A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes

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Abstract: A systematic investigation of the direction and degree of stereoselectivity in aldol addition reactions is presented involving achiral unsubstituted metal enolate and enolsilane nucleophiles and chiral aldehydes. The BF_3·OEt_2 mediated Mukaiyama aldol reaction with α-unsubstituted, β-alkoxy aldehydes afforded good levels of 1,3-*anti* induction in the absence of internal aldehyde chelation. The level of 1,3-induction was found to be primarily dependent on the electrostatic nature of the aldehyde β-substituent. A revised model for 1,3-asymmetric induction is presented to account for these results based primarily on minimization of internal electrostatic and steric repulsion between the aldehyde carbonyl moiety and the β-substituents. A full conformational analysis, corroborated by semiempirical (AM1) calculations, is presented to support the proposed model. The merged impact of α and β aldehyde substituents was also systematically investigated, and an integrated 1,2- and 1,3-asymmetric induction model is proposed that incorporates the salient features of the Felkin−Anh and revised 1,3-model. In accordance with this integrated model, uniformly high levels of Felkin, 1,3-*anti* diastereofacial selectivity are observed in Mukaiyama aldol reactions with *anti* substituted α-methyl-β-alkoxy aldehydes, which contain stereocontrol elements that are in a stereoreinforcing relationship. In contrast, variable levels of aldehyde facial induction were observed in the corresponding reactions with *syn* substituted aldehyde substrates, which contain stereocontrol elements in a non-reinforcing relationship. The direction of aldehyde facial induction in Mukaiyama aldol additions to the *syn* substituted aldehydes was found to be primarily dependent on the size of the enolsilane, with the first known examples of anti-Felkin selective Mukaiyama aldol reactions observed under conditions known to preclude chelation for the addition of the enolsilane of acetone. We conclude that dominant 1,2-stereoinduction will be found in those reactions proceeding with the reactants in an *antiperiplanar* relationship, favored by sterically encumbered enolsilane substituents, while dominant 1,3-stereoinduction will be manifest from a *synclinal* transition state, preferred for less bulky enolsilane substituents. By inspection, the *synclinal* transition state may be destabilized by an increase in the steric bulk of the Lewis acid, and in accordance with this prediction the trityl perchlorate mediated enolsilane addition resulted in a dramatic reversal of facial selectivity relative to the BF_3·OEt_2 mediated reaction. These trends were also documented in the mechanistically related addition of allylstannanes to *anti* and *syn* disubstituted chiral aldehydes.

Introduction

The formulation of models that successfully predict the stereochemical outcome of reactions at trigonal carbon centers has been a major preoccupation in synthesis design. One of the focal points in this area has been concerned with the elucidation of the control elements that dictate acyclic carbonyl π-facial selectivity in nucleophilic addition reactions.[1] A succession of predictive stereochemical models for carbonyl addition have been advanced since Cram's initial 1952 proposal.[2,3] Currently, the Felkin−Anh model[4] is widely invoked to interpret the contributions of torsional, steric, and electronic factors from the stereogenic center α to the reacting carbonyl.[5] Heteroatom substituents positioned either α or β to the carbonyl moiety raise the potential for transition state chelate organization, and this method has also been effectively utilized in the prediction of reaction diastereoselection.[6] Although significant effort has been expended in the development of transition state models that account for the influence of the proximal substituent on carbonyl facial induction, comparable models acknowledging the stereochemical impact of β substituents have been less well developed.[7] Recently we reported the results from an investigation of 1,3-asymmetric induction in the methyl ketone aldol reaction.[8] The highest levels of 1,3-stereoinduction are achieved

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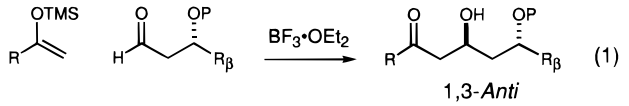
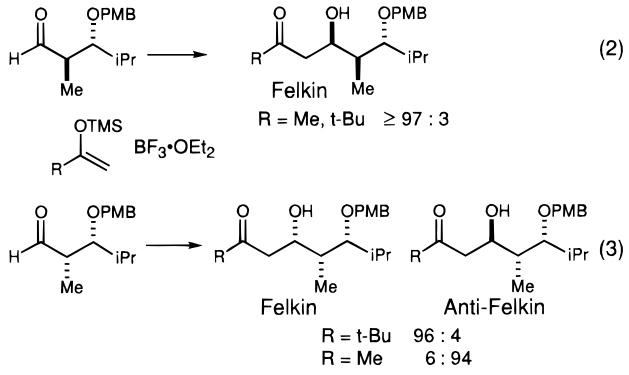
in the $BF_3{\cdot}OEt_2$ promoted enolsilane (Mukaiyama)[9] aldol variants (eq 1). The facial bias imparted to the carbonyl by the



(1)

aldehyde β-heteroatom substituent generally results in preferential formation of the 1,3-*anti* product diastereomer in these aldol processes. A stereochemical model is presented here to account for this preference, with observations on the contributions of electrostatic and steric effects to 1,3-asymmetric induction.

1,3-Asymmetric induction may also play an important role in the stereochemical outcome of additions to more complex aldehyde substrates that possess both α and β stereogenic centers.[10] For example, uniformly high levels of diastereofacial selectivity are observed in Mukaiyama aldol reactions with *anti* substituted α-methyl-β-alkoxy aldehydes (eq 2). In contrast, we have documented variable levels of aldehyde facial induction in the corresponding reactions with *syn* substituted aldehyde substrates (eq 3).[10] We have asserted that the diastereofacial



(2)

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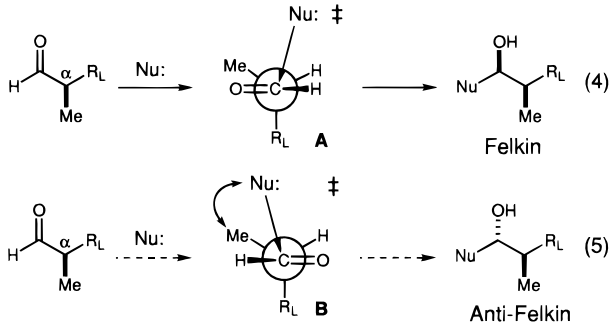
bias imposed on the carbonyl moiety is the result of stereocontrol from both the α and β stereocenters, and have concluded that, in some cases, the β-center appears to be the dominant stereocontrol element.[10] The purpose of the present investigation is to present an integrated α,β-stereoinduction model for Mukaiyama aldol reactions and related processes.

1,2-Asymmetric Induction Model. The sense of 1,2-asymmetric induction in many nucleophilic additions to α-methyl-substituted chiral aldehydes is consistent with predictions made by the Felkin−Anh paradigm.[4,5] The major tenet of this transition state model is the minimization of nonbonded interactions between the nucleophile and the substituents α to the carbonyl center. A staggered arrangement is preferred between the partially formed bond and the α substituents to minimize torsional strain, as is illustrated in transition states **A** and **B** (eqs 4 and 5).[11] *Ab initio* calculations by Houk have

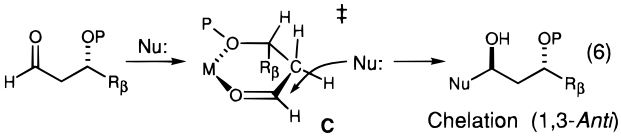


(4)

(5)

provided support for the Felkin hypothesis and indicate that when the α stereogenic center bears substituents of different size but of similar electronic character, steric factors favor nucleophilic attack on conformer **A** (eq 4).[5a,b] The largest substituent (R_L) is aligned *anti* to the forming bond, and the methyl group is disposed *syn* to the carbonyl moiety. Steric interactions between the nucleophile and α substituents are minimized in this transition state as the incoming nucleophile follows a Dunitz−Bürgi trajectory[12] over the proton of the α stereocenter. Based on this model, 1,2-asymmetric induction should increase as the steric demands of the nucleophile increase; this prediction has been borne out experimentally.[13]

1,3-Asymmetric Induction Models. The only well-established strategy for controlling aldehyde face selectivity *via* 1,3-induction involves internal chelation to a β-heteroatom substituent.[6c] Indeed, preferential formation of the 1,3-*anti* diastereomer is consistent with reaction through transition state **C** (eq 6), which involves nucleophilic attack on the less hindered



(6)

face of a conformationally locked, internally chelated intermediate. In these systems the chelating metal center (M) must possess a minimum of two open coordination sites to simultaneously complex both carbonyl[14] and ether oxygens. NMR spectroscopic experiments by Keck have established that the protecting group (P) must also permit effective bidentate complexation of the Lewis acid between the carbonyl and ether oxygen.[15]

In many diastereoselective reactions with β-heteroatom-substituted substrates, however, chelate organization is precluded due to either the nature of the coordinating metal species or the heteroatom protecting group. An illustrative example has been

(7) (a) Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, 1036−1047. (b) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011−4018. (c) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019−4026. (d) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732. (e) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1994**, *35*, 741−744.

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(12) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067. (b) Dunitz, J. D. *X-ray Analysis and the Structure of Organic Molecules*; Cornell University Press: Ithaca, NY, 1979. (c) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

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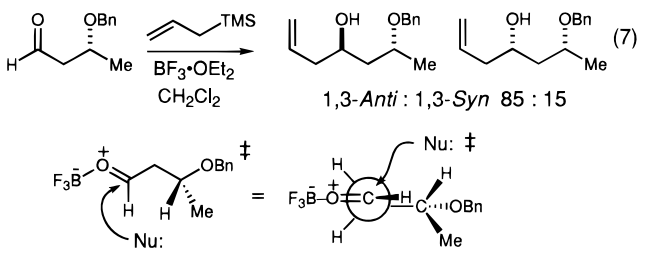
(14) For a review on Lewis acid carbonyl complexation: Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds, Part 1*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: New York, 1991; Chapter 10.

(15) (a) Keck, G. E., Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478−5480. (c) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896−906.

reported by Reetz, in which a stereoselective $BF_3{\cdot}OEt_2$ mediated allylsilane addition resulted in preferential formation of the 1,3-*anti*-substituted product (eq 7).[16] Due to the monodentate nature

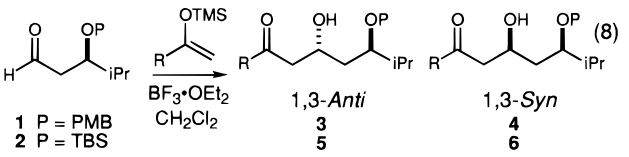


of the boron Lewis acid, chelation (eq 6) cannot be invoked to rationalize the observed *anti*-1,3-stereoinduction. An extension of Cram's polar 1,3-stereoinduction model[7c] has been proposed by Reetz to account for the diastereofacial selectivity in this system. In this model, minimization of electrostatic repulsion in the Lewis acid coordinated aldehyde complex results in formation of an extended intermediate that is attacked from the less hindered carbonyl diastereoface to provide that 1,3-*anti* product. Although the stereochemical outcome is consistent with this proposal, the Cram−Reetz model fails to acknowledge the importance of transition state torsional interactions. We propose herein an alternate 1,3 polar induction model, based primarily on electrostatic interactions within the aldehyde, that incorporates the staggered conformation of α-substituents present in the Felkin−Ahn model for 1,2-induction. The experimental results that led to the development of the modified 1,3-stereoinduction model are detailed in the following discussion.

Results and Discussion

We initiated a systematic investigation into 1,3-asymmetric induction by subjecting β-alkoxy aldehydes **1** and **2** to addition reactions with a series of methyl ketone derived enolsilane nucleophiles (eq 8, Table 1). The monodentate Lewis acid $BF_3{\cdot}OEt_2$ was utilized to preclude the intervention of chelate organization. These data indicate that good levels of 1,3-stereoinduction can be achieved in $BF_3{\cdot}OEt_2$ promoted Mukaiyama aldol reactions (1 equiv of $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C),[17] irrespective of the nature of the β-alkoxy protecting group (P) or the size of the enolsilane substituent (R).[18] This consistent predisposition for formation of the 1,3-*anti*-substituted product under nonchelate controlled conditions has been observed in numerous related Lewis acid promoted addition reactions.[19] These processes demonstrate that a useful degree of asymmetric induction can be achieved by remote substituent effects, although the origins of stereocontrol have not been systematically investigated.

Table 1.[a] Lewis Acid Promoted Aldol Reactions of Enolsilanes with β-Substituted Aldehydes **1** and **2** (Eq 8)

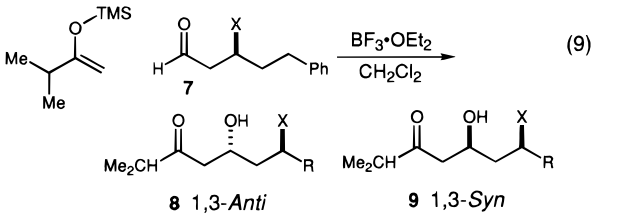


entry	R	**3**:**4** (P = PMB) (yield, %)	**5**:**6** (P = TBS) (yield, %)
A	*t*-Bu	89:11 (82)	84:16 (79)
B	*i*-Pr	92:08 (91)	80:20[b] (84)
C	Me	91:09 (89)	93:07 (87)

[a] All reactions were carried out with 1 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C. Ratios were determined by GLC analysis after silylation (TMS−imidazole) of the unpurified reaction mixtures unless otherwise noted. Yields are reported for the mixture of diastereomeric adducts. [b] Ratio was determined by integration of the ^1H NMR spectrum of the unpurified reaction mixture.

In order to assess the contribution from electrostatic and steric effects, other aldehyde substrates were subjected to the $BF_3{\cdot}OEt_2$ mediated aldol reactions (eqs 9 and 10). The facial bias of aldehyde **7a** (X = OPMB) was examined in an attempt to evaluate the electrostatic contribution to 1,3-stereoinduction. This substrate incorporates β-substituents of comparable size (OCH_2Ar vs CH_2CH_2Ar) but of different electronic character. Enolsilane addition to this aldehyde afforded an 81:19 mixture of products favoring the 1,3-*anti* diastereomer. The degree of aldehyde facial control was also examined in the presence of other β-heteroatom substituents. The reaction of β-OTBS substrate **7b** also preferentially afforded the 1,3-*anti* aldol adduct, but with slightly diminished selectivity relative to β-OPMB aldehyde **7a**. Unexpectedly, the tendency for 1,3-*anti* product formation was not observed in the reaction with aldehyde **7c** (X = OAc), and a 43:57 ratio of diastereomers favoring the 1,3-*syn* diastereomer was obtained. Finally, the unstable β-chloroaldehyde **7d** exhibited the highest level of 1,3-stereoinduction (83:17 *anti*:*syn*).

Table 2.[a] Aldehyde β-Substituent Influence on 1,3-Induction (Eq 9)



aldehyde	X	**8**:**9** (yield, %)
7a	OPMB	81:19 (87)
7b	OTBS	73:27 (90)
7c	OAc	43:57 (79)
7d	Cl	83:17 (84)

[a] See footnote *a* in Table 1.

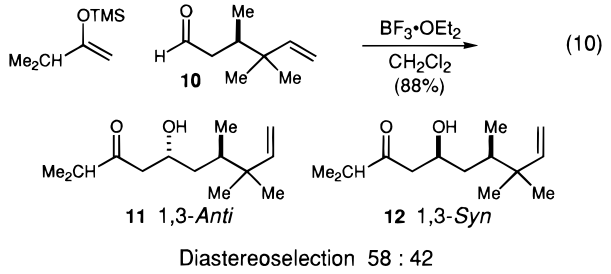
To establish the steric contribution to 1,3-stereoinduction in the absence of a polar β-substituent, aldehyde **10** possessing sterically differentiated β-alkyl substituents was synthesized. This substrate displayed low π-facial selectivity (58:42 *anti*:*syn*) in the $BF_3{\cdot}OEt_2$ promoted enolsilane aldol reaction, indicating that steric effects alone do not appear to strongly influence 1,3-stereoinduction.[18]

(16) (a) Reference 7d. (b) Reetz, M.; Kesseler, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1079−1080.

(17) For related examples; see: (a) Reference 7d. (b) Roy, R.; Rey, A. W. *Synlett* **1990**, 448−450. (c) Paterson, I.; Smith, J. *J. Org. Chem.* **1992**, *57*, 3261−3264. (d) Paterson, I.; Smith, J. D.; Ward, R. W. *Tetrahedron* **1995**, *51*, 9413−9436. (e) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768−7781. Similar trends have been reported in Mukaiyama aldol additions to β-thio-substituted aldehydes: (f) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, F. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456−461.

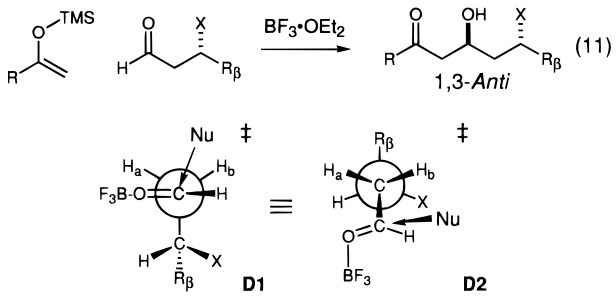
(18) Product stereochemical assignments are described in detail in the supporting information.

(19) Allylsilane additions: (a) Reference 7d; allylstannane additions. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31−42. (c) Reference 15b. (d) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schrieber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601. (e) Overly, K. R.; Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1990**, *31*, 4573−4576. [2 + 2] cycloadditions: (f) Pons, J.-M.; Pommier, A.; Lerpiniere, J.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1549−1551. (g) Pommier, A.; Pons, J.-M.; Kocienski, P. J.; Wong, L. *Synthesis* **1994**, 1294−1300. (h) Pommier, A.; Pons, J.-M.; Kocienski, P. J. *J. Org. Chem.* **1995**, *60*, 7334−7339.



Revised 1,3-Asymmetric Induction Polar Model. The revised 1,3-asymmetric induction model is derived from several assumptions common to the Felkin−Anh analysis for 1,2-asymmetric induction.[4,5] First, it is assumed that torsional effects will dictate that aldehyde transition state conformations adopt a staggered relationship between the forming bond and the aldehyde α-substituents. Second, it is assumed that the principal addition product evolves from that reactant-like transition structure wherein the β-stereogenic center is oriented *anti*, rather than *gauche*, to the forming bond since this geometry reduces nonbonded interactions between the aldehyde α substituents and the incoming nucleophile.[20]

Given the preceding assumptions concerning transition state geometry, we speculate that aldehyde face selectivity is governed by steric and electrostatic effects in the aldehyde that originate from interactions between the β-substituents and the carbonyl reaction center. Accordingly, minimization of electrostatic and steric repulsion between these substituents affords the preferred transition structure illustrated in two different perspectives (**D1** and **D2**) in eq 11. In the illustrated structures, the descriptor

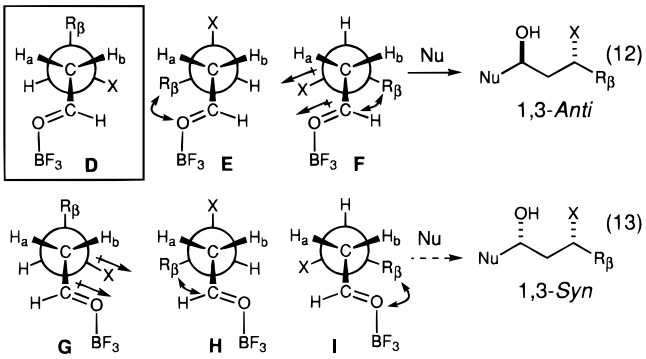


R_β denotes the β-carbon alkyl substituent, while X represents the polar heteroatom substituent (OR, Cl). This model, which leads to the 1,3-*anti* diastereomer, clearly depicts the staggered conformation of the α-substituents with respect to the incoming nucleophile **D1**, and the favored orientation of the β-stereocenter relative to the coordinated carbonyl moiety **D2**. The relevant steric and electronic interactions that favor this specific aldehyde rotamer in the transition state may be estimated in the conformational analysis of the constrained BF_3-coordinated aldehydes.

The perspective illustrated in model **D2** has been utilized to identify the important nonbonded interactions between the β-substituents and carbonyl moiety in this conformational analysis (eqs 12 and 13). Steric interactions in these aldehyde conformations are expected to be minimized when the β-alkyl substituent (R_β) is oriented *anti* to the C_α−C═O bond as in structures **D** and **G**. Therefore, conformers **E** and **I** are destablized by the *gauche* R_β↔C═O interaction. Structures **F** and **H** are also expected to become increasingly destabilized as

(20) It is not suggested that only transition states which maintain this *anti* orientation between the nucleophile and β-stereocenter are viable pathways involved in these processes. It is reasonable that transition structures possessing a *gauche* relationship between the β-stereogenic center and nucleophile should also be considered, although we propose that they contribute less to the distribution of energetically significant reaction pathways.

Table 3.[a] Relative $\Delta\Delta H$ (kcal/mol) of the Illustrated Conformations



entry	R_β	X	D	E	F	G	H	I
1	*t*-Bu	OMe	0.0	2.8	2.6	1.2	1.7	2.2
2	*t*-Bu	Cl	0.0	3.0	2.8	1.8	1.8	2.6
3	*t*-Bu	OAc	0.0	1.0	0.6	0.3	1.3	0.7
4	*t*-Bu	Me	0.1	2.2	1.2	0.0	1.3	2.1

[a] Relative energies were calculated at the semiempirical (AM1) level through a systematic conformational analysis. See ref 22.

R_β becomes larger, and the preferred alignment of this substituent *anti* to C_α−C═O thus becomes more important. When X is a polar heteroatom substituent, a destabilizing dipolar interaction between the C−X and the C═O bonds is present in structures **F** and **G**. Thus, by a process of elimination, we conclude that complementary minimization of destabilizing dipole and steric interactions favors nucleophilic addition to the exposed face of conformer **D**, affording the 1,3-*anti* diastereomer. Indeed, this conformer may also be stabilized by an attractive electrostatic interaction between the β-heteroatom substituent and the polarized carbonyl carbon.[21]

The relative conformational energies of the illustrated aldehyde complexes were investigated by semiempirical calculations (AM1).[22] A constrained 90° dihedral relationship between the carbonyl (C═O) and C_α−C_β bonds was imposed in these conformational analyses, which orients the β-stereogenic center perpendicular to the σ-framework of the carbonyl moiety in accord with the assumptions outlined above. Conformational searches were performed with full geometry optimization about the C_α−C_β bond (and C_β-X bond where applicable), and the relative energies (kcal/mol) are listed in Table 3. These calculations support the proposition that conformer **D** minimizes unfavorable interactions in substrates possessing the polar β-substituents (X = OR, halogen) (Table 3, entries 1 and 2). It is significant that the smaller energy variations calculated for the staggered rotamers of the model β-OAc aldehyde (Table 3, entry 3) are consistent with the low level of asymmetric induction noted for this substituent (cf. Table 2) relative to the other β-heteroatom substituents. *From these experimental and supporting computational data, we conclude that the nature of the oxygen protecting group employed in the reaction is an important consideration for optimal 1,3-induction.*

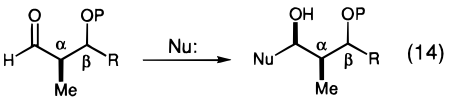
(21) For examples of potential transition state stabilization by similar electrostatic interactions: (a) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343−2346. (b) Yamamoto, Y.; Nemoto, H.; Kikuchi, R.; Komatsu, H.; Suzuki, I. *J. Am. Chem. Soc.* **1990**, *112*, 8598−8599. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117−4126. (d) Roush, W. R.; Ratz, A. M.; Jablonowski, J. A. *J. Org. Chem.* **1992**, *57*, 2047−2052.

(22) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909. These AM1 calculations were performed on the SPARTAN computational platform: Deppmeier, B. J.; Dreissen, A. J.; Hehre, W. J.; Johnson, H. C.; Leonard, J. M.; Yu, J.; Lou, L. SPARTAN SGI Version 3.1.2 GL, Wavefunction INC.: Irvine, CA.

