Tetrahedron Vol. 48, No. 11, pp. 2127-2142, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Diastereoselective *Anti* Aldol Reactions of Chiral Ethyl Ketones. Enantioselective Processes for the Synthesis of Polypropionate Natural Products.

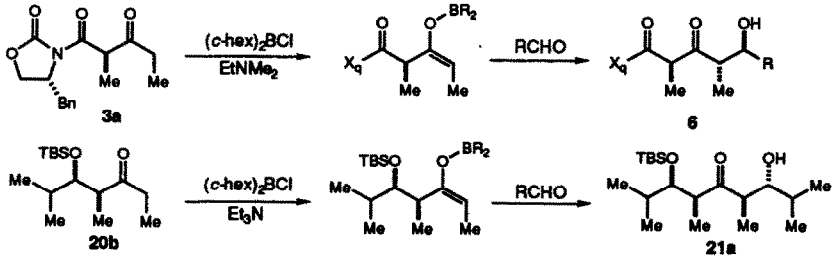
David A. Evans,* Howard P. Ng, J. Stephen Clark, and Dale L. Rieger

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts, U. S. A.

(*Received in USA* 19 *October* 1991)

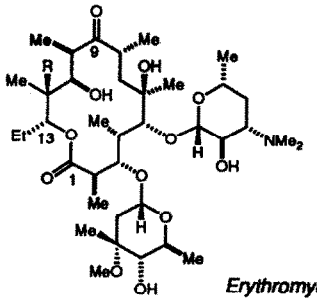
Key Words: Stereoselective *anti* aldol reactions; β-keto imides; (*E*) boron enolates; polypropionate synthesis.

Abstract: The diastereoselective *anti* aldol reactions of the β-keto imide **3a**, the related ethyl ketone **20b**, and its diastereomer **22b** have been studied. In these aldol reactions, the chiral ethyl ketones **3a** and **20b** were found to exhibit the opposite sense of asymmetric induction in the analogous *anti* aldol bond constructions from the derived (*E*) boron enolates. The relevance of this study to the synthesis of polypropionate natural products is discussed.

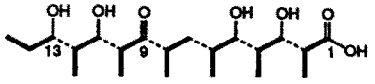


Introduction

The polyketides are an important family of naturally occurring substances which include antibiotics, ionophores, immunosuppressive and antitumor agents, and other bioactive materials of widespread importance in chemotherapy. The *in vivo* synthesis of these substances conforms either wholly or in part, to a variant of



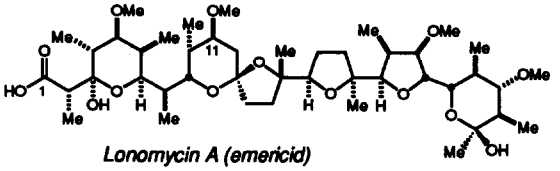
Erythromycin A, R = OH, Erythromycin B, R = H



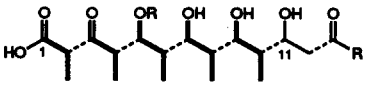
The 7 Propionate Subunits

the theme represented in fatty acid biosynthesis wherein either acetate or propionate constituents are assembled through a linear series of acylation and intervening refunctionalization operations.[1] The erythromycin antibiotics provide one of the best illustrations of polypropionate assemblage where the sole carbon source for the macrolide portion of these structures is derived from propionate.

In contrast to the motif expressed in erythromycin biosynthesis, the biosynthesis of the polyether antibiotics[2] such as lonomycin A[3] involves the incorporation of propionate as well as acetate and, on occasion, other low molecular weight carboxylic acid building blocks.



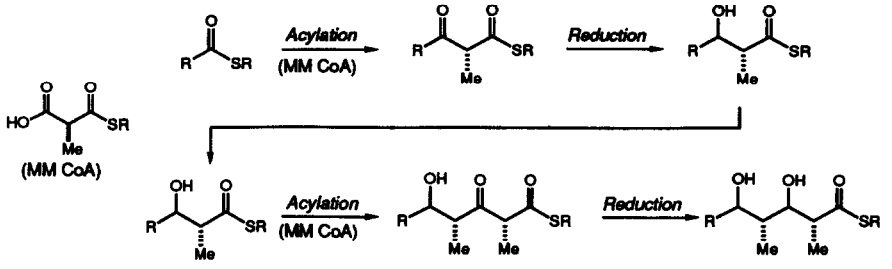
Lonomycin A (emericid)



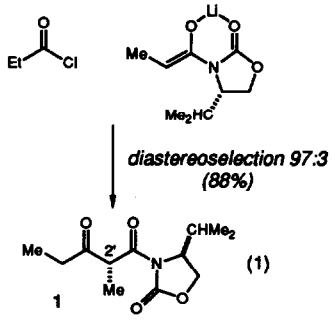
C_1–C_{10}: 5 propionate subunits

In the most recent model[4] for the assemblage process leading to the biosynthesis of propionate-derived natural products, methyl malonyl CoA, under the action of a polyketide synthase (PKS), is acylated by a starter thioester fragment installing the first propionate subunit and associated stereogenic center. In the subsequent events culminating in the completion of the first cycle, the acylation adduct is reduced, either partially or fully, and the new thioester readied for the next cycle (Scheme 1). The multienzyme complex associated with these two sets of transformations is referred to as a synthase unit (SU). Recently, the genes which govern the synthesis of the erythromycin macrolide have been identified.[4]

Scheme 1. Primary Steps in Polypropionate Biosynthesis: Two Synthase Unit Cycles.



Our interest in utilizing the primary steps in polypropionate biosynthesis as a stimulus for the development of analogous laboratory transformations originated with the observation that the primary biosynthetic acylation event could be effected to afford **1** whose newly formed 2' methyl-bearing stereogenic center could be retained during the course of a standard chromatographic purification (eq 1).[5] An X-ray structure of **1**



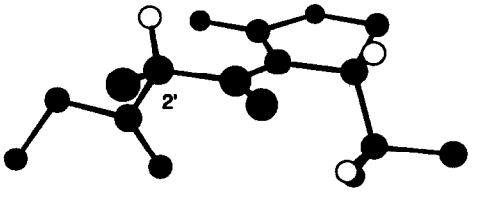
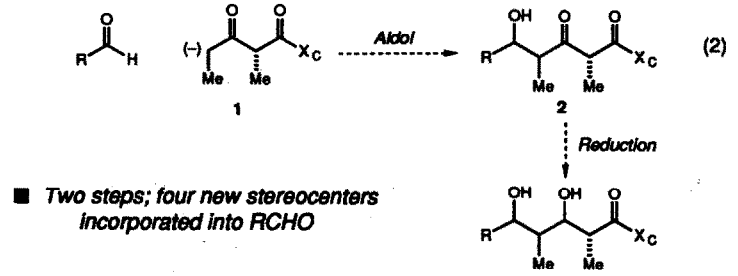


Figure 1. X-ray structure of β-ketoimide **1** (eq 1).

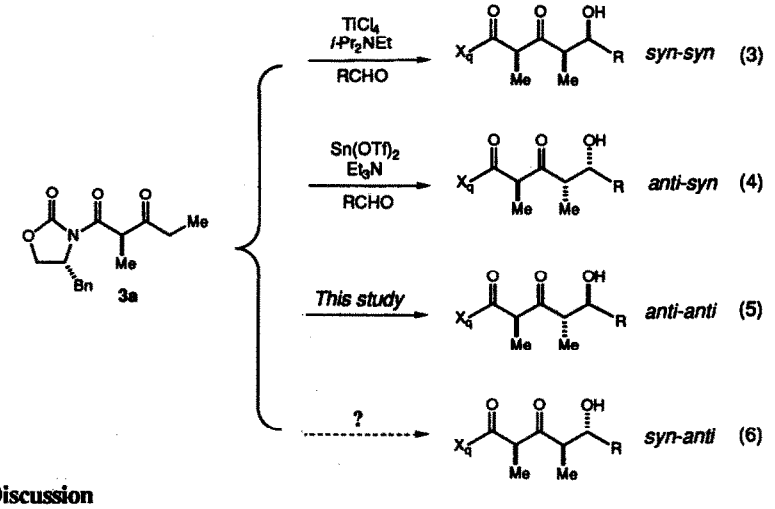
(Figure 1) suggested that the unexpectedly low kinetic acidity of **1** was most likely due to allylic strain conformational effects which orient the C-2' hydrogen in a conformation not conducive to overlap with the C-1' carbonyl moiety.

The preceding observation suggested that one might exploit dipropionyl imides such as **1** in subsequent aldol bond constructions to provide the adduct **2** (eq 2), the penultimate intermediate in the second iteration of the synthase unit (Scheme 1), if mild, kinetically controlled enolization conditions were employed. If this aldol methodology could be coupled with the appropriate stereoselective reductions[6,7] of **2**, one might then have a powerful set of bond constructions for the rapid assemblage of polypropionate natural products. For example, the application of both the Ti(IV) and Sn(II) aldol reactions illustrated below (eq 3, 4) to the synthesis of erythromycin is readily apparent. It is also noteworthy that the oxidation pattern found in the lonomycin A C_1-C_4 carboxyl terminus (*vide supra*) conforms to that found in aldol adduct **2**, and we have recently reported the application of this concept to the synthesis of the C_1-C_{11} polypropionate region of this polyether antibiotic.[8]



(2)

Of the four possible stereochemical variants of this basic bond construction, we have been able to develop the two *syn* aldol options shown below (eq 3, 4).[9] The subject of the present study is the development of one of the two remaining *anti* aldol options (eq 5).

