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A Divergent Synthesis of Essentially Enantiopure *syn*- and *anti*-Propionate Aldol Adducts Based on the Chiral 1,3,2-Oxazaborolidin-5-one-Promoted Asymmetric Aldol Reaction Followed by Diastereoselective Radical Reduction

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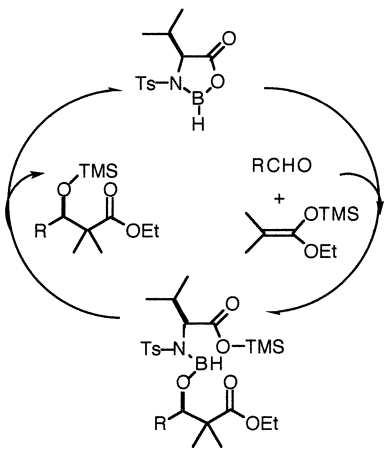
Essentially, enantiopure *syn*- and *anti*-propionate aldol adducts were divergently synthesized using a novel strategy which utilizes both the highly enantioselective 1,3,2-oxazaborolidin-5-one-promoted aldol reaction with a ketene silyl acetal derived from ethyl 2-bromo propionate and a highly diastereoselective radical debromination reaction. These procedures provide yields that increase to a level available for practical synthesis.

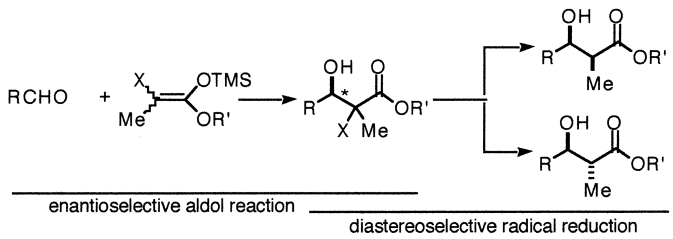
The enantioselective synthesis of *syn*- and *anti*-propionate aldol adducts is important in terms of the asymmetric synthesis of natural products which contain 1,3-diol moieties. Considerable success has been reported in the area of asymmetric aldol reactions with chiral nucleophiles which are related to propionate synthons and which are bound to a variety of chiral auxiliaries.[1] The chiral Lewis acid-promoted asymmetric aldol reaction, in which activated aldehydes react with silyl nucleophiles, is generally considered to be more practical and useful for the enantioselective construction of aldol adduct's skeletons, compared to asymmetric aldol reactions which involve chiral auxiliaries. In cases where a chiral Lewis acid can be successfully used as a catalyst, asymmetric aldol reactions are the reactions of choice. Even in the case where the chiral Lewis acid does not function as a superior catalyst, the semicatalytic or stoichiometric process is still quite useful (in such cases the Lewis acid is referred to as a promoter) and is more advantageous situations that require the binding and removal of chiral auxiliaries. A number of successful examples have been reported in the area of the chiral Lewis acid-catalyzed (promoted) enantioselective aldol reactions.[2] However, the diastereoselectively divergent synthesis of essentially enantiopure *syn*- and *anti*-propionate aldol adducts using chiral Lewis acid-mediated asymmetric aldol reactions has not yet been realized. In the case of chiral borane-catalyzed (promoted) aldol reactions with ketene silyl acetals, as these relate to propionate synthons, Yamamoto reported on a highly enantioselective synthesis of *syn*-propionate aldol adducts with chiral (acyloxy)borane reagents, derived from L- or D-tartaric acid, in which *syn* predominance is obtained independently of the geometry of the ketene silyl acetals, while the reaction using chiral 1,3,2-oxazaborolidin-5-ones resulted in the formation of a slight excess of *anti*-propionate aldol adducts with moderate enantioselectivity.[3] The resolution of divergent synthesis represents the most important serious problem remaining since our first report of the chiral 1,3,2-oxazaborolidin-5-one-mediated asymmetric aldol reaction.[4]



Scheme 1. A plausible mechanism.

Our chiral 1,3,2-oxazaborolidin-5-one-mediated asymmetric aldol reaction proceeds smoothly through a catalytic cycle, as shown in Scheme 1, which represents the most plausible mechanism. The supposed aldolate intermediate also appears to catalyze the aldol reaction because it is a trivalent neutral borane species, but in a somewhat lower enantioselectivity, as observed when a catalytic amount of 1,3,2-oxazaborolidin-5-one was used. In order to prevent a lowering of the enantioselectivity, 1,3,2-oxazaborolidin-5-one, in which the chiral ligands are recycled in nearly all cases, was used in a stoichiometric amount. The *si* facial selection is always observed in the reaction using (*S*)-1,3,2-oxazaborolidin-5-one.[4]

We report herein a new approach toward a diastereoselectively divergent synthesis of essentially enantiopure *syn*- and *anti*-propionate aldol adducts using the chiral 1,3,2-oxazaborolidin-5-one-promoted asymmetric aldol reaction, in conjunction with diastereoselective radical reduction.[5]



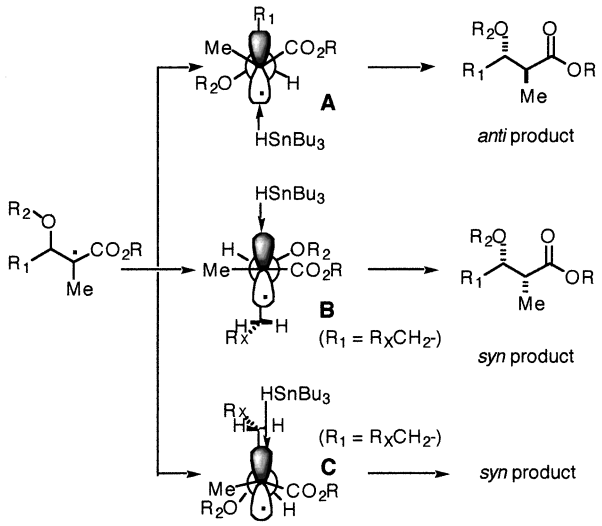
Scheme 2. The combination of enantioselective aldol reaction and diastereoselective radical reduction toward enantiopure *syn*- and *anti*-propionate aldol adducts.

Results and Discussion

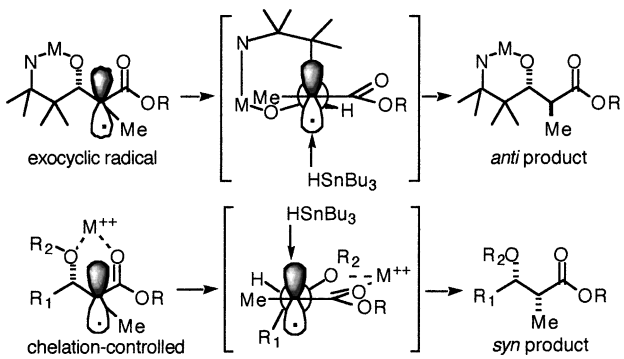
The appropriate steric bulkiness at the β-position of ketene silyl acetals is known to allow a high level of enantioselectivity in our chiral 1,3,2-oxazaborolidin-5-one-promoted aldol reaction; for example, a reaction with a ketene silyl acetal bearing a dithiolane resulted in the formation of essentially enantiopure acetate aldol adducts after desulfurization.[4g] Based on this strategy, a ketene silyl acetal was prepared from ethyl 2-(methylthio)propionate, which gave a mixture of an equal amount of *syn*- and *anti*-aldol products having an α-methylthio group with very high level of enantioselectivity in the aldol reaction, followed by desulfurization to afford the essentially enantiopure *syn*- and *anti*-propionate aldol adducts, but with poor diastereoselection.[4l] At that stage, the earlier studies were strongly in need of an effective diastereoselective desulfurization procedure, or its equivalent. An ideal approach to realizing both enantiopure *syn*- and *anti*-propionate aldol adducts is as follows. The asymmetric aldol reaction results in the formation of a mixture of enantiopure aldol adducts having an appropriate structure available for a subsequent diastereoselective elimination reaction and a sequential reaction with the resulting aldol adducts which takes place to divergently afford *syn*- and *anti*-propionate aldol adducts (Scheme 2). In order to realize this sequential strategy, it is necessary to find a highly diastereoselective transformation reaction which permits a divergent elimination of the X substituent at the α-position of enantiopure aldol adducts.[6] Fortunately, the radical-mediated hydrogen-transfer reactions, reported by Guindon, represent a possibility.[7]