Conclusions. The preceding analysis provides a stereochemical model for the 1,3-asymmetric induction that is in accord with the experimental data (Table 2, X = OPMB, OTBS, OAc, Cl). Elevated levels of 1,3-stereoinduction for a given β heteroatom should be observed as the steric requirements of the β-alkyl substituent (R_β) increase, and this trend is evident by comparing the data presented in Tables 1 and 2. This analysis also accounts for the low selectivity observed for aldehydes carrying sterically differentiated β substituents such as **10**. Replacement of the β-heteroatom with a methyl group (X = Me) greatly diminishes any polar interactions between the β-substituents and the carbonyl moiety. As a consequence, the energies of conformers **D** and **G**, which lead to diastereomeric products, may be similar. The AM1 level calculations support this conclusion and indicate that steric effects alone do not induce a significant carbonyl facial bias from the β-stereocenter (Table 3, entry 4).

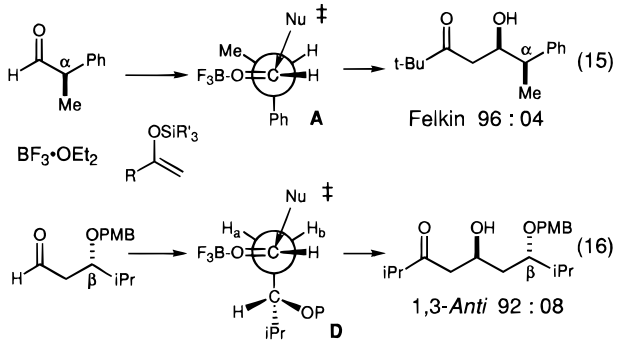
The revised 1,3-asymmetric induction model differs in a key respect from leading predictive theories for acyclic stereocontrol such as the Felkin−Anh[4a,b] and Cram−Reetz models.[7d] The relative energies between competing transition states in the latter stereochemical models are primarily based on interactions between the incoming nucleophile and the carbonyl substrate. Although intermolecular nonbonded interactions can clearly play an important role in dictating the facial selectivity of many carbonyl addition processes,[13] we propose that 1,3-stereoinduction is governed to a large extent by conformational effects that occur within the aldehyde.[23] This conclusion evolves from the assumption that steric interactions between the nucleophile and carbonyl substrate will essentially be identical during attack on either aldehyde diastereoface for competing transition states that orient the β-stereogenic center of the aldehyde *anti* to the incoming nucleophile.[20] If this is true, then the conformational preferences of the constrained ground state aldehyde geometries might also be manifest in the transition state.[24]

Merged 1,2- and 1,3-Asymmetric Induction. It is generally accepted that the stereogenic center α to the carbonyl dictates diastereofacial selectivity in nucleophilic additions to aldehydes bearing multiple stereocenters (eq 14). However, in the data

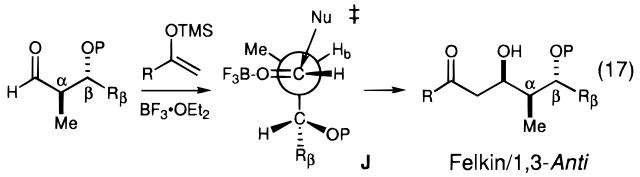


to be presented, we document cases where the β-stereocenter can exert the dominant influence on aldehyde facial selectivity by overriding the intrinsic bias imposed by the α-stereocenter. An integrated α,β-stereoinduction model that accounts for the impact of both α- and β-stereocenters is proposed by incorporating the salient features of the Felkin−Anh model and the revised 1,3-induction model presented above.

Excellent levels of selectivity are typically obtained in Mukaiyama aldol reactions with simple α-methyl-substituted chiral aldehydes (eq 15).[25] These Lewis acid promoted additions generally proceed with enhanced diastereoselectivity relative to the reactions of many standard organometallic reagents. The Felkin−Anh model **A**[4] has been invoked to account for the facial induction of these systems. As previously discussed, Mukaiyama aldol reactions also exhibit good levels of 1,3-stereoinduction with β-alkoxy aldehydes under non-chelate controlled reaction conditions (eq 16).[8] The facial bias conferred on the carbonyl moiety by the β-stereocenter is readily accommodated by the revised polar 1,3-stereoinduction model **D**. *These results suggest that there may exist stereochemical relationships between the* α *and* β *substituents that exert either complementary or opposing influences on the facial bias of the carbonyl moiety*.



For substrates bearing substituents at both the α and β positions, we propose that the Felkin−Anh and 1,3-asymmetric induction models may be integrated. For example, the merged α,β-stereoinduction model **J** is generated by replacing H_a in 1,3-stereoinduction model **D** (eq 16) with a methyl group. This affords a substrate bearing an *anti* relationship between α-methyl and β-alkoxy substituents where the relative configurations of these substituents *mutually reinforce* nucleophilic addition from the indicated aldehyde diastereoface (eq 17). This analysis leads to the conclusion that the reinforcing diastereomeric relationship found in the indicated *anti* aldehyde diastereomer should contribute to enhanced π-facial selectivity in carbonyl addition, and as a corollary, the nonreinforcing *syn* aldehyde diastereomers should exhibit either diminished or inverted selectivity (*vide infra*).



As predicted, excellent levels of diastereoselectivity are achieved in the BF_3•OEt_2 promoted Mukaiyama aldol reactions with *anti* substituted aldehydes **13** and **14** (eq 18, Table 4).[26] These results are readily accommodated by the merged α,β-stereoinduction model **J**, which predicts preferential formation of the Felkin/1,3-*anti* product diastereomer.

For the analogous *syn*-substituted aldehydes, the stereocontrol exerted individually by the α- and β-substituents directs nucleophilic addition to opposite diastereofaces of the carbonyl moiety. This arrangement of vicinal substituents is identified as a *nonreinforcing* relationship.[27] For example, substitution of a methyl group for H_b in 1,3-stereoinduction model **D** produces transition state **K** (eq 19). This structure preserves the configuration at the β-stereocenter that is important for 1,3-stereoinduction, but the problems inherent with anti-Felkin

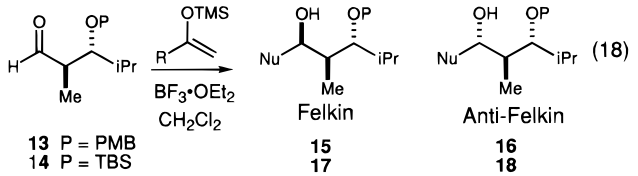
(23) Frenking and Reetz have recently postulated that conformational effects, rather than nonbonded interactions between the nucleophile and carbonyl substrate, are responsible for a significant portion of the energy difference between competing transition states involved in 1,2-stereoinduction. See ref 5f.

(24) Eurenius, K.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 9943−9946.

(25) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667−1668.

(26) For related examples: (a) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441−444. (b) Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 9065−9068. (c) Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K.-S. *Tetrahedron* **1995**, *51*, 9437−9466.

Table 4.[a] Lewis Acid Promoted Aldol Reactions of Enolsilanes with *anti*-Substituted α-Methyl-*β*-alkoxy Aldehydes (Eq 18)



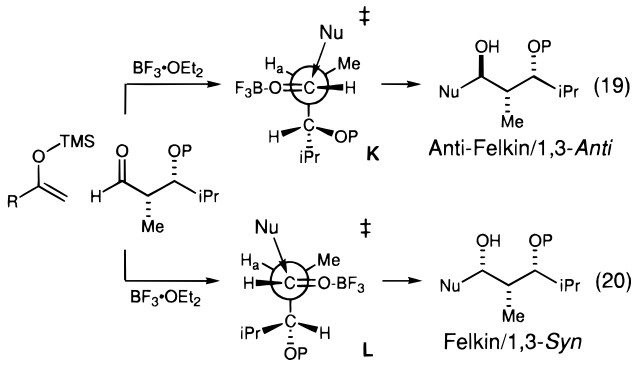
13 P = PMB
14 P = TBS

15 **17** **16** **18**

entry	R	**15**:**16** (P = PMB) (yield, %)	**17**:**18** (P = TBS) (yield, %)
A	*t*-Bu	99:01 (94)	99:01 (91)
B	*i*-Pr	98:02 (91)	95:05[b] (93)
C	Me	97:03 (86)	71:29 (85)

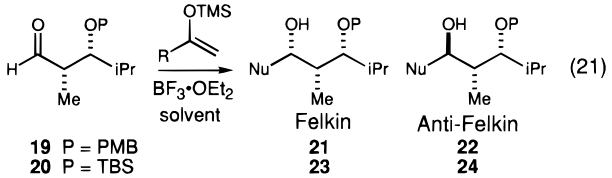
[a] See footnote *a* in Table 1. [b] Ratio was determined by integration of the ^{1}H NMR spectrum of the unpurified reaction mixture.

addition must be overcome in this transition state. On the other hand, any potential transition states affording the Felkin diastereomer, such as transition structure **L** (eq 20), must overcome the conformational preferences that dictate *β*-stereocontrol and favor formation of the 1,3-*anti* product.[28] It is clear from this simple analysis that the direction and degree of *syn* aldehyde diastereofacial selectivity cannot readily be predicted if both α and *β* stereocontrol elements are significant.



Accordingly, a wide range of stereoselectivities are observed in the BF_3•OEt_2 promoted Mukaiyama aldol additions to *syn* substituted aldehydes **19** and **20** (eq 21, Table 5). A particularly striking feature of these reactions is the dependence of aldehyde diastereofacial selectivity on the steric requirements of the enolsilane alkyl substituent (R). For *β*-OPMB aldehyde **19**, a turnover in carbonyl facial selectivity (Felkin → anti-Felkin) is observed upon decreasing the size of the enolsilane substituent **R** (*t*-Bu → Me). *This reversal in aldehyde facial induction is unprecedented and indicates that the β-stereocenter becomes the dominant control element as the steric demands of the enolsilane decrease*. To our knowledge these are the first examples of anti-Felkin selective Mukaiyama aldol reactions under conditions known to preclude chelate organization. The *β*-OPMB aldehyde **19** typically affords higher levels of 1,3-control relative to TBS-protected aldehyde **20**, and this same

Table 5.[a] Lewis Acid Promoted Aldol Reactions of Enolsilanes with *syn*-Substituted α-Methyl-*β*-Alkoxy Aldehydes (Eq 21)



19 P = PMB
20 P = TBS

21 **23** **22** **24**

entry	R	solvent	**21**:**22** (P = PMB) (yield, %)	**23**:**24** (P = TBS) (yield, %)
A	*t*-Bu	CH_2Cl_2	96:04 (89)	96:04 (93)
B	*t*-Bu	toluene	88:12 (75)	94:06 (81)
C	*i*-Pr	CH_2Cl_2	56:44 (98)	87:13 (91)
D	*i*-Pr	toluene	32:68 (86)	75:25 (83)
E	Me	CH_2Cl_2	17:83 (82)	58:42 (93)
F	Me	toluene	06:94 (92)	40:60 (95)

[a] See footnote *a* in Table 1; toluene was utilized in the indicated reactions.

stereochemical trend was observed in the additions to α-unsubstituted aldehydes (Tables 1 and 2). Furthermore, a decrease in the solvent polarity (CH_2Cl_2 → toluene) consistently provides a greater preponderance of the anti-Felkin diastereomer. The indicated solvent effects are consistent with the fact that 1,3-induction, which is based primarily on electrostatic interactions, is enhanced in nonpolar media relative to 1,2-induction, whose origins are primarily derived from nonbonded interactions in this family of substrates. The data in Table 5 illustrate that the interplay between 1,2- and 1,3-asymmetric induction is influenced by a number of factors, and conventional stereochemical models cannot be relied upon to accurately assess the facial bias associated with *syn* α,*β*-disubstituted aldehydes in these processes.

How does one explain the turnover in aldehyde diastereofacial selectivity from a 96:04 Felkin preference to a 94:06 anti-Felkin preference based on the size of the enolsilane component? *In the analysis of the stereochemical data for syn aldehyde* ***19*** *(Table 5), we conclude that dominant 1,2-stereoinduction will be found in those reactions proceeding through an antiperiplanar transition state, while dominant 1,3-stereoinduction will be manifest from a synclinal transition state*. Furthermore, it is proposed that the *antiperiplanar* transition state is favored by sterically encumbered enolsilane substituents, while the *synclinal* transition state is preferred for less bulky enolsilane substituents. The following discussion is provided to support these statements.

The aldehyde conformations depicted in structures **K** and **L** (eqs 19 and 20) have been incorporated into the Mukaiyama aldol transition states illustrated in Scheme 1. The weight of experimental evidence suggests that Mukaiyama aldol reactions proceed through open transition states[29] having either *synclinal* or *antiperiplanar* geometries, with no significant preference for either reactant orientation. By inspection, it is evident that nonbonded interactions between the enolsilane and the aldehyde α-substituent (Felkin Control) will be more significant within the subset of *antiperiplanar* transition structures. In fact, if electronic effects were to emerge as the dominant control element in a given reaction, one might expect this control element to require a synclinal reactant orientation that minimizes the impact of 1,2-induction.

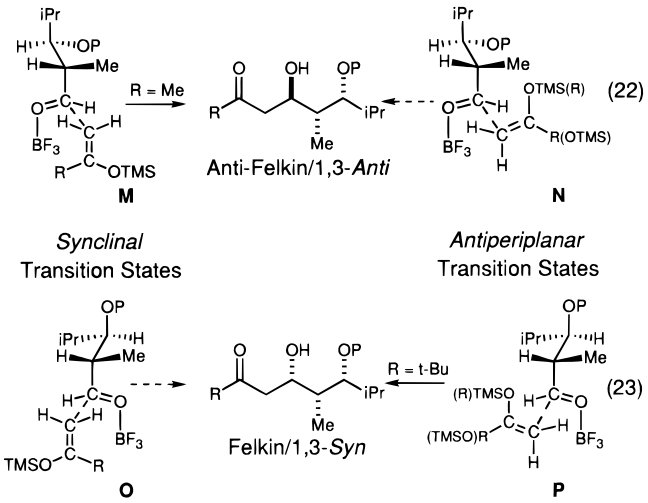
In the reactions with the pinacolone enolsilane (R = *t*-Bu), *synclinal* structures **M** and **O** are destabilized by the nonbonded

(27) The terms stereoreinforcing and nonreinforcing are explicitly distinguished from the related terms matched and mismatched. Stereoreinforcing and nonreinforcing refer to the relationship between stereocontrol elements on the same substrate, and therefore are intramolecular relationships. The terms matched and mismatched are reserved for relationships between stereocontrol elements on different substrates in double stereodifferentiating reactions, and are therefore intermolecular relationships. See: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30.

(28) Transition structure **L** may contribute largely to the formation of the Felkin/1,3-*syn* product diastereomer, because alternative structures generated by 120° rotations about the $C_\alpha-C_\beta$ bond are destabilized by nonbonded steric or dipolar interactions.

(29) For early discussions of open transition states: (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248−3249. (b) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107−7109.

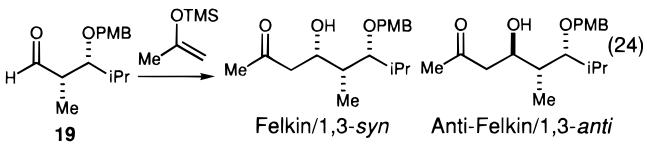
Scheme 1



interaction between the coordinated Lewis acid and *tert*-butyl substituent.[30] The destabilizing interactions in these *synclinal* orientations[31] may be alleviated upon reaction through an *antiperiplanar* transition state such as **N** or **P**. In this subset of transition states, 1,3-stereoinduction favors reaction through structure **N**. However, a consideration of steric interactions between the enol component and the aldehyde α-stereocenter in structures **N** and **P** leads to the conclusion that Felkin addition *via antiperiplanar* geometry **P** is favored. We believe that these steric interactions between the pinacolone enolsilane and the aldehyde substituents are strong enough to effectively preclude anti-Felkin addition and override the intrinsic facial bias imposed on the carbonyl by the *β*-stereocenter. Therefore, we conclude that the α-stereogenic center is the dominant control element in reactions proceeding through *antiperiplanar* transition states and addition to the Felkin aldehyde diastereoface is preferred.

As the steric demands of the enolsilane substituent R decrease (*t*-Bu → Me), the BF_3↔R interaction is attenuated in *synclinal* geometries **M** and **O**, and these geometries may become competitive with *antiperiplanar* structures.[32] In the *synclinal* transition states nonbonded interactions between the nucleophile and aldehyde α-stereocenter are significantly reduced, thereby diminishing the influence of Felkin control. This provides an opportunity for 1,3-asymmetric induction to play a more prominent role in dictating the sense of aldehyde facial selectivity. Synclinal structure **M** possesses the conformation at the *β*-stereocenter that benefits from the electrostatic effects that govern 1,3-stereoinduction (model **K**, eq 19). Therefore, we suggest that in the addition of the acetone enolsilane (R = Me), 1,3-asymmetric induction is the dominant stereochemical determinant and reaction through *synclinal* transition state **M** preferentially affords the anti-Felkin diastereomer.

Support for the Model. Based on the preceding analysis, the energies of the *synclinal* transition states relative to their *antiperiplanar* counterparts are critically dependent on the enolsilane↔Lewis acid interaction (R↔BF_3). By inspection, the *synclinal* transition state may be destabilized by an increase in either the steric bulk of the enolsilane substituent R (Me → *t*-Bu) or an increase in the size of the Lewis acid. It then follows that a more sterically encumbered Lewis acid moiety will decrease the anti-Felkin preference exhibited by the acetone enolsilane in addition to aldehyde **19**. Indeed, utilization of the sterically demanding Lewis acid trityl perchlorate[33] to catalyze the addition of the acetone enolsilane to aldehyde **19** resulted in the reversal of facial selectivity relative to the BF_3·OEt_2 mediated reaction (eq 24).[34] An 89:11 mixture of products



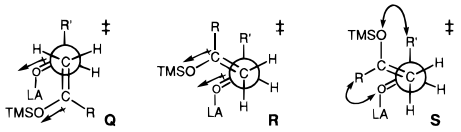
BF_3·OEt_2 / toluene	06 : 94
Ph_3CClO_4 / CH_2Cl_2	89 : 11

favoring the Felkin diastereomer was observed in the reaction catalyzed by this large Lewis acid. We postulate that reaction through a *synclinal* geometry (**M** or **O**) is now disfavored due to the enhanced nonbonded interaction between the enolsilane and the trityl moiety (R↔CPh_3).[35] Therefore, we conclude that Felkin addition through an *antiperiplanar* transition state analogous to **P** is now preferred. These data are also consistent with Heathcock's projection that increased steric requirements in the carbonyl-coordinated Lewis acid provide enhanced Felkin induction through an altered nucleophile trajectory during the addition process.[25,36]

We have also observed the above stereochemical trends in the related additions of allystannanes to these α,*β*-disubstituted aldehydes under conditions that preclude chelate organization (eqs 25 and 26).[37] For example, exclusive formation of the Felkin product was obtained in the additions of either allylstannane or *β*-methallylstannane to *anti* substituted aldehyde **13**, regardless of the Lewis acid employed (Table 6). On the other hand, dominant 1,3-stereoinduction selectively afforded the anti-Felkin isomer in the analogous BF_3·OEt_2 mediated additions to *syn* substituted aldehyde **19** (Table 7, entries A and B). As in the reaction with the acetone enolsilane, the trityl perchlorate-catalyzed process reverts the allylation of aldehyde **19** to Felkin control. These results illustrate that the integrated

(30) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037.

(31) *Synclinal* transition states **Q** and **R**, which orient the enolsilane substituent (OTMS) *syn* to the coordinated carbonyl (=O−BF_3), are energetically disfavored on the basis of electrostatic considerations. *Synclinal* structure **S** is disfavored by the indicated nonbonded interactions. (a) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707−709. (b) Reference 30. (c) Reference 9b.



(32) Nakamura, E.; Yamago, S.; Machii, D. *Tetrahedron Lett.* **1988**, *29*, 2207−2210.

(33) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759−1762. (b) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327−4330.

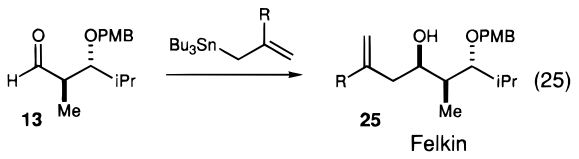
(34) The aldol product was isolated as the corresponding trimethylsilyl ether. Control experiments indicate that catalysis in this reaction is likely mediated by Ph_3CClO_4 and not by Me_3SiClO_4. For reports addressing the issue of catalysis by an active trialkylsily species in enolsilane addition reactions: (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326. (b) Reference 33b. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581.

(35) (a) Heathcock, C. H.; Walker, M. A. *J. Org. Chem.* **1991**, *56*, 5747−5750. (b) Reference 4e. (c) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99−111. (d) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655−1660.

(36) For a recent complementary study: Davis, A. P.; Plunkett, S. J. *J. Chem. Soc., Chem. Commun.* **1995**, 2173−2174.

(37) For a review of allylmetal addition reactions: (a) Yamamoto, Y.; Asoa, N. *Chem. Rev.* **1993**, *93*, 2207−2293. For recent insight into the transition state orientation of crotylstannane additions, see: (b) Marshall, J. A. *Chemtracts: Org. Chem.* **1992**, 75−98. (c) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889−7896.

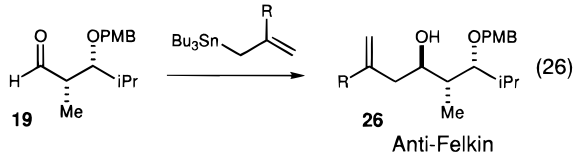
Table 6.[a] Allylstannane Addition to the *anit* Aldehyde (Eq 25)



entry	conditions	R	Felkin:*anti*-Felkin
A	$BF_3{\cdot}OEt_2$, toluene	Me	>99:1
B	$BF_3{\cdot}OEt_2$, toluene	H	>99:1
C	Ph_3CClO_4, CH_2Cl_2	H	>99:1

[a] See footnote *a* in Table 1.

Table 7.[a] Allylstannane Addition to the *syn* Aldehyde (Eq 26)

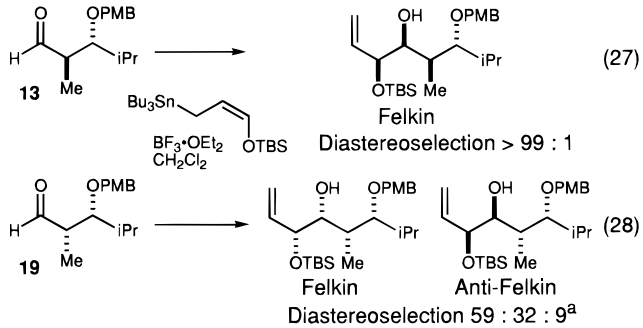


entry	conditions	R	Felkin:*anti*-Felkin
A	$BF_3{\cdot}OEt_2$, toluene	Me	20:80
B	$BF_3{\cdot}OEt_2$, toluene	H	13:87
C	Ph_3CClO_4, CH_2Cl_2	H	62:38

[a] See footnote *a* in Table 1.

α,*β*-stereoinduction models can be applied to other reactions which proceed through open transition states in direct analogy to the Mukaiyama aldol reactions.

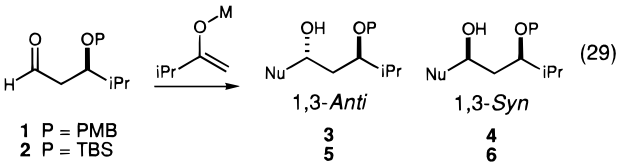
The cases examined thus far have all dealt with unsubstituted nucleophiles, such as allylmetal reagents or enolsilanes derived from methyl ketones. Based on the preceding analysis, we predict that substitution at the vinylic center of the nucleophile should increase steric interactions between the nucleophile and the α stereocenter of the aldehyde (Felkin control), thus decreasing the relative influence of 1,3-induction in determining carbonyl diastereofacial selectivity. However, in the additions of the vinylic OTBS substituted allystannane to aldehydes **13** and **19**, the effect of the *β*-stereocontrol element was still significant (eqs 27 and 28).[38] As anticipated, the addition of this allystannane to *anti* substituted aldehyde **13** resulted in extremely high Felkin selectivity. In contrast, the corresponding reaction with *syn* aldehyde **19** exhibited significantly diminished Felkin control, due to the nonreinforcing stereochemical influence of the α- and *β*-substituents.[39]



[a]The third unpictured product is the Felkin-3,4-*anti* diastereomer.

