of using **2** in order to examine the potential of the aldol strategy for use in polypropionate synthesis.



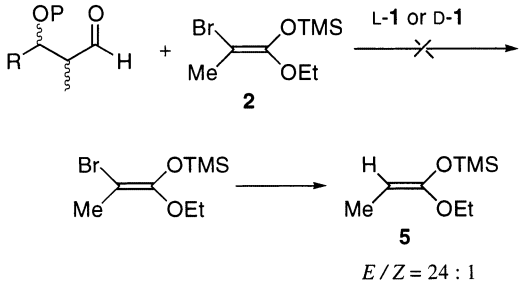
Scheme 1.

* Corresponding author. Tel.: +81-88-844-8295; fax: +81-88-844-8359; e-mail: kiyo@cc.kochi-u.ac.jp

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00405-0



Scheme 2. Iterative aldol strategy toward polypropionate units.



Scheme 3.

2. Results and discussion

The aldol reaction of chiral aldehydes having α-methyl and β-siloxy substituents represents a plausible model reaction for exploring the possibility that polypropionate units might be constructed using an iterative enantioselective and/or diastereoselective aldol strategy. The stereochemical prediction, however, is not so difficult in the Lewis acid-promoted Mukaiyama-type aldol reactions of aldehydes, which involve separately α-alkyl or β-siloxy substituents, from the standpoint of chelate-*syn*, chelate-*anti*, Felkin-*syn*, and Felkin-*anti* configurations.[3–5] In the case of chiral oxazaborolidinone-promoted asymmetric aldol reactions of α-chiral aldehydes, e.g. 2-phenylpropanal, with silyl ketene acetals, the newly generated stereogenic center is known to be constructed through the control induced by the stereogenic center of the promoter used, and is independent of the α-stereocenter of the aldehydes, that is, the so-called *promoter (catalyst) control* on acyclic stereoselection, as depicted in Fig. 1.[6] In the case of aldehydes having no α-substituents, the promoter control works more effectively in the enantioselective C–C bond forming reactions, supplying essentially pure 1,3-*syn*- and *anti*-polyol units, suitable for diastereoselective polyacetate synthesis.[7] However, the promoter control is prone to be diminished when the steric bulk of the α-substituent of the aldehyde is increased.[8] If promoter control can be realized in the present aldehyde system, which involves both α-methyl and β-siloxy substituents, the expected iterative aldol reactions toward the polypropionate synthesis might provide an ideal and straightforward strategy.

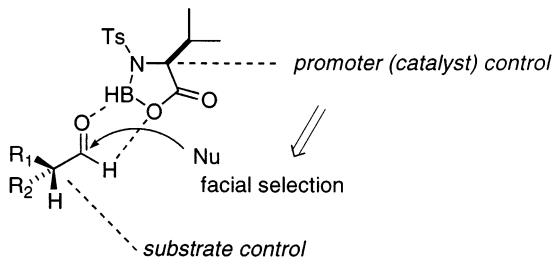
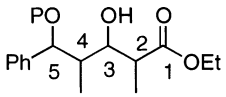
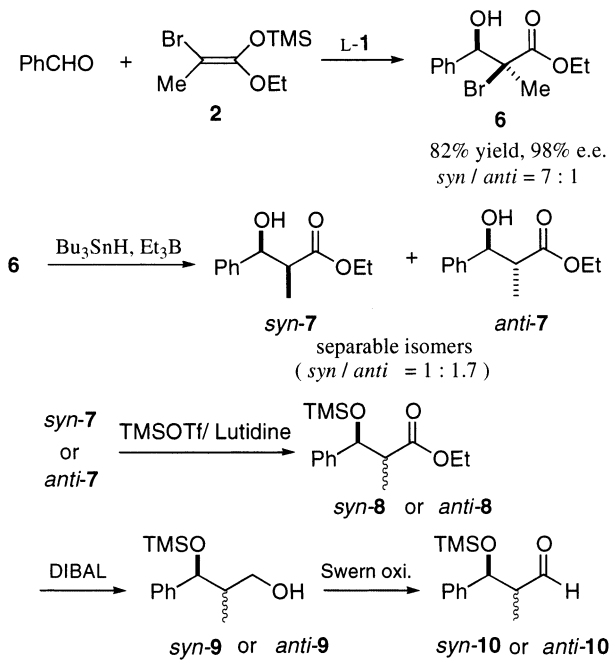


Figure 1.