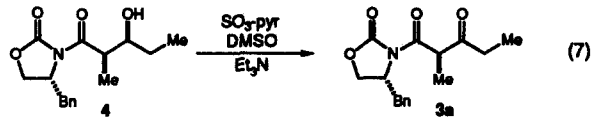


(3) (4) (5) (6)

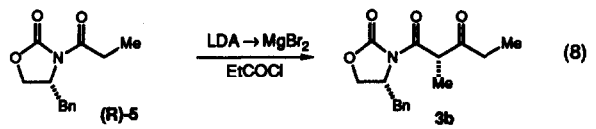
Results and Discussion

Synthesis of β–Ketoimide Substrates. The diastereomeric β-ketoimides **3a** and **3b** used in the study were prepared according to the two general methods previously reported (eq 7, 8).[5a] For the preparation of **3a**, the aldol adduct **4**,[10] synthesized from (*R*)-**5**, was oxidized by the method of Parikh and Doering[11] to provide a 95% yield of the crystalline imide **3a**. Alternatively, the direct acylation of the magnesium enolate derived

from (*R*)-**5**, with propionyl chloride (1.05 equiv) provided the expected diastereomer **3b** in 78% yield with kinetic diastereoselection of >20:1. Prior studies from this laboratory[9] had established that, although the dominant stereogenic center in the enolates derived from either **3a** or **3b** is the methyl-bearing center, some modulation of the reaction diastereoselectivity by the stereogenic center on the chiral auxiliary was noted in both the Ti(IV) and Sn(II) *syn* aldol reactions (eq 3, 4). Although a detailed explanation is still not possible for this subtle stereochemical bias, the observation that **3a** was consistently more diastereoselective than **3b** in the complementary *syn* aldol processes provided the impetus for initiating the present study with the former substrate. Subsequent control experiments (*vide infra)* now suggest that the effect of the remote center on the chiral auxiliary is minimal in at least one of the *anti* aldol processes (eq 5).



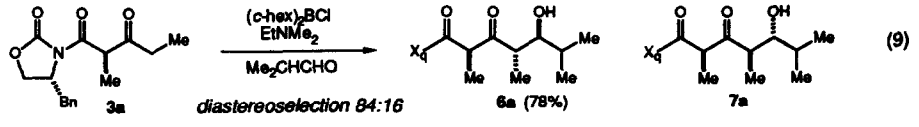
(7)



(8)

β–Ketoimide Aldol Reactions. The recent report by Brown[12] on the stereoselective generation of (*E*) enolates using the dicyclohexylchloroborane-triethylamine enolization procedure formed the basis of the present study on the enolization and aldol reactions of β-ketoimide **3a**. This substrate and the reaction of its derived (*E*) boron enolate with isobutyraldehyde provided the focal point for reaction optimization studies.

Not surprisingly, the outcome of this reaction is quite dependent on the solvent and amine used. As reported by Brown, diethyl ether proved to be the solvent of choice. Reactions performed in tetrahydrofuran or toluene resulted in lowered yields and selectivities while no reaction was observed in dichloromethane. A systematic variation in amine structure did not affect reaction diastereoselectivity but had a marked effect on product yield. The optimum amine was found to be *N,N*-dimethylethylamine. Triethylamine and *N*-ethylpiperidine afforded lower yields, while di-*iso*-propylethylamine, 2,6-lutidine, and secondary amines failed to effect enolization. In addition, product isolation conditions employing activated IRA-743 resin[13] to remove the boron contaminants proved superior to either the usual oxidation procedures using aqueous hydrogen peroxide or azeotropic methods using methanol for removing boronates through co-distillation. Epimerization of the C_2-center and/or loss of chiral auxiliary were observed when the latter two methods were used.



(9)

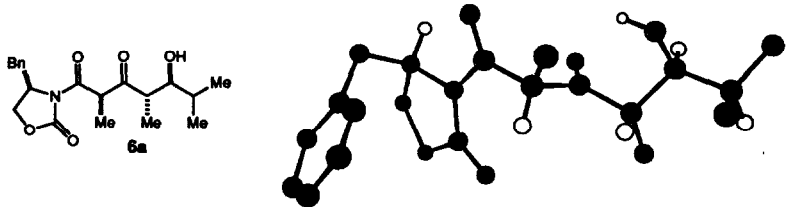
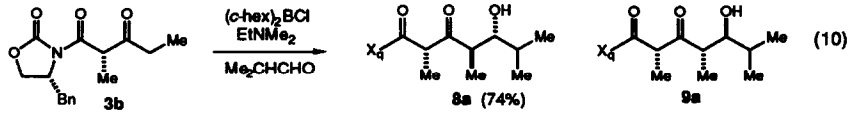


Figure 2. X-ray structure of aldol adduct **6a** (eq 9).

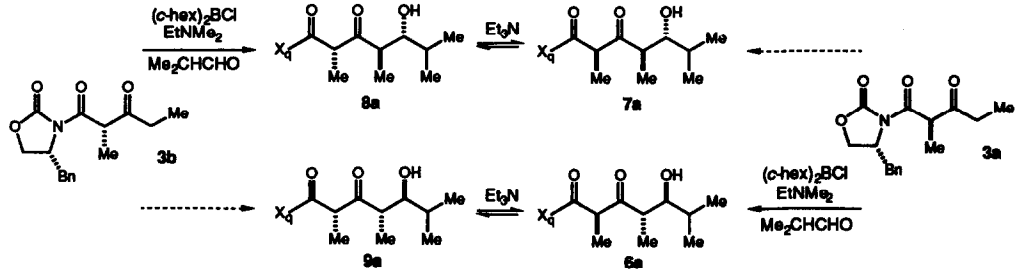
Using the preceding reaction conditions for the formation of the (*E*) enolate of **3a**, $(c\text{-hex})_2BCl$ with *N,N*-dimethylethylamine (Et_2O, 0 °C, 1 h), the subsequent aldol reaction with isobutyraldehyde (-78 °C, 3 h), afforded the crystalline-*anti-anti* aldol adduct **6a** in 78% yield accompanied by the other *anti* aldol adduct **7a** in a ratio of 84:16 (eq 9). The other two possible reaction diastereomers, which had been previously characterized,[9] were not observed thus indicating that the reaction exhibited a high level of *anti* aldol diastereoselection. The structure of **6a** was determined by X-ray crystallographic analysis.

The complementary aldol reaction was also carried out on the diastereomeric β-ketoimide **3b** with essentially the same stereochemical outcome and reaction diastereoselectivity (eq 10). The major and minor aldol adducts, **8a** and **9a**, respectively were purified by chromatography on silica gel and correlated with the aldol adducts **6a** and **7a** derived from β-ketoimide **3a** (eq 9) by triethylamine equilibration (CH_2Cl_2, 25 °C, 3 h). In this comparison (Scheme 2), the major product diastereomer **8a** derived from **3b**, upon epimerization, provided a new aldol diastereomer which proved to be identical with the minor product diastereomer **7a** produced in the aldol reaction of the diastereomeric β-ketoimide **3a**. In the analogous correlation, the major aldol diastereomer **6a** derived from **3a**, upon epimerization produced an aldol diastereomer which was identical with the minor aldol diastereomer **9a** produced in the aldol reaction of the diastereomeric β-ketoimide **3b**. These experiments thus provide a correlation between the aldol diastereomers of **3a** and **3b** and establish that the C-2' stereocenter is the dominant control element in the aldol reactions of both substrates.



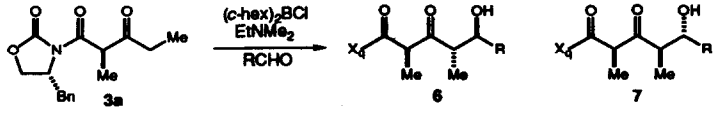
(10)

Scheme 2. Base Equilibration of the Aldol Adducts Derived from **3a** and **3b**.



The generality of the aldol reaction of **3a** was then evaluated with a variety of representative aldehydes (eq 11, Table I). In the instances studied, the isolated yields of major diastereomer ranged from 70-84% with fair to excellent reaction diastereoselection. It is noteworthy that the aldol reaction provided in entry E is a matched double stereodifferentiating process; and in accord with expectation, this process is significantly more diastereoselective than its achiral counterpart (entry A). With the stereochemical assignment of aldol adduct **6a** secured by X-ray crystallography (Figure 2), the absolute configurations of the remaining adducts **6b-6e** were assigned by analogy.

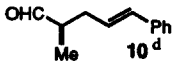
The sense of asymmetric induction observed in these reactions (eq 11) was unexpected and opposite to our *a priori* prediction based on a reactant-like transition state model wherein A(1, 3) allylic strain conformational considerations[14] would dispose the methyl and R_L substituents in the manner illustrated below.



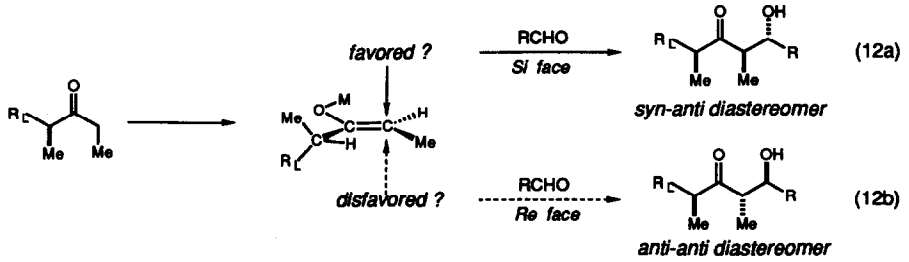
(11)

The assumption that the *N*-propionylimidazoyl moiety (R_L) is sterically more demanding than the methyl substituent appears to be reasonable. This conformational model leads to the clear prediction that the *si* face of the enolate should be more accessible to attacking electrophiles, thus leading to the conclusion that the *syn-anti* aldol diastereomer would be the major aldol product (eq 12a). ***The fact that these reactions proceed with the opposite sense of asymmetric induction to afford the anti-anti diastereomer (eq 12b) convincingly invalidates this naive postulate on the geometry of this aldol transition structure.*** This point will be revisited later in the discussion.

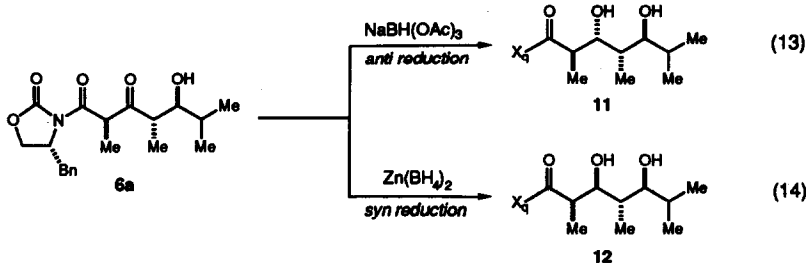
Table 1. *Anti* Aldol Reaction of **3a** with Representative Aldehydes (eq 11).

entry	aldehyde	yield, %[a]	ratio **6** : **7**[b]
A	OCH–$CHMe_2$	78 (**6a**)	84 : 16
B	OCH–$C(Me)=CH_2$	72 (**6b**)	92 : 8
C	OCH–CH_2CH_3	70 (**6c**)[c]	80 : 20
D	OCH–CH_2CH_2Ph	84 (**6d**)[c]	88 : 12
E		84 (**6e**)	97 : 3

[a] Values refer to isolated yield of major diastereomer **6**, unless otherwise noted.
[b] Ratios determined by HPLC. [c] Yield of purified mixture of diastereomers.
[d] The enantiomeric purity of this aldehyde was >98%.

