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Diastereoselective radical debromination approach toward divergent syntheses of *syn*- and *anti*-propionate units, coupled with enantioselective and/or diastereoselective Lewis acid-promoted aldol reactions

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Abstract—A practical methodology directed to the enantioselective synthesis of polypropionate backbones, available for the synthesis of polyketide natural products, has been developed by iterative enantio- and diastereoselective Lewis acid-promoted aldol reactions, followed by diastereoselective radical debromination reactions. A chiral oxazaborolidinone-promoted aldol reaction of a racemic aldehyde, derived from 2-methyl-1,3-propanediol, with a silylketene acetal from ethyl 2-bromopropionate, resulted in highly enantioselective formation of the corresponding bromo aldol adduct, followed by radical debromination with Bu_3SnH in the presence of Et_3B to divergently give *syn*- and *anti*-propionate aldols, which are versatile stereotriads. Furthermore, elongation of the propionate units has also been achieved: the $BF_3{\cdot}OEt_2$-promoted aldol reaction of chiral *syn*- and *anti*-α-methyl-β-protected-oxy aldehydes with the silyl nucleophile proceeded with essentially complete *syn*-selectivity while the $TiCl_4$-promoted aldol reaction resulted in fairly good *anti*-selectivity. The resulting bromo aldol adducts were divergently debrominated by the radical reduction to give a complete set of stereotetrads.

1. Introduction

Although a number of successful examples have been reported in the area of the enantioselective synthesis of *syn*- and *anti*-propionate aldol adducts, divergent synthesis of these compounds has not been realized to date.[1] After continuous studies on chiral oxazaborolidinone **1** promoted asymmetric aldol reactions,[2] we found however that the enantioselective aldol reaction with a silylketene acetal **2** derived from ethyl 2-bromopropionate, followed by diastereoselective debromination reactions, can resolve this problem to give divergently enantiopure *syn*- and *anti*-propionate aldol adducts.[3] The approach is available as part of the overall strategy for constructing both single propionate and iterative polypropionate units, as shown in Scheme 1. The bromo substituent in **2** has dual roles: the first is to provide a suitable steric bulkiness of the silyl nucleophile leading to very high enantioselectivity in the aldol condensation process and the second is to serve as a group which can be readily eliminated from the resulting intermediates in a subsequent radical reduction process.[4] Essentially enantiopure aldol adducts, obtained from the enantioselective aldol reaction at the first step, are divergently transferred to each corresponding *syn*- or *anti*-propionate by using distinctive, highly diastereoselective radical debrominations in the second step. The other part of the strategy appears in the diastereoselective aldol reactions of aldehydes, involving stereogenic centers, with the same nucleophile **2**, where the bulkiness of **2**, might work again effectively for the diastereoselectivity, followed by the same radical debromination procedures. We herein report versatile synthetic studies of propionate stereotriads and stereotetrads aiming at a general methodology, available for the asymmetric synthesis of polyketide natural products, which is based on Lewis acid-promoted aldol reactions coupled with radical reductions.

2. Results and discussion

2.1. Enantioselective synthesis of stereotriads available for construction of a variety of skeletons of polyketide natural products

Our strategy, developed in a divergent enantioselective synthesis of *syn*- and *anti*-propionate alodol adducts,[3]

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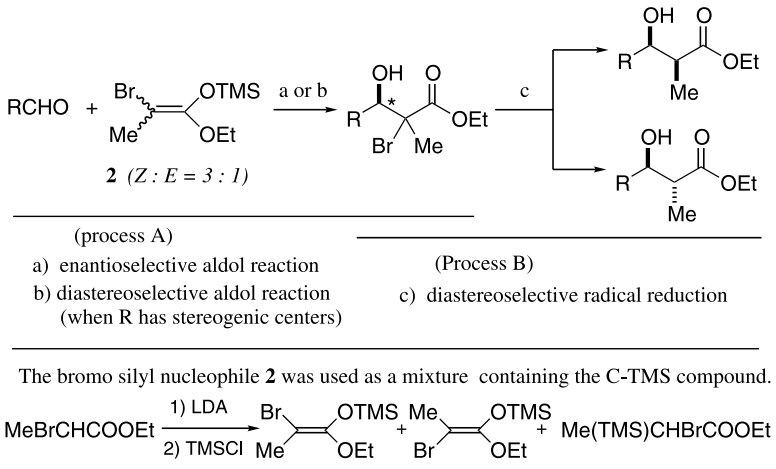
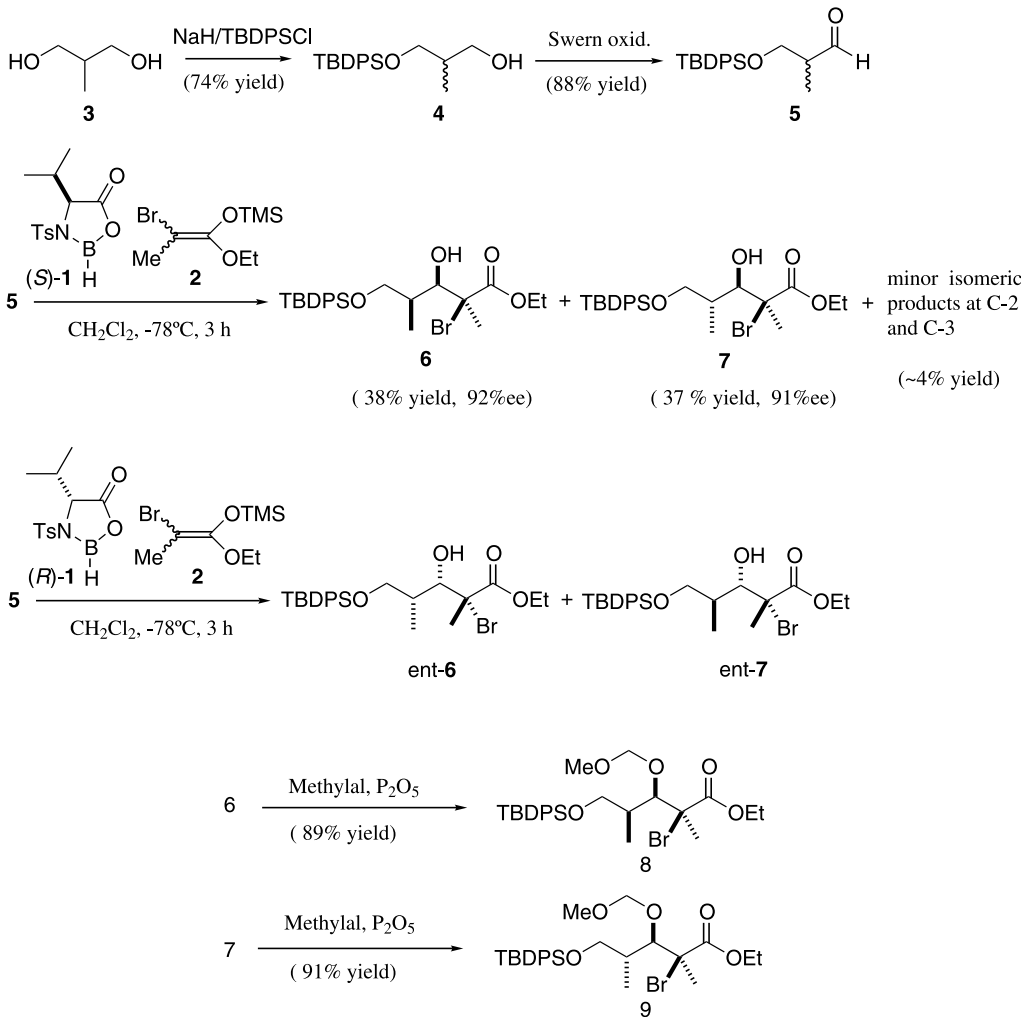


Scheme 1. Enantioselective or diastereoselective approach to propionate units.

was applied to the racemic aldehyde **5**, derived from a cheap achiral diol **3**,[5] which was chosen as a simple and suitable starting material because of it having a minimum propionate functionality for elongation. Provided the so-called 'catalyst control', where a newly created center is formed depending only on the chirality of the used catalysts (promoters) without any influence of the existing chiral centers of the aldehyde, is possible in this system of aldehyde **5** with silyl nucleophile **2** in the presence of chiral oxazaborolidinones, (*S*)-**1** and (*R*)-**1**, as observed in a previous report of the oxazaborolidi2none-promoted asymmetric aldol reaction with racemic aldehydes,[2h] we can expect to obtain a pair of highly enantioselective aldol adducts, essential for the enantioselective synthesis of propionate skeletons. A strategy to the quite effective enantioselective synthesis of versatile stereotriads has been preliminarily reported using a TBS-protected homologous aldehyde with respect to the enantioselective synthesis of (+)-discodermolide.[6]

After mono-protection of **3** with TBDPSCl/NaH, Swern oxidation gave aldehyde **5** in good yield. In the presence of a stoichiometric amount of chiral borane (*S*)-**1**, which was prepared in situ by stirring L-TsVal and BH_3·THF in CH_2Cl_2 at 0°C, the aldol reaction of **5** with **2** was carried out at −78°C for 3 h. The reaction proceeded smoothly to give a mixture of aldol adducts in 85% yield along with a small amount of isomers at C-2 and C-3 (~4% yield), as shown in Scheme 2. The major mixture was constituted of an almost 1:1 ratio of (+)-2,3-*syn*-3,4-*syn*-**6** and (−)-2,3-*syn*-3,4-*anti*-**7** which were determined to be 92% ee and 91% ee, respectively, by chiral HPLC analysis using Daicel Chiralcel OD-H. The same reaction with (*R*)-**1** also resulted in the production of the enantiomers (−)-**6** and (+)-**7** with nearly the same level of enantioselectivity. The stereocenter at C-3, installed during the reaction, is primarily controlled by the promoters (*S*)-**1** and (*R*)-**1**, respectively. The high enantioselectivity is achieved through an effective kinetic resolution where chiral pairs of enantiopure aldol adducts are in practice obtainable from a racemic starting material. An additional interesting selectivity leads to an excellent 2,3-*syn* relationship in the aldol adducts,[2u] although the stereochemistry at C-2 is not so important in this strategy involving the following radical debromination procedure. In the case of chiral oxazaborolidinone-promoted asymmetric aldol reactions of **5**, the predominance of the catalyst (promoter) control over the substrate control should be explained for the facial selection, as depicted in Figure 1.

In supplying effectively protected substrates to allow higher diastereoselectivity in the following radical debromination, bromo aldol adducts, **6** and **7**, were converted with methylal/P_2O_5 to the corresponding MOM-protected compounds, **8** and **9**, respectively, in good yields. After research by Guindon et al.[4] and our improved work,[3] diastereoselective reductive reactions via radicals α to the carboxyl ester function have become a promising method to obtain *syn*- and *anti*-propionates. The α-bromo ester is suitable as a precursor for the radical reduction with Bu_3SnH in the presence of a catalytic amount of Et_3B.[7] In radical debromination of α-bromo-β-protected-oxy-α-methyl esters with Bu_3SnH/Et_3B, *syn*-selectivity is generally observed while *anti*-selectivity is predominantly achieved in the presence of a large excess of $MgBr_2$·OEt_2, where the diastereoselectivity is explained by the dipole–dipole control for the former and the chelation control for the latter. Even β-hydroxy esters could accept the chelation control with $MgBr_2$·OEt_2.[3] The effects of β-hydroxy protection on the diastereoselectivity have been observed, to a considerable extent, but it is necessary to take into account the selection of an appropriate protecting group available for the practical procedure. If MOM-protection effectively affects



Scheme 2.

