A Study Directed to the Asymmetric Synthesis of the Antineoplastic Macrolide Acutiphycin under Enantioselective Acyclic Stereoselection Based on Chiral Oxazaborolidinone-Promoted Asymmetic Aldol Reactions

Syun-ichi Kiyooka* and Mostofa A. Hena

Department of Chemistry, Kochi University Akebono-cho, Kochi 780-8520, Japan

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A shortening of the reaction path can be realized by using a series of the chiral oxazaborolidinone-promoted aldol reaction with respect to the practical synthesis of the (+)-acutiphycin seco acid derivative **5**. The linear strategy is based on the utilization of five aldol reactions with a sequence of silyl nucleophiles, **7**, **8**, **35**, **10**, and **11**, in the presence of stoichiometric amounts of the promoter, **1** or **2**. The construction of the relative configuration between the stereogenic centers is diastereoselectively controlled by the stereochemistry of the promoter used in the enantioselective aldol reaction, which is nearly independent of that of the substrate (promoter control).

The chiral Lewis acid-promoted aldol reaction in which activated aldehydes react with silyl nucleophiles is generally considered to be more practical and useful for the enantioselective construction of aldol skeletons, compared with asymmetric aldol reactions involving chiral auxiliaries. When a chiral Lewis acid can be used successfully as a catalyst, the asymmetric aldol reaction is the reaction of choice. Even in the case where the chiral Lewis acid does not function as a catalyst, the stoichiometric process is still quite useful (in this case the Lewis acid is called a promoter) and more advantageous than the cases of requiring the binding and removal of chiral auxiliaries. This is because the chiral ligands contained by the promoter are recycled in nearly all cases. After the first report by Reetz, who converted a prototype of the Mukaiyama aldol reaction into an asymmetric version by introducing a chiral Lewis acid,[1a] a number of other successful examples appeared in this field; among these are the divalent tin-catalyzed asymmetric aldol reactions found and developed by Mukaiyama and Kobayashi[1b] and the chiral borane (CAB)-catalyzed asymmetric aldol reaction reported by Yamamoto.[1c] Reactions using a titanium reagent, reported by Carreira,[1d] and a copper reagent, reported by Evans,[1e] recently have also led to significantly higher levels of enantioselectivity. During this period, we also described a highly enantioselective aldol reaction, which is promoted by chiral oxazaborolidinones.[2a,b] Similar reactions have also been reported by Masamune[2c,d] and Corey.[2e]

(*S*)- and (*R*)-Oxazaborolidinones, **1** and **2**, respectively, were easily obtained in situ via the reaction of (*S*)- and (*R*)-*N*-tosylvalines with 1 equiv of BH_3·THF which promotes the aldol reaction of a variety of aldehydes with silyl ketene acetals with very high enantioselectivity (Scheme 1). The scope and limitation of the oxazaborolidinone-promoted aldol reaction has been summarized by surveying the stereochemical outcome of reactions which involve enantioselectivities which are acceptable for practical syntheses, even though a stoichiometric amount of the promoter is required.[3] In a stable conformation in the ground state of (*S*)-oxazaborolidinone **1**, as optimized using MOPAC-AM1,[4] one methyl group of the isopropyl substituent is necessarily located at the upper position of the five-membered ring (Figure 1). The stereochemical outcome (*si* facial selectivity) observed in the reaction using **1** can be explained based on the assumption that carbon−carbon bond formation takes place at the bottom of the five-membered ring, thus avoiding steric hindrance by the methyl group. Corey extended this view by suggesting that the conformation is fixed by a hydrogen bonding interaction between the Lewis acid and the aldehyde.[5] Thus, our oxazaborolidinone-promoted aldol reaction presumably proceeds via a transition state assembly, as depicted in Figure 1, in which no $\pi-\pi$ interactions between the aromatic moiety of the promoter and the aldehyde are involved.

Acyclic stereoselection methods, which have been developed in the past two decades, have been largely attained via the diastereoselective inter- and/or intramolecular chirality transfer of the stereochemistry of the first chiral center so that stereoselective construction of acyclic systems, which involve multiple chiral centers, is always affected by the stereochemistry of the substrates used in the reaction.[6] It might be expected that

(1) (a) Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind. (London)* **1986**, 824. (b) Kobayashi, S.; Uchio, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247−4252. (c) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483−3491. (d) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8838. (e) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815.

(2) (a) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278. (b) Kiyooka, S.-i.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927−4930. (c) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365−9366. (d) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729−1732. (e) Corey E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910.

(3) Kiyooka, S.-i. *Rev. Heteroatom Chem.* **1997**, *17*, 245−270.

(4) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(5) (a) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37−40. (b) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351−4354.

(6) (a) Gawly, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*, Pergamon: Oxford, 1996. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press: Boca Roton, 1995.

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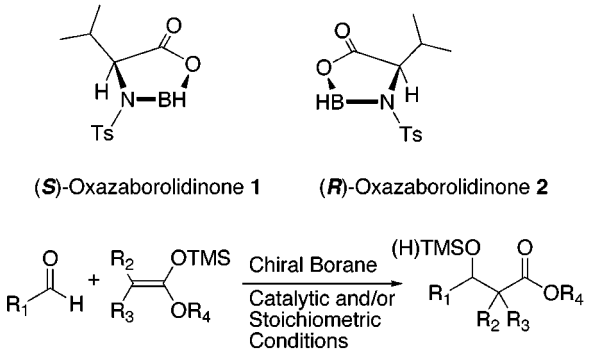
Scheme 1. General Feature of the Oxazaborolidinone-Promoted Asymmetric Aldol Reaction



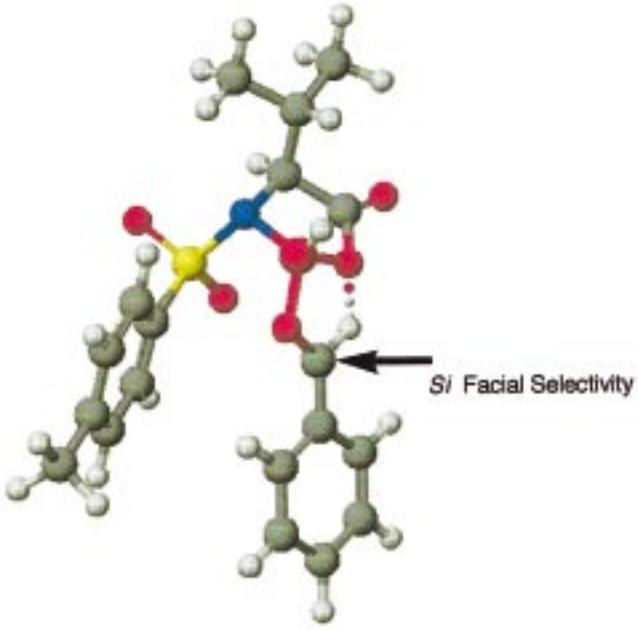


Figure 1.

acyclic stereoselection might evolve to highly efficient levels provided that the enantioselective carbon−carbon bond formation reactions proceed under complete promoter (catalyst) control with no stereochemical effects caused by substrates. During the development of the chiral oxazaborolidinone (**1** and **2**)-promoted asymmetric aldol reaction, we reported an interesting catalyst and/or promoter control[7] on reaction stereochemistry, in which the newly stereogenic center is created by the stereochemistry of the promoter and which is nearly independent of the substrate aldehyde even in the presence of an α-chiral center in the aldehyde.[8] This promoter control has proved to be remarkably straightforward for achieving enantioselective acyclic stereoselection.[8]

We report herein a highly enantioselective synthesis of a seco acid derivative via shortened reaction paths with the use of a series of chiral oxazaborolidinone-promoted aldol reactions toward a practical synthesis of (+)-acutiphycin (**3**).

Results and Discussion

Acutiphycin (**3**) has been shown to be cytotoxic to KB and NIH/3T3 cells and has significant antineoplastic in vivo against murine Lewis lung carcinoma. The structural elucidation of this novel macrolide, which was isolated from the alga *Osillatoria Acutissima*, its biological activity,[9] and spectral analysis, was reported originally by Moore in 1984.[10] The only known route for the synthesis of this macrolide was reported by Smith in 1995.[11] In this route Smith employed a Brown asymmetric allylboration, chelation-controlled introduction of a methyl group, a Still [2,3]-sigmatropic rearrangement, and a Cram enolate addition to generate the stereogenic centers of (+)-acutiphycin.

Despite the report of this macrolide synthesis it appeared to us that the acyclic stereocontrol for the creation of the chiral centers remains a challenging synthetic objective. The complex structure of marine macrolides such as acutiphycin serves as an exciting stage for exhibiting creative synthetic methodology.[12] Aldol reactions, which are auxiliary-, reagent-, and/or substrate-controlled, have been employed for constructing the acyclic structures which contain numerous stereogenic centers.[8] However, few precedents exist for the synthetic approaches using catalyst and/or promoter-controlled aldol reactions. When the stereochemistry of the catalyst (promoter) controls the newly created stereocenter, in preference to that of the substrate in the chiral catalyst and/or promoter-controlled aldol reaction, the reaction proves to be remarkably straightforward for achieving enantioselective acyclic stereoselection.

With our continuing studies on the chiral oxazaborolidinone-promoted asymmetric aldol reaction our aim was to achieve substantial shortening of paths toward complex targets by repeated aldol reactions. The methodology is based on promoter control where enantiomerically pure diastereomers can be provided by repeating the asymmetric aldol reactions controlled by the stereochemistry of the promoter.[8] Thus, our goal is to construct the seco acid **4** (Scheme 2) with a linear strategy using a series of five aldol reactions at the carbon−carbon bonds indicated with slanted lines in the seco acid derivative **6** of acutiphycin in Table 1. The key aldol reactions for this very simple and straightforward synthesis are listed, along with necessary reagents in the presence of a stoichiometric amount of the promoters.

Highly Enantioselective Synthesis of the C11−C22 Subunit. The introduction of the first stereogenic center into the acyclic system is very important because the initial enantiomerical purity will affect the selectivity of each of the subsequent reactions. As a result, an especially high enantioselectivity is demanded for the first reaction. In undertaking the construction of the (*R*)-stereogenic center at C17 of the C11−C22 segment, the reaction started with commercially available hexanal.

(7) The term "Catalyst control" was first introduced by Mukaiyama: (a) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, 831−834. (b) Soai, K.; Shimada, C.; Takeuchi, M. Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567−568.

(8) (a) Kiyooka, S.-i.; Kira, H.; Hena, M. A. *Tetrahedron Lett.* **1996**, *37*, 2597−2600. (b) Kiyooka, S.-i.; Maeda, H. *Tetrahedron: Asymmetry* **1997**, *8*, 3371−3374. (c) Kiyooka, S.-i.; Maeda, H.; Hena, M. A.; Uchida, M.; Kim, C.-S.; Horiike, M. *Tetrahedron Lett.* **1998**, *39*, 8287−8290. (d) Hena, M. A.; Kim, C.-S.; Horiike, M.; Kiyooka, S.-i. *Tetrahedron Lett.* **1999**, *40*, 1161−1164.

(9) Moore, R. E. *Pure Appl. Chem.* **1982**, *54*, 1919−1934.

(10) Barchi, J. J., Jr.; Moore, R. E.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193−8197.

(11) Smith, A. B., Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013−12014.

(12) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

Scheme 2. A Retrosynthesis of Acutiphycin

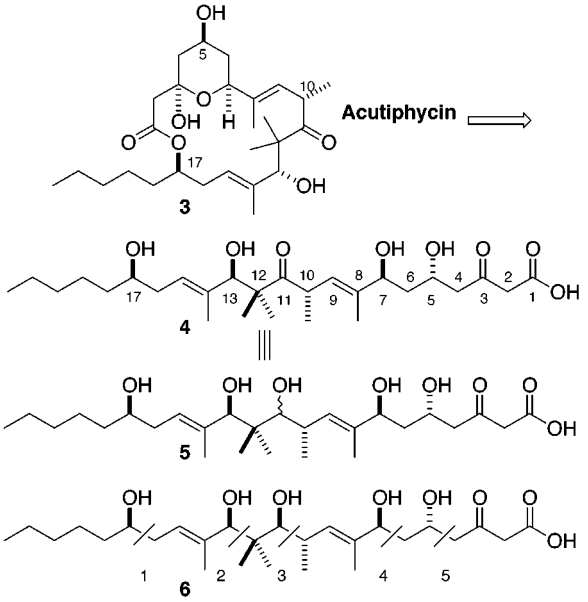
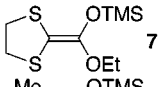
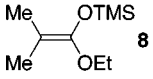
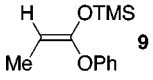
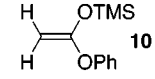
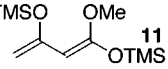


Table 1. A Linear Strategy toward the Seco Acid 6 of Acutiphycin on the Basis of Chiral Oxazaborolidinone-Promoted Asymmetric Aldol Reactions

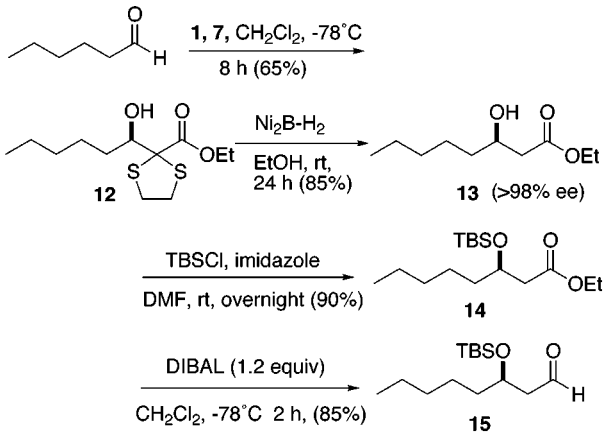
	Aldol Reaction	Promoter Complex	Silyl Nucleophile
1	The First Aldol Reaction	**1**	 **7**
2	The Second Aldol Reaction	**1**	 **8**
3	The Third Aldol Reaction	**1**[a]	 **9**
4	The Fourth Aldol Reaction	**1**	 **10**
5	The Fifth Aldol Reaction	**2**	 **11**

[a] At the beginning of this study we have considered that the planned third aldol reaction proceeds with the sense of anti selectivity.