Scheme 4. Relative stereochemical relationship appeared in the present aldol reaction. C(2)–C(3): 1,2-*syn*-/*anti*-diastereoselection; C(3)–C(4): Felkin or *anti*-Felkin selection; C(3)–C(5): 1,3-diol-*syn*-/*anti*-diastereoselection.

The three types of relative stereochemical relationships in the present aldol products should be considered, as follows; (1) C(2)–C(3): 1,2-*syn*-/*anti*-diastereoselection, (2) C(3)–C(4): Felkin or *anti*-Felkin selection, and (3) C(3)–C(5): 1,3-diol-*syn*-/*anti*-diastereoselection (Scheme 4). Homochiral α-methyl-β-siloxy aldehydes were prepared using our chiral oxazaborolidinone-promoted asymmetric aldol reactions, as shown in Scheme 5.[2] The reaction of benzaldehyde with bromo silyl nucleophile **2** in the presence of oxazaborolidinone, L-**1**, resulted in the essentially enantiopure aldol production of a mixture of *syn*- and *anti*-isomers **6** (ratio = 7:1) in good yield. The non-diastereoselective debromination of **6**



Scheme 5.

was carried out to give separable isomers of *syn*-**7** and *anti*-**7**[1,9] (*syn*/*anti*=1:1.7), both of which are available for the present synthesis, by treatment with Bu_3SnH containing a catalytic amount of Et_3B. After TMS protection of the β-hydroxyl group of *syn*-**7** and *anti*-**7**, starting aldehydes (*syn*-**10** and *anti*-**10**) were obtained by DIBAL reduction and subsequent Swern oxidation.

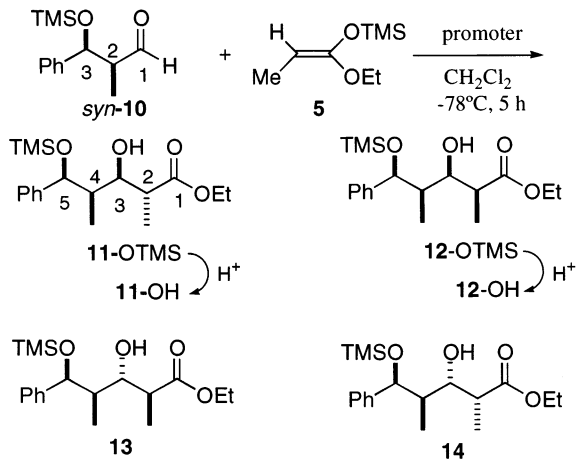
The Lewis acid-mediated aldol reaction of TMS-protected aldehydes (*syn*-**10** and *anti*-**10**) with silyl ketene acetal **5** was examined. After aldol reactions, the TMS-aldol adducts could be separated by silica-gel chromatography and the isomeric ratios in the aldol reactions were determined. Then, desilylation of the products was carried out to give the corresponding diols, followed by acetonization. The stereochemistry of the products of **11**, **12**, **15**, and **16** was confirmed by NOESY experiments, using the corresponding acetonides, **19**, **20**, **21**, and **22**, respectively. The aldol reaction of *syn*-α-methyl-β-siloxy aldehyde (*syn*-**10**) in the presence of L-**1** resulted in a 1:1 mixture of **11** and **12**, having 3,4-*syn* configuration, in 67% yield (Table 1).

This seemed to be normal and typical because the promoter control, effected by L-**1**, would be expected to produce the same configuration at C(3) via *re* facial selection. In addition, the random selection at C(2) on the 2,3-*syn* and *anti*-relationship also lies within the general tendency for reactions with the silyl nucleophile **5**.[10] Surprisingly, however, the aldol reaction in the presence of D-**1** gave a mixture of **11** and **12**, not a mixture of **13** and **14** as would be anticipated from the promoter control. These results strongly suggest that the configuration of the newly created stereogenic center at C(3) can be attributed to the effect of the existing stereocenters of *syn*-**10**. As a result, a reinvestigation of the stereochemistry of the reaction was then carried out using an achiral Lewis acid in order to obtain direct evidence for the existence of such *substrate control* in this system. A clear result was obtained in the reaction using $BF_3{\cdot}OEt_2$, which gave a 1:1 mixture of **11** and **12** in high yield. This finding supports that a highly reliable substrate control in the Felkin selection presents where the face of the aldehyde carbonyl allowed by mutual interactions with α- and β-substituents is being attacked by the incoming nucleophile. Moreover, it was found that the effectiveness of $BF_3{\cdot}OEt_2$ is noteworthy in the attainment of high 3,4-*syn* selection in the present system. Even in the case of aldol reactions in which *anti*-α-methyl-β-siloxy aldehyde (*anti*-**10**) is used, similar results were obtained (Table 2).