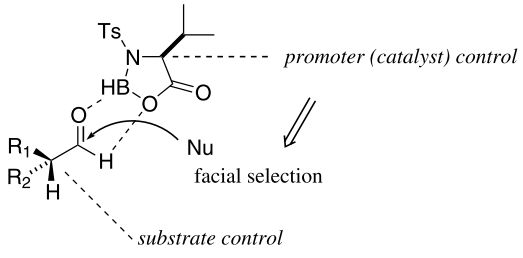


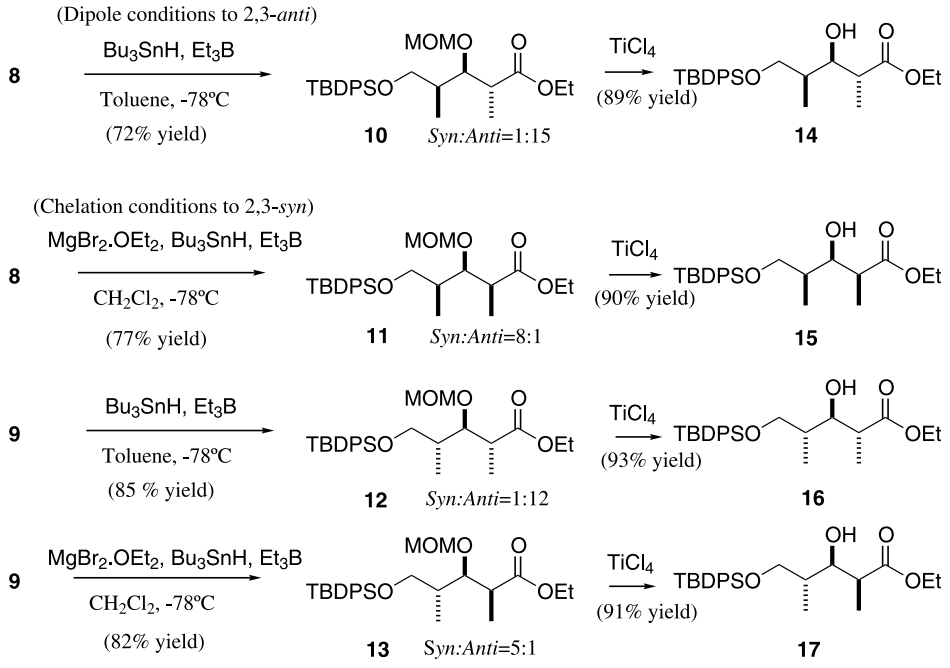
Figure 1.

both controls in the radical debromination by expecting enhanced dipole–dipole and chelation interactions, the MOM group should be chosen for their ease of protection and deprotection procedures.

As shown in Scheme 3, debromination of **8** and **9** under dipole conditions (Bu_3SnH/Et_3B in toluene at −78°C) results in fairly good 2,3-*anti* selection of 15:1 for **10** and 12:1 for **12**, respectively, in good yields. Debromination of **8** and **9** under chelation conditions (Bu_3SnH/Et_3B in the presence of $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 at −78°C) led to good 2,3-*syn* selection of 8:1 for **11** and 5:1 for **13**, respectively. After easy separation of the diastereoisomers at C-2 by flash-column chromatography, the debrominated major compounds, **10**–**13**, were selectively deprotected on treatment with 1 equiv of $TiCl_4$ in CH_2Cl_2 at rt, so as to derive the final stereotriads, **14**–**17**, without decomposition of the TBDPS protection. The methoxymethyl moiety might be expected to play a role for enhanced steric assistance in both dipole and chelation modes, depicted in Figure 2. Thus, the enantioselective synthesis of all stereotriads of ethyl 5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-3-hydroxypentanoate is necessarily achieved by using a sequence of the enantioselective aldol reaction and the following diastereoselective radical reduction reaction.

2.2. Diastereoselective synthesis of chiral stereotetrads available for construction of the polypropionate framework of polyketide natural products[8]

More straightforward approaches to the diastereoselective construction of polypropionates, possessing units with alternative hydroxyl and methyl groups, towards the versatile synthesis of biologically active polyketide natural products would be expected in a sequential procedure of a chiral oxazaborolidinone-promoted



Scheme 3.

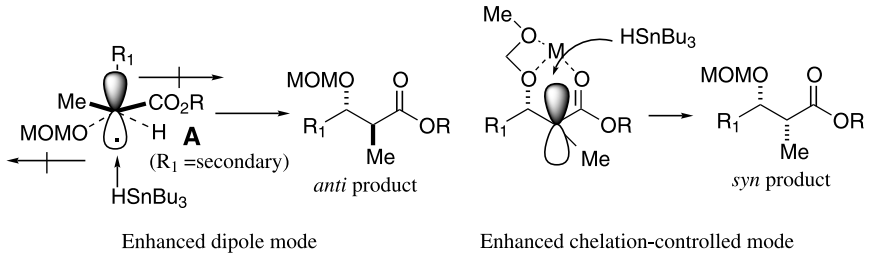
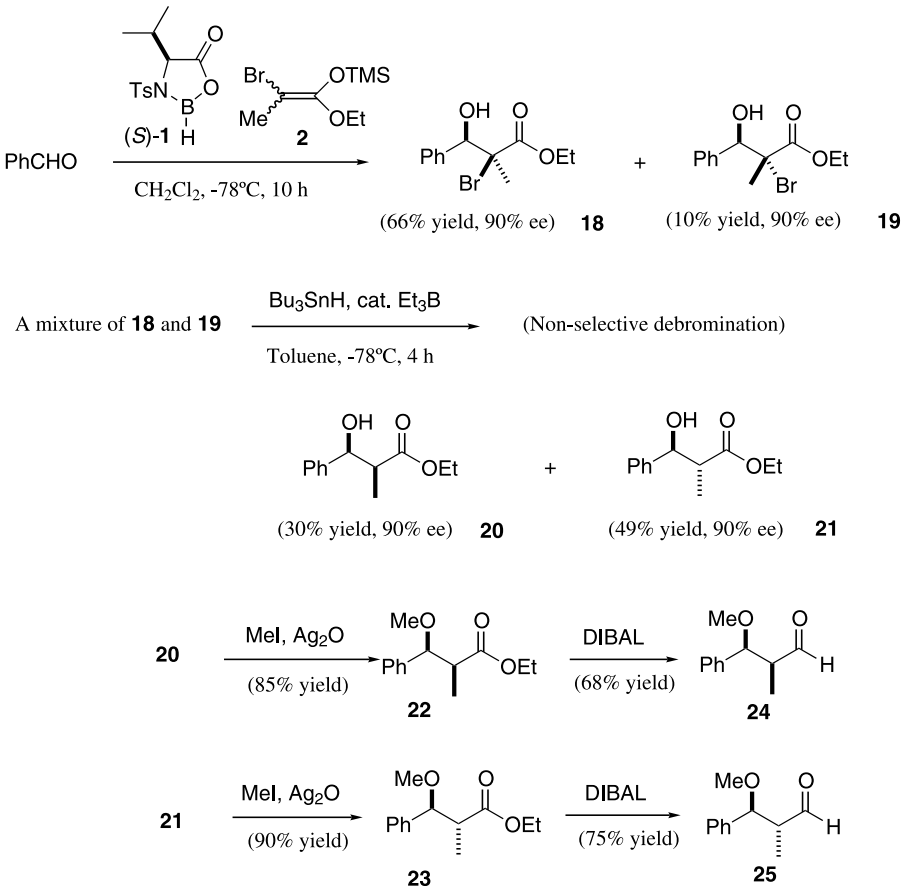


Figure 2. More effective assistance with methoxymethyl moiety.

enantioselective aldol reaction with silylketene acetal **2** and a radical debromination reaction, as mentioned above. However, the enantioselective aldol reaction did not work sufficiently well on the enantioselective diastereoselection in the iterative construction of the bulky propionate system, having alternative protected-oxy and methyl groups.[9] We then planned a diastereoselective approach using the classical Mukaiyama aldol reaction as an alternative to the enantioselective aldol reaction. Excellent *syn*-diastereoselection (Felkin–Anh control) has been recognized in the $BF_3{\cdot}OEt_2$-mediated aldol reaction of α-methyl-β-siloxy aldehydes with a silylketene acetal from ethyl propionate.[9,10] A complementary access is, however, needed to clarify the iterative *syn*- and *anti*-stereoselection necessary for the diastereoselective polypropionate construction because such systematic studies have been restricted to the case of aldehydes bearing only an α- or a β-stereocenter.[11] Typical bidentate Lewis acids, e.g. $TiCl_4$ and $SnCl_4$, were known to undergo chelation-controlled addition reactions in the case of the above aldehydes.[12] However, such Lewis acids were reported to exhibit little to no chelating capability in the aldol reaction of α-methyl-β-benzyloxy aldehydes bearing a β-substituent with enol silanes.[13]

We selected ethyl (2*S*,3*S*)- and (2*R*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionate, **20** and **21**, as the first propionate units in order to test the efficiency of our iterative aldol reaction strategy. The propionates, **20** and **21**, were prepared by our sequential method of chiral oxazaborolidinone-promoted aldol reaction, followed by debromination, as shown in Scheme 4. The enantioselective aldol reaction of benzaldehyde with silyl nucleophile **2** gave *syn*-selectively with a mixture of bromo aldol adducts composed of **18** (66%) and **19** (10%) with 90% ee.[3] The mixture was directly converted to the desired propionate aldols, **20** (30%) and **21** (49%) with 90% ee under non-selective conditions without protection of the hydroxy group (Bu_3SnH/Et_3B, in toluene at −78°C). Both highly enantiopure aldehydes *syn*-**24** and *anti*-**25**, were obtained by successive reactions of methylation (MeI/Ag_2O) and DIBAL reduction.

