Acknowledgment. We thank NSERCC and FCAR for generous financial assistance and the Sumitomo Chemical Co. Ltd. for granting a sabbatical leave to Y. Sakito. We also thank Dr. C.-M. Liu, Hoffmann-La Roche, for a sample of ionomycin Na salt. We acknowledge the assistance given by Dr. G. McCraw in the preparation of precursors to aldehyde **25**. We thank Professor D. A. Evans for providing us with spectroscopic data and other information on compound **13**.

Supplementary Material Available: Selected ^1H NMR and ^{13}C NMR spectra are listed (30 pages). Ordering information is given on any current masthead page.

Total Synthesis of the Polyether Antibiotic Ionomycin

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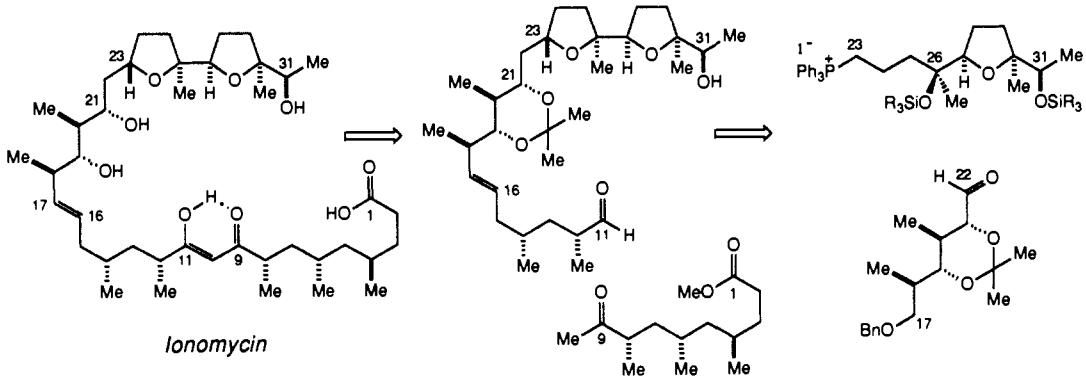
Abstract: A convergent asymmetric synthesis of the calcium ionophore ionomycin has been achieved through a route that is outlined below. The four illustrated subunits, which comprise the C_1–C_{10}, C_{11}–C_{16}, C_{17}–C_{22}, and C_{23}–C_{32} portions of ionomycin,



were constructed through the use of chiral enolate bond constructions wherein 9 of the 14 stereogenic centers were created. The remaining chirality at C_6, C_{21}, C_{26}, C_{30}, and C_{31} was incorporated through internal asymmetric induction. In the assemblage process, the ylide derived from the C_{23}–C_{32} synthon was coupled with the C_{17}–C_{22} aldehyde. The C_{23}–C_{26} tetrahydrofuranyl ring and associated C_{23} stereocenter were then established through intramolecular oxymercuration, which proceeded in a highly diastereoselective manner (≥93:7) with the desired stereochemical outcome. The C_{16}–C_{17} double bond was constructed through a Julia trans olefination sequence. The union of the C_1–C_{10} keto ester with the assembled C_{11}–C_{32} aldehyde was achieved through an aldol bond construction. Subsequent oxidation of the C_{11} alcohol afforded the fully protected ionomycin structure. Final deprotection provided synthetic ionomycin whose absolute configuration is in full agreement with that determined by X-ray crystallography.

Over the last three decades a large class of molecules, collectively known as polyether antibiotics, have been isolated from various strains of Streptomyces organisms.[3] It is now well appreciated that these unique structures, which characteristically contain a carboxylate group as well as from two to five additional oxygen ligands, are highly effective in the complexation of inorganic cations. Complexes generated from these "ionophores" are exceptionally hydrophobic and, as a result, facilitate the translocation of ions across membrane barriers. Membrane transport mechanisms provided by the polyether antibiotics induce a range of biological responses, which include ruminant growth promotion,[4] coccidiostatic activity,[5] and mammalian cardiovascular effects.[6] An excellent monograph provides an in-depth summary of the biology of this family of natural products.[7]

In 1978 Meyers and co-workers reported the isolation of the polyether antibiotic ionomycin, as its hexane-soluble calcium complex, from the organism *Streptomyces conglobatus*.[8] Subsequent competitive ion-binding studies have shown that the antibiotic exhibits a high propensity for divalent versus monovalent ions. The following hierarchy has been documented for the alkaline earth cations: $Ca^{2+} > Mg^{2+} \gg Sr^{2+}$ and Ba^{2+}.[9] The binding stoichiometry for these divalent ions was determined to be 1:1. The only other ionophore to exhibit similar selectivity for divalent cations is the "tridentate" ionophore calcimycin,[10,11] which shows little differentiation between calcium and magnesium as its 2:1 ligand/metal complex.

In 1979 the X-ray structure and absolute stereochemistry of both the calcium and cadmium complexes of ionomycin were

(1) Taken from the Ph.D. Thesis of R. L. Dow, Harvard University, 1985.
(2) Taken from the Ph.D. Thesis of T. L. Shih, California Institute of Technology, 1983.
(3) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vol. 1-2.
(4) Westley, J. W. *Annu. Rept. Med. Chem.* **1975**, *10*, 246-256.
(5) Mitrovic, M.; Schildknecht, E. G. *Poult. Sci.* **1974**, *53*, 1448.
(6) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501-530.
(7) Reference 3; Vol. 2, Chapters 5-9.
(8) Liu, W.-C.; Smith-Slusarchyk, D.; Astle, G.; Trejo, W. H.; Brown, W. E.; Meyers, E. *J. Antibiot.* **1978**, *31*, 815-819.
(9) (a) Liu, C.; Hermann, T. E. *J. Biol. Chem.* **1978**, *253*, 5892-5894. (b) Kauffman, R. F.; Taylor, R. W.; Pfeiffer, D. R. *Ibid.* **1980**, *255*, 2735-2739.
(10) (a) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932-1933. (b) Metal complexes: Smith, G. D.; Duax, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 1578-1580. (c) Chaney, M. O.; Jones, N. D.; Debono, M. *J. Antibiot.* **1976**, *29*, 424-427.
(11) For syntheses of calcimycin (A23187) see: (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789-6791. (b) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. J. *J. Org. Chem.* **1980**, *45*, 3537-3539. (c) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063-1066.

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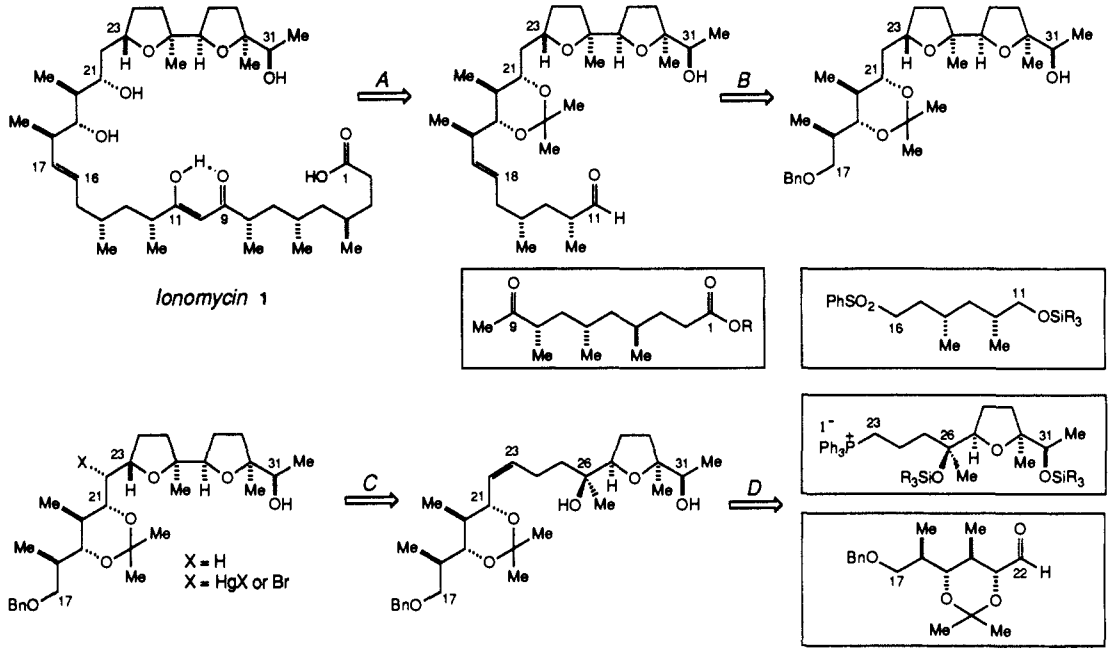
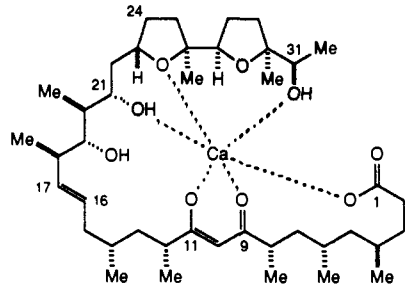
Scheme I



reported by Gougoutas and co-workers (Figure 1).[12] Prominent structural features of this ionophore include the presence of 14 stereogenic centers, and a β-dicarbonyl moiety that provides two of the six metal ligation points and accounts for ionomycin's intense ultraviolet absorption at 280 nm.

Ionomycin contains two unique architectural features that distinguish it from other members of the family of polyethers. First, this structure is the only example of a *doubly charged* ionophore thus affording the unique opportunity to form 1:1 charge-neutral hexacoordinate complexes with divalent cations. Second, in addition to the carboxylate ligand, the β-dicarbonyl at C_9–C_{11} provides the second charged ligation point. The presence of β-diketone ligands in these natural products is rare. Only one other ionophore has subsequently been reported to contain this moiety as part of a tetronic acid residue, which appears as the charged ligation site in the monovalent ion-selective ionophore M139603.[13]



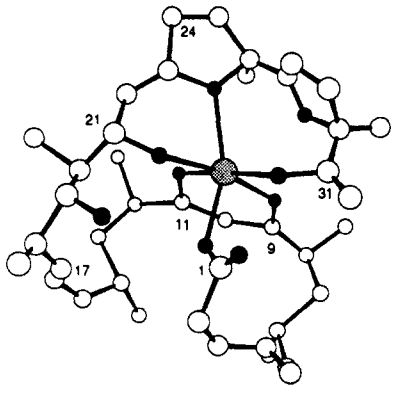


Figure 1. X-ray structure of ionomycin–calcium complex.

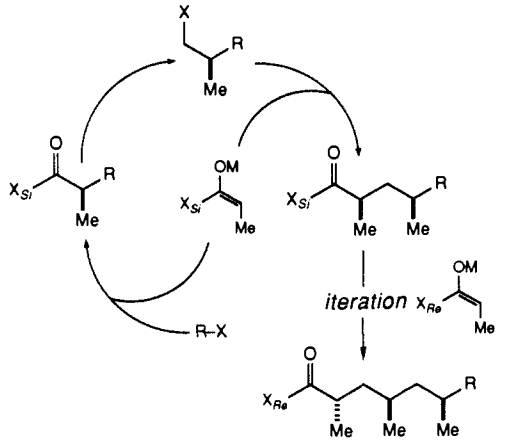
In conjunction with our interest in the development of stereoselective reactions relevant to the synthesis of polyether and macrolide antibiotics, we wish to describe our studies which have culminated in a successful asymmetric synthesis of ionomycin. As a stimulus for the utilization of reactions under parallel development in our laboratory, we elected to develop an approach to the synthesis of this ionophore that would rely on asymmetric bond constructions to contend with the stereochemical issues posed by the structure. This approach to the issue of absolute stereocontrol has also been followed in our recent synthesis of the polyether antibiotic X-206[14] and the macrolide antibiotic cytovaricin.[15] This arbitrary position complements the reasonable alternative of utilizing either the "chiral pool"[16] or chemical resolution to achieve the same objective.

Synthesis Plan

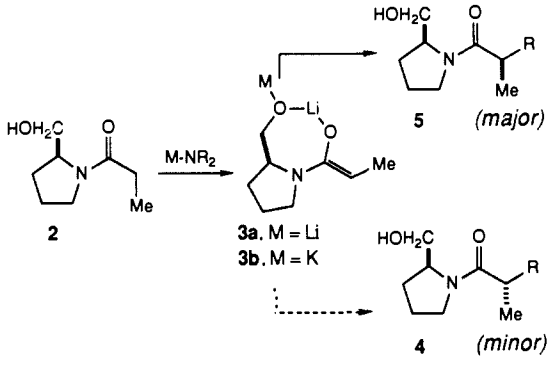
The identification of the ionomycin subunits was, with one exception, straightforward.[17] Both the trans double bond (C_{16}–C_{17}) and the β-dicarbonyl regions (C_9–C_{11}) are readily identifiable disconnection points (transforms A and B, Scheme I) that provide the illustrated C_1–C_{10} and C_{11}–C_{16} synthons, respectively. Each of these fragments contains the common theme of alternating methyl-bearing stereocenters characteristic of propionate-based natural products. Further simplification of the C_{17}–C_{32} synthon was somewhat obvious. In the interest of convergency, the decision was made to section this portion of the molecule at the C_{22}–C_{23} bond, a plan that necessitates the creation of the C_{23} stereocenter in conjunction with subunit assemblage (transforms C and D). On the basis of a rationale that will be presented later, we projected that this stereocenter might be in-

(12) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1979**, *101*, 3344–3353.
(13) Davies, D. H.; Snape, E. W.; Suter, P. J.; King, T. J.; Falshaw, C. P. *J. Chem. Soc., Chem. Commun.* **1981**, 1073–1074.
(14) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
(15) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J. A.; Stout, T. *J. Am. Chem. Soc.* **1990**, in press.
(16) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon: New York, 1983.
(17) The basic disconnection strategy and synthesis plan has been outlined by us: Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32.

Scheme II



Scheme III

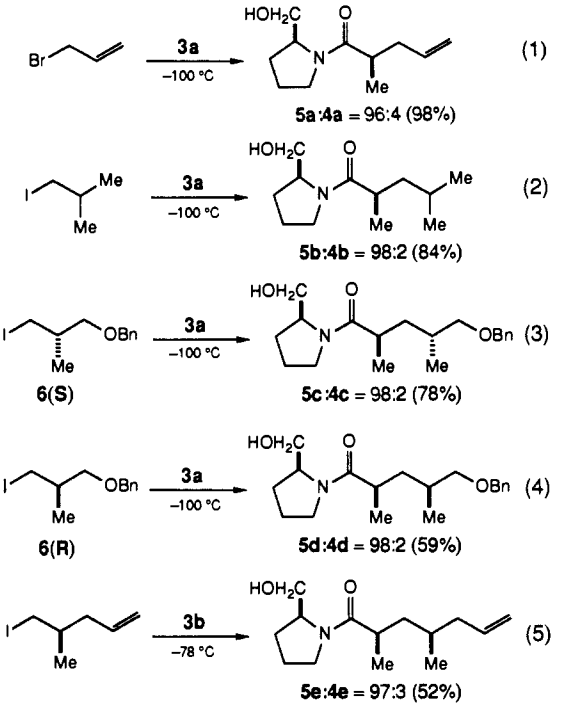


corporated into the associated tetrahydrofuran ring construction through an intramolecular oxymercuration or related halogen-induced haloetherification of the illustrated C_{17}–C_{32} (*Z*) olefin synthon. Collectively, these transforms provided the four illustrated subunits of comparable complexity. In the following sections, the construction and assemblage of these fragments leading to the first synthesis of ionomycin (**1**) will be presented.[1,2]

Acyclic 1,3-Dimethyl-Substituted Synthons. Chiral Propionate Enolates. One of the prominent structural features in ionomycin is the repeating pattern of alternating methyl substitution in the C_1–C_{14} region of the molecule. At the time this project was initiated, no concise solutions to the asymmetric synthesis of such fragments were available. In principle, the iterative use of chiral propionate enolates in the set of alkylation reactions illustrated in Scheme II might provide a general solution to this problem. Through this strategy, syn 1,3-dimethyl relationships might be accessible through the consecutive alkylation of two propionate enolates carrying the same chiral auxiliary (X_C), while either diastereomeric anti dimethyl relationship might be attained through the consecutive use of enantiomeric enolates.

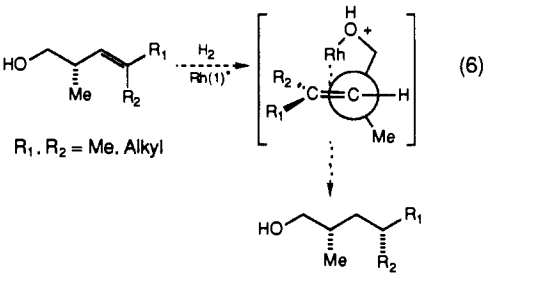
Our efforts to reduce this plan to practice provided the impetus for the development of enolates of sufficient nucleophilicity to react with β-branched alkyl halides with acceptable levels of reaction diastereoselectivity. Although the chiral oxazolidone carboximide derived enolates, under simultaneous development in this laboratory, did not possess sufficient nucleophilicity to participate in such alkylation reactions,[18] the lithium enolate derived from L-prolinol *N*-propionamide met the above criteria for both reactivity and selectivity for this application (Scheme III).[19] After an extensive screening of reaction variables, two common sets of alkylation conditions were established for optimal reaction diastereoselection. In Procedure A, amide **2** was treated with 2 equiv of lithium diisopropylamide (LDA), while for Procedure B, **2** was initially deprotonated with 1 equiv of potassium hydride followed by 1 equiv of LDA. In both instances the reaction solvent was 5% HMPA in tetrahydrofuran (THF). As a point of clarification, the illustrations depicting enolates **3a** and **3b** generated by these two procedures are employed for convenience and are not meant to convey any detailed structural information.

The representative enolate bond constructions illustrated below provide an overview of the effectiveness of this enolate nucleophile (eq 1–5). In one of the relevant reactions, alkylation of enolate



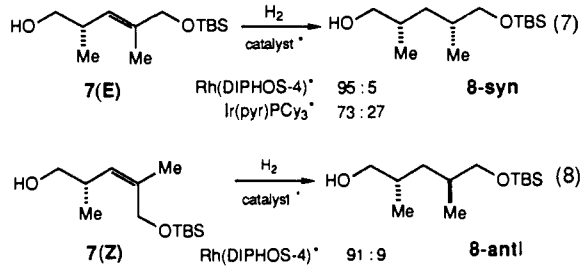
3a, the dilithium conjugate of **2**, with isobutyl iodide (−100 °C) afforded a high yield of the alkylation product **5b** with 98:2 diastereoselectivity (eq 2). For the synthesis of 1,3-dimethyl-substituted synthons, the alkylations of **3a** with iodides **6**(***S***) and **6**(***R***) afforded comparable reaction diastereoselections. During the course of this investigation, other mixed metal enolates such as the potassium/lithium conjugate **3b** exhibited comparable and sometimes improved alkylation stereoselectivity with certain families of alkylating agents at higher temperatures (−78 °C). These latter conditions were chosen for a related alkylation, which will be presented later (Scheme VI, **22b** → **23**). These experiments demonstrate that chiral enolates such as **3** are capable of functioning in the iterative assemblage of reduced polypropionate synthons relevant to the construction of the methyl-bearing stereocenters C_4, C_6, C_8, C_{12}, or C_{14} in ionomycin.

Directed Hydrogenation. Directed hydrogenation reactions[20] were also identified as being potentially valuable for the stereoselective construction of 1,3-dimethyl relationships (Scheme II). Through the intervention of allylic 1,3-strain conformational effects,[21] one might anticipate that the illustrated cationic rhodium–substrate complex could lead to the stereoselective hydrogenation of the trisubstituted olefin (eq 6). This reaction was



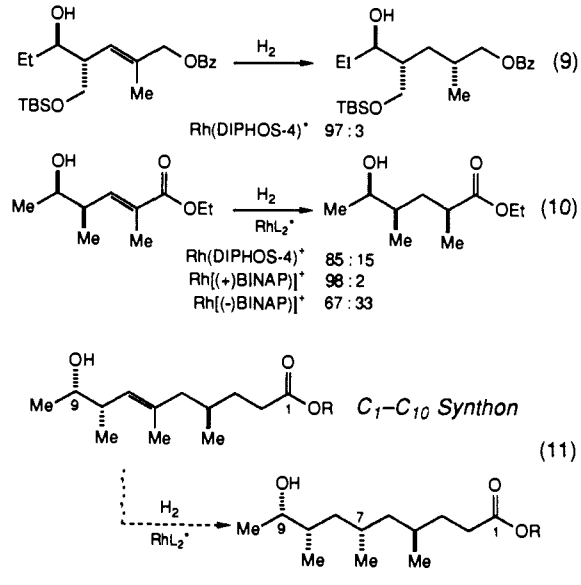
(18) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
(19) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236. Takacs, J. M. Ph.D. Thesis, California Institute of Technology, 1981.
(20) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.
(21) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

evaluated through the synthesis and hydrogenation of the enantiomerically pure (*E*) and (*Z*) homoallylic alcohols **7**(*E*) and **7**(*Z*) which were anticipated to provide the diastereomeric hydrogenation products **8-*syn*** and **8-*anti***, respectively, if hydroxyl directivity were operative in the reduction (eq 7, 8).[22] Hydrogenation of



7(*E*) (CH_2Cl_2, H_2 1200 psi, 25 °C, 2 h) in the presence of 3 mol % of [Rh(NBD)(DIPHOS)-4)]BF_4[23] afforded a 95:5 ratio of product diastereomers favoring **8-*syn*** as anticipated (eq 7). The analogous reduction of the isomeric (*Z*) olefin proved to be less stereoselective (eq 8) for no obvious reason. Attempts to elevate the stereoselectivity of these reactions through the use of the chiral rhodium catalysts derived from (+)- and (−)-BINAP[24] proved to be unsuccessful. During the course of this study we also had the occasion to evaluate the Crabtree catalyst,[25] Ir(pyr)PCy_3^+, in the reduction of **7**(*E*). In accord with related observations, the diastereoselectivity observed with this catalyst in acyclic hydroxy olefins is not as high as the analogous reactions utilizing the cationic rhodium catalyst.[22b,c]

Two additional examples of the directed reduction of more complex homoallylic alcohols that contain stereocenters at both the allylic and homoallylic positions were also investigated (eq 9, 10).[22b] In both cases, the allylic stereocenter controls the stereochemical outcome of the reaction as anticipated from the A-strain model (eq 6). In the latter example, the chiral BINAP ligand effected an enhancement in reaction diastereoselection through double stereodifferentiation.[26] These examples provided us with important analogies for the projected hydrogenation illustrated below (eq 11), which becomes a pivotal step in the synthesis of the C_1–C_{10} ionomycin subunit (vide infra).



(22) (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868. (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005–6008. (c) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637–4640.

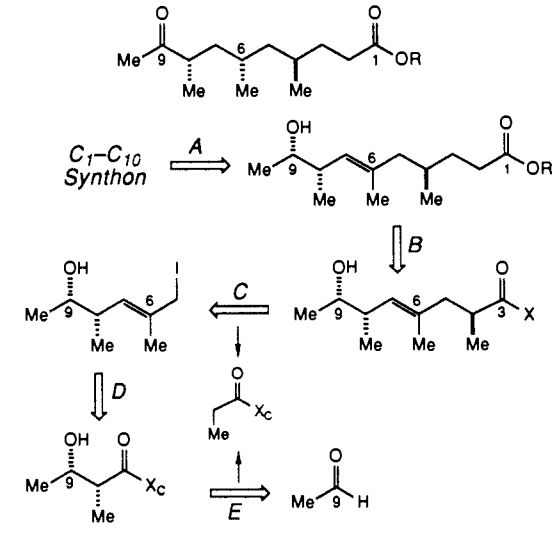
(23) For references associated with the synthesis of these catalysts see ref 20.

(24) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934.

(25) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.

(26) Each of the illustrated alcohols was enantiomerically pure and possessed the indicated absolute stereochemistry.

Scheme IV



In the following discussion, the application of these reactions to the synthesis of the C_1–C_{10} and C_{11}–C_{16} ionomycin synthons will be described.

Synthesis of Ionomycin Fragments. The C_1–C_{10} Subunit. The preceding methodological studies were instrumental in formulating an efficient approach to the synthesis of this portion of the target structure. The abbreviated synthesis plan is shown below (Scheme IV). The decision was made to carry the C_9 carbonyl function as its corresponding secondary alcohol until the final step of the synthesis to provide the opportunity for a directed hydrogenation reaction to establish the C_6 stereocenter (eq 11) and to create a readily available synthon wherein both the C_9 and C_8 stereocenters might be obtained through an enantioselective aldol reaction. As we had previously demonstrated in model studies (eq 9, 10), *either* C_9 hydroxyl configuration could serve equally well as a "directing group" for the hydrogenation. It was anticipated that all other stereochemical relationships in the molecule might be established through asymmetric alkylation (Transform C)[28] and aldol reactions (transform E)[27] from a common chiral propionate enolate. The reduction of this plan to practice is summarized in Scheme V.

The C_8 methyl-bearing stereocenter and associated C_8 hydroxyl group were introduced through a diastereoselective aldol addition of the boron enolate derived from the norephedrine-based chiral carboximide[27] **9** with acetaldehyde. This reaction afforded the crystalline aldol adduct **10** in 93% yield (>98% de). The alcohol was then protected in high yield (98%) as its *tert*-butyldimethylsilyl (TBS) ether (TBS-Cl, imidazole, DMF, 13 h, 25 °C) prior to removal of the chiral auxiliary. At the time that this work was carried out, one of the most reliable methods for excising this imide auxiliary was through lithium benzyloxide transesterification.[28,29] Accordingly, treatment of the TBS ether derived from **10** with LiOBn in THF (3.5 h, 0 °C) afforded an 84% yield of the desired benzyl ester **11**. In order to set up the homologation to the unsaturated ester **13**, the benzyl ester was reduced with diisobutylaluminum hydride to the monoprotected diol **12** (93%) and oxidized (Swern)[30] to the corresponding aldehyde. Condensation of this aldehyde with (carbethoxyethylidene)triphenylphosphorane afforded the α,β unsaturated ester **13** [79%, (*E*):(*Z*) 98:2]. In anticipation of staging the next enolate bond construction to create the C_4 methyl-bearing stereocenter, **13** was reduced with diiso-

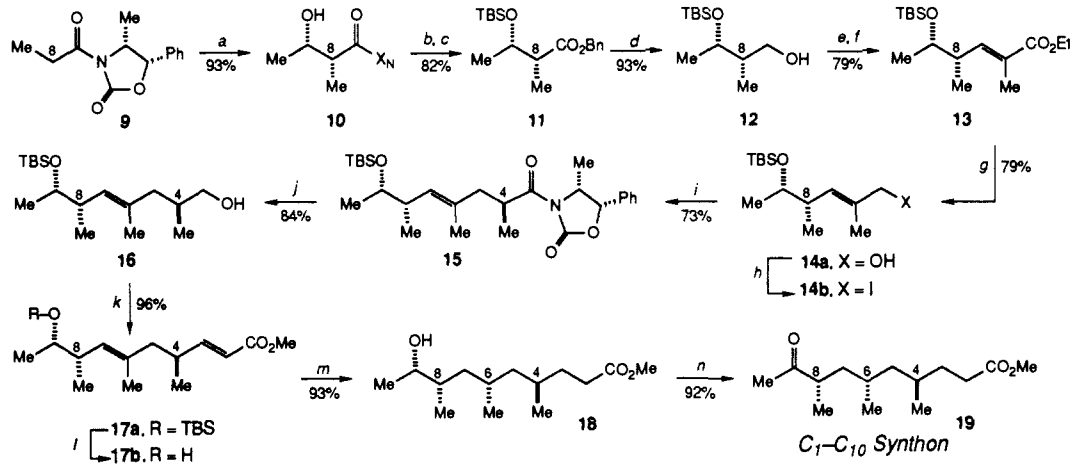
(27) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. For a detailed experimental procedure for these boron aldol reactions see: Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83–91.

(28) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(29) For a more recent general method for hydrolyzing *N*-acylcarboximides see: Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

(30) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

Scheme V[a]



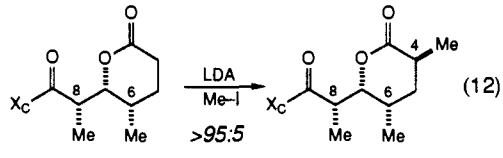
[a] (a) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; MeCHO; (b) TBSCl, Imidazole, DMF; (c) LiOBn, THF, 0 °C; (d) DIBAH, CH_2Cl_2, −78 → 0 °C; (e) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2; (f) $EtO_2CC(Me)=PPh_3$, Toluene, 70 °C; (g) DIBAH, CH_2Cl_2, −78 °C → 0 °C; (h) $(PhO)_3P$·MeI, DMF, 0 °C; (i) 9, $NaN(SiMe_3)_2$, THF, −78 → −50 °C; 14b; (j) $LiAlH_4$, THF; (k) $(ClCO)_2$, DMSO, Et_3N; $MeO_2CCH=PPh_3$, CH_2Cl_2; (l) HF-HOH, MeCN; (m) H_2, (Rh(NBD)DIPHOS)BF_4, CH_2Cl_2; (n) Pyr·SO_3, Et_3N, DMSO.

butylaluminum hydride (98%) to the primary allylic alcohol **14a**. In principle, this transformation could be accomplished with the chiral propionate enolates derived from either the prolinol (Scheme III) or the norephedrine (X_N) oxazolidone auxiliaries such as **9**. The decision to employ **9** in the transformation of **14b** to **15** was not based on the anticipated relative diastereoselectivities of the two enolate alkylations but on the relative ease of the reductive removal of the chiral imide auxiliary.

Allylic alcohol **14a** was transformed into its derived allylic iodide through the procedure of Landauer-Rydon with methyltriphenoxyphosphonium iodide in DMF.[31] Iodide **14b** was used in the subsequent alkylation reaction without chromatographic purification due to its sensitivity toward olefin isomerization. Alkylation of **14b** with 3 equiv of the sodium enolate derived from **9** (−50 °C, 10 h, THF) afforded the crystalline carboximide **15** in 73% yield from allylic alcohol **14a**. Diastereomer analysis (capillary GLC) of the unfractionated product indicated a 98:2 ratio of C_4 product diastereomers. The stereochemical assignment of **15** was based on ample precedent established in this laboratory.[32] Due to the modest reactivity of this enolate, the indicated allylic iodide was required for this transformation. Preliminary experiments with the analogous bromide suffered from the problem of low conversion. At this point, all that remained to complete the framework of the C_1–C_{10} fragment was the illustrated two-carbon chain extension (Scheme V). A three-step sequence consisting of reductive removal of the recyclable chiral auxiliary present in **15**, followed by Swern oxidation and condensation with (carbomethoxymethylidene)triphenylphosphorane provided **17a** in 81% overall yield from **15**.

With the carbon backbone in hand, attention was directed toward setting up the directed hydrogenation to establish the final methyl-bearing stereocenter at C_6. The diene alcohol **17b** necessary for investigating this reduction was produced in 97% yield with dilute aqueous hydrofluoric acid in acetonitrile.[33] Hydrogenation of **17b** with 5 mol % of the cationic rhodium catalyst, [Rh(NBD)DIPhOS-4]BF_4[34] (15 psi H_2, 25 °C, 12 h, CH_2Cl_2), afforded the fully saturated alcohol **18** in good yield and stereoselectivity [6(*S*):6(*R*) = 94:6]. In analogy with our previous observations (eq 7–10), the stereochemistry at C_6 was assigned as (*S*). Attempts at further enhancement of reaction diastereoselectivity by employing chiral rhodium catalysts proved unsuccessful in spite of the precedents that we had established in our methodological studies (eq 10).

An affirmation of the stereochemical integrity of **18** was also made by independent synthesis. During the course of this project, we developed an alternate approach to the C_1–C_{10} fragment **18**.[2] This synthesis, although longer than the present route, was unambiguous in its establishment of the C_6 stereocenter. One of the intermediates in this synthesis is the lactone illustrated in eq 12. In the successful execution of this synthesis, the construction



(12)

of the C_8 and C_6 stereocenters was accomplished with the previously discussed asymmetric aldol and alkylation reactions whereas the C_4 stereocenter was introduced through the illustrated lactone enolate alkylation. From this intermediate, the relative stereochemical relationships at C_6 and C_4 could be unequivocally determined by ^1H NMR spectroscopy, while the C_8 stereocenter, produced in the aldol bond construction, rested on sound precedent. Rigorous proof of the identity of the compounds produced by the two routes was forthcoming after Parikh oxidation (DMSO, SO_3–pyridine, Et_3N)[35] of **18** to **19** (92%).