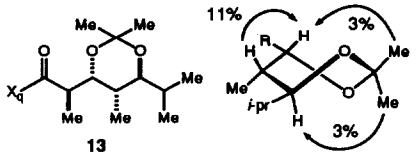


Stereoselective Reductions. The stereoselective reduction of these aldol adducts is invariably a necessary adjunct to their utility in polypropionate synthesis (Scheme 1, eq 2). Not unexpectedly, the reagent of choice for achieving either *syn*[6] or *anti*[7] reduction of a given *syn* or *anti* aldol diastereomer in this general series of compounds is not always the same. With the present set of aldol adducts, exemplified by **6a**, selective *anti* reduction (>99:1) to **11** can be achieved with either $NaBH(OAc)_3$ or $Me_4NBH(OAc)_3$ (eq 13).[8b]

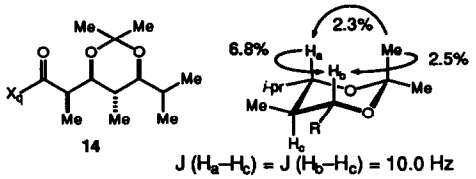


On the other hand, reduction of **6a** to the diastereomeric *syn* diol **12** is less straightforward. It was observed that $Zn(BH_4)_2$, the optimal reagent, exhibited modest *syn* selectivity (**12:11** 4:1, 89%). In a complementary procedure, reduction with $Et_2BOMe/NaBH_4$[15] resulted only in decomposition of starting material. Surprisingly, reduction of **6a** with DIBAL-H, a reagent known to afford *syn* diols in numerous instances,[16] afforded predominantly the *anti* diol **11** (>92:8), in 73% yield.

The stereochemical assignments of diols **11** and **12** were made through the respective acetonides **13** and **14** which were subjected to homonuclear decoupling, NOE, and ^{13}C NMR spectroscopic studies. The coupling constants and nuclear Overhauser enhancements reveal that acetonide **14**, derived from *syn* diol **12**, exists in the expected chair conformation. On the other hand, nuclear Overhauser enhancements of acetonide **13** indicate that it is in a twist-boat conformation. The ^{13}C resonances of the ketal and methyl acetonide carbons of acetonide **13** are 25.2, 23.3, and 100.3 ppm, indicative of an *anti* diol-derived acetonide.[17] Similarly, the corresponding ^{13}C resonances for acetonide **14** are 29.9, 19.0, and 97.8 ppm, confirming the complementary *syn* diol relationship.



13

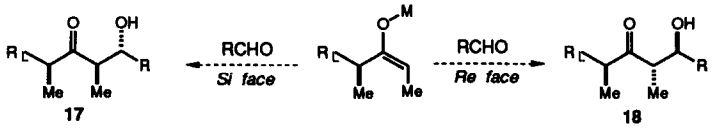


14

***Anti* Aldol Reactions of Related Chiral Ethyl Ketones.** The sense of asymmetric induction which is exhibited in *syn* aldol reactions of chiral (*Z*) enolates such as **15** has now been established in a number of instances for both boron and titanium enolates bearing a wide array of sterically dominant substituents, R_L.[18] Furthermore, transition state models have been proposed by both us[18c] and Paterson[19] to rationalize the sense of asymmetric induction observed in these processes. With the exception of the Sn(II) aldol reaction recently reported by us (eq 4),[9] and a lithium enolate aldol reaction reported by McCarthy,[20] the *syn* aldol reactions conform to the stereochemical outcome shown below.

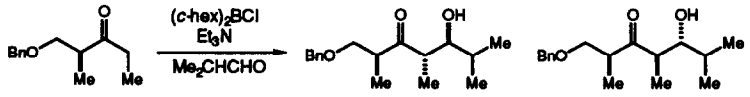
15 16

In contrast, there is little precedent for the sense of asymmetric induction which might be expected for the analogous *anti* aldol reactions of the analogous (*E*) enolates (eq 15) with the exception of the present study which reveals an unexpected sense of asymmetric induction to afford diastereomer **18** as the principal aldol adduct.



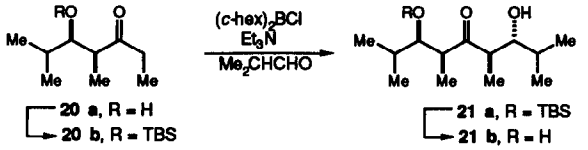
17 18 (15)

In one of the few related cases, Paterson[21] has reported that ethyl ketone **19** undergoes a highly diastereoselective *anti* aldol reaction *via* the derived (*E*) boron enolate (eq 16). The stereochemical outcome of this reaction appears to conform to the analogy generated in the present study (eq 11), but the levels of asymmetric induction are remarkable in view of the modest difference in steric requirements of the substituents (Me vs $BnOCH_2$) appended to the inducing stereogenic center in the enolate. On the basis of these stereochemical issues, we decided to further study this class of aldol bond constructions.

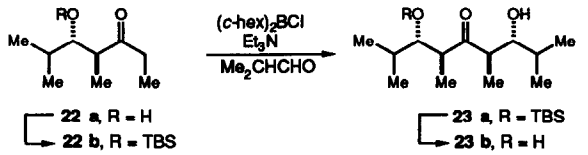


(16)

The two chiral ethyl ketones **20b** and **22b**, representative of substrates which might be employed in propionate-related bond constructions, were selected for study. These two ketones, previously prepared by McCarthy and Kageyama,[20] were subjected to the standard enolization conditions using chlorodicyclohexylborane and triethylamine in Et_2O at 0 °C to form the derived (*E*) boron enolates. Subsequent reaction with isobutyraldehyde at -78 °C afforded the *anti* aldol products **21a** and **23a** respectively (eq 17, 18). In both instances the reaction diastereoselection was excellent with the major aldol diastereomer predominating over the sum of the three minor diastereomers by ratios of 94:6 and 96:4 respectively. These experiments confirm that the selectivities for both the enolization and aldol addition steps are excellent.



anti diastereoselection = 94 : 6
90% yield (17)



anti diastereoselection = 96 : 4
75% yield (18)

The following experiments were carried out to secure the stereochemical assignments of the illustrated aldol adducts. Desilylation of **21a** (48% aqueous HF, CH_3CN) afforded the crystalline diol **21b**, mp 66-67 °C, whose structure was determined by single crystal X-ray analysis (Figure 3).

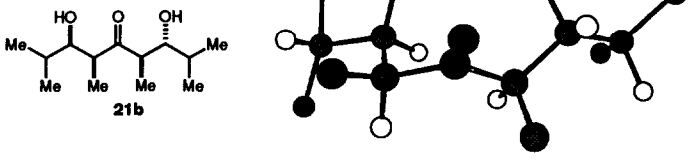
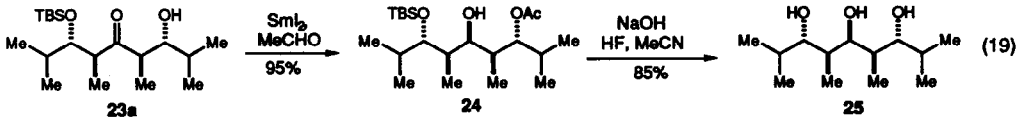


Figure 3. X-ray structure of aldol adduct **21b** (eq 17).

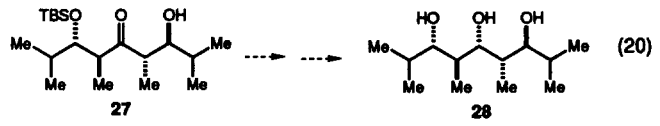
The relative stereochemistry of aldol adduct **23a** was secured by removing the silicon protecting group to provide the *meso* ketodiol **23b** which exhibited the expected 7-line ^{13}C NMR spectrum. In order to eliminate the possibility that the other *anti* aldol adduct **27** possessing latent C_2 symmetry was not produced, the illustrated set of transformations were carried out (eq 19). Thus, samarium-catalyzed Tishchenko reduction[7a] of **23a** was followed by deprotection to provide the *meso* triol **25**, whose structure also exhibited the characteristic 7-line ^{13}C NMR spectrum. If the aldol adduct had possessed structure **27**, the illustrated transformations (eq 20) would have broken the symmetry of the derived triol **28** and such structural features would have been readily ascertained in the ^{13}C NMR spectrum.

It is evident that the *anti* aldol reactions of β-ketoimide **3a** (eq 11) and the related ethyl ketones **20** and **22** (eq 17, 18) do not to exhibit the same sense of asymmetric induction based on an analysis of the the relative

steric requirements of the crucial substituents on the crucial stereogenic center adjacent to the incipient carbonyl in the aldol transition states. If the assumption that the *N*-propionylimidazoyl moiety, which was designated as the sterically dominant substituent is actually sterically subordinate to the methyl substituent, then the stereochemical outcome of the two families of reactions conform to the allylic strain steric model presented earlier (see Eq 12). However, at the present time, such a conclusion appears unwarranted.



(19)



(20)

Conclusions

We conclude from these data that the development of a general stereochemical rationalization for the reactions presented is not yet possible from the accumulated data. In fact, the preceding results underscore the lack of understanding which still surrounds the stereochemical aspects of this important family of reactions. Nevertheless, the general utility of these bond constructions to the synthesis of propionate natural products is quite evident. Applications of these reactions in the context of synthesis ventures will appear in due course.