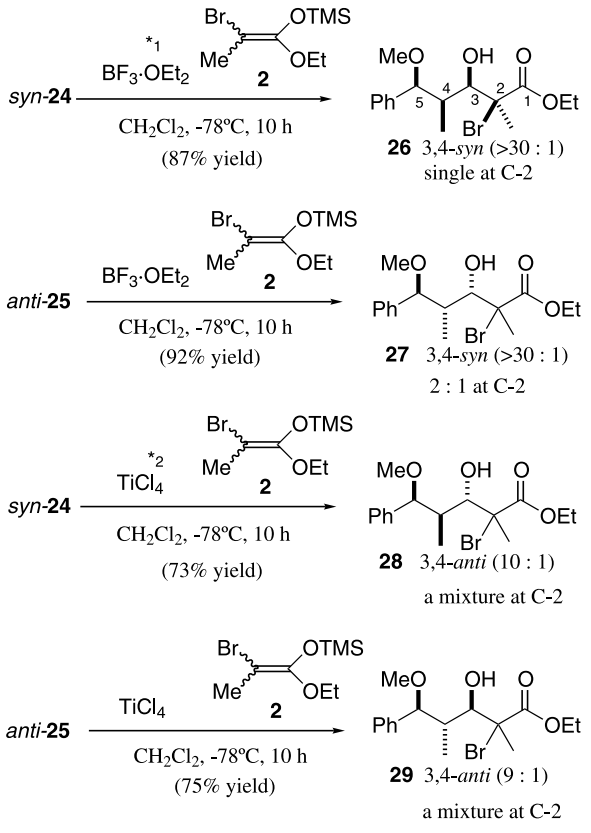
With respect to the process of introducing the stereogenic center at C-3, the Mukaiyama aldol reaction of the silylketene acetal **2** was examined by using $BF_3{\cdot}OEt_2$ and $TiCl_4$. As expected above, the $BF_3{\cdot}OEt_2$ (1 equiv.)-mediated addition reaction of **2** to diastereomeric aldehydes, *syn*-**24** and *anti*-**25**, resulted



Scheme 4.

in excellent 3,4-*syn*-selection to give Felkin–Anh controlled products, **26** (single at C-2) and **27** (2:1 at C-2), respectively, as shown in Scheme 5. Thus, the complete *syn*-selection was confirmed to be reproducible at least in this reaction system, although a relatively different contribution of the resident β-stereocenter has been reported for the Felkin–Anh controlled diastereoselectivity in the non-chelate-controlled addition reaction of similar aldehydes with enol silanes.[10] On the other hand, in spite of the predicted drawbacks of the lower chelation ability[13] of $TiCl_4$ to the aldehyde type in question, the $TiCl_4$ (1.7 equiv.)-mediated addition reaction of aldehydes, *syn*-**24** and *anti*-**25**, with **2** was also found to lead to fairly good 3,4-*anti* selection to give the desired chelate-controlled adducts, **28** (a mixture at C-2) and **29** (a mixture at C-2), respectively. The selectivity at C-2 in achiral Lewis acid-promoted reactions was not observed except in the case of **26** in contract to that in chiral oxazaborolidinone-promoted aldol reactions. The stereochemical outcomes in the above reactions are rationally predicted, as follows: The *syn*-adducts might be formed via the Felkin–Anh controlled addition modes where the major factor responsible for the high *syn*-selection is attributable to the potential differences in the steric bulkiness between the methyl group and the residual group, involving the methoxy substituent, at the C-2 of the aldehydes, as shown in Figure 3. In spite of the indefinite prediction of $TiCl_4$ chelation control on α-methyl-β-protected-oxy aldehydes as described above,[13] the $TiCl_4$-mediated reaction of the *syn*-aldehyde **24** with **2** resulted in fairly good *anti* selection (10:1). The reaction conditions are noteworthy in that trapped TMS *syn*-selective adducts, obtained through a catalytic reaction mode, were found when the amount of $TiCl_4$ used was not sufficient. When we used $SnCl_4$ under similar reaction conditions, very high *syn*-selection (30:1) was found, which implied a loss of the chelating ability of the Lewis acid. In the case of the *anti*-aldehyde **25**, if the chelation with $TiCl_4$ was possible, the *anti*-selectivity would be considerably diminished, because of the desired approach of the silyl nucleophile under the chelation control would be prevented by the β-methoxy substituent, oppositely directed relative to the α-methyl in the chelated conformer. Unexpectedly, the $TiCl_4$-mediated reaction led to remarkably good *anti*-selection (9:1). These results suggest that the chelation controls are surely possible in the $TiCl_4$-mediated reaction of both *syn*- and *anti*-aldehydes, **24** and **25**, as shown in Figure 3.

For the purpose of introducing a stereogenic center at C-2 in elongating the polypropionate chains, an appropriate choice of a β-hydroxy protecting group of aldol adducts was required while bearing in mind the stereochemical demands for the following debromination procedures directed to *syn*- and *anti*-selections. Surveying a number of protecting groups suitable for the following diastereoselective debromination reactions, we again



Scheme 5. *Reagents and conditions*: *1 $BF_3{\cdot}OEt_2$ (1 equiv.), CH_2Cl_2, −78°C, 1 h, 2 (1.5 equiv.); *2 $TiCl_4$ (2 equiv.), CH_2Cl_2, −78°C, 1 h, 2 (1.5 equiv.).

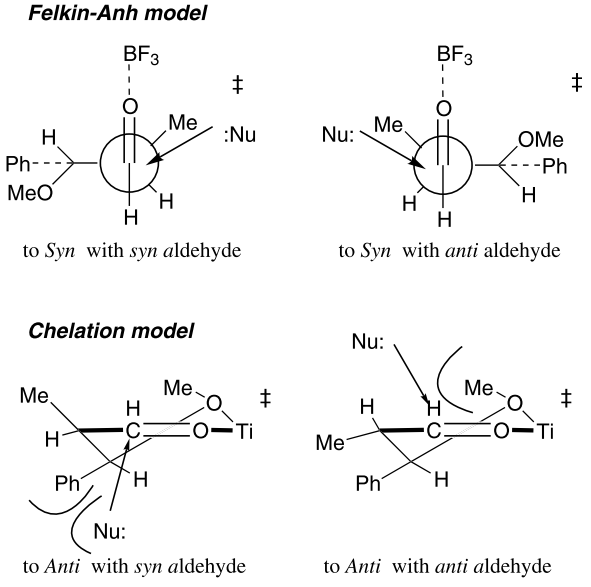


Figure 3.

selected a methoxymethyl (MOM) protection group, available for highly diastereoselective debrominations to the desired eight stereotetrads. The major aldol adducts, **26**–**29**, were treated with dimethoxymethane and P_2O_5 to give the corresponding MOM-protected esters, **30**–**33**, which consisted of isomers at the C-2 position. In the debromination processes, the MOM protection group allowed extremely high diastereoselection for both routes to the 2,3-*syn*-isomer via chelation control and the 2,3-*anti*-isomer via dipole control, as shown in Scheme 6. The MOM protection bearing two oxygens prevented the participation of the methoxy group at C-5 under the conditions of chelation control, while the two oxygens enhanced the transient dipole moment under the conditions of dipole control. The stereocenter at C-2 of the bromides did not contribute to the stereochemical outcome in the radical debromination process because the diastereoselection is achieved at the sp^2 carbon center of the radical species, generated by Et_3B. The 2,3-*syn*-selection can be attributed to the effective chelation of $MgBr_2$ to the ethoxycarbonyl and the MOM moiety while the 2,3-*anti*-selection was enhanced by the induced dipole–dipole repulsion between the ethoxycarbonyl and the MOM moiety, as indicated in Figure 2. After deprotection of the MOM group, followed by simple column chromatography, the expected eight stereotetrads of ethyl 3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate, **42**–**49**, were obtained essentially enantiopure and in good yield.

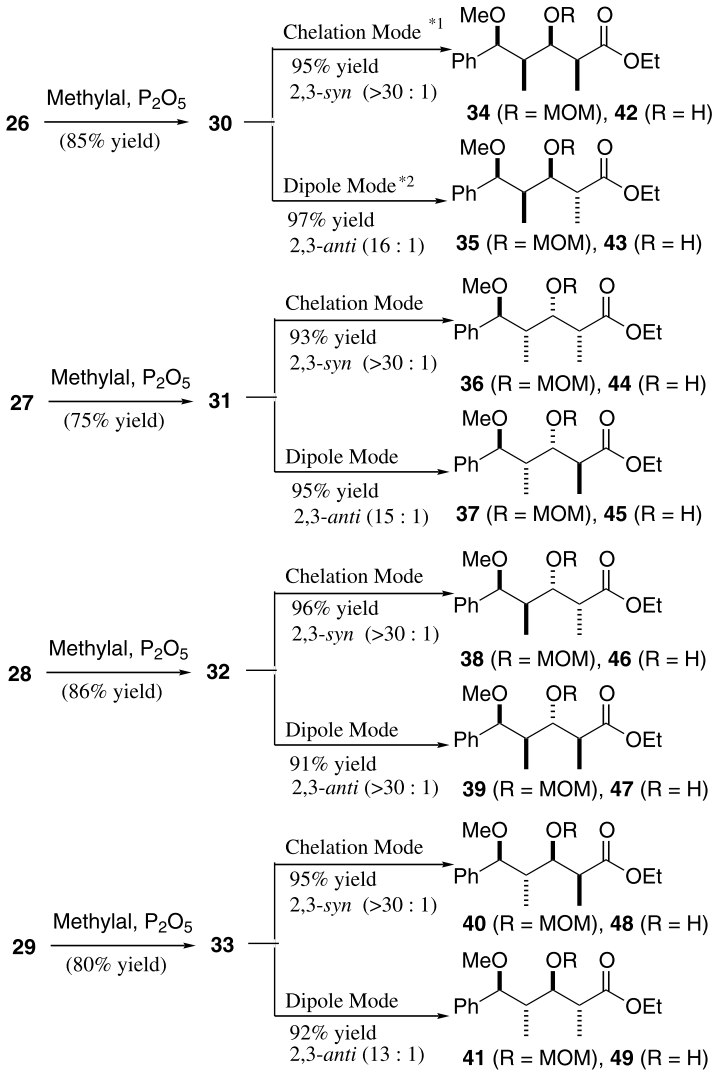
3. Conclusion

The sequence in Scheme 1 of the highly enantioselective and/or diastereoselective aldol reactions (process **A**) and the following highly diastereoselective radical debromination reaction (process **B**) has opened up a very versatile and iterative approach towards the divergent construction of polypropionate chains with acceptable selectivity in good overall yields. This straightforward strategy can tailor the desired configuration in question during the synthesis of a class of polyketide natural products. In the sequential process **A**, iterative aldol reactions as reliable discrete ways to the reverse diastereoselection can be simply achieved by the selection of classical Lewis acids, $BF_3{\cdot}OEt_2$ and $TiCl_4$. In process **B**, the MOM protection group effectively affects both debromination reaction modes so as to more predominantly allow an alternative diastereoselection.

4. Experimental

4.1. General

Infrared spectra (IR) were determined with a JASCO FT/IR-5300 Fourier-transform infrared spectrometer. ^1H NMR spectra were determined at 400 MHz 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, using DAICEL chiral columns. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Merck silica-gel 60 (230–400 mesh) was used for flash-column chromatography.



Scheme 6. *Reaction conditions*: The bromides, **27**, **28**, and **29** except **26**, were converted to the corresponding MOM-derivatives, **30**–**33**, without separation of isomers at C-2. The debromination procedures were done under the following conditions: *1 $MgBr_2{\cdot}OEt_2$ (7 equiv.), Bu_3SnH (5 equiv.), Et_3B (1 equiv.), CH_2Cl_2, −78°C, 15 h. *2 Bu_3SnH (4 equiv.), Et_3B (1 equiv.), toluene, −78°C, 2 h. The major products were isolated after deprotection of the MOM group through the acidic work-up procedure.

4.2. 2-Bromo-1-ethoxy-2-methyl-1-(trimethylsiloxy)-ethene 2

To a stirred solution of LDA (58 mmol) in THF (35 mL) (prepared in situ) at −78°C was added dropwise ethyl 2-bromopropionate (9.1 g, 50 mmol) over 5 min. After 15 min of stirring at the same temperature, TMSCl (9.0 g, 83 mmol) was added over 10 min. The reaction mixture was allowed to warm to ambient temperature after which THF was removed with a rotary evaporator and residue mixed with dry hexane and filtered. After removal of the solvent, the residue was distilled under a reduced pressure to give **2** (9.0 g, 71%, bp 73–74°C/0.1 mmHg), which contained ethyl 2-bromo-2-(trimethylsilyl)propionate (10–20%); IR (neat): 2962, 1655, 1251, 1219, 850 cm^{-1}; *Z*-isomer: ^1H NMR ($CDCl_3$): δ (ppm) = 0.22 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 3.84 (q, J = 7.1 Hz, 2H); *E*-isomer: ^1H NMR ($CDCl_3$): δ (ppm) = 0.19 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H), 2.08 (s, 3H), 3.88 (q, J = 7.1 Hz, 2H).