We briefly demonstrate here the feasibility of Guindon's methodology for stereocontrol through a radical reaction to propionate aldol adducts.[7] The stereochemical outcome of reactions involving an acyclic radical is rationalized by using the transition state models: A, B, and C in Scheme 3. These transition state models, which are predictive of the predominant product, take into consideration both steric and electronic factors. In A to the *anti* product, the opposition of the ester and electronegative OR_2 groups should reduce intramolecular electrostatic repulsions. In addition, an electronic effect is involved in the stabilization of an electron-poor radical by hyperconjugation with the best σ-donor substituent (R_1). In B to the *syn* product, 1,3-allylic strain appears to be a serious destabilizing factor. Guindon concluded that C is the preferred transition state model to give the *syn* product; on the basis of the assumption that the radical reaction proceeds through an early transition state, both models A and C bear a marked similarity to ground state conformer of the radical. The conclusion reached was that the ratio of *anti*- and *syn*-products would be dictated by the energy difference between transition states A and C. As shown in Scheme 4, more effective stereocontrolled systems have since been reported by Guindon;[7] the reaction which proceeds via an exocyclic radical gives, predominantly, the *anti* product and the reaction, which can be chelation-controlled with a variety of Lewis acids, shows a significant improvement in *syn*-selectivity.

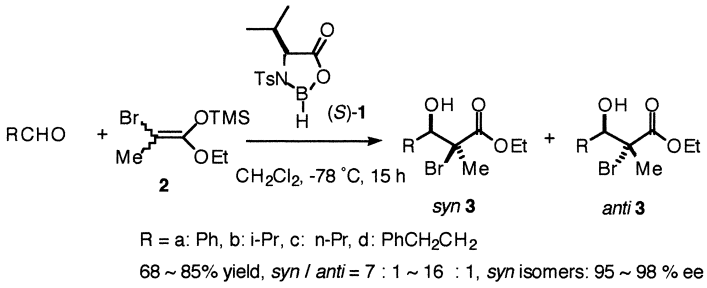
Thus, the two required reactions, an enantioselective aldol reaction and a diastereoselective radical reaction, appear to be feasible to achieve our strategy to divergently prepare enantiopure *syn*- and *anti*-propionate aldol adducts, as depicted in



Scheme 3. A rationale for the stereochemical outcome of highly diastereoselective hydrogen-transfer reactions.



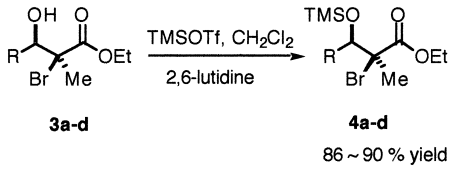
Scheme 4. More effectively stereocontrolled systems.



Scheme 5.

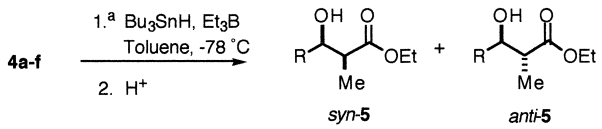
Scheme 2. As mentioned above, we are already aware that a large substituent at the β-position of ketene silyl acetals is responsible for the high enantioselectivity (approaching $>$ 98% ee) in the asymmetric aldol reaction in the presence of chiral 1,3,2-oxazaborolidin-5-one (*S*)-**1**, prepared in situ from L-Ts-Val and BH_3·THF.[4k] Based on this strategy, 2-bromo-2-methylketene ethyl silyl acetal **2** (bp 73–74 °C/0.1 mmHg, $E : Z = 1 : 2$) was chosen as an appropriate silyl nucleophile for this reaction sequence. 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; the second is that it has promise as a group which can be readily eliminated from the resulting intermediates in the radical reduction process. The reaction of a variety of aldehydes with the silyl nucleophile **2** proceeded in good yields under the standard conditions (CH_2Cl_2, -78 °C, 15 h) in the presence of a stoichiometric amount of chiral borane (*S*)-**1** (Scheme 5). A very high level of enantioselectivity was observed.[4u] The considerably high diastereoselection observed is particularly intriguing and appears to be beyond the scope derived from the general features of the asymmetric aldol reaction which proceeds independent of the geometry of the silyl nucleophiles used.[4r,u]

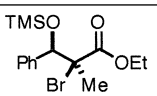
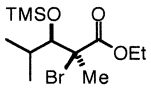
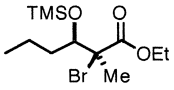
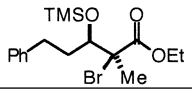
A systematic investigation of the influence of β-hydroxy protecting groups on diastereoselection was carried for the radical reduction of ethyl 2-bromo-2-methyl-3-phenyl-3-(protected hyroxy)propionates with Bu_3SnH and Et_3B[7h] and a methyl protected hydroxy function was found to be suitable for high *anti*-diastereoselection, compared with benzyl or isopropyl protection. However, the protecting group is not necessarily pertinent for the practical synthesis of polypropionates, because the procedures required for protection and deprotection are not simple. An easily eliminated TMS group seems to be the most convenient protecting group for such transformations, in that the protection is adequate. The above information prompted us to investigate the radical debromination reduction using starting compounds which contained a TMS protecting group. The TMS protected starting materials *syn*-**4a–d** were prepared from the corresponding aldol adducts *syn*-**3** with TMSOTf and 2,6-lutidine in CH_2Cl_2 in good yields (Scheme 6). Radical debromination reactions for a variety of essentially enantiopure aldols *syn*-**4a–d** were investigated under the conditions of Bu_3SnH and Et_3B in toluene at -78 °C, followed by deprotection of the TMS function with an acidic methanolic solution to afford the corresponding propionate aldol adducts **5**. Basically the observed diastereoselection involves the same level of *anti*-selection in the case where **4a** contains a phenyl



Scheme 6.

Table 1. Effect of C-3 Substituents in α-Bromo-β-TMS-oxy Esters on Diastereoselection in Radical Debromination Reaction



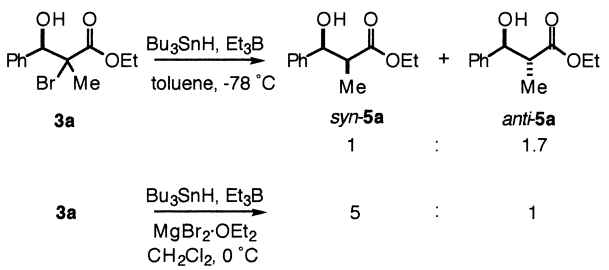
Entry	4a–f		Isolated yield/%	*syn*/*anti* ratio[b]
1		**4a**	**5a** 80	1 : 7.7
2		**4d**	**5b** 81	1 : 2.7
3		**4c**	**5c** 88	6.6 : 1
4		**4d**	**5d** 90	6.2 : 1

a) Conditions: 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, Toluene, -78 °C, overnight.
b) Determined by NMR analysis.

substituent on C-3, though the selectivity (1 : 7.7) is somewhat higher than that (1 : 4) observed for a similar system involving OTBS.[7h] A larger protecting group for the β-hydroxy function would likely destabilize an appropriate transition state to the *anti*-isomer. When R on C-3 has a methylene unit adjacent to the hydroxy carbon, the diastereoselection was reversed to *syn*-predominance (entries 3 and 4) which must have arisen from the transfer of hydrogen to a transition state C (Scheme 3). A conclusion on the effect of C-3 substituents, derived from Table 1, is that considerably large substituents prefer *anti*-selection and that linear substituents result in *syn*-selection, which is consistent with the known prediction that the ratio of *anti*- and *syn*-products would be dictated by the energy difference

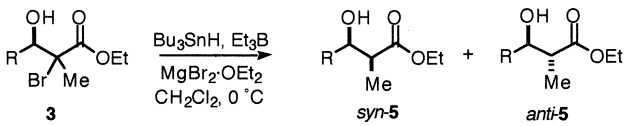
between transition states A and C.[7g] Unfortunately a general trend for diastereoselection in the debromination reaction of α-bromo-β-siloxy esters was not observed.