Experimental Section

General. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter using a sodium (589 nm, D line) lamp at the temperature indicated, and are reported as follows: $[\alpha]_D^{temp}$. Infrared spectra were taken on a Perkin-Elmer 781 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AM300, AM400, or AM500 spectrometers. Chemical shifts are reported in parts per million downfield from a tetramethylsilane internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (Hz), integration, and interpretation. ^1H NMR assignments for compounds containing the 4-(phenylmethyl)-2-oxazolidinone auxiliary are reported using the following notation: H_1 and H_2 represent the benzylic protons, H_3 the proton at the 4-position, and H_4 and H_5 the protons at the 5-position of the oxazolidinone ring. Chemical shifts of ^{13}C NMR spectra are reported in ppm from tetramethylsilane using the solvent resonance as an internal standard (deuterochloroform: 77.0 ppm, deuterobenzene: 128.0 ppm). Flash chromatography was performed on silica gel 60 (230-400 mesh, E.M. Science). Analytical high performance liquid chromatography (HPLC) was carried out on a Hewlett-Packard HP 1090 chromatograph equipped with a diode array detector using a Dupont Zorbax column (4.6 x 25 cm, 5 μm silica gel) employing solvents indicated. Mass spectra were obtained on a JEOL-SX1102 or AX-505 mass spectrometer. High resolution mass spectra were obtained by peak matching. Elemental analyses were performed by Spang Microanalytical Laboratories, Inc. (Eagle Harbor, MI) or Galbraith Laboratories (Knoxville, TN). Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen. When necessary, solvents were dried prior to use. Chlorodicyclohexylborane[22] ((c-hex)$_2$BCl), and zinc borohydride[23] ($Zn(BH_4)_2$) were prepared according to literature procedure, and were stored under an atmosphere of dry nitrogen in a Schlenck flask. All other reagents were used as received.

[[3-(2*R*)-4*R*]-3-(1-oxo-2-methyl-3-hydroxy-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (3a). [[3-(2*R*,3*S*)-4*R*]-3-(3-hydroxyl-2-methyl-1-oxo-propyl)-4-phenylmethyl]-2-oxazolidinone was prepared according to the published *Organic Syntheses* procedure.[10] A boron aldol addition with propanal was performed according to the procedure described therein. Thus, (4*R*)-3-(1-oxo-propyl)-4-phenylmethyl-oxazolidin-2-one (2.25 g, 9.65 mmol) in dichloromethane (40 mL) was enolized using dibutylboron triflate (2.64 mL, 10.61 mmol) and triethylamine (1.88 mL, 13.50 mmol), then caused to react with propanal (0.91 mL, 12.54 mmol). After oxidative workup and recrystallization (1:1 ether/hexanes) the aldol adduct was obtained as a colorless crystalline solid (2.46 g, 88%) identical to its enantiomer, previously synthesized:[9] mp 82-83 °C; IR (liquid film)

3700-3200, 3070, 3040, 2980, 2945, 2890, 1780, 1700, 1460, 1390, 1355, 1300, 1220, 1120, 975, 935, 770, 755, 710cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (m, 5H, aromatic C-H), 4.70 (m, 1H, H_3), 4.19 (m, 2H, H_4 and H_5), 3.86 (m, 1H, C_3-H), 3.79 (dq, J = 2.8, 7.0 Hz, 1H, C_2-H), 3.25 (dd, J = 3.3, 13.4 Hz, 1H, H_1), 2.92 (d, J = 3.2 Hz, 1H, OH), 2.79 (dd, J = 9.4, 13.4 Hz, 1H, H_2), 1.53 (m, 2H, C_4-H), 1.25 (d, J = 7.0 Hz, 3H, C_2-CH_3), 0.98 (t, J = 7.4 Hz, 3H, C_5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 153.0, 135.1, 129.4, 128.9, 127.4, 73.1, 66.2, 55.1, 41.9, 37.8, 26.9, 10.4, 10.3; TLC (40% EtOAc/hexanes) Rf 0.26. *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27. Found: C, 65.75; H, 7.07.

The aldol adduct **4** (2.43 g, 8.35 mmol) in dichloromethane and DMSO (40 mL each) was cooled to ca. -5 °C in a brine bath, and triethylamine (3.53 mL, 25.32 mmol) was added by syringe. A solution of sulfur trioxide-pyridine complex (4.03 g, 25.32 mmol) in DMSO (40 mL) was transferred by cannula at a rate slow enough to maintain a temperature under 0 °C in the reaction vessel. Three hours after the addition was complete, the reaction was judged complete by TLC (2:1 EtOAc/hexanes). The unpurified reaction mixture was diluted with ether (200 mL) and extracted with successive portions of 1 *M* $NaHSO_4$, $NaHCO_3$, and brine (200 mL each). The organic phase was dried over Na_2SO_4. After solvent removal *in vacuo*, a yellow solid was obtained. Following recrystallization (1:1 ether/pentane) **1** was obtained as a colorless crystalline solid (2.03 g). Concentration of the mother liquior *in vacuo*, followed by flash chromatography on silica gel afforded an additional 28 mg (total yield of 95%) of the crystalline compound, identical to its enantiomer, previously synthesized:[9] mp 76-77 °C. IR (liquid film) 3070, 3040, 2990, 2950, 2890, 1785, 1725, 1705, 1610, 1500, 1485, 1460, 1390, 1360, 1250, 1220, 1130, 1085, 1055, 1015, 980cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.18 (m, 5H, aromatic C-H), 4.74 (m, 1H, H_3), 4.60 (q, J = 7.5 Hz, 1H, C_2-H), 4.20 (m, 2H, H_4 and H_5), 3.30 (dd, J = 3.2, 13.4 Hz, 1H, H_1), 2.77 (dd, J = 9.6, 13.4 Hz, 1H, H_2), 2.65 (m, 2H, C_4-H), 1.43 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.07 (t, J = 7.2 Hz, 3H, C_5-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 170.2, 153.8, 135.2, 129.3, 128.9, 127.3, 66.5, 55.3, 52.6, 38.0, 34.0, 12.8, 7.5; $[\alpha]_D^{295}$ -149° (*c* 0.97, CH_2Cl_2); TLC (40% EtOAc/hexanes) Rf 0.46. *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.46; H, 6.53.

[[3-(2*S*)-4*R*]-3-(2-methyl-1,3-dioxo-pentyl)-4-(phenylmethyl)]-2-oxazolidinone (3b). To a cooled (-78°C) solution of 150 μL (1.05 mmol) of di-*iso*-propylamine in 2.0 mL of dry THF was added 0.724 mL (1.05 mmol) of *n*-butyllithium (1.45 M in hexane) dropwise. After stirring at -78 °C for 30 min, a solution of (4*R*)-3-(1-oxo-propyl)-4-phenylmethyl-2-oxazolinone (**5**) (233 mg, 1.00 mmol) in 5 mL of dry THF was added dropwise. The resulting mixture was stirred at -78 °C for 2 h. A solution of 282 mg (1.10 mmol) of anhydrous magnesium bromide-THF in 2.0 mL of dry THF was then added in one portion at -78 °C. After 1 min at -78 °C, propionyl chloride (0.113 mL, 1.30 mmol) was added very rapidly to the solution. After 5 min at -78 °C, the reaction was quenched at -78 °C with 5.0 mL of sat. aqueous ammonium chloride, warmed to room temperature and poured into CH_2Cl_2 and a small amount of sat. aqueous ammonium chloride. The aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed once with a small amount of water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography to give 226 mg (78%) of the desired β-ketoimide **3b** as a colorless oil and 49 mg of recovered imide **5**. Analysis by ^{1}H NMR indicated the presence of a single isomer (>20:1) of high purity: $[\alpha]_D^{297}$ +23.7 ° (*c* 1.13, CCl_4); IR (neat) 3070, 3040, 2990, 2950, 2890, 1780, 1720, 1610, 1590, 1500, 1485, 1460, 1390, 1250, 1220, 1130, 1085, 1055, 1010, 980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H, Ar-H), 4.68 (m, 1H, C_4-H), 4.53 (q, J = 7.3 Hz, 1H, H_3), 4.18-4.16 (m, 2H, H_4, H_5), 3.46 (dd, J = 3.3, 13.5 Hz, 1H, H_2), 2.8-2.59 (m, 3H, H_1, C_4-H), 1.42 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.10 (t, J = 7.2 Hz, 3H, C_5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 170.0, 153.6, 135.5, 129.4, 128.8, 127.1, 66.4, 55.3, 52.2, 37.5, 33.9, 12.6, 7.5. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.43; H, 6.67.

General *Anti*-aldol Procedure. To a cooled (0 °C) solution of β-ketoimide **3** (0.10 M) in Et_2O was added (*c*-hex)$_2$BCl (1.2 equiv) then $EtNMe_2$ (1.2 equiv). The resulting yellow suspension was stirred at 0 °C for 1 h, then cooled to -78 °C prior to addition of aldehyde (1.5 equiv). The reaction was stirred at -78 °C for 3 h, then allowed to warm to -20 °C over a 2 hour period before addition of 2:1 MeOH/sat. aqueous NH_4Cl solution (6 mL/mmol β-ketoimide). The mixture was stirred for an additonal 5 min at 0 °C then poured into CH_2Cl_2 (30 mL/mmol β-ketoimide) and water (5 mL/mmol β-ketoimide). The aqueous layer was separated and extracted further with CH_2Cl_2 (10 mL/mmol β-ketoimide). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (20 mL/mmol β-ketoimide) and stirred overnight with activated IRA-743 resin[13] (8 mL/mmol β-ketoimide). The solution was then filtered through a short column of silica gel with ethyl acetate and concentrated *in*

vacuo. Analysis of the unpurified mixture was accomplished by HPLC. Purification was accomplished by flash chromatography on silica gel.