4.3. (2*RS*)-3-(*tert*-Butyldiphenylsiloxy)-2-methyl-propanol 4

To a suspension of NaH (4.4 g, 100 mmol) in dry THF (150 mL) was slowly added 2-methyl-1,3-propanediol (9 g, 90 mmol) in dry THF (10 mL). After the mixture was stirred at rt for 45 min, TBDPSCl (24.7 g, 90 mmol) in THF (10 mL) was added. The mixture was stirred at rt for 15 h before quenching with water (25 mL). The solution was extracted with ether, dried over anhydrous $MgSO_4$, evaporated in vacuo, and purified by flash-column chromatography (10% ethyl acetate/hexane) to give **4** (21.9 g, 74%) as a colorless oil; IR (neat): 3389, 2961 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) = 0.83 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H), 1.92–2.07 (m, 1H), 2.65 (br s, 1H), 3.60 (dd, J = 10.3, 7.3 Hz, 1H), 3.66 (d, J = 6.4 Hz, 2H), 3.71 (dd, J = 10.3, 4.9 Hz, 1H), 7.37–7.43 (m, 6H), 7.66–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.2, 19.1, 26.8, 37.3, 67.5, 68.6, 127.7, 129.8, 133.2, 135.6. Anal. calcd for $C_{20}H_{28}O_2Si$: C, 73.12; H, 8.59. Found: C, 73.20; H, 8.67.

4.4. (2*RS*)-3-(*tert*-Butyldiphenylsiloxy)-2-methylpropanal 5

To a stirred and cooled (−78°C) solution of $(COCl)_2$ (5.4 mL, 63 mmol) in CH_2Cl_2 (100 mL) was added DMSO (8.3 mL, 117 mmol). After 10 min, alcohol **4** (12.9 g, 39 mmol) in dry CH_2Cl_2 (5 mL) was added. The mixture was stirred for 20 min after which Et_3N (21.7 mL, 156 mmol) was added. The solution was then allowed to rise to 0°C. After stirring for an additional 30 min, a mixture of water (13 mL), ether (50 mL) and benzene (25 mL) was added to quench the reaction. The organic phase was separated, washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified by flash-column chromatography (5% ethyl acetate/hexane) to give **5** (11.2 g, 88%) as a colorless oil; IR (neat): 2957, 2932, 2885, 2858, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.04 (s, 9H), 1.09 (d, J = 7.3 Hz, 3H), 2.55–3.0 (m, 1H), 3.86 (dd, J = 10.3, 5.4 Hz, 1H) [one of ABq in ABX], 3.90 (dd, J = 10.3, 5.9 Hz, 1H) [one of ABq in ABX], 7.24–7.43 (m, 6H), 7.63–7.65 (m, 4H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.3, 19.2, 26.7, 48.8, 64.1, 127.7, 129.8, 133.2, 135.6, 204.4. Anal. calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.45; H, 8.12.

4.5. Enantioselective aldol reaction of 5 in the presence of chiral borane (*S*)-1

Under an argon atmosphere, to a stirred solution of *N*-*p*-tosyl-(*S*)-valine (299 mg, 1.1 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 after which it was stirred for a further 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 where **5** (327 mg, 1 mmol) in CH_2Cl_2 (1 mL) was slowly added over 5 min. After 5 min, the silyl nucleophile **2** (760 mg, 3 mmol) was slowly introduced and stirred for 3 h at −78°C. The reaction was quenched by adding a buffer solution (10 mL, pH 6.8), extracted with ether, washed with a satd $NaHCO_3$ solution, followed with a satd NaCl solution and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude was evaporated, and purified by flash column chromatography (7% AcOEt in hexane) to afford a mixture of aldol adducts, **6** and **7**, (381 mg, 75%) and minor isomers (~4%) as a colorless oil, which was then separated into each isomer by silca-gel flash-column chromatography.

4.5.1. Ethyl (2*S*,3*R*,4*S*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-hydroxy-4-methylpentanoate 6. $[\alpha]_D^{24}$ = +1.4 (*c* 1.44, $CHCl_3$); IR (neat): 3529, 2935, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.97 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.89 (s, 3H), 1.87–2.07 (m, 1H), 2.65 (d, J = 4.9 Hz, 1H), 3.52 (dd, J = 9.8, 5.9 Hz, 1H) [one of ABq in ABX], 3.58 (dd, J = 9.8, 6.8 Hz, 1H) [one of ABq in ABX], 4.18 (dq, J = 9.7, 7.3 Hz, 2H), 4.28 (dd, J = 4.9, 2.5 Hz, 1H), 7.25–7.42 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.0, 13.8, 19.2, 24.2, 26.9, 37.4, 62.3, 67.8, 68.2, 74.8, 127.7, 129.7, 133.5, 135.6, 170.7. Anal. calcd for $C_{25}H_{35}BrO_4Si$: C, 59.16; H, 6.95. Found: C, 59.20; H, 7.02. The enantiomeric excess of the product was determined to be 92% by HPLC analysis using Chiralcel OD-H (eluent: hexane/2-propanol (99:1), 0.5 mL/min, 254 nm) (t_R of peak 1: 13.50 min, peak 2: 15.14 min).

4.5.2. Ethyl (2*S*,3*R*,4*R*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-hydroxy-4-methylpentanoate 7. $[\alpha]_D^{24}$ = −16.1 (*c* 1.23, $CHCl_3$); IR (neat): 3528, 2932, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.89 (d, J = 7.3 Hz, 3H), 1.07 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H), 1.78–1.84 (m, 1H), 1.86 (s, 3H), 3.43 (d, J = 3.9 Hz, 1H), 3.73 (dd, J = 10.3, 4.9 Hz, 1H), 3.84 (dd, J = 10.3, 4.4 Hz, 1H), 4.16–4.31 (m, 3H), 7.25–7.45 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.0, 13.7, 14.6, 19.2, 21.7, 26.9, 38.3, 62.0, 67.4, 68.6, 127.7, 129.8, 133.1, 135.6, 170.7. Anal. calcd for $C_{25}H_{35}BrO_4Si$: C, 59.16; H, 6.95. Found: C, 59.25; H, 6.84. The enantiomeric excess of the product was determined to be 91% by HPLC analysis using Chiralcel OD-H (eluent: *n*-hexane/2-propanol (99:1), 0.5 mL/min, 254 nm) (t_R of peak 1: 13.68 min, peak 2: 16.78 min).

4.6. Enantioselective aldol reaction of 5 in the presence of chiral borane (*R*)-1

The aldol condensation procedure described above for the preparation of **6** and **7** was employed using (*R*)-**1**.

4.6.1. Ethyl (2*R*,3*S*,4*R*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-hydroxy-4-methylpentanoate the enantiomer of 6. $[\alpha]_D^{24}$ = −1.2 (*c* 0.93, $CHCl_3$).

4.6.2. 2. Ethyl (2*R*,3*S*,4*S*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-hydroxy-4-methylpentanoate the enantiomer of 7. $[\alpha]_D^{24}$ = +15.1 (*c* 1.66, $CHCl_3$).

4.7. Methoxymethyl protection of aldol products

4.7.1. Ethyl (2*S*,3*R*,4*S*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-hydroxy-4-methylpentanoate 8. Under an argon atmosphere at rt, to a stirred solution of **6** (233 mg, 0.46 mmol) and dimethoxymethane (5 mL) in dry $CHCl_3$ (5 mL) was added P_2O_5 (500 mg). This solution was then stirred at the same temperature for 3 h. The reaction was quenched by the slow addition of water (5 mL) at 0°C, extracted with ether, washed with a satd $NaHCO_3$ solution and a satd NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The resulting oil was purified by flash column chromatography (5% AcOEt in hexane) to afford **8** (226 mg, 89%). $[\alpha]_D^{24}$ = +27.8 (*c* 1.50, $CHCl_3$); IR (neat): 2957, 2885, 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.99 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H), 1.80–1.89 (m, 1H), 1.89 (s, 3H), 3.31 (s, 3H), 3.47 (dd, J = 9.8, 7.8 Hz, 1H), 3.58 (dd, J = 9.8, 7.3 Hz, 1H), 4.05–4.25 (m, 2H), 4.18 (d, J = 2.0 Hz, 1H), 4.76 (ABq, J = 6.3 Hz, $\Delta\nu$ = 15.0 Hz, 2H), 7.25–7.44 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 12.0, 13.8, 19.2, 24.0, 26.8, 38.3, 56.3, 62.1, 66.7, 67.1, 81.7, 99.3, 127.6, 129.6, 133.6, 135.6, 170.2. Anal. calcd for $C_{27}H_{39}BrO_5Si$: C, 58.79; H, 7.13. Found: C, 58.69; H, 7.24.

4.7.2. Ethyl (2*S*,3*R*,4*R*)-2-bromo-5-(*tert*-butyldiphenylsiloxy)-3-methoxymethoxy-4-methylpentanoate 9. Compound **9** was prepared from **7** (91%) using the same procedure as **8**. $[\alpha]_D^{27}=+23.7$ (*c* 5.10, $CHCl_3$); IR (neat): 2957, 2932, 2885, 1732 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 1.05 (s, 9H), 1.06 (d, $J=6.8$ Hz, 3H), 1.32 (t, $J=7.1$ Hz, 3H), 1.65–1.74 (m, 1H), 1.74 (s, 3H), 3.20 (s, 3H), 3.56 (dd, $J=10.3$, 7.8 Hz, 1H), 3.80 (dd, $J=10.3$, 3.4 Hz, 1H), 4.05 (d, $J=4.9$ Hz, 1H), 4.25 (dq, $J=7.3$, 2.4 Hz, 2H), 4.73 (ABq, $J=6.8$ Hz, $\Delta\nu=27.8$ Hz, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.8, 16.5, 19.3, 21.8, 26.9, 39.5, 56.4, 62.0, 65.6, 65.9, 85.0, 100.0, 127.6, 129.6, 133.7, 135.6, 170.3. Anal. calcd for $C_{27}H_{39}BrO_5Si$: C, 58.79; H, 7.13. Found: C, 58.67; H, 7.21.

4.8. Radical debromination under dipole conditions

4.8.1. Ethyl (2*R*,3*R*,4*S*)-5-(*tert*-butyldiphenylsiloxy)-3-methoxymethoxy-2,4-dimethylpentanoate 10. Under an argon atmosphere, to a stirred solution of MOM-protected bromide **8** (552 mg, 1 mmol) in toluene (15 mL) at −78°C was added dropwise Bu_3SnH (0.8 mL, 3 mmol) and then Et_3B (0.6 mL, 0.6 mmol, 1 M soln in hexanes) in 1/3 portions every 15 min with the resulting mixture being left to stir for 2 h at the same temperature. The reaction was then quenched by the addition of water, extracted with ether, washed with a satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-column chromatography to afford compound **10** as a colorless oil (397 mg, 72%). The ratio of *anti*:*syn* was found to be 15:1 on the basis of NMR data. $[\alpha]_D^{27}=+4.0$ (*c* 7.50, $CHCl_3$); IR (neat): 2958, 2932, 2885, 2858, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.82 (d, $J=6.8$, 3H), 1.07 (s, 9H), 1.08 (d, $J=6.8$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 1.80–1.90 (m, 1H), 2.70 (dq, $J=9.3$, 7.3 Hz, 1H), 3.23 (s, 3H), 3.51 (dd, $J=9.8$, 6.4 Hz, 1H), 3.63 (dd, $J=9.8$, 7.3 Hz, 1H), 3.98 (dd, $J=9.8$, 2.0 Hz, 1H), 4.08–4.18 (m, 2H), 4.59 (ABq, $J=6.8$ Hz, $\Delta\nu=11.7$ Hz, 2H), 7.35–7.43 (m, 6H), 7.64–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 9.9, 14.1, 14.4, 19.2, 26.9, 37.1, 43.7, 55.9, 60.3, 66.1, 80.7, 98.5, 127.6, 129.6, 133.8, 135.6, 175.4. Anal. calcd for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found: C, 68.70; H, 8.61.