In comparison with *syn*-**10**, the reactions with *anti*-**10** in the presence of both chiral oxazaborolidinones proceeded in extremely low yields, which are presumably caused by the shielding of the allowed face of the aldehyde carbonyl with the bulk of the promoter and a slight difference in the ratio of 3,4-*syn* products (the 2,3-*anti* isomer **15** is preferred) was observed in the reaction in the presence of L-**1**. As expected from the substrate control, the aldol reaction of *syn*-**10** using $BF_3{\cdot}OEt_2$ also gave the *syn*-isomers in excellent yield.

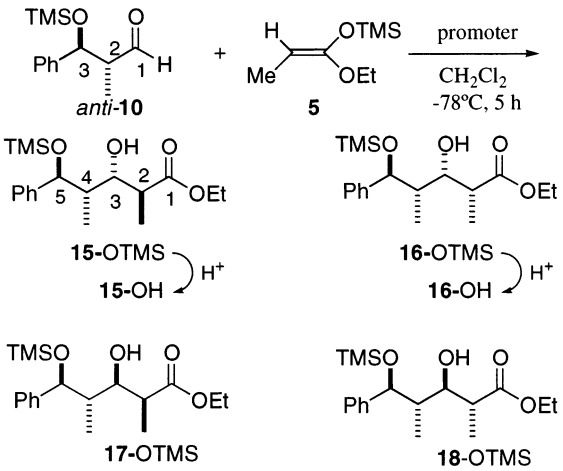
A similar system has been investigated consisting of (2*R*,3*R*)- and (2*S*,3*R*)-2,4-dimethyl-3-[(4-methoxybenzyl)pentanals **23** and **24** and enol silanes, **25** (Fig. 2), in $BF_3{\cdot}OEt_2$-mediated aldol reactions where Evans proposed the revised 1,3-asymmetric induction polar model in order to explain the influence of the electrostatic nature of the β-substituent on the facial selection of the carbonyl moiety, in addition to the Felkin–Anh prediction exerted on the α-substituent.[3] The observed diastereoselectivity was dependent on the size of nucle-

Table 1.



Entry	Promoter	Yield (%)	Product ratios			
			11	**12**	**13**	**14**
1	L-**1** (L-Ts-Val)	67	1	1	–	–
2	D-**1** (D-Ts-Val)	61	1.6	1	–	–
3	$BF_3{\cdot}OEt_2$	82	1	1	–	–

Table 2.



Entry	Promoter	Yield (%)	Product ratios			
			15	**16**	**17**	**18**
1	L-**1** (L-Ts-Val)	21	1.7	1	–	–
2	D-**1** (D-Ts-Val)	24	2	1	–	–
3	$BF_3{\cdot}OEt_2$	93	1	1	–	–

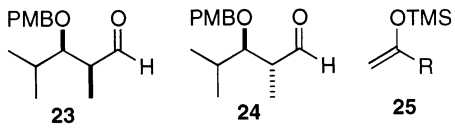


Figure 2.

ophiles and the stereochemistry at the β position of aldehydes was subsequently recognized to affect the total diastereoselection as a merged 1,2- and 1,3-asymmetric induction. However, the diastereofacial selection in our present system of *syn*-**10** and *anti*-**10** can be effectively accounted for using only the Felkin–Anh model without any consideration of a specific influence of β-substituents. The stereochemical outcome of the present reaction can be explained with some confidence using transition state models; **A** from *syn*-**10** and **B** from *anti*-**10**, as depicted in Fig. 3.

3. Conclusions

The stereogenic center at C(3) of the aldol products obtained from *syn*- and *anti*-**10** could not be controlled by the stereogenic center of the oxazaborolidinone used. The fact provides a serious limitation on the structure of aldehydes available for acyclic stereoselection under promoter (catalyst) control in chiral oxazaborolidinone-promoted asymmetric aldol reactions. However, for these aldehydes, $BF_3{\cdot}OEt_2$ was found to be a quite effective Lewis acid for essentially complete 3,4-*syn* stereoselection from the standpoint of substrate control. $BF_3{\cdot}OEt_2$ would be useful as an alternative Lewis acid for use in the iterative aldol strategy to achieve the expected polypropionate synthesis. A study of the diastereoselective construction between C(2) and C(3) in the system is currently underway.