We then planned to deal with the most simple case, that is, the absence of any protection for the β-hydroxy function of the starting bromo esters as a practical synthesis, since this would considerably shorten the number of reaction steps by eliminating the protection and deprotection steps. A preliminary trial (Scheme 7) was conducted using a mixture of *syn*- and *anti*-**3a** with Bu_3SnH and catalytic Et_3B to afford an unacceptable level of *syn* : *anti* selectivity (1 : 1.7). However, a reaction with Bu_3SnH and Et_3B in the presence of $MgBr_2{\cdot}OEt_2$, (chelation controlled conditions, reported by Guindon)[7c] gave predominantly *syn*-2-methyl-3-hydroxypropionate esters **5** (> 98% ee) in 87% yield with a *syn* : *anti* selectivity (5 : 1). It is noteworthy that the free hydroxy function did not interfere with the Lewis acid and did not prevent coordination; also, the radical from the β-hydroxy ester acted as a bidentate ligand. Reactions of a variety of aldol adducts were investigated following the same procedure described above. Each reduction resulted in a *syn*-diastereoselection of nearly the same level (moderately high), except for entry 2, where a 14-fold increase in *syn*-selectivity was observed, in good overall yields with very high enantioselectivity (Table 2). To account for the mechanism of the chelation-controlled radical reduction, a transition-state model can be proposed, as depicted in Scheme 8. First, the chelation of the carbonyl and hydroxy moieties to a bidented Lewis acid ($MgBr_2{\cdot}OEt_2$) as well as a homolytic cleavage of



Scheme 7.

Table 2. Diastereoselection of Chelation Controlled-Radical Debromination of α-Bromo-β-hydroxy Esters[a)]

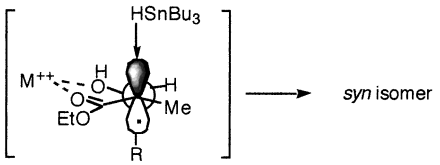


Entry	**3** (R)	Yield/%[b)]	*syn*/*anti*	% ee (*syn*)
1	Ph (**3a**)	87 (**5a**)	5 : 1	> 98
2	$(CH_3)_2CH$ (**3b**)	83 (**5b**)	> 70 : 1	> 98
3	$CH_3CH_2CH_2$ (**3c**)	79 (**5c**)	5 : 1	> 98
4	$PhCH_2CH_2$ (**3d**)	80 (**5d**)	6 : 1	> 98

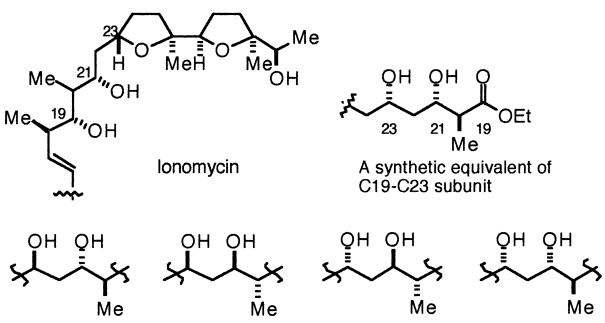
a) Reaction (0 °C) of non-protected bromo aldol adducts (a mixture of *syn*- and *anti*-isomers: **3a**; 7 : 1, **3b**; 16 : 1, **3c**; 10 : 1, **3d**; 9 : 1) was carried out with 2 equiv of Bu_3SnH and 0.2 equiv of Et_3B, and 5 equiv of $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2. b) Isolated yield.

the C–Br bond forces the substrate molecule into a transition state conformation in which the top face of the radical system is exposed to the delivery of a hydrogen atom, thus providing access to *syn*-diastereoselection. In addition, the R group, α, to the radical system plays an important role in bloking the down face of the radical system, thereby discouraging an attack by Bu_3SnH from that position. When the steric branch of the R group was increased, the *syn* selectivity was substantially enhanced (entry 2). Thus, an effective access to the practical synthesis of essentially enantiopure *syn*-propionate aldol adducts was achieved via the use of a chiral 1,3,2-oxazaborolidin-5-one-mediated aldol reaction coupled with a stereoselective radical reduction. The sequence of these reactions might provide a powerful approach for constructing chiral acyclic skeletons involving *syn*-propionate units, as found in the C1–C7 segment of Monensin.[8]

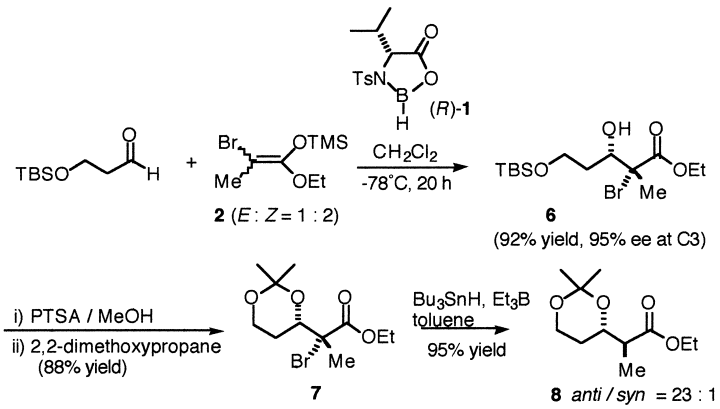
We next shifted our attention to an approach to the preparation of essentially enantiopure 2, 3-*anti*-propionate aldol adducts, according to the strategy, shown in Scheme 2, where the "exocyclic effect" could be used as a reliable methodology toward the *anti*-diastereoselective radical reduction. From the viewpoint of a practical synthesis, we planned to construct 2, 3-*anti*-propionate aldol adducts involving a 3, 5-*syn*- or *anti*-diol subunit. Such an enantiopure segment constitutes a typical unit found in a variety of natural products including the C16–C19 segment of scytophycin C,[9] the C4–C7 segment of discodermolide,[10] the C32–C35 subunit of the synthetic intermediate for rapamycin,[11] and the C19–C23 segment of ionomycin[12] (Scheme 9). We previously reported that a 1, 3-*syn*- or *anti*-diol can be stereoselectively prepared by applying a chiral (*S*)- or (*R*)-1,3,2-oxazaborolidin-5-one-promoted asymmetric aldol reaction to ketene silyl acetal **10**. Guindon has already reported that the *anti*-propionate aldol adducts can be obtained from a radical reduction of the acetals of 2-methyl-2-phenylseleno-3,5-dihydroxypentanoate derivatives with Bu_3SnH via non-chelation control with respect to an exocyclic



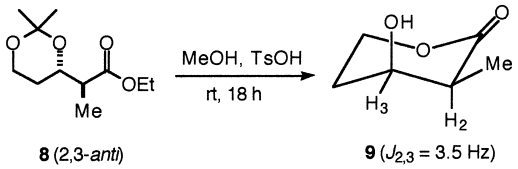
Scheme 8. A transition state model of chelation controlled-radical reduction.



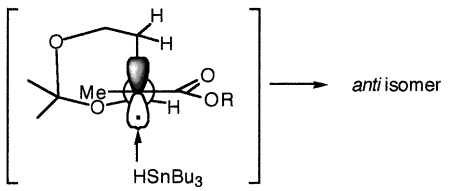
Scheme 9. Synthetic targets as enantiopure subunits.



Scheme 10.



Scheme 11.