4.8.2. Ethyl (2*R*,3*R*,4*R*)-5-(*tert*-butyldiphenylsiloxy)-3-methoxymethoxy-2,4-dimethylpentanoate 12. Employing the radical reduction procedure described for the preparation of **10**, the reaction of **9** gave **12** (85%). The ratio of *anti*:*syn* was found to be 12:1. $[\alpha]_D^{27}=-6.9$ (*c* 2.52, $CHCl_3$); IR (neat): 2957, 2932, 2886, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.98 (d, $J=6.8$ Hz, 3H), 1.07 (s, 9H), 1.11 (d, $J=7.3$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 1.92–2.02 (m, 1H), 2.85 (dq, $J=6.8$, 6.8 Hz, 1H), 3.26 (s, 3H), 3.61 (dd, $J=10.3$, 6.4 Hz, 1H), 3.73 (dd, $J=9.8$, 4.9 Hz, 1H), 3.77 (t, $J=5.9$ Hz, 1H), 4.12 (dq, $J=7.3$, 2.0 Hz, 2H), 4.58 (s, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 12.9, 14.2, 14.3, 19.3, 26.9, 37.8, 42.9, 55.9, 60.3, 65.2, 83.1, 98.1, 127.6, 129.6, 133.8, 135.7, 174.8. Anal. calcd for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found: C, 68.72; H, 8.65.

4.9. Radical debromination under chelation conditions

4.9.1. Ethyl (2*S*,3*R*,4*S*)-5-(*tert*-butyldiphenylsiloxy)-3-methoxymethoxy-2,4-dimethylpentanoate 11. Under an argon atmosphere, Mg turnings (78 mg, 3.2 mmol) were treated with 1,2-dibromoethane (603 mg, 3.2 mmol) at rt in dry ether (7 mL) until the reaction went to completion. To a stirred suspension of the residue and MOM-protected bromide **8** (254 mg, 0.46 mmol) in CH_2Cl_2 (6 mL) at −78°C was added Bu_3SnH dropwise (0.62 mL, 2.3 mmol) and then Et_3B (0.46 mL, 0.46 mmol, 1 M soln in hexanes) in 1/3 portions every 15 min with the resulting mixture being left to stir for 15 h at the same temperature. The reaction was then quenched by the addition of water, extracted with ether, washed with a satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-column chromatography to afford compound **11** (195 mg, 77%). The ratio of *syn*:*anti* was found to be 8:1 on the basis of NMR data. $[\alpha]_D^{27}=+9.3$ (*c* 1.91%, $CHCl_3$); IR (neat): 2957, 2930, 2885, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.91 (d, $J=6.8$ Hz, 3H), 1.06 (s, 9H), 1.19 (d, $J=7.3$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 1.77–1.91 (m, 1H), 2.72 (dq, $J=6.8$, 6.3 Hz, 1H), 3.31 (s, 3H), 3.50 (dd, $J=10.3$, 5.4 Hz, 1H), 3.58 (dd, $J=10.3$, 6.8 Hz, 1H), 4.01 (dd, $J=6.4$, 4.4 Hz, 1H), 4.15 (dq, $J=6.8$, 1.5 Hz, 1H), 4.64 (ABq, $J=7.1$ Hz, $\Delta\nu=19.5$ Hz, 2H), 7.35–7.43 (m, 6H), 7.64–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 11.7, 12.8, 14.1, 19.2, 26.9, 39.0, 42.9, 56.1, 60.4, 66.1, 80.8, 98.5, 127.6, 129.6, 133.6, 135.6, 175.0. Anal. calcd for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found: C, 68.52; H, 8.64.

4.9.2. Ethyl (2*S*,3*R*,4*R*)-5-(*tert*-butyldiphenylsiloxy)-3-methoxymethoxy-2,4-dimethylpentanoate 13. Employing the radical reduction procedure described for the preparation of **10**, the reaction of **11** gave **13** (82%). The ratio of *anti*:*syn* was found to be 5:1. $[\alpha]_D^{27}=-6.0$ (*c* 0.52, $CHCl_3$); IR (neat): 2959, 2931, 2885, 2858, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.99 (d, $J=6.8$ Hz, 3H), 1.07 (s, 9H), 1.13 (d, $J=7.3$ Hz, 3H), 1.25 (t, $J=7.1$ Hz, 3H), 1.80–1.90 (m, 1H), 2.67 (dq, $J=7.1$, 3.9 Hz, 1H), 3.19 (s, 3H), 3.63 (dd, $J=9.8$, 5.9 Hz, 1H), 3.73 (dd, $J=9.8$, 3.9 Hz, 1H), 3.96 (dd, $J=7.8$, 3.9 Hz, 1H), 4.12 (q, $J=7.1$ Hz, 2H), 4.49 (ABq, $J=6.6$ Hz, $\Delta\nu=32.8$ Hz, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.1, 14.1, 14.4, 19.3, 26.9, 39.0, 41.7, 56.0, 60.4, 65.5, 81.7, 98.2, 127.6, 129.6, 133.8, 135.7, 175.1. Anal. calcd for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found: C, 68.70; H, 8.45.

4.10. Deprotection of the MOM group of 10–13 with $TiCl_4$

4.10.1. Ethyl (2*R*,3*R*,4*S*)-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-3-hydroxypentanoate 14. To a stirred solution of the MOM-compound **10** (270 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL) at rt was added dropwise a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.85 mL, 0.85 mmol). The solution was stirred at the same temperature for 30 min. The reaction was then quenched with a buffer solution (3 mL, pH 6.8), followed by the addition of

water (3 mL), extracted with ether (10 mL), dried over anhydrous $MgSO_4$, and evaporated. The resulting oil was purified by flash-column chromatography (7% ethylacetate/hexane) to give MOM-deprotected product **14** (218 mg, 89%). $[\alpha]_D^{26} = -7.1$ (*c* 3.35, $CHCl_3$); IR (neat): 3520, 2957, 2885, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.91 (d, $J = 7.3$ Hz, 3H), 1.06 (s, 9H), 1.10 (d, $J = 7.3$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.72–1.83 (m, 1H), 2.59 (dq, $J = 7.1$, 6.8 Hz, 1H), 2.89 (d, $J = 4.4$ Hz, 1H), 3.65–3.75 (m, 2H), 3.98–4.03 (m, 1H), 4.12–4.25 (m, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 9.47, 14.1, 14.2, 19.2, 26.9, 36.7, 43.3, 60.5, 67.8, 74.3, 127.7, 129.7, 133.2, 135.6, 176.3. Anal. calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.11; H, 8.38.

4.10.2. Ethyl (2*S*,3*R*,4*S*)-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-3-hydroxypentanoate 15. $[\alpha]_D^{25} = +10.1$ (*c* 0.79, $CHCl_3$); IR (neat): 3517, 2957, 2885, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.01 (d, $J = 6.8$ Hz, 3H), 1.06 (s, 9H), 1.24 (d, $J = 7.3$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.67–1.78 (m, 1H), 2.65 (dq, $J = 7.3$, 6.8 Hz, 1H), 2.98 (d, $J = 2.9$ Hz, 1H), 3.61 (dd, $J = 10.3$, 4.9 Hz, 1H), 3.72 (dd, $J = 10.3$, 3.9 Hz, 1H), 3.99 (dt, $J = 7.3$, 3.6 Hz, 1H), 4.12 (dq, $J = 7.3$, 2.0 Hz, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.9, 13.2, 14.2, 19.2, 26.9, 37.4, 43.2, 60.4, 68.3, 74.8, 127.7, 129.8, 132.9, 135.6, 175.7. Anal. calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.00; H, 8.52.

4.10.3. Ethyl (2*R*,3*R*,4*R*)-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-3-hydroxypentanoate 16. $[\alpha]_D^{25} = -16.7$ (*c* 2.09, $CHCl_3$); IR (neat): 3500, 2957, 2885, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.99 (d, $J = 6.8$ Hz, 3H), 1.06 (s, 9H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.82–1.93 (m, 1H), 2.75 (dq, $J = 7.1$, 5.4 Hz, 1H), 3.42 (d, $J = 7.3$ Hz, 1H), 3.63 (dt, $J = 6.8$, 6.3 Hz, 1H), 3.73 (dq, $J = 10.3$, 4.9 Hz, 2H), 4.12–4.21 (m, 2H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.2, 14.4, 14.5, 19.2, 26.8, 38.0. 42.9, 60.4, 66.8, 77.2, 127.7, 129.7, 133.1, 135.6, 175.7; Anal. calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.09; H, 8.53.

4.10.4. Ethyl (2*S*,3*R*,4*R*)-5-(*tert*-butyldiphenylsiloxy)-2,4-dimethyl-3-hydroxypentanoate 17. $[\alpha]_D^{25} = -9.8$ (*c* 1.50, $CHCl_3$); IR (neat): 3495, 2957, 2885, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.88 (d, $J = 6.8$ Hz, 3H), 1.06 (s, 9H), 1.20 (d, $J = 7.3$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.72–1.83 (m, 1H), 2.61 (dq, $J = 6.8$, 3.9 Hz, 1H), 3.51 (d, $J = 3.4$ Hz, 1H), 3.71 (dd, $J = 10.3$, 5.9 Hz, 1H), 3.83 (dd, $J = 9.8$, 3.9 Hz, 1H), 3.96 (dt, $J = 12.0$, 3.9 Hz, 1H), 4.16 (q, $J = 6.8$ Hz, 1H), 7.25–7.43 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 9.8, 13.7, 14.2, 19.2, 26.9, 37.4, 42.4, 60.5, 67.9, 75.3, 127.7, 129.7, 133.0, 135.6, 175.9. Anal. calcd for $C_{25}H_{36}O_4Si$: C, 70.05; H, 8.47. Found: C, 70.12; H, 8.40.

4.11. Enantioselective aldol reaction of a benzaldehyde with 2 in the presence of (*S*)-1

Under an argon atmosphere, to a stirred solution of *N*-(*p*-toluenesulfonyl)-(*S*)-valine (19.5 g, 72 mmol) in dry CH_2Cl_2 (150 mL) at 0°C was added dropwise a 1 M solution of BH_3·THF in THF (60 mL, 60 mmol) over a period of 5 min after which it was left to stir at 0°C for 30 min. 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 after which benzaldehyde (6.1 mL, 60 mmol) in CH_2Cl_2 (10 mL) was slowly added over 5 min. After 5 min, **2** was also introduced over 5 min and the resulting solution stirred for 15 h at −78°C. The reaction mixture was quenched by the addition of buffer solution (10 mL, pH 6.8), extracted with ether, and washed with a satd $NaHCO_3$ solution, followed by the addition of a satd NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash-column chromatography (7% AcOEt in hexane) to afford a mixture of **18** and **19** (12.8 g, 73% yield), which could be separated into each isomer. The ratio of *syn*:*anti* was found to be 6.6:1): δ (ppm) = 13.7, 22.5, 62.4, 67.6, 77.1, 127.9, 128.0, 128.5, 136.8, 170.4. The enantiomeric excess of the *syn*-isomer was determined to be 90% ee by HPLC analysis using Chiralcel OD-H (t_R of peak 1: 24.04 min; t_R of peak 2: 27.31 min; eluent, hexane/2-propanol = 97.5:2.5, 0.5 mL/min). Anal. calcd for $C_{12}H_{15}O_3Br$: C, 50.17; H, 5.23. Found: C, 50.20; H, 5.21.