[[3-(2*R*,4*S*,5*S*),4*R*]-3-(5-Hydroxy-2,4,6-trimethyl-1,3-dioxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (6a). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3a** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg, 0.840 mmol), *iso*-butyraldehyde (760 mg, 1.05 mmol). Analysis of unpurified reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 84:16 ratio of **6a** to **7a**. Purification by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 196 mg (78%) of a white solid. Product was recrystallized from 1:1 hexane-Et_2O as a crystalline solid: mp 116.0-117.5 °C; $[\alpha]_D^{295}$ -45.8 ° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3540 (br), 3030, 2970, 2880, 1780, 1730, 1450, 1375, 1355, 1120, 1010, 985 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, Ar-**H**), 4.93 (q, J = 7.3 Hz, 1H, C_2-**H**), 4.79-4.73 (m, 1H, **H**$_3$), 4.29-4.17 (m, 2H, **H**$_4$, **H**$_5$), 3.59-3.47 (m, 1H, C_4-**H**), 3.31 (dd, J = 3.3, 13.3 Hz, 1H, **H**$_1$), 2.93 (quin, J = 7.2 Hz, 1H, C_3-**H**), 2.78 (dd, J = 9.7, 13.3 Hz, 1H, **H**$_2$), 1.80 (dq, J = 3.5, 6.8 Hz, 1H, C_6-**H**), 1.49 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.17 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.97 (d, J = 6.9 Hz, 3H, C_6-CH_3), 0.88 (d, J = 6.7 Hz, 3H, C_6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 170.6, 153.4, 135.1, 129.4, 128.9, 127.4, 77.6, 66.3, 55.4, 52.5, 47.1, 37.9, 29.5, 20.0, 14.6, 14.1, 12.9. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53. Found: C, 66.52; H, 7.60.

[[3-(2*R*,4*S*,5*R*),4*R*]-3-(5-Hydroxy-2,4,6-trimethyl-1,3-dioxo-hept-6-enyl)-4-(phenylmethyl)]-2-oxazolidinone (6b). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3a** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg, 0.84 mmol), methacrolein (196 mg, 2.10 mmol, transferred *via* cannula). Analysis of the unpurified reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 92:8 ratio of **6b** to **7b**. Purification by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 180 mg (72%) of a crystalline solid: mp 88.5-90.0 °C; $[\alpha]_D^{295}$ -99.7 ° (*c* 0.63, CCl_4); IR ($CHCl_3$) 3400 (br), 2990, 2950, 1790, 1720, 1705, 1600, 1455, 1380, 1360, 1210, 1120, 1010, 995, 905, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H, Ar-**H**), 4.95-4.89 (m, 3H, C_6-**H**$_2$, C_2-**H**), 4.80-4.71 (m, 1H, **H**$_3$), 4.28-4.17 (m, 3H, C_5-**H**, **H**$_4$, **H**$_5$), 3.31 (dd, J = 3.3, 13.3 Hz, 1H, **H**$_1$), 2.95-2.91 (m, 1H, C_4-**H**), 2.77 (dd, J = 9.7, 13.3 Hz, 1H, **H**$_2$), 1.73 (s, 3H, C_6-CH_3), 1.49 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.06 (d, J = 7.1 Hz, 3H, C_4-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 170.6, 153.4, 144.4, 135.0, 129.3, 128.9, 127.3, 114.5, 78.6, 66.3, 55.2, 52.9, 46.9, 37.8, 16.3, 14.3, 12.6. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.84; H, 7.01. Found: C, 67.02; H, 7.01.

[[3-(2*R*,4*R*,5*S*),4*R*]-3-(5-Hydroxy-2,4-dimethyl-1,3-dioxo-heptyl)-4-(phenylmethyl)]-2-oxazolidinone (6c). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3a** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg, 0.840 mmol), propionaldehyde (61 mg, 1.05 mmol). Analysis of the unpurified reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 80:20 ratio of **6c** to **7c**. Purification by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 170 mg (70%) of a mixture of **6c** and **7c** as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H, Ar-**H**), 4.89 (q, J = 7.3 Hz, 1H, C_2-**H** (**6c,7c**)), 4.76-4.68 (m, 1H, **H**$_3$ (**6c,7c**)), 4.27-4.08 (m, 2H, **H**$_4$, **H**$_5$ (**6c,7c**)), 3.62-3.54 (m, 1H, C_5-**H** (**6c,7c**)), 3.29-3.26 (m, 1H, **H**$_1$ (**6c,7c**)), 2.85-2.74 (m, 2H, **H**$_4$, C_4-**H** (**6c,7c**)), 1.46 (m, 3H, C_2-CH_3 (**6c,7c**)), 1.34 (d, J = 6.6 Hz, 0.8H, C_4-CH_3 (**7c**)), 1.18 (d, J = 7.1 Hz, 2.2H, C_4-CH_3 (**6c**)), 1.09 (t, J = 7.4 Hz, 0.8H, C_7-**H** (**7c**)), 0.96 (t, J = 7.4 Hz, 2.2H, C_7-**H** (**6c**)). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 65.69; H, 7.25. Found: C, 65.41; H, 7.20.

[[3-(2*R*,4*R*,5*S*),4*R*]-3-(5-Hydroxy-2,4-dimethyl-1,3-dioxo-9-phenyl-nonyl)-4-(phenylmethyl)]-2-oxazolidinone (6d). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3a** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg. 0.84 mmol), hydrocinnamaldehyde (141 mg, 1.05 mmol). Analysis of the unpurified reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 88:12 ratio of **6d** to **7d**. Purification by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 180 mg (81%) of a mixture of **6d** and **7d** as a clear, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.17 (m, 5H, Ar-H), 4.89 (m, 1H, C_2-**H** (**6d,7d**)), 4.76-4.68 (m, 1H, **H**$_3$ (**6d,7d**)), 4.27-4.08 (m, 2H, **H**$_4$, **H**$_5$ (**6d,7d**)), 3.66-3.58 (m, 1H, C_5-**H** (**6d,7d**)), 3.29-3.26 (m, 1H, **H**$_1$ (**6d,7d**)), 2.85-2.59 (m, 4H, **H**$_4$, C_4-**H**, C_7-**H**$_2$ (**6d,7d**)), 1.85-1.79 (m, 1H, C_6-**H** (**6d,7d**)), 1.69-1.61 (m, 1H, C_6-**H** (**6d,7d**)), 1.49-1.45 (m, 3H, C_2-CH_3 (**6d,7d**)), 1.19 (d, J = 7.1 Hz, 2.6H, C_4-CH_3 (**6d**)), 1.15 (d, J = 7.4 Hz, 0.5H, C_4-**H** (**7d**)). HRMS (FAB) *m/z*: Calcd for (M + Na$^+$): 466.1943. Found: 466.1927.

[[3(2*R*,4*S*,5*S*,6*R*,8*E*),4*R*]-3-(5-hydrox-2,4,6-trimethyl-1,3-dioxo-9-phenyl-8-nonenyl)-4-(phenylmethyl)]-2-oxazolidinone (6e). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3a** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg, 0.84 mmol), aldehyde **10** (146 mg, 1.2 mmol, in a 0.5 mL solution of anhydrous Et$_2$O, transferred *via* cannula). Analysis of the unpurified reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 97:3 ratio of **6e** to **7e**. Purification by flash chromatography on silica gel (20% ethyl acetate/hexane) afforded 272 mg (84%) of a colorless oil: $[\alpha]_D^{297}$ -86.3 ° (*c* 1.16, CCl_4); IR (CCl_4) 3640, 3550 (b), 3040, 2980 (br), 2950, 1790, 1750, 1720 (br), 1600, 1460, 1390, 1360, 1245, 1215, 1125, 1050, 1010, 970, 705, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (m, 10H, Ar-H), 6.40 (d, J = 15.8 Hz, 1H, C_9-H), 6.21 (quin, 1H, C_8-H), 4.90 (q, 1H, C_2-H), 4.71 (m, 1H, H_3), 4.17-4.09 (m, 2H, H_4, H_5), 3.83-3.79 (m, 1H, C_5-H), 3.25 (dd, J = 3.1, 13.3 Hz, 1H, H_1), 2.95 (m, 1H, C_4-H), 2.75 (dd, J = 9.5, 13.3 Hz, 1H, H_3), 2.46 (d, J=5.2 Hz, 1H, C_5-H), 2.32-2.18 (m, 2H, C_7-H_2), 1.77 (m, 1H, C_6-H), 1.48 (d, J=7.3 Hz, 3H, C_2-CH_3), 1.10 (d, J=7.1 Hz, 3H, C_4-CH_3), 0.91 (d, J=6.8 Hz, 3H, C_6-CH_3); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 211.8, 170.6, 153.3, 137.4, 135.0, 131.3, 129.2, 128.8, 128.7, 128.3, 126.8, 125.8, 75.0, 66.2, 55.1, 52.5, 47.4, 37.7, 34.6, 13.6, 12.7, 11.7. HRMS (FAB) *m/z*: Calcd for (M + Na$^+$): 486.2256. Found: 486.2253.

[[3-(2*S*,4*S*,5*S*),4*R*]-3-(5-Hydroxy-2,4,6-trimethyl-1,3-dioxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (7a). To a solution of 100 mg of imide **8a** in 5 mL CH_2Cl_2 was added two drops (approx. 12 mg) of triethylamine. The resulting solution was stirred at room temperature for 3 h, then concentrated *in vacuo*. The residue was filtered through a short column of silica gel with ethyl acetate. Analysis of the unpurified mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 80:20 ratio of **8a** to **7a**. Purification by flash chromatography on silica gel afforded 79 mg (79%) of imide **8a** and 19 mg (19%) of imide **7a**. Data for **7a**: $[\alpha]_D^{295}$ -9.5 ° (*c* 0.46, CCl_4). IR (CCl_4) 3570 (br), 2960, 2890, 1790, 1715, 1705, 1445, 1385, 1360, 1215, 1020, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 5H, Ar-H), 4.90 (q, d = 7.3 Hz, 1H, C_2-H), 4.73-4.65 (m, 1H, H_3), 4.20-4.16 (m, 2H, H_4, H_5), 3.62-3.57 (m, 1H, C_5-H), 3.44 (dd, J = 2.9, 13.5 Hz, 1H, H_1), 2.96 (q, J = 7.5 Hz, 1H, C_4-H), 2.78 (dd, J = 9.9, 13.4 Hz, 1H, H_2), 1.84-1.79 (m, 1H, C_6-H), 1.47 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.19 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.99 (d, J = 7.1 Hz, 3H, C_6-CH_3), 0.89 (d, J = 8.9 Hz, 3H, C_6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9, 170.3, 153.8, 135.0, 129.4, 129.0, 127.5, 77.9, 66.6, 55.6, 53.5, 48.3, 38.0, 29.6, 20.2, 14.6, 14.3, 13.0. HRMS (FAB) *m/z*: Calcd for (M + H): 362.1967. Found: 362.1963.