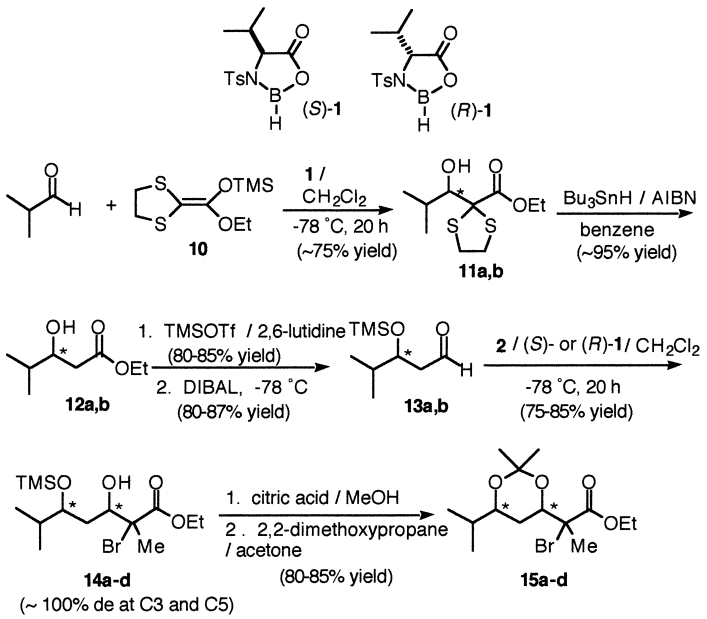
Scheme 12.

effect.[7] The above information persuaded us to investigate the following reactions: after acetalization of the diols derived from successive aldol reactions of an aldehyde with ketene silyl acetals, **10** and **2**, the subunits above might be prepared by debromination using an exocyclic effect controlled radical reduction.

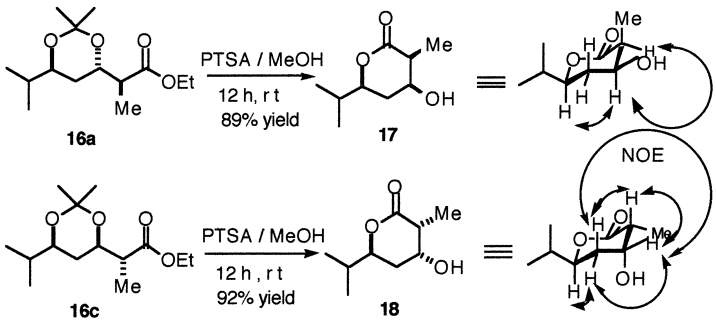
A preliminary trial was conducted with the corresponding epimeric bromide **7**. Bromide **7** was prepared by the chiral 1,3,2-oxazaborolidin-5-one-promoted asymmetric aldol reaction of 3-*t*-butyldimethylsiloxypropanal with **2** in a stoichiometric amount of chiral (*R*)-1,3,2-oxazaborolidin-5-one to give the corresponding α-bromo aldol adduct **6** in 92% yield with 95% ee at C3, followed by treatment with PTSA and 2,2-dimethoxypropane (88% yield), in a one pot reaction. The bromide **7** was then subjected to a hydrogen transfer reaction with Bu_3SnH with a catalytic amount of Et_3B in toluene at -78 °C with stirring overnight. The product **6** was preferentially obtained in a ratio of 23 : 1 in 95% yield (Scheme 10). The relative configuration of the reduced products **8** was deduced by correlating the ^{1}H NMR spectral data. A more rigorous stereochemical assignment was performed for the *anti*-reduction product **8** by subjecting it to acidic methanolic conditions to afford lactone **9** (Scheme 11). Lactone **9** shows a smaller H_2–H_3 coupling constant (3.5 Hz), proving that **8** contains a 2, 3-*anti* configuration. The *anti* selectivity was shown to be quite high in the case of the α-bromo system bearing an isopropylidene acetal moiety in the radical reductions. A rational explanation of the stereochemical outcome in the hydrogen transfer reaction can be given by using a transition model which effectively involved the so-called "exocyclic effect" (Scheme 12).

The epimeric bromides **15a–d** involving the enantiopure 1,3-diol unit required for the synthesis of the targets under consideration were prepared as follows (Scheme 13). The reaction of isobutanal with silyl nucleophile **10** proceeded smoothly in the presence of a stoichiometric amount of (*S*)- or (*R*)-chiral borane to afford the corresponding dithiolane aldol adducts in an essentially enantiopure state. The sequential procedure for desulfurization was carried out using Bu_3SnH with AIBN,[13] instead of Ni_2B-H_2,[4g] to give the enantiopure aldol adducts **12a,b** in nearly quantitative yields. The TMS protection of the hydroxy group in **12a,b** was achieved with TMSOTf and 2,6-lutidine, and the ethoxycarbonyl function in the resulting TMS protected aldol adducts was directly converted to the corresponding aldehydes to give **13a,b** upon the treatment of DIBAL at -78 °C. The second asymmetric aldol reaction of **13a,b**, in this sequence to **15a–d**, with silyl nucleophile **2** in the presence of (*S*)- or (*R*)-chiral borane furnished aldol adducts **14a–d** (100% de at C3 and C5) in good yields. The stereochemistry at the stereogenic center (C3) is completely controlled by only the stereochemistry of the chiral borane used, "promoter (catalyst) control" on the enantioselective acyclic stereoselection, so that each 3, 5-*syn*- or *anti*-diol unit is readily available in a pure state of the relative configuration. After deprotection of the TMS function in **14a–d**, the resulting diol was subjected to acetalization to give **15a–d**, which are epimeric only at C2.

The resultig epimeric bromides **15a–d** underwent a radical debromination reaction in the presence of Bu_3SnH and Et_3B in toluene, similar to the reaction applied to **7**, to afford the corresponding target compounds **16a–d** in high yields (86–92%) with excellent anti diastereoselectivity (33–36 : 1), as shown in Table 3. The stereochemistry of the major product was confirmed by the NMR study using their lactone derivatives (Scheme 14). By using silica-gel flash column chromatography, the target molecules were easily purified to give the enantiopure 2, 3-*anti*-propionate aldol adducts involving a 3, 5-syn- or *anti*-diol subunit. Thus, we were able to achieve effective access to the preparation of essentially enantiopure 2, 3-*anti*-



Scheme 13.



Scheme 14.

propionate aldol adducts involving a 3, 5-*syn*- or *anti*-diol subunit, which is available for the enantioselective synthesis of appropriate fragments of several complex macrolides, by using chiral 1,3,2-oxazaborolidin-5-one-promoted asymmetric aldol reactions coupled with an *anti*-diastereoselective radical reduction.

Conclusion

We report the successful divergent synthesis of essentially enantiopure *syn*- and *anti*-propionate aldol adducts by a new methodology which effectively merged two reactions: the enantioselective aldol reaction developed by Kiyooka[4] and the diastereoselective radical debromination developed by Guindon.[7]

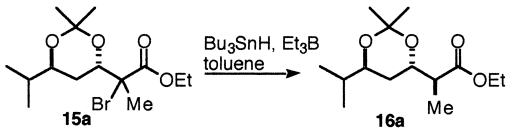
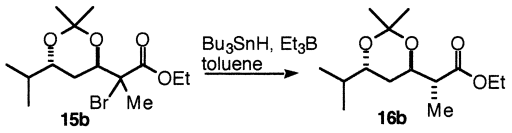
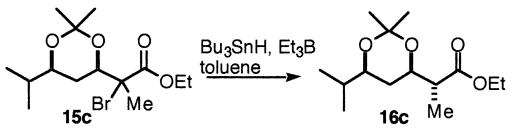
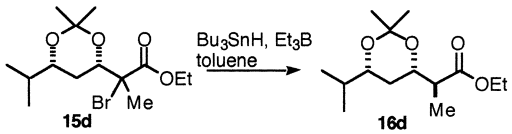
Experimental

General. Infrared spectra (IR) were determined with a JASCO FT/IR-5300 Fourier transform infrared spectrometer. ^{1}H NMR spectra were determined by a JEOL JNM-LA 400 (a superconducting, 400 MHz, FT instrument) spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet), coupling constant(s) in Hertz, number of protons. ^{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 and for thin-layer chromatography Merck silica-gel 60 TLC aluminum sheets were used.