Metal Enolate Nucleophiles.[40] Of the methyl ketone aldol reaction variants examined in Tables 8 and 9 (eqs 29 and 30), the $BF_3{\cdot}OEt_2$ promoted enolsilane additions proceed with enhanced levels of 1,3-*anti* stereocontrol relative to the corresponding metal enolate mediated bond constructions. It is of interest to note that this same stereochemical trend is also manifest in the related addition reactions of allylmetal nucleophiles with *β*-heteroatom-substituted aldehydes (eq 31, Table 10).[41] In the representative allylation reactions, the additions that are mediated by $BF_3{\cdot}OEt_2$ (entries A−C) consistently exhibit higher 1,3-*anti* stereoselectivity relative to the systems in which no external Lewis acid is required to induce reactivity (entries D−G). We speculate that the positively charged transition states of Lewis acid induced carbonyl addition reactions of neutral nucleophiles are intrinsically more polar than their pericyclic metal enolate and allylmetal counterparts. Electrostatic effects clearly play a significant role in influencing the stereochemical outcome of both the aldol and allylation processes, and perhaps this stereocontrol element assumes greater importance for those reactions proceeding through more polar open transition states. Of the enolate based aldol reactions, only the lithium aldol additions displayed moderate levels of 1,3-*anti* stereoselectivity.

Table 8.[a] Aldol Reactions with *β*-Substituted Aldehydes **1** and **2** (Eq 29)



entry	metal	**3**:**4** (P = PMB) (yield, %)	**5**:**6**[b] (P = TBS) (yield, %)
A	$TMS/BF_3{\cdot}OEt_2$	92:08 (91)	80:20 (84)
B	Li	71:29 (99)	76:24 (91)
C	$TiCl_n$	60:40 (98)	58:42 (88)
D	9-BBN	42:58 (82)	52:48 (79)

[a] Reactions were carried out in CH_2Cl_2 or THF (entry B) at −78 °C. See footnote *a* in Table 1. [b] Ratios were determined by integration of the ^1H NMR spectrum of the unpurified reaction mixtures.

1,3-Asymmetric induction might also play a critical role in achiral methyl ketone lithium enolate aldol reactions with α,*β*-disubstituted aldehydes (eqs 32 and 33).[42] The lithium aldol addition reactions with *anti* substituted aldehydes **13** and **14** (eq 32) afford the expected Felkin diastereomer with modest levels of selectivity (Table 11). In contrast, the anti-Felkin diastereomer is the major product in the corresponding additions to *syn* substituted aldehydes **19** and **20** (eq 33, Table 12).[43] It is tempting to conclude that the *β*-heteroatom substituent is the dominant stereocontrol element in this series of reactions;

(38) (a) Evans, D. A.; Coleman, P. J. Unpublished results, Department of Chemistry, Harvard University. For a related investigation of 1,2- and 1,3-induction with this allylstannane: (b) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139−142.

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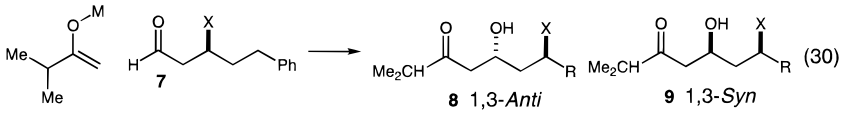
(40) (a) For a review of lithium enolates: Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 1624−1654. (b) The chlorotitanium enolates were generated by the standard procedure reported by us: Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047−1049. Boron enolates: (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 174−178. (d) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc*. **1970**, *101*, 6120−6123.

(41) (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc*. **1983**, *105*, 4833−4835. (b) Reference 19b.

(42) For a systematic investigation of lithium, titanium, and boron aldol reactions of methyl ketone enolates with complex aldehyde substrates: Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett*. **1995**, *36*, 3443−3446.

(43) For related lithium aldol reactions with *syn*-substituted aldehydes: Evans, D. A.; Gage, J. R. *Tetrahedron Lett*. **1990**, *33*, 6129−6132.

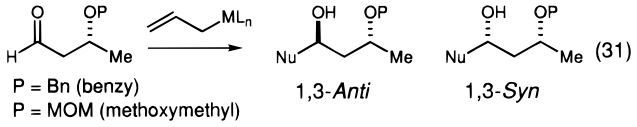
Table 9.[a] Aldehyde β-Substituent Influence on 1,3-Induction (Eq 30)



metal	**8**:**9** (**7a**, X = OPMB) (yield, %)	**8**:**9** (**7b**, X = OTBS) (yield, %)	**8**:**9** (**7d**, X = Cl) (yield, %)
TMS/BF_3•OEt_2	81:19 (87)	73:27 (90)	83:17 (84)
Li	53:47 (94)	61:39 (96)	80:20 (65)
$TiCl_n$	58:42 (84)	62:38 (93)	63:37 (75)
9-BBN	44:56 (77)	52:48 (82)	27:73 (68)

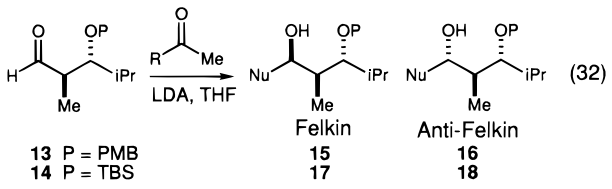
[a] All reactions were carried out at −78 °C in CH_2Cl_2 or THF (Li aldols). See footnote *a* in Table 1.

Table 10. Allylmetal Additions with β-Substituted Aldehydes (Eq 31)



entry	conditions	(P = Bn) *anti* : *syn*	(P = MOM) *anti* : *syn*	ref.
A	$SiMe_3$ BF_3•OEt_2	85 : 15		7d
B	$SnPh_3$ BF_3•OEt_2	79 : 21		15b
C	$SnMe_3$ BF_3•OEt_2		70 : 30	19b
D	$Ti(Oi\text{-}Pr)_3$	~50 : 50	47 : 53	41a,19b
E	$Ti(NEt_2)_3$	~50 : 50		41a
F	$B(OMe)_2$	63 : 37		41a
G	9-BBN		51 : 49	19b

Table 11.[a] Addition of Lithium Enolates to *anti* Aldehydes (Eq 32)

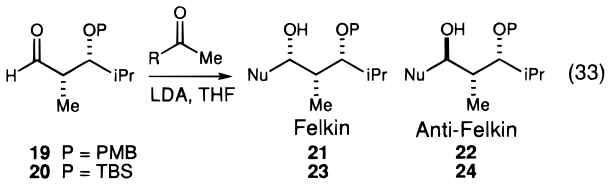


entry	R	**15**:**16** (P = PMB) (yield, %)	**17**:**18** (P = TBS) (yield, %)
A	*t*-Bu	67:33 (64)	58:42 (89)
B	*i*-Pr	72:28 (94)	65:35[b] (99)
C	Me	84:16 (78)	63:37 (94)

[a] Reactions carried out in THF at −78 °C. See footnote *a*, Table 1. [b] Ratio was determined by integration of the ^1H NMR spectrum of the unpurified reaction mixture.

however, the modest levels of induction observed with the α-unsubstituted aldehyde substrates (eq 29, Table 8) suggest that this control element is large. Further work in this area is warranted. It should also be noted that the propensity for anti-Felkin selectivity in the lithium enolate aldol reactions with *syn* substituted aldehydes (Table 12) is not observed in the more complex aldol bond constructions that have been reported in the syntheses of lonomycin A and monensin.[44] As the data reported in this manuscript illustrate, the stereogenic center proximal to the bond construction is not always the dominant stereochemical determinant governing carbonyl facial induction, and the complete architecture of the substrate should be considered. This problem can become exceedingly complex in the stereochemical analyses of reactions involving polyfunctional substrates. Therefore caution must be exercised when extending stereochemical models based on reactions of simple substrates to more complex systems.

Table 12.[a] Addition of Lithium Enolates to *syn* Aldehydes (Eq 33)



entry	R	**21**:**22** (P = PMB) (yield, %)	**23**:**24** (P = TBS) (yield, %)
A	*t*-Bu	11:89 (71)	08:92 (91)
B	*i*-Pr	14:86 (95)	13:87 (64)
C	Me	22:78 (73)	14:86 (88)

[a] Reactions carried out in THF at −78 °C. See footnote *a*, Table 1.

"Chelation Control." The principal evidence for β-heteroatom chelate organized carbonyl addition in lithium mediated aldol addition reactions has been based on product stereochemistry.[45] The documentation that β-heteroatom electronic effects afford the same predicted stereochemical outcome as the chelation addition model weakens the chelation control argument. The fact that the β-OTBS substituent[46,47] also affords the 1,3-*anti* diastereomer (Tables 8 and 9) or anti-Felkin product isomer (Table 12) with qualitatively similar levels of induction as the β-OPMB substituted aldehydes further undermines arguments for chelate organization in these reactions. Finally, neither kinetic nor stereochemical evidence has been observed for chelation in the reactions of lithium enolates in THF, even with α-alkoxy aldehydes.[48] We thus conclude that chelate organization in these addition reactions is unlikely.

(44) (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3348−3467. (b) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476−2478. (c) Fukaiyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262−263. (d) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120−2121. (e) Patel, P. V.; VanMiddlesworth, F.; Donauber, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603−4614.

(45) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526−5528.

(46) (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284. (b) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28* 279−280. (c) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697−703.

(47) Chen, X.;l Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784 and references cited therein. Evidence for the possible participation of an α-TBS ether in bidentate chelate organization is presented in this paper.

(48) (a) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302−1312. (b) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846−3856.

Conclusion

We have provided transition state models that incorporate the stereochemical impact of both α- and β-substituents of α,β-disubstituted aldehydes in Mukaiyama aldol addition reactions and related processes. Merged transition state model **J** illustrates the constructive relationship between α- and β-stereoinduction, and rationalizes the highly stereoregular nature of these processes when the α and β substituents are in the *anti* (stereoreinforcing) diastereomeric relationship as in aldehydes **13** and **14**. In contrast, when the aldehyde substituents are in the *syn* diastereomeric relationship, integration of the Felkin−Anh and 1,3-stereoinduction models (**K** and **L**) indicates that the facial bias conferred on the carbonyl from the α- and β-stereocenters is nonreinforcing. In the Mukaiyama aldol addition reactions with *syn* substituted aldehydes **19** and **20** we have proposed transition state models in which dominant Felkin control is suggested to occur through *antiperiplanar* reactant geometries, whereas dominant 1,3-induction may be achieved in reactions proceeding through *synclinal* transition states. Although this open transition model may be empirical and speculative, the stereochemical influence of many reaction parameters including nucleophile, aldehyde, Lewis acid structure, and solvent effects can all be rationalized. Dominant 1,3-stereoinduction is also apparent in the reactions of lithium enolates derived from simple methyl ketones with these aldehydes. The β-heteroatom substituent can clearly be an important stereochemical determinant and its stereochemical influence should be considered in nucleophilic addition reactions to complex aldehyde substrates.

Experimental Section

General Information.[49] Analytical gas−liquid chromatography (GLC) was performed on a Hewlett-Packard 5880A Series or 5990 Series gas chromatograph with a flame ionization detector and split mode capillary injection system, using either DB-1701, DB-1, or DX-2 fused silica columns (30 M × 0.32 mm) (J&W Scientific). Hydrogen was used as the carrier gas at the indicated pressures. For determination of diastereomeric ratios of thermally unstable aldol adducts by GLC, a sample of the unpurified product mixture was silylated (1-(trimethylsilyl)imidazole) or acetylated (acetic anhydride, pyridine) prior to analysis. All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware. Typically, all non-organometallic commercially obtained reagents were purified by distillation or recrystallization prior to use. Dichloromethane (CH_2Cl_2), triethylamine, diisopropylethylamine, and diisopropylamine were distilled from CaH_2 under an inert atmosphere of nitrogen. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from potassium/benzophenone ketyl. Methanol was distilled from $Mg(OMe)_2$. Dimethyl sulfoxide was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Isobutyraldehyde was freshly distilled from anhydrous $CaSO_4$ prior to use. 9-Borabicyclo[3.3.1]nonyl trifluoromethanesulfonate[40c,d] (9-BBN triflate) and freshly prepared samarium(II) iodide[50] were prepared according to literature procedures.

In the following paragraphs, the experimental details for the aldol reactions are followed by characterization of the aldol adducts. A general scheme for the stereochemical proof of aldol adducts is provided. A specific stereochemical proof for each aldol product is contained in the accompanying supporting information. General Procedures for the many reactions that were utilized repetitively in this investigation are also provided.

General Procedure for the $BF_3{\cdot}OEt_2$ Promoted Enolsilane Addition Reactions (Mukaiyama Aldol Reactions). Boron trifluoride etherate (1.0 equiv) was added dropwise to a 0.1 M solution of the enolsiliane (1.1 equiv) and the aldehyde (1.0 equiv) in CH_2Cl_2 at −78 °C. The reaction was stirred for the indicated amount of time, quenched at −78 °C by addition of an equivalent volume of saturated aqueous $NaHCO_3$, and then warmed to ambient temperature. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous washing was extracted once with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel chromatography. Reactions carried out in toluene were run under otherwise identical reaction conditions. Therefore, the pertinent results of these experiments may be obtained from the corresponding tables.

General Procedure for the Aldol Reactions of Lithium Enolates. The lithium diisopropylamide (LDA) was generated by addition of 1.05 equiv of *n*-butyllithium (2.5 M solution in hexanes) to a 0.1 M solution of diisopropylamine (1.1 equiv) in THF at −78 °C. After 10 min, 1.0 equiv of the indicated ketone was added dropwise and the resulting solution was stirred at −78 °C for 30 min. The aldehyde (0.9 equiv as a solution in THF) was added dropwise and the solution was stirred at −78 °C for 2 min. The reaction was quenched at −78 °C by addition of an equivalent volume of saturated aqueous NH_4Cl, and the mixture was warmed to ambient temperature. The mixture was diluted with Et_2O and washed once each with saturated aqueous NH_4Cl and brine. The aqueous washings were extracted once with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by chromatography.

General Procedure for the Aldol Reactions of Chlorotitanium Enolates. Titanium(IV) chloride (1.1 equiv) was added dropwise to a 0.1 M solution of 1.0 equiv of the ketone in CH_2Cl_2 at −78 °C, giving a yellow mixture. After 2 min, 1.2 equiv of diisopropylethylamine was added dropwise and the resulting deep red solution was stirred at −78 °C for 0.5 h. The aldehyde (0.9 equiv, as a solution in CH_2Cl_2) was added and the solution was stirred at −78 °C for the indicated amount of time. The reaction was quenched at −78 °C by addition of an equivalent volume of saturated aqueous NH_4Cl and the mixture was warmed to ambient temperature. This mixture was diluted with CH_2Cl_2 and washed once each with H_2O and saturated aqueous $NaHCO_3$. The aqueous washings were extracted once with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by chromatography.

General Procedure for the Aldol Reactions of 9-Borabicyclo-[3.3.1]nonyl (9-BBN) Enolates. To a 0.1 M solution of the ketone (1.0 equiv) in CH_2Cl_2 at −78 °C was added 1.1 equiv of 9-borabicyclo-[3.3.1]nonyl trifluoromethanesulfonate (9-BBN triflate) and 1.2 equiv of diisopropylethylamine. The resulting solution was stirred at −78 °C for 30 min and then 0.9 equiv of the aldehyde was added (as a solution in CH_2Cl_2). The solution is stirred at −78 °C for the indicated amount of time (ca. 1 h) and then quenched with 1:1 (v:v) 0.05 M pH 7 phosphate buffer and diluted with 2:1 (v:v) MeOH. After warming to 0 °C, 30% aqueous H_2O_2 (1 mL/mmol of boron Lewis acid) was added dropwise. The mixture was stirred at 0 °C for 1 h, then the volatiles were removed at aspirator pressure. The resulting residue was dissolved in Et_2O and washed with H_2O and brine. The aqueous washings were extracted with an additional portion of Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by chromatography.

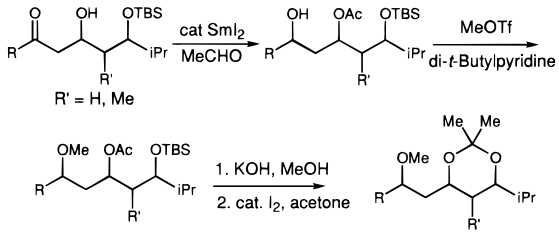
General Strategy for the Stereochemical Proofs of Aldol Addition Products Derived from β-OPMB Substituted Aldehydes: The configuration of the newly formed hydroxyl stereogenic center of these aldol adducts was established by determining its relationship to the stereocenter(s) originating from the aldehyde precursor. This strategy relied on intramolecular oxidative formation of the *p*-methoxybenzylidene acetal (PMP), which was accomplished by treatment of the PMB ether under anhydrous conditions with 2,3-dichloro-5,6-dicyanobezoquinone (DDQ).[51] Only a single diastereomer was obtained at the benzylidene acetal stereocenter in all cases. The relative stereochemistry of the acetal substituents was then ascertained by analysis of the vicinal proton coupling constants and NOE measurements. Specific stereochemical proof for all compounds, as well as full characterization of all intermediates, may be found in the supporting information.

(49) For a general discussion of the spectrometers employed and solvent drying procedures: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

(50) Girard, P.; Namy, J. K.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.

(51) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−892.

General Strategy for the Stereochemical Proofs of Aldol Addition Products Derived from *β*-OTBS Substituted Aldehydes. The configuration of the newly formed hydroxyl stereogenic center of these aldol adducts was also established by determining its relationship to the stereocenter(s) originating from the aldehyde precursor. For example, an *anti* selective Tischenko reduction[52] followed by methylation of the exposed hydroxyl moiety afforded the differentially protected triol. Selective removal of the silyl and acetate protecting groups followed by ketalization afforded the 1,3-diol acetonide. The relative stereochemistry of the dioxane substituents was then ascertained by analysis of the ^{1}H NMR spectroscopy vicinal coupling constants, NOE measurements, and ^{13}C NMR chemical shift of the acetal carbon.[53]



3-[(4-Methoxybenzyl)oxy]-4-methylpentanal (1). To a solution of 1.15 g (10.0 mmol) of 2-methyl-5-hexen-3-ol[54] in 40 mL of Et_2O at 0 °C was added 4.41 g (15.6 mmol) of the *p*-methoxybenzyl trichloroacidimidate as a solution in 5 mL of Et_2O (5 mL rinse). A catalytic amount (∼5 drops) of triflic acid was added, and the reaction was stirred for 1 h at 0 °C. The reaction was quenched with 40 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by MPLC (Michel−Miller size 11 column, 5→50% EtOAc in hexane gradient) afforded 628 mg (27%) of the desired benzyl ether as a yellow oil. To a solution of 599 mg (2.56 mmol) of the yellow oil and 4 drops of pyridine in 200 mL of CH_2Cl_2 and 70 mL of CH_3OH was added *ca*. 1 mg of sudan III indicator. The light red solution was cooled to −78 °C and a stream of ozone was passed through the reaction mixture until the solution became colorless (∼5 min). The solution was purged with O_2, then 1.88 mL (25.6 mmol) of dimethyl sulfide was added. The mixture was warmed to ambient temperature and stirred for 7 h. The volatiles were removed *in vacuo* and the residue was diluted with 40 mL of CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The layers were separated and the organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford 376 mg (66%) of aldehyde **1** as a colorless oil: IR (neat) 2080, 1724, 1612, 1514, 1486, 1248, 1173, 1083, 1034, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, J = 1.8 Hz, J = 2.7 Hz, 1 H, *H*C═O), 7.25 (m, 2 H, Ar*H*), 6.87 (m, 2 H, Ar*H*), 4.51 (d, J = 11.0 Hz, 1 H, ArC*H*), 4.44 (d, J = 11.0 Hz, 1 H, ArC*H*), 3.80 (s, 3 H, ArOCH_3), 3.76 (m, 1 H, PMBOC*H*), 2.61 (ddd, J = 2.7 Hz, J = 8.3 Hz, J = 16.3 Hz, 1 H, O═CC*H*H), 2.48 (ddd, J = 1.8 Hz, J = 3.7 Hz, J = 16.3 Hz, 1 H, O═CCH*H*), 2.01 (m, 1 H, C*H*(CH$_3$)$_2$), 0.94 (d, J = 6.9 Hz, 3 H, CH(CH_3)CH$_3$), 0.93 (d, J = 6.8 Hz, 3 H, CH(CH$_3$)CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 159.3, 130.5, 129.3, 113.8, 78.8, 71.4, 55.3, 45.0, 31.0, 18.4, 17.3. Exact mass calcd for $C_{14}H_{20}O_3$: 236.1412. Found: 236.1398 (EI).

3-((*tert*-Butyldimethylsilyl)oxy)-4-methylpentanal (2). To a solution of 1.99 g (17.4 mmol) of 2-methyl-5-hexen-3-ol and 2.64 mL (22.6 mmol) of 2,6-lutidine in 35 mL of CH_2Cl_2 at 0 °C was added 4.80 mL of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 30 min, 100 mL of H_2O was added to quench and the mixture was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 100 mL of H_2O and 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size D, 2% EtOAc in hexane) afforded 3.13 g (83%) of the silyl protected homoallylic alcohol as a colorless oil. To a solution of 2.40 g (10.5 mmol) of this olefin and 15 drops of pyridine in 200 mL of CH_2Cl_2 and 70 mL of CH_3OH was added *ca*. 4 mg of sudan III indicator. The light red solution was cooled to −78 °C and a stream of ozone was passed through the reaction mixture until the solution became colorless (*ca*. 10 min). The solution was purged with O_2, then 7.72 mL (105 mmol) of dimethyl sulfide was added. The mixture was warmed to ambient temperature and stirred for 8 h. The volatiles were removed *in vacuo* and the residue was dissolved in 250 mL of CH_2Cl_2 and 200 mL of saturated aqueous $NaHCO_3$. The layers were separated and the organic extract was washed with 200 mL of brine. The combined aqueous washings were extracted with 100 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size D, 5% EtOAc in hexane) afforded 1.79 g (74%) of the aldehyde as a colorless oil: IR (thin film) 2959, 2931, 2888, 2858, 2720, 1728, 1472, 1387, 1370, 1254, 1091, 1055, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (dd, 1 H, J = 3.0 Hz, J = 2.0 Hz), 4.00 (dt, 1 H, J = 7.2 Hz, J = 4.5 Hz), 2.49 (ddd, 1 H, J = 15.7 Hz, J = 7.2 Hz, J = 3.0 Hz), 2.39 (ddd, 1 H, J = 15.7 Hz, J = 4.4 Hz, J = 2.0 Hz), 1.76 (dseptets, 1 H, J = 6.8 Hz, J = 4.7 Hz), 0.87 (d, 3 H, J = 6.9 Hz), 0.85 (d, 3 H, J = 6.9 Hz), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 72.4, 47.2, 34.0, 25.7, 18.5, 18.0, 17.2, −4.6, −4.7. This aldehyde was too unstable to aquire high resolution mass spectral data.

Enolsilane Addition to Aldehyde 1, Table 1, Entry A. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (12 μL, 0.10 mmol), the trimethylsilyl enol ether of pinacolone (15 μL, 0.10 mmol), and the aldehyde **1** (24 mg, 0.10 mmol). The reaction was stirred for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) revealed an 11:89 ratio of diastereomers **4A** (t_r = 16.81 min) to **3A** (t_r = 18.17 min), respectively. Purification by flash chromatography (5% EtOAc in hexane) afforded 28 mg (82%) of a mixture of aldol diastereomers as a colorless oil.