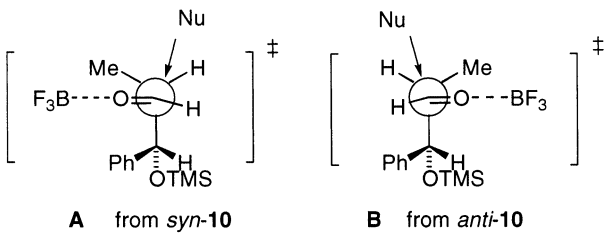


Figure 3.

4. Experimental

4.1. General

Infrared spectra (IR) were determined with a JASCO FT/IR-5300 Fourier-transform infrared spectrometer. ^{1}H NMR spectra were determined with a JEOL JNM-LA 400 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^{13}C NMR spectra were measured at 100 MHz with a JEOL JNM-LA 400 spectrometer. High performance liquid chromatography (HPLC) was done with a JASCO Model PU-980 liquid chromatograph. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Merck silica gel 60 (230–400 mesh) was used for flash-column chromatography and for thin-layer chromatography Merck silica gel 60 TLC aluminum sheets were used.

4.2. Ethyl (2*S*,3*S*)-2-methyl-3-phenyl-3-trimethylsiloxypropionate *syn*-8

To a stirred solution of ethyl (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate (907 mg, 4.36 mmol) in dry

CH_2Cl_2 (35 mL) at rt was added 2,6-lutidine (2.03 mL, 17.4 mmol) and the resulting mixture stirred for 15 min. Then, TMSOTf (1.13 mL, 6.54 mmol) was added and stirred for 2.5 h at the same temperature. Reaction was quenched by slow addition of satd NaCl (10 mL), extracted with ether, washed with satd NaCl, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash-column chromatography (1% AcOEt in *n*-hexane) to afford **8** (93%); $[\alpha]_D^{30}$ −45.1 (*c* 1.02, $CHCl_3$); IR (neat): 2959, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 2.66 (dq, J = 7.1, 6.8 Hz, 1H), 3.91–4.04 (m, 2H), 4.94 (d, J = 6.3 Hz, 1H), 7.19–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 12.0, 14.0, 49.0, 60.2, 75.9, 126.4, 127.3, 127.9, 143.1, 174.3. Anal. calcd for $C_{15}H_{24}O_3Si$: C, 64.25; H, 8.63. Found: C, 64.36; H, 8.57%.

4.2.1. Ethyl (2*R*,3*S*)-2-methyl-3-phenyl-3-trimethylsiloxypropionate *anti*-8. $[\alpha]_D^{30}$ −19.1 (*c* 1.00, $CHCl_3$); IR (neat): 2961, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0 (s, 9H), 0.91 (d, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.78 (dq, J = 9.5, 7.1 Hz, 1H), 4.19–4.32 (m, 2H), 4.75 (d, J = 9.3 Hz, 1H), 7.32–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 14.0, 14.4, 49.3, 60.4, 77.8, 127.1, 127.8, 128.2, 142.2, 175.5. Anal. calcd for $C_{15}H_{24}O_3Si$: C, 64.25; H, 8.63. Found: C, 64.19; H, 8.66%.

4.3. Reduction procedure: (2*R*,3*S*)-2-methyl-3-phenyl-3-trimethylsiloxypropanol *syn*-9

Under an argon atmosphere, to a stirred solution of *syn*-**8** (750 mg, 2.67 mmol) in dry CH_2Cl_2 (20 mL) at −78°C was added dropwise a solution of DIBAL in toluene (1 M, 8.01 mL, 8.01 mmol) over 30 min and was stirred at the same temperature for 2 h. The reaction was quenched by slow addition of MeOH (5 mL), followed by addition of distilled water (20 mL), extracted with ether, washed with satd NaCl, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash-column chromatography (15% AcOEt in *n*-hexane) to afford *syn*-**9** (546 mg, 86%); $[\alpha]_D^{24}$ −33.3 (*c* 1.14, $CHCl_3$); IR (neat): 3380, 2961 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 0.75 (d, J = 7.1 Hz, 3H), 1.96–2.05 (m, 1H), 2.37 (dd, J = 6.1, 4.6 Hz, 1H), 3.40–3.47 (m, 1H), 3.51–3.57 (m, 1H), 4.80 (d, J = 4.4 Hz, 1H), 7.19–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 11.8, 42.7, 65.7, 77.3, 126.7, 127.1, 127.9, 142.5.