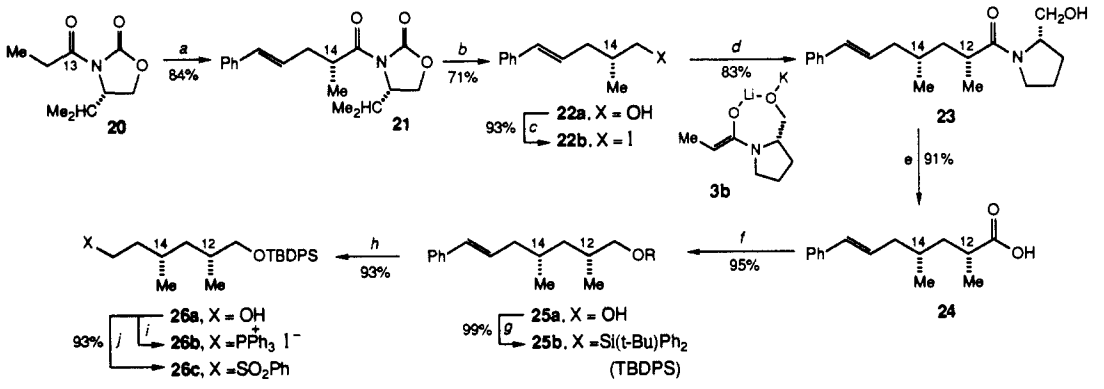
During the course of this study several other groups have also provided approaches to the synthesis of this synthon or a closely related variant. For example, the C_2–C_{10} fragment has been synthesized by Hanessian in a 29-step reaction sequence from L-glutamic acid.[36] In addition, a clever asymmetric synthesis of the C_1–C_9 synthon has been reported by Schreiber.[37] Other efforts by Weiler resulting in the synthesis of the racemic C_5–C_{15} portion of ionomycin without full stereocontrol have recently appeared.[38]

The C_{11}–C_{16} Subunit. Following our preliminary studies, several approaches to the synthesis of this synthon were developed (eq 4, 5). The route that was ultimately chosen was based on the iterative alkylation of chiral propionate enolates as previously outlined (Scheme II).

The synthesis of this subunit began with the generation of the C_{14} stereocenter by reaction of the lithium enolate derived from propionimide **20**[39] with cinnamyl bromide (−40 ≥ −20 °C, 2.5 h)

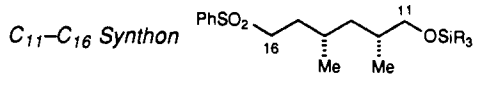
(31) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224–2234.
(32) See ref 28.
(33) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *20*, 3981–3982.
(34) [Rh(NBD)(DIPHOS-4)]BF_4 = norbornadiene[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate. For leading references to the preparation of this catalyst see ref 22a.
(35) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
(36) Hanessian, S.; Murray, P. J. *Can. J. Chem.* **1986**, *64*, 2231–2234.
(37) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5305.
(38) Shelly, K. P.; Weiler, L. *Can. J. Chem.* **1988**, *66*, 1359–1365.

Scheme VI[a]



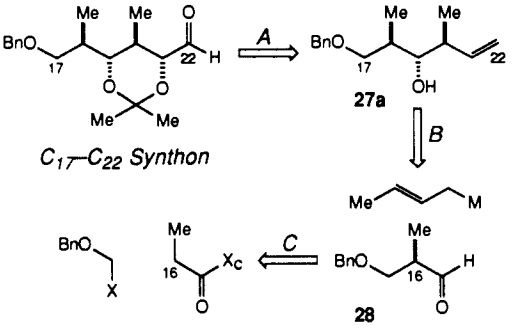
[a] (a) LDA, THF, −78 °C; PhCH=CHCH$_2$Br, −40 °C → 0 °C; (b) LiAlH$_4$, THF, 0 °C; (c) MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 0 °C; NaI, Me$_2$CO, 55 °C; (d) KH, LDA. HMPA, THF, −78 °C; 3b; (e) HCl(aq), 100 °C; NaOH; (f) LiAlH$_4$, Et$_2$O; (g) TBDPSCl, Et$_3$N, DMF; (h) O$_3$, EtOH; NaBH$_4$, H$_2$O/EtOH; (i) MeSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$; NaI, Me$_2$CO; PPh$_3$, MeCN, 50 °C; (j) (PhS)$_2$, (*n*-Bu)$_3$P, CH$_2$Cl$_2$; MCPBA, CH$_2$Cl$_2$.

providing the alkylation product **21** in 84% yield as a 98.7:1.3 14(*R*):14(*S*) mixture of diastereomers (Scheme VI). This material was then transformed into allyl iodide **22b** through the three-step sequence of reduction (LiAlH$_4$), mesylation (MsCl, Et$_3$N), and halogen displacement (NaI) to set up the next propionate alkylation. Since our carboximide-derived enolates do not possess sufficient nucleophilicity to react with alkyl iodides such as **22b**, the more nucleophilic prolinol amide enolate[19] **3** was employed for the next bond construction based on the favorable results that had been obtained from related alkylation reactions (eq 1–5). Reaction of **22b** with 1.1 equiv of the mixed potassium–lithium enolate **3b**, formed by the successive deprotonation of amide **2** with KH and LDA, afforded an 83% yield of the desired alkylation product **23** as a 97:3 12(*R*):12(*S*) mixture of diastereomers. Internally assisted hydrolysis (N → O acyl transfer) of **23** in refluxing 1 N aqueous HCl for 8 h followed by brief treatment with 2 N aqueous NaOH provided carboxylic acid **24** (91%),[19] which was reduced with LiAlH$_4$ in diethyl ether to afford the desired alcohol **25a** in 95% yield. GLC analysis revealed a 96:4 mixture of C$_{12}$ diastereomers, which established an upper limit of 1% for epimerization at C$_{12}$ during the amide hydrolysis and reduction steps. The C$_{11}$ hydroxyl group was then protected as its *tert*-butyldiphenylsilyl (TBDPS) ether **25b** (99%) so that the appropriate C$_{16}$ functionality could be introduced.



Ozonolysis of **25b** in the presence of Sudan III dye[40] as a reaction indicator followed by reduction of the hydroxyperoxide with sodium borohydride afforded alcohol **26a** in 96% yield. At this juncture, it was convenient to remove the C$_{12}$ diastereomer contaminant (ca. 4%) by medium-pressure liquid chromatography. From this intermediate, both the phosphonium salt **26b** and the sulfone **26c** were readily prepared as anticipated constituents for a trans olefin construction through either Schlosser–Wittig[41] or Julia[42] reactions. The phosphonium salt **26b** was prepared in 91% yield by sequential mesylation, sodium iodide treatment, and displacement with triphenylphosphine. The corresponding sulfone was synthesized by treatment of **26a** with phenyl disulfide and tri-*n*-butylphosphine[43] followed by oxidation with excess *m*-chloroperbenzoic acid to provide the desired sulfone **26c** in 93% yield.

Scheme VII



In related studies, this ionomycin fragment had also been subsequently prepared by Hanessian through a 25-step reaction sequence from L-glutamic acid,[36] and a closely related fragment has also been synthesized in racemic form by Weiler.[44]

The C$_{17}$–C$_{22}$ Subunit. The abbreviated synthesis plan for this fragment is outlined in Scheme VII. The selection of the acetonide protecting group for the C$_{19}$, C$_{21}$ diol functionality was made in anticipation that the C$_{21}$ stereocenter could be epimerized to the desired diastereomer through base equilibration of the aldehyde moiety in the event that kinetic control elements were ineffective in defining this center during its construction. The penultimate intermediate **27a**, from which the desired synthon might be readily constructed, was further disconnected to the well-recognized β-hydroxyisobutyric acid derived aldehyde **28**[45] and a crotylmetal organometallic (transform B). At the time this project was initiated, the development of chiral allylic organometallic reagents that would be suited for this synthesis had not yet been achieved.[46] In the present instance it was hoped that asymmetric induction from the chiral aldehyde might be realized through a chelate-controlled addition process.[47] In planning for this reaction, we hoped to employ the observations of Hiyama[48] and Heathcock,[49]

(39) (a) For a synthesis of the (*S*)-valine and (1*S*,2*R*)-norephedrine-derived chiral auxiliaries see: Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835. (b) For a detailed procedure for the synthesis of the (*S*)-phenylalanine-derived oxazolidone see: Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 77–82.

(40) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.

(41) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126.

(42) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. I* **1978**, 829. (c) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. I* **1980**, 1045. For a recent review see: Kocienski, P. *Phosphorus and Sulfur* **1985**, *24*, 97–127.

(43) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *16*, 1409–1412.

(44) Nicoll-Griffith, D.; Weiler, L. *J. Chem. Soc., Chem. Commun.* **1984**, 659–661.

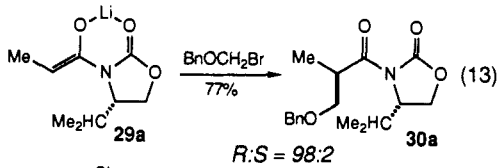
(45) (a) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203–214. (b) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925–944. (c) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117–2118. (d) Reference 11a.

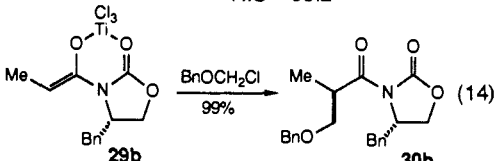
(46) For recent advances in this area see: Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979–3982. Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538. For a recent review of allylmetal reagents as enolate equivalents see: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489–503.

(47) It is noteworthy that chelate-controlled addition reactions can be achieved with this aldehyde with certain nucleophiles: Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035–1038. Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281–284 and references cited therein.

who noted that high levels of anti diastereoselection could be obtained in the addition of crotylchromium(III) reagents to aldehydes. The possible role that chelate organization might play in the addition process[50] with this organometallic reagent was one of the issues to be addressed.

The first objective was the development of a practical approach to the synthesis of the "Roche aldehyde" **28**, a chiral building block that has enjoyed considerable popularity in the synthesis of propionate-derived natural products.[45] Two relevant asymmetric alkylation reactions that result in the successful construction of O-protected β-hydroxyisobutyric acid derivatives are shown in eq 13 and 14. In work previously published, the alkylation of the

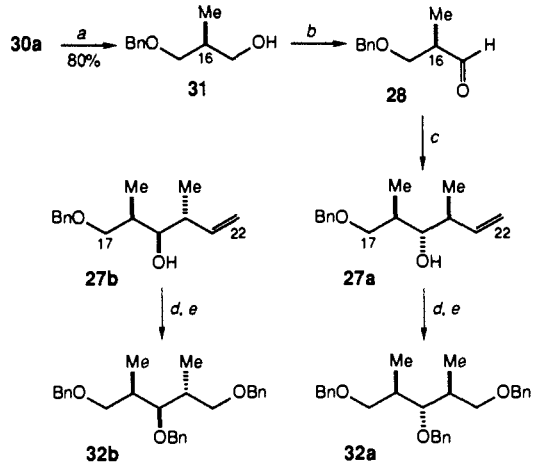




lithium enolate **29a** with bromomethyl benzyl ether (2 h, −40 °C) afforded the alkylation product **30a** in 77% yield with good diastereoselectivity (98:2).[18] In this reaction, the alkyl bromide is required for the reaction due to the modest nucleophilicity of the illustrated enolate. Recently, we have re-examined this reaction with more Lewis acidic metal enolates such as **29b**, and a substantial improvement in the practicality of the reaction has been achieved (eq 14).[51] Reduction of **30a** or **30b** ($LiAlH_4$, THF, 0–25 °C, 3 h) afforded an 80% yield of the primary alcohol **31**, which was oxidized (Swern) to aldehyde **28** (Scheme VIII). This oxidation procedure provided negligible racemization of this substrate, which readily racemizes (ca. 20%) on attempted oxidation with the $DMSO/SO_3$–pyridine procedure of Parikh.[35]

The addition of the crotylchromium reagent to **28** was accomplished with the crotyl bromide/chromous chloride reagent under the conditions described by Hiyama.[48] Analysis of the product mixture by gas chromatography revealed a rather disappointing 40:60 mixture of adducts **27a** and **27b**, respectively. The stereochemical assignment of these two isomers was accomplished through the illustrated two-step sequence, independently performed on each isomer, to provide tribenzyl ethers **32a** and **32b** (Scheme VIII). These diastereomers are readily distinguishable with ^{13}C NMR spectroscopy by the presence of the symmetry plane in **32a**. With this disappointing result in hand, attention was directed at probing the effects of solvent on the reaction diastereoselection. Unfortunately, this addition proved to be quite solvent-insensitive, and no improvement in selectivity was observed in solvents such as diethyl ether, toluene, or dimethylformamide. Similar observations have been reported by Kishi and Lewis for the reactions of **28**, as well as a number of other aldehydes, under these conditions.[52] These authors also revealed that increasing the steric

Scheme VIII



hindrance of the α-substituent in the aldehyde resulted in the selective formation of the undesired "Cram" product. It thus appears that the crotylchromium(III) reagents are not good candidates for chelate-controlled carbonyl addition. Additional studies with both crotyl–$TiClCp_2$ and crotyl–$ZrClCp_2$ afforded similar results.

At the time this impasse was reached, a reaction that was relevant to the generation of the C_{19}–C_{20} anti relationship with the correct absolute stereochemistry was discovered in these laboratories. It was found that the aldol addition of boryl enolates derived from crotonimide **33**[53] with aldehydes provided the crystalline syn, α-vinyl adducts such as **34** (Scheme IX).[54] These results provided a solution to the specific problem at hand when the carboximide portion of the aldol product was viewed as a latent methyl group. This plan was put into practice through the addition of the boryl enolate derived from **33** to aldehyde **28** to afford the desired syn adduct **34** in 58% overall yield based on starting alcohol **31**, the precursor to **28**.

As discussed earlier for the synthesis of the C_1–C_{10} synthon (**10** → **11**, Scheme V), reductive removal of the chiral auxiliary in imides such as **34** suffers from competing reaction at the endocyclic carbonyl group[29] as well as loss of the α stereocenter through accompanying olefin conjugation. A solution to this problem that relies upon activation of the exocyclic carbonyl toward nucleophilic attack through regeneration of the boron aldolate has been developed.[55] Reaction of **34** with tri-*n*-butylborane and glacial acetic acid at 25 °C[56] followed by reduction (0 °C, $LiBH_4$) provided diol **35a** in 89% yield (Scheme IX). The successful conversion of **35a** to **27a** was achieved by selective tosylation of the primary alcohol group (Ts–Cl, pyridine, 5 °C)[57] and reduction with lithium triethylborohydride[58] to provide **27a** in 92% yield from diol **35a**. This reaction sequence not only established the C_{19} and C_{20} stereocenters in a highly selective manner, but it also nearly doubled the overall yield of **27a** available through the prior route, which employed the chromium-mediated addition (Scheme VIII). All that remained to complete the synthesis of **4** was incorporation of the C_{21} and C_{22} oxygen atoms and subsequent functional group manipulations.

Bis-hydroxylation of **27a** under the Upjohn conditions (catalytic OsO_4, *N*-methylmorpholine *N*-oxide)[59] introduced the remaining

(48) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181. Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037–1040.

(49) Buse. C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, *19*, 1685–1688.

(50) For an excellent review see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

(51) Evans, D. A.; Urpi, F. *J. Org. Chem.* Submitted for publication. In conjunction with this study, a simple enolization protocol for the generation of the trichlorotitanium enolate **29b** has been discovered. Treatment of the imide *successively* with 1.05 equiv of $TiCl_4$ and then ethyldiisopropylamine (1.05 equiv, CH_2Cl_2, 0 °C, 1 h) resulted in the quantitative generation of **29b**. Subsequent treatment of this enolate with chloromethyl benzyl ether (2 equiv, 0 °C, 6 h) afforded a 99% yield of the illustrated alkylation product **30b** (eq 14). The detailed experimental procedure for this reaction has been provided.

(52) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343–2346.

(53) See the following paper for the full experimental details for the synthesis of these compounds: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

(54) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961–4964.

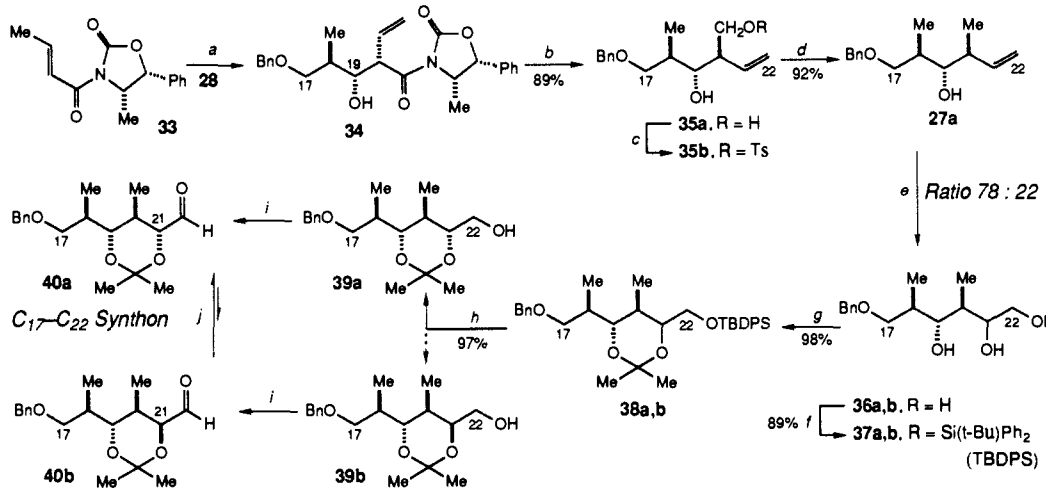
(55) Bartroli, J. Ph.D. Thesis, California Institute of Technology, 1984.

(56) This reaction produces the dibutylboryl acetate, which reacts with **34** to form the boron aldolate.

(57) Johnson, W. S.; Collins, J. C.; Pappo, R.; Rubin, M. B.; Kropp, P. J.; Johns, W. F.; Pike, J. E.; Bartmann, W. *J. Am. Chem. Soc.* **1963**, *85*, 1409–1430.

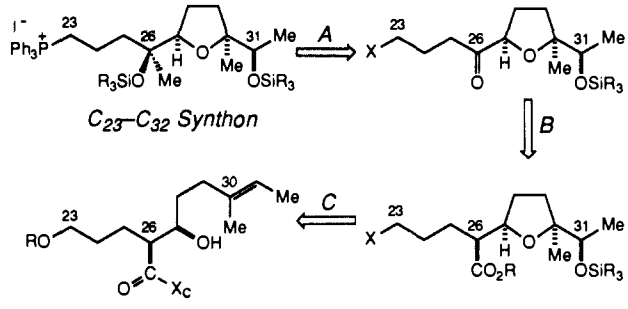
(58) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064–3066. (b) Holder, R. W.; Matturro, M. G. *Ibid.* **1977**, *42*, 2166–2168.

Scheme IX[a]

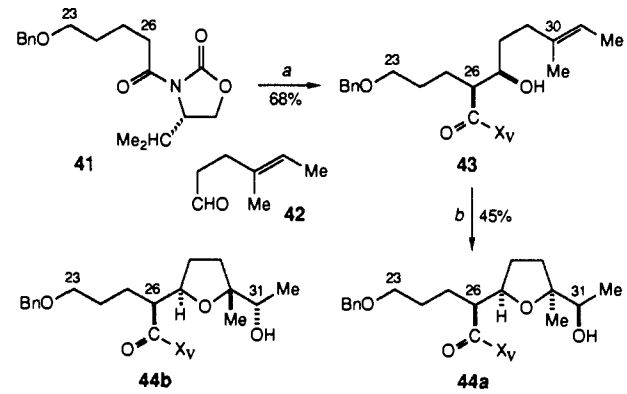


[a](a) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, 28, −78 °C; H_2O_2, MeOH; (b) Bu_3B, HOAc, THF; $LiBH_4$, THF, 0 °C; H_2O_2, MeOH; (c) *p*-$TolSO_2Cl$, Pyr, 5 °C; (d) $Li(Et)_3BH$, THF; H_2O_2, NaOH(aq), MeOH; (e) OsO_4, R_3N-O, H_2O/Me_2CO; (f) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (g) $Me_2C(OMe)_2$, CSA, Me_2CO; (h) $(n\text{-}Bu)_4NF$, THF; (i) Pyr·SO_3, Et_3N, DMSO; (j) K_2CO_3, MeOH.

Scheme X



Scheme XI



(a) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (b) MCPBA, EtOAc.

oxygen functionality. The triol product **36a**, which was a 78:22 mixture of C_{21} diastereomers, was selectively silylated[60] to provide diols **37a,b** in 89% overall yield from olefin **27a** (Scheme IX). This protection step was a necessary prelude to the establishment of the 1,3-diol (C_{19} and C_{21}), rather than the thermodynamically more stable 1,2-diol (C_{21} and C_{22}) acetonide.[61] Removal of the silyl protecting group with tetrabutylammonium fluoride afforded a mixture of chromatographically resolvable alcohols **39a** and **39b** in 95% overall yield from **37a**. It is significant that, rather than the expected equimolar mixture of these isomers, the *desired* diol precursor to acetonide **39a** was obtained as the major product. No explanation for the unanticipated asymmetric induction in this osmylation is apparent. This observation provides another useful example of acyclic stereocontrol in the osmylation process.[62]

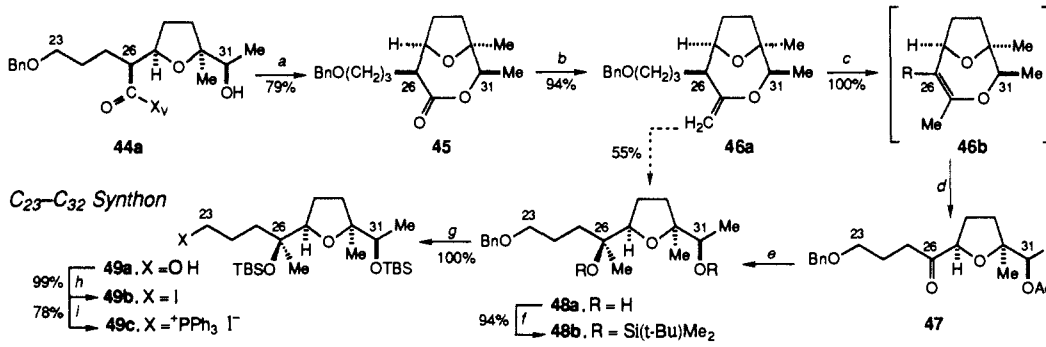
All that remained to complete the synthesis of the C_{17}–C_{22} subunit was equilibration of the C_{21} stereocenter in minor diastereomer **39b** (Scheme IX). This was accomplished by oxidation[35] and epimerization (potassium carbonate/methanol) of the resultant aldehyde **40b** providing an equilibrium mixture of **40a**:**40b** of 92:8.

The C_{23}–C_{32} Subunit. The plan for the synthesis of this portion of ionomycin is outlined below (Scheme X). Chelate-controlled addition of methylmagnesium bromide (transform A),[63] the execution of a "carboxy inversion" reaction[64] (transform B), and remote epoxidation[65] (transform C) reduce this fragment to an intermediate that might be readily assembled through an asymmetric aldol bond construction.

The synthesis was initiated with the aldol addition of the boryl enolate[27] derived from imide **41** and unsaturated aldehyde **42**,[66] which afforded **43** in 68% yield (97% diastereomeric purity by capillary GLC, Scheme XI). At this point, attempts to achieve a diastereoselective epoxidation of olefin **43** met with limited success. As expected from the precedent established by Kishi and co-workers,[65] the hydroxyl-directed vanadium(V)-catalyzed *tert*-butyl hydroperoxide epoxidation afforded a 1:4 ratio of epoxides, the precursors to tetrahydrofurans **44a** and **44b** favoring the undesired diastereomer **44b**. After attempts to invert the stereochemistry of the intermediate epoxides from this reaction failed,[65] the decision was made to pursue a nonselective epoxidation with *m*-chloroperbenzoic acid and subsequent acid-catalyzed cyclization (HOAc) which afforded a 1:1 mixture of tetrahydrofurans **44a** and **44b** readily separable by flash chromatog-

(59) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.
(60) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99–102.
(61) See for example: Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883–4886.
(62) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, in press.
(63) (a) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2745–2748. (b) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262–263. (c) Collum, D. B.; McDonald, J. H.; Still, W. C. *Ibid.* **1980**, *102*, 2117–2118.
(64) (a) Denny, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760–3761. (b) Suginome, H.; Uchida, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 943–946.
(65) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2741–2744. The sense of this epoxidation selectivity appeared to be of no consequence based on reports of epoxide isomer interconversion in related cases: Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935.
(66) Obtained by the reduction of ethyl (*E*)-4-methyl-4-hexanoate with $LiAlH_4$ followed by pyridinium chlorochromate oxidation. The ester was prepared through Claisen rearrangement. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

Scheme XII[a]

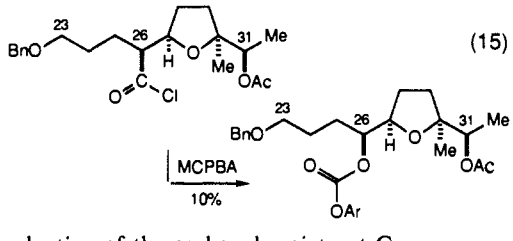


[a] (a) PhMgBr, THF; (b) $Cp_2TiCl(CH_2)AlMe_2$, Pyr, THF/Toluene, −45 °C −20 °C; (c) PPTS, CH_2Cl_2; (d) O_3, CH_2Cl_2/MeOH, −78 °C, Me_2S; (e) MeMgBr. CH_2Cl_2/Et_2O, −78 °C; (f) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; (g) H_2. Pd/C, EtOAc; (h) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C: NaI, $NaHCO_3$, Me_2CO; (i) PPh_3, Toluene/MeCN, 75 °C;

raphy.[67] The high chemical yield (90%), ease of diastereomer separation, and the timing of this step in the synthesis all reinforced the decision to use this approach for the construction of the illustrated synthon. Two pieces of evidence were employed to secure the stereochemical assignments of these diastereomeric tetrahydrofurans. First, a strong ^{1}NMR NOE between the methyl and hydrogen substituents on the two ring stereocenters secured the stereochemical assignment **44a**. This assignment was later confirmed chemically by the lactonization experiment (**44a** → **45**) illustrated in Scheme XII.

With the availability of tetrahydrofuran **44a**, the next objective became the incorporation of the C_{26} stereocenter, which required a formal oxidative decarboxylation, followed by addition of a methyl nucleophile to the derived ketone (Scheme X, transforms B and A). In the pursuit of this objective, it was discovered that the most expedient protocol for the removal of the valine-derived chiral auxiliary (HX_V) from the tetrahydrofuran **44a** was to exploit the propensity of this substrate to undergo lactonization to **45**, a reaction that was facilitated with phenylmagnesium bromide/lithium bromide in 79% yield (Scheme XII). Lactone **45** not only proved to be a useful intermediate (vide infra), but it also provided unequivocal evidence for the stereochemical assignment of the tetrahydrofuran **44a**.

At this point, our plan was to exploit the carboxy inversion reaction[64] to introduce the needed oxygen at C_{26} (eq 15). Accordingly, lactone **45** was transformed into the illustrated acid chloride which, upon treatment with MCPBA, afforded a low yield (ca. 10%) of the desired product. Efforts to improve the yield of this reaction were unsuccessful, and as a consequence, an alternative degradation strategy was developed (Scheme XII).

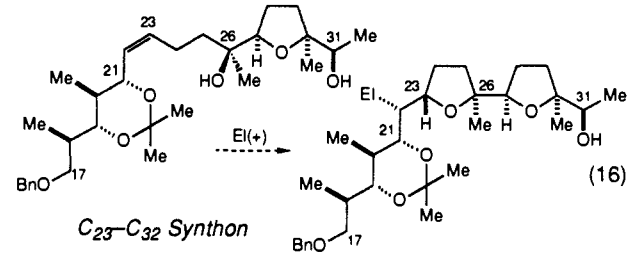


(15)

Introduction of the carbonyl moiety at C_{26} was approached through the oxidative cleavage of an enol derivative of lactone **46b** (Scheme XII). After attempts to effect a high-yield enolization/silylation (LDA, TMSCl) failed, the equivalent transformation was accomplished through a three-step sequence which was initiated by the formation of enol ether **46a** by employing the methylenating reagent discovered by Tebbe and developed by us.[68] Treatment of the exocyclic vinyl ether **46a** with a catalytic amount of pyridinium *p*-toluenesulfonate cleanly effected olefin isomerization to the endocyclic enol ether **46b**, which was subjected to ozonolysis with use of the conditions of Stotter[69] in the presence of Sudan 7B indicator[40] to provide ketone **47** after reduction with dimethyl sulfide. Since this intermediate was quite susceptible to epimerization at C_{27} upon exposure to silica, the unpurified ketone was immediately treated with methylmagnesium bromide to afford diol **48a** (Scheme XII) in a 55% overall yield from lactone **45**. In addition to this major diastereomer, 9% of another diastereomeric product was also isolated, which we speculate could either be isomeric at C_{26} or a product derived from addition to the C_{27} epimerization product. Protection of the C_{26} and C_{31} alcohols as *tert*-butyldimethylsilyl (TBS) ethers (TBS–OTf, Et_3N, 2 h, 0 °C, 94%) followed by debenzylation (H_2, Pd–C, EtOAc, 100%) set up the formation of the C_{23} phosphonium salt **49c**. Mesylation of **49a** (MsCl, Et_3N, 3 h, 0 °C) and iodide displacement (NaI, acetone, 18 h, 20 °C) of the derived mesylate afforded the iodide **49b** in 99% yield from its alcohol precursor. The synthesis of the phosphonium salt **49c** was then accomplished by heating the iodide with 1.5 equiv of triphenylphosphine (54 h, 75 °C) to afford, after crystallization, 78% of the hygroscopic phosphonium salt, mp 76–81 °C.

With each of the four ionomycin subunits in hand, their assemblage to ionomycin was undertaken through the experiments outlined in the following discussion.

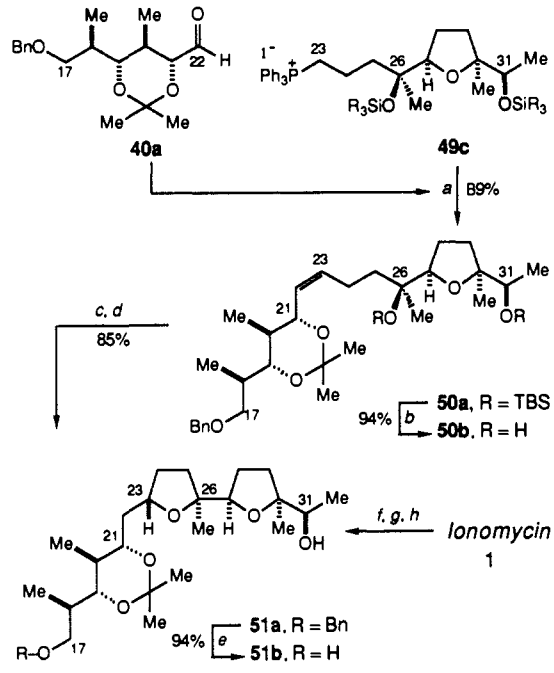
Assemblage of Subunits. Union of the C_{16}–C_{22} and C_{23}–C_{32} Fragments. Several factors influenced the decision to assemble the molecule from the C_{32} to the carboxyl terminus. First, this direction of assemblage delayed the incorporation of the most sensitive functionality (β-diketone and carboxylate) until the latter stages of the synthesis. Second, with the C_{17}–C_{32} fragment in hand, all assumptions dealing with the assignment of stereochemistry in this portion of the molecule could be checked through a direct comparison of this intermediate with the identical fragment derived from a projected degradation of ionomycin. The assemblage of this portion of the molecule was anticipated to begin with the union of C_{17}–C_{22} aldehyde with the C_{23}–C_{32} phosphorus ylide to provide the illustrated cis olefin (eq 16). The pivotal issue to be addressed was the stereochemical course of the electrophile-induced cyclization to form the second tetrahydrofuran ring and the associated C_{23} stereocenter.[70]



(16)

(67) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(68) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* **1980**, *102*, 3270–3272.
(69) Stotter, P. L.; Eppner, J. B. *Tetrahedron Lett.* **1973**, *14*, 2417–2420.
(70) For a recent review of this family of reactions see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6.