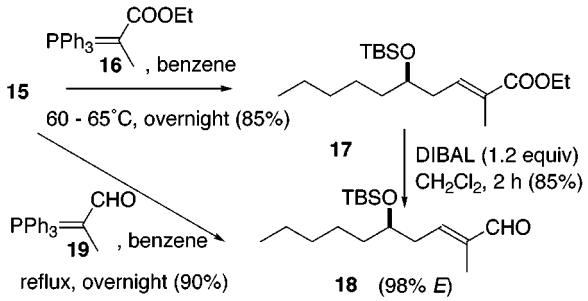
The (*S*)-oxazaborolidinone (**1**)-promoted aldol reaction between a variety of aldehydes and dithiolane silyl ketene acetal is known to provide the corresponding dithiolane aldols with very high enantioselectivities.[13] The necessity of using a dithiolane aldol rests in the fact that the reaction, without steric bulk at the α-position of the silyl ketene acetal, provides low enantiometric acetate aldols under conditions of the chiral oxazaborolidinone-promoted aldol reaction.[2a,b]

The dithiolane substituent of the silyl ketene acetal **7**, derived from ethyl dithiolane-2-carboxylate, enhanced the enantiometric purity of the aldol **13** up to >98% ee under the conditions mentioned above. Treatment of **12** with a large excess of nickel boride (prepared in situ from $NiCl_2$ and $NaBH_4$) for desulfurization, [14] provided the acetate aldol **13** (Scheme 3). The hydroxy group of **13** was protected with TBSCl−imidazole to give *tert*-butyldimethylsilyl ether **14**, followed by subsequent reduction with DIBAL to directly give the corresponding aldehyde **15**.

Scheme 3



Scheme 4



The olefinic bond between C14−C15 was introduced via a Wittig reaction (Scheme 4) using (α-carbethoxyethylidene)triphenylphosphorane (**16**). The resulting olefin **17** showed a *E*/*Z* ratio of 200:1. The *E*/*Z* geometry was identified by comparing the olefinic proton chemical shift with the data available in the literature.[15] The reduction of the ester group of **17** with DIBAL gave the corresponding aldehyde **18**. To reduce the number of the reaction steps, we used (α-formylethylidene)triphenylphosphorane (**19**)[16] to prepare the desired aldehyde **18** in one step. This reaction also showed an excellent *E*/*Z* ratio.

Our previous results promised a high enantioselectivity for the second chiral oxazaborolidinone-promoted aldol reaction using a silyl ketene acetal derived from ethyl isobutyrate.[2a,b] The reaction of olefinic aldehyde **18** with silyl nucleophile **20** proceeded well in the presence of chiral promoter **1** to give the TBS-acetal derivative **21** (the stereochemistry at the acetal carbon, however, was unclear) in 70% yield (Scheme 5). The resulting acetal **21** was converted to the corresponding aldehyde **23** by treatment with 80% AcOH. However, an attempt to protect the hydroxy group of **23** with TBSCl, unfortunately, failed. The protection of **21** was then carried out by using TBSOTf and 2,6-lutidine in CH_2Cl_2 to give the multiple TBS-protected compound **22**. However, hydrolysis of the acetal group of **22** with 80% AcOH did not give the desired products.

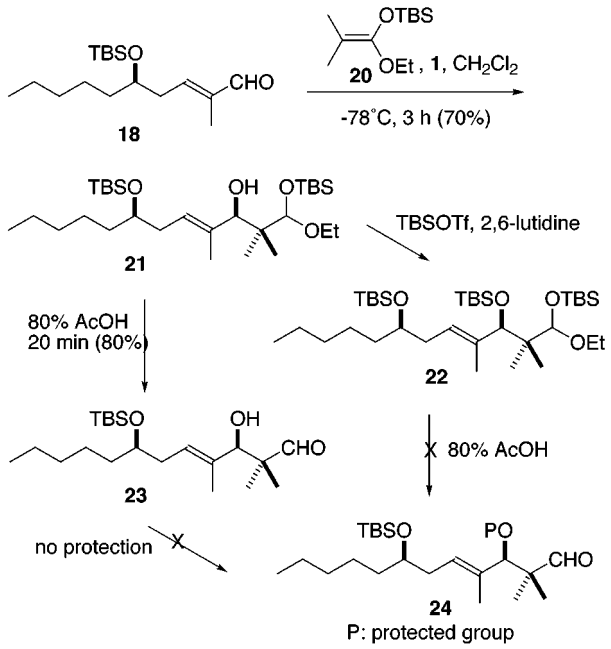
(13) Kiyooka, S.-i.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2181−2184.

(14) Flippin, L. A.; Dombroski, M. A. *Tetrahedron Lett.* **1985**, *26*, 2977−2980.

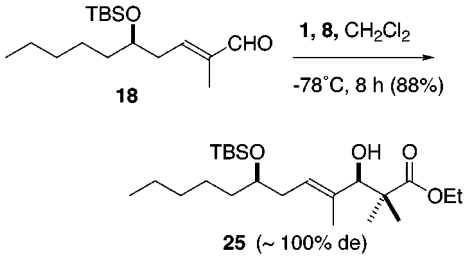
(15) (a) Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259−1262. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873−3888. (c) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(16) (a) Schlessinger, R. H.; Pross, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391−2394. (b) Trippet, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 1266−1272.

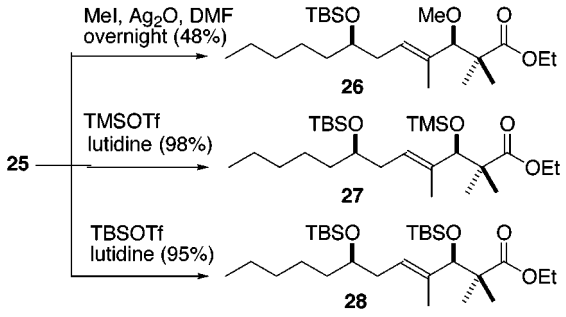
Scheme 5



Scheme 6

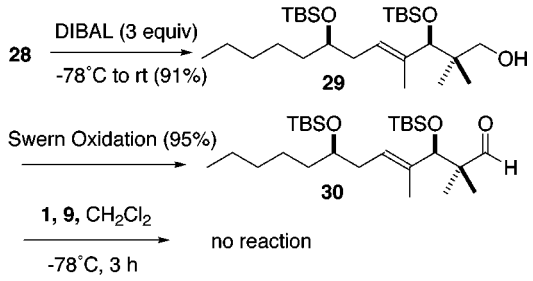


Scheme 7

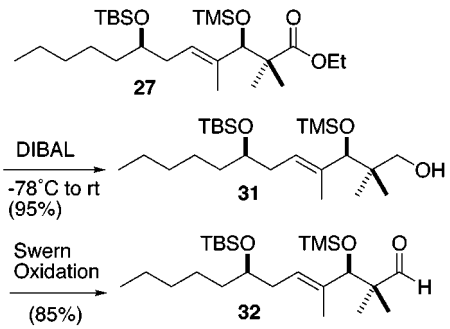


Thus, in the second chiral oxazaborolidinone-promoted aldol reaction trimethylsily ketene acetal **8** was used instead of *tert*-butyldimethylsilyl ketene acetal **20** to construct the isobutyrate aldol **25**. As expected, this reaction proceeded smoothly to give the corresponding aldol **25** as a single diastereomer in high yield (88%) (Scheme 6). Protection of the hindered hydroxy group of **25** was carried out with three different reagents to give methyl, trimethylsilyl, and *tert*-butyldimethylsilyl ethers (**26**, **27**, and **28**), respectively (Scheme 7). The TBS-protected ether **28** was treated with DIBAL in an usual manner (−78 °C, 2 h, quenched at −78 °C), but instead of giving the corresponding aldehyde remained largely unchanged with only a small portion converted to the corresponding alcohol. The protected aldol **28** was treated with DIBAL for 2 h at −78 °C, allowed to warm to room temperature, and quenched to give the corresponding

Scheme 8



Scheme 9



alcohol **29**, which, after Swern oxidation, gave the desired aldehyde **30**. However, the third chiral oxazaborolidinone-promoted aldol reaction of **30** with silyl ketene acetal **9** did not proceed, due presumably to steric hindrance around the aldehyde function which restricted the minimal approach required for coordination between the aldehyde and the chiral oxazaborolidinone (Scheme 8). Thus it became obvious that a smaller protecting group might lead to the expected result.

The subsequent direct reduction of *β*-trimethylsiloxy ester **27** to the corresponding aldehyde **32** by DIBAL under conditions at −78 °C proved to be more difficult than anticipated because of steric factors. Ester **27** was then reduced to alcohol **31**, followed by Swern oxidation to give the desired aldehyde **32** in good yield (Scheme 9).

Unexpected Selectivity in the Aldol Reaction with Pivalaldehyde as a Model of Highly Hindered Aldehydes. At the initial stage of our investigations we believed that the chiral oxazaborolidinone-promoted aldol reactions of the highly hindered aldehyde **32** with silyl nucleophile **9** proceed according to the mode of selectivity of anti preference on the basis of observations that follows (Scheme 10). The asymmetric aldol reaction of isobutyraldehyde with silyl nucleophile **9**, which gives largely the *E*-isomer (92%), resulted in a slight excess of *anti* diastereoselectivity with relatively lower enantioselectivity, compared with that of the minor syn isomer.[2b] In addition, we observed that the aldol reaction of pivalaldehyde with silyl nucleophile **10** proceeds with extremely high enantioselectivity (98% ee). On the basis of these two results, we strongly expected that the aldol reaction of pivalaldehyde with silyl nucleophile **35** (*E*/*Z* = 85:15) instead of **9** would preferentially give the anti isomer with very high enantioselectivity. However, the reaction with **9** did not proceed because of excess steric hindrance. We then explored the aldol reaction of pivaldehyde with **35** as a model reaction of **32** with **35**.

Very surprisingly, and contrary to our expectation, the syn isomer was obtained as the major product (22:1) in 96% ee. The diastereochemistry of the products was

Scheme 10

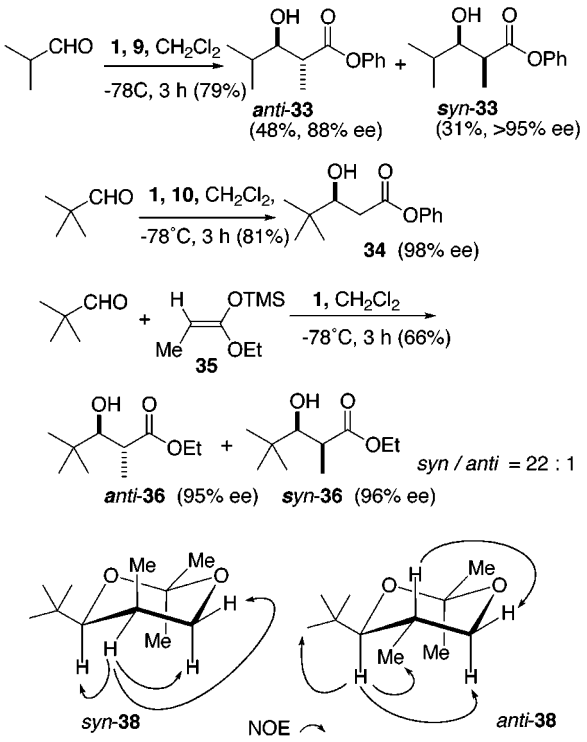


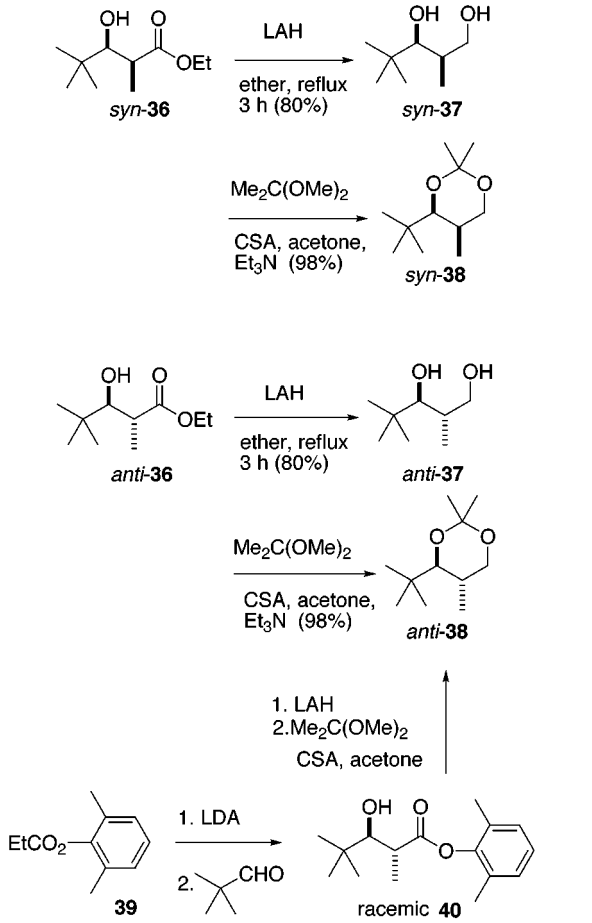
Figure 2. The NOEs detected for *syn*-**38** and *anti*-**38**.

assigned by a comparison of the acetonides, *syn*-**38** and *anti*-**38**,[17] derived from *syn*-**36** and *anti*-**36**, respectively. The NOEs of these compounds also confirmed the structures (Figure 2). *anti*-**38** was alternatively prepared via anti aldol **40** by a known stereoselective procedure using the enolate of **39**[18] (Scheme 11).