2-Bromo-1-ethoxy-1-trimethylsiloxypropene (2). To a stirred solution of LDA (58.3 mmol) in THF (35 mL) (prepared in situ) at −78 °C was added dropwise ethyl 2-bromopropionate (50 mmol) over 5 min. After 15 min of stirring at the same temperature, TMSCl (83.3 mmol) was added over 10 min. The reaction mixture was allowed to warm to ambient temperature and THF was removed with a rotary evaporator. The residue was mixed with dry hexane and filtered. After removal of the solvent, the residue was distilled under reduced pressure to give **2** (9.0 g, 71%, bp 73–74 °C/0.1 mmHg). IR (neat) 2962, 1655, 1251, 1219, 850 cm^{-1}. *Z*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 3.84 (q, J = 7.0 Hz, 2H). *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H), 2.08 (s, 3H), 3.88 (q, J = 7.0 Hz, 2H).

General Procedure for the Asymmetric Aldol Reaction in

Table 3. High *anti* Selection in Radical Reduction Controlled by Exocyclic Effect[a)]

Substrate	Product	Diastereomeric ratio[b)] *anti*/*syn* at C2–C3	Yield/%
 **15a**	**16a**	33 : 1	86
 **15b**	**16b**	36 : 1	92
 **15c**	**16c**	35 : 1	90
 **15d**	**16d**	33 : 1	88

a) All reactions were performed at a substrate concentration of 0.1 M using 2.0 equiv of Bu_3SnH with a catalytic amount of Et_3B. b) Diastereomeric ratio was determined from their ^1H NMR spectra.

the Presence of a Stoichiometric Amount of a Chiral Borane Complex. Ethyl (2*S*,3*R*)- and (2*R*,3*R*)-2-Bromo-3-hydroxy-2-methyl-3-phenylpropionates (3a). Under an argon atmosphere, to a stirred solution of (*S*)-1,3,2-oxazaborolidin-5-one (2.11 g, 7.78 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added dropwise a 1 M solution of THF·BH_3 in THF (7.01 ml, 7.01 mmol) over 5 min and the solution was stirred at 0 °C for 30 min. The resulting solution was then allowed to warm to ambient temperature, and was subsequently stirred for 30 min. The solution was then cooled to −78 °C and PhCHO (0.68 mL, 6.56 mmol) in CH_2Cl_2 (1 mL) was added slowly over 5 min. Then, **2** was introduced over 5 min and the mixture was stirred for 15 h at −78 °C. The reaction mixture was quenched by adding a buffer solution (10 mL, pH 6.8), extracted with CH_2Cl_2, and washed with sat. $NaHCO_3$, followed by sat. NaCl. After dried over anhydrous $MgSO_4$ and evaporated, the residue was purified by flash column chromatography (7% AcOEt in hexane) to separate **3** (1.45 g, 77.3% yield). *Syn* : *anti* ratio was found on the basis of NMR data of the crude products. The physical data of **3a–d** have been reported in ref. 4u. The enantiomeric purity was determined by HPLC analysis. **3a**: the retention times of peak-1: 24.04 min and peak-2: 27.31 min [eluent; hexane : 2-propanol (97.5 : 2.5), 0.5 mL min^{-1}, Column: CHIRALCEL OD]. **3b**: the retention times of peak-1: 14.26 min and peak-2: 18.87 min [eluent; hexane : 2-propanol (99.8 : 0.2), 1 mL min^{-1}, Column : CHIRALPAK AD]. **3c**: the retention times of peak-1: 28.56 min and peak-2: 30.90 min [eluent; hexane : 2-propanol (99 : 1), 0.5 mL min^{-1}, Column: CHIRALPAK AD]. **3d**: the retention times of peak-1: 20.04 min and peak-2: 24.28 min [eluent; hexane : 2-propanol (97 : 3), 0.5 mL min^{-1}, Column: CHIRALCEL OD]. Found: C, 50.20; H, 5.31%. Calcd for $C_{12}H_{15}BrO_3$: C, 50.19; H, 5.27%.

Silylation Procedure to *syn*-4a–d. To a stirred solution of **3a** (574 mg, 2 mmol) in dry CH_2Cl_2 (16 mL) at room temperature was added 2,6-lutidine (0.88 mL, 7.6 mmol) and stirred for 15 min. Then, TMSOTf (0.66 mL, 3 mmol) was added and the mixture was stirred for 2.5 h at the same temperature. The reaction was quenched by a slow addition of sat. NaCl (10 mL). The reaction mixture was extracted with ether, washed sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (1% AcOEt in hexane) to afford **4a**. Found: C, 50.10; H, 6.48%. Calcd for $C_{15}H_{23}BrO_3Si$: C, 50.14; H, 6.45%.

***syn*-4a** (86% yield):$[\alpha]_D^{20}$ −5.64 (*c* 1.24%, $CHCl_3$). IR (neat) 2961, 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H), 1.89 (t, J = 7.1 Hz, 3H), 1.69 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 5.22 (s, 1H), 7.18–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 0.0, 13.8, 21.8, 61.9, 67.0, 78.3, 127.7, 128.0, 128.1, 138.9, 170.2.

***syn*-4b** (92% yield):$[\alpha]_D^{21}$ −14.5 (*c* 2%, $CHCl_3$). IR (neat) 2962, 1736 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.65 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 1.35–1.41 (m, 1H), 1.59 (s, 3H), 3.91 (d, J = 2.9 Hz, 1H), 4.02 (dq, J = 1.7, 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 0.3, 13.3, 17.3, 21.6, 22.0, 31.0, 61.3, 67.0, 80.7, 170.5.

***syn*-4c** (88% yield):$[\alpha]_D^{21}$ +5.48 (*c* 1.64%, $CHCl_3$). IR (neat) 2961, 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.68 (t, J = 7.1 Hz, 3H), 0.92–1.07 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H), 1.12–1.34 (m, 2H), 1.56 (s, 3H), 3.99 (dd, J = 1.7, 7.6 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 0.9, 13.9, 13.9, 20.0, 21.5, 35.7, 61.9, 66.6, 77.3, 170.8.

***syn*-4d** (90% yield):$[\alpha]_D^{21}$ +21.25 (*c* 0.8%, $CHCl_3$). IR (neat) 2957, 1736 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.0 (s, 9H), 1.01 (t, J = 7.1 Hz, 3H), 1.29–1.49 (m, 2H), 1.53 (s, 3H), 2.28 (ddd, J = 6.1, 10.7, 13.4 Hz, 1H), 2.58 (ddd, J = 5.1, 10.9, 13.7 Hz, 1H), 3.95 (q, J = 7.1 Hz, 2H), 4.02 (dd, J = 2.2, 9.5 Hz, 1H), 6.88–7.04 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.8, 21.6, 33.3, 35.6, 61.9, 66.2, 77.5, 126.1, 128.3, 128.5, 141.4, 170.7.