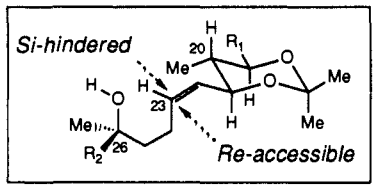
Scheme XIII[a]

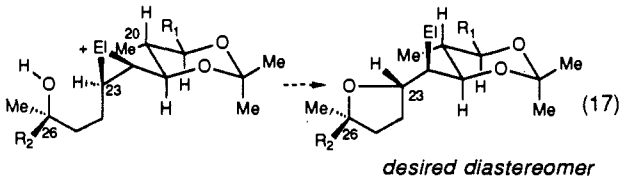


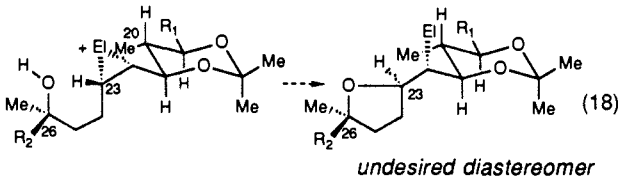
[a] (a) $NaN(TMS)_2$, Toluene, −78 °C; 40a; (b) Bu_4NF, THF, 80 °C; (c) $Hg(OAc)_2$, CH_2Cl_2, −78 to −20 °C; (d) $NaBH_4$, NaOH(aq), MeOH, −78 °C; (e) H_2, Pd/C, EtOAc; (f) CH_2N_2, Et_2O, 0 °C; $Me_2C(OMe)_2$, PPTS; (g) OsO_4, $NaIO_4$, THF/H_2O; (h) $LiAlH_4$, Et_2O.

We anticipated that this reaction, which might be accomplished with either electropositive halogen or mercuric ion, would proceed with the desired stereochemical outcome based upon the following logic. As a consequence of the C_{22} cis olefin geometry, the torsion angle around the C_{21}–C_{22} bond is strongly biased by allylic strain effects.[21] In the optimal conformation, the H–C_{21}–C_{22}–C_{23} dihedral angle should be nearly zero thereby positioning the C_{20} methyl group pendant to the acetonide ring, over the *Si*-face of the olefin. With such a dominant difference in the steric environments on the two olefin diastereofaces, we reasoned that a stereoselective bond construction could be realized.[71]

If the stereochemistry-determining step in the electrophile-induced ring closure is the competing formation of the illustrated olefin complexes (eq 17, 18), one might anticipate that the product derived from *Re*-face attack of electrophile (eq 17) would be the favored product. On the other hand, if reversible electrophile–olefin complexation is followed by a rate-determining intramolecular etherification, the stereochemical outcome of the reaction is clouded by steric factors that influence both the population of olefin complexes and the rate of their collapse from attack by the oxygen nucleophile. However, if the steric effects of olefin complexation are dominant, both kinetic options should result in the same stereochemical outcome. Prior literature suggests that the latter situation probably prevails.[72] From the results to follow, it is clear that the cyclization induced by mercuric acetate is highly stereoselective (93:7) in favor of the desired cyclization pathway (eq 17). The reactions culminating in the assemblage of this fragment are illustrated in Scheme XIII.







Condensation of aldehyde **40a** with the ylide derived from phosphonium salt **49c** under salt-free conditions[73] provided olefin **50a** (Scheme XIII) in 89% yield (97:3 cis:trans). Removal of the TBS protecting groups was accomplished by heating a THF solution of **92** in the presence of tetrabutylammonium fluoride (10 equiv, 36 h, 80 °C) affording diol **50b** (94%), which set the stage for construction of the second tetrahydrofuran ring and the associated C_{23} stereocenter. Internal oxymercuration of the C_{22} double bond by the C_{26} hydroxyl group was accomplished by reaction with mercuric acetate (2 equiv, CH_2Cl_2, 7 h, −78 to 20 °C) followed by reduction of the organomercurial with basic sodium borohydride providing an 85% yield of **51a**. Examination of the unpurified reaction mixture by capillary GLC revealed a 93:7 mixture of diastereomers from which the major isomer **51a** was isolated by chromatography.

In an independent set of experiments, ionomycin was sequentially converted into its corresponding methyl ester (CH_2N_2), treated with dimethoxypropane/pyridinium tosylate to prepare the C_{19}–C_{21} acetonide, and oxidized with aqueous osmium tetroxide/sodium periodate to give several fragments from which the aldehyde corresponding to the C_{23}–C_{32} portion of the ionophore was isolated.[2] Reduction of this aldehyde with $LiAlH_4$ afforded **51b**, which proved to be identical in all respects with synthetic **51b** prepared by debenzylation of **51a**. This correlation unequivocally established the integrity of all nine stereogenic centers in the C_{17}–C_{32} portion of ionomycin.

Incorporation of the C_{11}–C_{16} Subunit. Construction of the C_{16}–C_{17} trans-disubstituted olefin was initiated by reprotection of the sterically hindered C_{31} hydroxyl group in **51a** as the TBS ether, hydrogenolysis of the benzyl ether to give alcohol **52b** (94% overall yield), and subsequent Swern oxidation to aldehyde **53**. The initial plan for construction of the C_{16}–C_{17} bond was based on the trans-selective Schlosser–Wittig procedure.[41] However, even after considerable effort, this reaction could not effectively be applied to the union of aldehyde **53** and the ylide derived from phosphonium salt **26b** (Scheme VI). The Julia trans-olefination sequence was then accepted as the viable alternative (Scheme XIV).[42] This sequence was initiated by the reaction of aldehyde **53** with the lithium conjugate of sulfone **26c**. The diastereomeric mixture of β-acetoxysulfones **54**, obtained upon quenching the reaction with acetic anhydride, was reduced with sodium amalgam at −30 °C to give an 86:14 ratio (capillary GLC) of olefins favoring the trans isomer **55a** in a 70% yield from alcohol **52b**. Selective removal[74] of the primary silyl protecting group with tetrabutylammonium fluoride (7 equiv, 21 h, 25 °C) followed by separation of the minor cis olefin contaminant by medium-pressure chromatography afforded **55b** in 94% yield, based on the isomeric purity of the starting material. The trans olefin **55b** exhibits a 15.5 Hz coupling constant between the C_{16} and C_{17} protons, whereas the cis isomer has a corresponding 11 Hz coupling constant. With three-quarters of ionomycin successfully assembled, the next step involved generation of the β-diketone portion of the molecule.

(71) In our recent synthesis of the polyether antibiotic X-206 (ref 14) a related diastereoselective mercuric acetate cyclization was also achieved.

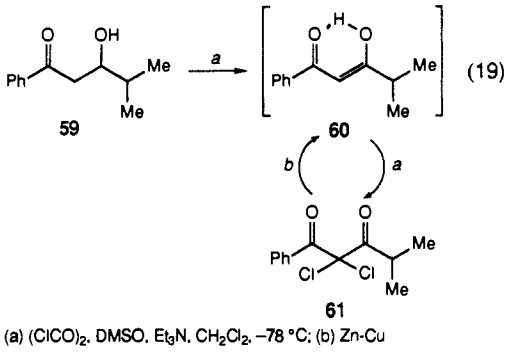
(72) For related cyclizations that formed the basis of a loose analogy see: Tanaka, O.; Tanaka, N.; Ohsawa, T.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1968**, *9*, 4235–4238.

(73) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694–1700.

(74) Studies on related systems had shown the C_{31}-*tert*-butyldimethylsiloxy group to be extremely resistant to cleavage by tetrabutylammonium fluoride.

Incorporation of the C_1–C_{10} Subunit. The final bond construction required the selective enolization of the methyl ketone moiety in the C_1–C_{10} subunit **19** (Scheme XIV). On the basis of literature precedent,[75] the enolate derived from methyl ketone **19**, generated with dibutylboryl triflate and diisopropylethylamine (−78 °C), was allowed to react with the aldehyde **56** corresponding to alcohol **55b**, providing a 1:1 mixture of diastereomeric aldol adducts[27] **57** in 85% yield based on **55b**. Alternatively, this same reaction could be carried out with the corresponding stannous enolate[76] in 70% yield, a process that presents an operationally simplified solution to performing this reaction on micromolar scale. Finally, oxidation of the diastereomeric aldol adducts **57** to β-diketone **58** represented the final step needed to secure the intact carbon skeleton of ionomycin.

Execution of this final oxidation in the synthesis of ionomycin proved considerably more difficult than initially expected. Due to the relatively small quantities of β-hydroxy ketone **57** available, a model substrate was chosen to investigate this reaction. The model employed was β-hydroxy ketone **59** (eq 19), which represented an attempt to approximate the steric environment of the corresponding functionality in **57**. Prior to this study, a report[77] on the oxidation of simple β-hydroxy ketones had shown the most effective conditions for this transformation to be those developed by Swern.[30] When **59** was subjected to an excess of the dichlorosulfonium chloride reagent (−78 °C), followed by treatment with triethylamine, a less polar (TLC) product was cleanly produced which proved to be the dichlorinated ketone **61** rather than the expected β-diketone **60**. The requirement for the use of an excess of oxidant (which is also the source of electrophilic chlorine) was relevant in the model system because only minute quantities of the actual substrate **57** would be available for oxidation at any given time. Even though it was found that **61** could be converted to **60** in >90% yield by reduction with zinc–copper couple,[78] other methods for effecting the oxidation of **59** under nonstoichiometric conditions were investigated. These attempts led to various products including **61**, the (methylthio)methyl ether of **59**, and the α,β-unsaturated ketone derived from **59**. In spite of the fact that the Collins oxidation[79] had been shown in the earlier study[77] to provide only low yields of β-diketones, a method based on this oxidation procedure was finally developed. The procedure involved formation of the oxidant, generated from chromium trioxide and pyridine, in the presence of Celite, which would presumably prevents loss of product in the precipitates associated with the Collins procedure. When **59** was exposed to these conditions (10 mol equiv of chromium) for a short time period (5 min), the resulting β-diketone **91** was generated in 80% yield. It thus appears that product occlusion in the inorganic precipitates from the Collins procedure is the principal source of the low yields observed earlier.[77] These oxidation conditions were applied to the ionomycin substrate **57** to provide the strongly ultraviolet active **58** in 72% yield (Scheme XIV).



(19)

(a) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (b) Zn-Cu

Deprotection. All that remained for the completion of the synthesis was removal of the three protecting groups present in **58**. In our preliminary studies, considerable effort was invested in the development of a set of protecting groups for ionomycin that could be removed without degradation of the natural product. We were particularly concerned about the possibility of acid- or base-catalyzed epimerization of the C_8 and C_{12} methyl groups flanking the β-dicarbonyl moiety during the deprotection sequence. Accordingly, the selection of protecting groups for the synthesis and the conditions for their removal were established by experiments executed on natural ionomycin.[1,2] The deprotection of synthetic **58** was initiated with the cleavage of the C_{31} TBS ether and accompanying acetonide hydrolysis by treatment with dilute HF in aqueous acetonitrile,[33] which removed both protecting groups within 1 h at room temperature providing triol **59** in 84% yield. Finally, hydrolysis of the methyl ester **59** with lithium hydroxide in aqueous dimethoxyethane afforded ionomycin (92% from **59**), which was isolated as the calcium complex following treatment of **1** with a buffered aqueous solution of calcium chloride. Ionomycin calcium complex prepared by this route proved to be identical in all respects (^1H NMR, ^{13}C NMR, IR, mp, HPLC, UV, and optical rotation) with an authentic sample of ionomycin.[80]

Conclusions

When the synthesis of ionomycin was first addressed, the development of both the proline and oxazolidone-based chiral enolates had just been undertaken. The stereochemical complexity and associated architectural features of this structure served as a focal point for the development of both enolate-based bond constructions and later the hydroxyl-directed hydrogenation reactions. The prospect of employing such reactions in an iterative fashion without being submerged in a morass of diastereomers stood as one of the goals for the application of this methodology to the synthesis of complex structures. These objectives were realized in the synthesis of this natural product.

Experimental Section

General. ^1H NMR spectra are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, dd = doublet of doublets, dq = doublet of quartets, dt = doublet of triplets), integration, coupling constant (Hz), and interpretation. ^{13}C NMR spectra were recorded on a JOEL FX-90Q (22.5 MHz) or a Bruker AM-300 (75 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Optical rotations are reported as follows $[\alpha]_D$, concentration, c (g/100 mL), and solvent. Melting points are uncorrected. Analytical gas–liquid chromatography was carried out on a Hewlett Packard 5880A chromatograph with a 25 m × 0.2 mm fused silica capillary column wall-coated with Carbowax 20M or a 30 m × 0.32 mm silica capillary column wall-coated with SE-54, DB-1, or DWAX-4. Data are reported as follows: column type, oven temperature, column head pressure, and retention time (t_r). Flash chromatography was performed according to the general procedure of Still,[67] employing EM Reagents 40–63 mm silica gel 60 or Whatman 37–53 mm silica gel LPS-2, with the amount and solvent system indicated. Medium-pressure chromatography (MPLC) was performed with EM Reagents Lobar silica gel 60 prepacked columns. Data are reported as follows: column size, solvent system, and flow rate. When necessary, solvents and reagents were dried in the traditional fashion prior to use.

General Acylation Procedure for the Preparation of Prolinol-Derived Hydroxyamides. To 1.0 equiv of amino alcohol was added dropwise (exothermic) 1.1 equiv of anhydride with stirring. Upon complete addition, the mixture was heated at ~70 °C for 10 min. The mixture was cooled, basified with aqueous NaOH, and extracted with three portions of CH_2Cl_2. The combined organic extracts were washed with 10% aqueous HCl and brine, dried (Na_2SO_4), and concentrated in vacuo to yield the hydroxyamide, which was evaporatively distilled prior to use.

(2*S*)-2-(Hydroxymethyl)-1-propionylpyrrolidine (2). Acylation of 23.9 g (0.24 mol) of (*S*)-prolinol[81] with 34 mL (34.5 g, 0.26 mol) of propionic

(75) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559–562. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

(76) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381–1384.

(77) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567–570.

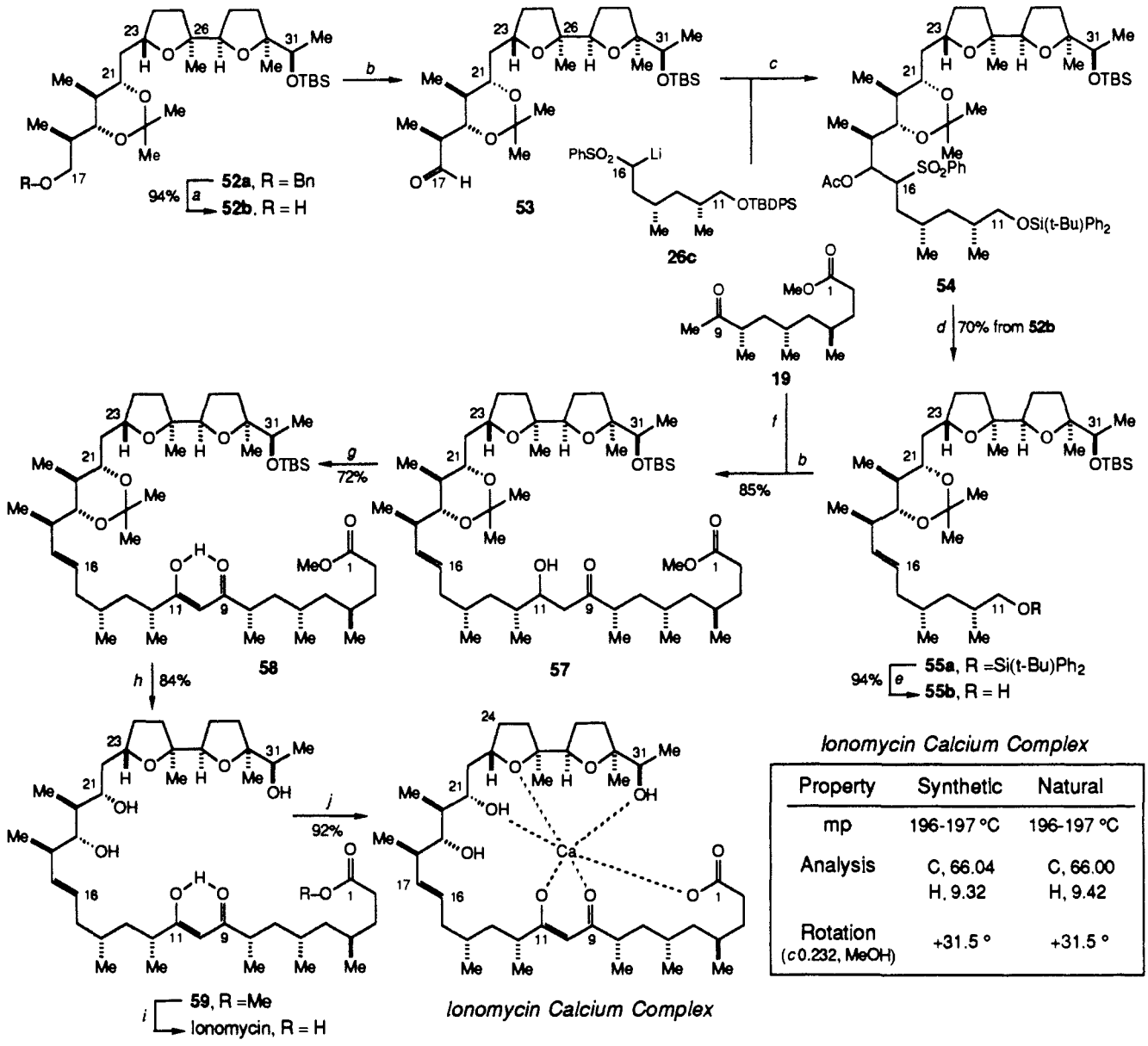
(78) Stephenson, L. M.; Gemmer, R. V.; Current, S. P. *J. Org. Chem.* **1977**, *42*, 212–214.

(79) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *9*, 3363–3366.

(80) The authors are grateful to The Squibb Institute for Medical Research for providing a generous sample of the calcium complex of ionomycin.

(81) Lane, C. F. U.S. Patent 3,935,280; *Chem. Abstr.* **1976**, *84*, 13510d.

Scheme XIV[a]



Ionomycin Calcium Complex

Property	Synthetic	Natural
mp	196-197 °C	196-197 °C
Analysis	C, 66.04 H, 9.32	C, 66.00 H, 9.42
Rotation (*c* 0.232, MeOH)	+31.5 °	+31.5 °

[a] (a) H_2, Pd/C, Me_2CO; (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) THF, −78 °C; 26c; Ac_2O; −78 °C to 20 °C; (d) Na(Hg), EtOAc/MeOH, −30 °C; (e) Bu_4NF, THF; 55b to corresponding aldehyde 56 by conditions (b) above; (f) Bu_2BOTf, $(i\text{-}Pr)_2(Et)N$, CH_2Cl_2, −78 °C; (g) CrO_3·Pyr, Celite, CH_2Cl_2; (h) HF, HOH, MeCN, 25 °C, (i) LiOH, HOH, Dioxane, 45 min, 25 °C; (j) pH 9 $CaCl_2$-HOH.

anhydride afforded 32.3 g (86%) of propionamide **2** as a light amber oil. Bulb-to-bulb distillation (110 °C, <0.001 mm) provided **2** as a colorless liquid that crystallized on standing: mp 38–40 °C; IR (neat) 3380, 2962, 2937, 2870, 1610, 1430 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.16 (br s, 1, O*H*), 4.20 (m, 1, CH), 3.67–3.39 (m, 4, N, O-CH_2), 2.31 [q, J = 9 Hz, 2, C(O)-CH_2], 2.13–1.58 (m, 4, CH_2-CH_2), 1.16 (t, J = 9 Hz, 3, CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 174.7 (s, *C*=O), 66.9 (t, *C*H_2-OH), 60.9 (d, *C*H), 47.8 (t, *C*H_2-N), 28.1 (t, *C*H_2-CH_2), 24.3 [t, C(O)-*C*H_2], 8.9 (q, *C*H_3); $[\alpha]_D$ = −65.3° (*c* 21.6, CH_2Cl_2). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.15; H, 9.65; N, 8.90.

General Procedures for the Enantioselective Alkylations of Chiral Hydroxyamide Derivatives. Preparation of Lithium Diisoproylamide (LDA). To a cooled (0 °C) solution of 1.2–1.5 equiv of diisopropylamine in THF (0.1–0.5 M) was added 1.0 equiv of *n*-butyllithium in hexane with stirring. Upon complete addition, the mixture was warmed to room temperature and used as a standard solution. **Lithium Enolate Alkylation Conditions.** To a stirred solution of 2.1 equiv of LDA in THF (0.1–0.5 M) was added 1.0 equiv of amide. The resulting solution was stirred at room temperature for 10–30 min, followed by the addition of 2.1 equiv of HMPA. The mixture was cooled to the desired alkylation temperature and 1.0–1.5 equiv of alkyl halide added dropwise, at a rate to maintain the desired temperature. The reaction mixture was stirred 3–12 h. **Mixed Metal Enolate Alkylation Conditions.** A slurry of 1.2–1.5 equiv of KH in mineral oil was washed with four portions of pentane to remove the oil. To the residue was added a sufficient volume of THF to yield a 0.1–0.5 M solution upon addition of 1.0 equiv of hydroxyamide. Upon cessation of gas evolution, 1.05–1.1 equiv of LDA was added. The resulting mixture was stirred at room temperature for 10–30 min. Following the addition of 2.1 equiv of HMPA, the reaction mixture was cooled to the desired alkylation temperature and 1.0–1.2 equiv of alkyl halide added dropwise, at a rate to maintain the desired temperature. The reaction mixture was stirred 3–6 h. **Standard Isolation Procedure.** The resulting reaction mixtures were quenched by dropwise addition of saturated aqueous ammonium chloride or water. This mixture was partitioned between solvent and water or brine and then the aqueous layer extracted with 1–3 portions of the indicated solvent. The combined organic extracts were dried (Na_2SO_4 or $MgSO_4$) and concentrated in vacuo to afford the alkylation product.

(2*S*,2′*R*)-2-(Hydroxymethyl)-1-(2′-methyl-4′-pentenoyl)pyrrolidine (5a, Eq 1). To a cooled (−100 °C) solution of lithium enolate derived from 6.88 g (43.8 mmol) of hydroxy-amide **2** in THF–HMPA was added 4.2 mL (5.87 g, 48.5 mmol) of allyl bromide. The reaction mixture was slowly warmed to −70 °C over 6 h and then quenched with saturated ammonium chloride solution. The standard isolation procedure, partitioning between ether–brine and extraction with three portions of CH_2Cl_2, afforded after chromatography on silica gel (350 g, EtOAc) 8.50 g (98%) of amide **5a** as a pale yellow liquid: IR ($CHCl_3$) 3350, 3075, 2975,

2875, 1615 (sh), 1605, 1457, 1435, 1330 cm^{-1}; ^1H NMR ^1H NMR (90 MHz, $CDCl_3$) δ 6.11–5.50 (m, 1, H_2C=C*H*), 5.20–4.87 (m, 3, H_2C=CH, O*H*), 4.19 (m, 1, N-C*H*), 3.73–3.28 (m, 4, N, O-CH_2), 2.83–1.50 [m, 7, C(O)-C*H*, C-CH_2-C], 1.16 (d, J = 7 Hz, 3, CH-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 177.1 (*C*=O), 136.0 (H_2C=*C*H), 116.6 (H_2C=*C*H), 66.8 (*C*H_2OH), 60.8 (N-*C*H), 47.8 (N-*C*H_2), 38.1 [C-(O)-*C*H-*C*-H_2], 37.8 [C(O)-*C*H-*C*H_2], 28.2 (*C*H_2), 24.4 (*C*H_2), 17.3 [96%, (*R*)-CH-*C*H_3], 16.6 [4%, (*S*)-CH-*C*H_3]; $[\alpha]_D$ (diastereomer ratio 96.5:3.5) = −84.9° (*c* 15.27, CH_2Cl_2). GLC analysis (–OTMS derivative, 50 m Carbowax, 190 °C) shows two peaks at 5.62 (96.2%) and 5.71 min (3.8%). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.22; H, 9.51.

(2*S*,2′*R*)-1-(2′,4′-Dimethylpentanoyl)-2-(hydroxymethyl)pyrrolidine (5b, Eq 2). To a cooled (−100 °C) solution of lithium enolate derived from 3.129 g (19.9 mmol) of hydroxyamide **2** in THF–HMPA was added 2.54 mL (4.04 g, 2.19 mmol) of isobutyl iodide. The reaction mixture was slowly warmed to −40 °C over 10 h and then quenched with water. The standard isolation procedure, partitioning between ether–brine and extraction with three portions of CH_2Cl_2, afforded after chromatography on silica gel (250 g, EtOAc) 3.56 g (84%) of amide **5b** as a clear liquid: IR (neat) 3390, 2955, 2930 (sh), 2865, 1630 (sh), 1610, 1458, 1430 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.16 (br, t, 1 O*H*), 4.20 (m, 1, N-C*H*), 3.78–3.33 (m, 4, N, O-CH_2), 2.53 [m, 1, C(O)-C*H*], 2.22–1.00 (m, 7, C-CH_2-C, CH_3-C*H*-CH_3), 1.19 [d, J = 7 Hz, 3, C(O)-CH-CH_3], 0.89 (d, J = 6 Hz, 6, CH_3-CH-CH_3; ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.2 (*C*=O), 67.1 (*C*H_2-OH), 60.8 (N-*C*H), 47.8 (N-*C*H_2), 42.7 [C-(O)-C-H=*C*H_2], 36.1 [C(O)-*C*H], 28.2 (*C*H_2), 25.9 (CH_3-*C*H-CH_3) 24.5 (*C*H_2), 23.0 (*C*H_3-CH-CH_3), 22.4 (CH_3-CH-*C*H_3), 17.8 [97%, (*R*)-C-(O)-*C*H-CH_3], 17.1 [3%, (*S*)-C(O)-*C*H-CH_3]; $[\alpha]_D$ (diastereomer ratio 97.4:2.6) = −66.6° (*c* 12.6, CH_2Cl_2). GLC analysis (25 m methyl silicone, 150 °C) shows two peaks at 12.94 (2.4%) and 13.42 min (97.6%). Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.47; H, 10.91; N, 6.71.

An authentic diastereomeric mixture of **5b** and the C_2-epimer **4b** was prepared by enolization of a sample of **5b** with LDA (THF, 25 °C, 45 min) followed by reprotonation with water. The standard isolation procedure (CH_2Cl_2) afforded a mixture of diastereomers as an amber oil: ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 177.8 (*C*=O), 66.4 (*C*H_2-OH), 60.8 (N-*C*H), 47.8 (N-*C*H_2), 43.4 [(*S*)-C(O)-CH-*C*H_2]. 42.6 [(*R*)-C(O)-CH-C*H*$_2$], 36.0 [C(O)-*C*H], 28.0 (*C*H_2), 25.9 [CH_3-*C*H-CH_3], 24.4 (*C*H_2), 22.9 (*C*H_3-CH-CH_3), 22.6 (CH_3-CH-*C*H_3), 17.7 [(*R*)-C(O)-CH-*C*H_3], 17.1 [(*S*)-C(O)-CH-*C*H_3]. A sample of this amide was hydrolyzed to the corresponding carboxylic acid for characterization: **(2*R*)-2,4-Dimethylpentanoic Acid.** Hydrolysis of 3.36 g (15.8 mmol) of amide **5b** in 100 mL of 1.0 N HCl afforded, after bulb-to-bulb distillation, 1.96 g (96%) of 2,4-dimethylpentanoic acid: $[\alpha]_D$ = −18.97° (neat). $[\alpha]_D$ = −21.9° (*c* 5.39, ether) (lit.[82] $[\alpha]_D$ = +19.4° (*c* 5.23, ether)).

(2*S*,2′*R*,4′*R*)-1-(5′-(Benzyloxy)-2′,4′-dimethylpentanoyl)-2-(hydroxymethyl)pyrrolidine (5c, Eq 3). To a cooled (−78 °C) solution of lithium enolate **3a** derived from 5.869 g (37.4 mmol) of hydroxyamide **2** in THF–HMPA was added 11.3 g (39.0 mmol) of (*S*)-3-(benzyloxy)-2-methylpropyl iodide[45b] (**6**(*S*)) as a 50% THF solution. The mixture was stirred at −78 °C for 6 h and then quenched with saturated NH_4Cl solution. The standard isolation procedure (hexane) afforded after chromatography on silica gel (300 g, EtOAc) 9.261 g (78%) of amide **5c** as a colorless oil: IR (neat) 3400, 3070, 3035, 2985, 2940, 2880, 1640 (sh), 1617, 1480 (sh), 1440 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.29 (s, 5, Ar), 5.12 (br s, 1 O*H*), 4.44 (s, 2, Ar*C*H_2O), 4.14 (m, 1, N-C*H*), 3.67–3.24 (m, 4, N, O-CH_2), 3.29 (d, J = 5 Hz, 2, ArCH_2OCH_2), 2.68 [m, 1, C(O)C*H*], 2.09–1.44 (m, 6, CH_2), 1.44–1.0 (m, 1, OCH_2-C*H*), 1.12 [d, J = 7 Hz, 3, C(O)-CH-CH_3], 0.96 (d, J = 6.5 Hz, 3, OCH_2-H-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.0 (*C*=O), 138.6 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 75.7 (ArCH_2), 73.0 (ArCH_2O*C*H_2), 67.3 (*C*H_2OH), 60.9 (N-*C*H), 47.6 (N-*C*H_2), 37.8 [HC-*C*H_2-CH], 35.8 [C(O)-*C*H], 31.4 (OCH_2-*C*H), 28.1 (*C*H_2), 24.3 (*C*H_2), 18.0 (overlapping *C*H_3); $[\alpha]_D$ = −50.0° (*c* 5.2, CH_2Cl_2). GLC analysis (15 m Carbowax 210 °C) showed peaks at 28.14 [(2*S*,4*R*), 1.8%], 27.36 [(2*R*,4*S*), 5.2%], and 28.87 min [(2*R*,4*R*), 92.9%]. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.48; H, 9.07.