4.11.1. Ethyl (2*R*,3*R*)-2-bromo-3-hydroxy-2-methyl-3-phenylpropionate 19. $[\alpha]_D^{26} = -38.6$ (*c* 3.00, $CHCl_3$); IR (neat): 3508, 1734 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.33 (t, $J = 7.1$ Hz, 3H), 1.79 (s, 3H), 3.22 (d, $J = 5.1$ Hz, 1H), 4.30 (dq, $J = 5.1$, 7.1 Hz, 2H), 5.31 (d, $J = 5.1$ Hz, 1H), 7.26–7.49 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.8, 22.1, 62.1, 62.5, 77.9, 127.7, 128.4, 128.5, 137.4, 171.2. The enantiomeric excess of the *syn*-isomer was determined to be 90% ee by HPLC analysis using Chiralcel OD-H (t_R of peak 1: 19.76 min; t_R of peak 2: 30.59 min; eluent, hexane/2-propanol = 98:2, 1 mL/min). Anal. calcd for $C_{12}H_{15}O_3Br$: C, 50.17; H, 5.23. Found: C, 50.15; H, 5.24.

4.12. Radical reduction of a mixture of 18 and 19

Under an argon atmosphere, to a stirred solution of (2*S*,3*R*)- and (2*R*,3*R*)-2-bromo-3-hydroxy-2-methyl-3-phenylpropionates in CH_2Cl_2 (6 mL) at −78°C was added dropwise Bu_3SnH (0.53 mL, 1.9 mmol) and then Et_3B (0.64 mL, 0.64 mmol, 1 M solution in THF) 1/3 portions every 15 min and then left to stir for 4 h at the same temperature. The reaction was then quenched by the addition of water, extracted with ether, washed with a satd NaCl solution and dried over anhydrous $MgSO_4$, evaporated. The residue was purified by flash-column chromatography (5% AcOEt in hexane) to afford **20** (30%) and **21** (49%), respectively.

4.12.1. Ethyl (2*S*,3*S*)-3-methoxy-2-methyl-3-phenylpropionate 20. $[\alpha]_D^{23} = -15.7$ (*c* 2.10, $CHCl_3$); IR (neat): 3477, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.13 (d, $J = 7.0$ Hz, 3H), 1.21 (t, $J = 7.0$ Hz, 3H), 2.77 (dq, $J = 2.9$, 7.0 Hz, 1H), 2.98 (d, $J = 3.1$ Hz, 1H), 4.12 (dq, $J = 4.1$, 7.0 Hz, 2H), 5.09 (dd, $J = 3.4$, 4.1 Hz, 1H), 7.25–7.68 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.8, 14.0, 46.4,

60.0, 70.3, 125.9, 127.4, 128.1, 141.4, 175.7. The enantiomeric excess of the *syn*-isomer was determined to be 90% ee by HPLC analysis using Chiralcel OD-H (t_R of peak 1: 11.64 min; t_R of peak 2: 12.47 min; eluent, hexane/2-propanol = 97:3, 1 mL/min). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.31; H, 7.70.

4.12.2. Ethyl (2*R*,3*S*)-3-methoxy-2-methyl-3-phenylpropionate 21. $[\alpha]_D^{23} = -42.3$ (*c* 2.50, $CHCl_3$); IR (neat): 3458, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.00 (d, $J = 7.3$ Hz, 3H), 1.25 (t, $J = 7.3$ Hz, 3H), 2.79 (dq, $J = 1.0$, 7.3 Hz, 1H), 2.98 (d, $J = 4.4$ Hz, 1H), 4.18 (q, $J = 7.3$ Hz, 2H), 4.75 (dd, $J = 4.4$, 8.2 Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.0, 14.4, 47.1, 60.6, 76.2, 126.6, 127.9, 128.3 141.6, 175.7. The enantiomeric excess of the *syn*-isomer was determined to be 90% ee by HPLC analysis using Chiralcel OD-H (t_R of peak 1: 15.09 min; t_R of peak 2: 25.43 min; eluent, hexane/2-propanol = 97:3, 1 mL/min). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 69.18; H, 7.71.

4.13. Methyl protection of 20 and 21

4.13.1. Ethyl (2*R*,3*S*)-3-methoxy-2-methyl-3-phenylpropionate 22. To a stirred solution of **20** (2.51 g, 12.5 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added methyl iodide (3.9 mL) and stirred for 15 min. Silver oxide (14.7 mg, 61.2 mmol) was added and the solution left to stir for 15 h. Methyl iodide (3.9 mL) was added and the solution stirred for 1 h at the same temperture. After addition of ether (20 mL), the solution was washed with a satd NH_4Cl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash-column chromatography (4% AcOEt in hexane) to afford **22** (85%). $[\alpha]_D^{25} = -34.0$ (*c* 1.00, $CHCl_3$); IR (neat): 2984, 1734 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.07 (d, $J = 7.0$ Hz, 3H), 1.22 (t, $J = 6.8$ Hz, 3H), 2.73 (quin, $J = 7.0$ Hz, 1H), 3.22 (s, 3H), 3.98 (Abq in ABX_3, $J = 7.0$, 10.8 Hz, $\Delta\nu = 14.8$ Hz, 2H), 4.40 (d, $J = 7.0$ Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 12.5, 13.9, 47.4, 57.1, 60.2, 84.5, 127.1, 127.7, 128.1, 139.7, 173.9. Anal. calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.20; H, 8.08.

4.13.2. Ethyl (2*S*,3*S*)-3-methoxy-2-methyl-3-phenylpropionate 23. $[\alpha]_D^{25} = -51.9$ (*c* 1.56, $CHCl_3$); IR (neat): 2982, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.86 (d, $J = 7.0$ Hz, 3H), 1.30 (t, $J = 7.0$ Hz, 3H), 2.73 (dq, $J = 7.3$, 9.7 Hz, 1H), 3.15 (s, 3H), 4.22 (Abq in ABX_3, $J = 7.0$, 11.3 Hz, $\Delta\nu = 22.9$ Hz, 2H), 4.24 (d, $J = 10.0$ Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 14.0, 14.2, 47.1, 56.7, 60.4, 85.9, 127.6, 128.1, 128.3, 138.9, 175.3. Anal. calcd for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.09; H, 8.11.

4.14. DIBAL reduction of 22 and 23

4.14.1. (2*S*,3*S*)-3-Methoxy-2-methyl-3-phenylpropanal 24. Under an argon atmosphere, to a stirred solution of **22** (1.46 g, 6.56 mmol) in dry CH_2Cl_2 (25 mL) at −78°C was added dropwise a 1 M solution of DIBAL in toluene (19.6 mL, 19.6 mmol) over 30 min. The resulting solution was then stirred at the same temperature for 2 h. The reaction was quenched by the slow addition of MeOH (1 mL). After addition of water (5 mL), the solution was extracted with ether, washed with a satd NaCl solution, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by flash-column chromatography (10% AcOEt in hexane) to afford **24** (798 mg, 68%). $[\alpha]_D^{24} = -61.2$ (*c* 0.98, $CHCl_3$); IR (neat): 2986, 1726 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 1.06 (d, $J = 7.0$ Hz, 3H), 1.22 (ddq, $J = 1.2$, 4.8, 7.0 Hz, 1H), 4.60 (d, $J = 4.8$ Hz, 1H), 7.25–7.39 (m, 5H), 9.81 (d, $J = 2.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 8.41, 53.0, 57.1, 82.4, 126.8, 127.8, 128.4, 138.9, 203.5.

4.14.2. (2*R*,3*S*)-3-Methoxy-2-methyl-3-phenylpropanal 25. $[\alpha]_D^{23} = -89.0$ (*c* 1.14, $CHCl_3$); IR (neat): 3030, 2982, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.83 (d, $J = 7.0$ Hz, 3H), 2.71 (ddq, $J = 1.1$, 7.0, 9.0 Hz, 1H), 3.18 (s, 3H), 4.27 (d, $J = 9$ Hz, 1H), 7.29–7.40 (m, 5H), 9.81 (d, $J = 2.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.9, 52.6, 56.7, 84.8, 127.3 128.2, 128.5, 138.7, 204.0.

4.15. *syn*-Selective $BF_3{\cdot}OEt_2$-promoted aldol reaction of *syn*-24 and *anti*-25

4.15.1. Ethyl (2*S*,3*R*,4*R*,5*S*)-2-bromo-3-hydroxy-5-methoxy-2,4-dimethyl-5-phenylpentanoate 26. Under an argon atmosphere, to a stirred solution of $BF_3{\cdot}OEt_2$ (0.88 mL, 7.01 mmol) in dry CH_2Cl_2 (35 mL) at −78°C was added dropwise the aldehyde *syn*-**24** (1.25 g, 7.01 mmol) over 5 min. After stirring at the same temperature for 15 min, bromo silyl nucleophile **2** (2.66 g, 10.5 mmol) was introduced over 10 min and the resulting solution 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 a satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude residue was purified by flash-column chromatography (8% AcOEt in *n*-hexane) to afford **26** as a single isomer (2.19 g, 87%). $[\alpha]_D^{20} = -17.0$ (*c* 1.06, $CHCl_3$); IR (neat): 3497, 2984, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.92 (d, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.87 (s, 3H), 1.92 (ddq, $J = 1.4$, 2.4, 4.6 Hz, 1H), 3.02 (d, $J = 3.2$ Hz, 1H), 3.29 (s, 3H), 4.25 (dq, $J = 2.2$, 7.1 Hz, 2H), 4.27 (d, $J = 1.7$ Hz, 1H), 4.28 (dd, $J = 4.9$, 8.8 Hz, 1H), 7.21–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 8.0, 13.9, 23.8, 41.9, 57.5, 62.3, 66.6, 77.2, 88.3, 126.9, 127.6, 128.2, 139.5, 170.7. Anal. calcd for $C_{16}H_{23}O_4Br$: C, 53.48; H, 6.41. Found: C, 53.52; H, 6.39.

4.15.2. Ethyl (2*R*,3*S*,4*S*,5*S*)-2-bromo-3-hydroxy-5-methoxy-2,4-dimethyl-5-phenylpentanoate 27. The bromo-aldol adducts of **27** and the isomer at C-2 were obtained from the reaction of the *anti*-**25** (2:1 ratio) (92%). $[\alpha]_D^{27} = -29.5$ (*c* 0.78, $CHCl_3$); IR (neat): 3526, 2984, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.92 (d, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.88 (s 3H), 1.91 (m, 1H), 3.03 (d, $J = 3.2$ Hz, 1H), 3.29 (s, 3H), 4.25 (dq, $J = 4.2$, 6.8 Hz, 2H), 4.27 (d, $J = 3.4$ Hz, 1H), 4.28 (dd, $J = 4.9$, 9.1 Hz, 1H), 7.19–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 8.0, 13.9, 23.7, 41.9, 57.5, 62.2, 66.6, 77.2, 88.3, 126.8, 127.6, 128.3, 139.5, 170.7. Anal.

calcd for $C_{16}H_{23}O_4Br$: C, 53.48; H, 6.41. Found: C, 53.54; H, 6.45.