General Procedure for the Chelation Controlled-Radical Reduction. Ethyl (2*S*,3*S*)- and (2*R*,3*S*)-3-Hydroxy-2-methyl-

3-phenylpropionates (5a). Under an argon atmosphere Mg turnings (180 mg, 7.1 mmol) were treated with 1,2-dibromoethane (1.32 g, 7.1 mmol) at room temperature in dry diethyl ether (15 mL) until the reaction was complete, and then the reaction mixture was evaporated. To a stirred suspension of the residue and **3a** (287 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added dropwise Bu_3SnH (1.34 mL, 5 mmol) and then Et_3B (0.6 mL, 0.6 mmol) in 1/3 portions every 15 min; the mixture was then stirred for 2 h at the same temperature. The reaction was quenched by adding *m*-dinitrobenzene followed by pouring into an aqueous $NaHCO_3$ solution; the reaction was extracted with CH_2Cl_2, and washed with sat.$NaHCO_3$, followed by sat. NaCl. After being dried over anhydrous $MgSO_4$ and evaporated, the residue was purified by flash column chromatography (4% AcOEt in hexane) to afford **5a**. The *syn* : *anti* ratio was found on the basis of NMR data of the crude products. The physical data of isolated isomers (**5a–d**) are reported in Ref. 4l. The enantiomeric purity of each isomer was determined by HPLC analysis. **5a** (87% yield): the retention times of peak-1: 21.78 min and peak-2: 24.79 min [eluent; hexane : 2-propanol (95 : 5), 0.5 mL min^{-1}, Column: CHIRALCEL OD]. **5b** (83% yield): the retention times of peak-1: 11.88 min and peak-2: 14.84 min [eluent; hexane : 2-propanol (99.7 : 0.3), 1 mL min^{-1}, Column: CHIRALCEL OD]. **5c** (79% yield): the retention times of peak-1: 15.19 min and peak-2: 17.52 min [eluent; hexane : 2-propanol (99.8 : 0.2), 1 mL min^{-1}, Column: CHIRALCEL OD]. **5d** (80% yield): the retention times of peak-1: 4.46 min and peak-2: 10.14 min [eluent; hexane : 2-propanol (95 : 5), 1 mL min^{-1}, Column: CHIRALCEL OD].

Ethyl (2*R*,3*S*)-2-Bromo-5-(*t*-butyldimethylsiloxy)-3-hydroxy-2-methylpentanoate (6). This product was produced from the reaction of 3-(*t*-butyldimethylsiloxy)propionaldehyde with **2** using a stoichiometric amount of (*R*)-1,3,2-oxazaborolidin-5-one (87% yield). *Syn* isomer was purified from a mixture, of which the *syn* : *anti* ratio was found to be 15 : 1 on the basis of NMR data.

$[\alpha]_D^{24}$ −2.28 (*c* 3.4%, $CHCl_3$). IR (neat) 3462, 1736 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.0 (s, 6H), 0.82 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H), 1.54–1.67 (m, 2H), 1.78 (s, 3H), 3.35 (d, J = 2.9 Hz, 1H), 3.71–3.82 (m, 2H), 4.15 (dt, J = 2.9, 9.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ −5.5, −5.5, 13.8, 18.2, 23.0, 25.8, 34.6, 61.2, 62.2, 66.6, 74.6, 170.51. The enantiomeric purity of *syn*-isomer was determined to be 95% ee by an HPLC analysis. The retention times of peak-1 was 24.46 min and peak-2 was 22.38 min [eluent; hexane : 2-propanol (99.8 : 0.2), 0.5 mL min^{-1}, Column: CHIRALPAK OD-H]. Found: C, 45.56; H, 7.85%. Calcd for $C_{14}H_{29}BrO_4Si$: C, 45.52; H, 7.91%.

Ethyl (2*R*,3*S*)-2-Bromo-3,5-isopropylidenedioxy-2-methylpentanoate (7). Under an argon atmosphere, to a stirred solution of **6** (370 mg, 1 mmol) in dry MeOH (5 mL) at a room temperature was added PTSA (20 mg); the mixture was stirred for 30 min. Then, 2,2-dimethoxypropane (5.0 mL, 40.9 mmol) was added and the mixture was further stirred for 30 min. The reaction was quenched by the slow addition of water (10 mL). The resulting mixture was extracted with ether, washed with sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (8% AcOEt in hexane) to afford **7** (88% yield). $[\alpha]_D^{21}$ +28.4 (*c* 2.03%, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 1.42 (s, 3H), 1.47 (s, 3H), 1.45–1.51 (m, 1H), 1.75 (dABq, J = 12.0, 5.4 Hz, $\Delta\nu$ = 21.2 Hz, 1H), 1.84 (s, 3H), 3.86 (ddd, J = 2.2, 5.6, 12.0 Hz, 1H), 3.96 (dt, J = 3.2, 12.0 Hz, 1H), 4.31 (dd, J = 11.5, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.9, 19.2, 23.1, 26.5, 29.5, 59.4, 62.2, 63.2, 73.6, 99.3, 169.8. Found: C, 44.75; H, 6.50%. Calcd for $C_{11}H_{19}BrO_4$: C, 44.76; H, 6.49%.

Ethyl (2*S*,3*S*)-3,5-Isopropylidenedioxy-2-methylpentanoate (8). Aldol adduct **8** was prepared according to the usual procedure using Bu_3SnH with a catalytic amount of Et_3B in toluene. $[\alpha]_D^{21}$ +20.1 (*c* 1.49%, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.46–1.50 (m, 1H), 1.59 (dABq, J = 12.0, 5.6 Hz, $\Delta\nu$ = 20.8 Hz, 1H), 2.48 (dq, J = 7.1, 7.5 Hz, 1H), 3.86 (ddd, J = 1.7, 5.4, 11.7 Hz, 1H), 3.97 (dt, J = 3.2, 12.0 Hz, 1H), 4.08 (ddd, J = 2.4, 8.3, 11.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 12.3, 14.2, 19.1, 27.9, 29.67, 45.6, 59.7, 60.2, 70.6, 98.4, 174.7. Found: C, 60.12; H, 9.31%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.

Lactone 9. Under an argon atmosphere, PTSA (20 mg) was added to a stirred solution of **8** (100 mg, 0.33 mmol) in dry MeOH (5 mL) at room temperature. The resulting solution was stirred for 12 h at the same temperature. The reaction was quenched by the slow addition of water (10 mL); then, the reaction mixture was extracted with ether, washed with sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (20% AcOEt in hexane) to afford the lactone **9** (80% yield). ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 3H), 1.97–2.04 (m, 1H), 2.15–2.23 (m, 1H), 2.62 (dq, J = 7.1, 3.7 Hz, 1H), 2.76 (d, J = 3.4 Hz, 1H), 4.24 (dt, J = 4.1, 4.2 Hz, 1H), 4.30 (dt, J = 5.8, 5.6 Hz, 1H), 4.56 (ddd, J = 4.9, 8.0, 11.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.9, 31.0, 41.3, 65.1, 67.2, 174.1.

2-[Ethoxy(trimethylsiloxy)methylene]-1,3-dithiolane (10). To a stirred solution (−78 °C) of LDA (125 mmol) in THF (250 mL) (prepared in situ) was added dropwise ethyl 2,2-(1,3-dithiolan-2-yl)acetate (100 mmol) for over 15 min. After 15 min of stirring at the same temperature, TMSCl (300 mmol) was added over 10 min. The reaction mixture was allowed to warm to ambient temperature, and stirred overnight. After THF was removed with a rotary evaporator, the residue was mixed with dry hexane and filtered. After removal of the solvent, the residue was distilled under reduced pressure to give **10** (18.2 g, 72%, bp 108–110 °C/0.1 mmHg). IR (neat) 2962, 1655, 1251, 1219, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.0 (s, 9H), 1.02 (t, J = 7.1 Hz, 3H), 3.02–3.59 (m, 4H), 3.60 (q, J = 7.1 Hz, 2H).

Ethyl (3*R*)-2,2-(Ethylenedithio)-3-hydroxy-4-methylpentanoate (11a). This product was produced from the reaction of isobutyraldehyde with **10** using a stoichiometric amount of (*S*)-1,3,2-oxazaborolidin-5-one (75% yield). $[\alpha]_D^{26}$ −44.6 (*c* 1.03%, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3H), 1.0 (d, J = 6.6 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.84 (octet, J = 6.6 Hz, 1H), 3.30 (d, J = 6.8 Hz, 1H), 3.25–3.40 (m, 4H), 3.95 (dd, J = 6.1, 6.4 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 18.4, 20.7, 33.1, 39.7, 40.0, 62.8, 76.2, 78.8, 171.6.