(2*S*,2′*R*,4′*S*)-1-(5′-(Benzyloxy)-2′,4′-dimethylpentanoyl)-2-(hydroxymethyl)pyrrolidine (5d, Eq 4). To a cooled (−100 °C) solution of lithium enolate derived from 3.132 g (19.9 mmol) of hydroxyamide **2** in THF–HMPA was added 6.0 g (20.7 mmol) of (*R*)-3-(benzyloxy)-2-methylpropyl iodide[45b] (**6**(*R*)) as a 50% THF solution. The mixture was slowly warmed to −40 °C over 12 h and then quenched with saturated NH_4Cl. The standard isolation procedure (ether) afforded after chromatography on silica gel (350 g, EtOAc) 3.768 g (59%) of amide **5d** as a pale yellow oil: IR (neat) 3410, 3100, 3075, 3040, 2975, 2945, 2880, 1642 (sh), 1618, 1492, 1468, 1460, 1440 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.32 (s, 5, Ar), 5.17 (br s, 1 O*H*), 4.47 (s, 2, Ar-CH_2), 3.50 [m, 1, N-C*H*], 3.67–3.23 (m, 6, N, O-CH_2), 2.70 [m, 1, C(O)-C*H*], 2.06–1.33 (m, CH_2, OCH_2-C*H*-CH_3), 1.10 [d, J = 7 Hz, 3, C(O)-CH-CH_3], 0.93 (d, J = 7 Hz, 3, OCH_2-CH-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.1 (*C*=O), 138.5 (Ar), 128.2 (Ar), 127.6 (Ar), 127.5 (Ar), 76.2 (Ar-*C*H_2), 73.1 (ArCH_2O-*C*H_2), 67.1 (*C*H_2OH), 60.8 (N-*C*H), 47.5 (N-*C*H_2), 38.0 [C(O)-CH-*C*H_2], 35.7 [C(O)-*C*H-CH_3], 31.5 (OCH_2-*C*H-CH_3), 28.0 (*C*H_2), 24.3 (*C*H_2), 17.8 (*C*H_3), 17.6 (*C*H_3); $[\alpha]_D$ (diastereomer ratio 1.7:95.5:2.8) = −50.5° (*c* 4.4, CH_2Cl_2). GLC analysis (25 m methyl silicone, 180 °C) showed peaks at 39.79 [(2*S*,4*S*), 1.8%], 40.83 [(2*R*,4*S*), 95.5%], and 41.42 min [(2*R*,4*R*), 2.7%]. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15. Found: C, 71.29; H, 9.10. A sample of this amide was hydrolyzed to the corresponding carboxylic acid for characterization: **(2*R*,4*S*)-5-(Benzyloxy)-2,4-dimethylpentanoic Acid.** Hydrolysis of 537 mg (1.68 mmol) of amide **5d** in 15 mL of 1.0 N HCl gave 363 mg (91%) of the indicated carboxylic acid: IR (neat) 3450–2350, 1732 (sh), 1705, 1603, 1493, 1463 (sh), 1452 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 10.48 (br s, 1, CO_2*H*), 7.30 (s, 5, Ar), 4.44 (s, 2, Ar-CH_2OCH_2), 3.24 (d, J = 5 Hz, 2, ArCH_2OC*H*$_2$), 2.52 [m, 1, C(O)-C*H*], 1.79 (m, 1, OCH_2-CH), 1.50 (overlapping d's, J = 7 Hz, 2, C*H*-C_2-CH), 1.12 (d, J = 7.5 Hz, 3, C(O)-CH-CH_3], 0.93 (d, J = 7 Hz, 3 OCH_2-CH-CH_3).

(2*S*,2′*R*,4′*R*)-1-(2′,4′-Dimethyl-6′-heptenoyl)-2-(hydroxymethyl)-pyrrolidine (5e, Eq 5). To a cooled (−78 °C) solution of mixed lithium–potassium enolate **3b** derived from 2.711 g (17.3 mmol) of hydroxyamide **2** in THF–HMPA was added 3.89 g (18.5 mmol) of (*R*)-1-iodo-2-methyl-4-pentene[83] as a 50% THF solution. The mixture was stirred at −78 °C for 6 h and then quenched with saturated NH_4Cl. The standard isolation procedure, partitioning between hexane–brine and extraction with two portions of ether, afforded after chromatography on silica gel (300 g, EtOAc) 2.135 g (52%) of amide **5e** as a yellow liquid: IR (neat) 3400, 3082, 2970, 2940, 2920, 2880, 1640 (sh), 1620, 1460, 1437 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.03–5.53 (m, 1, C=C*H*), 5.23–4.83 (m, 2, H_2C=C), 4.22 (m, 1, N-C*H*), 3.73–3.37 (m, 4, N, OCH_2), 2.69 [m, 1, C(O)-C*H*], 2.22–1.0 (m, 9, C*H*, CH_2), 1.13 [d, J = 7 Hz, 3, (C(O)-CH-CH_3], 0.87 (d, J = 6 Hz, 3, CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.0 (*C*=O), 136.9 (H_2C=*C*H), 115.9 (*C*H_2=CH), 67.2 (*C*H_2-OH), 60.8 (N-*C*H), 47.8 (N-*C*H_2), 41.3 (CH-*C*H_2), 40.5 (CH-*C*H_2), 35.7 [C(O)-*C*H], 30.4 (CH_2-*C*H-CH_2), 28.1 (*C*H_2), 24.4 (*C*H_2), 19.7 (*C*H_3), 18.2 [C(O)-CH-*C*H_3]; $[\alpha]_D$ (diastereomer ratio, 91.9:2.8:5.3) = −67.2° (*c* 3.59, CH_2Cl_2). GLC analysis (50 m Carbowax 175 °C) showed peaks at 38.71 [(2*R*,4*R*), 91.3%], 39.12 [(2*S*,4*R*), 3.0%], and 39.71 min [(2*R*,4*S*), 5.7%]. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53. Found: C, 69.31; H, 10.43.

An authentic diastereomeric mixture (2*R*,2*S*) of amide **5e** was prepared by enolization of a sample of (2*R*)-amide with LDA (THF, 25 °C, 15 min) followed by reprotonation with ammonium chloride solution. The standard isolation procedure (CH_2Cl_2) afforded a mixture of diastereomeric amides as an amber liquid: ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 178.0, 136.9, 115.9, 67.1, 61.0, 60.8, 47.8, 41.5, 41.3, 40.9, 40.5, 35.9, 35.7, 30.7, 30.5, 28.1, 24.4, 19.8, 19.5, 18.3 [(*R*), C(O)-CH-*C*H_3], 16.8 [(*S*), C(O)-CH-*C*H_3].

(4*S*)-3-Propionyl-4-isopropyl-1,3-oxazolidin-2-one (20).[84] Into a dried, 1-L, 3-necked flask equipped with a gas-inlet, mechanical stirrer, and an addition funnel was placed 25.8 g (0.200 mol) of (4*S*)-4-isopropyl-2-oxazolidinone.[39a] The apparatus was flushed with nitrogen and the flask charged with 400 mL of dry THF, the stirred solution was cooled to −78 °C, and 130 mL (1.70 M, 0.221 mol) of a hexane solution of *n*-butyllithium was added over a 15-min period. After the solution was stirred for 0.5 h at −78 °C, 19.1 mL (20.3 g, 0.224 mol) of propionyl chloride was added in one portion via hypodermic syringe. The reaction mixture was warmed to 0 °C and stirred for an additional 3 h. After the addition of 200 mL of a 1 M aqueous solution of K_2CO_3, the mixture was concentrated to a volume of ca. 200 mL on a rotary evaporator (30 °C, 30 mm). The residue was extracted with three 200-mL portions of CH_2Cl_2. The organic extracts were combined, washed with two 200-mL portions of saturated aqueous K_2CO_3 and brine, dried over anhydrous $MgSO_4$, and solvent removed in vacuo (30 °C, 30 mm). The residual liquid was distilled under reduced pressure through a 10-cm vacuum-jacketed Vigreux column, affording 33.3–36.0 g (90–97%) of **20** as a colorless liquid: bp 59–62 °C (0.01 mm); IR (neat) 2970, 2880, 1785, 1705, 1385, 1370, 1245, 1210, 1070 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ d 4.6–4.1 (m, 3 H, C_4-*H*, C_5-H_2), 2.95 (q, J = 7.6 Hz, 2 H, C_2'-H_2),

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(83) Prepared by the alkylation of enolate **3b** with allyl bromide, hydrolysis, reduction ($LiAlH_4$), mesylation (MsCl, Et_3N), and iodide displacement.

(84) This experiment was performed by D. J. Mathre, Department of Chemistry, California Institute of Technology.

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2.57–2.22 (m, 1 H, C_4-C*H*), 1.18 (t, J = 7.6 Hz, 3 H, C_3-H_3), 0.92 (overlapping d's, 6 H, $CH(CH_3)_2$); $[\alpha]_{589}$ = +91.9°, $[\alpha]_{577}$ = +96.0°, $[\alpha]_{546}$ = +109.5°, $[\alpha]_{435}$ = +186.2°, $[\alpha]_{365}$ = +293.9° (*c* 0.377, CH_2Cl_2). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.38; H, 8.30.

(4*S*,2′*R*)-3-(3′-(Benzyloxy)-2′-methylpropanoyl)-4-benzyl-1,3-oxazolidin-2-one (30b, Eq 14).[51] A solution of 1.165 g (5.0 mmol) of (4*S*)-3-propanoyl-4-benzyl-2-oxazolidinone[39b] in 20 mL of dry CH_2Cl_2 was cooled to 0 °C under nitrogen, and 0.575 mL (5.24 mmol) of $TiCl_4$ were added dropwise giving a homogeneous yellow solution of the derived enolate **29b**. After 5 min, 0.915 mL (5.25 mmol) of diisopropylethylamine was added (5 min) and the dark red mixture was stirred at 0 °C for 1 h. The resultant titanium enolate was treated with 1.39 mL (10.02 mmol) of benzyl chloromethyl ether for 6 h at 0 °C. A conventional isolation procedure afforded 2.65 g (150% mass balance) of unpurified adduct **30b**. Analysis by capillary GC (30 m × 0.32 mm DB-1, 200 °C, 15 psi) afforded a >99:1 ratio of (2*R*) (t_r = 14.20 min) to (2*S*) (t_r = 14.65 min) diastereomers. The title compound was isolated by MPLC (Michel-Miller column, size D, hexane/EtOAc 4:1) to give 1.753 g (99.3%) of the pure **30b** as a colorless oil: R_f 0.28 (20% EtOAc/hexane); IR (neat) 3065, 3030, 2980, 2940, 2870, 1782, 1705, 1290, 1355, 1220, 1120 cm^{-1}; MS (CI, e/m) 353 (M^+), 276, 262, 247; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.20 (m, 10 H, aromatic *H*'s), 4.77–4.69 (m, 1 H, CHN), 4.58 (s, 2 H, $OCH_2C_6H_5$), 4.26–4.13 (m, 3 H, $NCHCH_2O$ and CHCO), 3.84 (dd, J = 7.90, 8.96 Hz, 1 H, C*H*HOC_6H_5), 3.62 (dd, J = 5.32, 9.08 Hz, 1 H, C*H*HOC_6H_5), 3.26 (dd, J = 3.22, 13.45 Hz, 1 H, C*H*HC_6H_5) 2.75 (dd, J = 9.23, 13.47 Hz, 1 H, C*H*HC_6H_5), 1.22 (d, J = 6.88 Hz, 3 H, CH_3CHCO); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 175.2, 153.0, 138.13, 135.16, 129.34, 128.74, 128.20, 127.49, 127.42, 127.11, 73.12, 72.33, 65.89, 55.12, 38.39, 37.78, 13.92; $[\alpha]^{25}_D$ = +50.4° (*c* 1.55, CH_2Cl_2). Anal. Calcd for $C_{21}H_{22}NO_4$: C, 71.37; H, 6.56. Found: C, 71.32; H, 6.38.

(2*S*)-2-Methyl-3-(benzyloxy)-1-propanol (31).[45b] To a magnetically stirred, cooled (−78 °C) solution of 15.3 g (50.0 mmol) of imide **30a** in 100 mL of THF was added 50 mL (1 M in THF, 50 mmol) of $LiAlH_4$ dropwise over a 15-min period. After 0.5 h, the mixture was allowed to warm to 25 °C and then stirred for 2 h. The mixture was recooled to −78 °C and then cautiously quenched with 1.9 mL of water, 1.9 mL of 2 M aqueous NaOH, and 5.7 mL of water. The mixture was allowed to warm to 25 °C and stirred for 1 h. The mixture was filtered through a sintered glass filter and the precipitate washed with ether. The filtrate and washings were concentrated in vacuo. The product was isolated by flash chromatography (7 × 70 cm column, 85:15 CH_2Cl_2/ether) to afford after distillation (Kugelrohr, 90 °C, 0.01 mm) 6.8 g (76%) of (2*S*)-alcohol **31** as a colorless liquid: IR (CH_2Cl_2) 3640, 3540, 3060, 2970, 1265, 1090 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ d 7.2 (s, 5 H, aromatic *H*'s), 4.4 (s, 2 H, OCH_2Ph), 3.7–3.3 (m, 4 H, C_1-H_2, C_3-H_2), 2.47 (br s, 1 H, O*H*), 2.1 (m, 1 H, C_2-*H*), 0.9 (d, J = 8 Hz, 3 H, C_2-CH_3); $[\alpha]_{589}$ = +5.3° (*c* 2.2, EtOH) (lit.[45b,85] $[\alpha]_{589}$ = +4.97° (*c* 0.9, EtOH)). Further elution with ether afforded 4.8 g (74%) of recovered (4*S*)-valinol 2-oxazolidinone.

(4*R*,5*S*)-3-Propanoyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one (9).[4] A mechanically stirred solution of 88.6 g (0.500 mol) of (4*R*,5*S*)-norephedrine 2-oxazolidinone[39a] (0.5 M in THF) was metalated with 290 mL (1.74 M in hexane, 0.505 mol) of *n*-butyllithium and acylated with 52 mL (55 g, 0.60 mol) of propanoyl chloride according to the acylation procedure outlined for the synthesis of **20** to give 124 g (106% mass balance) of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 135 °C, 0.008 mm) to afford 110 g (94%) of **9** as a colorless viscous liquid: IR (CH_2Cl_2) 2990, 1785, 1710, 1370, 1350, 1245, 1220, 1200, 1150, 1125 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ d 7.33 (s, 5 H, aromatic *H*'s), 5.63 (d, J = 7.2 Hz, 1 H, C_5-*H*), 4.73 (qn, J = 6.8 Hz, 1 H, C_4-*H*), 2.93 (q, J = 7.5 Hz, 2 H, C_2-H_2), 1.17 (t, J = 7.2 Hz, 3 H, C_3-H_3), 0.88 (d, J = 6.8 Hz, 3 H, C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ d 173.7, 153.0, 133.5, 128.6, 125.6, 79.0, 54.7, 29.2, 14.5, 8.3; $[\alpha]_{589}$ = +43.4° (*c* 3.61, CH_2Cl_2). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48. Found: C, 67.17; H, 6.64.

(4*R*,5*S*,2′*R*,3′*S*)-5-(2′-Methyl-3′-hydroxybutanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (10). To a cooled (−78 °C) and stirred solution of 4.12 g (17.7 mmol) of imide **9** in CH_2Cl_2 (25 mL) was added 5.10 mL (20.3 mmol) of di-*n*-butylboryl triflate[75] over a 1-min period to produce a heterogeneous mixture. After 5 min, 3.20 mL (23.0 mmol) of triethylamine was added over 5 min, to produce a light tan solution. The reaction temperature was maintained at −78 °C for 30 min and then allowed to slowly warm to 0 °C and held at this temperature for 1 h. The solution was recooled (−78 °C) and 2.00 mL (35.3 mmol) of freshly distilled acetaldehyde was added in one portion. The reaction temperature was held at −78 °C for 45 min and then allowed to rise to 0 °C and maintained at this temperature for 1 h. The reaction mixture was quenched by the addition of 25 mL of phosphate buffer (pH 7), poured into a 500-mL flask containing 50 mL of MeOH, cooled to 0 °C, and treated with a solution of 25 mL of 30% aqueous H_2O_2 in 75 mL of MeOH for 1 h. The organic solvents were removed in vacuo, 75 mL of 10% aqueous $NaHCO_3$ was added, and the resultant solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to a colorless oil. Flash chromatography (250 g of silica, 50% EtOAc/hexane) afforded 4.58 g (93% yield) of **10** as a white solid which was recrystallized from ether/petroleum ether: mp 116–117 °C. Diastereomer analysis by GLC before and/or after chromatography (trimethylsilyl ether derivative, DB-1, 180 °C, 15 psi, t_r(**10**) = 4.53 min) indicated a diastereomer ratio of 99:1: IR (CCl_4) 3600–3300 (br), 2980, 2940, 2880, 1775, 1685, 1455, 1350, 1230, 1195, 1120, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.26 (m, 5 H, aromatic *H*'s), 5.69 (d, 1 H, C_5-*H*), 4.82 (qn, 1 H, C_4-*H*), 4.20 (m, 1 H, C_3-*H*), 3.77 (dq, 1 H, C_2-*H*), 2.92 (d, 1 H, O*H*), 1.27–1.23 (d, d, 6 H, C_2-CH_3, C_4-*H*'s), 0.89 (d, 3 H, C_4-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.15, 152.44, 133.04, 128.31, 125.31, 78.51, 67.58, 54.41, 43.27, 19.67, 13.92, 10.50; $[\alpha]_D$ +18.0° (*c* 3.5, CH_2Cl_2). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90. Found: C, 64.99; H, 7.12.

(4*R*,5*S*,2′*R*,3′*S*)-5-(2′-Methyl-3′-(dimethyl-*tert*-butylsiloxy)butanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (10a). To a stirred solution of 2.18 g (7.88 mmol) of **10** in DMF (10 mL) were added 1.07 g (15.7 mmol) of imidazole and 1.42 g (9.45 mmol) of *tert*-butyldimethylsilyl chloride. After 13 h at 25 °C, the reaction mixture was added to 20% CH_2Cl_2/hexane (150 mL) and was successively washed with 10% aqueous $NaHSO_4$ (50 mL) and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (300 g of silica, 10% EtOAc/hexane) afforded 3.03 g (98% yield) of a colorless oil: R_f 0.50 (15% EtOAc/hexane); IR (neat) 2960, 2935, 2890, 2860, 1780, 1700, 1343, 1233, 1195, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.29 (m, 5 H, aromatic *H*'s), 5.63 (d, 1 H, C_5-*H*), 4.73 (qn, 1 H, C_4-*H*), 4.11 (qn, 1 H, C_3-*H*), 3.85 (qn, 1 H, C_2-*H*), 1.25–1.17 (d, d, 6 H, C_2-CH_3, C_4-*H*'s), 0.91 (d, 3 H, C_4-CH_3), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (d, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.91, 152.61, 133.50, 128.60, 125.63, 78.75, 69.85. 55.14, 45.17, 25.76, 21.57, 17.94, 14.18, 12.33, −4.52, −4.98; $[\alpha]_D$ −1.1° (*c* 5.42, CH_2Cl_2).

(2*R*,3*S*)-3-((1,1-Dimethylethyl)dimethylsiloxy)-2-methylbutanoic Acid, Benzyl Ester (11). To a cooled (0 °C), stirred solution of 2.07 g (19.1 mmol) of benzyl alcohol in THF (9 mL) was added 8.74 mL (15.3 mmol) of a 1.75 M solution of *n*-butyllithium in hexane. The reaction temperature was maintained at 0 °C for 15 min, this solution was then added to a cooled (0 °C) solution of 3.00 g (7.65 mmol) of **10a** in THF (21 mL). The reaction mixture temperature was held at 0 °C for 3.5 h, added to water (80 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (300 g of silica, 5% EtOAc/hexane) afforded 2.07 g (84% yield) of a colorless oil: R_f 0.66 (15% EtOAc/hexane); IR (neat) 2955, 2930, 2890, 2855, 1735, 1460, 1380, 1255, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 5 H, aromatic *H*'s), 5.10 (q, 2 H, C_1-O*CH*'s), 4.08 (qn, 1 H, C_3-*H*), 2.45 (qn, 1 H, C_2), 1.20–1.10 (d, d, 6 H, C_2-CH_3, C_4-*H*'s), 0.85 (s, 9 H, C-$(CH_3)_3$), 0.03 (d, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.65, 136.15, 128.44, 128.08, 128.03, 69.59, 66.00, 47.65, 25.73, 21.85, 17.94, 12.07, −4.34, −4.99; $[\alpha]_D$ +7.2° (*c* 6.48, CH_2Cl_2). Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.29; H, 9.56.

(2*S*,3*S*)-3-((1,1-Dimethylethyl)dimethylsiloxy)-2-methyl-1-butanol (12). To a cooled (−78 °C), stirred solution of 18.50 g (57.36 mmol) of ester **11** in CH_2Cl_2 (100 mL) was added 126 mL (126 mmol) of a 1.0 M solution of diisobutylaluminum hydride over a 15-min period. The reaction temperature was held at −78 °C for 30 min and then allowed to rise to 0 °C and maintained at this temperature for an additional 30 min. Excess hydride reagent was quenched with MeOH (3 mL), and the reaction mixture was diluted in CH_2Cl_2 (200 mL). A solution of 250 mL (125 mmol) of a 0.5 M aqueous sodium potassium tartrate solution was then added over a 20-min period with stirring. This heterogeneous mixture, after stirring for 12 h at 25 °C, produced two clear layers. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (500 g of silica, 10% EtOAc/hexane) afforded a colorless oil, 11.64 g (93% yield): R_f 0.32 (15% EtOAc/hexane); IR (neat) 3600–3100 (br), 2960, 2930, 2890, 2860, 1470, 1460, 1255, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (m, 1 H, C_3-*H*), 3.73 (dd, 1 H, C_1-*H*), 3.52 (dd, 1 H, C_1-*H*), 1.97 (m, 1 H, C_2-*H*), 1.15 (d, 3 H, C_4-*H*'s), 0.90 (s, 9 H, C-$(CH_3)_3$), 0.80 (d, 3 H, C_2-CH_3), 0.09 (d, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.76, 65.25, 41.77, 25.68, 19.29, 17.81, 11.55, −4.60, −5.15; $[\alpha]_D$ +14.5° (*c* 5.50, CH_2Cl_2).

(2*E*,4*S*,5*S*)-5-((1,1-Dimethylethyl)dimethylsiloxy)-2,4-dimethyl-2-hexenoic Acid, Ethyl Ester (13). To a cooled (−78 °C), stirred solution

of 0.72 mL (8.3 mmol) of oxalyl chloride in CH_2Cl_2 (10 mL) was added 1.08 mL (15.2 mmol) of DMSO dropwise over a 2-min period. After an additional 5 min, this solution was added via cannula to a cooled (−78 °C), stirred solution of 1.50 g (6.89 mmol) of alcohol **12** in CH_2Cl_2 (15 mL).[30] The resulting white heterogeneous mixture was maintained at −78 °C for 30 min, and then 4.80 mL (34.4 mmol) of triethylamine was added to produce a thick white slurry. The reaction temperature was held at −78 °C for 20 min and then allowed to rise to 0 °C. The solution was diluted with 20% CH_2Cl_2/hexane (250 mL) and extracted successively with 10% aqueous $NaHSO_4$ (80 mL) and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. The resulting oil was dissolved in freshly distilled toluene (15 mL) and treated with 3.74 g (10.3 mmol) of (carbethoxyethylidene)triphenylphosphorane. The resulting yellow heterogeneous mixture was stirred at 70 °C for 12 h. After cooling, the reaction was diluted with hexane (40 mL), and the precipitated triphenylphosphine oxide was removed by filtration through a short plug of Celite with 20% EtOAc/hexane (150 mL) to elute the products. Concentration in vacuo provided a yellow oil, which was flash chromatographed (200 g of silica, 5% EtOAc/hexane) to afford a colorless oil, 1.64 g (79% from **12**). Olefin isomer analysis before and/or after chromatography (DB-1, 150 °C, 10 psi, t_r(**2*Z*-13**) = 2.87 min, t_r(**13**) = 3.79 min) revealed a ratio of **2*Z*-13**:**13** of 1.5:98.5:R_f 0.25 (5% EtOAc/hexane); IR (neat) 2965, 2945, 2900, 2870, 1715, 1650, 1250, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, 1 H, C_3-*H*), 4.18 (q, 2 H, C_1-C*H*'s), 3.67 (qn, 1 H, C_5-*H*), 2.48 (m, 1 H, C_4-*H*), 1.85 (s, 3 H, C_2-CH_3), 1.29 (t, 3 H, C_1-OCH_2CH_3), 1.11 (d, 3 H, C_6-*H*'s), 1.01 (d, 3 H, C_4-CH_3), 0.90 (s, 9 H, C-$(CH_3)_3$), 0.06 (s, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.15, 144.82, 126.93, 71.52, 60.22, 41.22, 25.79, 21.77, 17.99, 15.05, 14.18, 12.53, −4.37, −4.96; $[\alpha]_D$ −1.6° (*c* 4.76, CH_2Cl_2). This material was employed in the next experiment without further characterization.

(2*E*,4*S*,5*S*)-5-((1,1-Dimethylethyl)dimethylsiloxy)-2,4-dimethyl-2-hexen-2-ol (14a). To a cooled (−78 °C), stirred solution of 1.45 g (4.82 mmol) of ester **13** in CH_2Cl_2 (11 mL) was added 11.1 mL (11.1 mmol) of a 1 M solution of diisobutylaluminum hydride in CH_2Cl_2 over a 5-min period. The reaction was held at −78 °C for 30 min, allowed to rise to 0 °C, and maintained at this temperature for an additional 30 min. The resulting solution was added to 22.0 mL (11.0 mmol) of a 0.5 M solution of aqueous sodium potassium tartrate and stirring was continued for 4 h at 25 °C. After the addition of water (80 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (100 g of silica, 20% ethyl acetate/hexane) afforded **14a** as a colorless oil, 1.22 g (98% yield); R_f 0.26 (15% EtOAc/hexane); IR (neat) 3550–3100 (br), 2985, 2940, 2870, 1255, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (d, 1 H, C_3-*H*), 3.99 (br d, 2 H, C_1-*H*'s), 3.57 (qn, 1 H, C_5-*H*), 2.38 (m, 1 H, C_4-*H*), 1.68 (s, 3 H, C_2-CH_3), 1.50 (br t, 1 H, O*H*), 1.08 (d, 3 H, C_6-*H*'s), 0.95 (d, 3 H, C_4-CH_3), 0.90 (s, 9 H, C-$(CH_3)_3$), 0.05 (d, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.16, 129.20, 72.54, 68.62, 40.19, 26.02, 25.82, 21.54, 18.02, 16.69, 13.92, −4.42, −4.86; $[\alpha]_D$ +8.6° (*c* 3.59, CH_2Cl_2). Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.05; H, 11.70. Found: C, 64.94; H, 11.68.

(2*E*,4*S*,5*S*)-5-((1,1-Dimethylethyl)dimethylsiloxy)-2,4-dimethyl-1-iodo-2-hexene (14b). To a cooled (0 °C), stirred solution of 4.25 g (16.4 mmol) of alcohol **14a** in DMF (20 mL) was added a DMF solution (15 mL) of 8.18 g (18.1 mmol) of methyltriphenoxyphosphonium iodide[31] over a 5-min period, to produce an orange solution. The reaction mixture was warmed to 25 °C, maintained at this temperature for 15 min, and then diluted with hexane (500 mL). This solution was successively washed with cold aqueous 1 N NaOH (2 × 100 mL) and water (2 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford iodide **14b** as yellow oil, 6.34 g (105% mass balance); R_f 0.77 (15% EtOAc/hexane); IR (neat) 2960, 2930, 2890, 2860, 1255, 1155, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (d, 1 H, C_3-*H*), 3.94 (d, 2 H, C_1-*H*'s), 3.56 (qn, 1 H, C_5-*H*), 2.29 (m, 1 H, C_4-*H*), 1.79 (s, 3 H, C_2-CH_3), 1.08 (d, 3 H, C_6-*H*'s), 0.93 (d, 3 H, C_4-CH_3), 0.90 (s, 9 H, C-$(CH_3)_3$), 0.05 (s, 6 H, Si-$(CH_3)_2$). There was also approximately 5% of what appeared to be the *Z* olefin isomer present (^1H NMR). This material was employed in the next experiment without further purification.

(2′*S*,4*R*,4′*E*,5*S*,6′*S*,7′*S*)-3-(7′-((1″,1″-Dimethylethyl)dimethylsiloxy)-2′,4′,6′-trimethyl-4′-octenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (15). A stirred solution of 9.95 (54.3 mmol) of sodium bis(trimethylsilyl)amide in THF (75 mL) was prepared and cooled to −78 °C. In a separate flask, a cooled (−78 °C) solution of 11.5 g (49.3 mmol) of imide **9** in THF (25 mL) was prepared and subsequently transferred via cannula to the amide base solution over a 15-min period. After maintaining the reaction temperature at −78 °C for 30 min, iodide **14b** (prepared in the previous experiment) was added neat over a 15-min period. This solution was warmed to −50 °C and held at this temperature for 10 h. Saturated aqueous NH_4Cl (60 mL) was added, and the THF was removed in vacuo. The resulting mixture was added to 10% aqueous HCl (200 mL) and was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with water (100 mL), dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to give a red oil. Flash chromatography (600 g of silica, 5% EtOAc/hexane) afforded **15** as a white solid, 5.69 g (73% from **14a**). Diastereomer analysis before and/or after chromatography (DB-5, 250 °C, 15 psi, t_r(**2*R*-15**) = 6.51 min, t_r(**15**) = 7.32 min) revealed a ratio of **2*R*-15**:**15** of 1.9:98.1: mp 80.5–81.5 °C; R_f 0.36 (15% EtOAc/hexane); IR (CCl_4) 2965, 2935, 2860, 1790, 1705, 1368, 1343, 1238, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.27 (m, 5 H, aromatic *H*'s), 5.67 (d, 1 H, C_5-*H*), 5.00 (d, 1 H, C_5-*H*), 4.80 (qn, 1 H, C_4-*H*), 4.00 (m, 1 H, C_2-*H*), 3.50 (qn, 1 H, C_7-*H*), 2.52 (dd, 1 H, C_3-*H*), 2.33 (m, 1 H, C_6-*H*), 1.98 (dd, 1 H, C_3-*H*), 1.68 (s, 3 H, C_4-CH_3), 1.13 (d, 3 H, C_2-CH_3), 1.08 (d, 3 H, C_8-*H*'s), 0.93–0.85 (m, 15 H, C_4-CH_3, C_6-CH_3, C-$(CH_3)_3$), 0.05 (s, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.89, 152.65, 133.56, 131.57, 131.15, 128.68, 125.67, 78.71, 72.83, 54.83, 43.90, 40.89, 35.86, 25.90, 21.80, 18.10, 17.16, 16.42, 16.06, 14.62, −4.26, −4.76; $[\alpha]_D$ +13.3° (*c* 4.20, CH_2Cl_2). Anal. Calcd for $C_{27}H_{43}NO_4Si$: C, 68.45; H, 9.15. Found: C, 68.75; H, 9.21.

(2*S*,4*E*,6*S*,7*S*)-7-((1,1-Dimethylethyl)dimethylsiloxy)-2,4,6-trimethyl-4-octen-1-ol (16). To a cooled (−78 °C), stirred solution of 0.240 g (0.507 mmol) of **15** in THF (5 mL) was added 1.0 mL (1.0 mmol) of a 1 M solution of $LiAlH_4$ in THF over a 2-min period. The reaction temperature was held at −78 °C for 10 min, allowed to rise to 0 °C, and maintained at this temperature for an additional 60 min. Water (0.2 mL) and 1 N aqueous NaOH (0.1 mL) were added to produce a heterogeneous mixture, which was stirred at 25 °C for 30 min.[86] The resulting mixture was filtered, the solids were washed with ether (75 mL), and the filtrate was concentrated in vacuo to give a colorless oil. Flash chromatography (25 g of silica, 15% EtOAc/hexane) afforded alcohol **16** as a colorless oil, 0.127 g (84% yield); R_f 0.20 (15% EtOAc/hexane); IR (neat) 3600–3100 (br), 2960, 2935, 2900, 2865, 1455, 1370, 1250, 1090, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (d, 1 H, C_5-*H*), 3.58–3.40 (m, 3 H, C_1-*H*'s, C_7-*H*), 2.35 (m, 1 H, C_6-*H*), 2.09 (dd, 1 H, C_3-*H*), 1.94–1.75 (m, 2 H, C_2-*H*, C_3-*H*), 1.62 (s, 3 H, C_4-CH_3), 1.43 (s, 1 H, O*H*), 1.08 (d, 3 H, C_8-*H*'s), 0.95–0.85 (m, 15 H, C_2-CH_3, C_6-CH_3, C-$(CH_3)_3$), 0.05 (s, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.01, 130.12, 72.88, 68.52, 68.44, 44.50, 40.76, 33.80, 25.91, 21.72, 18.10, 17.08, 16.63, 16.36, −4.28, −4.76; $[\alpha]_D$ +0.9° (*c* 6.06, CH_2Cl_2). Anal. Calcd for $C_{17}H_{36}O_2Si$: C, 67.93; H, 12.07. Found: C, 67.72; H, 12.27.