4.3.1. (2*S*,3*S*)-2-Methyl-3-phenyl-3-trimethylsiloxypropanol *anti*-9. $[\alpha]_D^{29}$ −60.5 (*c* 1.00, $CHCl_3$); IR (neat): 3420, 2961 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 0.79 (d, J = 7.1 Hz, 3H), 1.91–2.04 (m, 1H), 3.18 (dd, J = 6.8, 4.1 Hz, 1H), 3.58–3.69 (m, 2H), 4.54 (d, J = 7.3 Hz, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 14.2, 42.8, 66.9, 81.4, 126.7, 127.5, 128.2, 143.4.

4.4. Oxidation procedure: (2*S*,3*S*)-2-methyl-3-phenyl-3-trimethylsiloxypropanal *syn*-10

Under an argon atmosphere, to a stirred solution of $(COCl)_2$ (0.38 mL, 4.38 mmol) in dry CH_2Cl_2 at −78°C was added dropwise DMSO (0.58 mL, 8.22 mmol) over 5 min. After stirring for 10 min at the same temperature, *syn*-**9** (650 mg, 2.74 mmol) was added and the mixture was stirred for 20 min before Et_3N (1.53 mL, 10.96 mmol) was added. The reaction mixture was allowed to warm up to 0°C and additionally stirred for 30 min before quenched with a mixture of water (1.0 mL), ether (4.0 mL), and benzene (2.0 mL). The organic phase was separated, washed with water followed with satd NaCl, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash-column chromatography (5% AcOEt in *n*-hexane) to afford *syn*-**10** (480 mg, 74%); $[\alpha]_D^{20}$ −37.9 (*c* 2.19, $CHCl_3$); IR (neat): 2959, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 1.0 (d, J = 7.1 Hz, 3H), 2.53–2.62 (m, 1H), 5.13 (d, J = 4.4 Hz, 1H), 7.20–7.32 (m, 5H), 9.71 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 8.0, 54.5, 73.9, 126.1, 127.4, 128.2, 142.3, 204.3.

4.4.1. (2*R*,3*S*)-2-Methyl-3-phenyl-3-trimethylsiloxypropanal *anti*-10. $[\alpha]_D^{19}$ −95.6 (*c* 1.21, $CHCl_3$); IR (neat): 2961, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 0.89 (d, J = 7.1 Hz, 3H), 2.67–2.77 (m, 1H), 4.77 (d, J = 7.8 Hz, 1H), 7.27–7.37 (m, 5H), 9.80 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 11.1, 54.2, 76.6, 126.6, 127.8, 128.4, 142.2, 204.7.

4.5. General procedure: chiral oxazaborolidinone-promoted asymmetric aldol reaction of *syn*-10

Under an argon atmosphere, to a stirred solution of *N*-*p*-tosyl-(*S*)-valine (331 mg, 1.22 mmol) in dry CH_2Cl_2 (5 mL) at 0°C was added dropwise a 1 M solution of BH_3·THF in THF (1.02 mL, 1.02 mmol) over 5 min, and was further stirred for 30 min at the same temperature. The resulting solution was then allowed to warm to ambient temperature and subsequently stirred for 30 min. The solution was then cooled to −78°C and *syn*-**10** (240 mg, 1.02 mmol) in CH_2Cl_2 (1 mL) was added slowly over 5 min. After 5 min, 1-ethoxy-2-methyl-1-trimethylsiloxy-1-propene (267 mg, 1.53 mmol) was introduced slowly and stirred for 15 h at −78°C. The reaction was quenched by adding a buffer solution (10 mL, pH 6.8), extracted with ether, washed with satd $NaHCO_3$ solution, followed with satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude was evaporated, and purified by flash-column chromatography (7% AcOEt in *n*-hexane) to afford a mixture of aldol adducts in 1: 1 ratio (197 mg, 57%).