4.15.3. Ethyl (2*S*,3*S*,4*S*,5*S*)-2-bromo-3-hydroxy-5-methoxy-2,4-dimethyl-5-phenylpentanoate the isomer of 27. $[\alpha]_D^{25} = -64.6$ (*c* 1.01, $CHCl_3$); IR (neat): 3349, 2982, 1734 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.65 (d, $J = 6.8$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.92 (s, 3H), 2.24 (ddq, $J = 1.2$, 6B, 8.3 Hz, 1H), 3.21 (s, 3H), 3.38 (d, $J = 7.3$ Hz, 1H), 4.08 (d, $J = 8.0$ Hz, 1H), 4.24 (ABq in ABX_3, $J = 7.1$, 10.9 Hz, $\Delta\nu = 10.0$ Hz, 2H), 4.61 (dd, $J = 7.1$, 1.5 Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.7, 13.8, 24.9, 40.6, 57.1, 62.4, 63.5, 74.9, 86.5, 127.5, 127.8, 128.3, 140.4, 171.6.

4.16. *anti*-Selective $TiCl_4$-promoted aldol reaction of *syn*-24 and *anti*-25

4.16.1. Ethyl (3*S*,4*S*,5*S*)-2-bromo-2,4-dimethyl-3-hydroxy-5-methoxy-5-phenylpropionate 28. Under an argon atmosphere, to a stirred solution of $TiCl_4$ (0.36 mL, 3.29 mmol) in dry CH_2Cl_2 (15 mL) at −78°C was added dropwise the aldehyde *syn*-**24** (278 mg, 1.64 mmol) over 5 min. After stirring at the temperature for an additional 30 min, silylketene acetal **2** (624 mg, 2.47 mmol) was introduced over 5 min and the resulting solution stirred for another hour at −78°C. The reaction was quenched with a buffer solution (3 mL, pH 6.8), extracted with ether, washed with a satd NaCl solution and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude residue was purified by flash-column chromatography (10% AcOEt in hexane) to afford a mixture of **28** and the C-2 isomer (10:1 ratio) (363 mg, 73%), accompanied by a small amount of 3,4-*syn* isomers. ^1H NMR ($CDCl_3$): δ (ppm) = 0.69 (d, $J = 7.3$ Hz, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.90 (s, 3H), 2.01 (m, 1H), 3.31 (s, 3H), 3.57 (dd, $J = 2.6$, 3.4 Hz, 1H), 4.22 (m, 2H), 4.33 (dd, $J = 3.4$, 7.3 Hz, 1H), 4.83 (d, $J = 2.2$ Hz, 1H), 7.23–7.37 (m, 5H). Anal. calcd for $C_{16}H_{23}O_4Br$: C, 53.48; H, 6.41. Found: C, 53.46; H, 6.43.

4.16.1.1. The C-2 isomer of 28. ^1H NMR ($CDCl_3$): δ (ppm) = 0.93 (d, $J = 7.3$ Hz, 3H), 1.28 (t, $J = 7.3$ Hz, 3H), 2.05 (s, 3H), 2.14 (ddq, $J = 2.2$, 4.6, 7.0 Hz, 1H), 3.30 (s, 3H), 4.08 (t, $J = 5.2$ Hz, 1H), 4.24 (q, $J = 7.0$ Hz, 2H), 4.27 (d, $J = 5.4$ Hz, 1H), 4.90 (d, $J = 2.4$ Hz, 1H), 7.24–7.38 (m, 5H).

4.16.2. Ethyl (3*R*,4*R*,5*S*)-2-bromo-2,4-dimethyl-3-hydroxy-5-methoxy-5-phenylpropionate 29. The bromo-aldol adducts were obtained from the reaction of the *anti*-**25** as a mixture at C-2 (9:1 ratio) (75%). $[\alpha]_D^{27} = -48.1$ (*c* 0.54, $CHCl_3$); IR (neat): 3447, 2984, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.70 (d, $J = 6.8$ Hz, 3H), 1.33 (t, $J = 7.0$ Hz, 3H), 2.03 (s, 3H), 2.27 (ddq, $J = 4.6$, 7.0, 10.0 Hz, 1H), 2.98 (s, 3H), 4.10 (d, $J = 7.3$ Hz, 1H), 4.12 (t, $J = 4.9$ Hz, 1H), 4.27 (ABq in ABH_3, $J = 7.0$, 10.7 Hz, $\Delta\nu = 38$ Hz, 2H), 5.16 (d, $J = 7.8$ Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.7, 16.9, 25.0, 41.8, 55.3, 62.0, 81.3, 86.2, 126.4, 127.7, 128.1, 128.4, 139.7, 171.3. Anal. calcd for $C_{16}H_{23}O_4Br$: C, 53.48; H, 6.41. Found: C, 53.54; H, 6.45.

4.16.2.1. The C-2 isomer of 29. ^1H NMR ($CDCl_3$): δ (ppm) = 0.54 (d, $J = 7.0$ Hz, 3H), 1.24 (t, $J = 7.3$ Hz, 3H), 1.92 (s, 3H), 2.12 (m, 1H), 3.17 (s, 3H), 4.21 (m, 2H), 4.25 (m, 2H), 4.66 (d, $J = 3.9$ Hz, 1H), 7.25–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 8.9, 14.26, 24.6, 45.9, 61.4, 64.7, 80.7, 86.93, 126.8, 127.6, 127.8, 128.2, 140.2, 173.6.

4.17. A typical procedure of a *syn*-selective radical debromination reaction from 26–29 to 42, 44, 46, and 48

4.17.1. Ethyl (2*S*,3*R*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 42. Under an argon atmosphere, Mg turnings (78 mg, 3.2 mmol) were treated with 1,2-dibromoethane (603 mg, 3.2 mmol) at rt in dry ether (7 mL) until the reaction went to completion. To a stirred suspension of the residue and MOM-protected bromide **30** (193 mg, 0.46 mmol), which was prepared from **26** according to the standard procedure for **8** (85%) and used without further purification, in CH_2Cl_2 (6 mL) at −78°C was added dropwise Bu_3SnH (0.62 mL, 2.3 mmol) and then Et_3B (0.46 mL, 0.46 mmol, 1 M soln in hexanes) in 1/3 portions every 15 min with the resulting mixture being left to stir for 15 h at the temperature. The reaction was quenched by the addition of water, extracted with ether, washed with a satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-column chromatography to afford compound **34** (140 mg, 95%). The ratio of *syn*:*anti* was found to be >30:1 on the basis of NMR data. Compound **34** (136 mg, 0.4 mmol) was then dissolved in a solution of THF (1 mL), water (1 mL), and 6 M hydrochloric acid (1 mL). After being stirred at rt for 3 h, the solution was extracted with ether, washed with a satd Na_2CO_3 solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-column chromatography (15% AcOEt in hexane) to afford **42** (91 mg, 85%). $[\alpha]_D^{28} = -44.6$ (*c* 0.56, $CHCl_3$); IR (neat): 3489, 2980, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.84 (d, $J = 7.0$ Hz, 3H), 1.22 (t, $J = 7.3$ Hz, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.73 (ddq, $J = 2.2$, 3.4, 7.0 Hz, 1H), 2.61 (dq, $J = 6.8$, 9.0 Hz, 1H), 3.30 (s, 3H), 3.46 (d, $J = 1.7$ Hz, 1H), 3.98 (ddd, $J = 1.7$, 2.2, 9.2 Hz, 1H), 4.10 (ABq in ABX_3, $J = 7.3$, 10.8 Hz, $\Delta\nu = 9.3$ Hz, 2H), 4.43 (d, $J = 3.4$ Hz, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 5.8, 14.1, 14.4, 42.4, 43.7, 57.1, 60.2, 76.3, 88.4, 126.5, 127.4, 128.2, 139.6, 175.1. Anal. calcd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57. Found: C, 68.61; H, 8.59.

4.17.2. Ethyl (2*R*,3*S*,4*S*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 44. $[\alpha]_D^{28} = -57.1$ (*c* 0.98, $CHCl_3$); IR (neat): 3504, 2980, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.90 (d, $J = 7.0$ Hz, 3H), 1.12 (t, $J = 7.3$ Hz, 3H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.85 (ddq, $J = 1.9$, 7.0, 7.2 Hz, 1H), 2.60 (dq, $J = 6.8$, 9.0 Hz, 1H), 3.07 (d, $J = 4.1$ Hz, 1H), 3.24 (s, 3H), 3.94 (ddd, $J = 1.9$, 3.9, 9.0 Hz, 1H), 4.01 (ABq in ABX_3, $J = 3.6$, 7.0 Hz, $\Delta\nu = 7.1$ Hz, 2H), 4.21 (d, $J = 6.1$ Hz, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 11.3, 14.0, 14.5, 42.6, 43.9, 57.4, 60.1, 72.0, 87.7, 126.8, 127.6, 128.3, 140.2, 174.9.

4.17.3. Ethyl (2*R*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 46. $[\alpha]_D^{28} = -72.4$ (*c* 0.69, $CHCl_3$); IR (neat): 3493, 2980, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) = 0.76 (d, $J = 7.0$ Hz, 3H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.76 (ddq, $J = 2.6$, 7.3, 7.5 Hz, 1H), 2.65 (dq, $J = 5.1$, 7.0 Hz, 1H), 3.31 (s, 3H), 3.59 (d, $J = 5.1$ Hz, 1H), 3.92 (dt, $J = 5.3$, 7.0 Hz, 1H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.78 (d, $J = 2.4$ Hz, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.0, 11.1, 14.1, 41.9, 42.9, 57.3, 60.5, 74.0, 83.2, 126.7, 127.0, 128.1, 140.0, 176.1.

4.17.4. Ethyl (2*S*,3*R*,4*S*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 48. $[\alpha]_D^{28} = -41.6$ (*c* 1.44, $CHCl_3$); IR (neat): 3468, 3063, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.58 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 2.01 (ddq, $J = 7.0$, 7.9, 9.0 Hz, 1H), 2.59 (dq, $J = 2.6$, 7.3 Hz, 1H), 3.17 (s, 3H), 3.99 (ddd, $J = 1.7$, 2.4, 9.0 Hz, 1H), 4.18 (ABq in ABX_3, $J = 7.3$, 9.0 Hz, $\Delta\nu = 8.0$ Hz, 2H), 4.24 (d, $J = 8.0$ Hz, 1H), 4.48 (dd, $J = 1.2$, 1.7 Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 8.6, 12.3, 14.1, 41.5, 42.0, 56.3, 60.5, 75.6, 88.6, 127.8, 127.9, 128.2, 139.3, 175.6.