(2*E*,4*S*,6*E*,8*S*,9*S*)-9-((1,1-Dimethylethyl)dimethylsiloxy)-4,6,8-trimethyl-2,6-decadienoic Acid, Methyl Ester (17a). To a cooled (−78 °C), stirred solution of 0.22 mL (2.5 mmol) of oxalyl chloride in CH_2Cl_2 (8 mL) was added 0.36 mL (5.1 mmol) of DMSO dropwise over a 1-min period.[30] After an additional 3 min, this solution was added via cannula to a cooled (−78 °C) solution of 0.587 g (1.95 mmol) of alcohol **16** in CH_2Cl_2 (4 mL). The resulting heterogeneous mixture was stirred at −78 °C for 30 min, and 1.36 mL (9.76 mmol) of triethylamine was added to produce a thick white slurry. After being stirred at −78 °C for 15 min, the mixture was allowed to warm slowly to 0 °C, diluted with 20% diethylether/hexane (200 mL), and then successively washed with 10% aqueous $NaHSO_4$ (50 mL) and water (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting oil, 0.581 g (100% material balance), was dissolved in CH_2Cl_2 (6 mL), and 1.31 g (3.91 mmol) of (carbomethoxymethylidene)triphenylphosphorane was added. The resulting solution was stirred at 25 °C for 12 h. Concentration in vacuo gave a white mass, which upon flash chromatography (75 g of silica, 5% ethyl acetate/hexane) afforded ester **17a** as a colorless oil, 0.668 g (96% yield from **16**). Olefin isomer analysis before and/or after chromatography (DB-1, 200 °C, 5 psi, t_r(**2*Z*-17a**) = 4.34, t_r(**17a**) = 5.33) revealed a ratio of **2*Z*-17a**:**17a** of 2.2:97.8: R_f 0.58 (15% ethyl acetate/hexane); IR (neat) 2960, 2935, 2860, 1730, 1660, 1260, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, 1 H, C_3-*H*), 5.77 (d, 1 H, C_2-*H*), 4.95 (d, 1 H, C_7-*H*), 3.73 (s, 3 H, OCH_3), 3.51 (qn, 1 H, C_9-*H*), 2.50 (qn, 1 H, C_4-*H*), 2.32 (m, 1 H, C_8-*H*), 2.10 (dd, 1 H, C_5-*H*), 1.95 (dd, 1 H, C_5-*H*), 1.60 (s, 3 H, C_6-CH_3), 1.08 (d, 3 H, C_{10}-*H*'s), 1.00 (d, 3 H, C_4-CH_3), 0.93 (d, 3 H, C_8-CH_3), 0.90 (s, 9 H, C-$(CH_3)_3$), 0.05 (s, 6 H, Si-$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.13, 154.53, 131.55, 131.03, 118.98, 72.76, 51.21, 46.63, 40.82, 34.53, 25.87, 21.72, 18.74, 18.07, 17.10, 16.31, −4.29, −4.79; $[\alpha]_D$ −2.8° (*c* 5.94, CH_2Cl_2). Anal. Calcd for $C_{20}H_{38}O_3Si$: C, 67.74; H, 10.80. Found: C, 67.79; H, 11.01.

(2*E*,4*S*,6*E*,8*S*,9*S*)-9-Hydroxy-4,6,8-trimethyl-2,6-decadienoic Acid, Methyl Ester (17b). A solution of 0.644 g (1.82 mmol) of ester **17a** in 95:5 acetonitrile/48% aqueous HF (8 mL) was allowed to stand at 25 °C for 1 h. This solution was then added to saturated aqueous $NaHCO_3$

(50 mL) and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to give a colorless oil. Flash chromatography (70 g of silica, 25% EtOAc/hexane) afforded the hydroxy ester **17b** as an oil that solidified upon standing, 0.426 g (97% yield): mp 33.5–34.5 °C; R_f 0.10 (15% EtOAc/hexane); IR (neat) 3600–3100 (br), 2960, 2920, 2870, 1725, 1655, 1435, 1275, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, 1 H, C_3-*H*), 5.69 (d, 1 H, C_2-*H*), 4.90 (d, 1 H, C_7-*H*), 3.67 (s, 3 H, OCH_3), 3.50 (br t, 1 H, C_9-*H*), 2.50–2.30 (m, 2 H, C_4-*H*, C_8-*H*), 2.05 (dd, 1 H, C_5-*H*), 1.93 (dd, 1 H, C_5-*H*), 1.57 (s, 3 H, C_6-CH_3), 1.40 (br s, 1 H, O*H*), 1.06 (d, 3 H, C_{10}-*H*'s), 0.95 (d, 3 H, C_4-CH_3), 0.89 (d, 3 H, C_8-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.85, 154.06, 132.70, 129.88, 119.08, 71.81, 50.94, 46.48, 40.03, 34.46, 20.60, 18.73, 16.46, 16.30; $[\alpha]_D$ −26.0° (*c* 3.92, CH_2Cl_2). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.91; H, 9.96.

(4*R*,6*S*,8*S*,9*S*)-9-Hydroxy-4,6,8-trimethyldecanoic Acid, Methyl Ester (18). A solution of 0.135 g (0.636 mmol) of diene alcohol **17b** and 22.5 mg (31.7 μmol) of norbornadiene[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate[34] in 3 mL of CH_2Cl_2 was stirred under 1 atm of H_2 gas for 12 h. The resulting solution was filtered through a short plug of silica gel (50% EtOAc/hexane) and concentrated in vacuo to give a colorless oil, 0.114 g (93% yield). Diastereomer analysis (DWAX-4, 170 °C, 10 psi, t_r(**18**) = 6.77 min, t_r(6*R*-**18**) = 7.00 min) revealed a ratio of **18**:6*R*-**18** of 93.5:6.5. The two diasteromers (R_f(**18**) = 0.25, R_f(6*R*-**18**) = 0.22; 25% EtOAc/hexane) were separated by medium-pressure chromatography (Lobar C column, 15% ethyl acetate/hexane, flow rate 15 mL): R_f 0.25 (25% EtOAc/hexane); IR (neat) 3600–3100 (br), 2960, 2930, 1740, 1460, 1440, 1380, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (m, 1 H, C_9-*H*), 3.68 (s, 3 H, OCH_3), 2.35 (t, 2 H, C_2-*H*'s), 1.72–0.83 (m, 22 H, C_3-*H*'s, C_4-*H*, C_4-CH_3, C_5-*H*'s, C_6-*H*, C_6-CH_3, C_7-*H*'s, C_8-*H*, C_8-CH_3, C_{10}-*H*'s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.39, 70.62, 51.32, 43.96, 41.08, 36.81, 32.69, 31.71, 29.67, 27.44, 20.49, 20.36, 19.04, 14.28; $[\alpha]_D$ −35.8° (*c* 1.22, CH_2Cl_2). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.55; H, 11.57.

(4*R*,6*S*,8*S*)-9-Oxo-4,6,8-trimethyldecanoic Acid, Methyl Ester (19). To a solution of 66.5 mg (0.272 mmol) of alcohol **18** in DMSO (4 mL) was added 0.26 mL (1.86 mmol) of triethylamine, followed by 0.13 g (0.82 mmol) of pyridine–SO_3 complex.[35] The resulting solution was stirred at 25 °C for 40 min, added to 10% aqueous $NaHSO_4$ (50 mL), and extracted with ether (2 × 70 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give **19** as a oil. Flash chromatography (10 g of silica, 15% EtOAc/hexane) afforded 60.7 mg (92% yield) of a colorless oil: R_f 0.24 (15% EtOAc/hexane); IR (neat) 2965, 2930, 1745, 1718, 1175 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 3.68 (s, 3 H, OCH_3), 2.63 (m, 1H, C_8-*H*), 2.34 (dt, 2 H, C_2-*H*'s), 2.14 (s, 3 H, C_{10}-*H*'s), 1.68–1.42 (m, 5 H), 1.17–1.04 (m, 6 H), 0.84 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.43, 174.27, 51.34; 44.93, 44.34, 41.31, 32.83, 31.84, 29.81, 28.20, 27.69, 19.66, 19.00, 16.96; $[\alpha]_D$ −14.5° (*c* 1.22, CH_2Cl_2). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.42; H, 10.86.

(2′*R*,4′*E*,4*S*)-3-(2′-Methyl-5′-phenyl-4′-pentenoyl)-4-isopropyl-1,3-oxazolidin-2-one (21). To a cooled (0 °C) solution of 7.01 mL (50.0 mmol) of diisopropylamine in THF was added 31.2 mL (50.0 mmol) of a 1 M hexane solution of *n*-butyllithium over a 20-min period. The resulting yellow solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of 8.33 g (45.0 mmol) of imide **20** in THF (8 mL) was then added over a 20-min period. The reaction mixture was maintained at −78 °C for 1 h, and 13.3 g (67.5 mmol) of cinnamyl bromide was added over a 10-min period. The reaction temperature was maintained at −40 to −20 °C for 1 h then allowed to rise to 0 °C and held at this temperature an additional 2.2 h, producing an orange solution. Aqueous saturated NH_4Cl (30 mL) was added, and the THF was removed in vacuo. Water (30 mL) was added, the resulting mixture was extracted with ether (3 × 100 mL), and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting orange oil was flash chromatographed (600 g of silica, 25% ethyl acetate/hexane) to afford the alkylated imide **21** as a light yellow oil, 11.43 g (84% yield). Diastereomer analysis before and/or after chromatography (SE-54, 10 psi, t_r(2*S*-**21**) = 9.91 min, t_r(**21**) = 10.48 min) revealed a ratio of 2*S*-**21**:**21** of 1.3:98.7: R_f 0.55 (40% ethyl acetate/hexane); IR ($CHCl_3$) 3030, 2985, 2940, 2880, 1775, 1695, 1490, 1455, 1385, 1300, 1220, 1120, 1085, 1055 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.28 (s, 5 H, aromatic *H*'s), 6.60–5.98 (m, 2 H, C_4-*H*, C_5-*H*), 4.60–3.75 (m, 4 H, C_2-*H*, C_4-*H*, C_5-*H*'s), 2.88–2.10 (m, 3 H, C_3-*H*'s, C_4-C*H*), 1.23 (d, 3 H, C_2-CH_3), 0.83 (dd, 6 H, C_4-$C(CH_3)_2$); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 176.57, 153.82, 137.54, 132.44, 128.48, 127.31, 126.92, 126.20, 63.29, 58.62, 37.76, 28.59, 18.00, 16.51, 14.49; $[\alpha]_D$ +20.2° (*c* 2.12, CH_2Cl_2). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.60; H, 7.70.

(2*R*,4*E*)-2-Methyl-5-phenyl-4-penten-1-ol (22a). To a cooled (−78 °C), stirred solution of 11.20 g (37.16 mmol) of **21** in THF (35 mL) was added 37.2 mL (37.2 mmol) of a 1 M THF solution of $LiAlH_4$ over a 30-min period. The reaction temperature was held at −78 °C for 15 min, allowed to rise to 0 °C, and maintained at this temperature for an additional 1.2 h. Water (4 mL) and 20% aqueous NaOH (1 mL) were added dropwise to give a heterogeneous mixture, which was stirred at 25 °C for 10 min. The white solids were filtered and washed with ether, giving a yellow filtrate, which was concentrated in vacuo to give **22a** as a yellow oil. Flash chromatography (400 g of silica, 15% ether/CH_2Cl_2) afforded a golden oil, 4.66 g (71% yield): R_f 0.48 (15% diethyl ether/CH_2Cl_2); IR ($CHCl_3$) 3600–3100 (br), 3010, 2960, 2920, 2870, 1595, 1490, 1445, 1215, 1025 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.35–7.05 (m, 5 H, aromatic *H*'s), 6.50–5.84 (m, 2 H, C_4-*H*, C_5-*H*), 3.47 (br d, 2 H, C_1-*H*'s), 2.48–1.57 (m, 4 H, C_2-H, C_3-*H*'s, O*H*), 0.95 (d, 3 H, C_2-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.58, 131.34, 128.68, 128.35, 126.86, 125.95, 67.72, 36.98, 36.07, 16.38; $[\alpha]_D$ +6.1° (*c* 1.72, CH_2Cl_2). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.32.

(2*R*,4*E*)-1-Iodo-2-methyl-5-phenyl-4-pentene (22b). To a cooled (0 °C), stirred solution of 2.29 g (13.0 mmol) of alcohol **22a** and 2.72 mL (19.5 mmol) of triethylamine in CH_2Cl_2 (30 mL) was added 1.21 mL (15.6 mmol) of methanesulfonyl chloride. The temperature of the resulting heterogeneous yellow mixture was maintained at 0 °C for 30 min. Water (30 mL) was added, followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, to afford a yellow oil, 3.34 g (101% material balance). This oil was dissolved in a solution of 40 mL of saturated NaI in acetone and 0.2 mL of diisopropylethylamine was added. The resulting heterogeneous mixture was stirred at 55 °C for 4 h. After the mixture was cooled to 25 °C, water (30 mL) was added, followed by extraction with ether (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to an orange oil. Flash chromatography (200 g of silica, 5% EtOAc/hexane) afforded **22b** as a golden oil, 3.46 g (93% from **22a**): R_f 0.65 (15% EtOAc/hexane); IR (neat) 3090, 3070, 3035, 2970, 2935, 2845, 1605, 1500 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.40–7.10 (m, 5 H, aromatic *H*'s), 6.58–5.83 (m, 2 H, C_4-*H*, C_5-*H*), 3.14 (d, 2 H, C_1-*H*'s), 2.30–2.06 (m, 2 H, C_3-*H*'s), 1.84–1.38 (m, 1 H, C_2-*H*), 1.00 (d, 3 H, C_2-CH_3). This material was immediately carried on to the next experiment.

(2*S*,2′*R*,4′*R*,6′*E*)-1-(2′,4′-Dimethyl-7′-phenyl-6′-heptenoyl)-2-(hydroxymethyl)pyrrolidine (23). A solution of 2.09 g (13.3 mmol) of the prolinol-derived propionamide **2**[19] in THF (40 mL) was added to 0.95 g (23.6 mmol) of KH. After 10 min at 25 °C, a cooled (0 °C) solution of LDA (prepared by stirring a cooled (0 °C) THF (25 mL) solution of 2.24 mL (16.0 mmol) of diisopropylamine and 9.4 mL (15 mmol) of a 1.56 M hexane solution of *n*-butyllithium for 30 min) was added with stirring, and the temperature was maintained at 25 °C for 30 min. After the enolate **3b** was cooled to −78 °C, 4.86 mL (28.0 mmol) of hexamethylphosphoric triamide was added. A solution of 3.46 g (12.1 mmol) of iodide **22b** in THF (12 mL) was added over a 7-min period. The reaction was maintained at −78 °C for 7 h, allowed to rise to −35 °C over a 1-h period, and quenched with water (60 mL). The resulting mixture was extracted with EtOAc (3 × 100 mL), and the combined extracts were washed with saturated aqueous NaCl (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to a golden oil. Flash chromatography (300 g of silica, EtOAc) afforded 3.15 g (83% yield based on **22b**) of **23** as an oil. Diastereomer analysis before and/or after chromatography (SE-54, 230 °C, 15 psi, t_r(2*S*-**23**) = 2.29 min, t_r(**23**) = 2.66 min) revealed a ratio of 2*S*-**23**:**23** of 2.7:97.3: R_f 0.32 (EtOAc); IR ($CHCl_3$) 3500–3150 (br), 2985, 2930, 2905, 2885, 1605, 1445, 1215, 1080 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.43–7.12 (m, 5 H, aromatic *H*'s), 6.53–5.85 (m, 2 H, C_6-*H*, C_7-*H*), 5.09 (t, 1 H, O*H*), 4.22 (m, 1 H, C_2-*H*), 3.70–3.34 (m, 4 H, C_2-CH_2, C_5-*H*'s), 2.70 (qn, 1 H, C_2-*H*), 2.45–1.00 (m, 9 H, C_3-*H*'s, C_4-*H*, C_5-*H*'s, C_3-*H*'s, C_4-*H*'s), 1.14 (d, 3 H, C_2-CH_3), 0.95 (d, 3 H, C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 177.94, 137.64, 131.34, 128.80, 128.42, 126.86, 125.88, 67.26, 65.77, 60.83, 47.83, 40.49, 35.81, 30.93, 28.14, 24.37, 19.95, 18.13; $[\alpha]_D$ −43.0° (*c* 3.98, CH_2Cl_2). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27. Found: C, 75.99; H, 9.43.

(2*R*,4*R*,6*E*)-2,4-Dimethyl-7-phenyl-6-heptenoic Acid (24). An emulsion of 3.10 g (9.83 mmol) of amide **23** and 70 mL of 1 N aqueous HCl was stirred vigorously at reflux for 8 h. The resulting emulsion was cooled to 0 °C, 2 N aqueous NaOH (40 mL) was added, and the reaction temperature was maintained at 0 °C for 10 min. The reaction mixture was reacidified to pH = 3 with concentrated HCl and extracted with ether (3 × 150 mL), and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The isolated oil was flash chromatographed (300 g of silica, EtOAc) to afford the acid **24** as an oil, 2.08 g (91% yield): R_f 0.67 (EtOAc); IR ($CHCl_3$) 3600–2200

(br), 1700, 1455, 1375, 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 11.33 (br s, 1 H, COO*H*), 7.43–7.08 (m, 5 H, aromatic *H*'s), 6.52–5.89 (m, 2 H, C_6-*H*, C_7-*H*), 2.58 (m, 1 H, C_2-*H*), 2.30–1.00 (m, 5 H, C_3-*H*'s, C_4-*H*, C_5-*H*'s), 1.20 (d, 3 H, C_2-CH_3), 0.95 (d, 3 H, C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 183.66, 137.64, 131.40, 128.54, 128.42, 126.79, 125.95, 40.75, 40.49, 37.30, 31.06, 19.30, 17.74, 16.77; $[\alpha]_D$ −3.4° (*c* 4.16, CH_2Cl_2). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.84.

(2*R*,4*R*,6*E*)-2,4-Dimethyl-7-phenyl-6-hepten-1-ol (25a). To a cooled (0 °C), stirred ether (40 mL) solution of 2.00 g (8.60 mmol) of acid **24** was added 11.2 mL (11.2 mmol) of a 1 M solution of $LiAlH_4$ in ether, and the resulting solution was warmed slowly to 25 °C. The reaction temperature was maintained at 25 °C for 1.5 h, and then water (2 mL) and 20% aqueous NaOH (0.5 mL) were added dropwise to give a heterogeneous mixture, which was stirred at 25 °C for 15 min.[87] The solids thus obtained were removed by filtration and washed with ether (150 mL). The combined filtrates were concentrated in vacuo and flash chromatographed (30% EtOAc/hexane) to afford the primary alcohol **25a** as a golden oil, 1.80 g (95% yield). Diastereomer analysis (SE-54, 145 °C, 5 psi, t_r(**25a**) = 11.02 min, t_r(2*S*-**25a**) = 11.24 min) revealed a ratio of **25a**:2*S*-**25a** of 96:4: R_f 0.47 (40% EtOAc/hexane); IR ($CHCl_3$) 3600–3250 (br), 2960, 2920, 2880, 1450, 1375, 1205, 1020 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.42–7.09 (m, 5 H, aromatic *H*'s), 6.50–5.94 (m, 2 H, C_6-*H*, C_7-*H*), 3.63–3.17 (m, 2 H, C_1-*H*'s), 2.42–0.80 (7, 7 H, C_2-*H*, C_3-*H*'s, C_4-*H*, C_5-*H*'s, O*H*), 0.93 (d, 6 H, C_2-CH_3, C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.77, 131.14, 129.20, 128.42, 126.79, 125.88, 67.98, 40.55, 40.10, 33.08, 30.54, 20.28, 17.29; $[\alpha]_D$ +10.5° (*c* 4.20, CH_2Cl_2). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.40; H, 10.34.

(4*R*,6*R*,1*E*)-4,6-Dimethyl-7-((1,1-dimethylethenyl)diphenylsiloxy)-1-phenyl-1-heptene (25b). To a solution of 1.71 g (7.83 mmol) of alcohol **25a** in DMF (15 mL) was added 1.63 mL (11.7 mmol) of triethylamine, followed by 2.5 mL (9.5 mmol) of *tert*-butyldiphenylsilyl chloride. After the mixture was stirred at 25 °C for 20 h water (30 mL) was added. The resulting mixture was extracted with ether (2 × 75 mL), and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a golden oil. Flash chromatography (300 g of silica, 5% EtOAc/hexane) afforded 3.56 g (99% yield) of the TBS ether **25b** as an oil: R_f 0.67 (15% EtOAc/hexane); IR ($CHCl_3$) 3000, 2940, 2910, 2860, 1455, 1420, 1105, 1080 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.80–6.90 (m, 15 H, aromatic *H*'s), 6.48–5.93 (m, 2 H, C_6-*H*, C_7-*H*), 3.64–3.30 (m, 2 H, C_1-*H*'s), 2.38–0.70 (m, 6 H, C_2-*H*, C_3-*H*'s, C_4-*H*, C_5-*H*'s), 1.10 (s, 9 H, $C(CH_3)_3$), 0.94 (dd, 6 H, C_2-CH_3, C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.84, 135.56, 134.07, 131.08, 129.46, 129.32, 128.42, 127.57, 126.73, 125.95, 68.82, 40.68, 40.36, 33.21, 30.61, 26.90, 20.21, 19.30, 17.74; $[\alpha]_D$ +7.4° (*c* 4.31, CH_2Cl_2). Anal. Calcd for $C_{31}H_{40}OSi$: C, 81.52; H, 8.83. Found: C, 81.67; H, 8.81.

(2*R*,4*R*)-2,4-Dimethyl-1-(diphenyl-*tert*-butylsiloxy)hexan-6-ol (26a). A solution of 1.59 g (3.48 mmol) of olefin **25b** in anhydrous EtOH (50 mL) was prepared in a 100-mL 3-necked round-bottom flask (equipped with a pipet inlet and drying tube outlet). To this solution was added Sudan III indicator (4 mg), so as to produce a red solution.[40] After the mixture was cooled to −78 °C, a gaseous solution of ozone in oxygen was passed through the reaction mixture until the dye bleached. Nitrogen was then bubbled through the reaction mixture for 5 min and a solution of 1.32 g (34.9 mmol) of $NaBH_4$ in 50% aqueous EtOH (20 mL) was added. This solution was warmed to 25 °C and then stirred for 10 h, and 40 mL of 1 N aqueous NaOH was added. Ethanol was removed in vacuo, and the resulting mixture was extraced with ether (3 × 150 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a yellow oil. Flash chromatography (250 g of silica, 25% EtOAc/hexane) afforded 1.29 g (96% yield) of the primary alcohol **26a** as an oil. Diastereomer analysis before and/or after chromatography (DB-5, 230 °C, 10 psi, t_r(**26a**) = 6.31 min, t_r(2*S*-**26a**) = 6.56 min) revealed a diastereomer ratio of 96.1:3.9. Diastereomer **26a** elutes first on silica gel chromatography and was isolated in a pure state by medium-pressure chromatography (C size column, 15% EtOAc/hexane, flow rate = 8 mL/min): R_f 0.56 (40% EtOAc/hexane); IR ($CHCl_3$) 3600–3100 (br), 2970, 2940, 2870, 1480, 1470, 1435, 1395, 1115 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.80–7.15 (m, 10 H, aromatic *H*'s), 3.75–3.28 (m, 4 H, C_1-*H*'s, C_6-*H*'s), 1.95–0.80 (m, 7 H, C_2-*H*, C_3-*H*'s, C_4-*H*, C_5-*H*'s, O*H*), 1.08 (s, 9 H, $C(CH_3)_3$), 0.90 (dd, 6 H, C_2-CH_3), C_4-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 135.63, 134.59, 134.13, 129.52, 127.57, 68.89, 61.02, 41.33, 39.84, 33.21, 27.10, 26.97, 20.34, 19.37, 17.74, 15.27; $[\alpha]_D$ +3.2° (*c* 3.02, CH_2Cl_2). Anal. Calcd for $C_{24}H_{36}O_2Si$: C, 74.94; H, 9.43. Found: C, 74.96; H, 9.46.

(2*R*,4*S*)-2,4-Dimethyl-1-((1,1-dimethylethyl)diphenylsiloxy)-6-(phenylsulfonyl)hexane (26c). To a stirred solution of 0.217 g (0.564 mmol) of alcohol **26a** and 0.135 g (0.620 mmol) of phenyl disulfide in CH_2Cl_2 (4 mL) was added 0.15 g (0.62 mmol) of tri-*n*-butylphosphine. After 2 h at 25 °C, 5 mL of EtOH and 2 mL of 1 N aqueous NaOH were added. The resulting yellow solution was stirred at 25 °C for 20 min, 20 mL of 0.5 N aqueous NaOH was added, and this mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined extacts were washed with water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an oil. This material was employed in the next experiment without further purification.

To a stirred, cooled (0 °C) solution of the phenyl sulfide corresponding to **26a** (prepared in the previous experiment) in CH_2Cl_2 (5 mL) was added 0.58 g (3.36 mmol) of *m*-chloroperbenzoic acid. The reaction temperature was held at 0 °C for 10 min, allowed to rise to 25 °C, and maintained at this temperature for an additional 2 h. A 10% aqueous $NaHCO_3$ solution (25 mL) was added, and this mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were washed with water (25 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a golden oil. Flash chromatography (50 g of silica, 15% ethyl acetate/hexane) afforded sulfone **26c** as a colorless oil, 0.267 g (93% yield): R_f 0.25 (15% EtOAc/hexane); IR (neat) 2960, 2930, 2860, 1445, 1425, 1320, 1305, 1150, 1110, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97–7.32 (m, 15 H, aromatic *H*'s), 3.50–3.35 (m, 2 H, C_1-*H*'s), 3.14–2.95 (m, 2 H, C_6-*H*'s), 1.79–0.75 (m, 6 H, C_2-*H*, C_3-*H*'s, C_4-*H*, C_5-*H*'s), 1.03 (s, 9 H, C-$(CH_3)_3$), 0.87 (d, 3 H, CH_3), 0.80 (d, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.06, 135.75, 135.39, 133.64, 133.42, 129.44, 129.07, 127.80, 127.48, 68.31, 53.98, 40.17, 32.76, 29.05, 28.76, 26.73, 19.58, 19.11, 17.41; $[\alpha]_D$ +9.9° (*c* 3.46, CH_2Cl_2).

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-2,4-dimethyl-3-hydroxy-5-hexene (27a) and (2*R*,3*S*,4*R*)-1-(Benzyloxy)-2,4-dimethyl-3-hydroxy-5-hexene (27b). To a solution of 20.0 mL (248 mmol) of pyridine in 250 mL of CH_2Cl_2 at 0 °C was added 12.4 g (120 mmol) of chromium trioxide with vigorous overhead stirring. The reaction temperature was held at 0 °C for 15 min and then allowed to rise to 0 °C and maintained at this temperature for an additional 30 min. A solution of 2.70 g (15.0 mmol) of alcohol **31**[18] in 25 mL of CH_2Cl_2 was added over a 5-min period. After an additional 30 min, the reaction mixture was decanted, and the residue was washed with CH_2Cl_2 (4 × 75 mL). The combined organic layers were concentrated in vacuo, the residue taken up in ether (75 mL), and the resulting brown solution filtered through a short plug of silica, eluting with ether. The filtrate was concentrated in vacuo to afford 2.32 g (87% material balance) of the aldehyde **28** as an oil. For the analogous oxidation to produce enantiomerically pure **28** see the procedure for the synthesis of **34** below. Due to the sensitive nature of this aldehyde, it was employed in the next experiment without further purification.

To a slurry of 6.40 g (52.1 mmol) of anhydrous chromous chloride in 60 mL of THF at 0 °C was added a solution of the aldehyde **28** (prepared in the previous experiment) in 4 mL of THF. A solution of 3.32 g (26.0 mmol) of freshly distilled crotyl bromide (containing 20% 3-bromo-1-butene) in 3 mL of THF was then added over a 15-min period. After the solution was stirred at 25 °C for 5 h, water (50 mL) was added, and THF was removed in vacuo. The residue was extracted with ether (3 × 75 mL); the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a green oil. Purification by Kugelrohr distillation (bp 130–135 °C, 20 mTorr) afforded a colorless oil, 2.46 g (70% from **31**). Diastereomer analysis (DB-1, 145 °C, 10 psi, t_r(**27a**) = 4.32 min, t_r(**27b**) = 4.52 min) revealed a ratio of **27a**:**27b** of 40.1:59.9. Diastereomer resolution was accomplished by preparative HPLC (7% EtOAc/hexane). **27a**: R_f 0.48 (25% EtOAc/hexane); IR (neat) 3700–3200 (br), 3080, 3040, 2970, 2935, 2880, 1640, 1455, 1420, 1365, 1150–1050 (br), 1000 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5 H, aromatic *H*'s), 6.18–5.70 (m, 1 H, C_5-*H*), 5.20–4.91 (m, 2 H, C_6-*H*'s), 4.50 (s, 2 H, OCH_2Ph), 3.62–3.17 (m, 4 H, C_1-*H*'s, C_3-*H*, O*H*), 2.52–2.17 (m, 1 H, C_4-*H*), 1.92 (qn, 1 H, C_2-*H*), 1.12 (d, 3 H, C_4-CH_3), 0.91 (d, 3 H, C_2-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 139.85, 137.84, 128.42, 127.64, 115.16, 79.54, 75.26, 73.50, 41.14, 36.26, 17.68, 13.97; $[\alpha]_D$ −13.0° (*c* 5.54, CH_2Cl_2). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.80; H, 9.46. Found: C, 76.72; H, 9.23. **27b**: R_f 0.45 (25% EtOAc/hexane); IR (neat) 3700–3200 (br), 3080, 3040, 2970, 2935, 2880, 1640, 1455, 1420, 1365, 1150–1050 (br), 1000 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5 H, aromatic *H*'s), 6.07–5.56 (m, 1 H, C_5-*H*), 5.28–4.87 (m, 2 H, C_6-*H*'s), 4.50 (s, 2 H, OCH_2Ph), 3.68–3.30 (m, 3 H, C_1-*H*'s, C_3-*H*), 2.50–1.72 (m, 3 H, C_2-*H*, C_4-*H*, O*H*), 0.95 (d, 6 H, C_2-CH_3, C_4-CH_3). The stereochemical assignments of these diastereomers were made by conversion of each isomer to the bis-benzyl ethers **32a** and **32b** as discussed in the text.

(2′*S*,3′*R*,4*R*,4′*S*,5*S*)-3-(2′-Ethenyl-3′-hydroxy-4′-methyl-5′-(benzyloxy)pentanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (34). To a cooled (−78 °C), stirred solution of 0.95 mL (10.9 mmol) of oxalyl chloride in CH_2Cl_2 (40 mL) was added 1.55 mL (21.8 mmol) of DMSO dropwise over a 3-min period.[30] After an additional 5 min, a solution of 1.64 g

(87) Brown. C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918.

(9.10 mmol) of alcohol **31** in CH_2Cl_2 (6 mL) was added over a 5-min period. The resulting white heterogeneous mixture was stirred at −78 °C for 30 min, and 6.34 mL (45.5 mmol) of triethylamine was added to produce a thick white slurry. After being stirred for 15 min, 10% aqueous $NaHSO_4$ (80 mL) was added to the reaction mixture, followed by extraction with 20% ether/hexane (3 × 100 mL). The combined extracts were washed with water (2 × 75 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a golden oil, 1.57 g (97% material balance). Due to the sensitive nature of aldehyde **28**, it was employed in the next experiment without further purification.