The result, which involved an unexpected switching of diastereoselectivity along with very high enantioselectivity in the reaction with pivaldehyde, was very surprising. This unexpected switching of diastereoselectivity observed in the reaction of the bulky aldehyde can be explained on the basis of Corey's hydrogen bond model between the aldehyde hydrogen and the promoter boranering oxygen[5] that the reaction presumably proceeds through **A** or **C**, shown in Figure 3 where **B** is destabilized by gauche interactions between the methyl and *tert*-butyl groups and between the *tert*-butyl and enol groups.[18] In any event the validity of the aldol reaction with **35** was verified on introducing, in a syn-selective manner, a methyl group into such a highly sterically hindered skeleton in acyclic systems.

Construction of the Stereocenter at C10. In the presence of a stoichiometric amount of chiral borane **1**, aldehyde **32** smoothly underwent an aldol condensation with 3 equiv of **35** at −78 °C for 24 h to give a mixture of the aldols, **41**−**44**, in 92% yield. An extended reaction time (>20 h) is necessary in order to obtain acceptable yields. The results are summarized in Scheme 12 and Table 2. The stereochemistry of the products was assigned by a comparison of the observed *J* values indicating the relative stereochemistry between C2 and C3. In

Scheme 11



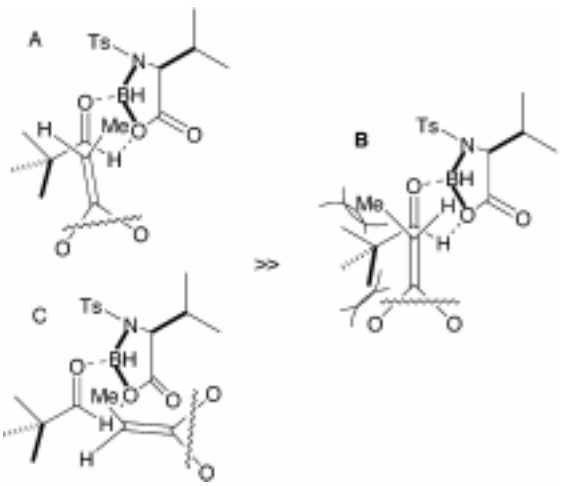


Figure 3. Transition state assemblies to syn aldol.

this system, adjacent to a quaternary carbon, the coupling constants of syn isomers are larger than those of anti isomers, contrary to common cases,[19] as shown in Table 3. The NOE experiments of the acetonide **46** derived from **41** confirmed the stereochemistry (Scheme 13, Figure 4). The ratio of **41** + **43** to **42** + **44** corresponds to the diastereofacial selectivity while each ratio of **41** to **43** and **42** to **44** corresponds to the enantiofacial selectivity in the reaction. High syn (10:1) predominance was observed and each syn and anti product showed a

(17) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727−1732.

(18) Gennari, C. *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, 1988; pp 53−71.

(19) Mulzer, J.; Zippel, M.; Brüntrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108−1134.

Scheme 12

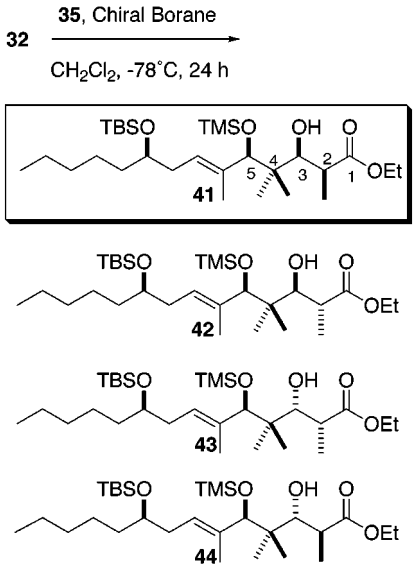
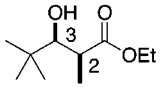
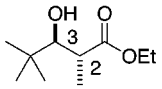
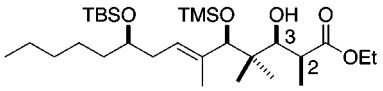
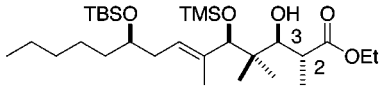


Table 2. Chiral Oxazaborolidinone-Promoted Aldol Reaction with Aldehyde 32

chiral borane	yield (%)	syn/anti[a]	syn[b] **41**/**43**	anti[b] **42**/**44**
1 (L-valine)	92	10:1	12:1	10:1
2 (D-valine)	54	4.5:1	4:1	1.5:1

[a] The syn/anti ratio (**41** + **43**/**42** + **44**) is corresponding to the diastereoselectivity of the reaction. [b] The each syn (**41**/**43**) and anti (**42**/**44**) ratio is corresponding to the enantioselectivity of the reaction.

Table 3. The List of the Characteristic Vicinal Coupling Constants ($J_{2,3}$) Related to the Relative Stereochemistry between C2 and C3 in the System Having a Tertiary Substituent at C3

compound	$J_{2,3}$ (Hz)
 *syn*-**36**	4.6
 *anti*-**36**	2.0
 **41**[a]	6.6
 **42**	4.1

[a] The relative stereochemistry of C2 and C3 of **41** was confirmed on the basis of NOE experiments of the acetonide derivative, which was prepared from LAH reduction of **41** followed by acetonization.

considerably high enantiofacial selectivity which can be attributed to the inherent si-facial selectivity of the chiral oxazaborolidinone **1**. Promoter control apparently exists, which is independent of the stereochemistry of the substrate. However, when chiral borane **2**, derived from D-valine, was used, the yield was considerably lower (54%). The stereochemical response was poor for each diastereo- and enantioselevtivity; but a similar preponderance was observed for the each selectivity, compared with the reaction with **1**. To explore the possibility that substrate control operates as giving a preference to (*S*)-

Scheme 13

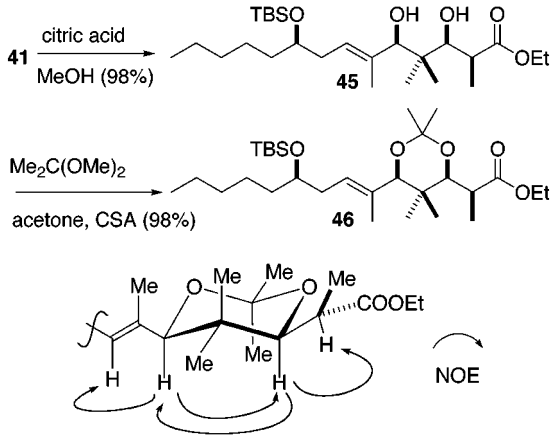


Figure 4. The NOEs detected for compund **46**.

Scheme 14

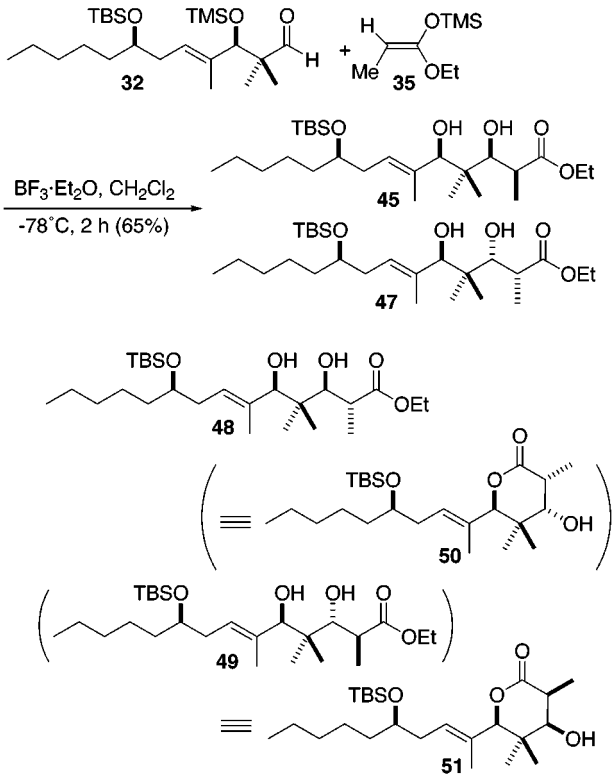


Table 4. Product Ratios Observed in the BF_3-Catalyzed Aldol Reaction of 32 with 35 (Scheme 14)

45:**47**:**48**:**51** = 1:1:1:1
2,3-syn/2,3-anti = 1:1
3,5-syn/3,5-anti = 1:1

configuration at C3 of the products in the reaction with **2**, we carried out the reaction of **32** with **35** in the presence of achiral Lewis acid, BF_3·OEt_2. The BF_3-catalyzed reaction gave four products, **45**, **47**, **48**, and **51**, as shown in Scheme 14. It was obvious that no substrate control appears, relative to C2 and C3 (Table 4). Consequently, the syn preference observed in the presence of chiral promoter **2** cannot be ascribed to any type of substrate control.

The enhanced syn selectivity in the presence of chiral promoter **1** can be rationally explained by using Figure 5. The spatial orientation of the siloxy group at C3 is presumably fixed by the introduction of two methyl

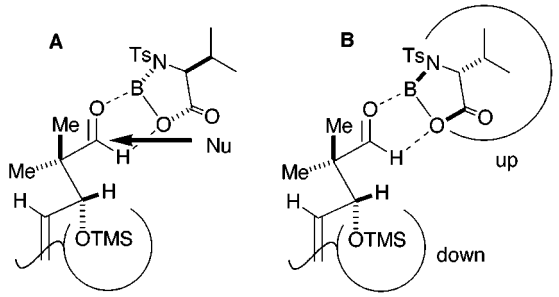
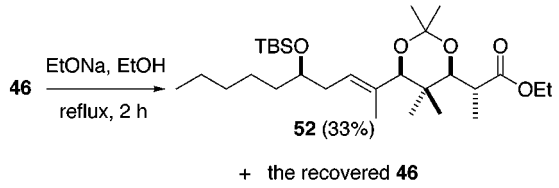


Figure 5. A transition state model explaining the unexpected switch of diastereoselectivity.

Scheme 15



groups at C2, which affect the conformation of the entire aldehyde, and, when the chiral borane coordinates to the aldehyde, an adequate fit between the stereocenters of the catalyst and the substrate (at C3) might be achieved to provide stereochemical outcome expected from promoter control. An effective approach of the silyl nucleophile may take place via a path, such as **A** for the case of promoter control with **1** where an adequate space is open to the nucleophile. On the other hand, the reaction with **2** (from D-valine) diminished promoter control and substrate control because of stereochemically unsuitable interactions where the TMSO group and oxazaborolidinone moiety reversely locate relative to the face of the five-membered ring involving the carbonyl group, shown in **B**.

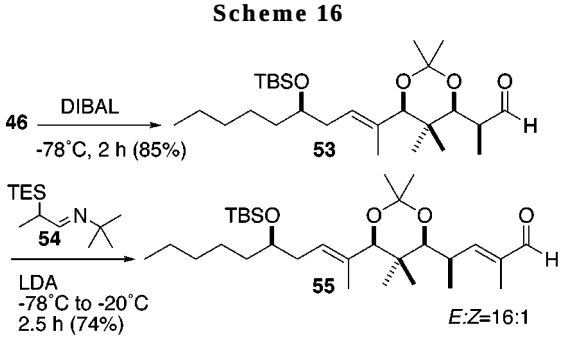
The stereochemistry at C2 of the major product **41** was opposite relative to that at C10 in acutiphycin. From the standpoint of the total synthesis of acutiphycin, this is not necessarily a serious disadvantage. After cyclization to the macrolactone, epimerization at C10 would overcome this problem.

We alternatively considered the epimerization at C10 related to the target molecule at this stage. When the major isomer **46** from the aldol reaction was treated with sodium ethoxide under thermodynamic conditions, the expected isomer **52** was isolated in 33% yield along with recovered **46** (Scheme 15).