4.6. Ethyl (2*R*,3*R*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-5-phenyl-5-trimethylsiloxypentanoate 11-OTMS

$[\alpha]_D^{19}$ −28.0 (*c* 1.11, $CHCl_3$); IR (neat): 3516, 2976, 2900, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 0.92 (d, J = 7.1 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H), 1.25

(t, $J=7.1$ Hz, 3H), 1.79 (dq, $J=6.8$, 2.2 Hz, 1H), 2.58 (dq, $J=9.3$, 7.1 Hz, 1H), 3.04 (d, $J=3.4$ Hz, 1H), 3.65 (ddd, $J=9.0$, 3.2, 2.2 Hz, 1H), 4.07–4.20 (m, 2H), 4.79 (d, $J=5.8$ Hz, 1H), 7.21–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 7.0, 13.8, 14.1, 42.3, 43.5, 60.5, 74.7, 78.7, 126.5, 127.2, 128.0, 143.2, 176.1.

4.6.1. Ethyl (2*S*,3*R*,4*R*,5*S*) - 3 - hydroxy - 2,4 - dimethyl-5-phenyl-5-trimethylsiloxypentanoate 12-OTMS. $[\alpha]_D^{22}$ −33.2 (*c* 0.84, $CHCl_3$); IR (neat): 3510, 2978, 2889, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.0 (s, 9H), 0.79 (d, $J=7.1$ Hz, 3H), 1.19 (d, $J=7.1$ Hz, 3H), 1.22 (t, $J=6.8$ Hz, 3H), 1.63–1.71 (m, 1H), 2.59 (dq, $J=8.8$, 7.1 Hz, 1H), 2.99 (d, $J=2.4$ Hz, 1H), 3.85 (dt, $J=8.5$, 2.2 Hz, 1H), 4.01–4.12 (m, 2H), 4.85 (d, $J=3.9$ Hz, 1H), 7.17–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 0.0, 6.3, 13.9, 14.1, 43.1, 43.7, 60.2, 75.5, 79.1, 126.2, 127.0, 127.9, 142.9, 175.2.

4.7. General procedure: $BF_3{\cdot}OEt_2$-mediated aldol reaction of *anti*-10

Under an argon atmosphere, to a stirred solution of *anti*-**10** (710 mg, 3.0 mmol) in dry CH_2Cl_2 (10 mL) at −78°C was added dropwise $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) over 5 min. After stirring at the same temperature for 10 min, 1-ethoxy-2-methyl-1-trimethylsiloxy-1-propene (1.1 g, 6.0 mmol) was introduced over 5 min and stirred for an additional 1 h at −78°C. The reaction was quenched with a buffer solution (10 mL, pH 6.8), extracted with ether, washed with satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude was evaporated, and purified by flash-column chromatography (20% AcOEt in *n*-hexane) to afford a mixture of **15**-OH and **16**-OH in a 1:1 ratio (738 mg, 93%).

4.8. Desilylation procedure: ethyl (2*R*,3*R*,4*R*,5*S*)-3,5-dihydroxy-2,4-dimethyl-5-phenylpentanoate 11-OH

Under an argon atmosphere, to a stirred solution of **11**-OTMS (108 mg, 0.32 mmol) in dry MeOH (5 mL) at rt was added citric acid (403 mg, 1.92 mmol) and was stirred at rt for 30 min. The reaction was quenched with water, extracted with ether, washed with satd $NaHCO_3$, followed with satd NaCl, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude was evaporated, and purified by flash-column chromatography (13% AcOEt in *n*-hexane) to afford **11**-OH (80 mg, 94%); $[\alpha]_D^{22}$ −5.5 (*c* 1.83, $CHCl_3$); IR (neat): 3441, 2980, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.82 (d, $J=7.1$ Hz, 3H), 1.12 (d, $J=7.3$ Hz, 3H), 1.28 (t, $J=7.1$ Hz, 3H), 1.81–1.90 (m, 1H), 2.62 (dq, $J=9.0$, 7.1 Hz, 1H), 3.58 (d, $J=1.4$ Hz, 1H), 3.65 (d, $J=3.2$ Hz, 1H), 4.19 (q, $J=7.1$ Hz, 2H), 5.04 (br s, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 4.3, 13.8, 14.1, 40.9, 43.4, 60.9, 77.4, 78.1, 125.8, 127.0, 128.1, 143.2, 176.3. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.89; H, 8.31%.