Ethyl (3*S*)-2,2-(Ethylenedithio)-3-hydroxy-4-methylpentanoate (11b). This product was produced from the reaction with **10** using a stoichiometric amount of (*R*)-1,3,2-oxazaborolidin-5-one (71% yield). $[\alpha]_D^{26}$ +45.0 (*c* 1.2%, $CHCl_3$).

General Procedure for the Desulfurization. Ethyl (3S)-3-Hydroxy-4-methylpentanoate (12a). To a stirred solution of **11a** (765 mg, 3 mmol) in dry benzene (5 mL) at room temperature were added Bu_3SnH (1.76 mL, 6 mmol) and AIBN (150 mg). The resulting mixture was refluxed for 1.5 h at 80 °C, allowed to cool, evaporated, and purified by flash column chromatography (5% AcOEt in hexane) to afford **12a** (95% yield). $[\alpha]_D^{26}$ −28.54 (*c* 1.15%, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.60–1.70 (m,

1H), 2.33 (dd, J = 10.0, 15.6 Hz, 1H), 2.42 (dd, J = 2.8, 16.4 Hz, 1H), 2.85 (d, J = 4.0 Hz, 1H), 3.68–3.73 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.1, 17.7, 18.3, 33.1, 38.4, 60.6, 72.6, 173.4.

Ethyl (3*R*)-3-Hydroxy-4-methylpentanoate (12b). Aldol adduct **12b** was prepared from **11b** (91% yield). $[\alpha]_D^{26}$ +27.91 (*c* 1.57%, $CHCl_3$).

(3*S*)-4-Methyl-3-trimethylsiloxypentanal (13a). To a stirred solution of **12a** (300 mg, 1.87 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added 2,6-lutidine (0.86 mL, 7.48 mmol); the mixture was stirred for 15 min. Then, TMSOTf (0.61 mL, 2.8 mmol) was added and the mixture was stirred for 2.5 h at the same temperature. The reaction was quenched by the slow addition of sat. NaCl (10 mL); the reaction mixture was then extracted with ether, washed with sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (1% AcOEt in hexane) to afford TMS-protected product (92% yield). Under an argon atmosphere, to a stirred solution of the TMS-protected product (254 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added dropwise a 1 M solution of DIBAL in toluene (1.32 mL, 1.32 mmol) over 30 min; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the slow addition of water (5 mL), extracted with ether, washed with sat. NaCl, dried over anhydrous $MgSO_4$, evaporated and purified by flash column chromatography (4% AcOEt in hexane) to afford **13a** (84% yield). ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 1.59–1.67 (m, 1H), 2.24–2.48 (m, 2H), 3.87–3.92 (m, 1H), 9.69 (s, 1H).

(3*R*)-4-Methyl-3-trimethylsiloxypentanal (13b). Aldehyde **13b** was prepared from **12b** according to the procedure of **13a**.

Ethyl (2*R*,3*S*,5*S*)-2-Bromo-3-hydroxy-2,6-dimethyl-5-trimethylsiloxyheptanoate (14a). From an aldol reaction between **13a** and **2** using a stoichiometric amount of (*R*)-1,3,2-oxazaborolidin-5-one, **14a** was prepared (75% yield). Found: C, 45.62; H, 7.89%. Calcd for $C_{14}H_{29}BrO_4Si$: C, 45.52; H, 7.91%. $[\alpha]_D^{26}$ −9.37 (*c* 1.6%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.72 (d, J = 7.1 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.31–1.43 (m, 2H), 1.61 (octet, J = 6.6 Hz, 1H), 1.70 (s, 3H), 3.11 (s, 1H), 3.59 (dt, J = 3.2, 6.6 Hz, 1H), 4.03 (br.d, J = 9.8 Hz, 1H), 4.07–4.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 0.0, 13.5, 17.7, 18.1, 22.7, 33.1, 34.6, 61.9, 67.5, 72.2, 74.2, 170.3.

Ethyl (2*R*,3*R*,5*R*)-2-Bromo-3-hydroxy-2,6-dimethyl-5-trimethylsiloxyheptanoate (14b). From an aldol reaction between **13b** and **2** using a stoichiometric amount of (*S*)-1,3,2-oxazaborolidin-5-one, **14b** was prepared (78% yield). $[\alpha]_D^{26}$ +7.5 (*c* 2%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.72 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.31–1.43 (m, 2H), 1.61 (octet, J = 6.6 Hz, 1H), 1.70 (s, 3H), 3.09 (d, J = 3.4 Hz, 1H), 3.59 (ddd, J = 2.9, 5.9, 8.6 Hz, 1H), 4.03 (dt, J = 2.9, 10.0 Hz, 1H), 4.07–4.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 0.0, 13.5, 17.7, 18.1, 22.7, 33.1, 34.6, 61.9, 67.5, 72.2, 74.2, 170.3.

Ethyl (2*R*,3*R*,5*S*)-2-Bromo-3-hydroxy-2,6-dimethyl-5-trimethylsiloxyheptanoate (14c). From an aldol reaction between **13c** and **2** using a stoichiometric amount of (*S*)-1,3,2-oxazaborolidin-5-one, **14c** was prepared (71% yield). $[\alpha]_D^{26}$ −4.37 (*c* 1.6%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.66 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.35–1.40 (m, 2H), 1.60–1.70 (m, 1H), 1.70 (s, 3H), 3.34 (d, J = 2.2 Hz, 1H), 3.66 (dt, J = 3.9, 6.2 Hz, 1H), 4.0 (dt, J = 2.2, 5.6 Hz, 1H), 4.09 (dq, J = 2.4, 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 0.0, 13.5, 16.7, 17.0, 22.3, 32.4, 33.8, 61.7, 65.7, 75.0, 76.4, 170.0.

Ethyl (2*R*,3*S*,5*R*)-2-Bromo-3-hydroxy-2,6-dimethyl-5-trimethylsiloxyheptanoate (14d). From the aldol reaction between **13d** and **2** using a stoichiometric amount of (*R*)-1,3,2-oxazaborolidin-5-one, **14d** was prepared (71% yield). $[\alpha]_D^{26}$ +8.0 (*c* 3%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 9H), 0.67 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.37–1.49 (m, 2H), 1.62–1.70 (m, 1H), 1.70 (s, 3H), 3.34 (s, 1H), 3.64–3.68 (m, 1H), 3.98–4.03 (m, 1H), 4.07–4.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 0.0, 13.5, 16.7, 17.0, 22.3, 32.4, 33.8, 61.7, 65.7, 74.9, 76.4, 170.0.

Ethyl (2*R*,3*S*,5*S*)-2-Bromo-3,5-isopropylidenedioxy-2,6-dimethyl heptanoate (15a). Under an argon atmosphere, to a stirred solution of **14a** (80 mg, 0.21 mmol) in dry MeOH (5 mL) at room temperature was added citric acid (200 mg); the mixture was stirred for 15 min. Then, 2,2-dimethoxypropane (2.5 mL, 20.5 mmol) was added and further stirred for 30 min. The resulting solution was evaporated, followed by the addition of dry acetone (10 mL) and then 2,2-dimethoxypropane (2.5 mL, 20.5 mmol), and stirred for 30 min. The reaction was quenched by the slow addition of water (10 mL), extracted with ether, washed with sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (4% AcOEt in hexane) to afford **15a** (82% yield). $[\alpha]_D^{26}$ −21.69 (*c* 1.06%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.56–1.67 (m, 2H), 1.72–1.79 (m, 1H), 1.82 (s, 3H), 3.39 (ddd, J = 7.3, 7.6, 10.0 Hz, 1H), 4.20 (dd, J = 6.7, 9.5 Hz, 1H), 4.22–4.29 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 17.6, 18.6, 23.5, 24.1, 24.2, 32.3, 32.8, 62.2, 64.1, 71.5, 71.9, 101.0, 169.0. Found: C, 49.77; H, 7.34%. Calcd for $C_{14}H_{25}BrO_4$: C, 49.86; H, 7.47%.