(5*R,7*R**)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,8-trimethyl-3-nonanone (3A).** Ir (thin film) 3512, 2968, 2936, 2875, 2837, 1709, 1613, 1514, 1470, 1390, 1255, 1030, 840, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.4 Hz), 6.85 (d, 2 H, J = 8.8 Hz), 4.52 and 4.42 (AB, 2 H, J = 10.4 Hz), 4.22 (m, 1 H), 3.78 (s, 3 H), 3.51 (m, 1 H), 2.65 (dd, 1 H, J = 3.2 and 18 Hz), 2.56 (dd, 1 H, J = 8.4 and 18 Hz), 1.98 (m, 1 H), 1.50 (m, 2 H), 1.09 (s, 9 H), 0.92 (d, 3 H, J = 6.8 Hz), 0.89 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5, 159.2, 130.9, 129.5, 113.8, 80.6, 72.1, 64.9, 55.3, 44.3, 43.7, 36.8, 30.5, 26.3, 18.7, 17.3. Exact mass calcd for $C_{20}H_{32}O_4Na$: 359.2198. Found: 359.2204 (FAB, MNBA, added NaI).

(5*S,7*R**)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,8-trimethyl-3-nonanone (4A).** IR (thin film) 3512, 2968, 2936, 2875, 2837, 1709, 1613, 1514, 1470, 1390, 1255, 1030, 840, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2 H, J = 8.1 Hz), 6.82 (d, 2 H, J = 8.4 Hz), 4.50 and 4.33 (AB, 2 H, J = 11.1 Hz), 4.16 (m, 1 H), 3.75 (s, 3 H), 3.46 (m, 1 H), 2.65 (dd, 1 H, J = 6.9 and 17.4 Hz), 2.48 (dd, 1 H, J = 5.1 and 17.4 Hz), 2.03 (m, 1 H), 1.56 (m, 2 H), 1.07 (s, 9 H), 0.87 (d, 3 H, J = 7.2 Hz), 0.85 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 159.2, 130.4, 129.4, 113.8, 82.9, 70.6, 67.3, 55.2, 44.2, 43.6, 35.6, 29.4, 26.2, 18.3, 16.6. Exact mass calcd for $C_{20}H_{32}O_4Na$: 359.2198. Found: 359.2193 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 1, Table 1, Entry B. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (37 μL, 0.30 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (52.2 mg, 0.330 mmol), and aldehyde **1** (71 mg, 0.30 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure, affording 88 mg (91%) of a mixture of aldol diastereomers as a colorless oil. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated an 8:92 ratio of **4B** (t_r = 6.38 min) to **3B** (t_r = 6.81 min), respectively.

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Lithium Enolate Addition to Aldehyde 1, Table 8, Entry B. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (119 μL of a 2.52 M solution, 0.300 mmol), diisopropylamine (42 μL, 0.30 mmol), 3-methyl-2-butanone (32 μL, 0.30 mmol), and the aldehyde **1** (74.4 mg, 0.315 mmol, as a solution in 1 mL of THF). The reaction was quenched and isolated as described in the general lithium aldol procedure, affording 96 mg (99%) of a mixture of aldol diastereomers as a colorless oil. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated a 29:71 ratio of **4B** (t_r = 6.38 min) to **3B** (t_r = 6.80 min), respectively.

Titanium Enolate Addition to Aldehyde 1, Table 8, Entry C. The following reagents were combined in the amounts indicated according to the general procedure; titanium(IV) chloride (36 μL, 0.33 mmol), isopropyl methyl ketone (32 μL, 0.30 mmol), diisopropylethylamine (63 μL, 0.36 mmol), and the aldehyde **1** (74.4 mg, 0.315 mmol, as a solution in 0.5 mL of CH_2Cl_2). The reaction was allowed to proceed 10 min at −78 °C, quenched, and isolated as described in the general titanium aldol procedure, affording 94 mg (98%) of a colorless oil. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated a 40:60 ratio of **4B** (t_r = 6.39 min) to **3B** (t_r = 6.81 min), respectively. Purification by flash chromatography (5% EtOAc in CH_2Cl_2) afforded 40 mg (41%) of **4B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy) and 23 mg (24%) of **3B** as a colorless oil (>95% diasteromerically pure by ^{1}H NMR spectroscopy).

9-BBN Enolate Addition to Aldehyde 1, Table 8, Entry D. The following reagents were combined in the amounts indicated according to the general procedure: 9-BBN triflate (745 μL of a 0.5 M solution in hexane, 0.372 mmol), 3-methyl-2-butanone (36 μL, 0.34 mmol), diisopropylethylamine (71 μL, 0.41 mmol), and the aldehyde **1** (80 mg, 0.34 mmol, as a solution in 0.5 mL of CH_2Cl_2). The reaction was allowed to proceed 15 min then subjected to the standard isolation procedure. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated a 58:42 ratio of **4B** (t_r = 6.57 min) to **3B** (t_r = 7.01 min), respectively. Purification by flash chromatography (30% EtOAc in hexane) afforded 90 mg (82%) of a mixture of the two diastereomers (58:42 by ^{1}H NMR spectroscopy).

(5*R,7*R**)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,8-dimethyl-3-nonanone (3B).** IR ($CHCl_3$) 3508 (br), 3007, 2964, 2875, 1701, 1612, 1514, 1466, 1249, 1063, 1036, 907 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 9.5 Hz, 2 H, Ar*H*), 6.88 (d, J = 8.6 Hz, 2 H), 4.54 (d, J = 10.8 Hz, 1 H), 4.46 (d, J = 10.8 Hz, 1 H), 4.28 (m, 1 H), 3.80 (s, 3 H), 3.53 (m, 1 H), 3.42 (d, J = 3.2 Hz, 1 H), 2.58 (m, 3 H), 2.00 (m, 1 H), 1.54 (m, 2 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 159.2, 130.9, 129.5, 113.8, 80.7, 72.0, 64.9, 55.3, 47.2, 41.4, 36.7, 30.5, 18.7, 18.0, 17.3. Exact mass calcd for $C_{19}H_{30}O_4Na$: 345.2042. Found: 345.2061 (FAB, MNBA, added NaI).

(5*S,7*R**)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,8-dimethyl-3-nonanone (4B).** IR ($CHCl_3$) 3472 (br), 3008, 2967, 2936, 1705, 1612, 1514, 1466, 1386, 1368, 1303, 1250, 1066, 1036, 824 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 2 H), 6.86 (m, 2 H), 4.56 (d, J = 10.9 Hz), 4.37 (d, J = 10.9 Hz), 4.21 (m, 1 H), 3.80 (d, J = 1.7 Hz), 3.80 (s, 3 H), 3.52 (m, 1 H), 2.65 (dd, J = 7.5 Hz, J = 16.9 Hz), 2.57 (septet, J = 6.9 Hz, 1 H), 2.49 (dd, J = 4.8 Hz, J = 16.9 Hz), 2.09 (m, 1 H), 1.59 (m, 2 H), 1.08 (d, J = 6.9 Hz, 6 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 159.3, 130.4, 129.4, 113.9, 83.0, 70.6, 67.4, 55.2, 47.3, 41.4, 35.6, 29.4, 18.3, 17.9, 16.5. Exact mass calcd for $C_{19}H_{30}O_4$: 322.2144. Found: 322.2159 (EI).

Enolsilane Addition to Aldehyde 1, Table 1, Entry C. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (8 μL, 68 μmol), the trimethylsilyl enol ether of acetone (11 μL, 68 μmol), and the aldehyde **1** (16 mg, 68 μmol). The reaction was stirred for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) revealed a 91:9 ratio of the diastereomers **3C** (t_r = 18.96 min) and **4C** (t_r = 20.75 min), respectively. Purification by flash chromatography (5% EtOAc in hexane) afforded 18 mg (89%) of a mixture of the aldol diastereomers as a colorless oil.

(4*R,6*R**)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-7-methyl-2-octanone (3C).** IR (thin film) 3510, 2961, 2361, 1705, 1514, 1470, 1390, 1255, 1030, 840, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.4 Hz), 6.85 (d, 2 H, J = 8.5 Hz), 4.52 and 4.42 (AB, 2 H, J = 10.8 Hz), 4.25 (m, 1 H), 3.77 (s, 3 H), 3.45 (m, 1 H), 2.54 (d, 2 H, J = 6.4 Hz), 2.12 (s, 3 H), 1.98 (m, 1 H), 1.50 (m, 2 H), 0.90 (d, 3 H, J = 7.8 Hz), 0.87 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 159.2, 130.8, 129.5, 113.8, 80.6, 71.9, 64.8, 55.2, 50.5, 36.4, 30.7, 30.4, 18.7, 17.3. Exact mass calcd for $C_{17}H_{26}O_4$: 294.1831. Found: 294.1821 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 2, Table 1, Entry A. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (45 μL, 0.37 mmol), the trimethylsilyl enol ether of acetone (72 mg, 0.55 mmol), and aldehyde **1** (85 mg, 0.37 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure, affording 84 mg (79%) of a mixture of aldol diastereomers as a colorless oil. Silylation and GLC analysis (DB-1701, 155 °C, 10 psi) indicated an 16:84 ratio of **6A** (t_r = 14.80 min) to **5A** (t_r = 15.19 min), respectively. Purification by flash chromatography (20% EtOAc in hexane) afforded a sample of product **5A** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) as a colorless oil.

(5*R,7*R**)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-2,2,8-trimethyl-3-nonanone (5A).** IR (thin film) 3512 (br), 2958, 2930, 2857, 1699, 1412, 1387, 1368, 1252, 1074, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (m, 1 H), 3.77 (q, 1 H, J = 5.3 Hz), 3.46 (d, 1 H, J = 2.5 Hz), 2.63 (d, 2 H, J = 6.6 Hz), 1.82 (m, 1 H), 1.46 (m, 2 H), 1.13 (s, 9 H), 0.89 (s, 9 H), 0.87 (d, 3 H, J = 7.0 Hz), 0.86 (d, 3 H, J = 6.9 Hz), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1, 74.0, 64.5, 44.3, 44.1, 38.4, 33.4, 26.3, 25.9, 18.7, 18.1, 17.0, −4.5, −4.5. Exact mass calcd for $C_{18}H_{39}O_3Si$: 331.2668. Found: 331.2665 (CI, NH_3 atmosphere).

Enolsilane Addition to Aldehyde 2, Table 1, Entry B. The following reagents were combined in the amounts indicated according to the general silyl enol ether aldol procedure: boron trifluoride etherate (96 μL, 0.78 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (124 mg, 0.783 mmol), and the aldehyde **2** (180 mg, 0.781 mmol). The reaction was allowed to proceed for 10 min at −78 °C, quenched, and isolated as described in the general procedure. The silylated or acetylated diastereomer derivatives were not adequately resolved by GLC analysis. Therefore, diastereomeric ratios were determined by integration of the H*H*OH carbinol methine signals at 4.15 and 4.25 ppm for **6B** and **5B**, respectively. ^{1}H NMR spectrum of the unpurified reaction mixture revealed an 80:20 ratio of **5B**:**6B**. Purification by MPLC (Michel−Miller column size C, 2.5% EtOAc in CH_2Cl_2) provided 150 mg (61%) of **5B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 30 mg (12%) of a mixture of diastereomers, and 27 mg (11%) of **6B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Lithium Enolate Addition to Aldehyde 2, Table 8, Entry B. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (334 μL, 0.835 mmol) of a 2.50 M solution in hexanes, diisopropylamine (117 μL, 0.835 mmol), isopropyl methyl ketone (89 μL, 0.80 mmol), and the aldehyde **2** (175 mg, 0.759 mmol, as a solution in 0.40 mL of THF). The ^{1}H NMR spectrum of the unpurified reaction mixture revealed a 76:24 ratio of **5B**:**6B**. Purification by MPLC (Michel−Miller column size C, 2.5% EtOAc in CH_2Cl_2) provided 130 mg (62%) of **5B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 33 mg (16%) of a mixture of diastereomers, and 28 mg (13%) of **6B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Titanium Enolate Addition to Aldehyde 2, Table 8, Entry C. The following reagents were combined in the amounts indicated according to the general procedure: titanium(IV) chloride (80 μL, 0.73 mmol), isopropyl methyl ketone (71 μL, 0.66 mmol), diisopropylethylamine (138 μL, 0.794 mmol), and the aldehyde **2** (160 mg, 0.694 mmol, as a solution in 0.30 mL of CH_2Cl_2). The reaction was allowed to proceed 30 min at −78 °C, quenched, and isolated as described in the general titanium aldol procedure. ^{1}H NMR spectroscopy of the unpurified reaction mixture revealed a 58:42 ratio of **5B**:**6B**. Purification by

MPLC (Michel−Miller column size C, 10% EtOAc in hexane) provided 184 mg (88%) of a mixture of the aldol isomers as a colorless oil.

9-BBN Enolate Addition to Aldehyde 2, Table 8, Entry D. The following reagents were combined in the amounts indicated according to the general 9-BBN aldol procedure: 9-BBN triflate (1.46 mL, 0.727 mmol, as a 0.5 M solution in hexanes), 3-methyl-2-butanone (71 μL, 0.66 mmol), diisopropylethylamine (138 μL, 0.794 mmol), and the aldehyde **2** (160 mg, 0.694 mmol, as a solution in 0.30 mL of CH_2Cl_2). The reaction was allowed to proceed 20 min at −78 °C then subjected to the standard isolation procedure. ^{1}H NMR spectroscopy of the unpurified reaction mixture revealed a 52:48 ratio of **5B**:**6B**. Purification by MPLC (Michel−Miller column size C, 10% EtOAc in hexane) provided 166 mg (79%) of a mixture of the aldol isomers as a colorless oil.

(5*R,7*R**)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,8-dimethyl-3-nonanone (5B).** IR (thin film) 3510 (br), 2958, 2931, 2895, 2858, 1706, 1471, 1386, 1252, 1069, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (m, 1 H), 3.75 (m, 1 H), 3.43 (br s, 1 H), 2.66−2.54 (m, 3 H), 1.82 (m, 1 H), 1.51−1.43 (m, 2 H), 1.10 (d, 6 H, J = 7.0 Hz), 0.89 (s, 9 H), 0.87 (d, 6 H, J = 6.9 Hz), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 74.2, 64.5, 47.6, 41.4, 38.3, 33.3, 25.9, 18.7, 18.1, 17.9, 17.1, −4.5, −4.5. Exact mass calcd for $C_{17}H_{36}O_3SiNa$: 339.2331. Found: 339.2337 (FAB, MNBA, added NaI).

(5*S,7*R**)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,8-dimethyl-3-nonanone (6B).** IR (thin film) 3504 (br), 2959, 2931, 2872, 2858, 1707, 1612, 1471, 1386, 1252, 1050, 1036, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15, (m, 1 H), 3.75 (m, 1 H), 3.44 (br s, 1 H), 3.63−2.54 (m, 3 H), 1.80 (dseptets, 1 H, J = 6.9 Hz, J = 3.9 Hz), 1.61−1.47 (m, 2 H), 1.09 (d, 6 H, J = 7.0 Hz), 0.88 (s, 9 H), 0.88 (d, 3 H, J = 6.8 Hz), 0.81 (d, 3 H, J = 6.9 Hz), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 75.6, 66.4, 47.2, 41.4, 38.3, 32.8, 25.9, 18.0, 17.9, 17.6, 17.0, −4.3, −4.5. Exact mass calcd for $C_{17}H_{36}O_3SiNa$: 339.2331. Found: 339.2337 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 2, Table 1, Entry C. The following reagents were combined in the amounts indicated according to the general silyl enol ether aldol procedure: boron trifluoride etherate (107 μL, 0.87 mmol), the trimethylsilyl enol ether of pinacolone (165 mg, 0.955 mmol), and the aldehyde **2** (200 mg, 0.870 mmol). The reaction was allowed to proceed for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 170 °C, 10 psi) revealed a 93:7 ratio of **5C**:**6C**, respectively. Purification by MPLC (Michel−Miller column size C, 5% EtOAc in hexane) provided 232 mg (81%) of **5C** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy) and 16 mg (6%) of **6C** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

(4*R,6*R**)-6-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-7-methyl-2-octanone (5C).** IR (thin film) 3486 (br), 2957, 2930, 2895, 2857, 1712, 1472, 1386, 1361, 1078, 1051, 836, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (m, 1 H), 3.73 (q, 1 H, J = 5.2 Hz), 3.41 (d, 1 H, J = 2.5 Hz), 2.57 (m, 2 H), 2.12 (s, 3 H), 1.83 (m, 1 H), 1.46 (m, 2 H), 0.88 (s, 9 H), 0.86 (d, 3 H, J = 6.9 Hz), 0.85 (d, 3 H, J = 6.8 Hz), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 74.4, 64.5, 51.0, 38.2, 33.2, 30.7, 25.9, 18.8, 18.0, 17.1, −4.5, −4.5. Exact mass calcd for $C_{15}H_{33}O_3Si$: 289.2199. Found: 289.2204 (EI).

Preparation of Aldehydes 7a−7d: 3-Hydroxy-5-phenyl-*N*-methoxy-*N*-methylpentanamide. Lithium diisopropylamide (LDA) was generated by addition of 373 μL (5.82 mmol) of *n*-butyllithium (1.56 M solution in hexanes) to a solution of 815 μL (5.82 mmol) of diisopropylamine in 28 mL of THF at −78 °C. After 10 min, a solution of 600 mg (5.82 mmol) of *N*-acetyl-*N*,*O*-dimethylhydroxylamine in 0.75 mL of THF was added dropwise (0.25 mL THF rinse) and the resulting solution was stirred at −78 °C for 30 min. Then 845 μL (6.98 mmol) of isobutyraldehyde was added dropwise and the solution was stirred at −78 °C for 10 min. The reaction was quenched at −78 °C by the addition of saturated aqueous NH_4Cl, and the mixture was warmed to ambient temperature. The mixture was diluted with Et_2O and washed once each with saturated aqueous NH_4Cl and brine. The aqueous washings were extracted once with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size C, 60−70% EtOAc in hexane) provided 1.12 g (81%) of the title compound as a colorless oil. IR (film) 3476 (br), 3064, 3013, 2940, 1641, 1496, 1454, 1423, 1390, 1001, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5 H), 4.04 (m, 1 H), 3.90 (br s, 1 H), 3.67 (s, 3 H), 3.18 (s, 3 H), 2.86 (m, 1 H), 3.75−2.62 (m, 3 H), 2.48 (m, 1 H), 1.89 (m, 1 H), 1.74 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.6, 141.9, 128.3, 128.2, 125.6, 67.0, 61.1, 38.1, 31.7. Exact mass calcd for $C_{13}H_{20}O_3N$: 237.1365. Found: 237.1358 (EI).

3-[(4-Methoxybenzyl)oxy]-5-phenylpentanal (7a). To a solution of 300 mg (1.26 mmol) of the alcohol and 464 mg (1.64 mmol) of the *p*-methoxybenzyl trichloroacidimidate in 6.3 mL of Et_2O at room temperature was added 10 μL of trifluoromethanesulfonic acid. After 10 min, the reaction was diluted with 40 mL of saturated aqueous $NaHCO_3$ and 40 mL of Et_2O. The layers were separated and the organic extract was washed with 30 mL of saturated aqueous $NaHCO_3$. The combine aqueous washings were extracted with 40 mL of Et_2O. The combine organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size B, 20→40% EtOAc in hexane) provided 325 mg (72%) of the desired benzyl ether as a colorless oil. To a solution of 600 mg (1.68 mmol) of the amide in 8 mL of THF at −78 °C was added 1.34 mL (2.01 mmol) of a 1.5 M solution of DIBAL-H in toluene. After stirring at −78 °C for 30 min, the solution was transferred into a 1:1 mixture of Et_2O:1 M aqueous HCl (40 mL at 0 °C). The mixture was allowed to warm to ambient temperature and stirred for 30 min, and then the layers were separated. The organic extract was washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size B, 30% EtOAc in hexane) provided 428 mg (85%) of aldehyde **7a** as a colorless oil: IR (thin film) 3061, 3026, 2934, 2836, 1723, 1612, 1586, 1513, 1454, 1302, 1248, 1034, 822, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, 1 H, J = 2.2 Hz), 7.33−7.15 (m, 7 H), 6.92−6.89 (m, 2 H), 4.49 (s, 2 H), 3.98 (m, 1 H), 3.81 (s, 3 H), 2.80−2.57 (m, 4 H), 2.06−1.85 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 159.3, 141.5, 130.1, 129.8, 129.4, 128.4, 128.3, 125.9, 113.8, 73.2, 70.9, 55.2, 48.2, 36.1, 31.3.

3-((*tert*-Butyldimethylsilyl)oxy)-5-phenylpentanal (7b). To a solution of 803 mg (3.38 mmol) of the alcohol and 512 μL (4.40 mmol) of 2,6-lutidine in 11 mL of CH_2Cl_2 at 0 °C was added 933 μL (4.06 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 30 min, 25 mL of H_2O was added to quench and the mixture was extracted with two 25-mL portions of CH_2Cl_2. The combined organic extracts were washed with 25 mL of H_2O and 25 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size C, 25% EtOAc in hexane) afforded 1.15 g (96%) of the protected amide as a colorless oil. To a solution of 781 mg (2.22 mmol) of the Weinreb amide in 8 mL of THF at −78 °C was added 1.34 mL (2.44 mmol) of a 1.5 M solution of DIBAL-H in toluene. After stirring at −78 °C for 30 min, the solution was transferred into a 1:1 mixture of Et_2O:1 M aqueous HCl (40 mL at 0 °C). The mixture was allowed to warm to ambient temperature and the layers were separated. The organic extract was washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size B, 10% EtOAc in hexane) provided 428 mg (85%) of aldehyde **7b** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, 1 H, J = 2.4 Hz), 7.33−7.26 (m, 2 H), 7.23−7.17 (m, 3 H), 4.27 (m, 1 H), 2.72−2.55 (m, 4 H), 1.91−1.85 (m, 2 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 141.7, 128.4, 128.3, 125.9, 67.7, 50.7, 39.5, 31.4, 25.9, 18.0, −4.5, −4.7.

3-Acetoxy-5-phenylpentanal (7c). To a solution of 989 mg (4.17 mmol) of the alcohol, 590 μL (6.25 mmol) of acetic anhydride, and 929 μL (6.67 mmol) of triethylamine in 8 mL of CH_2Cl_2 at ambient temperature was added a catalytic amount (∼5 mg) of dimethylaminopyridine. The solution was stirred for 4 h at ambient temperature then diluted with 50 mL of Et_2O. This was washed with two 30-mL portions of saturated aqueous NH_4Cl. The organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size B, 50% EtOAc in hexane) provided 1035 mg (97%) of the desired acetate as a colorless oil. To a solution of 780 mg (2.79 mmol) of the Weinreb amide in 28 mL of THF at −78 °C was added 1.86 mL (2.79 mmol) of a 1.5 M solution of DIBAL-H

in toluene. After stirring at −78 °C for 15 min, the solution was transferred into a 1:1 mixture of Et_2O:1 M aqueous HCl (40 mL of 0 °C). The mixture was allowed to warm to ambient temperature and the layers were separated. The organic extract was washed with 30 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford 579 mg (94%) of the aldehyde **7c** as a colorless oil. The ^{1}H NMR spectrum of the unpurified reaction mixture shows only the desired aldehyde: IR (film) 3027, 2933, 2859, 2735, 1737, 1603, 1496, 1454, 1374, 1240, 1047, 751, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (dd, 1 H, J = 2.7 Hz, J = 1.7 Hz), 7.31−7.15 (m, 5 H), 5.33 (m, 1 H), 2.74−2.59 (m, 4 H), 2.04−1.86 (m, 2 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 170.4, 140.7, 128.4, 128.2, 125.8, 68.6, 48.0, 35.7, 31.6, 20.8.