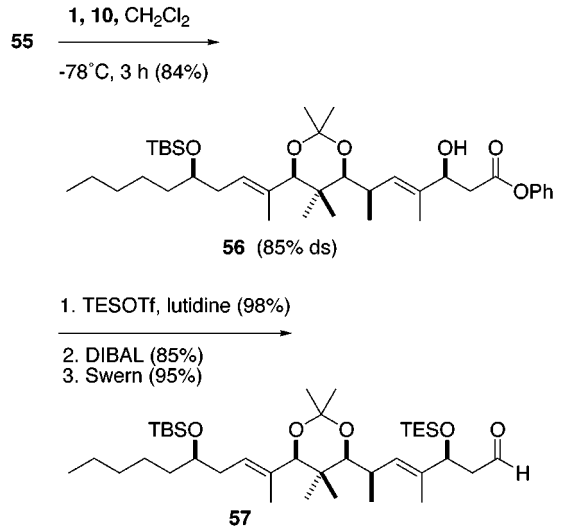
Enantioselective Bond Extension to the C1−C10 Subunit. The economic homologation of the aldehyde moiety, which is accompanied by double bond formation, was addressed in the next step. An effective reagent **54** for this purpose has been reported.[20] The aldehyde **53**, directly obtained by the DIBAL reduction of **46**, was treated with the α-silyl imine **54** under LDA conditions to give the α,β-unsaturated aldehyde **55** with very high *E* geometry (16:1) in 74% yield (Scheme 16).

The next step is the introduction of an acetate aldol unit by a fourth aldol reaction. Although the best reagent for high enantioselectivity is generally considered to be the dithiolane silyl nucleophile **7**, we were not able to use it for this step because the desulfurization process under a hydrogen atmosphere reduces the double bonds in the acyclic subtrate **55**. The reaction of **55** with unsubstituted silyl nucleophile **10** in the presence of chiral borane **1** proceeded smoothly to give aldol **56** in 84% yield with 85% de. Fortunately, the undesired isomer was easily separated by flash column chromatography. After TES protection, the last aldehyde **57** was prepared via a two-step procedure (DIBAL reduction and Swern oxidation) in good yield (Scheme 17).

Scheme 16



Scheme 17



Provided that an acetoacetate unit can be enantioselectively introduced by the fifth aldol reaction, the synthesis of the linear seco acid of acutiphycin can now be realized. Adequate reagents, such as silyl nucleophile **58**[21] and disilyl nucleophile **11**,[22] have been prepared. Highly enantioselective chiral Lewis acid-catalyzed aldol reactions using **58** have been reported by two groups,[23] but the reagent **58** gave unacceptable results in our chiral oxazaborolidinone-promoted aldol reaction, only 16% ee of **59** for benzaldehyde, as shown in Scheme 18. The fifth aldol reaction for the final stage was achieved using disilyl nucleophile **11**. The reaction of benzaldehyde in the presence of chiral borane **1** gave aldol **60** in 72% yield with 61% ee in a model reaction. After protection and reduction, the fifth aldol reaction of **57** with disilyl

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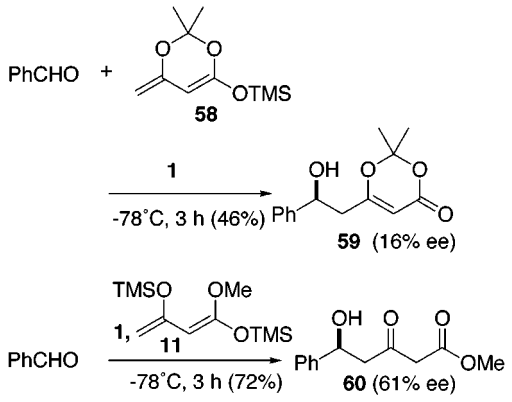
(21) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91−95.

(22) Yamamoto, K.; Suzuki, S.; Tsuji, J. *Chem. Lett.* **1978**, 649−652.

(23) (a) Sato, M. Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pham. Bull.* **1994**, *42*, 839−845. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360−12361.

Scheme 18



Scheme 19

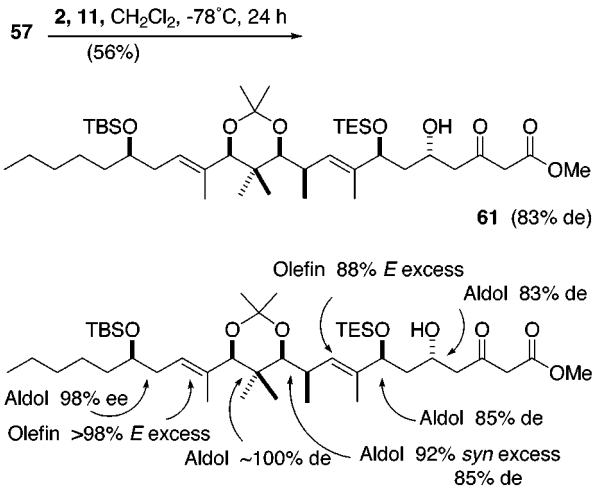


Figure 6. Each selectivity found in the reaction sequence.

nucleophile **11** in the presence of **2** permitted a straightforward synthesis of the C10-epi seco acid derivative **61** of acutiphycin with 83% de. The final compound **61** was easily separated from the isomer by flash column chromatography (Scheme 19).

Conclusion

The synthesis of the (+)-acutiphycin seco acid derivative **5** having six stereogenic centers was achieved from hexanal by a linear strategy using the chiral oxazaborolidinone-promoted asymmetric aldol reaction in only 16 steps. The excellent to good enantioselectivities in the five aldol reaction sequences and the high *E* selection in the two olefination steps were obtained, as shown in Figure 6. On the route to the synthesis of **61** no special separation of isomers was required, presumably because of the high purity of each reaction product. Such high selective reactions allow for the shortening of the pathway to this complex target. It is clear that the chiral oxazaborolidinone-promoted asymmetric aldol reaction is practical for the construction of the carbon backbones having multichiral centers with enantioselective acyclic stereoselection.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Dichloromethane, diisopropylamine, and triethylamine were distilled from calcium hydride under a nitrogen atmosphere. Dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and 2,6-lutidine were distilled from calcium hydride under reduced pressure. Oxalyl chloride was distilled prior to use. All reactions involving organometallic reagents were conducted under an argon atmosphere. Infrared spectra are reported in wavenumber (cm^{-1}). All proton NMR spectra were measured in $CDCl_3$ solvent, and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.00) as internal standard. Data are tabulated in the following order: multiplicity, coupling constants in hertz, number of protons. All carbon NMR spectra were measured in $CDCl_3$ solvent, and chemical shifts are reported as δ values in parts per million relative to $CDCl_3$ (δ 77.0) as internal standard.

1-Ethoxy-1-(trimethylsiloxy)-2,2-(ethylenedithio)ethene (7). To a solution of diisopropylamine (0.77 mL, 5.5 mmol) in dry THF (25 mL) at 0 °C was added *n*-BuLi (3.45 mL, 5.5 mmol, 1.6 M in hexane) dropwise. The solution was cooled to −78 °C, and ethyl dithiolanecarboxylate (0.70 mL, 5.0 mmol) was added dropwise over 30 min. After 25 min, chlorotrimethylsilane (1.27 mL, 10 mmol) was added, and the solution was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent in vacuo, the residue was diluted with dry hexane and filtered through Celite. After removal of the hexane in vacuo, the residual oil was distilled (bp 108−109 °C/ 0.1 mmHg) to give the pure silyl nucleophile **7** as a yellow oil (937 mg, 75%). IR (film) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ (ppm) 3.82 (q, J = 7.0 Hz, 2H), 3.21 (brs, 4H), 1.20 (t, J = 7.0 Hz, 3H), 0.19 (s, 9H).

Ethyl (3*R*)-2,2-(Ethylenedithio)-3-hydroxyoctanoate (12). To a solution of *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added BH_3·THF (1.0 mL, 1.0 mmol, 1 M in THF). The solution was allowed to stir for 30 min at 0 °C and then additionally for 30 min at room temperature. The solution was cooled to −78 °C, and hexanal (100.1 mg, 1 mmol) in CH_2Cl_2 (1 mL) was added slowly over 5 min. After stirring for 5 min, **7** (275 mg, 1.1 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min, the reaction mixture was stirred for 3 h, and a buffer solution (5 mL, pH 6.86) was added to quench the reaction. The reaction mixture was allowed to warm to room temperature. After phases were separated, the organic phase was diluted with ether, washed with sat. aq $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated in vacuo. Flash column chromatography (10% ethyl acetate/hexane) provided the pure aldol **12** (180.9 mg, 65%, 98% ee, CHIRALCEL OD, 1.5% 2-propanol/hexane, 1.0 mL/min, R_f 20.5 min, λ 210 nm). $[\alpha]^{24}_D$ +10.0 (*c* 1.4, $CHCl_3$). IR (film) 3490, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.25 (q, J = 7.0 Hz, 2H), 4.05 (d, J = 9.7 Hz, 1H), 3.33−3.42 (m, 4H), 2.82 (brs, 1H), 1.33−1.67 (m, 8H), 1.32 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.8, 75.8, 75.5, 62.2, 39.9, 39.8, 34.0, 31.4, 26.1, 22.4, 13.9, 13.8. Anal. Calcd for $C_{12}H_{22}O_3S_2$: C, 51.76; H, 7.96. Found: C, 51.70; H, 8.01.

Ethyl (3*R*)-3-Hydroxyoctanoate (13). To a solution of **12** (1.1 g, 4.0 mmol) in ethanol (40 mL) was mixed anhydrous $NiCl_2$ (25.9 g, 0.2 mol), and the mixture was kept under H_2 pressure. Then the mixture was cooled to −10 °C, and $NaBH_4$ (3.8 g, 0.1 mol) was added in portions while the mixture was stirred vigorously with a mechanical stirrer. The same temperature was maintained until the evolution of gas was ceased. The resulting black mixture was allowed to warm to room temperature and stirred vigorously for 16 h. The reaction mixture was filtered, and the solvent ethanol was removed in vacuo. The concentrated residue was diluted with ether, washed with water, and dried over $MgSO_4$. After evaporation of the ether, the crude material was purified by flash column chromatography to give acetate aldol **13** (640 mg, 85%, 98% ee, CHIRALCEL OD, 5% 2-propanol/hexane, 0.5 mL/min, R_f 11.9 min, λ 210 nm) as a colorless oil. $[\alpha]^{24}_D$ −22.0 (*c* 1.0, $CHCl_3$); IR (film) 3485, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.17 (q, J = 7.0 Hz, 2H), 3.97−4.12 (m, 1H), 3.05 (brs, 1H), 2.49 (dd, J = 16.3, 3.4 Hz, 1H), 2.39 (dd, J = 16.3, 9.0

Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.25−1.54 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.9, 67.9, 60.5, 41.3, 36.4, 31.6, 25.0, 22.5, 14.1, 13.9. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.82; H, 10.68.

Ethyl (3*R*)-3-(*tert*-Butyldimethylsiloxy)octanoate (14). To a solution of imidazole (0.82 g, 12.0 mmol) in DMF (5 mL) was added TBSCl (0.91 g, 6.0 mmol) in DMF (2 mL) over 2.5 min. The solution was stirred at room temperature for 10 min. A solution of **13** (0.75 g, 4.0 mmol) in DMF (1 mL) was introduced dropwise, and the solution was allowed to stir overnight. The reaction mixture was poured into ice−water, extracted with ether, washed with sat. aq NH_4Cl solution and brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude residue was purified by flash column chromatography (2.5% ethyl acetate/hexane) to give TBS ether **14** (1.10 g, 90%) as a colorless oil. $[\alpha]^{24}_D$ −15.0 (*c* 1.2, $CHCl_3$); IR (film) 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.11 (q, J = 7.0 Hz, 2H), 4.07 (m, 1H), 2.38 (dd, J = 14.6, 7.1 Hz, 1H), 2.33 (dd, J = 14.6, 5.9 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.21−1.44 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 171.8, 69.4, 60.1, 42.6, 37.5, 31.8, 25.7, 24.5, 22.5, 17.9, 14.1, 13.9, −4.5, −4.8. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.47; H, 11.41.

(3*R*)-3-(*tert*-Butyldimethylsiloxy)octanal (15). To a cooled (−78 °C) solution of ester **14** (302 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added DIBAL (1.2 mL, 1.2 mmol, 1 M in toluene) over a period of 30 min, the reaction mixture was allowed to stir at −78 °C for 2 h, and MeOH was added to quench the reaction. After 15 min water (2 mL) was added, the resulting mixture was then allowed to warm to room temperature and stirred vigorously to form a precipitate. Workup procedures were carried out with filtration of precipitate, separation of phases, washing with water and brine, drying over $MgSO_4$, and evaporation of the solvent. Purification of the residue by flash column chromatography (2.5% ethyl acetate/hexane) provided aldehyde **15** (219 mg, 85%) as a colorless oil. $[\alpha]^{24}_D$ −5.0 (*c* 1.0, $CHCl_3$); IR (film) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.75 (t, J = 2.4 Hz, 1H). 4.13 (quin, J = 5.8 Hz, 1H), 2.45 (dd, J = 5.6, 2.4 Hz, 2H), 1.22−1.51(m, 8H), 0.85 (t, J = 6.8 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 202.4, 68.2, 50.7, 37.7, 31.7, 25.6, 24.7, 22.5, 17.9, 13.9, −4.5, −4.7. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.12; H, 11.78.