Ethyl (2*R*,3*R*,5*R*)-2-Bromo-3,5-isopropylidenedioxy-2,6-dimethyl heptanoate (15b). $[\alpha]_D^{26}$ −15.85 (*c* 0.82%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.56–1.67 (m, 2H), 1.76 (ddd, J = 5.6, 9.5, 12.4 Hz, 1H), 1.82 (s, 3H), 3.40 (ddd, J = 6.1, 7.3, 9.8 Hz, 1H), 4.20 (dd, J = 6.6, 9.8 Hz, 1H), 4.21–4.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 17.6, 18.6, 23.5, 24.1, 24.2, 32.3, 32.8, 62.2, 64.1, 71.5, 71.9, 101.0, 169.9.

Ethyl (2*R*,3*R*,5*S*)-2-Bromo-3,5-isopropylidenedioxy-2,6-dimethyl heptanoate (15c). $[\alpha]_D^{26}$ −23.12 (*c* 1.6%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.18–1.33 (m, 1H), 1.39–1.43 (m, 1H), 1.49–1.59 (m, 1H), 1.76 (s, 3H), 3.41 (ddd, J = 2.2, 6.6, 11.2 Hz, 1H), 4.13–4.22 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 13.9, 17.7, 18.3, 19.6, 23.1, 28.8, 29.9, 33.1, 62.1, 63.5, 73.6, 74.0, 99.1, 169.9.

Ethyl (2*R*,3*S*,5*R*)-2-Bromo-3,5-isopropylidenedioxy-2,6-dimethyl heptanoate (15d). $[a]_D^{26}$ +21.05 (*c* 1.9%, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.35–1.43 (m, 1H), 1.41 (s, 3H), 1.43 (s, 3H), 1.46–1.50 (m, 1H), 1.62 (octet, J = 6.8 Hz, 1H), 1.83 (s, 3H), 3.50 (ddd, J = 2.2, 6.6, 11.2 Hz, 1H), 4.23–4.24 (m, 1H), 4.27 (dq, J = 2.2, 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9, 17.7, 18.2, 19.6, 23.1, 28.8, 29.9, 32.9, 62.0, 63.5, 73.6, 73.9, 99.1, 169.9.

Ethyl (2*S*,3*S*,5*S*)-3,5-Isopropylidenedioxy-2,6-dimethylheptanoate (16a). Under an argon atmosphere, to a stirred solution of **15a** in dry toluene (10 mL) at −78 °C was added dropwise Bu_3SnH (0.12 mL, 0.48 mmol), followed by Et_3B (0.1 mL, 0.07 mmol); the mixture was stirred for 2 h at the same temperature. The reaction was quenched by adding water (5 mL), extracted

with MeCN, and washed with sat. $NaHCO_3$, followed by sat. NaCl. The solution was dried over anhydrous $MgSO_4$ and after filtration the solvent was evaporated. The residue was purified by flash column chromatography (2.5% AcOEt in hexane) to afford **16a** (86% yield). *Syn* : *anti* ratio was determined on the basis of NMR data. $[\alpha]_D^{24}$ −37.09 (*c* 0.62%, $CHCl_3$). IR (neat) 1739 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.29 (s, 3H), 1.30 (s, 3H), 1.52–1.69 (m, 3H), 2.28 (dq, J = 7.1, 7.1 Hz, 1H), 3.41 (dt, J = 7.1, 9.3 Hz, 1H), 3.93 (dt, J = 5.8, 9.5 Hz, 1H), 4.14 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.5, 14.2, 17.6, 18.7, 24.1, 24.2, 32.9, 33.9, 45.6, 60.2, 68.5, 71.6, 100.5, 174.8. Found: C, 64.98; H, 10.21%. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14%.

Ethyl (2*R*,3*R*,5*R*)-3,5-Isopropylidenedioxy-2,6-dimethylheptanoate (16b). $[\alpha]_D^{24}$ +37.0 (*c* 0.62%, $CHCl_3$). IR (neat) 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.29 (s, 3H), 1.30 (s, 3H), 1.52–1.69 (m, 3H), 2.48 (dq, J = 7.1, 7.3 Hz, 1H), 3.41 (dt, J = 6.4, 9.0 Hz, 1H), 3.94 (dt, J = 6.1, 9.3 Hz, 1H), 4.14 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 12.5, 14.2, 17.6, 18.7, 24.1, 24.2, 32.9, 33.9, 45.6, 60.2, 68.4, 71.5, 100.5, 174.7.

Ethyl (2*R*,3*R*,5*S*)-3,5-Isopropylidenedioxy-2,6-dimethylheptanoate (16c). $[\alpha]_D^{24}$ −14.2 (*c* 0.42%, $CHCl_3$). IR (neat) 1739 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.12 (dt, J = 11.7, 12.0 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.49 (dt, J = 2.2, 12.4 Hz, 1H), 1.58–1.66 (m, 1H), 2.48 (dq, J = 7.3, 7.5 Hz, 1H), 3.50 (ddd, J = 2.2, 6.6, 11.5 Hz, 1H), 4.01 (ddd, J = 2.4, 8.3, 11.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 12.3, 14.2, 17.6, 18.3, 19.6, 30.0, 30.1, 33.0, 45.6, 60.2, 70.9, 73.7, 98.3, 174.8.

Ethyl (2*S*,3*S*,5*R*)-3,5-Isopropylidenedioxy-2,6-dimethylheptanoate (16d). $[\alpha]_D^{24}$ +13.9 (*c* 0.62%, $CHCl_3$). IR (neat) 1738 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H), 1.12 (dt, J = 11.7, 12.0 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.49 (dt, J = 2.2, 12.4 Hz, 1H), 1.58–1.66 (m, 1H), 2.48 (dq, J = 7.1, 7.3 Hz, 1H), 3.50 (ddd, J = 2.1, 6.6, 11.2 Hz, 1H), 4.01 (ddd, J = 2.4, 8.3, 11.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 12.3, 14.2, 17.6, 18.3, 19.6, 30.0, 30.1, 33.0, 45.6, 60.2, 70.9, 73.7, 98.3, 174.8.

Lactone 17. Under an argon atmosphere, to a stirred solution of **16a** (30 mg, 0.11 mmol) in dry MeOH (3 mL) at room temperature was added PTSA (10 mg); the mixture was stirred for 12 h at the same temperature. The reaction was quenched by the slow addition of water (5 mL), extracted with ether, washed with sat. NaCl, and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was purified by flash column chromatography (20% AcOEt in hexane) to afford lactone (89% yield). ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 7.1 Hz, 3H), 1.70 (ddd, J = 3.9, 11.5, 15.1 Hz, 1H), 1.79 (d, J = 3.9 Hz, 1H), 1.86–1.95 (m, 1H), 2.35 (ddd, J = 4.2, 8.0, 14.9 Hz, 1H), 2.69 (dq, J = 4.4, 7.1 Hz, 1H), 3.97 (ddd, J = 4.2, 6.1, 11.0 Hz, 1H), 4.29 (dd, J = 3.6, 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 10.9, 17.8, 17.8, 32.2, 34.7, 40.2, 67.7, 80.3, 173.9.

Lactone 18. From **16c**, lactone **18** was obtained (83% yield). IR (neat) 1707 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 1.33 (d, J = 7.3 Hz, 3H), 1.78 (dd, J = 12.4, 13.7 Hz, 1H), 1.86–1.94 (m, 1H), 1.94 (d, J = 3.2 Hz, 1H), 2.04 (ddd, J = 3.6, 3.9, 13.9 Hz, 1H), 2.50 (dq, J = 3.2, 7.1 Hz, 1H), 4.21 (s, 1H), 4.55 (ddd, J = 3.7, 5.6, 12.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 12.6, 17.5, 17.6, 32.5, 32.8, 41.4, 67.5, 80.5, 173.9.

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