To a cooled (−78 °C), stirred solution of 1.93 g (9.81 mmol) of imide **33**[53] in CH_2Cl_2 (14 mL) was added 1.64 mL (11.8 mmol) of triethylamine, followed by the addition of 2.59 mL (10.3 mmol) of di-*n*-butylboryl triflate.[75] The resulting heterogeneous mixture was maintained at −78 °C for 30 min. Upon slow warming to 0 °C, a light yellow solution was produced which was held at this temperature for 20 min. After recooling (−78 °C), aldehyde **28** (prepared in the previous experiment) was added neat in one portion. The reaction temperature was held at −78 °C for 18 h and then allowed to rise to 0 °C, and 10 mL of phosphate buffer (pH 7) was added. This mixture was dissolved in 30 mL of MeOH at 0 °C and treated with a solution of 30% aqueous H_2O_2 (10 mL) in MeOH (10 mL) for 1 h. After removal of organic solvents in vacuo, 80 mL of 10% aqueous $NaHCO_3$ was added, and this mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an oil. Diastereomer analysis (trimethylsilyl) ether derivative, DB-1, 210 °C, 15 psi, t_r(**34**) = 5.64 min, t_r(**4*R*-34**) = 6.03 min) revealed a ratio of **34**:**4*R*-34** of 95:5. Flash chromatography (350 g, 4% ethyl ether/CH_2Cl_2) afforded the aldol adduct **34** as an oil, 1.99 g (58% from **31**). This oil crystallized upon standing: mp 73.0–73.5 °C (recrystallized from hexane); R_f 0.37 (6% ether/CH_2Cl_2); IR ($CHCl_3$) 3600–3300 (br), 3010, 2970, 2930, 2880, 1775, 1690, 1380, 1210, 1090 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.30 (s, 5 H, aromatic *H*'s), 6.28–5.80 (m, 1 H, C_2-C*H*), 5.48–5.18 (m, 2 H, C_2-C-CH_2), 4.69 (dd, 1 H, C_2-*H*), 4.54–4.27 (m, 1 H, C_4-*H*), 4.45 (s, 2 H, OCH_2Ph), 4.11 (d, 2 H, C_5-*H*'s), 3.90 (m, 1 H, C_3-*H*), 3.55 (br d, 3 H, C_5-*H*'s, O*H*), 2.33 (m, 1 H, C_4-*H*), 1.95 (qn, 1 H, C_4-*H*), 1.08–0.74 (m, 9 H, C_4-CH_3, C_4-C(CH_3)$_2$); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 173.65, 153.50, 138.16, 132.12, 128.28, 127.57, 120.42, 74.41, 73.57, 73.31, 63.10, 58.42, 50.43, 36.26, 28.27, 17.87, 14.56, 13.78; $[\alpha]_D$ +13.8° (*c* 3.58, CH_2Cl_2). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.78. Found: C, 67.25; H, 7.73.

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-3-hydroxy-4-(hydroxymethyl)-2-methyl-5-hexene (35a). To a solution of 0.925 g (2.46 mmol) of **34** in THF (8 mL) was added 0.5 mL of glacial acetic acid and 0.72 mL (3.0 mmol) of tri-*n*-butylborane. The resulting solution was stirred at 25 °C for 1.5 h. After the solution was cooled to 0 °C, 2.5 mL (4.9 mmol) of a 2 M solution of lithium borohydride in THF was added over a 5-min period. The reaction temperature was held at 0 °C for 1.5 h and the allowed to rise to 25 °C and maintained at this temperature for an additional 30 min. After recooling (0 °C), MeOH (20 mL) and pH 7 aqueous phosphate buffer (10 mL) were added; this solution was then treated with 5 mL of 30% aqueous H_2O_2 in 10 mL of MeOH. The reaction temperature was allowed to rise to 25 °C and held at this temperature for 1.5 h, and then the organic solvents were removed in vacuo. The resulting mixture was added to 10% aqueous $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to give the diol **35a** as an oil. Flash chromatography (125 g of silica, ether) afforded a golden oil, 0.548 g (89% yield): R_f 0.37 (ether); IR (neat) 3700–3100 (br), 3080, 3040, 2970, 2930, 2880, 1640, 1450, 1420, 1365, 1150–1030 (br) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.30 (s, 5 H, aromatic *H*'s), 6.22–5.73 (m, 1 H, C_5-*H*), 5.30–4.98 (m, 2 H, C_6-*H*'s), 4.48 (s, 2 H, OCH_2Ph), 4.02 (br s, 1 H, O*H*), 3.84–3.32 (m, 5 H, C_1-*H*'s, C_3-*H*, C_4-CH_2), 2.57 (br s, 1 H, O*H*), 2.48–1.68 (m, 2 H, C_2-*H*, C_4-*H*), 0.80 (d, 3 H, C_2-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 137.64, 135.17, 128.09, 127.31, 117.37, 75.52, 75.19, 73.11, 64.40, 48.68, 36.33, 13.13; $[\alpha]_D$ −23.3° (*c* 3.18, CH_2Cl_2). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 72.06; H, 8.95.

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-3-hydroxy-2-methyl-4-((((4-methylphenyl)sulfonyl)oxy)methyl)-5-hexene (35b). To a cooled (5 °C) solution of 0.545 g (2.18 mmol) of diol **35a** in pyridine (5 mL) was added 0.50 g (2.6 mmol) of *p*-toluenesulfonyl chloride, and the reaction mixture was maintained at 5 °C for 18 h. Ethyl acetate (3 mL) and 5% aqueous $NaHCO_3$ (3 mL) were added to the heterogeneous reaction mixture, and the resulting solution was stirred at 25 °C for 15 min. An additional portion of 5% aqueous $NaHCO_3$ (50 mL) was then added, followed by extraction with CH_2Cl_2 (3 × 70 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 0.908 g (103% material balance) of tosylate **35b** as an oil: R_f 0.31 (25% EtOAc/hexane); ^1H NMR (90 MHz, $CDCl_3$) δ 7.90–7.18 (m, 9 H, aromatic *H*'s), 5.97–5.49 (m, 1 H, C_5-*H*), 5.28–4.98 (m, 2 H, C_6-*H*'s), 4.49 (s, 2 H, OCH_2Ph), 4.33–3.85 (m, 2 H, C_4-CH_2), 3.78–3.32 (m, 4 H, C_1-*H*'s, C_3-*H*, O*H*), 2.78–2.37 (m, 1 H, C_4-*H*), 2.43 (s, 3 H, aromatic CH_3), 2.10–1.63 (m, 1 H, C_2-*H*), 0.73 (d, 3 H, C_2-CH_3). This material was employed in the next reaction without further purification.

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-2,4-dimethyl-3-hydroxy-5-hexene (27a). To a cooled (0 °C), stirred solution of 0.881 g (2.18 mmol) of **35b** (prepared in the previous experiment) in THF (3 mL) was added 10.9 mL (10.9 mmol) of a 1 M THF solution of lithium triethylborohydride over a 5-min period. After 10 min, the resulting solution was warmed to 25 °C and held at this temperature for 24 h. The reaction solution was recooled to 0 °C, and 9 mL of MeOH, 9 mL of 1 N aqueous NaOH, and 9 mL of 30% aqueous H_2O_2 were then *cautiously* added. The resulting heterogeneous mixture was warmed to 60 °C and stirred for 2 h. After the solution was cooled to 25 °C, 5% aqueous $NaHCO_3$ (80 mL) was added and this mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was flashed chromatographed (75 g of silica, 10% EtOAc/hexane) to afford 0.468 g (92% from **35a**) of **27a** as a colorless oil: R_f 0.48 (25% EtOAc/hexane); IR (neat) 3700–3200 (br), 3080, 3040, 2970, 2935, 2880, 1640, 1455, 1420, 1365, 1150–1050 (br), 1000 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5 H, aromatic *H*'s), 6.18–5.70 (m, 1 H, C_5-*H*), 5.20–4.91 (m, 2 H, C_6-*H*'s), 4.50 (s, 2 H, OCH_2Ph), 3.62–3.17 (m, 4 H, C_1-*H*'s, C_3-*H*, O*H*), 2.52–2.17 (m, 1 H, C_4-*H*), 1.92 (qn, 1 H, C_2-*H*), 1.12 (d, 3 H, C_4-CH_3), 0.91 (d, 3 H, C_2-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 139.85, 137.84, 128.42, 127.64, 115.16, 79.54, 75.26, 73.50, 41.14, 36.26, 17.68, 13.97; $[\alpha]_D$ −13.0° (*c* 5.54, CH_2Cl_2). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.80; H, 9.46. Found: C, 76.72; H, 9.23.

(2*R*,3*R*,4*S*,5*R*,*S*)-1-(Benzyloxy)-2,4-dimethyl-3,5,6-hexanetriol (36a, 36b). To a solution of 1.05 g (4.47 mmol) of olefin **27a** in 10 mL of 50% aqueous acetone was added 0.64 g (6.7 mmol) of *N*-methylmorpholine *N*-oxide monohydrate and 0.28 mL (0.04 mmol) of a 0.16 M aqueous osmium tetroxide solution. The resulting two-phase mixture was stirred at 25 °C for 10 h, producing a black single-phase solution. After removal of acetone in vacuo, the residue was acidified (pH 2) with 3 N aqueous sulfuric acid. The reaction mixture was extracted with ether (4 × 50 mL); the combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 1.30 g (108% material balance) of the diastereomeric triols **36a** and **36b** as a black oil: IR (neat) 3600–3100 (br), 2970, 2940, 2880, 1450, 1070; ^1H NMR (90 MHz, $CDCl_3$) δ 7.32 (s, 5 H, aromatic *H*'s), 4.47 (s, 2 H, OCH_2Ph), 3.95–3.32 (m, 9 H, C_1-*H*'s, C_3-*H*, C_5-*H*, C_6-*H*'s, O*H*), 2.20–1.72 (m, 2 H, C_2-*H*, C_4-*H*), 1.30–0.73 (m, 6 H, C_2-CH_3, C_4-CH_3). This material was employed in the next experiment without further purification.

(2*R*,3*R*,4*S*,5*R*,*S*)-1-(Benzyloxy)-2,4-dimethyl-6-(diphenyl-*tert*-butylsiloxy)-2,4-hexanediol (37a, 37b). To a solution of unpurified diastereomeric triols **36a** and **36b** (prepared in the previous experiment) in CH_2Cl_2 (20 mL) were added 0.94 mL (6.7 mmol) of triethylamine, 0.05 g (0.45 mmol) of 4-(dimethylamino)pyridine, and 1.74 mL (6.71 mmol) of *tert*-butyldiphenylsilyl chloride. The reaction mixture was stirred at 25 °C for 12 h and then concentrated in vacuo. The resulting residue was flash chromatographed (250 g of silica, 15% EtOAc/hexane) to afford 2.01 g (89% from **27a**) of a diastereomeric mixture of **37a,b** as a light yellow oil: R_f 0.55 (40% ethyl acetate/hexane); IR (neat) 3650–3150 (br), 3080, 2970, 2940, 2870, 1590, 1460, 1430, 1390, 1360, 1110 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.80–7.20 (m, 15 H, aromatic *H*'s), 4.55–4.47 (s, s, 2 H, OCH_2Ph), 4.25–3.35 (m, C_1-*H*'s, C_3-*H*, C_5-*H*, C_6-*H*'s, O*H*), 2.20–1.80 (m, 2 H, C_2-*H*, C_4-*H*), 1.35–0.75 (m, 15 H, C_2-CH_3, C_4-CH_3, C(CH_3)$_3$).

(1′*R*,4*R*,5*S*,6*R*,*S*)-4-(2′-(Benzyloxy)-1′-methylethyl)-6-((diphenyl-*tert*-butylsiloxy)methyl)-2,2,5-trimethyl-1,3-dioxane (38a, 38b). To a solution of 2.01 g (3.97 mmol) of the diastereomeric diols **37a,b** in anhydrous acetone (20 mL) was added 3.31 g (31.8 mmol) of 2,2-dimethoxypropane and 92 mg (0.40 mmol) of *d,l*-camphorsulfonic acid. The resulting yellow solution was stirred at 25 °C for 2 h and quenched with triethylamine (1 mL), and the organic solvents were removed in vacuo. Water (10 mL) was added, followed by extraction with ether (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 2.13 g (98% mass balance) of the silyl acetonides **38a,b** as an oil: R_f 0.45 (15% EtOAc/hexane); IR (neat) 3080, 2970, 2945, 2870, 1460, 1430, 1380, 1205, 1175, 1115 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.70–7.20 (m, 15 H, aromatic *H*'s), 4.45 (d, 2 H, OCH_2Ph), 3.80–3.15 (m, 6 H, C_1'-*H*'s, C_5-*H*, C_6-*H*, C_6-CH_2), 2.25–1.65 (m, 2 H, C_2-*H*, C_5-*H*), 1.50–0.60 (m, 21 H, C_2'-CH_3, C_2-(CH_3)$_2$, C_5-CH_3, C(CH_3)$_3$). This material was employed in the next experiment without further purification.

(1′*R*,4*R*,5*S*,6*R*,*S*)-4-(2′-(Benzyloxy)-1′-methylethyl)-6-(hydroxymethyl)-2,2,5-trimethyl-1,3-dioxane (39a, 39b). To a solution of the diastereomeric acetonides **38a,b** (prepared in the previous experiment)

in THF (20 mL) was added 7.80 mL (7.80 mmol) of a 1 N THF solution of Bu_4NF. The resulting orange solution was stirred at 25 °C for 10 h and then concentrated in vacuo to give a dark orange oil. Flash chromatography (175 g of silica, 25% EtOAc/hexane) afforded 1.19 g (97% from **37a,b**) of the diastereomeric acetonides **39a,b** as an oil. Diastereomer analysis (DB-1, 150 °C for 8 min then 20 deg/min to 200 °C, 15 psi, t_r(**39a**) = 10.45 min, t_r(**39b**) = 10.70 min) revealed a ratio of **39a**:**39b** of 77.7:22.3. These diastereomers were separated by medium-pressure liquid chromatography (size C column, 15% ether/CH_2Cl_2, flow rate 10 mL/min).

39a: R_f 0.36 (15% ether/CH_2Cl_2); IR (neat) 3650–3200 (br), 3000, 2970, 2940, 2880, 1450, 1380, 1260, 1205, 1170, 1100, 1050, 1015 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.32 (s, 5 H, aromatic *H*'s), 4.42 (s 2 H, OCH_2Ph), 3.86–3.12 (m, 6 H, C_1'-*H*'s, C_4-*H*, C_6-*H*, C_6-CH_2), 2.40–1.60 (m, 3 H, C_2'-*H*, C_5-*H*, *OH*), 1.40 (s, 3 H, C_2-CH_3), 1.35 (s, 3 H, C_2-CH_3), 1.03 (d, 3 H, C_5-CH_3), 0.80 (d, 3 H, C_2'-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 138.81, 128.28, 127.44, 98.20, 75.26, 73.05, 71.36, 63.62, 34.12, 31.58, 29.96, 19.50, 15.99, 11.96; $[\alpha]_D$ +5.5° (*c* 5.24, CH_2Cl_2). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.15; H, 9.14.

39b: R_f 0.22 (15% ether/CH_2Cl_2); IR (neat) 3650–3150 (br), 3000, 2940, 2880, 1460, 1385, 1230, 1180, 1110, 1025 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.33 (s, 5 H, aromatic *H*'s), 4.45 (s, 2 H, OCH_2Ph), 3.98–3.14 (m, 6 H, C_1'-*H*'s, C_4-*H*, C_6-*H*, C_6-CH_2), 2.13–1.68 (m, 3 H, C_2'-*H*, C_5k-*H*, *OH*), 1.33 (s, 6 H, C_2-$(CH_3)_2$), 1.02 (d, 3 H, C_5-CH_3), 0.82 (d, 3 H, C_2'-CH_3); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 138.68, 128.28, 127.44, 100.54, 76.23, 73.11, 72.07, 70.64, 62.45, 37.43, 34.83, 25.41, 23.46, 14.36, 12.54; $[\alpha]_D$ −1.9° (*c* 0.80, CH_2Cl_2).

(1′*R*,4*R*,5*S*,6*R*)-4-(2′-(Benzyloxy)-1′-methylethyl)-6-formyl-2,2,5-trimethyl-1,3-dioxane (40a). To a solution of 0.40 g (1.3 mmol) of alcohol **39a** in DMSO (6 mL) was successively added 1.2 mL (8.6 mmol) of triethylamine and 0.62 g (3.9 mmol) of SO_3–pyridine complex.[35] The resulting solution was stirred at 25 °C for 45 min. A 10% aqueous solution (40 mL) of $NaHSO_4$ was added, and this mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to provide aldehyde **40a** as a golden oil. Flash chromatography (60 g of silica, 25% EtOAc/hexane) afforded 0.38 g (95% yield) of **40a** as a colorless oil: R_f 0.62 (20% ether/CH_2Cl_2); ^1H NMR (90 MHz, CCl_4) δ 7.20 (s, 5 H, aromatic *H*'s), 4.40 (s, 2 H, OCH_2Ph), 3.70–3.05 (m, 4 H, C_1'-*H*'s, C_4-*H*, C_6-*H*), 2.30–1.60 (m, 2 H, C_2'-*H*, C_5-*H*), 1.38 (s, 6 H, C_2-CH_3), 0.95 (d, 3 H, C_5-CH_3), 0.85 (d, 3 H, C_2'-CH_3). The diastereomeric aldehydes **40a** and **40b** can be analyzed by capillary GLC (DB-1, 170 °C, 10 psi, t_r(**40a**) = 4.63 min, t_r(**40b**) = 4.91 min).

(+)-(4*S*)-3-(5′-(Benzyloxy)pentanoyl)-4-isopropyl-1,3-oxazolidin-2-one (41). The title compound was prepared in direct analogy to the procedure described earlier for *N*-propionyl imide **20**, using 50 g (0.22 mol) of 5-(benzyloxy)pentanoyl chloride and 28 g (0.22 mol) of (*S*)-valine-derived oxazolidone.[39] Flash chromatographic purification (300 g of silica gel, 5.5 × 42 cm, 1:4 EtOAc/hexane, 175 mL fractions) of 4 × 18 g portions of material afforded 52.4 g (75%) of **41** as a colorless oil: IR (neat) 2958, 2860, 1776, 1695, 1480, 1445, 1380, 1294, 1240, 1200, 1095, 1018, 729, 688 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 (d, 3 H, J = 4.5 Hz, CH_3), 0.90 (d, 3 H, J = 4.5 Hz, CH_3), 1.66 (m, 4 H, $-CH_2CH_2$), 2.30 [m, 1 H, $CH(CH_3)_2$], 2.87 [t, 2 H, J = 6 Hz, $-C(O)CH_2$], 3.43 (t, 2 H, J = 6 Hz, $ROCH_2$), 4.15 (m, 3 H), 4.40 (s, 2 H, $PhCH_2O$), 7.21 (s, 5 H, aromatic *H*'s); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) 14.49, 17.81, 21.06, 28.01, 28.85, 34.64, 57.64, 62.32, 69.41, 72.33, 126.99, 127.77, 138.49, 152.66, 171.63; $[\alpha]^{25}_D$ = +43.8° (*c* 3.15, CH_2Cl_2). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69, H, 7.89; N, 4.39. Found: C, 67.65; H, 7.78; N, 4.30.

(+)-(2′*S*,3′*R*,4*S*,6′*E*)-3(2′-(3″-(benzyloxy)propyl)-3′-hydroxy-6′-methyl-6′-octenoyl)-4-isopropyl-1,3-oxazolidin-2-one (43). Into a 250-mL 3-necked flask equipped with a 2-way stopcock valve, a magnetic spin bar, and a thermometer was weighed 8.24 mg (25.8 mmol) of *N*-acyl oxazolidinone **41**. Oxygen was excluded by the sequential evacuation and filling of the rubber septum-sealed system with argon. Freshly distilled CH_2Cl_2 (70 mL) was added and the mixture was cooled to −78 °C. To this solution was added dropwise 7.5 mL (30.6 mmol, 1.2 equiv) of di-*n*-butylboryl trifluoromethanesulfonate.[75] Any precipitate formed during this addition was allowed to dissolve by briefly warming the system to −40 °C. Triethylamine (5.68 mL, 40.8 mmol, 1.5 equiv) was then added at a rate that maintained the internal temperature below −65 °C. The solution was stirred at −78 °C for 30 min and 1 h at 0 °C to form the boryl enolate. To this cooled (−78 °C) solution was added 3 g (26.8 mmol) of freshly distilled (*E*)-4-methyl-4-hexenal (**42**)[66] in a single portion. After 30 min at −78 °C and 1 h at 0 °C, 50 mL of a pH 7 phosphate buffer was added to quench the reaction. A precooled (−20 °C) mixture of 100 mL of MeOH and 20 mL of a 30% hydrogen peroxide solution was then added to oxidize the boron complexes. After being stirred at 0 °C for 1 h the reaction mixture was transferred to a separatory funnel containing 150 mL of a 5% sodium bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 11.3 g (100% mass balance) of material. Diastereomer analysis (SE-54, 220 °C, t_r(major) = 16.81 min, t_r(minor) = 17.39 min) gave a ratio of 96.8:3.2. Flash chromatographic purification (300 g of silica gel, 5.5 × 42 cm, 1:4 EtOAc/hexane, 175-mL fractions) afforded 7.6 g (68%) of the aldol adduct **43** (R_f = 0.50 silica gel, 50% EtOAc/hexane, minor isomer not resolved) as a colorless oil: IR (CCl_4) 3500, 2975, 2940, 2880, 1780, 1695, 1452, 1389, 1302, 1205, 1102, 1056, 1028 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.84 (d, 3 H, J = 5 Hz, CH_3), 0.90 (d, 3 H, J = 6 Hz, CH_3), 1.53 (m, 9 H, $-CH_2CH_2-$, $CMe{=}CHCH_3$), 158 [s, 3 H, $C(CH_3){=}CHCH_3$] 2.0 (t, 2 H, J = 8 Hz, $CH_2CH{=}CR_2$), 2.21 [m, 1 H, $CH(CH_3)_2$], 2.60 (d, 1 H, J = 3 Hz, *OH*), 3.40 (t, 2 H, J = 6 Hz, $ROCH_2$), 3.67 [m, 1 H, $-CH(OH)-$], 4.2 (m, 4 H), 4.40 (s, 2 H, $PhCH_2$-O), 5.15 (m, 1 H, vinyl H), 7.21 (s, 5 H, aromatic *H*'s); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) 13.19, 14.43, 15.53, 17.87, 23.85, 27.23, 28.01, 31.71, 35.81, 46.92, 58.10, 62.26, 69.47, 71.36, 72.40, 118.21, 127.18, 127.83, 134.98, 138.29, 153.05, 174.82; $[\alpha]^{25}_D$ = +34.1° (*c* 2.59, CH_2Cl_2). Calcd exact mass for $C_{25}H_{37}NO_5$: 431.2672. Found: 431.2659.

(+)-(4*S*)-3-[5-(Benzyloxy)-(2*S*)-{(2*R*,5*S*)-5-methyl-5-[(1*R*)-1-hydroxyethyl]tetrahydrofuranyl}pentanoyl]-4-isopropyl-1,3-oxazolidin-2-one (44a). The unpurified aldol adduct **43**, (31 g, 71.9 mmol) was dissolved in 300 mL of EtOAc. To this cooled solution (0 °C) was added a solution of 39 g (180 mmol) of 80% pure technical grade *m*-chloroperoxybenzoic acid (MCPBA) in 100 mL of EtOAc. The reaction was stirred at 20 °C for 24 h before 65 mL of acetic acid was added. After an additional 10 h at 20 °C the excess MCPBA was consumed by the addition of 35 mL of dimethyl sulfide followed by overnight stirring. The solvent was removed in vacuo, and the resulting white solid (*m*-chlorobenzoic acid) and oily products were taken up in 500 mL of ether. All acidic byproducts were neutralized through the sequential addition of 200 mL of water followed by cautious addition of solid $NaHCO_3$. Successive extraction of the ethereal solution with water and saturated brine removed most of the acids and DMSO. The ethereal solution was dried ($MgSO_4$) and concentrated in vacuo to give a golden oil. Flash chromatographic purification in 7-g batches (300 g of silica gel, 5.5 × 42 cm, 1:4 ether/CH_2Cl_2) resulted in two major components, **44a** and **44b**, with **44a** eluting first, and afforded 14.5 g of **44a** (45%) as a colorless oil: IR (neat) 3510, 2975, 2949, 2882, 1780, 1694, 1488, 1452, 1387, 1372, 1365, 1300, 1235, 1205, 1097, 1020, 734, 696 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 [d, 3 H, J = 6 Hz, $CH(CH_3)CH_3$], 0.90 [d, 3 H, J = 6 Hz, $CH(CH_3)CH_3$], 1.02 (d, 3 H, J = 7 Hz, $C(OH)H$-CH_3), 1.08 (s, 3 H, R_3C-CH_3), 1.7 (m, 9 H, $-CH_2-$), 2.28 (s, 1 H, *OH*), 3.40 (t, 2 H, J = 6 Hz, OCH_2R), 3.53 [q, 1 H, J = 7 Hz, $CH(OH)CH_3$], 4.2 (m, 5 H), 4.40 (s, 2 H, $PhCH_2O$), 7.2 (s, 5 H, aromatic *H*'s); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) 14.49, 17.42, 17.81, 22.55, 26.32, 26.84, 28.20, 28.85, 30.41, 45.10, 58.03, 62.32, 69.34, 71.68, 72.33, 77.92, 86.04, 126.86, 127.12, 127.77, 138.42, 152.66, 173.71; $[\alpha]^{25}_D$ = +34.2° (*c* 3.2, CH_2Cl_2); R_f = 0.36 silica gel, 1:4 ether/CH_2Cl_2). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09, H, 8.33; N, 3.13. Found: C, 67.00; H, 8.27; N, 3.28.

(+)-(4*S*)-3-[5-(Benzyloxy)-(2*S*)-2-[(2*R*,5*R*)-5-methyl-5-[(1*S*)-1-hydroxyethyl]tetrahydrofuranyl]pentanoyl]-4-isopropyl-1,3-oxazolidin-2-one (44b). The title compound, **44b** (14 g, 45%), was isolated in the chromatographic purification of **44a**. IR (neat) 3500, 2978, 2940, 2884, 1780, 1690, 1641, 1486, 1450, 1383, 1362, 1299, 1240, 1220, 1200, 1120, 1089, 1054, 908, 748, 703 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.83 [d, 3 H, J = 6 Hz, $CH(CH_3)CH_3$], 0.90 [d, 3 H, J = 6 Hz, $CH(CH_3)CH_3$], 1.0 (d, 3 H, J = 6 Hz, $CH(OH)H$-CH_3), 1.0 (s, 3 H, R_3C-CH_3), 1.7 (m, 8 H, $-CH_2-$), 2.30 [m, 1 H, $CH(CH_3)CH_2$] 2.4 (s, 1 H *OH*) 3.36 (t, 2 H, J = 6 Hz, OCH_2), 3.57 [q, 1 H, J = 6 Hz, $CH(OH)CH_3$], 4.2 (m, 5 H), 4.40 (s, 2 H, OCH_2Ph), 7.2 (s, 5 H, aromatic *H*'s); ^{13}C NMR (CCl_4) δ (TMS) 14.69, 17.35, 17.87, 23.59, 26.06, 27.16, 28.53, 30.22, 45.75, 58.23, 62.39, 69.47, 71.75, 72.40, 81.04, 86.04, 126.92, 127.18, 127.83, 138.49, 152.98, 173.45; $[\alpha]^{25}_D$ = +64.6° (*c* 1.56, CH_2Cl_2); R_f = 0.24 silica gel, 1:4 ether/CH_2Cl_2). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09, H, 8.33; N, 3.13. Found: C, 67.12; H, 8.29; N, 3.24.

(1*S*,2*R*,5*S*,6*R*)-5-(3′-(Benzyloxy)propyl)-1,2-dimethyl-3,9-dioxabicyclo[4.2.1]nonan-4-one (45). To a cooled solution (−78 °C) of 9.75 g (21.8 mmol) of diastereomer **44a** in 220 mL of anhydrous THF was added dropwise 10 mL (24 mmol) of a 2.4 M solution of PhMgBr in ether to form the magnesium alkoxide. The solution was stirred at −78 °C for 2 h before 1.5 g (17.2 mmol) of anhydrous LiBr was added. After the mixture was stirred an additional 24 h at 20 °C, the solvent was removed in vacuo and the residue was flash eluted through a column of silica gel (200 g, 5.5 × 42 cm), eluting with 2 L of CH_2Cl_2 followed by 1 L of 1:1 ether/CH_2Cl_2. The solvents were removed in vacuo to afford

the unpurified lactone. Chromatographic purification (MPLC, Merck size C Lobar silica gel column, 5% ether/CH_2Cl_2, 20-mL fractions) afforded 5.5 g (79%) of pure lactone **45** as a colorless oil: IR (neat) 2990, 2955, 2875, 1731, 1464, 1451, 1383, 1213, 1178, 1088, 1062, 891, 733, 695 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.18 (d, 3 H, J = 6.5 Hz, O-CHCH_3), 1.20 (s, 3 H, C-CH_3), 1.3–2.4 (m, 8 H, –CH_2–), 2.76 [t, 1 H, J = 6.5 Hz, –CH_2CHC(O)–], 3.40 (t, 2 H, J = 5 Hz, ROC$H_2$$CH_2$), 4.06 (dd, 1 H, J = 8.3 Hz, J = 1 Hz, tetrahydrofuranyl methine), 4.39 (q, 1 H, J = 6.5 Hz, CO_2-CHCH_3), 4.41 (s, 2 H, PhCH_2O), 7.20 (s, 5 H); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.86 (d, 3 H, J = 6.5 Hz, CHCH_3), 0.92 (s, 3 H quaternary CH_3), 1.08 (dt, 2 H, J_d = 5.5 Hz, J_t = 12.5 Hz, –CH_2-CH_2CHCO_2–), 1.34 (m, 1 H), 1.67 (m, 3 H), 1.97 (m, 2 H), 2.72 [t, 1 H, J = 6.5 Hz, –CH_2CHC(O)–], 3.30 (m, 2 H, PhCH_2OCH_2), 3.98 (d, 1 H, J = 8.3 Hz, tetrahydrofuranyl methine), 4.08 (q, 1 H, J = 6.5 Hz, CO_2-CHCH_3), 4.31 (s, 2 H, PhCH_2O), 7.10 (t, J = 7.3 Hz) 7.18 (t, J = 7.5 Hz), 7.32 (d, J = 7.3 Hz); ^{13}C NMR (CCl_4 δ (TMS) 18.00, 23.53, 26.00, 27.23, 28.98, 30.48, 51.86, 69.67, 72.33, 77.73, 82.34, 84.48, 126.92, 127.12, 127.83, 138.49. 172.48; $[\alpha]^{25}_D$ = +59.5° (c 1.99, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67, H, 8.23. Found: C, 71.52; H, 8.15.

(1*S*,2*R*,5*S*,6*R*)-5-(3′-(Benzyloxy)propyl)-1,2-dimethyl-4-methyene-3,9-dioxabicyclo[4.2.1]nonane (46a). A solution of 4.5 g (14.2 mmol) of bicyclic lactone **45** in 57 mL of anhydrous THF under an argon atmosphere was cooled to –45 °C with an acetonitrile–dry ice bath. To this solution was added 0.7 mL of freshly distilled pyridine followed by a cooled solution (–45 °C) of 6.1 g (19.3 mmol) of Tebbe's reagent[68] in 28 mL of anhydrous toluene. The reaction temperature was maintained at –45 °C for 40 min and then allowed to warm to 20 °C over 2 h. After an additional 45 min at 20 °C, the red solution was cooled to 0 °C and quenched cautiously with 6 mL of a 15% aqueous NaOH solution. The evolution of methane gas was accompanied by a change in color to a blue solution over 1 h at 20 °C. Ether (60 mL) was added and the resulting slurry was filtered through 300 g of neutral activity III alumina (5.5 × 42 cm column) with 1 L of hexane followed by 500 mL of ether. Evaporation of the solvent in vacuo afforded 4.2 g (94%) of **46a** as a yellow oil: IR (neat) 2990, 2950, 2880, 1649, 1470, 1458, 1381, 1367, 1351, 1253, 1099, 1078, 1046, 1025, 980, 854, 731 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.05 (s, 3 H), 1.11 (d, 3 H, J = 7 Hz, OCH-CH_3), 1.2–2.3 (m, 8 H), 2.66 (q, 1 H, J = 6 Hz, allylic H), 3.33 (t, 2 H, J = 6 Hz, PhCH_2OCH_2), 3.56 (q, 1 H, J = 7 Hz, OCH-CH_3), 4.20 (m, 1 H, tetrahydrofuranyl methine), 4.22 (s, 1 H, vinyl H), 4.38 (s, 2 H, PhCH_2O), 4.48 (s, 1 H, vinyl H) 7.21 (s, 5 H, aromatic H's); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 1.04 (s, 3 H), 1.07 (d, 3 H, J = 7 Hz, OCH-CH_3), 1.24–1.55 (m, 4 H), 1.64 (m, 1 H), 1.77 (m, 1 H), 2.04 (m, 1 H), 2.18 (m, 1 H), 2.78 (dt, 1 H, J_d = 8 Hz, J_t = 7 Hz, allylic H), 3.25 (m, 2 H, PhCH_2OCH_2CH_2), 3.70 (q, 1 H, J = 7 Hz, OCH-CH_3), 4.30 (m, 1 H, tetrahydrofuranyl methine), 4.32 (s, 2 H, PhCH_2O), 4.35 (s, 1 H, vinyl H), 4.73 (s, 1 H, vinyl H), 7.11 (t, 1 H, J = 7.5 Hz), 7.19 (t, 2 H, J = 7.5 Hz), 7.27 (d, 2 H, J = 7 Hz); ^{13}C NMR (CCl_4) δ (TMS) 17.87, 23.33, 27.42, 27.62, 27.81, 31.19, 48.61, 69.67, 72.40, 78.44, 86.17, 88.38, 99.11, 126.99, 127.77, 138.42, 166.56; $[\alpha]^{25}_D$ = +42.4° (c 1.04, CH_2Cl_2); R_f = 0.57 (not stable to silica gel; gets converted to **46b**, 1:4 ether/CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91, H, 8.92. Found: C, 75.80; H, 8.80.