Ethyl (2*E*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-2-methyldec-2-enoate (17). A mixture of aldehyde (258 mg, 1.00 mmol) and (α-carbethoxyethylidene)triphenylphosphorane (402 mg, 1.1 mmol) in dry benzene (10 mL) was heated at 60−65 °C under a nitrogen atmosphere with stirring. After 3 h the solution was cooled to room temperature and evaporated to dryness, and ether (10 mL) was mixed. The precipitate was removed by filtration and evaporation of the filtrate gave a crude product (*E*:*Z*, 200:1; ^{1}H NMR). The crude was purified by flash chromatography (10% ethyl acetate/hexane) to give (*E*)-olefin **17** (291 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) 6.76 (t, J = 6.6 Hz, 1H) 4.14 (q, J = 7.0 Hz, 2H), 3.64−3.72 (m, 1H), 2.26 (t, J = 6.6 Hz, 2H), 1.79 (s, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.20−1.39 (m, 8H), 0.84 (brs, 12H), 0.01 (s, 6H). Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.61; H, 11.18. Found: C, 66.73; H, 11.23.

(2*E*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-2-methyldec-2-enal (18). A mixture of aldehyde **15** (258 mg, 1.00 mmol) and (α-formylethylidene)triphenylphosphorane (350 mg, 1.1 mmol) in dry benzene (15 mL) was refluxed under a nitrogen atmosphere with stirring for 18 h. The solution was then allowed to cool to room temperature, the benzene was removed in vacuo, and the concentrated material was diluted with ether (10 mL). The solid was removed by filtration, and evaporation of the filtrate gave a crude product (*E*:*Z*, 99:1; ^{1}H NMR). The crude was purified by flash chromatography to give (*E*)-olefin **18** (268 mg, 90%) as a colorless oil. $[\alpha]^{23}_D$ +14.0 (*c* 1.5, $CHCl_3$). IR (film) 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.35 (s, 1H). 6.55 (t, J = 7.3 Hz, 1H), 3.81 (quin, J = 5.8 Hz, 1H), 2.48 (t, J = 6.8 Hz, 2H), 1.72 (s, 3H), 1.17−1.45 (m, 8H), 0.86 (s, 9H), 0.84 (t, J = 6.5 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 194.9, 151.1, 140.2, 71.1, 37.3, 36.6, 31.8, 25.7, 24.9, 22.5, 17.9, 13.8, 9.3, −4.6. Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.26; H, 11.51.

Aldehyde **18** was also obtained from **17**, employing a DIBAL reduction procedure similar to that for aldehyde **15**. **17** (342 mg, 1 mmol) and DIBAL (1.2 mL, 1.2 mmol, 1 M in toluene) in CH_2Cl_2 (10 mL) at −78 °C for 2 h afforded aldehyde **18** (256 mg, 89%) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil.

(α-Formylethylidene)triphenylphosphorane (19). *n*-Butyllithium (6.9 mL, 11.0 mmol, 1.6 M in toluene) was added dropwise to a stirred suspension of ethyltriphenylphosphonium iodide (10.0 mmol) in THF (33 mL) at 22 °C under a nitrogen atmosphere. The resulting red solution was stirred for 1 h and then cooled to 0 °C. Freshly sublimed potassium *tert*-butoxide (1.24 g, 11.0 mmol) was added followed by a rapid addition of ethyl formate (2.02 mL, 25 mmol). The buff-colored reaction mixture was kept at 0 °C for 15 min and then quenched with 1 M HCl (12.5 mL). Dichloromethane (75 mL) was added to the reaction mixture and the pH of the aqueous layer adjusted to pH 8 by adding 10% NaOH (aq) solution, followed by stirring at 0 °C for 0.5 h. The aqueous layer was separated and extracted further with CH_2Cl_2 (50 mL). The combined organic extracts were dried and evaporated in vacuo to give an oil that was crystallized from CH_2Cl_2/Et_2O to afford a white solid (84%, mp 180−182 °C). Recrystallization from benzene/hexane afforded a material (overall 78%, mp 213-217 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.04 (d, J = 2.4 Hz, 1H), 7.50−7.71 (m, 15H), 1.88 (dd, J = 13.6, 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 178.9, 178.7, 133.7, 133.6, 132.7, 132.5, 129.0, 128.9, 124.5, 123.6, 10.6.

(4*E*,3*R*,7*R*)-1,7-Bis(*tert*-butyldimethylsiloxy)-1-ethoxy-3-hydroxy-2,2,4-trimethyldodec-4-ene (21). The aldol condensation procedure described for the preparation of aldol **12** was employed with aldehyde **18** (298 mg, 1 mmol), **20** (253 mg, 1.1 mmol), BH_3·THF (1.0 mL, 1.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol), and CH_2Cl_2 (5 mL) at −78 °C for 3 h to give **21** (371 mg, 70%) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{23}_D$ +25.0 (*c* 1.0, $CHCl_3$); IR (film) 3516 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ (ppm) 5.32 (t, J = 7.0 Hz, 1H) 4.50 (s, 1H), 4.32 (s, 1H), 3.84 (q, J = 7.0 Hz, 2H), 3.35 (quin, J = 5.8 Hz, 1H), 2.16 (t, J = 6.1 Hz, 2H), 1.89 (brs, 1H), 1.60 (s, 3H), 1.20−1.45 (m, 8H), 1.25 (t, J = 7.0 Hz, 3H), 1.09 (s, 3H), 0.89 (s, 9H), 0.87 (t, J = 6.5 Hz, 3H), 0.84 (s, 9H), 0.72 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.01 (s, 6H).

(4*E*,3*R*,7*R*)-1,3,7-Tris(*tert*-butyldimethylsiloxy)-1-ethoxy-2,2,4-trimethyldodec-4-ene (22). Employing a similar procedure described for the preparation of TMS ether **27** with a change in reaction time (7 h), alcohol **21** (531 mg, 1 mmol), 2,6-lutidine (0.44 mL, 3.8 mmol), TBSOTf (0.41 mL, 1.8 mmol), and CH_2Cl_2 (5 mL) afforded TBS ether **22** (613 mg, 95%) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil. ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.34 (t, J = 7.0 Hz, 1H), 4.57 (s, 1H), 4.13 (s, 1H), 3.68 (q, J = 7.0 Hz, 2H), 3.28 (quin, J = 5.8 Hz, 1H), 2.15 (t, J = 6.8 Hz, 2H), 1.57 (s, 3H), 1.22−1.45 (m, 8H), 1.17 (t, J = 7.0 Hz, 3H), 1.04 (s, 3H), 0.88 (s, 27H), 0.87 (t, J = 6.8 Hz, 3H), 0.69 (s, 3H), 0.05 (brs, 18H).

Ethyl (4*E*,3*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,2,4-trimethyldodec-4-enoate (25). The aldol condensation procedure described for aldol **12** was employed using aldehyde **18** (298 mg, 1.0 mmol), **8** (207 mg, 1.1 mmol), BH_3·THF (1.0 mL, 1.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol), and CH_2Cl_2 (5 mL) at −78 °C for 3 h to give aldol **25** (282 mg, 68%, ∼100% de; ^{1}H NMR) after flash column chromatography (5% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{24}_D$ +12.0 (*c* 1.0, $CHCl_3$); IR (film) 3442, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.40 (t, J = 7.0 Hz, 1H), 4.16 (dq, J = 7.0, 1.2 Hz, 2H), 4.05 (d, J = 6.0 Hz, 1H), 3.69 (quin, J = 6.3 Hz, 1H), 3.22 (d, J = 6.0 Hz, 1H), 2.18 (brt, J = 6.8 Hz, 2H), 1.57 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.22 (s, 3H), 1.19−1.40 (m, 8H), 1.12 (s, 3H), 0.88 (s, 9H), 0.87 (t, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.9, 135.3, 126.0, 83.0, 71.9, 60.7, 46.1, 36.6, 35.6, 31.9, 25.8, 25.0, 24.1, 22.5, 20.9, 18.0, 13.9, 13.0,

−4.4, −4.6. Anal. Calcd for $C_{23}H_{46}O_4Si$: C, 66.61; H, 11.18. Found: C, 66.53; H, 11.09.

Ethyl (4*E*,3*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-3-methoxy-2,2,4-trimethyldodec-4-enoate (26). To a stirred solution of alcohol **25** (414 mg, 1 mmol) in DMF (5 mL) at room temperature was added MeI (0.19 mL, 3 mmol). Silver(I) oxide (463 mg, 2.0 mmol) was added to the reaction mixture in portions over a period of 1.5 h. After stirring the mixture overnight at room temperature, CH_2Cl_2 (20 mL) was poured into the mixture which was concentrated in vacuo. The resulting residue was diluted with ether and washed with water and brine. After drying over $MgSO_4$, the solvent was evaporated to a crude resedue. The crude was purified by flash chromatography (2% ethyl acetate/hexane) to give ether **26** (205 mg, 48%) as a colorless oil. $[\alpha]^{24}_D$ +30.0 (*c* 1.0, $CHCl_3$); IR (film) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.44 (t, J = 7.0 Hz, 1H), 4.13 (ddq, J = 30.4, 10.8, 7.0 Hz, 2H), 3.77 (s, 1H), 3.72 (quin, J = 6.0 Hz, 1H), 3.16 (s, 3H), 2.24 (dt, J = 6.6, 6.4 Hz, 2H), 1.58 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.23−1.45 (m, 8H), 1.14 (s, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.87 (t, J = 6.6 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 176.8, 132.7, 127.8, 90.9, 71.9, 60.2, 56.7, 47.6, 36.6, 35.8, 31.9, 25.8, 25.0, 23.0, 22.6, 20.1, 18.1, 14.2, 14.0, 13.5, −4.3, −4.5. Anal. Calcd for $C_{24}H_{48}O_4Si$: C, 67.24; H, 11.28. Found: C, 67.27; H, 11.26.

Ethyl (4*E*,3*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2,4-trimethyl-3-(trimethylsiloxy)dodec-4-enoate (27). To a solution of alcohol **25** (414 mg, 1 mmol) and 2,6-lutidine (0.44 mL, 3.8 mmol) in CH_2Cl_2 (5 mL) was added TMSOTf (0.33 mL, 1.8 mmol). The mixture was stirred at room temperature for 20 min. Water (1 mL) was added to quench the reaction. The solution was extracted with ether, dried over $MgSO_4$, and evaporated in vacuo. The crude was purified by flash column chromatography (2% ethyl acetate/hexane) to give ether **27** (477 mg, 98%) as a colorless oil. $[\alpha]^{24}_D$ +21.0 (*c* 1.0, $CHCl_3$); IR (film) 1736 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.38 (t, J = 7.0 Hz, 1H), 4.29 (s, 1H), 4.08 (ddq, J = 25.1, 10.7, 7.0 Hz, 2H), 3.69 (quin, J = 6.0 Hz, 1H), 2.17 (m, 2H), 1.57 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.22−1.40 (m, 8H), 1.12 (s, 3H), 1.03 (s, 3H), 0.89 (s, 9H), 0.88 (t, J = 6.5 Hz, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.1, 136.1, 125.3, 82.3, 72.0, 60.3, 48.8, 36.4, 35.8, 32.0, 25.9, 25.3, 22.7, 22.1, 20.8, 18.2, 14.2, 14.1, 13.9, 0.0, −4.2, −4.4. Anal. Calcd for $C_{26}H_{54}O_4Si_2$: C, 64.14; H, 11.18. Found: C, 64.03; H, 11.22.

Ethyl (4*E*,3*R*,7*R*)-3,7-Bis(*tert*-butyldimethylsiloxy)-2,2,4-trimethyldodec-4-enoate (28). Employing a similar procedure to that for the preparation of TMS ether **27** with the exception in reaction time (7 h), alcohol **25** (414 mg, 1 mmol), TBSOTf (0.41 mL, 1.8 mmol), and 2,6-lutidine (0.44 mL, 3.8 mmol) in CH_2Cl_2 (5 mL) afforded TBS ether **28** (501 mg, 95%) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil. IR (film): 1736 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz) δ (ppm) 5.35 (t, J = 7.0 Hz, 1H), 4.25 (s, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.63−3.65 (m, 1H), 2.11 (t, J = 6.8 Hz, 2H), 1.55 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.18−1.40 (m, 8H), 1.02 (s, 3H), 0.98 (s, 3H), 0.83 (t, J = 6.8 Hz, 3H), 0.82 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ (ppm) 176.7, 136.0, 125.5, 82.4, 71.9, 60.2, 48.8, 36.6, 35.7, 35.5, 32.0, 25.9, 25.8, 25.2, 22.7, 22.3, 21.1, 18.1, 14.1, 14.0, 13.9, −4.2, −4.5, −4.8, −5.4.