3-Chloro-5-phenyl-*N*-methoxy-*N*-methylpentanamide. To a solution of 1.09 g (4.59 mmol) of the β-hydroxyamide in 15.3 mL of a 1:1 solution of MeCN/CCl_4 at 0 °C was added 1.57 g (5.97 mmol) of triphenylphosphine.[55] The colorless solution was stirred at 0 °C for 8 h, then diluted with 40 mL of CH_2Cl_2 and washed with 40 mL of H_2O. The aqueous phase was extracted with 20 mL of CH_2Cl_2. The combined organic extracts were washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size C, 25% EtOAc in hexane) provided 973 mg (83%) of the desired β-chloroamide as a white solid and 146 mg (12%) of the α,β-unsaturated amide as a colorless oil. Data for the β-chloroamide: IR ($CHCl_3$) 3065, 3014, 2970, 2940, 1654, 1496, 1454, 1390, 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.19 (m, 5 H), 4.41 (m, 1 H), 3.69 (s, 3 H), 3.20 (s, 1 H), 3.08 (m, 1 H), 2.93 (m, 1 H), 2.81−2.70 (m, 2 H), 2.15 (m, 1 H), 2.04 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 140.8, 128.5, 128.5, 126.1, 61.3, 57.7, 40.9, 39.9, 32.7, 32.0. Exact mass calcd for $C_{13}H_{29}NO_2Cl$: 256.1109. Found: 256.1098 (EI).

3-Chloro-5-phenylpentanal (7d). To a solution of 256 mg (1.00 mmol) of the Weinreb amide in 5 mL of THF at −78 °C was added 800 μL (1.20 mmol) of a 1.5 M solution of DIBAL-H in toluene. After stirring at −78 °C for 10 min, the solution was transferred into a 1:1 mixture of Et_2O:1 M aqueous HCl (40 mL at 0 °C). The mixture was stirred for 10 min at 0 °C then the layers were separated. The organic extract was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 195 mg (99%) of the aldehyde **7d** as a light yellow oil. The aldehyde is extremely unstable and must be used immediately: ^{1}H NMR (400 MHz, C_6D_6) δ 9.12 (br s, 1 H), 7.22−6.98 (m, 5 H), 3.88 (m, 1 H), 2.70−2.42 (m, 2 H), 2.29 (m, 1 H), 1.90 (m, 1 H), 1.70−1.50 (m, 2 H). This aldehyde was found to be too unstable for further characterization.

Enolsilane Addition to Aldehyde 7a.[56] The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (41 μL, 0.34 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (58 mg, 0.37 mmol), and aldehyde **7a** (100 mg, 0.335 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 250 °C, 15 psi) indicated a 19:81 ratio of the 1,3-*syn* adduct (t_r = 14.86 min) to the 1,3-*anti* isomer (t_r = 15.74 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) afforded 67 mg (52%) of **8a** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 35 mg (27%) of a mixture of diastereomers, and 10 mg (8%) of **9a** as a colorless oil (>95% diastereomerically pure by ^{1}H spectroscopy).

(5*R,7*S**)-5-Hydroxy-7-[(4-methoxybenzyl)oxy]-2-methyl-9-phenyl-3-nonanone (8a).** IR (thin film) 3486 (br), 3061, 3026, 2933, 2871, 1706, 1612, 1586, 1513, 1465, 1302, 1249, 1068, 1035, 822, 734, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 4 H), 7.21−7.16 (m, 3 H), 6.90−6.86 (m, 2 H), 4.53 (d, 1 H, J = 10.9 Hz), 4.46 (d, 1 H, J = 10.9 Hz), 4.32 (m, 1 H), 3.80 (s, 3 H), 3.75 (m, 1 H), 3.44 (br s, 1 H), 2.71−2.51 (m, 5 H), 2.01−1.82 (m, 2 H, $PhCH_2CH_2$), 1.76−1.58 (m, 2 H), 1.11 (d, 3 H, J = 6.9 Hz), 1.10 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 159.3, 142.2, 130.5, 129.6, 128.4, 128.3, 128.3, 125.8, 113.8, 75.3, 71.2, 64.9, 55.3, 47.1, 40.5, 35.8, 31.4, 18.0, 18.0. Exact mass calcd for $C_{24}H_{32}O_4Na$: 407.2198. Found: 407.2192 (FAB, MNBA, added NaI).

(55) For a review of this transformation: Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.

(5*S,7*S**)-5-Hydroxy-7-[(4-methoxybenzyl)oxy]-2-methyl-9-phenyl-3-nonanone (9a).** IR (thin film) 3477 (br), 3062, 3026, 2934, 2871, 1707, 1612, 1586, 1514, 1454, 1302, 1249, 1064, 1034, 821, 751, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.16 (m, 7 H), 6.92−6.86 (m, 2 H), 4.53 (d, 1 H, J = 14.2 Hz), 4.42 (d, 1 H, J = 14.2 Hz), 4.32 (m, 1 H), 3.80 (s, 3 H), 3.70 (m, 1 H), 3.66 (br s, 1 H), 2.71−2.48 (m, 5 H), 1.97−1.89 (m, 2 H), 1.83 (m, 1 H), 1.58 (m, 1 H), 1.09 (d, 6 H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 159.2, 142.0, 130.2, 129.5, 128.4, 128.3, 128.1, 125.8, 113.8, 78.0, 70.2, 66.6, 47.0, 41.4, 40.3, 35.2, 31.0, 17.9, 17.9. Exact mass calcd for $C_{24}H_{32}O_4Na$: 407.2198. Found: 407.2200 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 7b.[56] The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (32 μL, 0.26 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (45 mg, 0.28 mmol), and aldehyde **7b** (75 mg, 0.26 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 200 °C, 15 psi) indicated a 27:73 ratio of **9b** (t_r = 17.68 min) to **8b** (t_r = 18.04 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) afforded 87 mg (90%) of a mixture of aldol diastereomers. All attempts to separate aldol adducts **8b** and **9b** were unsuccessful.

(5*R,7*S**)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2-methyl-9-phenyl-3-nonanone (8b).** IR (thin film) 3505 (br), 3062, 3027, 2953, 2930, 2857, 1706, 1603, 1496, 1471, 1384, 1255, 1069, 1035, 836, 776, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 2 H), 7.21−7.16 (m, 3 H), 4.34 (m, 1 H), 4.05 (m, 1 H), 3.58 (br d, 1 H, J = 2.3 Hz), 2.71−2.54 (m, 5 H), 1.88 (m, 2 H), 1.63 (m, 2 H), 1.11 (d, 6 H, J = 6.9 Hz), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{1}13C NMR (100 MHz, $CDCl_3$) δ 215.2, 142.3, 128.4, 128.3, 125.7, 69.8, 64.5, 55.3, 47.5, 42.0, 41.4, 38.9, 31.5, 31.3, 25.8, 18.0, −4.5, −4.7.

(5*S,7*S**)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2-methyl-9-phenyl-3-nonanone (9b).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 2 H), 7.21−7.16 (m, 3 H), 4.19 (m, 1 H), 4.01 (m, 1 H), 3.47 (br d, 1 H, J = 2.2 Hz), 2.71−2.54 (m, 5 H), 1.85−1.65 (m, 4 H), 1.11 (d, 3 H, J = 6.9 Hz), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H).

Enolsilane Addition to Aldehyde 7c.[56] The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (34 μL, 0.28 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (53 mg, 0.33 mmol), and aldehyde **7c** (61 mg, 0.28 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Analysis by analytical HPLC (Zorbax, 20% EtOAc in hexane) indicated a 43:57 mixture of **8c**:**9c**, respectively. Purification by MPLC (Michel−Miller column size B, 40% EtOAc in hexane) afforded 67 mg (79%) of a mixture of aldol diastereomers. A related experiment afforded 125 mg of a mixture of aldol diastereomers which was purified by MPLC (Michel−Miller column size B, 10% EtOAc in hexane) affording 47 mg (31%) of **8c** (diastereomerically pure by ^{1}H NMR spectroscopy), 48 mg (31%) of a mixture of isomers, and 30 mg (20%) of aldol adduct **9c** (diastereomerically pure by ^{1}H NMR spectroscopy).

(5*R,7*S**)-7-Acetoxy-5-hydroxy-2-methyl-9-phenyl-3-nonanone (8c).** IR (thin film) 3505 (br), 3065, 3028, 2971, 2934, 1736, 1712, 1604, 1454, 1375, 1247, 1038, 911, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (m, 2 H), 7.20−7.13 (m, 3 H), 5.13 (m, 1 H), 4.02 (m, 1 H), 3.37 (br d, 1 H, J = 3.6 Hz), 2.72−2.48 (m, 5 H), 2.06 (s, 3 H), 2.01−1.81 (m, 2 H), 1.70−1.60 (m, 2 H), 1.11 (d, 3 H, J = 6.9 Hz), 1.09 (d, 3 H, J 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 171.7, 141.3, 128.4, 128.3, 125.9, 71.0, 64.0, 46.7, 41.7, 41.5, 36.5, 31.8, 21.1, 17.9, 17.9. Exact mass calcd for $C_{18}H_{27}O_4$: 307.1909. Found: 307.1912 (CI).

(5*S,7*S**)-7-Acetoxy-5-hydroxy-2-methyl-9-phenyl-3-nonanone (9c).** IR (thin film) 3496 (br), 3062, 3027, 2969, 2934, 2874, 1734, 1710, 1603, 1454, 1373, 1244, 1030, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2 H), 7.21−7.15 (m, 3 H), 5.05 (m, 1 H), 4.08 (m, 1 H), 3.30 (br d, 1 H, J = 3.4 Hz), 2.75−2.48 (m, 5 H), 2.03 (s, 3 H,

(56) Standard procedures were utilized for the metal enolate mediated aldol addition reactions with this aldehyde substrate. The diastereomeric ratios and isolated yields for the combined mixtures of isomers are contained in Table 9.

$CH_3C{=}O$), 1.98−1.85 (m, 3 H), 1.64 (m, 1 H), 1.09 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 170.9, 141.4, 128.4, 128.3, 125.9, 71.3, 65.1, 46.1, 41.4, 40.7, 36.1, 31.7, 21.2, 18.0, 17.9. Exact mass calcd for $C_{18}H_{27}O_4$: 307.1909. Found: 307.1908 (CI).

Enolsilane Addition to Aldehyde 7d.[56] The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (41 μL, 0.34 mmol), the trimethylsilyl enol ether of 3-methyl-2-butanone (58 mg, 0.37 mmol), and the freshly prepared aldehyde **7d** (100 mg, 0.335 mmol). The reaction was stirred for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GC/MS analysis (DB-1701, 220 °C, 15 psi) indicated a 17:83 ratio of **9d** (t_r = 7.38 min) to **8d** (t_r = 8.70 min), respectively. Purification by MPLC (Michel−Miller column size B, 20% EtOAc in hexane) afforded 78 mg (84%) of a mixture of an inseparable mixture of aldol diastereomers as a colorless oil.

(5*S,7*S**)-7-Chloro-5-hydroxy-2-methyl-9-phenyl-3-nonanone (8d).** IR (thin film) 3472 (br), 3062, 3027, 2969, 2933, 2874, 1706, 1603, 1496, 1454, 1384, 1288, 1257, 1095, 1030, 836, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2 H), 7.23−7.17 (m, 3 H), 4.37 (m, 1 H), 4.24 (m, 1 H), 3.31 (br d, 1 H, $J = 2.5$ Hz), 2.91 (m, 1 H), 2.75 (m, 1 H), 3.69−2.51 (m, 3 H), 2.07−1.97 (m, 2 H), 1.86 (m, 2 H), 1.69 (m, 1 H), 1.11 (d, 6 H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 141.0, 128.4, 128.4, 126.0, 64.7, 59.6, 46.5, 45.1, 41.4, 40.8, 32.7, 18.0, 17.9.

(5*R,7*S**)-7-Chloro-5-hydroxy-2-methyl-9-phenyl-3-nonanone (9d).** ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2 H), 7.23−7.17 (m, 3 H), 4.24 (m, 1 H), 4.06 (m, 1 H), 3.29 (br s, 1 H), 2.91 (m, 1 H), 2.75 (m, 1 H), 2.69−2.51 (m, 3 H), 2.20−2.02 (m, 2 H), 1.85 (m, 2 H), 1.69 (m, 1 H), 1.10 (d, 6 H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 141.0, 128.4, 128.4, 126.0, 65.2, 59.4, 45.8, 44.6, 40.8, 39.4, 32.5, 17.9, 17.9.

3,4,4-Trimethyl-5-hexenal (10). To a solution of 2.85 g (13.5 mmol) of 3-methyl-2-butene phenylsulfone in 100 mL of THF at −78 °C was added 9.46 mL (13.5 mmol) of a 1.43 M solution of *sec*-butyllithium. After 10 min at −78 °C, (*E*)-crotonaldehyde (2.24 mL, 27.1 mmol) was added and the solution was warmed to 0 °C. After 20 min at 0 °C, the reaction was quenched by the addition of 25 mL of saturated aqueous $NaHCO_3$. The mixture was diluted with 300 mL of ether, and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, affording a yellow oil. Purification by flash chromatography (30% EtOAc in hexane) afforded 3.29 g (87%) of the pure 5-hydroxy-2-methyl-4-(phenylsulfonyl)-2,6-octadiene as a 3:1 mixture of diastereomers by ^1H NMR spectroscopy. This material was reduced according to the procedure of Inomata and coworkers.[57] Thus the allylic phenylsulfone (3.650 g, 13.0 mmol) was dissolved in 150 mL of THF and cooled to −23 °C. To this solution was added 32.5 mL (65.1 mmol) of a 2.0 M solution of $LiBH_4$. After 15 min at −23 °C, a cooled (−23 °C) solution of 914 mg (1.3 mmol) of palladium dichloride bis(triphenylphosphine) in 65 mL was added and the solution was stirred at −23 °C for 24 h. An additional 914 mg (1.3 mmol) of palladium dichloride bis(triphenylphosphine) was added and the solution was stirred an additional 24 h at −23 °C. The reaction was then quenched at −23 °C with 15 mL of MeOH, then 20 mL of saturated aqueous NH_4Cl. The mixture was warmed to ambient temperature and diluted with 150 mL of ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated *in vacuo*. Purification by flash chromatography afforded 1.29 g (71%) of 5-hydroxy-2-methyl-2,6-octadiene as a colorless oil. This material was dissolved in 10 mL of THF and added *via cannula* to a suspension of 553 mg (13.8 mmol) of KH and 4.50 g (18.4 mmol) of 18-crown-6 in 150 mL of THF at ambient temperature. The suspension was then heated to 50 °C for 13 h, cooled to 0 °C, and quenched by the dropwise addition of 10 mL of saturated aqueous NH_4Cl. The mixture was diluted with 50 mL of ether, washed sequentially with 150 mL of saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography afforded 768 mg (60%) of the aldehyde as a colorless oil: IR ($CHCl_3$) 3084, 2970, 1721, 1639, 1602, 1463, 1415, 1377, 1007, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (dd, 1 H, $J = 1.1$ Hz, $J = 3.0$ Hz), 5.75 (dd, 1 H, $J = 10.8$ Hz, $J = 17.5$ Hz), 4.98 (dd, 2 H, $J = 10.7$ Hz, $J = 16.2$ Hz), 2.54 (dd, 1 H, $J = 2.5$ Hz, $J = 16.1$ Hz), 2.09 (ddd, 1 H, $J = 3.1$ Hz, $J = 10.2$ Hz, $J = 16.5$ Hz), 1.99 (m, 1 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 0.90 (d, 3 H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 146.9, 111.9, 47.1, 39.1, 36.4, 24.8, 22.7, 15.2. Exact mass calcd for $C_9H_{16}O$: 140.1201. Found: 140.1203 (EI).

Enolsilane Addition to Aldehyde 10. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: the aldehyde **10** (67 mg, 0.48 mmol), the trimethylsilyl enol ether of 2-methyl-3-pentanone (84 mg, 0.53 mmol), and $BF_3{\cdot}OEt_2$ (59 μL, 0.48 mmol). After 10 min at −78 °C, the reaction was quenched and the products isolated as described in the general procedure, yielding 96.0 mg (88%) of the mixture of aldol diastereomers as a clear oil. ^1H NMR spectroscopy indicated the absence of starting materials or impurities, only the aldol products **11**:**12** in a 58:42 ratio, respectively. Purification of 54 mg of a related mixture by flash chromatography (30% Et_2O in hexane) afforded 10.5 mg of diastereomer **11** (diastereomerically pure by ^1H NMR spectroscopy) and 5.0 mg of diastereomer **12** (diastereomerically pure by ^1H NMR spectroscopy).

(5*R,7*R**)-5-Hydroxy-7,8,8-trimethyl-9-decen-3-one (11).** IR ($CHCl_3$) 3556 (br), 2972, 2938, 2977, 1700, 1467, 1386, 1302, 1094, 1040, 1007 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (dd, 1 H, $J = 10.9$ Hz, $J = 17.5$ Hz), 4.93 (dd, 2 H, $J = 10.8$ Hz, $J = 15.3$ Hz), 4.08 (m, 1 H), 3.03 (dd, 1 H, $J = 1.3$ Hz, $J = 3.5$ Hz), 2.59 (m, 3 H), 1.63 (m, 2 H), 1.11 (d, 3 H), 1.10 (d, 3 H, $J = 7.0$ Hz), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.87 (d, 3 H, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 147.9, 110.8, 65.5, 47.6, 41.4, 39.3, 38.6, 37.3, 24.6, 23.1, 18.0, 18.0, 13.9. Exact mass calcd for $C_{14}H_{26}O_2Na$: 249.1830. Found: 249.1837 (FAB, MNBA, added NaI).

(5*S,7*R**)-5-Hydroxy-7,8,8-trimethyl-9-decen-3-one (12).** IR ($CHCl_3$) 3542 (br), 3083, 2972, 2936, 2247, 1700, 1467, 1386, 1299, 1097, 1048, 1007 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (dd, 1 H, $J = 10.8$ Hz, $J = 17.4$ Hz), 4.94 (dd, 1 H, $J = 1.4$ Hz, $J = 12.2$ Hz), 4.91 (dd, 1 H, $J = 1.4$ Hz, $J = 17.5$ Hz), 4.02 (m, 1 H), 2.67 (dd, 1 H, $J = 2.3$ Hz, $J = 17.7$ Hz), 2.59 (sept, 1 H, 6.9 Hz), 2.44 (dd, 1 H, $J = 9.3$ Hz, $J = 17.7$ Hz), 1.55 (m, 1 H), 1.23 (m, 2 H), 1.10 (d, 6 H, $J = 6.9$ Hz), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.88 (d, 3 H, $J = 6.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3, 147.6, 111.2, 67.6, 46.0, 41.5, 39.6, 39.3, 38.7, 24.5, 23.0, 18.0, 18.0, 15.2. Exact mass calcd for $C_{14}H_{26}O_2Na$: 249.1830. Found: 249.1839 (FAB, MNBA, added NaI).

(2*R*,3*R*)-2,4-Dimethyl-3-[(4-methoxybenzyl)oxy]pentanal (13). To a solution of titanium(IV) chloride (5.08 mL, 46.3 mmol) in 250 mL of CH_2Cl_2 at 0 °C was added 4.59 mL (15.4 mmol) of titanium(IV) isopropoxide. After 5 min, 12.0 g (51.4 mmol) of the propionyl (4*R*)-oxazolidinone (as a solution in 50 mL of CH_2Cl_2) was added, resulting in a yellow solution with a white precipitate. After 5 min, 10.8 mL (61.7 mmol) of diisopropylethylamine was added and the resulting deep red enolate solution was stirred at 0 °C for 1 h. In a separate flask, freshly distilled isobutyraldehyde (9.34 mL, 103 mmol) was added to a solution of diethylaluminum chloride (69.0 mL of a 25.4% solution in THF, 129 mmol) in 100 mL of CH_2Cl_2 at −78 °C. After 15 min the enolate solution was cooled to −78 °C and the aldehyde solution was added *via* cannula, rinsing with two 10-mL portions of CH_2Cl_2. After 1.5 h the reaction was quenched at −78 °C by addition of 30 mL of saturated aqueous NH_4Cl (gas evolution). The mixture was slowly warmed to ambient temperature with the addition of an additional 1 L of saturated aqueous NH_4Cl. After stirring 2 h at ambient temperature the aluminum salts were dissolved by the addition of 120 mL of 3 M aqueous HCl. The aqueous layer was extracted with two additional 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 300 mL of saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated *in vacuo* HPLC analysis (DuPont Zorbax, 30% EtOAc in hexane) of the unpurified mixture indicated 10% of unreacted propionyl oxazolidinone (t_f = 3.55 min), and a 71:29 mixture of the 2*S*,3*S*-diastereomer (t_r = 4.17 min) and the minor 2*S*,3*R*-diastereomer (t_r = 5.00 min), respectively. Purification by flash chromatography (15% EtOAc in hexane) afforded 1.05 g (9%) of the propionyl oxazolidinone, 9.13 g (58%) of the 2*S*,3*S*-diastereomer as a white crystalline solid (≥97% diastereomerically pure by ^1H NMR spectroscopy), and 4.00 g (25%) of the 2*S*,3*R*-diastereomer as a white crystalline

(57) Inomata, K.; Igarashi, S.; Mohri, M.; Yamamoto, T.; Kinoshita, H.; Kotake, H. *Chem. Lett.* **1987**, 707−710.

solid. To a solution of 8.32 g (27.3 mmol) of the *anti* substituted (2*S*,3*S*)-*β*-hydroxyimide and 1.16 mL (27.3 mmol) of MeOH in 91 mL of THF at 0 °C was slowly added 13.6 mL (27.3 mmol) of a 2.0 M solution of $LiBH_4$ in THF (gas evolution). After being stirred for 1 h at 0 °C the reaction mixture was quenched by the addition of 125 mL of 1.0 M aqueous sodium potassium tartrate and stirred for an additional 20 min. The mixture was then diluted with 200 mL of CH_2Cl_2 and 100 mL of 1.0 M aqueous sodium potassium tartrate. The layers were separated and the aqueous layer was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This provided 8.25 g of a mixture of the chiral auxiliary and the desired diol as a white solid. To a solution of this white solid and 5.96 g (32.7 mmol) of the dimethylacetal of anisaldehyde in 110 mL of CH_2Cl_2 at ambient temperature was added 5 mg (catalytic amount) of *p*-toluenesulfonic acid. After 2 h the reaction was diluted with 150 mL of CH_2Cl_2 and 150 mL of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4,a nd concentrated *in vacuo*. The white solid was purified by MPLC (Michel−Miller column size D, 10% EtOAc in hexane) to provide 5.42 g (79%) of the benzylidene acetal as a colorless oil. To a solution of 3.15 g (12.6 mmol) of the benzylidene acetal in 63.0 mL of CH_2Cl_2 at 0 °C was added 21.0 mL (31.5 mmol) of a 1.5 M solution of DIBAL-H in toluene. After 1 h the solution was transferred by cannula into a rapidly stirring mixture of 200 mL of 1:1 CH_2Cl_2:1 N aqueous HCl at 0 °C. The mixture was stirred for 30 min at ambient temperature then the layers were separated. The aqueous phase was extracted with two 75-mL portions of CH_2Cl_2. The combined organic extracts were washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 3.15 g (99%) of the 3-benzyl alcohol as a colorless oil. To a solution of 105 μL (1.20 mmol) of oxalyl chloride in 4.5 mL of CH_2Cl_2 at −78 °C was added 170 μL (2.4 mmol) of DMSO (gas evolution). After 10 min, a solution of 252 mg (1.00 mmol) of the alcohol in 0.50 mL of CH_2Cl_2 was added. The cloudy white mixture was stirred for 15 min then 697 μL (5.00 mmol) of triethylamine was added. The reaction was stirred at −78 °C for 40 min then quenched by the addition of 5 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature then diluted with 30 mL of CH_2Cl_2 and 30 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with two 15-mL portions of CH_2Cl_2. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR spectroscopy of the unpurified aldehyde was very clean. Purification by MPLC (Michel−Miller column size B, 15% EtOAc in hexane) provided 239 mg (95%) of aldehyde **13** as a colorless oil: $[\alpha]_D^{22}$ −44.9° (*c* 1.32, $CHCl_3$); IR (thin film) 2964, 2936, 2875, 2836, 2724, 1723, 1613, 1586, 1514, 1465, 1386, 1302, 1249, 1037, 823, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (d, 1 H, J = 2.2 Hz), 7.26−7.23 (m, 2 H), 6.89−6.86 (m, 2 H), 4.50 (AB, 2 H, J_{AB} = 10.8 Hz, $\Delta\nu$ = 20.4 Hz, CH_2Ar), 3.80 (s, 3 H), 3.40 (t, 1 H, J = 5.6 Hz), 2.67 (ddd, 1 H, J = 7.3 Hz, J = 5.6 Hz, J = 2.2 Hz), 1.94 (octet, 1 H, J = 6.8 Hz), 1.11 (d, 3 H, J = 7.0 Hz), 0.99 (d, 3 H, J = 6.7 Hz), 0.94 (d, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 159.3, 130.5, 129.2, 113.8, 85.7, 73.8, 55.2, 48.9, 30.9, 19.5, 17.8, 11.4. Exact mass calcd for $C_{15}H_{22}O_3Na$: 273.1467. Found 273.1452 (FAB, MNBA, added NaI).