[[3-(2*S*,4*R*,5*R*),4*R*]-3-(5-Hydroxy-2,4,6-trimethyl-1,3-dioxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (8a). The following reagents in the quantities indicated were combined using the general *anti*-aldol procedure: β-ketoimide **3b** (202 mg, 0.700 mmol), (*c*-hex)$_2$BCl (179 mg, 0.840 mmol), EtNMe$_2$ (61 mg, 0.84 mmol), *iso*-butyraldehyde (760 mg, 1.05 mmol). Analysis of unpurified the reaction mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 83:17 ratio of **8a** to **9a**. Purification by flash chromatography on silica gel (20% EtOAc/hexane) afforded 186 mg (74%) of a clear oil: $[\alpha]_D^{295}$ -11.0° (*c* 1.19, CCl_4); IR (CCl_4) 3560 (br), 2960, 2890, 1790, 1715, 1705, 1445, 1385, 1360, 1215, 1020, 990 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 5H, Ar-H), 4.90 (q, d = 7.3 Hz, 1H, C_2-H), 4.73-4.65 (m, 1H, H_3), 4.20-4.16 (m, 2H, H_4, H_5), 3.62-3.57 (m, 1H, C_5-H), 3.44 (dd, J = 2.9, 13.5 Hz, 1H, H_1), 2.96 (q, J = 7.5 Hz, 1H, C_4-H), 2.78 (dd, J = 9.9, 13.4 Hz, 1H, H_2), 1.84-1.79 (m, 1H, C_6-H), 1.47 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.19 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.99 (d, J = 7.1 Hz, 3H, C_6-CH_3), 0.89 (d, J = 8.9 Hz, 3H, C_6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 170.4, 153.3, 135.3, 129.3, 128.8, 127.1, 77.5, 66.2, 55.3, 52.1, 47.2, 37.4, 29.4, 20.0, 14.5, 14.0, 12.6. HRMS (FAB) *m/z*: Calcd for (M + Na$^+$): 384.1787. Found: 384.1812.

[[3-(2*S*,4*S*,5*S*),4*R*]-3-(5-Hydroxy-2,4,6-trimethyl-1,3-dioxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (9a). To a solution of 200 mg of imide **6a** in 10 mL CH_2Cl_2 was added four drops (approx. 24 mg) of triethylamine. The resulting solution was stirred at room temperature for 5 h, then concentrated *in vacuo*. The residue was filtered through a short column of silica gel with ethyl acetate. Analysis of the unpurified mixture by HPLC (75/24/1 hexanes-EtOAc-CH_2Cl_2, flow rate 2 mL/min, 254 nm) showed a 65:35 ratio of **6a** to **9a**. Purification by flash chromatography on silica gel afforded 111 mg (55%) of imide **8a** and 59 mg (30%) of imide **9a**. Data for **9a**: $[\alpha]_D^{295}$ -61.5 ° (*c* 0.81, CCl_4). IR (CCl_4) 3570 (br), 2970, 2880, 1785, 1720, 1705, 1455, 1390, 1360, 1210, 995 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H, Ar-H), 4.87 (q, d = 7.2 Hz, 1H, C_2-H), 4.71-4.70 (m, 1H, H_3), 4.21-4.19 (m, 2H, H_4, H_5), 3.51-3.47 (m, 1H, C_5-H), 3.48 (dd, J = 3.3, 13.5 Hz, 1H, H_1), 3.07-3.00 (m, 2H, C_4-H, OH), 2.77 (dd, J = 10.3, 13.5 Hz, 1H, H_2), 1.84-1.75 (m, 1H, C_6-H), 1.51 (d, J = 7.3 Hz, 3H, C_2-CH_3), 1.08 (d, J = 7.0 Hz, 3H, C_4-CH_3), 1.00 (d, J = 6.8 Hz, 3H, C_6-CH_3), 0.90 (d, J = 6.8 Hz, 3H, C_6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 170.2, 153.6, 135.4, 129.4, 129.0,

127.3, 77.8, 66.4, 55.8, 53.3, 48.3, 37.5, 29.5, 20.1, 14.5, 14.3, 12.7. HRMS (FAB) *m/z*: Calcd for (M + H): 362.1967. Found: 362.1968.

(2*R*,4*E*)-2-Methyl-5-phenyl-pent-4-en-1-al (10): To a solution of 700 mg (2.0 mmol) of [[3-(2*S*)-(4*S*)]-3(2-methyl-1-oxo-5-phenyl-pent-4-ene)-4-(phenylmethyl)]-2-oxazolidinone[24] in 40 mL of anhydrous Et_2O was added 40 uL (2.2 mmol) of water. This suspension was chilled to 0 °C and 1.1 mL (2.0 M in THF, 2.2 mmol) of $LiBH_4$ solution was added dropwise. The ice bath was removed and a white precipitate soon began to form. After stirring for 1 h at ambient temperature, 1M aqueous NaOH solution (20 mL) was slowly added, and the mixture stirred until both layers became clear (1 minute). The mixture was then poured into 40 mL of water and 40 mL of Et_2O. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated (*in vacuo*) to a milky white liquid. Chromatography on silica gel (20% ethyl acetate/hexane) produced 333 mg (95%) of the desired alcohol,which was carried on the the next experiment.

To a solution of 1.57 mL (18.0 mmol) of oxalyl chloride in 30 mL of CH_2Cl_2 at -78 °C was added 2.55 mL (36.0 mmol) of DMSO, resulting in gas evolution. After stirring at -78 °C for 20 min, 2.64 g (15.0 mmol) of the above alcohol (dissolved in 30 mL of CH_2Cl_2) was added quickly *via* cannula. The resulting milky white solution was stirred for 15 min, then 5.01 mL (36.0 mmol) of triethylamine was added. The mixture was allowed to warm to 0 °C over 1 h, warmed to ambient temperature and poured into 150 mL of Et_2O and 150 mL of a 1:1 brine-water solution. The organic layer was separated and washed with 150 mL of 150 mL of a 1:1 brine-water solution, then with 100 mL of brine. The combined aqueous washes were extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography on silica gel (5% ethyl acetate/hexane) produced 2.51g (96%) of aldehyde **10** as a slightly yellow oil: $[\alpha]_D$ -6.07 ° (*c* 2.39, CCl_4); IR (CCl_4) 3080, 3060, 3030, 2980, 2940, 2810, 2710, 1745, 1600, 1500, 1450, 1135 (b), 980, 965, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, J = 1.4 Hz, 1 H, C_1-H), 7.32-7.15 (m, 5 H, Ar-H), 6.38 (d, J = 15.8 Hz, 1 H, C_5-H), 6.10 (quin, 1 H, C_4-H), 2.58-2.52 (m, 1 H, C_3-H), 2.47-2.41 (m, 1 H, C_2-H), 2.28-2.22 (m, 1 H, C_3-H), 1.10 (d, J = 2.5 Hz, 3 H, CH_3); ^{13}C NMR δ 204.1, 136.9, 132.2, 128.3, 127.0, 126.4, 125.9, 46.0, 33.7, 12.9. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.45; H, 8.25.

[[3-(2R,3R,4S,5S),4R]-3-(3,5-Dihydroxy-2,4,6-trimethyl-1-oxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (11). $Me_4NBH(OAc)_3$ (908 mg, 3.45 mmol) was dissolved in dry MeCN (3.0 mL) and glacial acetic acid (3.0 mL). The aldol product **6a** (249.5 mg) dissolved in MeCN (5.0 mL) was added to this solution at room temperature and the reaction stirred for 2.75 h. The mixture was then transferred *via* cannula to a rapidly stirring biphasic mixture of CH_2Cl_2 (60 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL). The mixture was stirred for 5 min and the mixture then placed in separatory funnel. The organic layer was separated and washed with brine (40 mL). The combined aqueous layers were then extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were then combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Analysis of the unpurified mixture by HPLC (10% *i*-PrOH-hexane, flow rate 2 mL/min, 254 nm) showed a >99:1 ratio of **7** to **6**. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel (EtOAc-hexane, 3:2) to afford the diol (202.5 mg, 81%) as a gum that solidified on standing: mp 95-99 °C; $[\alpha]_D^{295}$ -49.8 ° (*c* 0.93, CCl_4); IR (CCl_4) 3520 (br), 2970, 2945, 1795, 1700, 1550, 1385, 1260, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H, Ar-H), 4.69-4.64 (m, 1H, H_3), 4.25-4.16 (m, 3H, C_3-H, H_4, H_5), 3.97-3.92 (m, 1H, C_2-H), 3.24-3.18 (m, 3H, C_5-H, H_1, OH), 2.73 (dd, J = 9.5, 13.4 Hz, 1H, H_2), 2.44 (d, J = 7.1, 1H, OH), 1.87-1.80 (m, 2H, C_4-H, C_6-H), 1.08 (d, J = 7.0, 3H, C_2-CH_3), 0.98 (d, J = 7.1 Hz, 3H, C_4-CH_3), 0.94 (d, J = 6.6 Hz, 3H, C_6-CH_3), 0.85 (d, J = 6.7 Hz, 3H, C_6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 153.4, 135.2, 129.4, 128.8, 127.2, 81.3, 73.2, 66.1, 55.2, 41.0, 37.9, 34.4, 30.9, 19.4, 18.2, 14.2, 10.5. HRMS (FAB) *m/z*: Calcd for (M + Na^+): 386.1943. Found: 386.1944.