(1*S*,2*R*,6*R*,4*Z*)-5-(3′-(Benzyloxy)propyl)-1,2,4-trimethyl-3,9-dioxabicyclo[4.2.1]non-4-ene (46b). To 4.0 g (12.6 mmol) of **46a** in 68 mL of CH_2Cl_2 was added 0.59 g (2.3 mmol) of anhydrous pyridinium tosylate. After the mixture was stirred at 20 °C for 6 h, the solvent was removed in vacuo. The residue was taken up in ether, filtered to remove the pyridinium tosylate, and extracted successively with 5% aqueous Na_2CO_3, water, and brine. The ethereal solution was dried (Na_2SO_4) and concentrated in vacuo to afford 4 g (100%) of **46b** as an oil. A small portion (100 mg) was flash chromatographed (10 g of silica gel, 20% EtOAc/hexane) to provide an analytical sample. IR (neat) 2984, 2950, 2870, 1710, 1680, 1492, 1454, 1442, 1378, 1364, 1301, 1274, 1239, 1200, 1186, 1145, 1115, 1097, 1069, 1026, 884, 726, 680 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.09 (d, 3 H, J = 7 Hz, OCHCH_3), 1.10 (s, 3 H), 1–2.4 (m, 8 H), 1.69 (s, 3 H, vinylic methyl), 3.36 (t, 2 H, J = 6 Hz, PhCH_2OCH_2CH_2), 3.42 (q, 1 H, J = 7 Hz, OCH-CH_3), 4.20 (dd, 1 H, J = 3 Hz, 9 Hz, allylic methine) 4.40 (s, 2 H, PhCH_2O), 7.21 (s, 5 H); ^{13}C NMR (CCl_4) δ (TMS) 17.48. 18.46, 23.33, 28.46, 28.85, 31.00, 33.60, 68.43, 72.27, 79.16, 85.33, 125.88, 126.92, 127.70, 138.36, 150.51; $[\alpha]^{25}_D$ = +53.3° (c 2.16, CH_2Cl_2); R_f = 0.57 (silica gel, 1:4 ether/CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91, H, 8.92. Found: C, 75.95; H, 8.92.

(1′*R*,2*R*,5*S*)-5-(1′-Acetoxyethyl)-5-methyl-2-(1″-oxo-4″-(benzyloxy)butyl)tetrahydrofuran (47). To 1.6 g (5.06 mmol) of **46b** in 40 mL of CH_2Cl_2 was added 6 mg of Sudan 7B dye.[40] This solution was protected from moisture with a calcium chloride packed drying tube and cooled to –78 °C, and a stream of ozone in oxygen was bubbled through the solution until the red color of the indicator dye was discharged. The flow of ozone was terminated, and 8 mL of dimethyl sulfide was added. After 1 h at –78 °C and 1 h at 20 °C, the solvent was removed in vacuo. The residue was taken up in ether and extracted with water and brine, and the ethereal solution was dried (anhydrous Na_2SO_4) and concentrated to give 1.5 g of unpurified ketone **47** (GC analysis, 30 meter DB-1, 225 °C, t_r = 3.77 min, shows 75–80% purity). A small sample (100 mg) was flash chromatographed (7 g of silica gel, 1 × 30 cm, 5% ether/CH_2Cl_2, 0.3-mL fractions) to give analytically pure material. It was noted that upon prolonged exposure to silica gel, the α-stereocenter proximal to the ketone was epimerized to give a 1:1 mixture of diastereomers. IR (CCl_4) 2985, 2950, 2878, 1736, 1719, 1451, 1374, 1245, 1099, 1060, 1029 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.17 (s, 3 H), 1.20 (d, 3 H, J = 7 Hz, OCHCH_3), 1.3–2.3 (m, 6 H), 1.92 [s, 3 H, OC(O)CH_3], 2.58 [t, 2 H, J = 7 Hz, CH_2CH_2C(O)–], 3.40 (t, 2 H, J = 6 Hz, –OCH_2CH_2–), 4.22 (m, 1 H, tetrahydrofuranyl methine), 4.40 (s, 2 H, PhCH_2O), 4.80 (q, 1 H, J = 7 Hz, CH(CH_3)OC(O)CH_3), 7.21 (s, 5 H); ^{13}C NMR (CCl_4) δ (TMS) 15.27, 20.67, 21.84, 23.01, 28.40, 33.53, 34.31, 68.69, 72.27, 73.44, 82.92, 85.13, 127.12, 127.77, 138.23, 168.12, 208.42; $[\alpha]^{25}_D$ = +24.0° (c 0.99, CH_2Cl_2); R_f = 0.48 (silica gel, 1:4 ether/CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94, H, 8.10. Found: C, 68.86; H, 8.04.

(1″*R*,1′*R*,2*R*,5*S*)-5-(1′-Hydroxyethyl)-5-methyl-2-(1″-hydroxy-1″-methyl-4″-(benzyloxy)butyl)tetrahydrofuran (48a). The unpurified keto–ester **47**, (1.5 g, 4.3 mmol) was taken up in 4 mL of distilled CH_2Cl_2 and added, dropwise, to a cooled (–78 °C) solution of 25 mL of CH_2Cl_2 and 24 mL of a 2.8 M solution of methylmagnesium bromide in ether. After 8 h at –78 °C, the reaction was stirred an additional 2 h at 20 °C. The solution was then cooled (–78 °C) before a saturated aqueous solution of NH_4Cl was added to quench the excess Grignard reagent. The product was isolated from an aqueous workup by ether extraction (3 × 100 mL). The ethereal extracts were combined and dried over anhydrous Na_2SO_4. The entire procedure was repeated on the same scale. The combined unpurified product (ca. 3 g) was flash chromatographed (125 g of silica gel, 4 × 40 cm, 1:1 ether/CH_2Cl_2, 8-mL fractions) to give 1.78 g (55%) of **48a** (eluting last) and 0.30 g (9%) of another isomer (eluting first) as oils (64% from **46a**): IR (neat) 3420, 2984, 2950, 2880, 1498, 1456, 1379, 1108, 1085, 1031, 1019, 911, 738, 699 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 1.03 (d, 3 H, J = 6.5 Hz, OCH-CH_3), 1.06 (s, 3 H, tetrahydrofuranyl methyl), 1.18 (s, 3 H, C(OH)CH_3], 1.2–2.3 (m, 8 H, CH_2), 3.37 (t, 2 H, J = 6.5 Hz, PhCH_2OCH_2), 3.7 (m, 2 H, methines), 3.9 (br s, 2 H, OH's), 4.40 (s, 2 H, PhCH_2O), 7.20 (s, 5, aromatic H's); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 1.03 (s, 3 H, tetrahydrofuranyl methyl), 1.08 (d, 3 H, J = 6.5 Hz, OCHCH_3), 1.28 (m, 1 H), 1.33 (s, 3 H), 1.38 (m, 1 H), 1.47 (m, 1 H), 1.58 (m, 1 H), 1.63 (m, 1 H), 1.74 (m, 1 H), 2.09 (m, 1 H), 2.20 (m, 1 H), 3.28 (t, 2 H, J = 6.5 Hz, PhCH_2OCH_2), 3.70 (dd, 1 H, J = 7 Hz, tetrahydrofuranyl methine), 3.75 (br s, 1 H, OH), 3.87 (q, 1 H, J = 6.5 Hz, OCHCH_3), 4.30 (s, 2 H, OCH_2Ph), 4.32 (br s, 1 H, OH), 7.1–7.3 (m, 5 H, aromatic H's); ^{13}C NMR (CCl_4) δ TMS) 18.13, 23.72, 23.92, 24.37, 26.26, 30.41, 35.42, 70.38, 72.46, 72.72, 72.98, 83.83, 86.11, 127.12, 127.90, 138.29; $[\alpha]^{25}_D$ = –7.29° (c 3.38, CH_2Cl_2). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.53; H, 9.17.

(1″*R*,1′*R*,2*R*,5*S*)-5-(1′-(*tert*-Butyldimethylsiloxy)ethyl)-5-methyl-2-(1″-(*tert*-butyldimethylsiloxy)-1″-methyl-4″-(benzyloxy)butyl)tetrahydrofuran (48b). To a cooled solution (0 °C) of 1.37 g (4.23 mmol) of **48a** in 10 mL of CH_2Cl_2 under an argon atmosphere was added 2.4 mL (17.3 mmol) of triethylamine followed by 2.4 mL (10.9 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBS triflate). After 2 h at 0 °C, the reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ solution. The CH_2Cl_2 layer was concentrated in vacuo. The residue was chromatographed (80 g silica gel, 4 × 46 cm, CH_2Cl_2) to afford 2.19 g (94%) of bis-silylated product **48b** as a colorless oil: IR (neat) 2964, 2940, 2895, 2868, 1460, 1370, 1254, 1100, 1074, 1004, 837, 810, 773, 731, 693 cm^{-1}; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.07 (s, 6 H, silyl CH_3), 0.17 (s, 6 H, silyl CH_3), 0.96 (s, 9 H, 1-butyl group), 1.0 (s, 9 H, *tert*-butyl group), 1.17 (s, 3 H), 1.20 (s, 3 H), 1.25 (d, 3 H, J = 6.5 Hz, ≡SiOCHCH_3), 1.2–2 (m, 8 H, methylenes), 3.34 (br t, 2 H ROCH_2CH_2), 3.70 (q, 1 H, J = 6.5 Hz, ≡SiOC$_H$CH_3), 3.83 (m, 1 H, tetrahydrofuranyl methine), 4.41 (s, 2 H, OCH_2Ph), 7.2 (m, 5 H, aromatic H's); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.069 (s, 3 H), 0.075 (s, 3 H), 0.169 (s, 3 H), 0.174 (s, 3 H), 0.97 (s, 9 H), 1.01 (s, 9 H), 1.175 (s, 3 H), 1.19 (s, 3 H), 1.27 (d, 3 H, J = 6.5 Hz, ≡SiOCHCH_3), 1.57 (m, 2 H), 1.7–1.9 (m, 6 H), 3.35 (m, 2 H, –OCH_2CH_2–), 3.70 (q, 1 H, J = 6.5 Hz, ≡SiOCHCH_3), 3.86 (t, 1 H, J = 7 Hz, tetrahydrofuranyl methine), 4.35 (s, 2 H, PhCH_2O), 7.1–7.3 (m, 5 H); ^{13}C NMR (CCl_4) δ (TMS) –5.00, –3.96, –2.08, 17.74, 18.26, 18.59, 23.01, 23.85, 25.74, 36.13, 36.85, 70.32, 72.33, 73.57, 76.10, 82.99, 84.74, 126.92, 127.77; $[\alpha]^{25}_D$ = –3.73° (c 3.91, CH_2Cl_2); R_f = 0.66 (silica gel, 10% ether/CH_2Cl_2). Anal. Calcd for $C_{31}H_{58}O_4Si_2$: C, 67.58; H,

10.61. Found: C, 67.69; H, 10.51.

(1″*S*,1′*R*,2*R*,5*S*)-2-(1″-(*tert*-Butyldimethylsiloxy)-1″-methyl-4″-iodobutyl)-5-(1′-(*tert*-butyldimethylsiloxy)ethyl)-5-methyltetrahydrofuran (49b). To 1.8 g (3.27 mmol) of benzyl ether **48b** in 40 mL of EtOAc was added 0.30 g of a 10% Pd/C hydrogenolysis catalyst. This mixture was transferred to a Parr hydrogenation apparatus and maintained under 4 atm of hydrogen for 19 h at 20 °C. The mixture was filtered through Celite to remove the catalyst. Evaporation of the solvent in vacuo gave 1.51 g (100%) of pure primary alcohol **49a**: IR (neat) 3360, 2965, 2942, 2890, 2868, 1473, 1461, 1371, 1258, 1252, 1102, 1065, 1009, 835, 772 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.03 (s, 3 H), 0.05 (s, 3 H), 0.10 (s, 6 H), 0.88 (s, 18 H, *tert*-butyl groups), 1.10 (d, 9 H), 1.3–1.9 (m, 8 H), 2.77 (s, 1 H, O*H*), 3.50 (t, 2 H, J = 6 Hz, HOCH_2), 3.52 (q, 1 H, J = 6 Hz, ≡SiO-C*H*CH_3), 3.80 (t, 1 H, J = 6 Hz, tetrahydrofuranyl methine); ^{13}C NMR (CCl_4) δ (TMS) −5.00, −3.96, −2.08, 17.74, 18.26, 18.65, 23.01, 35.74, 25.87, 26.58, 36.00, 36.59, 62.58, 73.44, 76.10, 82.66, 84.94; $[\alpha]^{25}_D$ = −4.60° (*c* 1.77, CH_2Cl_2); R_f = 0.44 (silica gel, 20% ether/CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

To a cooled solution (0 °C) of 1.5 g (3.25 mmol) of alcohol **49a** in 18 mL of CH_2Cl_2 was added 0.92 mL (6.6 mmol) of triethylamine and 0.46 mL (5.94 mmol) of methanesulfonyl chloride. After 3 h, the solvent was removed in vacuo. The residue was taken up in EtOAc and extracted with ice water. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to give 1.88 g of unpurified mesylate (R_f = 0.73 (silica gel, 20% ether/CH_2Cl_2)): IR (neat) 2968, 2945, 2898, 2870, 1474, 1463, 1361, 1259, 1252, 1179, 1102, 1071, 971, 835, 772 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (m, 12 H, silyl methyls), 0.85 (s, 18 H, *tert*-butyl groups), 1.03 (s, 3 H), 1.06 (d, 3 H, J = 6 Hz), 1.10 (s, 3 H), 1.3–2.0 (m, 8 H), 2.81 (s, 3 H, CH_3SO_3), 3.50 (q, 1 H, J = 6 Hz), 3.75 (t, 1 H, J = 6 Hz, tetrahydrofuranyl methine), 4.10 (t, 2 H, J = 6 Hz, CH_3SO_2-OCH_2). This material was carried on without purification to the next reaction.

The unpurified mesylate (1.88 g) derived from 1.5 g (3.25 mmol) of alcohol **49a** was dissolved in 40 mL of anhydrous acetone. To this solution was added 9.3 g of anhydrous NaI, 0.37 g of $NaHCO_3$, and 2 drops of diisopropylethylamine. After protecting the reaction from light with aluminum foil, the reaction was allowed to stir for 18 h (20 °C), the acetone was removed in vacuo, and the residue was taken up in EtOAc. After filtration through Celite the solvent was concentrated in vacuo. Flash chromatographic purification (50 g of silica gel, 3 × 30 cm, 20% EtOAc/hexane, 8-mL fractions) of the residue afforded 1.84 g (99% **49a**) of the unstable iodide **49b** (stored in a foil-wrapped container at −20 °C): IR (CCl_4) δ 2967, 2940, 2895, 2869, 1471, 1460, 1370, 1361, 1252, 1100, 1004, 832, 770, cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.03 (s, 3 H), 0.05 (s, 3 H), 0.10 (s, 6 H), 0.88 (s, 9 H, *tert*-butyl group), 0.89 (s, 9 H, *tert*-butyl group), 1.07 (s, 3 H), 1.13 (d, 3 H, J = 6 Hz, ≡SiO-CHCH_3) 1.14 (s, 3 H), 1.2–2.1 (m, 8 H), 3.18 (t, 2 H, J = 6 Hz, RCH_2), 3.42 (q, 1 H, J = 6 Hz, ≡SiOC*H*CH_3), 3.8 (t, 1 H, J = 6 Hz, tetrahydrofuranyl methine); ^{13}C NMR (CCl_4) δ (TMS) −5.00, −3.96, −2.08, 6.56, 17.74, 18.26, 18.65, 22.94, 25.74, 25.87, 27.55, 36.00, 41.20, 73.44, 75.84, 82.86, 85.00; $[\alpha]^{25}_D$ = −3.1° (*c* 5.5, CH_2Cl_2); R_f = 0.75 (silica gel, 20% EtOAc/hexane). Anal. Calcd for $C_{24}H_{51}IO_3PSi_2$: C, 50.51; H, 9.01. Found: C, 50.63; H, 8.86.

Phosphonium Iodide 49c. To a solution of 1.3 g (4.96 mmol) of triphenylphosphine and 0.14 mL of diisopropylethylamine in 20 mL of distilled toluene and 20 mL of distilled acetonitrile was added 1.84 g (3.22 mmol) of iodide **49b**. The reaction mixture was heated to 75 °C under a nitrogen atmosphere for 54 h. The solution was cooled and the solvents removed in vacuo with the appropriate care to exclude moisture from the hygroscopic residue. The gummy residue was transferred to a centrifuge tube with CH_2Cl_2, and the solvent was evaporated under a stream of dry nitrogen at 80 °C. The phosphonium salt was then washed with 3 × 50-mL portions by dry hexane to remove excess triphenylphosphine. The resulting white hygroscopic solid was dried under vacuum at 60 °C for 10 h to give 2.1 g (78%) of **49c**: mp 76–81 °C; ^1H NMR (90 MHz, benzene-d_6) δ (TMS) 0.20 (s, 12 H), 0.90 (s, 9 H, 1.01 (s, 9 H), 1.19 (s, 3 H), 1.23 (s, 3 H), 1.35 (d, 3 H, J = 6 Hz), 1.2–2.5 (m, 8 H), 3.8 (m, 3 H), 4.5 (br m, 1 H), 7.25 (br m), 7.85 (br m). Anal. Calcd for $C_{42}H_{66}IO_3PSi_2$: C, 60.56; H, 7.99. Found: C, 60.21; H, 7.78.

C_{17}–C_{32} Fragment 50a (Scheme XIII). To a solution of 582 mg (0.70 mmol) of phosphonium salt **49c** in 5.4 mL of toluene was added 1.45 mL (0.83 mmol) of a 0.575 M solution of sodium bis(trimethylsilyl)amide[87] in toluene. After 15 min at 20 °C, the orange solution was cooled to −78 °C for 30 min. A solution of 200 mg (0.65 mmol) of aldehyde **40a** in 0.200 mL of toluene was added. After 15 min, the cooling bath was removed and the reaction mixture was stirred an additional 30 min at 20 °C. The triphenylphosphine oxide was precipitated by the addition of hexane, the mixture was filtered through Celite, the filtrate was concentrated in vacuo, and the residue was flash chromatographed (10 g of silica gel, 1.5 × 30 cm, CH_2Cl_2) to afford 424 mg (89%) of **50a** as a light yellow oil. GLC analysis (SE-54, 260 °C, t_r(major) = 15.14 min, t_r(minor) = 14.12 min) gave a *Z*:*E* isomer ratio of 97.3:2.7: IR (neat) 2966, 2944, 2868, 1460, 1378, 1371, 1258, 1204, 1170, 1100, 1049, 1008, 990, 939, 912, 887, 836, 810, 772, 732, 695, 681, 662 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (m, 12 H, SiMe_2), 0.70 (d, 3 H, J = 6 Hz), 0.89 (s, 18 H, *tert*-butyl groups), 1.0 (d, 3 H, J = 7 Hz), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.29 (s, 3 H, acetonide geminal methyl), 1.39 (s, 3 H, acetonide geminal methyl), 1.4–2.3 (m, 1 O*H*), 3.1–4.2 (m, 6 H), 4.4 (s, 2 H, PhCH_2O), 5.0–5.6 (m, 2 H, olefinic H), 7.2 (s, 5 H, aromatic *H*'s); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.07 [s, 6 H, =Si-(CH_3)$_2$], 0.15 [s, 3 H, Si(CH_3)$_2$], 0.17 [s, 3 H, =Si(CH_3)$_2$], 0.83 [d, 3 H, J = 7 Hz, PhCH$_2$OCH$_2$CH(CH_3)CH(OR)], 0.98 (s, 9 H, *t-Bu*Si≡), 1.02 (s, 9 H, *t-Bu*Si≡), 1.18 (s, 3 H, methyl in tetrahydrofuran ring), 1.18 (d, 3 H, J = 7 Hz, methyl in acetonide ring), 1.19 [s, 3 H, –C-(OSiR$_3$)CH_3–], 1.27 (d, 3 H, J = 6 Hz, –CH(CH_3)OSiR$_3$–], 1.49 (s, 3 H, axial methyl in acetonide ring), 1.53 (s, 3 H, equatorial methyl in acetonide ring), 1.60 [m, 1 H, –CCH$_3$(OSiR$_3$)CH_2–], 1.75 [m, 3 H, tetrahydrofuranyl methylene and –CCH_3(OSiR$_3$)CH_2–], 1.85 (m, 2 H, tetrahydrofuranyl methylene), 2.27 (m, 2 H, methine), 2.34 (m, 2 H, –CH_2CH=CH–), 3.39 (dd, 1 H, J = 9.7 Hz, PhCH$_2$OC*H*(H)], 3.57 (dd, 1 H, J = 10, 2 Hz, BnOCH$_2$-CH(CH$_3$)C*H*(OR)], 3.69 [q, 1 H, J = 6 Hz, C*H*(CH$_3$)OSiR$_3$], 3.83 (dd, 1 H, J = 9, 6 Hz, PhCH$_2$OCH_2], 3.89 [t, 1 H, J = 7 Hz, tetrahydrofuranyl methine), 4.33 (d, 1 H, J = 12 Hz, PhCH_2O), 4.36 (d, 1 H, J = 12 Hz, PhCH_2O) 4.44 [dd, 1 H, J = 10, 8 Hz, –C*H*(OR)CH=CH–], 5.48–5.59 (m, 2 H, J_{cis} = 11 Hz, –C*H*=C*H*–), 7.09 (t, 1 H, J = 7.5 Hz), 7.18 (t, 2 H, J = 7.5 Hz), 7.31 (br d, 2 H, J = 7.5 Hz); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) −5.00, −3.96, −2.01, 12.02, 15.99, 17.74, 18.26, 18.59, 19.24, 22.23, 22.98, 25.74, 25.87, 30.02, 34.18, 35.81, 36.13, 40.03, 70.45, 70.97, 72.66, 73.57, 76.10, 77.34, 82.60, 84.87, 97.35, 126.86, 127.77, 129.59, 132.83, 138.62; $[\alpha]^{25}_D$ = +6.59° (*c* 2.78, CH_2Cl_2). Anal. Calcd for $C_{42}H_{76}O_6Si_2$: C, 68.80, H, 10.45. Found: C, 68.94; H, 10.40.

C_{17}–C_{32} Fragment 50b (Scheme XIII). To a solution of 2.5 g (9.56 mmol) of anhydrous Bu_4NF in 4 mL of THF in a re-sealable tube was added a solution of 550 mg (0.75 mmol) of **50a** in 6 mL of THF. The mixture was heated to 80 °C for 36 h in the sealed tube, the solvent was removed in vacuo, and the residue was introduced onto a silica gel column (40 g, 3 × 40 cm, packed in hexane) and flash eluted with 50% EtOAc/hexane (100-mL fractions). Concentration of the product-containing fractions 2–5 afforded 356 mg (94%) of diol **50b** as a liquid: IR (neat) 3410, 2980, 2945, 2882, 1656, 1498, 1455, 1380, 1350, 1255, 1205, 1172, 1130, 1103, 1080, 1046, 1030, 1011, 995, 940, 911, 891, 735, 697 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.71 [d, 3 H, J = 6 Hz, PhCH$_2$OCH$_2$CH(CH_3)], 0.96 (d, 3 H, J = 7 Hz, acetonide methyl), 1.05 [d, 3 H, J = 6 Hz, CH(OH)CH_3), 1.09 (s, 3 H, tetrahydrofuranyl methyl), 1.20 (s, 3 H, –CH$_2$C(OH)CH_3)–], 1.30 (s, 3 H, axial acetonide methyl), 1.40 (s, 3 H, equatorial acetonide methyl), 0.9–2.3 (m, 10 H), 3.10–3.80 (m, 6 H), 4.10 [dd, 1 H, J = 10, 8 Hz, –C*H*(OR)CH=CH–], 4.40 (s, 2 H, PhCH_2O), 5.0–5.70 (m, 2 H, C*H*=C*H*), 7.21 (s, 5 H, aromatic *H*'s); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.74 (d, 3 H, J = 6.6 Hz, acetonide methyl), 1.00 (d, 3 H, J = 6.3 Hz, CH_3CH(OH)], 1.02 (s, 3 H, tetrahydrofuranyl methyl), 1.18 (d, 3 H, J = 7.1 Hz, PhCH$_2$OCH$_2$CH(CH_3)], 1.2–1.3 (m, 2 H), 1.31 [s, 3 H, –CH$_2$C(OH)-CH_3–], 1.40 (s, 3 H, axial acetonide methyl), 1.45 (m, 1 H), 1.53 (s, 3 H, equatorial acetonide methyl), 1.59 (m, 1 H), 1.85 (m, 1 H), 2.00 (m, 1 H), 2.14 (m, 1 H), 2.2–2.3 (m, 3 H), 338 (dd, 1 H, J = 9.2, 7.1 Hz), 3.44 (dd, 1 H, J = 2.0, 10.2 Hz), 3.68 (dd, 1 H, J = 6.6, 7.7 Hz), 3.80 (q, 1 H, J = 6.3 Hz, CH$_3$C*H*(OH)], 3.82 (dd, 1 H, J = 6.1, 7.7 Hz), 4.32 (dd, 1 H, J = 7.7, 10.2 Hz), 4.36 (ABq, 2 H, J_{AB} = 12.2 Hz, PhCH_2O), 5.49 (m, 2 H, vinyl *H*), 7.08–7.33 (m, 5 H aromatic *H*'s); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) 11.96, 15.86, 18.13, 19.17, 22.23, 24.09, 24.32, 26.26, 29.96, 30.41, 34.18, 35.87, 38.15, 70.38, 70.90, 72.72, 73.11, 77.33, 83.64, 86.11, 97.55, 126.86, 127.77, 129.59, 133.35, 138.55; $[\alpha]^{25}_D$ = +15.7° (*c* 2.40, CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

Bis-Tetrahydrofuran Fragment 51a (Scheme XIII). To a cooled solution (−78 °C) of 356 mg (0.71 mmol) of **50b** in 14 mL of CH_2Cl_2 was added 460 mg (1.4 mmol) of mercuric acetate. The heterogeneous mixture was warmed to 20 °C over 6 h and stirred at 20 °C an additional 7 h. A solution of 1.7 g of $NaBH_4$, 2.5 mL of a 15% aqueous NaOH solution, 5 mL of water, and 30 mL of MeOH was prepared and added in one portion to the cooled reaction mixture (−78 °C). The mixture was stirred at 20 °C for 30 min, 50 mL of water was added, and the solution was extracted with ether (3 × 100 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated in vacuo to afford 347 mg of unpurified products. GLC analysis (SE-54, 250 °C, t_r(major) = 3.99 min, t_r(minor) = 4.97 min) gave a C_{23} diastereomer ratio of 93:7. Diastereoselection as high as 96.8:3.2 has been observed in smaller scale cyclization reactions. The unpurified product was chromatographed (25 g of

silica gel, 2 × 30 cm, 20% ether/CH_2Cl_2, 8-mL fractions, major diastereomer eluted first in fraction 11–17) to afford 301 mg (85%) of **51a** as a colorless oil: IR (CCl_4) 3440, 2974, 2940, 2875, 1451, 1385, 1302, 1264, 1245, 1203, 1173, 1123, 1100, 1075, 1029, 1012, 999, 990, 982, 987, 916, 881 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.80 (d, 3 H, J = 6 Hz, $PhCH_2OCH_2CHMe$), 0.96 (d, 3 H, J = 6 Hz, acetonide CH_3), 1.0 [d, 3 H, J = 6.5 Hz, $CH(CH_3)OH$], 1.05 [s, 3 H, $CH_3CH(OH)C(CH_3)O$], 1.20 (s, 3 H, central tetrahydrofuranyl methyl), 1.26 (s, 3 H, axial acetonide methyl), 1.35 (s, 3 H, equatorial acetonide methyl), 1.3–2.3 (m, 12 H), 3.1–4.2 (m, 8 H), 4.4 (s, 2 H, $PhCH_2O$), 7.21 (s, 5 H, aromatic H's); ^1H NMR (500 MHz, benzene-d_6) δ (TMS) 0.66 (d, 3 H, J = 6.6 Hz, acetonide methyl), 1.05 (s, 3 H, terminal tetrahydrofuranyl methyl), 1.12 [d, 3 H, J = 6.4 Hz, $CH_3CH(OH)$], 1.17 (d, 3 H, J = 7.1 Hz, $PhCH_2OCH_2CH(CH_3)$]. 1.20–1.28 (m, 1 H), 1.29 (s, 3 H, central tetrahydrofuranyl methyl), 1.35 (s, 3 H, axial acetonide methyl), 1.35–1.41 (m, 1 H), 1.45 (s, 3 H, equatorial acetonide methyl), 1.46–1.61 (m, 3 H), 1.72 (m, 2 H), 1.79 (m, 1 H), 1.91 (m, 1 H), 2.00 (m, 1 H), 2.20 (m, 2 H), 3.33 (dd, 1 H, J = 2.0, 10.2 Hz), 3.40 (dd, 1 H, J = 7.7, 8.7 Hz), 3.45 (m, 1 H), 3.80 (d, 1 H, J = 8.7 Hz), 3.80 (dd, 1 H, J = 9.2, 11.2 Hz), 3.95 [q, 1 H, J = 6.4 Hz, $CH_3CH(OH)$], 4.1 (br s, 1 H, OH), 4.25 (m, 1 H, central tetrahydrofuranyl methine), 4.38 (ABq, 2 H, J_{AB} = 9.2 Hz, $PhCH_2O$), 7.09–7.33 (m, 5 H, aromatic H's); ^{13}C NMR (22.5 MHz, CCl_4) δ (TMS) 12.09, 15.99, 17.68, 19.11, 24.31, 25.87, 27.42, 30.02, 30.41, 30.74, 34.05, 34.77, 35.29, 38.86, 70.90, 71.94, 72.72, 77.47, 77.73, 83.70, 86.82, 97.16, 126.86, 127.83, 138.62; $[\alpha]^{25}_D$ = −7.24° (c 1, 57, CH_2Cl_2). R_f = 0.54 (silica gel, 50% ether/CH_2Cl_2). Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.52. *Note*: The other minor diastereomer can be isolated in the later chromatography fractions.