(2*R*,3*R*)-2,4-Dimethyl-3-((*tert*-butyldimethylsilyl)oxy)pentanal (14). To a solution of 7.36 g (24.1 mmol) of the *β*-hydroxyimide used in the preparation of **13** in 100 mL of THF at 0 °C was added 3.37 mL (28.9 mmol) of 2,6-lutidine and 6.09 mL (26.5 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 15 min at 0 °C the reaction was quenched by the addition of 5 mL of MeOH. After an additional 5 min the reaction was washed with 100 mL of pH 4 aqueous $NaHSO_4$ and 100 mL of saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* yielding 10.11 g (100%) of the pure material as a white crystalline solid, which was carried on without purification. To a solution of 3.21 mL (43.4 mmol) of ethanethiol in 120 mL of THF at −78 °C was added 13.5 mL (33.7 mmol) of a 2.5 M solution of butyllithium in hexanes. After 10 min the solution was warmed to 0 °C, and 10.11 g (24.09 mmol) of the silyl-protected aldol adduct was added *via* cannula, as a solution in 10 mL of THF. After 15 min at 0 °C, the reaction was quenched by the slow addition of 50 mL of H_2O. The organic layer was extracted, and the aqueous layer was washed with an additional 30 mL of Et_2O. The combined organic layers were washed wtih brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc in hexane) afforded 10.89 g (92%) of the pure thioester as a colorless oil. The column was flushed (33% EtOAc in CH_2Cl_2) affording 3.74 g (87%) of the recovered oxazolidinone. To a solution of 6.74 g (22.1 mmol) of the thioester in 240 mL of acetone at ambient temperature was added 3.50 g (3.30 mmol) of 10% palladium on carbon. To this well-stirred mixture was slowly added 5.30 mL (33.2 mmol) of triethylsilane (gas evolution). After 10 min, an additional 5.30 mL of triethylsilane was added. After 45 min the reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue was purified by flash chromatography (50% CH_2Cl_2 in hexane) affording 5.19 g (96%) of the aldehyde *ent*-**4** as a colorless liquid; $[\alpha]_D^{21}$ +35.7° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 2959, 2858, 1719, 1472, 1389, 1258, 1038, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, J = 2.5 Hz, 1 H, *H*C═O), 3.67 (dd, J = 4.1 Hz, J = 5.0 Hz, 1 H, TBSOC*H*), 2.53 (m, 1 H, C*H*C═O), 1.84 (m, 1 H, C*H*(CH_3)$_2$), 1.10 (d, J = 7.1 Hz, 3 H, CH(C*H*$_3$)C═O), 0.92 (d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)CH$_3$), 0.90 (d, J = 6.9 Hz, 3 H, CH(CH$_3$)C*H*$_3$), 0.89 (s, 9 H, SIC(C*H*$_3$)$_3$), 0.07 (s, 3 H, SiC*H*$_3$), 0.06 (s, 3 H, SiC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 79.2, 49.9, 32.9, 25.9, 18.8, 18.2, 12.0, −4.1, −4.3. This material proved too unstable to obtain a high resolution mass spectral analysis.

Enolsilane Addition to Aldehyde 13, Table 4, Entry A. The following reagents were combined in the amounts indicated according to the general enolsilane addition procedure: boron trifluoride etherate (38 μL, 0.32 mmol), pinacolone trimethylsilyl enol ether (50 μL, 0.32 mmol), and aldehyde **13** (80 mg, 0.32 mmol). The reaction was allowed to proceed for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) indicated the presence of a single isomer **15A** (t_r = 14.21 min). Purification by flash chromatography (10% EtOAc in hexane) provided 105 mg (94%) of **15A** as a colorless oil.

Lithium Enolate Addition to Aldehyde 13, Table 11, Entry A. The following reagents were combined the the amounts indicated according to the general procedure: butyllithium (28 μL of a 1.45 M solution, 0.40 mmol), diisopropylamine (56 μL, 0.40 mmol), pinacolone (50 μL, 0.40 mmol), and the aldehyde **13** (100 mg, 0.40 mmol, as a solution in THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the general lithium aldol procedure. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) indicated a 67:33 ratio of **15A** (t_r = 14.21 min) to **16A** (t_r = 12.29 min), respectively. Purification by flash chromatography (10% EtOAc in hexane) provided 90 mg (64%) of a mixture of aldol diastereomers as a colorless oil.

(5*R*,6*S*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,6,8-tetramethyl-3-nonanone (15A). $[\alpha]^{23}_D$ −12.3° (*c* 1.5, CH_2Cl_2); IR (CH_2Cl_2) 3508 (br), 2968, 1700, 1614, 1515, 1465, 1249, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.7 Hz), 6.83 (d, 2 H, J = 8.4 Hz), 4.57 and 4.53 (AB, 2 H, J = 11.1 Hz), 4.47 (m, 1 H), 3.77 (s, 3 H), 3.50 (d, 2 H, J = 1.2 Hz), 3.22 (t, 1 H, J = 6.0 Hz), 2.67 (dd, 1 H, J = 7.5 Hz, J = 17.4 Hz), 2.55 (dd, 1 H, J = 5.1 Hz, J = 17.4 Hz), 1.99 (m, 1 H), 1.70 (m, 1 H), 1.11 (s, 9 H), 1.00 (d, 3 H, J = 6.6 Hz), 0.96 (d, 3 H, J = 6.6 Hz), 0.95 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 216.5, 159.3, 129.4, 113.9, 88.7, 75.8, 66.5, 55.3, 44.4, 41.3, 39.3, 30.8, 26.4, 20.3, 17.7, 11.1. Exact mass calcd for $C_{21}H_{34}O_4Na$: 373.2355. Found: 373.2352 (FAB, MNBA, added NaI).

(5*S*,6*S*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,6,8-tetramethyl-3-nonanone (16A). $[\alpha]^{23}_D$ −40.9° (*c* 0.75, CH_2Cl_2); IR (CH_2Cl_2) 3508 (br), 2969, 1693, 1613, 1514, 1466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2 H), 6.85 (m, 2 H), 4.51 and 4.45 (AB, 2 H, J = 10.4 Hz), 4.22 (m, 1 H), 3.77 (s, 3 H), 3.11 (t, 1 H, J = 5.6 Hz), 2.79 (dd, 1 H, J = 2.4 Hz, J = 17.6 Hz), 2.54 (dd, 1 H, J = 9.6 Hz, J = 17.6 Hz), 1.95 (m, 1 H), 1.87 (m, 1 H), 1.06 (s, 9 H), 0.98 (d, 3 H, J = 6.8 Hz), 0.95 (d, 3 H, J = 6.8 Hz), 0.92 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 217.8, 159.1, 130.9, 129.1, 113.7, 87.6, 74.6, 68.8, 55.3, 44.4, 40.6, 40.3, 31.1, 26.2, 20.4, 17.8, 13.4. Exact mass calcd for $C_{21}H_{34}O_4Na$: 373.2355. Found: 373.2361 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 13, Table 4, Entry B. The following reagents were combined in the amounts indicated according to the general silyl enol ether aldol procedure: boron trifluoride etherate (37 μL, 0.30 mmol), the enol ether (52.2 mg, 0.330 mmol), and the aldehyde **13** (75 mg, 0.30 mmol). The reaction was allowed to proceed for 30 min at −78 °C, quenched, and isolated as described in the general Mukaiyama aldol procedure, affording 96 mg (95%) of a colorless oil. The ^{1}H NMR spectrum of the unpurified reaction mixture indicated no unreacted starting material, and the pure major diastereomer. Silylation and GLC analysis (DB-1, 190 °C, 10 psi) indicated a 2:98 ratio of the 5*S*-diastereomer **16B** (t_r = 9.64 min) and the 5*R*-diastereomer **15B** (t_r = 10.82 min), respectively. Purification of a related 31:69 mixture of **16B**:**15B** by flash chromatography (8% EtOAc, 32% CH_2Cl_2 in hexane) afforded 99 mg (60%) of the **15B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy), and 58 mg (31%) of **16B** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Lithium Enolate Addition to Aldehyde 13, Table 11, Entry B. The following reagents were combined in the amounts indicated according to the general procedure: methyllithium (210 μL of a 1.43 M solution, 0.300 mmol), diisopropylamine (42 μL, 0.30 mmol), isopropyl methyl ketone (32 μL, 0.30 mmol), and the aldehyde **13** (79 mg, 0.32 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 10 min, quenched, and isolated as described in the general lithium aldol procedure, affording 95 mg (94%) of a colorless oil. Silylation and GLC analysis (DB-1, 190 °C, 10 psi) indicated a 28:72 ratio of **16B** (t_r = 9.64 min) and **15B** (t_r = 10.82 min), respectively.

(5*R*,6*S*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,6,8-trimethyl-3-nonanone (15B). $[\alpha]^{23}_D$ 1.7° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 3476 (br), 2971, 1704, 1613, 1466, 1385, 1302, 1250, 1174, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.59 (d, J = 10.4 Hz, 1 H), 4.55 (d, J = 10.4 Hz, 1 H), 4.50 (m, 1 H), 3.79 (s, 3 H), 3.46 (d, J = 1.5 Hz, 1 H), 3.21 (t, J = 5.8 Hz, 1 H), 2.69 (dd, J = 8.3 Hz, J = 17.0 Hz, 1 H), 2.60 (sept, J = 7.0 Hz, 1 H), 2.49 (dd, J = 4.7 Hz, J = 17.0 Hz, 1 H), 2.02 (m, 1 H), 1.72 (m, 1 H), 1.09 (d, J = 7.0 Hz, 6 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 159.3, 130.7, 129.4, 113.9, 89.0, 75.7, 66.6, 55.3, 45.1, 41.4 38.7, 30.8, 20.2, 18.1, 17.9, 17.9, 11.3. Exact mass calcd for $C_{20}H_{32}O_4$: 336.2300. Found: 336.2310 (EI).

(5*S*,6*S*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,6,8-trimethyl-3-nonanone (16B). $[\alpha]^{23}_D$ −41.5° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3489 (br), 3011, 2969, 2935, 1710, 1613, 1514, 1466, 1364, 1249, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.54 (d, J = 10.6 Hz, 1 H), 4.50 (d, J = 10.6 Hz, 1 H), 4.23 (m, 1 H), 3.80 (s, 3 H), 3.54 (d, J = 2.3 Hz, 1 H), 3.14 (dd, J = 5.0 Hz, J = 6.4 Hz, 1 H), 2.69 (dd, J = 2.5 Hz, J = 16.9 Hz, 1 H), 2.56 (m, 2 H), 1.93 (m, 2 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.06 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.9, 159.2, 130.8, 129.2, 113.8, 87.9, 74.6, 69.3, 55.2, 44.0, 41.5, 40.8, 31.2, 20.5, 18.0, 17.9, 17.5, 13.7. Exact mass calcd for $C_{20}H_{32}O_4Na$: 359.2198. Found: 359.2202 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 13, Table 4, Entry C. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (20 μL, 0.12 mmol), acetone trimethylsilyl enol ether (16 μL, 0.12 mmol), and the aldehyde **22** (30 mg, 0.12 mmol). The reaction was allowed to proceed for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) indicated a 3:97 ratio of anti-Felkin isomer **16C** (t_r = 10.23 min) to the Felkin diastereomer **15C** (t_r = 11.28 min), respectively. Purification by flash chromatography (10% EtOAc in hexane) provided 31 mg (86%) of **15C** as a colorless oil.

Lithium Enolate Addition of Aldehyde 13, Table 11, Entry C. The following reagents were combined in the amounts indicated according to the general lithium aldol procedure: butyllithium (280 μL of a 1.45 M solution, 0.400 mmol), diisopropylamine (56 μL, 0.40 mmol), acetone (30 μL, 0.40 mmol), and the aldehyde **13** (100 mg, 0.400 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 5 min, quenched, and isolated as described in the general lithium aldol procedure, affording 96 mg (78%) of a colorless oil. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) indicated a 16:84 ratio of **16C** (t_r = 11.39 min) and **15C** (t_r = 12.54 min), respectively.

(4*R*,5*S*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-2-octanone (15C). $[\alpha]^{23}_D$ −6.9° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) 3482 (br), 2966, 2964, 2361, 1710, 1613, 1514, 1464 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.24 (m, 2 H), 6.86−6.84 (m, 2 H), 4.58 and 4.51 (AB, 2 H, J = 10.2 Hz), 4.46 (m, 1 H), 3.77 (s, 3 H), 3.43 (s, 1 H), 3.19 (t, 1 H, J = 5.4 Hz), 2.68 (dd, 1 H, J = 8.7 Hz, J = 16.5 Hz), 2.39 (dd, 1 H, J = 4.2 Hz, J = 16.5 Hz), 2.15 (s, 3 H), 2.00 (m, 1 H), 1.69 (m, 1 H), 0.98 (m, 9 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.8, 159.2, 130.5, 129.4, 113.8, 89.2, 75.7, 66.6, 55.2, 48.4, 38.5, 30.8, 30.7, 20.1, 18.0, 11.4. Exact mass calcd for $C_{18}H_{28}O_4Na$: 331.1885. Found: 331.1874 (FAB, MNBA, added Na).

Enolsilane Addition to Aldehyde 14, Table 4, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (48 μL, 0.39 mmol), pinacolone trimethylsilyl enol ether (93 μL, 0.43 mmol), and the aldehyde **14** (96 mg, 0.39 mmol). The reaction was allowed to proceed for 30 min at −78 °C, quenched, and isolated as described in the general procedure. Acetylation and GLC analysis (DB-1701, 180 °C, 10 psi) revealed the presence of a single aldol diastereomer (t_r = 14.03 min). Purification by MPLC (Michel−Miller column size B, 10% EtOAc in hexane) provided 123 mg (91%) of **17A** (>99% pure by GLC analysis) as a colorless oil.

Lithium Enolate Addition to Aldehyde 14, Table 11, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (284 μL of a 2.52 M solution in hexanes, 0.716 mmol), diisopropylamine (105 μL, 0.722 mmol), pinacolone (85 μL, 0.682 mmol), and the aldehyde **14** (150 mg, 0.614 mmol, as a solution in THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the general lithium aldol procedure. Silylation and GLC analysis (DB-1701, 180 °C, 10 psi) indicated a 58:42 ratio of **17A**:**18A**. Purification by MPLC (Michel−Miller column size C, 5→10% EtOAc in hexane) afforded 92 mg (44%) of **17A** (diastereomerically pure by ^{1}H NMR spectroscopy), 64 mg (30%) of a mixture of diastereomers, and 32 mg (15%) of **18A** (diastereomerically pure by ^{1}H NMR spectroscopy), all as colorless oils.

(5*R*,6*S*,7*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,2,6,8-tetramethyl-3-nonanone (17A). $[\alpha]^{22}_D$ −1.1° (*c* 2.10, CH_2Cl_2); IR (film) 3507 (br), 2960, 2858, 1704, 1474, 1387, 1368, 1255, 1052, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (br t, 1 H, J = 6.4 Hz), 3.52 (d, 1 H, J = 1.0 Hz), 3.47 (dd, 1 H, J = 5.8 Hz, J = 4.3 Hz), 2.64 (dq, 2 H, J = 17.8 Hz, J = 7.1 Hz), 1.94 (octet, 1 H, J = 6.8 Hz), 1.68 (m, 1 H), 1.12 (s, 9 H), 0.96 (d, 3 H, J = 6.9 Hz), 0.93 (d, 3 H, J = 6.8 Hz), 0.91 (d, 3 H, J = 6.4 Hz), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 82.4, 66.7, 44.3, 41.4, 38.2, 31.8, 26.3, 26.2, 19.7, 18.5, 18.4, 11.6, −3.7, −3.8. Exact mass calcd for $C_{19}H_{41}O_3$: 345.2825. Found: 345.2836 (CI, NH_3 atmosphere).

(5*S*,6*S*,7*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,2,6,8-tetramethyl-3-nonanone (18A). $[\alpha]^{22}_D$ −44.6° (*c* 2.80, CH_2Cl_2); IR (film) 3456 (br), 2959, 2931, 2856, 1697, 1472, 1387, 1388, 1367, 1252, 1052, 836, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (br t, 1 H, J = 8.1 Hz), 3.51 (t, 1 H, J = 4.8 Hz), 3.44 (br s, 1 H), 2.75 (dd, 1 H, J = 17.7 Hz, J = 2.3 Hz), 2.54 (dd, 1 H, J = 17.7 Hz, J = 9.3 Hz), 1.90−1.77 (m, 2 H), 1.14 (s, 9 H), 0.91 (s, 9 H), 0.91 (d, 3 H, J = 6.4 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 0.87 (d, 3 H, J = 7.1 Hz), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 79.5, 68.8, 44.4, 42.1, 40.5, 31.9, 26.4, 26.2, 20.2, 18.3, 18.2, 13.3, −3.9, −4.1. Exact mass calcd for $C_{19}H_{41}O_3$: 345.2825. Found: 345.2814 (CI, NH_3 atmosphere).

Enolsilane Addition to Aldehyde 14, Table 4, Entry B. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (37 μL, 0.30 mmol), isopropyl methyl ketone trimethylsilyl enol ether (52 mg, 0.33 mmol), and the aldehyde **14** (73 mg, 0.30 mmol). The reaction was allowed to proceed for 50 min at −78 °C, quenched, and isolated as described in the general procedure, affording 92 mg (93%) of a colorless oil. The ^{1}H NMR spectrum of the unpurified reaction mixture (400 MHz, $CDCl_3$) indicated the two products **17B** and **18B**

in a 95:5 ratio, respectively (determined by integration of the carbinol protons at 4.54 (**17B**) and 4.12 ppm (**18B**). Purification of 101 mg of a related 47:53 mixture of **17B**:**18B** respectively by flash chromatography (2.5% EtOAc, 22.5% CH_2Cl_2 in hexane) afforded 23 mg of **17B** as a colorless oil (≥96% diastereomerically pure by ^{1}H NMR spectroscopy).

Lithium Enolate Addition to Aldehyde 14, Table 11, Entry B. The following reagents were combined in the amounts indicated according to the general lithium aldol procedure: butyllithium (119 μL of a 2.52 M solution, 0.300 mmol), diisopropylamine (42 μL, 0.30 mmol), isopropyl methyl ketone (32.1 μL, 0.300 mmol), and the aldehyde **14** (77 mg, 0.32 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the lithium aldol procedure, affording 98.3 mg (99%) of a mixture of aldol diastereomers as a colorless oil. The ^{1}H NMR spectrum of the unpurified reaction mixture (400 MHz, $CDCl_3$) indicated a 65:35 ratio of **17B**:**18B**.

(5*R*,6*S*,7*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyl-3-nonanone (17B). $[\alpha]^{23}_D$ 5.2° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 3463 (br), 2963, 2932, 1705, 1467, 1386, 1256, 1049, 1015, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (m, 1 H), 3.48 (m, 2 H), 2.71 (dd, J = 7.6 Hz, J = 17.1 Hz, 1 H), 2.62 (sept, J = 6.9 Hz, 1 H), 2.51 (dd, J = 5.3 Hz, J = 17.1 Hz, 1 H), 1.95 (m, 1 H), 1.69 (m, 1 H), 1.11 (d, J = 7.0 Hz, 6 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 7.1 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 82.7, 66.8, 45.2, 41.4, 38.3, 32.0, 26.2, 19.7, 18.7, 18.4, 18.2, 17.9, 11.8, −3.8, −3.8. Exact mass calcd for $C_{18}H_{38}O_3SiNa$: 353.2488. Found: 353.2462 (FAB, MNBA, added NaI).

(5*S*,6*S*,7*R*)-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyl-3-nonanone (18B). $[\alpha]^{23}_D$ −27.5° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3501 (br), 2961, 2932, 1702, 1468, 1386, 1256, 1212, 1051, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (m, 1 H), 3.49 (m, 2 H), 2.72 (dd, J = 2.4 Hz, J = 16.9 Hz, 1 H), 2.64 (sept, J = 6.9 Hz, 1 H), 2.51 (dd, J = 9.4 Hz, J = 16.9 Hz, 1 H), 1.83 (m, 2 H), 1.11 (d, J = 6.9 Hz, 6 H), 0.93 (d, J = 6.2 Hz, 3 H), 0.92 (s, 9 H), 0.89 (d, J = 7.3 Hz, 3 H), 0.87 (d, J = 7.6 Hz, 3 H, CHC*H*$_3$), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 80.1, 69.3, 44.4, 41.9, 41.4, 32.3, 26.1, 19.9, 18.3, 18.1, 18.1, 18.0, 13.9, −3.9, −4.1. Exact mass calcd for $C_{18}H_{38}O_3SiNa$: 353.2488. Found: 353.2471 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 14, Table 4, Entry C. The following reagents were combined in the amounts indicated according to the general enolsilane addition procedure: boron trifluoride etherate (61 μL, 0.50 mmol), acetone trimethylsilyl enol ether (98 mg, 0.75 mmol), and the aldehyde **14** (122 mg, 0.500 mmol). The reaction was allowed to proceed for 10 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 145 °C, 15 psi) revealed a 29:71 ratio of anti-Felkin isomer **18C** (t_r = 16.91 min) and the Felkin diastereomer **17C** (t_r = 17.24 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) provided 85 mg (56%) of **17C** (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 13 mg (10%) of a mixture of isomers, and 28 mg (19%) of **18C** (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Lithium Enolate Addition to Aldehyde 14, Table 11, Entry C. The following reagents were combined in the amounts indicated according to the general lithium aldol procedure: butyllithium (139 μL of a 2.52 M solution, 0.350 mmol), diisopropylamine (51 μL, 0.37 mmol), acetone (24 μL, 0.33 mmol), and the aldehyde **14** (73 mg, 0.30 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 5 min, quenched, and isolated as described in the lithium aldol procedure. Silylation and GLC analysis (DB-1701, 180 °C, 10 psi) revealed a 37:63 ratio of anti-Felkin isomer **18C** (t_r = 17.14 min) and the Felkin diastereomer **17C** (t_r = 17.49 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) provided 44 mg (48%) of **17C** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy), 18 mg (20%) of a mixture of diastereomers, and 24 mg (26%) of **18C** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) as colorless oils.