(4*E*,3*R*,7*R*)-3,7-bis(*tert*-Butyldimethylsiloxy)-2,2,4-trimethyldodec-4-enol (29). To a stirred (−78 °C) solution of ester **28** (528 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added DIBAL (3.0 mL, 3.0 mmol, 1M in toluene) over a period of 30 min. After stirring for 2 h at the same temperature, the solution was allowed to warm to room temperature and stirred additionally for 2 h. Methanol (2.0 mL) was added to the reaction mixture at room temperature, after 15 min water (2 mL) was added, and the resulting solution was stirred vigorously until a precipitate was formed. The precipitate was filtered off, and layers were separated. The organic phase was dried over $MgSO_4$, and evaporated. The crude material was purified by column chromatography (10% ethyl acetate/hexane) to give **29** (443 mg, 91%) as a colorless oil. IR (film) 3445 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ (ppm) 5.38 (t, J = 6.8 Hz, 1H), 3.92 (s, 1H), 3.63−3.67 (m, 1H), 3.46 (dd, J = 34.0, 10.7 Hz, 2H), 2.95 (brs, 1H), 2.35 (t, J = 6.6 Hz, 2H), 1.62 (s, 3H), 1.20−1.50 (m, 8H), 1.03 (s, 3H), 0.93 (t, J = 6.6 Hz, 3H), 0.92 (s, 18H), 0.69 (s, 3H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 22.5 MHz): δ (ppm) 136.6, 125.2, 86.5, 78.4, 71.0, 39.7, 36.6, 35.5, 32.0, 25.9, 25.2, 23.5, 22.6, 22.2, 18.1, 14.0, −4.3, −4.5, −4.6, −5.3. Anal. Calcd for $C_{27}H_{58}O_3Si_2$: C, 66.60; H, 12.01. Found: C, 66.58; H, 12.04.

(4*E*,3*R*,7*R*)-3,7-Bis(*tert*-butyldimethylsiloxy)-2,2,4-trimethyldodec-4-enal (30). To a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.13 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) was added DMSO (0.14 mL, 2 mmol). After 10 min, **29** (487 mg, 1 mmol) in dry CH_2Cl_2 (3 mL) was added. The mixture was stirred for 20 min and Et_3N (0.42 mL, 3.0 mmol) was added. The temperature of the mixture was allowed to rise to 0 °C. After stirring for an additional 30 min, a mixture of water (0.5 mL), ether (10 mL), and benzene (2.5 mL) was added. The organic phase was separated, washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography of the crude residue (1% ethyl acetate/hexane) gave **30** (461 mg, 95%) as a pure colorless oil. IR (film) 2710, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ (ppm) 9.66 (s,1H), 5.37 (t, J = 6.8 Hz, 1H), 4.09 (s, 1H), 3.68 (quin, J = 5.0 Hz, 1H), 2.15 (t, J = 6.8 Hz, 2H), 1.52 (s, 3H), 1.20−1.48 (m, 8H), 0.98 (s, 3H), 0.96 (s, 3H), 0.87 (t, J = 6.8 Hz, 3H), 0.86 (s, 18H), 0.03 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 206.3. 135.7, 125.9, 83.8, 71.8, 51.0, 36.7, 35.5, 32.0, 25.9, 25.8, 25.2, 22.7, 20.6, 18.1, 14.0, 13.4, −4.2, −4.4, −4.6, −5.3.

(4*E*,3*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2,4-trimethyl-3-(trimethylsiloxy)dodec-4-enol (31). Using a procedure similar to that for the preparation of alcohol **29**, ester **27** (486.8 mg, 1 mmol), DIBAL (3.0 mL, 3.0 mmol, 1 M in toluene), and CH_2Cl_2 (5 mL) gave alcohol **31** (391.4 mg, 88%) after flash column chromatography (10% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{24}_D$ +23.0 (*c* 0.3, $CHCl_3$); IR (film) 3422 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.36 (t, J = 7.0 Hz, 1H), 3.89 (s, 1H), 3.70 (quin, J = 5.6 Hz, 1H), 3.59 (dd, J = 10.2, 3.6 Hz, 1H), 3.33 (dd, J = 6.6, 3.6 Hz, 1H),), 3.28 (dd, J = 10.2, 6.6 Hz, 1H), 2.19 (t, J = 6.3 Hz, 2H), 1.65 (s, 3H), 1.20−1.38 (m, 8H), 0.97 (s, 3H), 0.88 (s, 9H), 0.87 (t, J = 5.1 Hz, 3H), 0.76 (s, 3H), 0.08 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 136.6, 125.4, 87.1, 72.0, 71.8, 39.4, 36.7, 35.7, 32.1, 26.0, 25.3, 23.8, 22.7, 21.8, 18.2, 14.1, 13.9, 0.0, −4.2, −4.4. Anal. Calcd for $C_{24}H_{52}O_3Si_2$: C, 64.80; H, 11.78. Found: C, 64.89; H, 11.85.

(4*E*,3*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2,4-trimethyl-3-(trimethylsiloxy)dodec-4-enal (32). Employing the oxidation procedure described for the preparation of aldehyde **30**, alcohol **31** (445 mg, 1.0 mmol), $(COCl)_2$ (0.13 mL, 1.5 mmol), DMSO (0.14 mL, 2.0 mmol), Et_3N (0.42 mL, 3.0 mmol), and CH_2Cl_2 (10 mL) gave aldehyde **32** (354 mg, 80%), after flash column chromatography (2.5% ethyl acetate/hexane), as a colorless oil. $[\alpha]^{24}_D$ +19.4 (*c* 1.0, $CHCl_3$); IR (film) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.67 (s, 1H), 5.39 (t, J = 7.0 Hz, 1H), 4.07 (s, 1H), 3.69 (quin, J = 5.6 Hz, 1H), 2.17 (t, J = 6.2 Hz, 2H), 1.54 (s, 3H), 1.20−1.41 (m, 8H), 1.00 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.07 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 206.9, 135.8, 125.7, 83.6, 71.9, 50.9, 36.4, 35.6, 32.0, 31.9, 25.9, 25.2, 22.7, 20.5, 18.1, 18.0, 14.1, 13.3, 0.0, −4.2, −4.4. Anal. Calcd for $C_{24}H_{50}O_3Si_2$: C, 65.10; H, 11.38. Found: C, 64.97; H, 11.42.

Phenyl (3*S*)-3-Hydroxy-4,4-dimethylpentanoate (34). The aldol condensation procedure described for the preparation of aldol **12** was employed with pivalaldehyde (258 mg, 3 mmol), **10** (687 mg, 3.3 mmol), BH_3·THF (3.0 mL, 3.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol), and CH_2Cl_2 (15 mL) at −78 °C for 3 h to give acetate aldol **34** (500 mg, 75%, 98% ee, CHIRALCEL OD, 1% 2-propanol/hexane, 0.5 mL/min, R_f 22.2 min, λ 254 nm), after flash column chromatography (10% ethyl acetate/hexane), as a colorless oil. $[\alpha]^{24}_D$ −36.0 (*c* 1.0, $CHCl_3$); IR (film) 3489, 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.85−7.25 (m, 5H), 3.69 (brd, J = 10.4 Hz, 1H), 2.64 (dd, J = 16.3, 2.2 Hz, 1H), 2.57 (brs, 1H),

2.48 (dd, J = 16.3, 10.7 Hz, 1H), 0.82 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 172.3, 150.4, 129.4, 125.9, 121.4, 75.5, 36.8, 34.4, 25.5. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.10.

1-Ethoxy-1-(trimethylsiloxy)prop-1-ene (35). Using a similar procedure to that described for the preparation of silyl ketene acetal **7**, ethyl propionate (1.4 mL, 10.0 mmol), lithium diisopropylamide (11.0 mmol), TMSCl (3.2 mL, 25.0 mmol), and THF (15 mL) at −78 °C gave silyl ketene acetal **35** (1.48 g, 75%, *E*:*Z*, 24:1) on bulb to bulb distillation (bp 60−61 °C/20 mmHg) as a colorless oil. IR (film) 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (q, J = 7.0 Hz, 2H), 3.72 (q, J = 6.6 Hz, 1H), 1.49 (d, J = 6.6 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 0.2 1 (s, 9H).

Ethyl (2*S*,3*S*)-3-Hydroxy-2,4,4-trimethylpentanoate (*syn*-36) and Ethyl (2*R*,3*S*)-3-Hydroxy-2,4,4-trimethylpentanoate (*anti*-36). Using the aldol condensation procedure identical to that described for aldol **12**, pivalaldehyde (258 mg, 3.0 mmol), **35** (575 mg, 3.3 mmol), BH_3·THF (3.0 mL, 3.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (0.90 g, 3.3 mmol), and CH_2Cl_2 (5 mL) at −78 °C for 3 h afforded acetate aldol *anti*-**36** (17 mg, 3%, 96% ee, CHIRALPAC AD, 2% 2-propanol/hexane, 0.5 mL/min, R_f 23.5 min, λ 210 nm) and *syn*-**36** (367 mg, 65%, 96% ee, CHIRALPAC AD, 2% 2-propanol/hexane, 0.5 mL/min, R_f 22.2 min, λ 210 nm) after flash column chromatography (2% ethyl acetate/hexane). ***anti*-36**. $[\alpha]^{24}_D$ +10.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.15 (dq, J = 7.0, 0.7 Hz, 2H), 3.71 (d, J = 9.7 Hz, 1H), 3.17 (dd, J = 9.5, 2.0 Hz, 1H), 2.73 (dq, J = 7.0, 2.0 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.4, 82.5, 60.5, 38.2, 35.9, 26.0, 18.0, 13.8. ***syn*-36.** $[\alpha]^{24}_D$ −12.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.06 (q, J = 7.0 Hz, 2H), 3.56 (t, J = 4.6 Hz, 1H), 2.60 (dq, J = 7.0, 4.6 Hz, 1H), 2.37 (brs, 1H), 1.19 (t, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.0, 78.0, 60.4, 41.1, 35.4, 26.4, 13.9, 12.9.

(2*S*,3*S*)-1,3-Isopropylidene-2,4,4-trimethylpentane-1,3-diol (*anti*-38). To a stirred solution of diol *anti*-**37** (131 mg, 0.9 mmol) in dry acetone (5 mL) was added successively acetone dimethylacetal (0.22 mL, 1.8 mmol) and camphor-10-sulfonic acid (23 mg, 0.1 mmol), and the reaction mixture was stirred for 20 min at room temperature. The reaction was quenched by adding Et_3N (0.21 mL, 0.15 mmol). The solution was evaporated. The resulting residue was dissolved in ether. The solution was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the crude material was purified by column chromatography (2% ethyl acetate/hexane) to give acetonide *anti*-**38** (182 mg, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.63 (dd, J = 11.2, 4.6 Hz, 1H), 3.23 (dd, J = 11.2, 5.4 Hz, 1H), 2.96 (d, J = 8.4 Hz, 1H), 1.69−1.79 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 98.7, 81.4, 65.3, 34.6, 31.7, 27.3, 26.2, 21.7, 17.5.

(2*R*,3*S*)-1,3-Isopropylidene-2,4,4-trimethylpentane-1,3-diol (*syn*-38). Using the above procedure described for *anti*-**38**, *syn*-**38** was prepared (178 mg, 96%) from *syn*-**37**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.98 (dd, J = 11.2, 2.7 Hz, 1H), 3.45 (dd, J = 11.2, 1.7 Hz, 1H), 3.44 (brs, 1H), 1.52 (ddq, J = 7.0, 2.2, 1.9 Hz, 1H), 1.32 (s, 3H), 1.31 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 98.6, 78.4, 69.4, 34.0, 31.2, 29.6, 26.5, 18.6, 13.0.

Ethyl (6*E*,2S,3S,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,4,6-tetramethyl-5-(trimethylsiloxy)tetradec-6-enoate (41) and Ethyl (6*E*,2*R*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,4,6-tetramethyl-5-(trimethylsiloxy)tetradec-6-enoate (42). Using the aldol condensation procedure identical to that described for aldol **12**, aldehyde **32** (1.80 g, 4 mmol), **35** (1.4 g, 8 mmol), BH_3·THF (6.0 mL, 6.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (1.80 g, 6.6 mmol), and CH_2Cl_2 (12 mL) at −78 °C for 24 h afforded aldol **41** (1.78 g, 84%) and aldol **42** (174 mg, 8%) after flash column chromatography (2.5% ethyl acetate/hexane) as colorless oils. **Aldol 41**. $[\alpha]^{24}_D$ +8.0 (*c* 1.0, $CHCl_3$); IR (film) 3485, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.37 (t, J = 6.8 Hz, 1H), 4.13 (ddq, J = 19.7, 10.7, 7.0 Hz, 2H), 3.99 (s, 1H), 3.93 (dd, J = 6.6, 1.7 Hz, 1H), 3.71 (d, J = 1.7 Hz, 1H), 3.70 (quin, J = 5.5 Hz, 1H), 2.65 (dq, J = 7.0, 6.6 Hz, 1H), 2.18 (brt, J = 6.8 Hz, 2H), 1.59 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H), 1.22−1.41 (m, 8H), 0.92 (s, 3H), 0.89 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.70 (s, 3H), 0.10 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 176.7, 136.3, 126.3, 87.5, 77.7, 71.8, 60.2, 43.0, 41.6, 36.7, 35.6, 32.0, 25.9, 25.2, 22.6, 21.5, 18.1, 16.9, 14.1, 14.0, 13.8, 0.0, −4.3, −4.5. Anal. Calcd for $C_{29}H_{60}O_5Si_2$: C, 63.92; H, 11.10. Found: C, 64.02; H, 11.15. **Aldol 42**. $[\alpha]^{24}_D$ +21.0 (*c* 0.5, $CHCl_3$); IR (film) 3485, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.37 (t, J = 7.0 Hz, 1H), 4.25 (d, J = 5.6 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 4.00 (s, 1H), 3.70 (quin, J = 6.0 Hz, 1H), 3.63 (dd, J = 5.3, 4.1 Hz, 1H), 2.69 (dq, J = 7.0, 4.1 Hz, 1H), 2.20 (brt, J = 7.0 Hz, 2H), 1.65 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.22−1.41 (m, 8H), 0.89 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.07 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 176.8, 136.3, 125.8, 85.5, 78.7, 71.9, 60.4, 42.8, 40.8, 36.7, 35.8, 32.1, 26.0, 25.3, 22.7, 21.3, 18.2, 17.6, 14.5, 14.2, 14.1, 0.0, −4.3, −4.5. Anal. Calcd for $C_{29}H_{60}O_5Si_2$: C, 63.92; H, 11.10. Found: C, 63.87; H, 11.21.