4.8.1. Ethyl (2*S*,3*R*,4*R*,5*S*)-3,5-dihydroxy-2,4-dimethyl-5-phenylpentanoate 12-OH. $[\alpha]_D^{22}$ −8.3 (*c* 1.08, $CHCl_3$); IR (neat): 3434, 2980, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.82 (d, $J=7.1$ Hz, 3H), 1.23 (t, $J=7.1$ Hz, 3H), 1.28 (d, $J=6.8$ Hz, 3H), 1.77–1.84 (m, 1H), 2.65 (dq, $J=8.6$, 7.1 Hz, 1H), 3.08 (br s, 1H), 3.36 (d, $J=3.2$ Hz, 1H), 4.0–4.08 (m, 1H), 4.12 (dq, $J=7.1$, 2.2 Hz, 1H), 4.98 (s, 1H), 7.23–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 5.0, 14.1, 14.2, 42.1, 43.7, 60.5, 76.9, 78.2, 125.6, 127.2, 128.2, 143.0, 175.2. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.54; H, 8.28%.

4.8.2. Ethyl (2*S*,3*S*,4*S*,5*S*)-3,5-dihydroxy-2,4-dimethyl-5-phenylpentanoate 15-OH. $[\alpha]_D^{26}$ −24.0 (*c* 0.25, $CHCl_3$); IR (neat): 3414, 2988, 2939, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.98 (d, $J=7.1$ Hz, 3H), 1.18 (t, $J=7.1$ Hz, 3H), 1.22 (d, $J=6.8$ Hz, 3H), 1.89–1.96 (m, 1H), 2.64 (dq, $J=8.8$, 7.1 Hz, 1H), 2.73 (d, $J=4.4$ Hz, 1H), 2.89 (d, $J=4.6$ Hz, 1H), 3.96 (ddd, $J=8.8$, 4.9, 2.2 Hz, 1H), 4.06 (dq, $J=7.1$, 2.9 Hz, 2H), 4.75 (t, $J=5.1$ Hz, 1H), 7.12–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.0, 14.1, 14.3, 42.1, 43.7, 60.4, 72.2, 78.2, 126.0, 127.5, 128.4, 143.4, 175.0. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.37; H, 8.41%.

4.8.3. Ethyl (2*R*,3*S*,4*S*,5*S*)-3,5-dihydroxy-2,4-dimethyl-5-phenylpentanoate 16-OH. $[\alpha]_D^{25}$ −50.0 (*c* 0.50, $CHCl_3$); IR (neat): 3445, 2978, 2939, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.98 (d, $J=7.1$ Hz, 3H), 1.02 (d, $J=7.1$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 1.91–1.98 (m, 1H), 2.58 (dq, $J=9.3$, 7.1 Hz, 1H), 3.30 (d, $J=5.9$ Hz, 1H), 3.36 (d, $J=3.6$ Hz, 1H), 4.01 (ddd, $J=9.5$, 3.6, 2.2 Hz, 1H), 4.13 (dq, $J=11.7$, 7.1 Hz, 2H), 4.76 (t, $J=5.8$ Hz, 1H), 7.22–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.1, 13.7, 14.1, 40.4, 43.2, 60.8, 72.0, 77.7, 126.0, 127.3, 128.4, 143.8, 176.3. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.55; H, 8.25%.

4.9. General procedure for the acetonide preparation: ethyl (2*R*,3*R*,4*R*,5*S*)-3,5-dihydroxy-3,5-*O*-isopropylidene-2,4-dimethyl-5-phenylpentanoate 19

Under a nitrogen atmosphere, to a stirred solution of **11**-OH (57 mg, 0.21 mmol) in dry acetone (5 mL) and 2,2-dimethoxypropane (0.13 mL, 1.06 mmol) at rt was added camphor-10-sulphonic acid (5 mg) and was stirred for 20 min. Reaction was quenched by slow addition of Et_3N (0.1 mL) followed with distilled water, extracted with ether, washed with satd NaCl, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash-column chromatography (5% AcOEt in *n*-hexane) to afford **19** (55 mg, 85%); $[\alpha]_D^{20}$ −35.6 (*c* 1.04, $CHCl_3$); IR (neat): 2984, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.62 (d, $J=6.8$ Hz, 3H), 1.09 (d, $J=7.1$ Hz, 3H), 1.27 (t, $J=7.1$ Hz, 3H), 1.48 (s, 3H), 1.49 (s, 3H), 1.73–1.80 (m, 1H), 2.57 (dq, $J=10.2$, 7.1 Hz, 1H), 4.18 (q, $J=7.1$ Hz, 2H), 4.29 (dd, $J=10.2$, 2.2 Hz, 1H), 5.11 (d, $J=2.4$ Hz, 1H), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 4.8, 12.5, 14.3, 19.3, 29.8, 34.4, 42.5, 60.3, 74.7, 74.9, 99.3, 125.6, 126.9, 128.1, 140.9, 175.4. Anal. calcd for

$C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 71.02; H, 8.63%.