[[3-(2*R*,3*S*,4*S*,5*S*),4*R*]-3-(3,5-Dihydroxy-2,4,6-trimethyl-1-oxo-heptyl)-4-(phenyl-methyl)]-2-oxazolidinone (12). To a solution of aldol adduct **6a** (501.7 mg, 1.388 mmol) in 100 mL of CH_2Cl_2 at -78 °C was added dropwise a 0.20M solution of $Zn(BH_4)_2$ in Et_2O (10.4 ml, 2.08 mmol). The reaction was stirred for 1 h at -78 °C, then warmed to 0 °C and stirred for 15 min. The reaction was quenched by transferring the reaction mixture *via* cannula to a rapidly stirring solution of 1N HCl at 0 °C. The mixture was then poured into CH_2Cl_2 (200 ml). The organic layer was separated and washed successively with a saturated aqueous solution of $NaHCO_3$ (100 ml) and brine (100 ml). The combined aqueous layers were then extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to a solid white foam. Analysis of unpurified reaction mixture by HPLC (75/25 hexanes-EtOAc, flow rate 2 mL/min, 254 nm) showed a 4:1 ratio of **12** to **11**. Purification by flash column chromatography on silica gel

(hexane-EtOAc, 1:1) afforded the product (445.2 mg, 89%) (mixture of isomers **12** and **11**) as a solid. The product (**12**) was crystallized from Et_2O-hexane to afford 394 mg (70%) of a powder: mp 128.0-128.5 °C; $[\alpha]_D^{295}$ -25.7 ° (*c* 0.83, CCl_4); IR (CCl_4) 3500 (br), 2970, 2940, 2880, 1790, 1680, 1455, 1380, 1370, 1240, 1210, 1195, 1110, 985, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H, Ar-H), 4.72 (m, 1H, H_3), 4.29-4.18 (m, 3H, H_4, H_5, OH), 3.99-3.93 (m, 2H, C_2-H, C_3-H), 3.48 (d, J = 8.8 Hz, 1H, C_5-H), 3.27 (dd, J = 3.3, 13.4 Hz, 1H, H_1), 2.79 (dd, J = 9.5, 13.4 Hz, 1H, H_2), 1.88 (m, 1H, C_4-H), 1.74 (m, 1H, C_5-H), 1.27 (d, J = 6.9 Hz, 3H, C_4-CH_3), 1.01 (d, J = 6.9 Hz, 3H, C_4-CH_3), 0.87 (d, J = 6.8 Hz, 3H, C_6-CH_3), 0.81 (d, J = 6.9 Hz, 3H, C_6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 152.9, 135.0, 129.4, 128.9, 127.4, 80.6, 76.8, 66.2, 55.2, 39.9, 37.9, 37.7, 29.9, 20.2, 13.9, 12.9, 9.4. Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04. Found: C, 66.17; H, 8.17.

[4*S*,5*S*,6*R*,6(1*R*,2(4*R*))]-4-(1-Methyl-ethyl)-6-(1-methyl-2-oxo-2-*N*-(4-(phenylmethyl)-2-oxazolidinyl))-2,2,5-trimethyl-1,3-dioxane (13). To a stirred solution of imide **11** (86 mg, 0.24 mmol) in 1.0 mL acetone and 1.0 mL 2,2-dimethoxypropane was added 2 mg camphorsulphonic acid. This mixture was stirred at room temperature overnight, then concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (15% EtOAc/hexane) gave 77 mg (81%) of the title compound as a crystalline solid: mp 115-116 °C; $[\alpha]_D^{296}$ -49.4 ° (*c* 1.08, CCl_4); IR (CCl_4) 2960, 2940, 2880, 1790, 1710, 1370, 1340, 1255, 1245, 1220, 1020, 995, 970 cm^{-1}; ^1H NMR (400 MHz, CDCl3) d 7.34-7.20 (m, 5H, Ar-H), 4.66-4.60 (m, 1H, C_6-C_4'-H), 4.14-4.12 (m, 2H, C_6-C_5'-H), 4.01-3.98 (m, 2H, C_6-H, C_6-C_1-H), 3.23 (dd, J = 3.3, 13.4 Hz, 1H, CH_2-Ar), 3.03 (dd, J = 5.2, 6.8 Hz, 1H, C_4-H), 2.80 (dd, J = 9.5, 13.4 Hz, 1H, CH_2-Ar). 1.82 (dt, J = 3.4, 6.7 Hz, 1H, C_5-H), 1.77-1.70 (m, 1H, C_4-C_1-H), 1.26 (s, 3H, C_2-CH_3), 1.24 (s, 3H, C_2-CH_3), 1.13 (d, J = 4.2 Hz, 3H, C_6-C_1-CH_3), 0.95-0.91 (m, 9H, C_5-CH_3, C_4-C_1-CH_3, C_4-C_2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 175.5, 153.2, 135.3, 129.4, 128.8, 127.2, 100.3, 79.1, 71.3, 65.9, 55.3, 37.9, 37.7, 34.3, 31.9, 25.2, 23.3, 18.7, 17.6, 13.0, 12.6. Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24. Found: C, 68.48; H, 8.15.

[4S,5S,6S,6(1R,2(4R))]-4-(1-Methyl-ethyl)-6-(1-methyl-2-oxo-2-*N*-(4-(phenylmethyl)-2-oxazolidinyl-))-2,2,5-trimethyl-1,3-dioxane (15). To a stirred solution of imide **12** (30 mg, 0.82 mmol) in 1.0 mL acetone and 1.0 mL 2,2-dimethoxypropane was added 1 mg of camphorsulphonic acid. This was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was purified by preparative-TLC (1 mm plate; 30% ethyl acetate/hexane) to give 31 mg (94%) of the title compound as a colorless oil: $[\alpha]_D^{296}$ -27.6° (*c* 1.05, CCl_4); IR (CCl_4) 2970, 2930, 1780, 1710, 1600, 1365, 1350, 1265, 1230, 1170, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.14 (m, 5H, Ar-H), 4.50-4.47 (m, 1H, C_6-C_4'-H), 4.11-4.03 (m, 2H, C_6-C_5'-H), 3.91 (dt, J = 3.1, 6.9 Hz, 1H, C_6-C_1-H), 3.80 (dd, J = 3.1, 10.0 Hz, 1H, C_6-H), 3.30 (dd, J = 3.1, 13.3 Hz, 1H, CH_2-Ar), 3.23 (dd, J = 2.2, 10.0 Hz, 1H, C_4-H), 2.68 (dd, J = 9.9, 13.3 Hz, 1H, CH_2-Ar). 1.83-1.79 (m, 1H, C_4-C_1-H), 1.53-1.46 (m, 1H, C_5-H), 1.23 (s, 3H, C_2-CH_3), 1.22 (s, 3H, C_2-CH_3), 1.12 (d, J = 46.9 Hz, 3H, C_6-C_1-CH_3), 0.84 (d, J = 6.9 Hz, 3H, C_4-C_2-CH_3), 0.76 (d, J = 6.8 Hz, 3H, C_4-C_2-CH_3), 0.72 (d, J = 6.7 Hz, 3H, C_5-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 153.4, 135.5, 129.4, 128.9, 127.2, 97.8, 77.7, 74.1, 66.2, 56.3, 40.2, 37.6, 33.2, 29.9, 28.0, 20.0, 19.4, 14.2, 10.9, 8.9. HRMS (FAB) *m/z*: Calcd for (M + Na^+): 426.2256. Found: 426.2261.

(3*R,4*S**,6*R**,7*R**)-3-*tert*-Butyldimethylsilyloxy-7-hydroxy-2,4,6,8-tetramethyl-5-nonanone (21a).** The following reagents were combined in the amounts indicated according to the general *anti*-aldol procedure: (*c*-hex)$_2$BCl (420 mg, 423 μL, 1.98 mmol), (3*R**,4*S**)-3-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5-heptanone (**20b**)[20] (512 mg, 1.88 mmol), triethylamine (209 mg, 288 μL, 2.07 mmol), and *iso*-butyraldehyde (149 mg, 188 μL, 2.07 mmol). Purification by flash chromatography on silica gel (5% EtOAc/hexane, then 10% EtOAc/hexane) gave 544.7 mg (84%) of the *syn-syn-anti* product (SSA) diastereomer **21a** as a white solid and 38.9 mg (6%) of a mixture of other aldol diastereomers. This chromatography fraction was shown by ^1H NMR integration to be a 10.8:1:1.1 mixture of SAA:SSA:SSS isomers (integration of dd resonances at δ 3.83, 3.77, and 3.68, respectively). The overall stereoselectivity of the reaction was calculated to be 16.9:1.0:0.1 SSA:SAA:SSS isomers (d.s. = 94:6).

Data for **21a**: mp 54-55 °C; IR ($CHCl_3$) 3520, 2950, 1695, 1465, 1255, 1050, 1000, 985, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (dd, J = 5.9, 3.5 Hz, 1H, CHOTBS), 3.48 (m, 1H, CHOH), 2.87 (m, 2H, CH_3CHC=O), 2.48 (d, J = 6.0 Hz, 1H, OH), 1.74 (m, 1H, $(CH_3)_2CH$CHOH), 1.67 (m, 1H, $(CH_3)_2$CHCHOTBS), 1.12 (d, J = 7.1 Hz, 3H, CH_3CHC=O), 1.11 (d, J = 7.2 Hz, 3H, CH_3CHC=O), 0.97 (d, J = 6.8 Hz, 3H, $(CH_3)_2$CHCHOH), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.91 (d, J = 6.5 Hz, 3H, $(CH_3)_2$CHCHOH), 0.90 (d, J = 6.7 Hz, 3H, $(CH_3)_2$CHCHOTBS), 0.88 (d, J = 6.7 Hz, 3H, $(CH_3)_2$CHCHOTBS), 0.08 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 218.7, 78.1, 76.5, 50.0, 48.4, 33.2, 30.0, 26.1, 20.1,

20.0, 17.1, 15.5, 14.4, 13.7, -3.8, -4.2. Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70. Found: C, 66.29; H, 11.68.