Ethyl (6*E*,2R,3R,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,4,6-tetramethyl-5-(trimethylsiloxy)tetradec-6-enoate (43) and Ethyl (6*E*,2*S*,3*R*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,4,6-tetramethyl-5-(trimethylsiloxy)tetradec-6-enoate (44). Using the aldol condensation procedure identical to that described for aldol **12**, aldehyde **32** (0.90 g, 2.0 mmol), **35** (0.70 g, 4 mmol), BH_3·THF (3.0 mL, 3.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*R*)-valine (0.45 g, 3.3 mmol), and CH_2Cl_2 (12 mL) at −78 °C for 24 h afforded aldol **43** (479 mg, 44%) and aldol **44** (109 mg, 10%) after flash column chromatography (2.5% ethyl acetate/hexane) as colorless oils. **Aldol 43**. $[\alpha]^{24}_D$ +10.0 (*c* 0.5, $CHCl_3$). IR (film) 3481, 1714 cm^{-1}; The ^{1}H NMR spectra suggested the existence of three rotamers (4:2:1). The peaks of the major rotamer are presented here. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.36 (dd, J = 12.9, 6.8 Hz, 1H), 4.12 (ddq, J = 10.7, 7.0, 1.9 Hz, 2H), 3.29 (s, 1H), 3.89 (s, 1H), 3.71 (quin, J = 6.8 Hz, 1H), 3.65 (d, J = 1.9 Hz, 1H), 2.65 (quin, J = 6.8 Hz, 1H), 2.18 (brt, J = 5.8 Hz, 2H), 1.65 (s, 3H), 1.22−1.41 (m, 8H), 1.25 (t, J = 7.0 Hz, 3H), 1.24 (d, J = 7.0 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.77 (s, 3H), 0.10 (s, 3H), 0.08 (s, 9H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 176.9, 136.6, 125.4, 87.0, 77.9, 72.0, 60.4, 43.1, 41.8, 36.7, 35.7, 32.1, 26.0, 25.3, 23.8, 22.9, 22.7, 18.2, 16.9, 14.1, 14.0, 13.9, 0.0, −4.2, −4.4. **Aldol 44.** $[\alpha]^{24}_D$ +22.0 (*c* 0.5, $CHCl_3$); IR (film) 3484, 1712 cm^{-1}; The ^{1}H NMR spectra suggested the existence of two rotamers (1.5:1). The peaks of the major rotamer are presented here. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.38 (dd, J = 15.1, 7.5 Hz, 1H), 4.21 (d, J = 5.6 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 4.00 (s, 1H), 3.70 (quin, J = 5.6 Hz, 1H), 3.63 (dd, J = 5.7, 5.6 Hz, 1H), 2.70 (dq, J = 7.0, 3.9 Hz, 1H), 2.18 (brt, J = 6.8 Hz, 2H), 1.65 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.21−1.45 (m, 8H), 0.89 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.86 (s, 3H), 0.72 (s, 3H), 0.06 (s, 3H), 0.05 (s, 9H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.6, 136.5, 125.6, 83.6, 79.1, 72.1, 60.6, 44.1, 39.0, 36.8, 35.9, 32.1, 26.0, 25.2, 22.7, 21.3, 19.8, 19.5, 17.9, 14.3, 14.2, 14.1, 0.1, −4.2, −4.4.

Ethyl (6*E*,2*S*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-2,4,4,6-tetramethyltetradec-6-enoate (45). To a stirred solution of TMS ether **41** (97.5 mg, 0.179 mmol) in anhydrous MeOH (10 mL) was added anhydrous citric acid (166 mg, 0.86 mmol). The reaction mixture was stirred at 23 °C for 15 min, and then the solvent was removed in vacuo. The residue was partitioned between H_2O (5 mL) and ether (20 mL), the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with sat. aq $NaHCO_3$ aq solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue afforded diol **45** (82.9 mg, 98%) after flash column chromatography (15% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{24}_D$ +25.0 (*c* 0.2, $CHCl_3$); IR (film) 3383, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.43 (t, J = 7.0 Hz, 1H), 4.14 (q, J

= 7.0 Hz, 2H), 4.05 (s, 1H), 3.99 (d, *J* = 5.1 Hz, 1H), 3.70 (brs, 1H), 3.69 (quin, *J* = 6.1 Hz, 1H), 3.01 (brs, 1H), 2.72 (dq, *J* = 7.0, 5.1 Hz, 1H), 2.20 (brt, *J* = 7.0 Hz, 2H), 1.66 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.22−1.43 (m, 8H), 0.99 (s, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.68 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.0, 136.4, 126.3, 86.6, 79.2. 72.0, 60.5, 42.3, 41.2, 36.7, 35.6, 31.9, 25.8, 25.0, 22.6, 22.1, 18.0, 15.5, 14.6, 14.1, 14.0, 13.3, −4.3, −4.5. Anal. Calcd for $C_{26}H_{52}O_5Si$: C, 66.05; H, 11.09. Found: C, 66.02; H, 11.13.

Ethyl (6*E*,2*S*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-3,5-isopropylidene-2,4,4,6-tetramethyltetradec-6-enoate (46). Using a similar procedure to that described for the preparation of acetonide *syn*-**38**, diol **45** (472 mg, 1 mmol), acetone dimethylacetal (0.25 mL, 2.0 mmol) and camphor-10-sulfonic acid (23 mg, 0.1 mmol) in dry acetone (5 mL) afforded acetonide **46** (502 mg, 98%) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{24}_D$ −5.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.38 (t, *J* = 7.0 Hz, 1H), 4.11 (dq, *J* = 7.0, 1.0 Hz, 2H), 3.97, (s, 1H), 3.86 (d, *J* = 8.0 Hz, 1H), 3.69 (quin, *J* = 5.8 Hz, 1H), 2.61 (dq, *J* = 8.0, 7.0 Hz, 1H), 2.20 (t, *J* = 6.3 Hz, 2H), 1.65 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.22−1.44 (m, 8H), 1.16 (d, *J* = 6.8 Hz, 6H), 0.91 (s, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.60 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 176.0, 133.1, 127.0, 98.7, 83.9, 78.0, 71.9, 60.4, 40.1, 38.2, 36.9, 35.6, 31.9, 29.9, 25.9, 25.0, 22.6, 21.3, 19.4, 18.0, 15.0, 14.9, 14.7, 14.1, 14.0, −4.3, −4.5. Anal. Calcd for $C_{29}H_{56}O_5Si$: C, 67.92; H, 11.01. Found: C, 68.01; H, 11.08.

BF_3·OEt_2-Catalyzed Aldol Condensation between Aldehyde 32 and Silyl Nucleophile 35. To a cooled (−78 °C) and stirred solution of aldehyde **32** (354 mg, 0.8 mmol) in CH_2Cl_2 (4 mL) was added freshly distilled BF_3·OEt_2 (0.21 mL, 1.6 mmol) dropwise, and after an interval of 10 min silyl nucleophile **35** (169.5 mg, 0.9 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 2 h a buffer solution (2 mL, pH 6.86) was added to quench the reaction. Workup procedures were carried out with separation of phases, drying over $MgSO_4$, and evaporation in vacuo. Flash chromatography afforded **45**, **47**, and **48** as a mixture (40 mg) with a ratio of 1:1:1 (the ratio was determined from ^{1}H NMR) and **51** (10 mg).

Ethyl (6*E*,2*R*,3*R*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-2,4,4,6-tetramethyltetradec-6-enoate (47). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.43 (t, *J* = 7.0 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.10 (d, *J* = 3.4 Hz, 1H), 3.87 (dd, *J* = 5.4, 5.1 Hz, 1H), 3.69 (quin, *J* = 6.1 Hz, 1H), 3.50 (d, *J* = 5.1 Hz, 1H), 2.80 (d, *J* = 3.4 Hz, 1H), 2.72 (m, 1H), 2.21 (brs, 2H), 1.70 (s, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.22−1.43 (m, 8H), 0.93 (s, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.04 (s, 6H). Anal. Calcd for $C_{26}H_{52}O_5Si$: C, 66.05; H, 11.09. Found: C, 66.07; H, 11.12.

Ethyl (6*E*,2*R*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-2,4,4,6-tetramethyltetradec-6-enoate (48). IR (film) 3420, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.37 (t, *J* = 7.0 Hz, 1H), 4.50 (d, *J* = 8.5 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.69 (quin, *J* = 6.1 Hz, 1H), 3.62 (dd, *J* = 8.5, 2.2 Hz, 1H), 3.49 (d, *J* = 6.8 Hz, 1H), 2.69 (dq, *J* = 7.0, 2.2 Hz, 1H), 2.19 (brt, *J* = 7.0 Hz, 2H), 1.70 (s, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.22−1.43 (m, 8H), 0.89 (s, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.84 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 177.7, 136.4, 125.5, 85.0, 80.3, 72.0, 60.9, 42.2, 38.5, 36.7, 35.8, 31.9, 25.8, 25.1, 22.6, 22.2, 20.6, 18.0, 14.4, 14.0, 13.9, −4.3, −4.5. Anal. Calcd for $C_{26}H_{52}O_5Si$: C, 66.05; H, 11.09. Found: C, 65.98; H, 11.13.

(6*E*,2*S*,3*R*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4,4,6-trimethyltetradec-6-en-5-olide (51). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.46 (t, *J* = 7.0 Hz, 1H), 4.29 (s, 1H), 3.72 (quin, *J* = 5.5 Hz, 1H), 3.37 (dd, *J* = 10.2, 4.4 Hz, 1H), 2.48 (dq, *J* = 10.2, 7.0 Hz, 1H), 2.23 (brt, *J* = 7.0 Hz, 2H), 1.86 (d, *J* = 4.4 Hz, 1H), 1.69 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.20−1.44 (m, 8H), 0.97 (s, 3H), 0.93 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

Ethyl (6*E*,2*R*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-3,5-isopropylidene-2,4,4,6-tetramethyltetradec-6-enoate (52). To a solution of NaOEt (544 mg, 8.0 mmol) in ethanol (20 mL) was added **46** (410 mg, 0.8 mmol) in EtOH (5 mL). After refluxing for 2 h, the solution was concentrated, diluted with ether, washed with water, and dried over $MgSO_4$. After removal of the solvent, a crude residue was purified by flash column chromatography (2% ethyl acetate/hexane) to give **52** (164 mg, 40%) as a colorless oil. $[\alpha]^{24}_D$ +13.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.39 (t, *J* = 7.0 Hz, 1H), 4.12 (ddq, *J* = 21.4, 10.7, 7.0 Hz, 2H), 3.94, (s, 1H), 3.70 (quin, *J* = 5.8 Hz, 1H), 3.69 (d, *J* = 7.8 Hz, 1H), 2.69 (dq, *J* = 7.5, 7.0 Hz, 1H), 2.21 (t, *J* = 6.3, 2H), 1.65 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.22−1.34 (m, 8H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 175.0, 133.0, 127.4, 98.3, 83.8, 80.4, 71.9, 60.0, 42.6, 37.4, 35.6, 31.9, 31.5, 29.8, 25.8, 25.0, 22.6, 22.0, 18.9, 18.0, 16.4, 14.8, 14.2, 14.1, 14.0, −4.4, −4.5. Anal. Calcd for $C_{29}H_{56}O_5Si$: C, 67.92; H, 11.01. Found: C, 67.85; H, 10.97.

(6*E*,2*S*,3*S*,5*R*,9*R*)-9-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-3,5-isopropylidene-2,4,4,6-tetramethyltetradec-6-enal (53). Employing a similar reduction procedure to that described for aldehyde **15**, ester **46** (342 mg, 1 mmol), and DIBAL (1.2 mL, 1.2 mmol, 1 M in toluene) in CH_2Cl_2 (10 mL) at −78 °C for 2 h afforded aldehyde **53** (417 mg, 89%) after flash column chromatography (2% ethyl acetate/hexane) as a colorless oil. $[\alpha]^{24}_D$ −5.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.60 (d, *J* = 2.2 Hz, 1H), 5.39 (t, *J* = 7.0 Hz, 1H), 4.01 (d, *J* = 4.8 Hz, 1H), 4.00 (s, 1H), 3.70 (quin, *J* = 5.8 Hz, 1H), 2.54 (ddq, *J* = 7.0, 4.8, 2.2 Hz, 1H), 2.21 (t, *J* = 6.3 Hz, 2H), 1.66 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.20−1.44 (m, 8H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.71 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 203.7, 133.0, 127.0, 98.7, 83.8, 75.5, 71.9, 46.8, 38.1, 36.9, 35.6, 31.9, 29.8, 25.9, 25.1, 22.6, 22.0, 19.2, 18.1, 15.6, 14.9, 14.0, 10.2, −4.3, −4.5. Anal. Calcd for $C_{27}H_{52}O_4Si$: C, 69.18; H, 11.18. Found: C, 69.51; H, 11.22.