(4*R*,5*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-5,7-dimethyl-2-octanone (17C). $[\alpha]^{23}_D$ −2.4° (*c* 1.79, CH_2Cl_2); IR (film) 3500 (br), 2958, 2858, 1713, 1473, 1387, 1361, 1255, 1050, 837, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (m, 1 H, C*H*OH), 3.48−3.43 (m, 2 H), 2.70 (A of ABX, 1 H, J_{AB} = 16.5 Hz, J_{AX} = 8.4 Hz), 2.40 (B of ABX, 1 H, J_{AB} = 16.5 Hz, J_{BX} = 4.6 Hz), 2.18 (s, 3 H), 1.95 (octet, 1 H, J = 6.7 Hz), 1.66 (m, 1 H), 0.96 (d, 3 H, J = 7.2 Hz), 0.94 (d, 3 H, J = 6.9 Hz), 0.93 (d, 3 H, J = 6.8 Hz), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 83.0, 66.9, 48.7, 38.2, 32.1, 30.9, 26.2, 19.6, 19.0, 18.4, 12.0, −3.7, −3.8. Exact mass calcd for $C_{16}H_{35}O_3Si$: 303.2355. Found: 303.2352 (CI, NH_3 atmosphere).

(4*S*,5*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-5,7-dimethyl-2-octanone (18C). $[\alpha]^{23}_D$ −17.2° (*c* 1.25, CH_2Cl_2); IR (film) 3507 (br), 2958, 2930, 2858, 1713, 1472, 1388, 1361, 1253, 1053, 836, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 1 H), 3.52 (br s, 1 H), 3.47 (t, 1 H, J = 4.9 Hz), 2.66 (A of ABX, 1 H, J_{AB} = 16.2 Hz, J_{AX} = 2.7 Hz), 2.47 (B of ABX, 1 H, J_{AB} = 16.2 Hz, J_{BX} = 9.6 Hz), 2.19 (s, 3 H), 1.86−1.74 (m, 2 H), 0.92 (d, 3 H, J = 6.8 Hz), 0.92 (s, 9 H), 0.88 (d, 3 H, J = 6.8 Hz), 0.85 (d, 3 H, J = 7.1 Hz), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 80.7, 68.7, 47.9, 41.6, 32.7, 30.8, 26.1, 19.6, 18.3, 18.0, 14.6, −4.0, −4.2. Exact mass calcd for $C_{16}H_{35}O_3Si$: 303.2355. Found: 303.2355 (CI, NH_3 atmosphere).

(2*S*,3*R*)-2,4-Dimethyl-3-[(4-methoxybenzyl)oxy]pentanal (19). Di-*n*-butylboryl trifluoromethanesulfonate (18.0 g, 16.6 mL, 65.8 mmol) was added to a solution of 13.93 g (59.80 mmol) of (*S*)-3-(1-oxo-1-propyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one in 120 mL of CH_2Cl_2 at such a rate to maintain the internal temperature below +3 °C (thermocouple thermometer). Triethylamine (7.20 g, 10.0 mL, 71.8 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was cooled to −78 °C and 6.5 mL (5.2 g, 72 mmol) of freshly distilled isobutyraldehyde was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by addition of 60 mL of pH = 7 aqueous phosphate buffer solution and 180 mL of MeOH (internal temperature below +10 °C, bath temperature = −10 °C). A solution of 120 mL of MeOH and 60 mL of 30% aqueous H_2O_2 was added carefully (internal temperature below +10 °C) and the resulting solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure and the residue was extracted with three 200-mL portions of Et_2O. The combined organic extracts were washed with 200 mL of saturated aqueous $NaHCO_3$ and 200 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ and purified by flash chromatography (40% EtOAc in hexane) to give 18.03 g (99%) of the *syn* aldol adduct as a white solid. To a solution of 9.05 g (29.6 mmol) of this aldol adduct and 1.27 mL (29.6 mmol) of MeOH in 118 mL of THF at 0 °C was slowly added 14.8 mL (29.6 mmol) of a 2.0 M solution of $LiBH_4$ in THF (gas evolution). After the mixture was stirred 45 min at 0 °C the reaction was quenched by the addition of 150 mL of 1.0 M aqueous sodium potassium tartrate and stirred for an additional 10 min. The mixture was then diluted with 300 mL of CH_2Cl_2 and 150 mL of 1.0 M aqueous sodium potassium tartrate. The layers were separated and the aqueous layer was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 300 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This provided 9.10 g of a mixture of the chiral auxiliary and the desired diol as a white solid. To a solution of this white solid and 6.14 g (32.6 mmol) of the dimethylacetal of anisaldehyde in 120 mL of CH_2Cl_2 at ambient temperature was added 5 mg (catalytic amount) of *p*-toluenesulfonic acid. After 3 h the reaction was diluted with 100 mL of CH_2Cl_2 and 200 mL of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with two 100-mL portions of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The oily white solid was triturated in 40 mL of hexane at 0 °C for 15 min. The white solid was collected on a Büchner funnel and washed with 40 mL of cold hexane. This afforded 4.90 g (93%) of the recovered oxazolidinone. The filtrate was concentrated and then purified by MPLC (Michel−Miller column size D, 5→10% EtOAc in hexane gradient) to provide 6.87 g (93%) of the benzylidene acetal as a white solid. To a solution of 986 mg (3.94 mmol) of the acetal in 19.7 mL of CH_2Cl_2 at 0 °C was added 6.56 mL (9.85 mmol) of a 1.5

M solution of DIBAL-H in toluene. After 45 min the solution was transferred by cannula into a rapidly stirring mixture of 120 mL of 1:1 CH_2Cl_2:1 N aqueous HCl at 0 °C. The mixture was stirred for 30 min at ambient temperature then the layers were separated. The aqueous phase was extracted with two 30-mL portions of CH_2Cl_2. The combined organic extracts were washed with 60 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford 978 mg (98%) of the 3-benzyloxy alcohol as a colorless oil. To a solution of 166 μL (1.90 mmol) of oxalyl chloride in 7.4 mL of CH_2Cl_2 at −78 °C was added 270 μL (3.80 mmol) of DMSO (gas evolution). After 10 min, a solution of 400 mg (1.59 mmol) of the alcohol in 0.50 mL of CH_2Cl_2 was added forming a cloudy white mixture. This was stirred for 15 min then 1105 μL (9.50 mmol) of triethylamine was added. The reaction was stirred at −78 °C for 45 min then quenched by the addition of 10 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature then diluted with 30 mL of CH_2Cl_2 and 30 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with two 15-mL portions of CH_2Cl_2. The combined organic extracts were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR spectroscopy of the unpurified aldehyde was very clean. Purification by MPLC (Michel−Miller column size B, 15% EtOAc in hexane) provided 358 mg (90%) of the aldehyde **19** as a colorless oil: $[\alpha]^{23}_D$ +56.0° (*c* 0.58, CH_2Cl_2); IR (thin film) 2962, 2874, 2837, 2715, 1723, 1613, 1586, 1514, 1466, 1385, 1302, 1249, 1174, 1036, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, 1 H, J = 1.0 Hz), 7.26−7.21 (m, 2 H), 6.87−6.83 (m, 2 H), 4.41 (s, 2 H), 3.80 (s, 3 H), 3.58 (dd, 1 H, J = 7.5 Hz, J = 3.5 Hz), 2.60 (ddd, 1 H, J = 7.0 Hz, J = 3.5 Hz, J = 1.0 Hz), 1.90 (octet, 1 H, J = 7.0 Hz), 1.16 (d, 3 H, J = 7.1 Hz), 1.03 (d, 3 H, J = 6.7 Hz, (CH_3)$_2$CH), 0.94 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 159.2, 130.4, 129.2, 113.7, 83.3, 73.5, 55.2, 49.2, 31.2, 19.6, 18.9, 8.1. Exact mass calcd for $C_{15}H_{22}O_3Na$: 273.1467. Found 273.1454 (FAB, MNBA, added NaI).

(2*S*,3*R*)-2,4-Dimethyl-3-(*tert*-butylsilyloxy)pentanal (20). To a suspension of 12.5 g (128 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 66 mL of THF at 0 °C was added 65 mL (130 mmol) of a 2.0 M solution of trimethylsilane in toluene (gas evolution). The resulting solution was stirred at ambient temperature for 30 min and then cooled to −15 °C. A solution of 13.1 g (42.9 mmol) of the β-hydroxy imide used in the synthesis of aldehyde **19** (*vide supra*) in 66 mL of THF was added by cannula and the resulting mixture was stirred at 0 °C for 2.5 h. This solution was transferred by cannula to a well-stirred mixture of 330 mL of CH_2Cl_2 and 665 mL of 0.5 N aqueous HCl. After the mixture was stirred at 0 °C for 1 h, the organic phase was separated. The aqueous phase was extracted with three 200-mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and purified by flash chromatography (80% Et_2O in hexane) to give 7.17 g (88%) of the *N*-methoxy-*N*-methyl amide as a white solid. To a solution of 7.10 g (37.6 mmol) of the β-hydroxy amide in 38 mL of CH_2Cl_2 at ambient temperature were added 5.0 mL (4.60 g, 43.0 mmol) of 2,6-lutidine and 9.0 mL (10.0 g, 39.0 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 15 min, 75 mL of H_2O was added to quench and the mixture was extracted with 75 mL of Et_2O. The organic extract was washed with 40 mL of H_2O and 40 mL of brine. The combined aqueous washings were extracted with 40 mL of Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$ and purified by flash chromatography (10% EtOAc in hexane, then 25% EtOAc in hexane) to give 11.28 g (99%) of the silyl ether as a colorless oil. A solution of diisobutylaluminum hydride in toluene (1.0 M, 33.3 mL, 33.3 mmol) was added to a solution of 5.05 g (16.6 mmol) of the *N*-methoxy-*N*-methyl amide in 166 mL of THF at 0 °C. After 30 min, 24 mL of EtOAc was added carefully to quench the excess hydride followed by 33 mL of H_2O. This solution was diluted with 300 mL of Et_2O and 150 mL of H_2O. Enough 1 N aqueous HCl (200 mL) was added to dissolve the aluminum salts and the phases were separated. The aqueous phase was extracted with two 100-mL portions of Et_2O. The combined organic extracts were washed with 200 mL of saturated aqueous $NaHCO_3$ and 200 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by MPLC (Michel−Miller column size B, CH_2Cl_2) provided 3.50 g (86%) of the aldehyde **20** as a colorless oil: $[\alpha]^{20}_D$ +60.8° (*c* 0.365, $CHCl_3$); IR (neat) 2960, 1730, 1250, 1100, 1050, 1030, 835, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, J = 0.8 Hz, 1 H), 3.89 (dd, J = 5.5 Hz, J = 3.9 Hz, 1 H), 2.50 (dqd, J = 7.0 Hz, J = 3.9 Hz, J = 0.7 Hz, 1 H), 1.81 (m, 1 H), 1.09 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 76.2, 50.4, 32.1, 25.8, 19.6, 18.2, 18.1, 8.4, −4.2, −4.4. This material was too unstable to acquire a high resolution mass spectral analysis.

Enolsilane Addition to Aldehyde 19, Table 5, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (100 μL, 0.800 mmol), pinacolone trimethylsilyl enol ether (130 μL, 0.800 mmol), and the aldehyde **19** (200 mg, 0.800 mmol). The reaction was allowed to proceed for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Acylation and GLC analysis (DB-1701, 210 °C, 15 psi) indicated a 4:96 ratio of anti-Felkin isomer **22A** (t_r = 21.42 min) and the Felkin diastereomer **21A** (t_r = 22.90 min), respectively. Purification by flash chromatography (10% EtOAc in hexane) provided 250 mg (89%) of the aldol adduct **21A** as a colorless oil.

Lithium Enolate Addition to Aldehyde 19, Table 12, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (300 μL of a 1.47 M solution, 0.440 mmol), diisopropylamine (60 μL, 0.44 mmol), pinacolone (55 μL, 0.44 mmol), and the aldehyde **19** (100 mg, 0.44 mmol, as a solution in 0.2 mL of THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the general lithium aldol procedure. Silylation and GLC analysis (DB-1701, 210 °C, 15 psi) indicated a 11:89 ratio of **21A**:**22A**. Purification by flash chromatography (10% EtOAc in hexane) provided 140 mg (71%) of a mixture of aldol adducts as a colorless oil.

(5*S*,6*R*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,6,8-tetramethyl-3-octanone (21A). $[\alpha]^{23}_D$ −45° (*c* 1.5, CH_2Cl_2); IR (CH_2Cl_2) 3508 (br), 2969, 1696, 1514, 1264, 1065, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2 H), 6.83 (m, 2 H), 4.58 and 4.46 (AB, 2 H, J = 12.9 Hz), 4.15 (m, 1 H), 3.77 (s, 3 H), 3.29 (dd, 1 H, J = 5.4 Hz, J = 7.5 Hz), 3.24 (d, 1 H, J = 2.4 Hz, O*H*), 2.63 (m, 2 H), 1.98 (m, 1 H), 1.75 (m, 1 H), 1.10 (s, 9 H), 0.97 (m, 9 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 216.7, 160.2, 159.2, 131.1, 129.1, 113.9, 87.0, 73.8, 70.4, 55.3, 44.4, 41.2, 39.6, 30.9, 26.3, 19.8, 18.5, 8.6. Exact mass calcd for $C_{21}H_{34}O_4Na$: 373.2355. Found: 373.2364 (FAB, MNBA, added NaI).

(5*R*,6*R*,7*R*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,2,6,8-tetramethyl-3-octanone (22A). $[\alpha]^{23}_D$ +20.5° (*c* 1.75, CH_2Cl_2); IR (CH_2Cl_2) 3508 (br), 2969, 1696, 1514, 1264, 1065, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.4 Hz), 6.83 (d, 2 H, J = 8.7 Hz), 4.59 and 4.54 (AB, 2 H, J = 11.1 Hz), 3.91 (m, 1 H), 3.77 (s, 3 H), 3.53 (d, 1 H, J = 3.5 Hz), 3.49 (dd, 1 H, J = 1.9 Hz, J = 8.8 Hz), 2.80 (dd, 1 H, J = 2.1 Hz, J = 18 Hz), 2.49 (dd, 1 H, J = 9.3 Hz, J = 18 Hz), 1.73 (m, 2 H), 1.11 (s, 9 H), 1.02 (d, 3 H, J = 6.6 Hz), 0.83 (m, 6 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 218.3, 158.9, 131.5, 129.1, 113.6, 83.6, 74.2, 69.5, 55.2, 44.5, 41.2, 40.1, 31.2, 26.3, 20.1, 19.5, 9.9. Exact mass calcd for $C_{21}H_{34}O_4Na$: 373.2355. Found: 373.2357 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 19, Table 5, Entry C. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (50 μL, 0.41 mmol), isopropyl methyl ketone trimethylsilyl enol ether (71 mg, 0.45 mmol), and the aldehyde *ent*-**19** (102 mg, 0.407 mmol). The reaction was allowed to proceed for 30 min at −78 °C, quenched, and isolated as described in the general Mukaiyama aldol procedure, affording 126 mg (98%) of a colorless oil. The ^{1}H NMR spectrum of the unpurified reaction mixture indicated no unreacted starting material, and the two products in an 55:45 ratio. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated an 56:44 ratio of the 5*R*-diastereomer *ent*-**21C** (t_r = 7.85 min) and the 5*S*-diastereomer *ent*-**22C** (t_r = 8.06 min), respectively.

Lithium Enolate Addition to Aldehyde 19, Table 12, Entry B. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (124 μL of a 2.41 M solution, 0.300 mmol), diisopropylamine (42 μL, 0.30 mmol), isopropyl methyl ketone (32 μL, 0.30 mmol), and the aldehyde *ent*-**19** (79 mg, 0.32 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 10 min, quenched, and isolated as described

in general lithium aldol procedure, affording 96 mg (95%) of a the mixture of diastereomeric products as a colorless oil. Silylation and GLC analysis (DB-1, 200 °C, 10 psi) indicated a 14:86 ratio of *ent*-**21C**:*ent*-**22C**, respectively.

(5*R*,6*S*,7*S*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,6,8-trimethyl-3-nonanone (*ent*-21C). $[\alpha]^{23}_D$ 49.5° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3708 (br), 2972, 1702, 1613, 1514, 1466, 1386, 1302, 1249, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2 H), 6.87 (m, 2 H), 4.60 (d, J = 10.6 Hz, 1 H), 4.49 (d, J = 10.6 Hz, 1 H), 4.20 (m, 1 H), 3.80 (s, 3 H), 3.32 (dd, J = 4.3 Hz, J = 6.4 Hz, 1 H), 3.23 (d, J = 1.9 Hz, 1 H), 2.68 (dd, J = 8.5 Hz, J = 17.2 Hz, 1 H), 2.59 (sept, J = 6.9 Hz, 1 H), 2.55 (dd, J = 3.9 Hz, J = 17.2 Hz, 1 H), 2.01 (m, 1 H), 1.74 (m, 1 H), 1.09 (d, J = 6.9 Hz, 6 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.96 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 159.2, 130.8, 129.2, 113.8, 87.3, 73.9, 70.4, 55.3, 44.9, 41.5, 39.4, 30.9, 19.8, 18.6, 18.0, 18.0, 8.3. Exact mass calcd for $C_{20}H_{32}O_4Na$: 359.2198. Found: 359.2186 (FAB, MNBA, added NaI).

(5*S*,6*S*,7*S*)-7-[(4-Methoxybenzyl)oxy]-5-hydroxy-2,6,8-trimethyl-3-nonanone (*ent*-22C). $[\alpha]^{23}_D$ −20.0° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 3620 (br), 3015, 2975, 1699, 1612, 1514, 1466, 1386, 1248, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.59 (m, 2 H), 3.96 (m, 1 H), 3.80 (s, 3 H), 3.50 (m, 2 H), 2.79 (dd, J = 2.4 Hz, J = 17.6 Hz, 1 H), 2.60 (sept, J = 7.0 Hz, 1 H), 2.52 (dd, J = 9.3 Hz, J = 17.6 Hz, 1 H), 1.87 (m, 1 H), 1.77 (m, 1 H), 1.11 (d, J = 7.0 Hz, 3 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 159.0, 131.4, 129.1, 113.7, 83.7, 74.2, 69.6, 55.2, 44.6, 41.5, 40.2, 31.1, 20.0, 19.6, 18.1, 18.0, 10.0. Exact mass calcd for $C_{20}H_{32}O_4$: 336.2300. Found: 336.2305 (EI).

Enolsilane Addition to Aldehyde 19, Table 5, Entry E. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (24 μL, 0.20 mmol), acetone trimethylsilyl enol ether (33 μL, 0.20 mmol), and the aldehyde **19** (50 mg, 0.20 mmol). The reaction was allowed to proceed for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Silation and GLC analysis (DB-1701, 210 °C, 10 psi) indicated a 83:17 ratio of anti-Felkin isomer **22E** (t_r = 15.27 min) and the Felkin diastereomer **21E** (t_r = 15.03 min), respectively. Purification by flash column (10% EtOAc in hexane) provided 50 mg (82%) of a mixture of aldol adducts as a colorless oil.

Lithium Enolate Addition to Aldehyde 19, Table 12, Entry C. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (1.3 mL of a 1.6 M solution, 0.2.0 mmol), diisopropylamine (290 μL, 2.1 mmol), acetone (150 μL, 0.2.0 mmol), and the aldehyde **19** (100 mg, 0.40 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 30 min, quenched, and isolated as described in the general lithium aldol procedure, affording 90 mg (73%) of a the mixture of diastereomeric products as a colorless oil. Silylation and GLC analysis (DB-1701, 215 °C, 10 psi) indicated a 22:78 ratio of **21E** (t_r = 9.11 min) and **22E**, (t_r = 9.24 min) respectively.

(4*S*,5*R*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-2-octanone (21E). $[\alpha]^{23}_D$ −49° (*c* 0.2, CH_2Cl_2); IR ($CHCl_3$) 3708 (br), 2963, 1709, 1514, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.4 Hz, Ar*H*), 6.85 (d, 2 H, J = 8.7 Hz, Ar*H*), 4.59 and 4.45 (AB, 2 H, J = 10.8 Hz, ArCH_2), 4.18 (m, 1 H, HOC*H*), 3.77 (s, 3 H, ArOCH_3), 3.28 (dd, 1 H, J = 4.2 Hz, J = 6.6 Hz, PMBOC*H*), 3.18 (d, 1 H, J = 1.8 Hz, O*H*), 2.65 (dd, 1 H, J = 8.7 Hz, J = 17.1 Hz, O═CC*H*H), 2.45 (dd, 1 H, J = 3.6 Hz, J = 17.1 Hz, O═CCH*H*), 2.13 (s, 3 H, O═CCH_3), 2.13 (m, 1 H, PMBOCHC*H*$(CH_3)_2$), 1.69 (m, 1 H, HOCHC*H*CHOPMB), 1.09 (d, 3 H, J = 6.6 Hz, HOCHCHCH_3), 0.94 (d, 3 H, J = 4.2 Hz, PMBOCHCH(CH_3)CH_3), 0.91 (d, 3 H, J = 3.9 Hz, PMBOCHCH(CH_3)CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.3, 159.2, 130.6, 129.3, 113.9, 87.5, 73.9, 70.5, 55.3, 48.4, 39.3, 30.9, 19.7, 18.7, 8.0. Exact mass calcd for $C_{18}H_{28}O_4Na$: 331.1885. Found: 331.1888 (FAB, MNBA, added NaI).

(4*R*,5*R*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-2-octanone (22E). $[\alpha]^{23}_D$ +14° (*c* 1.75, CH_2Cl_2); IR ($CHCl_3$) 3516 (br), 2962, 1708, 1613, 1514, 1466, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 7.9 Hz), 6.85 (d, 2 H, J = 8.6 Hz), 4.56 (s, 2 H), 3.95 (m, 1 H), 3.78 (s, 3 H), 3.47 (dd, 1 H, J = 2.1 Hz, J = 8.4 Hz), 3.29 (s, 1 H), 2.73 (dd, 1 H, J = 2.7 Hz, J = 17.4 Hz), 2.46 (dd, 1 H, J = 9.3 Hz, J = 17.4 Hz), 2.14 (s, 3 H), 1.86 (m, 1 H), 1.73 (m, 1 H), 1.02 (d, 3 H, J = 6.6 Hz), 0.86 (d, 3 H, J = 7.2 Hz), 0.83 (d, 3 H, J = 7.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.4, 160, 131.2, 129.2, 113.7, 83.8, 74.1, 69.5, 55.2, 48.0, 40.1, 30.9, 30.8, 19.9, 19.6, 10.1. Exact mass calcd for $C_{18}H_{28}O_4$: 308.1988. Found: 308.2001 (EI).

Enolsilane Addition to Aldehyde 20, Table 5, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (49 μL, 0.40 mmol), pinacolone trimethylsilyl enol ether (95 μL, 0.44 mmol), and the aldehyde **20** (98 mg, 0.40 mmol). The reaction was allowed to proceed for 30 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 180 °C, 10 psi) indicated a 4:96 ratio of anti-Felkin isomer **24A** (t_r = 9.95 min) and the Felkin diastereomer **23A** (t_r = 10.34 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) provided 128 mg (93%) of the Felkin adduct **23A** (>99% pure by GLC analysis) as a colorless oil.

Lithium Enolate Addition to Aldehyde 20, Table 12, Entry A. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (292 μL of a 1.60 M solution, 0.467 mmol), diisopropylamine (69 μL, 0.49 mmol), pinacolone (56 μL, 0.44 mmol), and the aldehyde **20** (98 mg, 0.40 mmol, as a solution in THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the general lithium aldol procedure. Silylation and GLC analysis (DB-1701, 180 °C, 10 psi) indicated a 8:92 ratio of anti-Felkin isomer **24A** (t_r = 9.95 min) and the Felkin diastereomer **23A** (t_r = 10.34 min), respectively. Purification by MPLC (Michel−Miller column size B, 5% EtOAc in hexane) provided 119 mg (86%) of the Felkin adduct **23A** (>99% pure by GLC analysis) as a colorless oil and 7 mg (5%) of the minor diastereomer **24A** as a colorless oil.