4.9.1. Ethyl (2*S*,3*R*,4*R*,5*S*)-3,5-dihydroxy-3,5-*O*-isopropylidene-2,4-dimethyl-5-phenylpentanoate 20. $[\alpha]_D^{22}$ −10.7 (*c* 1.31, $CHCl_3$); IR (neat): 2990, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.62 (d, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.47 (s, 6H), 1.67–1.73 (m, 1H), 2.58 (dq, J = 10.0, 6.8 Hz, 1H), 4.04–4.13 (m, 3H), 5.04 (d, J = 2.4 Hz, 1H), 7.15–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 5.3, 14.1, 15.1, 19.6, 29.9, 35.8, 42.4, 60.3, 74.5, 74.8, 99.5, 125.5, 126.8, 128.0, 140.8, 174.6. Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.77; H, 8.32%.

4.9.2. Ethyl (2*S*,3*S*,4*S*,5*S*)-3,5-dihydroxy-3,5-*O*-isopropylidene-2,4-dimethyl-5-phenylpentanoate 21. $[\alpha]_D^{19}$ −56.6 (*c* 0.32, $CHCl_3$); IR (neat): 2984, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.94 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 2.04–2.12 (m, 1H), 2.61 (dq, J = 11.0, 6.8 Hz, 1H), 4.09–4.25 (m, 4H), 7.26–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.1, 13.3, 14.2, 23.6, 24.5, 39.7, 41.3, 60.3, 70.9, 77.6, 101.5, 126.8, 127.7, 128.5, 141.9, 175.1. Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.82; H, 8.37%.

4.9.3. Ethyl (2*R*,3*S*,4*S*,5*S*)-3,5-dihydroxy-3,5-*O*-isopropylidene-2,4-dimethyl-5-phenylpentanoate 22. $[\alpha]_D^{20}$ −24.4 (*c* 0.16, $CHCl_3$); IR (neat): 2986, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.87 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 2.16–2.24 (m, 1H), 2.61 (dq, J = 10.7, 6.8 Hz, 1H), 4.11 (q, J = 7.1 Hz, 3H), 4.15 (dd, J = 10.8, 5.12 Hz, 1H), 4.19 (d, J = 8.3 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.5, 14.1, 15.7, 23.9, 24.5, 40.7, 40.8, 60.4, 70.9, 77.8, 101.5, 127.2, 127.8, 128.5, 141.6, 174.8. Anal. calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 71.42; H, 8.60%.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

References

1. (a) Kiyooka, S.-i.; Shahid, K. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1537–1542; (b) Kiyooka, S.-i.; Shahid, K. A. *Tetrahedron Lett*. **2000**, *41*, 2633–2637.
2. Kiyooka, S.-i.; Shahid, K. A. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 1485–1495 and references cited therein.
3. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc*. **1996**, *118*, 4322–4343.
4. Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeshini, R. *Tetrahedron* **1986**, *42*, 893–909.
5. Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095–1120; in the review, the more complex cases of merged 1,2- and 1,3-asymmetric inductions applied to natural product synthesis also are summarized.
6. (a) Kiyooka, S.-i.; Kira, H.; Hena, M. A. *Tetrahedron Lett*. **1996**, *37*, 2597–2600; (b) Kiyooka, S.-i.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett*. **2000**, *41*, 6599–6603.
7. (a) Kiyooka, S.-i.; Maeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371–3374; (b) Kiyooka, S.-i.; Hena, M. A.; Yabukami, T.; Murai, K.; Goto, F. *Tetrahedron Lett*. **2000**, *41*, 6599–6603.
8. (a) Kiyooka, S.-i.; Maeda, H.; Hena, M. A.; Uchida, M.; Kim, C.-S.; Horiike, M. *Tetrahedron Lett*. **1988**, *39*, 8287–8290; (b) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem*. **1999**, *64*, 5511–5523.
9. Hena, M. A.; Terauchi, S.; Kim, C.-S.; Horiike, M.; Kiyooka, S.-i. *Tetrahedron: Asymmetry* **1998**, *9*, 1883–1890.
10. Kiyooka, S.-i.; Kaneko, Y.; Kume, K. *Tetrahedron Lett*. **1992**, *33*, 4927–4930.