4.18. A typical procedure of *anti*-selective radical debromination reaction from 26–29 to 43, 45, 47, and 49

4.18.1. Ethyl (2*R*,3*R*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 43. Under an argon atmosphere, to a stirred solution of **30** (92 mg, 0.22 mmol), which was prepared from **26** according to the standard procedure for **8** (85%) and used without further purification, in toluene (3 mL) at −78°C was added dropwise Bu_3SnH (0.2 mL, 0.88 mmol) and then Et_3B (0.22 mL, 0.22 mmol, 1 M soln in hexanes) in 1/3 portions every 15 min and the resulting mixture left to stir for 2 h at the temperature. The reaction was then quenched by the addition of water, extracted with ether, washed with a satd NaCl solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography to afford compound **35** (73 mg, 97%). The ratio of *syn*:*anti* was found to be 16:1 on the basis of NMR data. Compound **35** (51 mg, 0.15 mmol) was dissolved in a solution of THF (1 mL), water (1 mL), and 6 M hydrochloric acid (0.5 mL). The solution was stirred at rt for 3 h, extracted with ether, washed with a satd Na_2CO_3 solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-column chromatography (15% AcOEt in hexane) to afford **43** (38 mg, 90%). $[\alpha]_D^{28} = -34.6$ (*c* 0.78, $CHCl_3$); IR (neat): 3501, 2980, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.90 (d, $J = 7.1$ Hz, 3H), 1.25 (d, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 6.8$ Hz, 3H), 1.82 (ddq, $J = 2.0$, 4.6, 6.8 Hz, 1H), 2.59 (dq, $J = 7.1$, 9.3 Hz, 1H), 3.26 (s, 3H), 3.51 (d, $J = 2.7$ Hz, 1H), 3.86 (ddd, $J = 2.0$, 2.5, 9.3 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.40 (d, $J = 4.9$ Hz, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 6.2, 13.9, 14.2, 41.1, 43.5, 57.1, 60.6, 76.0, 88.0, 126.9, 127.5, 128.3, 140.0, 176.2. Anal. calcd for $C_{16}H_{24}O_4$0: C, 68.57; H, 8.57. Found: C, 68.43; H, 8.61.

4.18.2. Ethyl (2*S*,3*S*,4*S*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 45. $[\alpha]_D^{28} = -66.9$ (*c* 1.18, $CHCl_3$); IR (neat): 3508, 2978, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.74 (d, $J = 7.1$ Hz, 3H), 1.05 (d, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.87 (ddq, $J = 2.0$, 7.4, 7.6 Hz, 1H), 2.58 (dq, $J = 7.3$, 9.5 Hz, 1H), 3.03 (d, $J = 4.2$ Hz, 1H), 3.20 (s, 3H), 4.16 (d, $J = 7.8$ Hz, 1H), 4.17 (dq, $J = 0.5$, 7.0 Hz, 2H), 4.22 (ddd, $J = 2.0$, 4.2, 9.5 Hz, 1H), 7.25–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 9.7, 14.0, 14.1, 41.0, 43.5, 57.1, 60.5, 71.6, 86.3, 127.3, 127.6, 128.3, 140.7, 176.3.

4.18.3. Ethyl (2*S*,3*S*,4*R*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 47. $[\alpha]_D^{28} = -50.0$ (*c* 1.32, $CHCl_3$); IR (neat): 3503, 2980, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.81 (d, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.31 (d, $J = 7.1$ Hz, 3H), 1.80 (dquin, $J = 2.4$, 7.1 Hz, 1H), 2.74 (dq, $J = 2.0$, 7.1 Hz, 1H), 3.32 (s, 3H), 3.57 (d, $J = 3.2$ Hz, 1H), 3.68 (ddd, $J = 2.0$, 3.9, 7.1 Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.72 (d, $J = 2.4$ Hz, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 10.2, 14.2, 15.1, 42.7, 43.4, 57.4, 60.5, 76.2, 83.0, 126.6, 127.1, 128.2, 140.3, 176.0.

4.18.4. Ethyl (2*R*,3*R*,4*S*,5*S*)-3-hydroxy-2,4-dimethyl-5-methoxy-5-phenylpentanoate 49. $[\alpha]_D^{28} = -67.0$ (*c* 1.18, $CHCl_3$); IR (neat): 3481, 2980, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) = 0.65 (d, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.28 (d, $J = 7.3$ Hz, 3H), 2.13 (dq, $J = 7.0$, 7.6 Hz, 1H), 2.76 (dq, $J = 3.7$, 6.8 Hz, 1H), 3.17 (s, 3H), 3.51 (ddd, $J = 3.7$, 6.1, 8.0 Hz, 1H), 4.08 (d, $J = 6.1$ Hz, 1H), 4.18 (ABq in ABX_3, $J = 7.1$, 9.4 Hz, $\Delta\nu = 7.6$ Hz, 2H), 4.31 (d, $J = 7.6$ Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ (ppm) = 13.0, 14.2, 14.7, 42.3, 42.8, 56.4, 60.4, 77.5, 86.9, 127.8, 127.9, 128.2, 139.6, 175.6.

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References

1. For enantioselective syntheses of *syn*-propionate aldol adducts, see: (a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079; (b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568; (c) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876–2878; (d) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (e) Hsiao, C. L.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206; (f) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495; (g) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772; (h) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*,

4247–4252; (i) Oppolzer, W.; Lienard, P. *Tetrahedron Lett*. **1993**, *34*, 4321–4324; (j) Yan, T. H.; Lee, H.-C.; Tan, C.-W. *Tetrahedron Lett*. **1993**, *34*, 3559–3562; (k) Davis, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett*. **1994**, *35*, 2373–2376; (l) Goh, J. B.; Lagu, B. R.; Wurster, J.; Liotta, D. C. *Tetrahedron Lett*. **1994**, *35*, 6029–6032; (m) Boeckman, R. K.; Johnson, A. T.; Musselman, R. A. *Tetrahedron Lett*. **1994**, *35*, 8521–8524; (n) Miyake, T.; Seki, M.; Nakamura, Y.; Ohmizu, H. *Tetrahedron Lett*. **1996**, *37*, 3129–3132. For enantioselective syntheses of *anti*-propionate aldol adducts, see: (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309–2315; (b) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc*. **1985**, *107*, 5812–5813; (c) Narasaka, K. Miwa, T. *Chem. Lett*. **1985**, 1217–1220; (d) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; (e) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc*. **1990**, *112*, 9672–9674; (f) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc*. **1990**, *112*, 4976–4977; (g) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem*. **1990**, *55*, 173–181; (h) Walker, M. A.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 5747–5750; (i) Oppolzer, W.; Strarkemann, C.; Rodrigenz, I.; Bernardinelli, G. *Tetrahedron Lett*. **1991**, *32*, 61–64. Reactions in the above literatures are sometimes stereodivergent by modifying the reaction conditions. For enantioselective syntheses of propionate aldol adducts using chiral Lewis acids, see: Ishihara, K. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed. Chiral B(III) Lewis Acids; Wiley-VCH: Weinheim, 2000; Chapter 5, pp. 135–189.

2. (a) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem*. **1991**, *56*, 2276–2278; (b) Kiyooka, S.-i.; Kaneko, Y.; Kume, K. *Tetrahedron Lett*. **1992**, *33*, 4927–4930; (c) Kiyooka, S.-i.; Kido, Y.; Kaneko, Y. *Tetrahedron Lett*. **1994**, *35*, 5243–5246; (d) Kaneko, Y.; Matsuo, T.; Kiyooka, S.-i. *Tetrahedron Lett*. **1994**, *35*, 4107–4110; (e) Kaneko, Y.; Kiyooka, S.-i. *Mem. Fac. Sci. Kochi Univ. Ser. C* **1994**, *15*, 9–14; (f) Kiyooka, S.-i.; Kaneko, Y.; Harada, Y.; Matsuo, T. *Tetrahedron Lett*. **1995**, *36*, 2821–2822; (g) Kiyooka, S.-i.; Hena, M. A. *Tetrahedron:Asymmetry* **1996**, *7*, 2181–2184; (h) Kiyooka, S.-i.; Kira, H.; Hena, M. A. *Tetrahedron Lett*. **1996**, *37*, 2597–2600; (i) Kiyooka, S.-i.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett*. **1997**, *38*, 3553–3556; (j) Kiyooka, S.-i.; Maeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371–3374; (k) Kiyooka, S.-i. *Rev. Heteroatom Chem*. **1977**, *17*, 245–270; (l) Hena, M. A.; Terauchi, S.; Kim, C.-S.; Horiike, M.; Kiyooka, S.-i. *Tetrahedron: Asymmetry* **1998**, *9*, 1883–1890; (m) Kiyooka, S.-i.; Maeda, H.; Hena, M. A.; Uchida, M.; Kim, C.-S.; Horiike, M. *Tetrahedron Lett*. **1998**, *39*, 8287–8290; (n) Hena, M. A.; Kim, C.-S.; Horiike, M.; Kiyooka, S.-i. *Tetrahedron Lett*. **1999**, *40*, 1161–1164; (o) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem*. **1999**, *64*, 5511–5523; (p) Kiyooka, S.-i.; Hena, M. A.; Goto, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2871–2879; (q) Kiyooka, S.-i.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett*. **1999**, *40*, 6447–6449; (r) Kiyooka, S.-i.; Shahid, K. A. *Tetrahedron Lett*. **2000**, *41*, 2633–2637; (s) Kiyooka, S.-i.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett*. **2000**, *41*, 6599–6603; (t) Kiyooka, S.-i.; Hena, M. A.; Yabukami, T.; Murai, K.; Goto, F. *Tetrahedron Lett*. **2000**, *41*, 7511–7516; (u) Kiyooka, S.-i.; Shahid, K. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1537–1542.
3. Kiyooka, S.-i.; Shahid, K. A. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 1485–1495.
4. (a) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavalée, J.-F. *Tetrahedron Lett*. **1990**, *31*, 2845–2848; (b) Guindon, Y.; Lavalée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett*. **1991**, *32*, 27–30; (c) Guindon, Y.; Lavalée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc*. **1991**, *113*, 9701–9702; (d) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavalée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem*. **1994**, *59*, 1166–1178; (e) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Benchequroun, M.; Murtagh, L.; Ghiro, É.; Jung, G. *J. Org. Chem*. **1995**, *60*, 288–289; (f) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc*. **1997**, *119*, 9289–9290; (g) Guindon, Y.; Faucher, A. M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem*. **1997**, *62*, 9276–9283; (h) Guindon, Y.; Rancourt, J. *J. Org. Chem*. **1998**, *63*, 6554–6565; (i) Guindon, Y.; Jung, G.; Guérin, B.; Ogilvie, W. W. *Synlett* **1998**, 213–220.
5. 2-Methyl-1,3-propanediol was purchased from Aldrich (1 L, 4,100 yen in 2000–2001 catalog).
6. (a) Shahid, K. A.; Li, Y.-N.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett*. **2002**, *43*, 6373–6376; (b) Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett*. **2002**, *43*, 6377–6381; (c) Corrigendum: Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett*. **2003**, *44*, 1519–1520.
7. Nozaki, K.; Oshima, K.; Uchimoto, K. *Tetrahedron* **1989**, *45*, 923–933.
8. A preliminary report: Kiyooka, S.-i.; Shiinoki, M.; Nakata, K.; Goto, F. *Tetrahedron Lett*. **2002**, *43*, 5377–5380.
9. Kiyooka, S.-i.; Shahid, K. A.; Murai, K.; Li, Y.-N.; Okazaki, M.; Shuto, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 2343–2349.
10. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc*. **1996**, *118*, 4322–4343.
11. Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095–1120 and references cited therein.
12. (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 556–569; (b) Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, T. A. *J. Org. Chem*. **1984**, *49*, 4214–4223; (c) Gennari, C. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, 1989; pp. 53–71.
13. Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc*. **2001**, *123*, 10840–10852.