(3*R,4*S**,6*R**,7*R**)-3,7-Dihydroxy-2,4,6,8-tetramethyl-5-nonanone (21b).** To a solution of ketone **21a** (66.5 mg, 0.193 mmol) in 1 mL CH_3CN was added four drops of aqueous HF (48%). This was stirred at ambient temperature for 1h, then quenched by addition of 10 mL of a saturated aqueous solution of sodium bicarbonate. This mixture was then extracted with Et_2O (3 X 15 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromotography on silica gel gave 43.3 mg (99%) of a white, crystalline solid: mp 66-67 °C; IR ($CHCl_3$) 3480, 2970, 1710, 1460, 1380, 1135, 1110, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (m, 2H, CHOH), 2.99 (dq, J = 8.6 Hz, J = 7.0 Hz, 1H, anti $CH_3CHC{=}O$), 2.85 (qd, J = 7.0, 2.4 Hz, 1H, syn $CH_3CHC{=}O$), 1.80 (m, 1H, syn $(CH_3)_2CH$), 1.70 (m, 1H, anti $(CH_3)_2CH$), 1.08 (d, J = 7.0 Hz, 3H, syn $CH_3CHC{=}O$), 1.05 (d, J = 7.0 Hz, 3H, anti $(CH_3)_2CH$), 1.03 (d, J = 7.3 Hz, 3H, anti $CH_3CHC{=}O$), 0.98 (d, J = 6.9 Hz, 3H, $(CH_3)_2CH$), 0.91 (d, J = 6.8 Hz, 3H, syn $(CH_3)_2CH$), 0.88 (d, J = 6.7 Hz, 3H, anti $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.4, 77.8, 75.5, 49.1, 46.9, 30.4, 29.3, 19.8, 19.6, 18.9, 14.3, 14.2, 7.7. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.94; H, 11.25.

(3*S,4*S**,6*R**,7*R**)-3-*tert*-Butyldimethylsilyloxy-7-hydroxy-2,4,6,8-tetramethyl-5-nonanone (23a).** The following reagents were combined in the amounts indicated according to the general *anti*-aldol procedure: (*c*-hex)$_2$BCl (272 mg, 274 μL, 1.28 mmol), (3*S*,4*S*)-3-*tert*-butyldimethylsilyloxy-2,4-dimethyl-5-heptanone (**22b**)[20] (331 mg, 1.22 mmol), triethylamine (136 mg, 187 μL, 1.34 mmol), and *iso*-butyraldehyde (96.0 mg, 122 μL, 1.34 mmol). Purification by flash chromatography on silica gel (5% EtOAc/hexane) gave 305 mg (73%) of pure **23a** as a colorless oil: IR (neat) 3500, 2960, 1710, 1460, 1250, 1050, 1000, 990, 835, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (dd, J = 7.1, 3.3 Hz, 1H, CHOTBS), 3.46 (ddd, J = 8.4, 4.8, 3.5 Hz, 1H, CHOH), 3.10 (quin, J = 7.1 Hz, 1H, $CH_3CHCHOTBS$), 2.91 (d, J = 4.8 Hz, 1H, OH), 2.84 (dq, J = 8.3, 7.0 Hz, 1H, $CH_3CHCHOH$), 1.79 (m, 2H, $(CH_3)_2CH$), 1.04 (d, J = 7.0 Hz, 3H, $CH_3CHCHOH$), 1.03 (d, J = 7.1 Hz, 3H, $CH_3CHCHOTBS$), 0.99 (d, J = 6.8 Hz, 3H, $(CH_3)_2CH$), 0.92 (d, J = 7.0 Hz, 6H, $(CH_3)_2CH$, 0.90 (d, J = 6.9 Hz, 3H, $(CH_3)_2CH$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2, 77.9, 77.7, 51.0, 49.1, 31.6, 29.5, 26.0, 20.1, 19.3, 18.3, 17.8, 14.5, 13.7, 12.8, -4.0, -4.8. Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70. Found: C, 66.25; H, 11.63. A portion of the unpurified product (ca. 5 mg) was desilylated and acetylated to give the corresponding diacetates. GLC analysis of this mixture showed a 176:7.5 ratio of isomers (d.s. = 96:4).[25]

(3*S,4*R**,5*S**,6*R**,7*R**)-7-Acetoxy-3-*tert*-butyldimethylsilyl-oxy-2,4,6,8-tetramethyl-5-nonanol (24).** A 0.1 M solution of SmI_2 in THF (1.52 mL, 0.152 mmol) was added to a solution of 131 mg (0.381 mmol) of the β-hydroxy ketone **23b** and 335 mg (425 μL, 7.62 mmol) of acetaldehyde in 1.3 mL of THF at 0 °C under N_2 in the dark. This mixture was stirred at 0 °C for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench and the mixture was warmed to ambient temperature. Et_2O (20 mL) was added and the mixture was washed with 10 mL of H_2O and 10 mL of brine. The combined aqueous washings were extracted with 10 mL of Et_2O. The combined organic extracts were dried over anhydrous magnesium sulfate and purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give 140.3 mg (95%) of **16** as a colorless oil: IR (neat) 3530, 2970, 1725, 1475, 1465, 1390, 1370, 1250, 1055, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (dd, J = 8.0, 3.9 Hz, 1H, CHOAc), 3.61 (dt, J = 5.9, 3.3 Hz, 1H, CHOH), 3.40 (dd, J = 5.0, 3.4 Hz, 1H, CHOTBS), 2.88 (d, J = 3.1 Hz, 1H, OH), 2.09 (s, 3H, O_2CCH_3), 1.97 (m, 1H, $(CH_3)_2CHCHOAc$), 1.77 (m, 3H, C2-, C4-, and C6-CH), 1.06 (d, J = 7.0 Hz, 3H, CH_3CH), 0.94 (d, J = 7.0 Hz, 3H, CH_3CH), 0.92 (d, J = 6.6 Hz, 3H, CH_3CH), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.90 (d, J = 7.4 Hz, 3H, CH_3CH), 0.90 (d, J = 6.7 Hz, 3H, $(CH_3)_2CHCHOAc$), 0.89 (d, J = 6.7 Hz, 3H, $(CH_3)_2CHCHOAc$), 0.08 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 79.8, 79.7, 70.9, 40.2, 38.0, 30.9, 28.5, 26.0, 21.0, 20.8, 20.2, 18.8, 18.2, 15.6, 12.8, 10.5, -3.9, -4.4. Anal. Calcd for $C_{21}H_{44}O_4Si$: C, 64.90; H, 11.41. Found: C, 65.00; H, 11.29.

(3*S,4*S**,5*R**,6*R**,7*R**)-2,4,6,8-Tetramethyl-3,5,7-nonanetriol (25).** Aqueous NaOH (15%, 0.5 mL) was added to a solution of 138 mg (0.356 mmol) of **24** in 2 mL of MeOH at ambient temperature. After stirring 15 h, the solvent was removed at aspirator pressure and the residue was diluted with 10 mL of H_2O and extracted with three 15 mL portions of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the unpurified dihydroxy silyl ether as a colorless oil.

Aqueous HF (48%, 300 μL) was added to a solution of the unpurified dihydroxy silyl ether in 6 mL of CH_3CN at ambient temperature. After stirring 1 h, 10 mL of saturated aqueous $NaHCO_3$ was added to quench

the acid and the mixture was extracted with three 15 mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate and purified by flash column chromatography on silica gel (75% EtOAc/hexane) to give 70.5 mg (85%) of triol **24** as a white, crystalline solid: mp 100-101 °C; IR ($CHCl_3$) 3450, 2970, 1460, 1385, 1090, 985, 970, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (m, 1H, C5-CHOH), 3.51 (br d, J = 3.3 Hz, 1H, OH), 3.27 (q, J = 5.0 Hz, 2H, $(CH_3)_2CHCHOH$), 2.97 (d, J = 4.6 Hz, 2H, OH), 1.88 (m, 2H, C4- and C6-$CHCH_3$), 1.82 (m, 2H, $(CH_3)_2CH$), 1.05 (d, J = 7.1 Hz, 6H, C4- and C6-$CHCH_3$), 0.96 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 0.90 (d, J = 6.8 Hz, 6H, $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.1, 72.5, 37.8, 30.9, 19.6, 17.3, 13.5. Anal. Calcd for $C_{13}H_{28}O_3$: C, 67.20; H, 12.15. Found: C, 67.05; H, 12.21.

Acknowledgment: Support has been provided by the NIH, the NSF, and Merck. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) provided NMR facilities. A postdoctoral fellowships for D. L. R. (American Cancer Society) and J. S. C. (NATO) are gratefully acknowledged.

References and Notes

1) (a) Hutchinson, C. R. *Accounts Chem. Res.* **1983**, *16*, 7-14. (b) Omura, S.; Tanaka, Y. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press, New York, 1984; pp 199-299. (c) Cane, D. E.; Liang, T.-C.; Taylor, P. B.; Chang, C.; Yang, C.-C. *J. Am. Chem. Soc.* **1986**, *108*, 4957-4964.
2) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
3) (a) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, 4147-4150. (b) Riche, C.; Pascard-Billy, C. *J. Chem. Soc., Chem. Commun.* **1975**, 951-952.
4) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675-679.
5) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154-1156. Related observations have also been made with our carboximide enolates: (b) DiPardo, R. M.; Bock, M.G. *Tetrahedron Lett.* **1983**, *24*, 4805-4808.
6) For the reduction of β-hydroxyketones to *syn* 1,3-diols see: (a) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190-5192, and references cited therein.
7) For the reduction of β-hydroxyketones to *anti* 1,3-diols see: (a) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. (c) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761-3770.
8) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192-5194.
9) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868.
10) For a detailed procedure for the synthesis of (*S*)-**5** and its subsequent boron enolate derived aldol addition see: Evans, D. A.; Gage, J. R. *Organic Syntheses* **1989**, *68*, 83-91.
11) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
12) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442.
13) Hicks, K. B.; Simpson, G. L.; Bradbury, A. G. *Carbohydrate Res.* **1986**, *147*, 39-48.
14) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.
15) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, 155-158.
16) (a) See ref. 9. (b) Kiyooka, H.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009-3012.
17) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.
18) (a) Patterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229-1232. (b) Enders, D.; Lohray, B. B. *Angew. Chem. Int. Ed. Eng.* **1988**, *27*, 581-583. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049. (d) For an earlier relevant case see: Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568.
19) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Patterson, I. *Tetrahedron* **1991**, *47*, 3471-3484.
20) McCarthy, P. A.; Kageyama, M. J. *J. Org. Chem.* **1987**, *52*, 4681-4686.
21) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121-7124.
22) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417-2421.
23) Gensler, W. J.; Johnson, F.; Sloan, A. B. D. *J. Am. Chem. Soc.* **1960**, *82*, 6074-6081.
24) Evans. D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.
25) A small amount (<1%) of what may be the *anti/anti* isomer was also detected by GLC. However, since this isomer was never isolated and fully characterized, this small impurity was omitted in calculating the diastereoselectivity of this reaction.