(5*S*,6*R*,7*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-2,2,6,8-tetramethyl-3-nonone (23A). $[\alpha]^{21}_D$ +21.7° (c 0.46, $CHCl_3$); IR ($CHCl_3$) 3562 (br), 2959, 2932, 2858, 1693, 1472, 1387, 1366, 1257, 1100, 1067, 1005, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (m, 1 H), 3.55 (t, J = 4.2 Hz, 1 H), 3.05 (d, J = 2.8 Hz, 1 H), 2.73 (dd, J = 2.8 Hz, J = 17.9 Hz, 1 H), 2.59 (dd, J = 9.1 Hz, J = 17.8 Hz, 1 H), 1.86 (m, 1 H), 1.65 (m, 1 H), 1.15 (s, 9 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.92 (s, J = 6.7 Hz, 3 H), 0.91 (s, 9 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.6, 78.4, 69.5, 44.4, 41.5, 40.8, 32.2, 26.3, 26.1, 19.6, 18.4, 18.1, 10.4, −3.6, −3.9. Exact mass calcd for $C_{19}H_{41}O_3Si$: 345.2848. Found: 345.2825 (CI, NH_3 atmosphere).

(5*R*,6*R*,7*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-hydroxy-2,2,6,8-tetramethyl-3-nonone (24A). $[\alpha]^{22}_D$ +30.5° (*c* 0.75, CH_2Cl_2); IR ($CHCl_3$) 3524 (br), 2960, 2931, 1694, 1473, 1386, 1366, 1077, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88−3.33 (m, 1 H), 3.78 (dd, J = 1.8 Hz, J = 6.7 Hz, 1 H), 3.46 (d, J = 3.0 Hz, 1 H), 2.74 (dd, J = 2.3 Hz, J = 17.6 Hz, 1 H), 2.52 (dd, J = 9.2 Hz, J = 17.7 Hz, 1 H), 1.71 (m, 2 H), 1.15 (s, 9 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 7.0 Hz, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.0, 76.3, 69.2, 44.5, 41.2, 40.7, 32.3, 26.3, 26.2, 19.9, 19.6, 18.5, 10.7, −3.9, −4.0. Exact mass calcd for $C_{19}H_{40}O_3SiNa$: 367.2644. Found: 367.2657 (FAB, MNBA, added NaI).

Enolsilane Addition to Aldehyde 20, Table 5, Entry C. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure: boron trifluoride etherate (39 μL, 0.32 mmol), the enolsilane (56 mg, 0.35 mmol), and the aldehyde *ent*-**20** (78 mg, 0.32 mmol). The reaction was allowed to proceed for 3 h at −78 °C, quenched, and isolated as described in the general procedure, affording 96.0 mg (91%) of a colorless oil. The ^1H NMR spectrum of the unpurified reaction mixture indicated the two products in an 82:18 ratio. Silylation and GLC analysis (DB-1, 160 °C, 3.5 psi) revealed a 13:87 ratio of the 5*S*-diastereomer *ent*-**24C** (t_r = 21.27 min) and the 5*R*-diastereomer *ent*-**23C** (t_r = 21.47 min), respectively.

Lithium Enolate Addition to Aldehyde 20, Table 12, Entry B. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (200 μL of a 2.51 M solution, 0.500 mmol), diisopropylamine (70 μL, 0.50 mmol), isopropyl methyl ketone (54 μL, 0.50 mmol), and the aldehyde *ent*-**20** (122 mg, 0.500 mmol, as a solution in 1 mL of THF). The reaction was allowed

to proceed at −78 °C for 10 min, quenched, and isolated as described in the general lithium aldol procedure, affording 148 mg (89%) of a colorless oil. Acylation and GLC analysis (DB-1701, 200 °C, 10 psi) revealed a 87:13 ratio of the the 5*S*-diastereomer *ent*-**24C** (t_r = 7.68 min) and the 5*R*-diastereomer *ent*-**23C** (t_r = 8.05 min), respectively. Purification by flash chromatography (10% EtOAc in hexane) afforded 98 mg (59%) of the 5*S*-diastereomer *ent*-**24C** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy) and 9 mg (5%) of the 5*R*-diastereomer *ent*-**23C** as a colorless oil (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

(5*R*,6*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyl-3-nonanone (*ent*-23C). $[\alpha]^{21}_D$ −28.8° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3468 (br), 2960, 2860, 1670, 1472, 1406, 1386, 1363, 1254, 1123, 1074, 1026, 1006, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (m, 1 H), 3.77 (dd, J = 1.8 Hz, J = 6.4 Hz, 1 H), 3.51 (d, J = 2.0 Hz, 1 H), 2.72 (dd, J = 2.5 Hz, J = 17.3 Hz, 1 H), 2.63 (sept, J = 6.9 Hz, 1 H), 2.50 (dd, J = 9.1 Hz, J = 17.3 Hz, 1 H), 1.77 (m, 1 H), 1.68 (m, 1 H), 1.11 (d, J = 6.9 Hz, 6 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.79 (d, J = 7.0 Hz, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 76.7, 69.3, 44.9, 41.5, 41.1, 32.1, 26.1, 19.8, 19.7, 18.4, 18.1, 17.9, 11.0, −4.0, −4.1. Exact mass calcd for $C_{18}H_{39}O_3Si$: 331.2668. Found: 331.2684 (CI, NH_3 atmosphere).

(5*S*,6*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,6,8-trimethyl-3-nonanone (*ent*-24C). $[\alpha]^{21}_D$ +27.2° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) 3536 (br), 2960, 2854, 1700, 1472, 1405, 1386, 1362, 1257, 1125, 1110, 1051, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 1 H), 3.56 (t, J = 4.2 Hz, 1 H), 2.98 (s, 1 H), 2.70−2.58 (m, 3 H), 1.86 (m, 1 H), 1.64 (m, 1 H), 1.12 (d, J = 7.0 Hz, 6 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 78.4, 69.6, 45.1, 40.6, 32.3, 26.1, 19.5, 18.4, 18.1, 18.1, 18.0, 10.2, −3.6, −4.0. Exact mass calcd for $C_{18}H_{39}O_3Si$: 331.2668. Found: 331.2671 (CI, NH_3 atmosphere).

Enolsilane Addition to Aldehyde 20, Table 5, Entry E. The following reagents were combined in the amounts indicated according to the general procedure: boron trifluoride etherate (71 μL, 0.50 mmol), acetone trimethylsilyl enol ether (98 mg, 0.75 mmol), and the aldehyde **20** (122 mg, 0.500 mmol). The reaction was allowed to proceed for 15 min at −78 °C, quenched, and isolated as described in the general procedure. Acetylation and GLC analysis (DB-1701, 180 °C, 10 psi) indicated a 42:58 ratio of anti-Felkin isomer **23E** (t_r = 10.00 min) and the Felkin diastereomer **24E** (t_r = 10.58 min), respectively. Purification by MPLC (Michel−Miller column size B, 8% EtOAc in hexane) provided 34 mg (28%) of the anti-Felkin adduct **24E** (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 21 mg (19%) of a mixture of isomers, and 56 mg (46%) of the Felkin adduct **23E** (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Lithium Enolate Addition to Aldehyde 20, Table 12, Entry C. The following reagents were combined in the amounts indicated according to the general procedure: butyllithium (146 μL of a 1.6 M solution, 0.23 mmol), diisopropylamine (34 μL, 0.24 mmol), acetone (16 μL, 0.22 mmol), and the aldehyde **19** (49 mg, 0.20 mmol, as a solution in 1 mL of THF). The reaction was allowed to proceed at −78 °C for 2 min, quenched, and isolated as described in the general lithium aldol procedure. Acylation and GLC analysis (DB-1701, 180 °C, 10 psi) indicated a 86:14 ratio of **23E**:**24E**, respectively. Purification by MPLC (Michel−Miller size B, 5% EtOAc in hexane) afforded 43 mg (70%) of **24E** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) and 11 mg (18%) of a mixture of diastereomers.

(4*S*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-5,7-dimethyl-2-octanone (23E). $[\alpha]^{23}_D$ −26.7° (*c* 1.05, CH_2Cl_2); IR (film) 3466 (br), 2958, 2930, 2857, 1713, 1472, 1387, 1361, 1253, 1046, 836, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (m, 1 H), 3.54 (t, 1 H, J = 4.2 Hz), 2.83 (br d, 1 H, J = 3.0 Hz), 2.60 (m, 2 H), 2.18 (s, 3 H), 1.84 (dseptets, 1 H, J = 6.9 Hz), 1.61 (m, 1 H), 0.93 (d, 3 H, J = 7.0 Hz), 0.90 (s, 9 H), 0.89 (d, 3 H, J = 7.0 Hz), 0.86 (d, 3 H, J = 7.0 Hz), 0.06 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 78.5, 69.6, 48.5, 40.5, 32.4, 30.8, 20.1, 19.4, 18.4, 18.2, 10.0, −3.6, −4.0. Exact mass calcd for $C_{16}H_{35}O_3Si$: 303.2355. Found: 303.2343 (CI, NH_3 atmosphere).

(4*R*,5*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-5,7-dimethyl-2-octanone (24E). $[\alpha]^{23}_D$ +23.4° (*c* 3.05, CH_2Cl_2); IR (film) 3473 (br), 2954, 2858, 1711, 1473, 1386, 1360, 1253, 1064, 837, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$0 δ 3.93 (m, 1 H), 3.72 (dd, 1 H, J = 6.1 Hz, J = 2.1 Hz), 3.56 (d, 1 H, J = 3.0 Hz), 2.68 (dd, 1 H, J = 16.9 Hz, J = 2.6 Hz), 2.46 (dd, 1 H, J = 16.9 Hz, J = 9.2 Hz), 2.19 (s, 3 H), 1.78 (octet, 1 H, J = 6.7 Hz), 1.68 (m, 1 H), 0.93 (d, 3 H, J = 6.8 Hz), 0.89 (s, 9 H), 0.88 (d, 3 H, J = 7.0 Hz), 0.78 (d, 3 H, J = 7.0 Hz), 0.10 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 77.4, 69.5, 48.4, 41.4, 31.8, 30.9, 26.1, 20.1, 19.6, 18.4, 11.4, −4.1, −4.1. Exact mass calcd for $C_{16}H_{35}O_3Si$: 303.2355. Found: 303.2361 (CI, NH_3 atmosphere).

***β*-Methallylstannane Addition to Aldehyde 13, Table 6, Entry A.** The following reagents were combined in the amounts indicated according to the general allylstannane addition procedure using toluene as the solvent: boron trifluoride etherate (10 μL, 0.077 mmol), methallyltri-*n*-butylstannane (14 mg, 0.046 mmol), and the aldehyde **13** (10 mg, 0.052 mmol). The reaction was allowed to proceed for 13 min at −78 °C, quenched and isolated as described in the general procedure. Silylation and GLC analysis (DB-1701, 190 °C, 15 psi) indicated a 99:1 ratio of the 4*R*-diasteromer **25A** (t_r = 18.12 min) and the 4*S*-diasteromer (t_r = 17.35 min), respectively. Purification by silica gel chromatography afforded 12 mg (86% yield) of the product **25A** as a colorless oil.

(4*R*,5*S*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-2,5,7-trimethyl-1-octene (25A). $[\alpha]^{23}_D$ −17.3° (*c* 0.56, CH_2Cl_2); IR (CH_2Cl_2) 3495 (br), 2963, 1613, 1514, 1463, 1301, 1249, 1173, 1037 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.04 (dd, 4 H, J = 101 Hz, 8.7 Hz, Ar*H*), 4.77 (d, 2 H, J = 9.8 Hz, CH_2Ar), 4.55 9dd, 2 H, J = 11.7 Hz, 10.4 Hz, C=CH_2), 4.15 (t, 1 H, J = 6.38 Hz, C*H*OH), 3.77 (s, 3 H, CH_3OAr), 3.15 (dd, 1 H, J = 7.23 Hz, 4.16 Hz, C*H*OPMB), 3.09 (s, O*H*), 2.28 (ddd, 2 H, J = 63.4 Hz, 16.3 Hz, 7.8 Hz, CH_2CHOH), 1.97 (m, 1 H, CH_3C*H*CHOH), 1.76 (s, 3 H, CH_3C=C), 1.70 (1H, $(CH_3)_2$C*H*), 1.02 (d, 6 H, J = 8.8 Hz, $(CH_3)_2$CH), 0.91 (d, 3 H, J = 6.8 Hz, CH_3CHCHOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.1, 143.4, 130.8, 129.6, 114.2, 112.8, 90.8, 76.1, 68.2, 55.6, 43.6, 38.0, 31.4, 22.8, 20.3, 19.0, 11.6. Exact mass calcd for $C_{19}H_{30}O_3$: 306.4454. Found: 306.21950 (EI).

Allylstannane Addition to Aldehyde 13, Table 6, Entry B. The following reagents were combined in the amounts indicated according to the general enolsilane procedure, except the nucleophile is allylstannane: boron trifluoride etherate (30 μL, 0.25 mmol), allyltributylstannane (72 μL, 0.25 mmol), and the aldehyde *rac*-**13** (56 mg, 0.23 mmol). The reaction was allowed to proceed for 30 min at −78 °C, quenched, and isolated as described in the general procedure. GLC analysis (DB-1, 200 °C, 10 psi) indicated the presence of a single diastereomer **25B** (t_r = 7.25 min). Purification by flash column (20% EtOAc in hexane) provided 62.3 mg (95%) of the Felkin isomer **25B** (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Allylstannane Addition to Aldehyde 13, Table 6, Entry C. To a suspension of 48 mg (0.14 mmol) of Ph_3CClO_4 in 0.5 mL of CH_2Cl_2 at −78 °C was added a solution of 32 mg (0.13 mmol) of aldehyde **13** in 0.25 mL of CH_2Cl_2, rinsing with 0.5 mL CH_2Cl_2. After 5 min at −78 °C, this solution was transferred *via cannula* to a solution of 110 μL (0.38 mmol) of allyltributylstannane in 0.75 mL of CH_2Cl_2 at −78 °C. After 10 min at −78 °C, the reaction was quenched by addition of 1 mL of Et_3N, then 5 mL of saturated aqueous NH_4Cl. The mixture was diluted with 20 mL of Et_2O and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo* affording 157.8 mg of a clear oil. GLC analysis (DB-1, 200 °C, 10 psi) indicated the presence of a single diastereomer (t_r = 10.72 min). Purification by flash chromatography (5% EtOAc, 45% CH_2Cl_2 in hexane) afforded 23.4 mg (64%) of **25B** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) as a colorless oil.

(4*R*,5*S*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-1-octene (25B). IR ($CHCl_3$) 3466 (br), 3007, 2964, 2875, 1613, 1514, 1465, 1303, 1250, 1174, 1081, 1036, 920, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2 H), 6.86 (m, 2 H), 5.79 (m, 1 H), 5.10 (dd, J = 1.4 Hz, J = 15.4 Hz, 1 H), 5.05 (dd, J = 0.8 Hz, J = 10.2 Hz, 1 H), 4.55 (quartet, J = 10.3 Hz, 2 H), 4.03 (t, J = 7.6 Hz, 1 H), 3.79 (s, 3 H), 3.35 (s, 1 H), 3.14 (dd, J = 3.5 Hz, J = 7.8 Hz, 1 H), 2.31 (m, 1 H), 2.10 (m, 1 H), 1.99 (m, 1 H), 1.79 (m, 1 H), 1.05 (d, J = 7.1

Hz, 3 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.5, 130.4, 129.3, 116.8, 113.8, 91.0, 69.9, 55.2, 39.2, 37.2, 31.1, 19.8, 19.1, 11.4. Exact mass calcd for $C_{18}H_{32}NO_3$: 310.2382. Found: 310.2389 (CI, NH_3 atmosphere).

***β*-Methallylstannane Addition to Aldehyde 19, Table 7, Entry A.** The following reagents were combined in the amounts indicated according to the general procedure for the $BF_3{\cdot}OEt_2$ mediated addition reactions using only toluene as the solvent: boron trifluoride etherate (20 μL, 0.16 mmol), the methallyltri-*n*-butylstannane (34 mg, 0.10 mmol), and the aldehyde **19** (23 mg, 0.094 mmol). The reaction was allowed to proceed for 11 min at −78 °C, quenched, and isolated as described in the general procedure. Silylation and GLC analysis of the unpurified mixture (DB-1701, 180 °C, 15 psi) indicated a 80:20 ratio of the 4*R*-diasteromer **26A** (t_r = 26.93 min) and the 4*S*-diastereomer (t_r = 26.33 min) respectively. Purification by silica gel chromatography provided 13.4 mg (86% yield) of a mixture of diastereomeric products as a colorless oil.

(4*R*,5*R*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-2,5,7-trimethyl-1-octene (26A). $[\alpha]^{23}_D$ −35.5° (*c* 0.35 CH_2Cl_2); IR (CH_2Cl_2) 3474 (br), 2959, 2361, 1646, 1612, 1514, 1457, 1381, 1301, 1247, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (dd, 4 H, J = 127 Hz, 8.6 Hz), 4.84 (d, 2 H, J = 27.9 Hz), 4.57 (s, 2 H, J = 17.2 Hz, 10.5 Hz), 3.78 (s, 3 H), 3.60 (m, 1 H), 3.47 (dd, 1 H, J = 8.4 Hz, 2.3 Hz), 2.35 (d, 1 H, J = 13.9 Hz), 2.00 (dd, 2 H, J = 13.5 Hz, 10.1 Hz), 2.86 (m, 1 H), 1.73 (s, 3 H), 1.70 (m, 1 H), 1.03 (d, 3 H, J = 6.6 Hz), 0.87 (d, 6 H, J = 6.9 Hz, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 131.8, 129.6, 129.5, 114.0, 84.9, 74.4, 70.4, 55.6, 44.5, 40.9, 31.4, 30.0, 22.6, 20.3, 20.0, 10.7. Exact mass calcd for $C_{19}H_{30}O_3$: 306.4454. Found: 306.21950 (EI).

(4*S*,5*R*,6*R*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-2,5,7-trimethyl-1-octene. $[\alpha]^{23}_D$ −3.2° (*c* 0.26 CH_2Cl_2); IR (CH_2Cl_2) 3486 (br), 3072, 2960, 1644, 1612, 1586, 1513, 1463, 1382, 1301, 1248, 1173, 1083, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (ddd, 4 H, J = 125 Hz, 6.6 Hz, 2.1 Hz), 4.77 (dd, 2 H, J = 18.7 Hz, 0.7 Hz), 4.54 (dd, 2 H, J = 17.2 Hz, 10.5 Hz), 3.90 (t, 1 H), 3.77 (s, 3 H), 3.24 (dd, 1 H, J = 7.1 Hz, 1.9 Hz), 2.71 (s, 1 H), 2.21 (m, 2 H), 2.07 (m, 1 H), 1.73 (s, 3 H), 1.01 (d, 3 H, J = 6.7 Hz), 0.91 (dd, 6 H, J = 5.6 Hz, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 130.8, 129.6, 125.8, 114.2, 113.2, 89.2, 74.3, 72.7, 55.6, 43.9, 39.0, 31.3, 22.8, 19.9, 19.3, 7.5. Exact mass calcd for $C_{19}H_{30}O_3$: 306.4454. Found: 306.21950 (EI).

Allylstannane Addition to Aldehyde *ent*-19, Table 7, Entry B. The following reagents were combined in the amounts indicated according to the general Mukaiyama aldol procedure using toluene as solvent: boron trifluoride etherate (13 μL, 0.11 mmol), allyltri-*n*-butylstannane (33 μL, 0.11 mmol), and the aldehyde *ent*-**19** (24 mg, 0.098 mmol). The reaction was allowed to proceed for 10 min at −78 °C, quenched, and isolated as described in the general procedure. GLC analysis (DB-1, 200 °C, 10 psi) indicated a 87:13 ratio of the anti-Felkin isomer *ent*-**26B** (t_r = 7.00 min) and the Felkin isomer (t_r = 7.46 min), respectively. Purification by flash chromatography (20% EtOAc in hexane) provided 25 mg (86%) of an 86:14 mixture of aldol diastereomers free of impurities by ^{1}H NMR spectroscopy. Purification of 285 mg of a related 75:25 mixture of anti-Felkin and Felkin diastereomers respectively (35% Et_2O in hexane) provided 50 mg (41%) of the anti-Felkin isomer **26B** (>95% diastereomerically pure by ^{1}H NMR spectroscopy), 31 mg (25%) of a mixture of isomers, and 11 mg (9%) of the Felkin diasteromer (>95% diastereomerically pure by ^{1}H NMR spectroscopy).

Allylstannane Addition to Aldehyde 19, Table 7, Entry C. To a solution of 40 mg (0.12 mmol) of Ph_3CClO_4 in 0.5 mL of CH_2Cl_2 at −78 °C was added a solution of 26 mg (0.11 mmol) of aldehyde **19** in 0.25 mL of CH_2Cl_2, rinsing with 0.25 mL of CH_2Cl_2. After 5 min at −78 °C, this solution was transferred *via cannula* to a solution of 91.5 μL (0.31 mmol) of allyltributylstannane in 0.75 mL CH_2Cl_2 at −78 °C. After 30 min at −78 °C, the reaction was quenched by the addition of 1 mL of Et_3N, followed by 3 mL of saturated aqueous NH_4Cl. The mixture was diluted with 25 mL of Et_2O and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*, to give 144 mg of a colorless oil. GLC analysis (DB-1, 200 °C, 10 psi) indicated a 38:62 mixture of the anti-Felkin adduct **26B** (t_r = 6.99 min) and the Felkin diastereomer (t_r = 7.49 min), respectively. Purification by flash chromatography (35% Et_2O in hexane) afforded 7 mg (23%) of the anti-Felkin diastereomer **26B** (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) and 10 mg (34%) of the Felkin diastereomer (≥95% diastereomerically pure by ^{1}H NMR spectroscopy) as colorless oils.

(4*S*,5*S*,6*S*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-1-octene (26B). $[\alpha]^{23}_D$ +32° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 3467 (br), 3008, 2962, 2874, 1612, 1514, 1466, 1302, 1249, 1174, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2H), 5.85 (m, 1H), 5.16 (d, J = 5.1 Hz, 2 H), 4.60 (d, J = 10.9 Hz, 1 H), 4.56 (d, J = 10.9 Hz, 1 H), 3.80 (s, 3 H), 3.61 (m, 1 H), 3.45 (dd, J = 2.3 Hz, J = 8.1 Hz), 2.42 (m, 2 H), 2.13 (m, 1 H), 1.92 (octet, J = 7.8 Hz, 1 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.1, 131.2, 129.2, 118.2, 113.7, 84.7, 73.7, 72.4, 55.3, 39.9, 39.8, 30.8, 19.9, 19.9, 10.9. Exact mass calcd for $C_{18}H_{32}NO_3$: 310.2382. Found: 310.2390 (CI, NH_3 atmosphere).

(4*R*,5*S*,6*S*)-6-[(4-Methoxybenzyl)oxy]-4-hydroxy-5,7-dimethyl-1-octene. $[\alpha]^{23}_D$ +48° (*c* 0.34, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 2977, 1613, 1514, 1465, 1384, 1302, 1250, 1174, 1111, 1034, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.82 (m, 1 H), 5.11 (m, 2 H), 4.62 (d, J = 10.4 Hz, 1 H), 4.49 (d, J = 10.4 Hz, 1 H), 3.83 (m, 1 H), 3.80 (s, 3 H), 3.27 (dd, J = 3.5 Hz, J = 7.4 Hz, 1 H), 2.93 (s, 1 H), 2.29 (m, 1 H), 2.22 (m, 1 H), 2.01 (octet, J = 6.9 Hz, 1 H), 1.77 (m, 1 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.4, 130.4, 129.4, 117.2, 113.9, 89.3, 74.6, 74.0, 55.3, 39.7, 38.3, 31.0, 19.6, 19.1, 6.8. Exact mass calcd for $C_{18}H_{32}NO_3$: 310.2382. Found: 310.2379 (CI, NH_3 atmosophere).

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Supporting Information Available: Experimental procedures for compounds indicated in the text and structure proofs of all reaction products (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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