α-Triethylsilyl *tert*-Butylimine of Propanal (54). To a cooled (−78 °C) solution of lithium diisopropylamide (1.1 equiv) in THF (7 mL) was added the *tert*-butylimine of propanal (113 mg, 1.0 mmol). The resulting yellow solution was stirred for 30 min, TESCl (0.14 mL, 1.0 mmol) was added. The resulting mixture was stirred with gradual warming to 0 °C over a period of 3.5 h. The reaction was quenched with water and extracted with ether. The combined ether extracts were washed with brine and dried over K_2CO_3. Removal of the ether, followed by distillation (bp 54−55 °C/0.22 mmHg) gave **54** (141 mg, 71%) as a clear oil. IR (neat) 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.56 (d, *J* = 7.0 Hz, 1H), 2.05 (quin, *J* = 7.0 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.15 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 9H), 0.58 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 29.8, 29.0, 12.8, 7.4, 6.5, 5.7, 2.2.

(2*E*,8*E*,4*R*,5*S*,7*R*,11*R*)-11-(*tert*-Butyldimethylsiloxy)-5,7-dihydroxy-5,7-isopropylidene-2,4,6,6,8-pentamethylhexadeca-2,8-dienal (55). To a solution (0 °C) of lithium diisopropylamide (1.0 equiv) was added **54** (199 mg, 1.0 mmol) dropwise over a period of 5 min. The resulting yellow to red solution was stirred for 15 min. The solution was cooled to −78 °C, and aldehyde **53** (468 mg, 1.0 mmol) in THF (1 mL) was added. The resulting mixture was stirred with gradual warming to −20 °C over a period of 2.5 h. The reaction was quenched with water (2 mL), and oxalic acid was added to reach the pH at 4.5 and stirred for 30 min. The solution was poured into brine (10 mL) and extracted with ether. The combined ether extracts were washed with sat. aq $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to give a crude material (*E*:*Z*, 16:1; ^{1}H NMR). Purification by flash column chromatography (1% ethyl acetate/hexane) afforded aldehyde **55** (376 mg, 74%) as a clear oil. $[\alpha]^{24}_D$ −5.5 (*c* 0.9, $CHCl_3$); IR (film) 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.41 (s, 1H), 6.44 (d, *J* = 10.4 Hz, 1H), 5.38 (t, *J* = 7.0 Hz, 1H), 3.93 (s, 1H), 3.69 (quin, *J* = 5.6 Hz, 1H), 3.47 (d, *J* = 7.0 Hz, 1H), 2.93 (ddq, *J* = 10.4, 7.0, 6.8 Hz, 1H), 2.20 (brt, *J* = 6.3 Hz,

2H), 1.77 (s, 3H), 1.65 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.22−1.47 (m, 8H), 1.06 (d, J = 6.8 Hz, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.70 (s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 195.4, 158.5, 135.9, 133.0, 127.2, 98.5, 83.8, 80.6, 71.9, 38.3, 36.9, 35.6, 34.9, 31.9, 29.9, 25.9, 25.1, 22.6, 22.4, 19.2, 18.1, 16.6, 15.4, 14.9, 14.0, 9.1, −4.3, −4.5. Anal. Calcd for $C_{30}H_{56}O_4Si$: C, 70.81; H, 11.09. Found: C, 70.67; H, 11.13.

Phenyl (4*E*,10*E*,3*S*,6*R*,7*S*,9*R*,13*R*)-13-(*tert*-Butyldimethylsiloxy)-7,9-isopropylidene-3,7,9-trihydroxy-4,6,8,8,10-pentamethyloctadeca-4,10-dienoate (56). Employing an aldol condensation procedure described for the preparation of aldol **12**, aldehyde **55** (508 mg, 1 mmol), **10** (229 mg, 1.1 mmol), BH_3·THF (1.0 mL, 1.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol), and CH_2Cl_2 (5 mL) at −78 °C for 3 h afforded acetate aldol **56** (541 mg, 84%, 85% de, ^{1}H NMR) after flash column chromatography (2% ethyl acetate/hexane) as a colorless oil (the undesired counter isomer was separated during flash column chromatography). $[\alpha]^{24}_D$ +5.0 (*c* 0.8, $CHCl_3$); IR (film) 3439, 1759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.37 (t, J = 7.3 Hz, 2H), 7.22 (d, J = 7.3 Hz, 1H), 7.08 (d, J = 8.2 Hz, 2H), 5.47 (d, J = 10.0 Hz, 1H), 5.35 (t, J = 7.0 Hz, 1H), 4.52 (br d, J = 8.8 Hz, 1H), 3.89 (s, 1H), 3.68 (quin, J = 5.6 Hz, 1H), 3.33 (d, J = 7.0 Hz, 1H), 2.78 (dd, J = 16.1, 9.3 Hz, 1H), 2.68 (dd, J = 16.1, 3.4 Hz, 1H), 2.62 (br s, 1H), 2.61−2.65 (m, 1H), 2.19 (br t, J = 6.3 Hz, 2H), 1.74 (s, 3H), 1.64, (s, 3H), 1.42, (s, 3H), 1.40, (s, 3H), 1.19−1.42 (m, 8H), 0.96 (d, J = 6.6 Hz, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H), 0.72 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 170.9, 150.4, 133.2, 132.4, 131.5, 129.4, 126.9, 125.9, 121.4, 98.2, 83.9, 81.2, 73.3, 72.0, 40.0, 38.1, 36.8, 35.7, 33.5, 31.9, 30.0, 25.8, 25.0, 22.6, 19.2, 18.0, 17.8, 15.3, 14.9, 14.0, 11.8, −4.3, −4.5. Anal. Calcd for $C_{38}H_{64}O_6Si$: C, 70.76; H, 10.00. Found: C, 70.33; H, 10.04.

(4*E*,10*E*,3*S*,6*R*,7*S*,9*R*,13*R*)-13-(*tert*-Butyldimethylsiloxy)-7,9-dihydroxy-7,9-isopropylidene-4,6,8,8,10-pentamethyl-3-(triethylsiloxy)octadeca-4,10-dienal (57). Employing a procedure analogous to that for the preparation of TMS ether **27,** alcohol **56** (645 mg, 1 mmol), TESOTf (0.31 mL, 1.8 mmol), 2,6-lutidine (0.44 mL, 3.8 mmol), and CH_2Cl_2 (5 mL) afforded TES ether (purified by flash column chromatography, 1% ethyl acetate/hexane). The TES ether was then reduced to the corresponding alcohol using a procedure similar to that described for the preparation of alcohol **29**. The alcohol was then oxidized using a Swern oxidation procedure described for the preparation of aldehyde **30** to give aldehyde **57** (534 mg, 79% overall) after flash column chromatography (1% ethyl acetate/hexane) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.74 (t, J = 2.4 Hz, 1H), 5.36 (t, J = 7.0 Hz, 1H), 5.34 (d, J = 10.2 Hz, 1H), 4.53 (dd, J = 8.2, 4.3 Hz, 1H), 3.88 (s, 1H), 3.68 (quin, J = 5.6 Hz, 1H), 3.30 (d, J = 7.0 Hz, 1H), 2.67 (ddd, J = 15.3, 8.2, 2.6 Hz, 1H), 2.58 (ddq, J = 10.2, 7.0, 6.8 Hz, 1H), 2.33 (ddd, J = 15.3, 4.3, 2.4 Hz, 1H), 2.19 (br t, J = 6.3 Hz, 2H), 1.64 (s, 3H), 1.62 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.20−1.44 (m, 8H), 0.95 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.8 Hz, 9H), 0.88 (t, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.67 (s, 3H), 0.57 (q, J = 7.8 Hz, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.8, 133.2, 132.7, 132.0, 126.9, 98.2, 83.9, 81.1, 74.0, 72.0, 49.5, 38.1, 36.9, 35.7, 33.4, 31.9, 30.0, 25.9, 25.0, 22.6, 22.5, 19.2, 18.0, 17.3, 15.3, 14.9, 14.0, 10.9, 6.7, 4.7, −4.3, −4.5. Anal. Calcd for $C_{38}H_{74}O_5Si_2$: C, 68.41; H, 11.18. Found: C, 68.31; H, 11.21.

6-(2-Hydroxy-2-phenylethyl)-2,2-dimethyl-1,3-dioxin-4-one (59). Using the aldol condensation procedure identical to that described for aldol **12**, benzaldehyde (212 mg, 1.0 mmol), **58** (472 mg, 2.2 mmol), BH_3·THF (2.0 mL, 2.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (0.60 g, 2.2 mmol), and CH_2Cl_2 (10 mL) at −78 °C for 3 h afforded **59** (377 mg, 76%, 16% ee, CHIRALPAK AD, 7% 2-propanol/hexane, R_f 26.0 min, 1 mL/min, λ 254 nm), after flash column chromatography, as a colorless oil. IR (film) 3376, 1721, 1628 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.27−7.37 (m, 5H), 5.29 (s, 1H), 4.97 (br quin, J = 4.1 Hz, 1H), 2.68 (dd, J = 14.6, 8.7 Hz, 1H), 2.59 (dd, J = 14.6, 4.9 Hz, 1H), 2.57 (br s, 1H), 1.66 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 168.8, 161.6, 142.7, 128.0, 127.4, 125.3, 106.2, 94.5, 70.1, 42.5, 24.7, 23.9. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.82; H, 6.59.

Methyl (5*S*)-5-Hydroxy-3-oxo-5-phenylpentanoate (60). Using a similar procedure described above, benzaldehyde (106 mg, 1.0 mmol), **11** (286 mg, 1.1 mmol), BH_3·THF (1.0 mL, 1.0 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*S*)-valine (298 mg, 1.1 mmol), and CH_2Cl_2 (10 mL) at −78 °C for 3 h afforded **60** (160 mg, 72%, 61% ee, CHIRALPAK AD, R_f 51.5 min, 4% 2-propanol/hexane, 1 mL/min, λ 254 nm), after flash column chromatography, as a colorless oil. IR (film) 3476, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.24−7.36 (m, 5H), 5.18 (dt, J = 9.0, 3.2 Hz, 1H), 3.72 (s, 3H), 3.48 (s, 2H), 2.99 (dd, J = 17.3, 3.2 Hz, 1H), 2.94 (d, 3.2 Hz, 1H), 2.90 (dd, J = 17.3, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 202.7, 167.2, 142.4, 128.6, 127.8, 125.6, 69.8, 52.5, 51.5, 49.6. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.02; H, 6.40.

Methyl (8*E*,14*E*,5*S*,7*S*,10R,11S,13*R*,17*R*)-17-(*tert*-Butyldimethylsiloxy)-5,11,13-trihydroxy-11,13-isopropylidene-8,10,12,12,14-pentamethyl-3-oxo-7-(triethylsiloxy)-docosa-8,14-dienoate (61). Using a similar aldol condensation procedure described, aldehyde **57** (600 mg, 0.9 mmol), **11** (260 mg, 1.0 mmol), BH_3·THF (0.9 mL, 0.9 mmol, 1 M in THF), *N*-(*p*-toluenesulfonyl)-(*R*)-valine (271 mg, 1.0 mmol), and CH_2Cl_2 (4 mL) at −78 °C for 3 h afforded aldol **61** (528 mg, 75%, 83% de, ^{1}H NMR), after flash column chromatography (2.5% ethyl acetate/hexane), as a colorless oil. $[\alpha]^{24}_D$ +16.6 (*c* 0.3, $CHCl_3$); IR (film) 3503, 1747, 1700, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.36 (t, J = 7.0 Hz, 1H), 5.35 (d, J = 10.0 Hz, 1H), 4.31 (dd, J = 7.0, 2.2 Hz, 1H), 4.23−4.30 (m, 1H), 3.89 (s, 1H), 3.73 (s, 3H), 3.69 (quin, J = 5.6 Hz, 1H), 3.48 (s, 2H), 3.32 (d, J = 7.0 Hz, 1H), 3.27 (d, J = 2.9 Hz, 1H), 2.67 (d, J = 6.0 Hz, 2H), 2.60 (ddq, J = 10.0, 7.0, 6.6 Hz, 1H), 2.20 (brt, J = 6.4 Hz, 2H), 1.64 (s, 3H), 1.58 (s, 3H), 1.43 (s, 3H), 1.41, (s, 3H), 1.20−1.40 (m, 10H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.89 (s, 3H), 0.88 (s, 9H), 0.87 (t, J = 7.0 Hz, 3H), 0.70 (s, 3H), 0.59 (q, J = 7.8 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 202.8, 167.3, 133.3, 133.0, 131.1, 126.8, 98.1, 83.9, 81.1, 75.2, 72.0, 64.5, 52.3, 50.1, 49.5, 41.3, 38.1, 36.8, 35.7, 33.4, 31.9, 30.0, 25.9, 25.0, 22.6, 22.5, 19.2, 18.0, 17.4, 15.3, 14.9, 14.0, 11.7, 6.8, 4.7, −4.4, −4.5. Anal. Calcd for $C_{43}H_{82}O_8Si_2$: C, 65.94; H, 10.55. Found: C, 65.03; H, 10.61.

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Supporting Information Available: ^{1}H NMR spectra (28 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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