Bis-THF Fragment 52a (Scheme XIV). To a cooled (0 °C) solution of 305 mg (0.60 mmol) of **51a** in 12 mL of CH_2Cl_2 under nitrogen was added 1.2 mL (8.6 mmol) of freshly distilled triethylamine and 0.75 mL (3.4 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 1.5 h at 0 °C, the reaction was quenched with 10 mL of a saturated aqueous $NaHCO_3$ solution and stirred an additional 1 h at 20 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was flash chromatographed (10 g of silica gel, 1.5 × 30 cm, ether), collecting the UV-active fraction. Evaporation of the solvent in vacuo afforded 374 mg (100%) of silyl ether **52a** as a yellow oil: IR (neat) 2970, 2945, 2869, 1460, 1452, 1377, 1370, 1258, 1205, 1175, 1100, 1029, 921, 831, 810, 772, 734, 695 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 (s, 6 H, $-Si(CH_3)_2-$], 0.79 [d, 3 H, J = 6 Hz, $PhCH_2OCH_2CH(CH_3)$], 0.89 (s, 9 H, *tert*-butyl group), 0.96 (d, 3 H, J = 7 Hz, $CH_3CH(OH)$], 1.05 (s, 6 H, quaternary tetrahydrofuranyl methyls), 1.10 (d, 3 H, acetonide methyl), 1.25 (s, 3 H, axial acetonide methyl). 1.31 (s, 3 H, equatorial acetonide methyl), 1.4–2.2 (m, 12 H), 3.05–4.20 (m, 7 H), 4.39 (s, 2 H, $PhCH_2O$), 7.2 (s, 5 H, aromatic H's); ^{13}C NMR (CCl_4) δ (TMS) −5.00, −4.03, 12.02, 15.99, 18.00, 18.13, 19.04, 23.40, 25.74, 26.45, 29.96, 31.19, 34.05, 34.83, 35.29, 35.87, 38.73, 70.97, 72.01, 72.59, 73.24, 76.36, 77.40, 82.73, 83.83, 84.74, 97.03, 126.79, 127.70, 138.55; $[\alpha]^{25}_D$ = −16.6° (c 0.976, CH_2Cl_2). R_f = 0.76 (silica gel, 50% ether/CH_2Cl_2). The title compound was carried on to the subsequent experiment without further characterization.

Bis-Tetrahydrofuran Synthon 52b (Scheme XIV). A solution of 55.2 mg (89.2 μmol) of **52a** and 20 mg of 10% Pd/C in 4 mL of acetone was stirred at 20 °C under 1 atm of H_2 for 3 h. The catalyst was removed by filtration through Celite. Evaporation of the solvent in vacuo afforded 44.5 mg (94%) of **52b** as an oil: IR (CCl_4) 3440, 2970, 2950, 2870, 1462, 1379, 1260, 1206, 1178, 1100, 1050, 1044, 920, 838, 832, 775 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ (TMS) 0.05 [s, 6 H, $-Si(CH_3)_2-$], 0.77 (d, 3 H, J = 6.5 Hz), 0.87 (s, 9 H, *tert*-butyl group), 1.02 (d, 3 H), 1.05 (s, 6 H, tetrahydrofuranyl methyls), 1.09 (d, 3 H), 1.30 (s, 3 H, axial acetonide methyl), 1.31 (s, 3 H, equatorial acetonide methyl), 1.4–2.1 (m, 12 H), 3.3–4.2 (m, 7 H); ^{13}C NMR (CCl_4) δ (TMS) −4.94, −3.96, 12.02, 15.40, 17.81, 18.20, 18.78, 19.11, 23.53, 25.74, 26.51, 30.09, 31.45, 34.57, 35.42, 35.87, 38.60, 62.58, 71.94, 73.37, 76.10, 79.42, 82.92, 83.83, 84.87, 97.42; $[\alpha]^{25}_D$ = −23.3° (c 1.47, CH_2Cl_2). The title compound was carried on to the next assembly stage without further characterization.

(2*R*,4*R*,6*E*,8*R*,9*R*,10*S*,11*S*,12(2*S*,5*S*(2*R*,5*S*(*R*))))-1-((1,1-Dimethylethyl)diphenylsiloxy)-9,11-((1-methylethylidene)dioxy)-2,4,8,10-tetramethyl-12-(tetrahydro-5-methyl-5-(tetrahydro-5-(1-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-5-methyl-2-furanyl)-2-furanyl)-6-dodecene (55a) (Scheme XIV). To a cooled (−78 °C), stirred solution of 44 μL (0.50 mmol) of oxalyl chloride in CH_2Cl_2 (0.5 mL) was added 71 μL (1.0 mmol) of DMSO dropwise.[30] After 2 min at −78 °C, this solution was added via cannula to a cooled (−78 °C), stirred solution of 98.1 mg (186 mmol) of alcohol **52b** in CH_2Cl_2 (2 mL). The resulting heterogeneous mixture was held at −78 °C for 30 min, and 0.35 mL (2.5 mmol) of triethylamine was added dropwise to produce a thick white slurry. After 15 min at this temperature, 20 mL of aqueous phosphate buffer (pH = 7) was added, followed by extraction with ether (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting aldehyde **53** was passed through a short plug of silica, eluting with ether, to afford a golden oil. This oil was employed in the next experiment without further purification.

To a cooled (−78 °C), stirred solution of 131 mg (257 μmol) of sulfone **26c** in THF (1.4 mL) was added 158 μL (265 μmol) of a 1.64 M hexane solution of *n*-butyllithium, and the resulting yellow solution was maintained at −78 °C for 30 min. This solution was added to a cooled −78 °C) flask containing aldehyde **53** (prepared in the previous experiment). The reaction temperature was maintained at −78 °C for 1 h, followed by the addition of 0.09 mL (1.0 mmol) of acetic anhydride. The resulting light yellow solution was allowed to warm slowly to 25 °C over a 1.5-h period and was then held at this temperature for an additional 1.5 h. Saturated aqueous ammonium chloride (20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford acetoxysulfones **54** as a yellow oil. This oil was employed in the next experiment without further purification.

To a cooled (−30 °C), stirred solution of the diastereomeric acetoxysulfones **54** (prepared in the previous experiment) in anhydrous MeOH (1.5 mL) and anhydrous EtOAc (0.7 mL) was added 1.0 g (4.5% sodium be weight) of sodium amalgam. The temperature of the resulting heterogeneous mixture was maintained at −30 °C for 20 h. Dilute aqueous hydrochloric acid (20 mL) was added and the liquid phase was decanted from the solids. This solution was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide a yellow oil. Isomer analysis before and/or after chromatography (DB-1, 300 °C, 15 psi, t_r(**55a**) = 23.81 min, t_r(**6*Z*-55a**) = 24.80 min) revealed a cis:trans olefin ratio of 86.2:13.8. Flash chromatography (30 g of silica, 5% EtOAc/hexane) afforded a colorless oil, 114 mg (70% from **52b**). This material was analyzed as a mixture of olefin isomers: R_f 0.28 (5% EtOAc/hexane; IR (neat) 2965, 2940, 2865, 1455, 1425, 1375, 1255, 1200, 1100 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 7.70–7.18 (m, 10 H, aromatic H's), 5.40–5.13 (m, 2 H, C_6-H, C_7-H), 4.15–3.03 (m, 7 H, C_1-H's, C_9-H, C_{11}-H, C_2'-H, C_2''-H, C_5''-CH), 2.30–0.52 (m, 63 H, $C(CH_3)_3$, C_2-H, C_2-CH_3, C_3-H's, C_4-H, C_4-CH_3, C_5-H's, C_8-H, C_8-CH_3, C_{10}-H, C_{10}-CH_3, C_{12}-H's, $C(CH_3)_2$, C_3'-H's, C_4'-H's, C_5'-CH_3, C_3''-H's, C_4''-H's, C_5''-CH_3, $C_5''CCH_3$, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (22.5 MHz, CCl_4) δ 135.63, 134.39, 132.83, 129.39, 128.94, 127.50, 97.42, 85.26, 84.35, 84.25, 78.31, 76.94, 74.02, 72.14, 69.47, 41.27, 40.23, 39.71, 38.67, 36.33, 36.00, 35.42, 33.73, 31.58, 31.06, 30.28, 27.23, 26.77, 26.00, 23.59, 20.15, 19.43, 18.39, 17.87, 11.70, −3.90, −4.61.

(2*R*,4*R*,6*E*,8*R*,9*R*,10*S*,11*S*,12(2*S*,5*S*(2*R*,5*S*(*R*))))-1-Hydroxy-9,11-((1-methylethylidene)dioxy)-2,4,8,10-tetramethyl-12-(tetrahydro-5-methyl-5-(tetrahydro-5-(1-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-5-methyl-2-furanyl)-2-furanyl)-6-dodecene (55b) (Scheme XIV). To 114.0 mg (129.9 μmol) of a 86.2:13.8 mixture of **55a** and its cis olefin contaminant was added 3.0 mL (900 μmol) of a 0.3 M THF solution of Bu_4NF. The resulting yellow solution was stirred at 25 °C for 21 h, diluted with water (15 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a golden oil. This material was first passed through 30 g of silica (eluting with 30% EtOAc/hexane) to remove polar impurities, and then the olefin isomers were separated by MPLC (size A column, 10% EtOAc/hexane, flow rate 3 mL/min) to afford pure **55b** as a golden oil, 67.1 mg (94% yield based on isomeric purity of the starting material): R_f 0.13 (15% EtOAc/hexane); IR (neat) 3650–3100 (br), 2965, 2940, 2875, 1460, 1375, 1255, 1200, 1100 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.73 (dd, 1 H, J = 8.5 Hz, J = 15.5 Hz, C_7-H), 5.39 (qn, 1 H, J = 15.5 Hz, C_6-H), 4.38 (m, 1 H, C_2'-H), 3.96 (t, 1 H, C_2''-H), 3.76 (q, 1 H, C_5''-CH), 3.54 (dt, 1 H, C_{11}-H), 3.35–3.17 (m, 3 H, C_1-H's, C_9-H), 2.38 (qn, 1 H, C_8-H), 2.13–0.81 (m, 18 H, C_2-H, C_3-H's, C_4-H, C_5-H's, C_{10}-H, C_{12}-H's, C_3'-H's, C_4'-H's, C_3''-H's, C_4''-H's, OH), 1.51 (s, 3 H, $C(CH_3)_2$), 1.33 (s, 3 H, $C(CH_3)_2$), 1.28 (d, 3 H, C_8-CH_3), 1.27 (s, 3 H, C_5'-CH_3), 1.22 (d, 3 H, C_5''-CCH_3), 1.21 (s, 3 H, C_5''-CH_3), 0.97 (s, 9 H, $C(CH_3)_3$), 0.88 (d, d, 6 H, C_2-CH_3, C_4-CH_3), 0.66 (d, 3 H, C_{10}-CH_3), 0.05 (d, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.67, 128.80, 96.46, 85.38, 84.33, 83.44, 77.88, 77.09, 73.35, 71.93, 68.25, 40.41, 39.53, 39.26, 38.45, 36.26, 35.91, 34.28, 33.26, 31.28, 30.49, 30.05, 26.96, 25.78, 23.95, 20.26, 19.39, 19.24, 18.46, 18.25, 17.85, 17.26, 11.52, −3.97, −4.87; $[\alpha]_D$ = −27.5° (c 0.30, CH_2Cl_2). Anal. Calcd for $C_{37}H_{70}O_6Si$: C, 69.54; H, 11.04. Found: C, 69.69; H, 11.07.

6*Z*-55b: R_f 0.07 (15% EtOAc/hexane); ^1H NMR (500 MHz, C_6D_6) δ 5.89 (t, 1 H, J = 11 Hz, C_7-H), 5.46 (m, 1 H, J = 11 Hz, C_6-H), 4.39 (m, 1 H, C_2'-H), 3.96 (t, 1 H, C_2''-H), 3.76 (q, 1 H, C_5''-H), 3.55 (dt, 1 H, C_{11}-H), 3.36 (dd, 1 H, C_9-H), 3.28 (dd, 1 H, C_1-H), 3.15 (dd, 1 H, C_1-H), 2.78 (qn, 1 H, C_8-H), 1.09–0.83 (m, 18 H, C_2-H, C_3-H's, C_4-H,

C_5-*H*'s, C_{10}-*H*, C_{12}-*H*'s, C_3'-*H*'s, C_4'-*H*'s, C_3''-*H*'s, C_4''-*H*'s, O*H*), 1.52 (s, 3 H, $C(CH_3)_2$), 1.36 (s, 3 H, $C(CH_3)_2$), 1.29 (d, 3 H, C_8-CH_3), 1.27 (s, 3 H, C_5'-CH_3), 1.22 (s, 3 H, C_5''-CH_3), 1.21 (d, 3 H, C_5''-CCH_3), 0.97 (s, 9 H, $C(CH_3)_3$), 0.89 (t, 6 H, C_2-CH_3, C_4-CH_3), 0.72 (d, 3 H, C_{10}-CH_3), 0.07 (d, 6 H, $Si(CH_3)_2$).

(4*R*,6*S*,8*S*,11*S*,12*R*,14*R*,16*E*,18*R*,19*R*,20*S*,21*S*,22(2*S*,5*S*-(2*R*,5*S*(*R*)))-4,6,8,12,14,18,20-Heptamethyl-11-hydroxy-19,21-((1-methylethylidene)dioxy)-9-oxo-22-(tetrahydro-5-methyl-5-(tetrahydro-5-(1-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-5-methyl-2-furanyl)-2-furanyl)-16-docosenoic Acid, Methyl Ester (57) and 11*R*-57. Boron-Mediated Aldol Reaction. To a cooled (−60 °C), stirred solution of 0.09 mL (1.0 mmol) of oxalyl chloride in CH_2Cl_2 (1.0 mL) was added 0.14 mL (2.0 mmol) of dimethylsulfoxide dropwise.[30] The resulting solution was maintained at −60 °C for 2 min and then a portion (0.2 mL) was added via cannula to a cooled (−60 °C), stirred solution of 13.8 mg (21.6 μmol) of alcohol **55b** in CH_2Cl_2 (2.0 mL). The reaction temperature was held at −60 °C for 25 min, and then 0.35 mL (2.5 mmol) of triethylamine was added to produce a thick white slurry. This mixture was stirred an additional 20 min, added to 20 mL of pH 7 aqueous phosphate buffer, and extracted with ether (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The aldehyde derived from **55b** was filtered through a short plug of silica (eluting with ether) to afford a golden oil, which was employed in the next experiment without further purification.

To a cooled (−78 °C), stirred solution of 8.7 mg (36 μmol) of ketone **19** in CH_2Cl_2 (0.6 mL) were successively added 11.7 μL (46.7 μmol) of di-*n*-butylboryl triflate[75] and 9.4 μL (54 μmol) of diisopropylethylamine. The reaction temperature was held at −78 °C for 30 min and then added via cannula to a cooled (−78 °C), stirred solution of the aldehyde corresponding to **55b** (prepared in the previous experiment) in CH_2Cl_2 (0.2 mL). The temperature of the resulting solution was maintained at −78 °C for 1 h, allowed to rise to 0 °C, and held at this temperature for an additional 1.5 h. The reaction mixture was quenched with 0.5 mL of pH 7 aqueous phosphate buffer and 2 mL of MeOH. This quench was followed by dropwise addition of 0.5 mL of a solution of 30% aqueous H_2O_2 in 2 mL of MeOH, and the resulting solution was held at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ (15 mL) was added, followed by extraction with ether (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give **57** as an oil. Flash chromatography (20 g of silica, 15% EtOAc/hexane) afforded a colorless oil, 16.0 mg (85% from **55b**): R_f 0.18 (15% EtOAc/hexane); IR (neat) 3600–3300 (br), 2965, 2935, 1745, 1710, 1460, 1380, 1255, 1205, 1175, 1100 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.77 (dd, 1 H, *J* = 8.5 Hz, *J* = 15.5 Hz, C_{17}-*H*), 5.42 (m, 1 H, *J* = 15.5 Hz, C_{16}-*H*), 4.39 (m, 1 H, C_2'-*H*), 4.01 (m, 1 H, C_{11}-*H*), 3.97 (t, 1 H, C_2''-*H*), 3.78 (q, 1 H, C_5''-C*CH*), 3.56 (dt, 1 H, C_{21}-*H*), 3.40 (s, 3 H, OCH_3), 3.31 (dd, 1 H, C_{19}-*H*), 3.23 (br s, 1 H, O*H*), 2.50–0.90 (m, 31 H, C_2-*H*'s, C_3-*H*'s, C_4-*H*, C_5-*H*'s, C_6-*H*, C_7-*H*'s, C_8-*H*, C_{10}-*H*'s, C_{12}-*H*, C_{13}-*H*'s, C_{14}-*H*, C_{15}-*H*'s, C_{18}-*H*, C_{20}-*H*, C_{22}-*H*'s, C_3'-*H*'s, C_4'-*H*'s, C_3''-*H*'s, C_4''-*H*'s), 1.51 (s, 3 H, $C(CH_3)_2$), 1.34 (s, 3 H, $C(CH_3)_2$), 1.30 (d, 3 H, C_{18}-CH_3), 1.29 (s, 3 H, C_5'-CH_3), 1.24 (d, 3 H, C_5''-CCH_3), 1.23 (s, 3 H, C_5''-CH_3), 0.98 (s, 9 H, $C(CH_3)_3$), 0.96–0.90 (m, 9 H, C_8-CH_3, C_{12}-CH_3, C_{14}-CH_3), 0.79–0.67 (d, d, d, 9 H, C_4-CH_3, C_6-CH_3, C_{20}-CH_3), 0.08 (d, 6 H, $Si(CH_3)_2$). Anal. Calcd for $C_{51}H_{94}O_9Si$: C, 69.65; H, 10.78. Found: C, 69.73; H, 10.76.

Tin-Mediated Aldol Reaction. In direct analogy to the previous experiment, 65.0 mg (102 μmol) of the alcohol **55b** was subjected to a Swern oxidation to give the aldehyde derived from **55b**, which was carried on to the next step. To a cooled (−78 °C), stirred slurry of 49.3 mg (300 μmol) of stannous triflate[76] in CH_2Cl_2 (1.0 mL) was added 48 μL (350 μmol) of freshly distilled *N*-ethylpiperidine. To this yellow mixture was added a cooled (−78 °C) solution of 49.3 mg (203 mmol) of ketone **19** in CH_2Cl_2 (5 mL) via cannula. The reaction temperature was held at −78 °C for 1 h, and this yellow mixture was then added via cannula to a cooled (−78 °C), stirred solution of the aldehyde corresponding to **55b** (prepared in the previous experiment) in CH_2Cl_2 (1.0 mL). The reaction temperature was maintained for 2 h at −78 °C. The reaction mixture was added to pH 7 aqueous phosphate buffer (30 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (20 g of silica, 1% MeOH/CH_2Cl_2) afforded **57** as an oil, 63.0 mg (70% from **55b**). This material possessed the same spectral characteristics as the product obtained in the boron-mediated reaction described above.

(4*R*,6*S*,8*S*,10*Z*,12*R*,14*R*,16*E*,18*R*,19*R*,20*S*,21*S*,22(2*S*,5*S*-(2*R*,5*S*(*R*)))-4,6,8,12,14,18,20-Heptamethyl-11-hydroxy-19,21-((1-methylethylidene)dioxy)-9-oxo-22-(tetrahydro-5-methyl-5-(tetrahydro-5-(1-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-5-methyl-2-furanyl)-2-furanyl)-10,16-docosadienoic Acid, Methyl Ester (58). To a slurry of 0.40 g of Celite in 4.0 mL of CH_2Cl_2 was added 95 μL (1.2 mmol) of pyridine, followed by 59 mg (0.59 mmol) of CrO_3 (dried in vacuo prior to use). The resulting slurry was stirred at 25 °C for 30 min, producing a red heterogeneous mixture. To the reaction mixture was added a CH_2Cl_2 (4 mL) solution of 51.9 mg (59.0 μmol) of **57**, and this slurry was stirred vigorously for 15 min. The dark red reaction mixture was then poured into 1 N aqueous HCl (30 mL) and was extracted with ether (2 × 60 mL). The combined light-red extracts were filtered through a short plug of Florasil, followed by further elution with 60 mL of ether. The resulting colorless filtrate was dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (10 g of silica, 7% EtOAc/hexane) afforded 37.4 mg (72%) of **58** as an oil: R_f 0.42 (15% EtOAc/hexane); IR (neat) 2970, 2935, 2880, 1745, 1680-1530 (br), 1460, 1380, 1255, 1205, 1175, 1100 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.73 (dd, 1 H, *J* = 8.5 Hz, *J* = 15.5 Hz, C_{17}-*H*), 5.42 (s, 1 H, C_{10}-*H*), 5.35 (m, 1 H, *J* = 15.5, C_{16}-*H*), 4.38 (m, 1 H, C_2'-*H*), 3.96 (t, 1 H, C_2''-*H*), 3.77 (q, 1 H, C_5''-*H*), 3.55 (dt, 1 H, C_{21}-*H*), 3.40 (s, 3 H, OCH_3), 3.30 (dd, 1 H, C_{19}-*H*), 2.44–0.90 (m, 29 H, C_2-*H*'s, C_3-*H*'s, C_4-*H*, C_5-*H*'s, C_6-*H*, C_7-*H*'s, C_8-*H*, C_{12}-*H*, C_{13}-*H*'s, C_{14}-*H*, C_{15}-*H*'s, C_{18}-*H*, C_{20}-*H*, C_{22}-*H*'s, C_3'-*H*'s, C_4'-*H*'s, C_3''-*H*'s, C_4''-*H*'s), 1.50 (s, 3 H, $C(CH_3)_2$), 1.33 (s, 3 H, $C(CH_3)_2$), 1.29 (d, 3 H, C_{18}-CH_3), 1.28 (s, 3 H, C_5'-CH_3), 1.23 (d, 3 H, C_5''-CCH_3), 1.22 (s, 3 H, C_5''-CH_3), 1.10–1.05 (d, d, 6 H, C_8-CH_3, C_{12}-CH_3), 0.97 (s, 9 H, $C(CH_3)_3$), 0.90–0.64 (d, d, d, d, C_4-CH_3, C_6-CH_3, C_{14}-CH_3, C_{20}-CH_3), 0.08 (d, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.67, 198.51, 174.27, 132.91, 128.81, 97.52, 97.03, 85.43, 84.42, 83.50, 77.87, 77.14, 73.46, 72.01, 51.34, 44.52, 42.47, 41.30, 40.28, 39.40, 38.52, 36.40, 36.00, 34.38, 32.77, 31.86, 31.33, 30.99, 30.13, 29.84, 29.68, 28.11, 27.04, 25.85, 23.98, 19.55, 19.45, 19.31, 19.07, 18.58, 18.48, 18.30, 17.93, 11.57, −3.93, −4.82; $[\alpha]_D$ = −30.5° (*c* 1.18, CH_2Cl_2). Anal. Calcd for $C_{51}H_{92}O_9Si$: C, 69.81; H, 10.57. Found: C, 69.89; H, 10.57.

(4*R*,6*S*,8*S*,10*Z*,12*R*,14*R*,16*E*,18*R*,19*R*,20*S*,21*S*,22(2*S*,5*S*-(2*R*,5*S*(*R*)))-4,6,8,12,14,18,20-Heptamethyl-9-oxo-11,19,21-trihydroxy-22-(tetrahydro-5-methyl-5-(tetrahydro-5-(1-hydroxyethyl)-5-methyl-2-furanyl)-2-furanyl)-10,16-docosadienoic Acid, Methyl Ester (59) (Scheme XIV). A solution of 23.7 mg (27.0 μmol) of **58** in 5 mL of 95:5 (by volume) acetonitrile/40% aqueous HF was stirred vigorously at 25 °C for 1 h. The reaction solution was then added to pH 7 aqueous phosphate buffer (25 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. Flash chromatography (5 g of silica, 50% EtOAc/hexane) afforded 16.3 mg (84%) of ionomycin methyl ester **59** as a colorless oil: R_f 0.20 (50% EtOAc/hexane); IR (neat) 3650–3150 (br), 2975, 2935, 2880, 1745, 1680–1530 (br), 1460, 1380, 1075 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.85 (dd, 1 H, *J* = 8.5 Hz, *J* = 15.5 Hz, C_{17}-*H*), 5.45 (m, 1 H, *J* = 15.5 Hz, C_{16}-*H*), 5.44 (s, 1 H, C_{10}-*H*), 3.99 (m, 1 H, C_2'-*H*), 3.88 (dt, 1 H, C_{21}-*H*), 3.80 (q, 1 H, C_5''-*H*), 3.69 (t, 1 H, C_2''-*H*), 3.53 (dd, 1 H, C_{19}-*H*), 3.40 (s, 3 H, OCH_3), 2.50–0.90 (m, 29 H, C_2-*H*'s, C_3-*H*'s, C_4-*H*, C_5-*H*'s, C_6-*H*, C_7-*H*'s, C_8-*H*, C_{12}-*H*, C_{13}-*H*'s, C_{14}-*H*, C_{15}-*H*'s, C_{18}-*H*, C_{20}-*H*, C_{22}-*H*'s, C_3'-*H*'s, C_4'-*H*'s, C_3''-*H*'s, C_4''-*H*'s), 1.36 (d, 3 H, C_{18}-CH_3), 1.17 (s, C_5''-CH_3), 1.13–1.06 (d, d, 6 H, C_8-CH_3, C_{12}-CH_3), 1.01 (s, 3 H, C_5'-CH_3), 0.92–0.70 (d, d, d, d, 12 H, C_4-CH_3, C_6-CH_3, C_{14}-CH_3, C_{20}-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.62, 174.30, 132.52, 129.38, 97.05, 86.84, 85.59, 83.64, 81.41, 79.14, 76.14, 72.84, 51.37, 44.48, 42.48, 42.06, 41.08, 40.96, 40.35, 40.27, 40.22, 39.80, 34.02, 32.77, 32.46, 31.85, 30.98, 30.54, 29.81, 29.68, 28.09, 27.58, 25.35, 23.40, 19.61, 19.55, 19.05, 18.60, 18.43, 17.53, 12.82; $[\alpha]_D$ = −12.3° (*c* 0.43, CH_2Cl_2). Anal. Calcd for $C_{42}H_{74}O_9$: C, 69.77; H, 10.32. Found: C, 69.72; H, 10.13.

Ionomycin Calcium Salt (1). To a stirred solution of 16.2 mg (22.4 μmol) of ionomycin methyl ester **59** in freshly distilled dimethoxyethane (4.0 mL) was added 0.5 mL of water and 1.0 mL (1.0 mmol) of 1 N aqueous LiOH. The reaction temperature was held at 25 °C for 45 min (a fine precipitate formed after 10 min); the reaction mixture was then added to pH 7 aqueous phosphate buffer (40 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo. The free ionomycin ligand thus obtained was employed in the next experiment without purification.

To a solution of ionomycin **1** (prepared in the previous experiment) in CH_2Cl_2 (10 mL) was added 10 mL of a pH 9 buffered aqueous calcium chloride solution.[81] The resulting two-phase system was vigorously stirred for 4 h at 25 °C; the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to afford an off-white solid. Flash chromatography (2 g of silica, EtOAc followed by acetone) afforded 15.3 mg (92% yield overall from **59**) as a white solid: mp 196–197 °C; R_f 0.14 (4% MeOH/CH_2Cl_2); IR ($CHCl_3$) 3600–3150 (br), 2980, 2940, 2880, 2850, 1613, 1560, 1505, 1467, 1445, 1380, 1325, 1175, 1117, 1085, 1058 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, *c* 18 mg/mL) δ 5.80–5.57 (m, 2 H, C_{16}-*H*, C_{17}-*H*), 5.41 (s, 1 H, C_{10}-*H*), 4.78 (q, 1 H, C_5''-C*H*), 3.83 (m, 1 H), 3.60

(m, 1 H), 3.37 (dd, 1 H), 3.28 (dd, 1 H), 2.63–0.76 (m, 32 H, C_2-H's, C_3-H's, C_4-H, C_5-H's, C_6-H, C_7-H's, C_8-H, C_{12}-H, C_{13}-H's, C_{14}-H, C_{15}-H's, C_{18}-H, C_{20}-H, C_{22}-H's, C_3'-H's, C_4'-H's, C_3''-H's, C_4''-H's, OH). 1.29 (d, 3 H), 1.25 (d, 3 H). 1.21 (d, 3 H), 1.19 (d, 3 H), 1.15 (d, 3 H), 1.12 (d, 3 H), 1.09 (s, 3 H), 1.08 (d, 3 H), 0.88 (s, 3 H), 0.61 (d, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, c 10 mg/mL) δ 195.31, 193.69, 182.71, 131.94, 130.66, 100.53, 87.46, 84.45, 82.82, 82.79, 80.89, 76.69, 69.57, 46.86, 42.85, 42.07, 41.81, 41.47, 40.50, 39.95, 39.64, 39.48, 36.59, 34.29, 33.59, 32.99, 32.44, 28.99, 28.52, 27.90, 26.44, 26.34, 23.53, 21.75, 21.17, 21.01, 19.85, 19.45, 19.40, 18.46, 12.20; $[\alpha]_D$ = +31.5° (c 0.232, MeOH). The ultraviolet light absorption spectrum (in 3% aqueous 0.1 M calcium chloride/MeOH) has a maximum at 294 nm. This product co-eluted with an authentic sample of the calcium salt of ionomycin on reverse-phase HPLC (Vydac reverse-phase C_{18} column, 3% 0.1 M aqueous calcium chloride/MeOH, flow rate 2.0 mL/min, t_r = 4.9 min). Anal. Calcd for $C_{41}H_{70}O_9Ca$: C, 65.91; H, 9.44. Found: C, 66.04; H, 9.32.

Acknowledgment. Support has been provided by the National Institutes of Health, the National Science Foundation, and Merck. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

Enzymes as Synthetic Catalysts: Mechanistic and Active-Site Considerations of Natural and Modified Chymotrypsin†

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Abstract: This paper describes the mechanistic investigation of α-chymotrypsin and [Met_{192}-sulfoxide]-α-chymotrypsin-catalyzed peptide synthesis in a kinetically controlled process (i.e., aminolysis) and the relative stabilities of both enzymes in different conditions. Partitioning parameters for various nucleophiles (including D- and L-amino acids) competing with water for the acyl enzyme intermediate were determined. These parameters provide insights into the active-site geometries of both the native and the oxidized enzymes. α-Chymotrypsin with D-isomer selectivity in the hydrolysis of α-methyl-α-nitro esters was used for the synthesis of a D-L pseudopeptide. Molecular modeling together with kinetic results was used to explain the unusual phenomena in hydrolysis and synthesis catalyzed by the native and modified enzymes. α-Chymotrypsin methylated at the ϵ_2-N of the active-site histidine was shown to be an effective catalyst for peptide synthesis in the kinetically controlled process. No peptide bond hydrolysis was observed. Energy diagrams for hydrolyses of activated substrates catalyzed by the native, the methylated, and the organic cosolvent modified enzymes are constructed to understand the effects of methylation and organic cosolvents on catalysis and binding.

In previous papers,[1-8] we have examined various enzymatic systems and attempted to assess these systems for the efficiency in synthesizing certain peptides. These enzymatic systems allow for peptide bond formation in a catalytic regimen under mild conditions, without detectable racemization, and with minimal functional protection.[9] Several problems, however, still remain that hinder the wide acceptance of enzymatic syntheses. High enzymatic specificity often limits the residues between which bonds can be synthesized. Undesired hydrolysis of peptide bonds catalyzed by the enzyme is always troublesome. The optimal conditions for synthesis can be deleterious to the stability of the enzymes, limiting their reuse as catalysts. In addition, enantioselectivity varies or may even be reversed, depending on the substrate employed[10] or the condition used.[9]

One possible solution to some of these problems lies in enzyme derivation, either through chemical or biological means. One example of the use of a derivatized enzyme has already been reported,[3] where methylation of the enzyme active-site histidine converted α-chymotrypsin to a peptide ligase. Both our work and the earlier kinetic work on this protein[11-13] demonstrated that after the methylation the acyl donor binding site (the S_1 subsite) and the nucleophile binding site (the S_1' subsite, see below) are unchanged. The methylated chymotrypsin has been used as a catalyst for synthesis of peptides in a kinetic approach (i.e., aminolysis of amino acid or peptide esters).[3]

To investigate the kinetics of enzyme-catalyzed peptide synthesis, a technique for quantifying the efficiency of amino acid nucleophiles in a kinetic approach is used to examine the reaction of acyl intermediate with available nucleophiles (eq 1). The efficiency of a nucleophile is determined by p as shown in eq 2, where [H] and [P] are the final concentrations of the hydrolysis product (acid) and peptide product, respectively, and [N] is the nucleophile concentration. Determination of p for a given nucleophile at various concentrations allows for the calculation of a partition ratio for the nucleophile, as well as an affinity constant of the nucleophile for the enzyme. Knowing these parameters for different enzyme derivatives also allows for mapping of small

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† This research was supported by NSF Grant CHE 8806182 and DOE (DE-AC0376SF00098) to C.H.W. and Welch Foundation Grant A-328 to E.F.M. A portion of this paper has been taken from the Ph.D. dissertation of J.B.W. from the Department of Chemistry, Texas A&M University.

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0002-7863/90/1512-5313$02.50/0