Thus, the conduction seems to occur at a rate governed by both the segmental mobility of side chains and the ion–dipole interactions, although ion–ion interactions will become important at higher concentrations of salt.[1,6-8]

Conclusions

The complexes of new polyelectrolytes carrying a pendant oligo(oxyethylene)cyclotriphosphazene and $LiClO_4$ have high ionic conductivities at ambient temperatures. The conductivities of the complexes are predominantly governed by the ion–dipole interactions and the segmental mobility of side chains without receiving any restriction of the mobility of backbone. In addition, it is suggested that the morphology of host polymer also influences conductivity. The effectiveness of the mobility of the backbone on the conductivity has been discussed previously.[1] This paper, however, offers the evidence that other structural factors rather than the mobility of the main chain is a key for a successful polymeric solid-state ionic conductor. The polycascade electrolyte has many advantages, i.e., a fast ion transport, a small conductivity temperature dependence, and a electrochemically stable polystyrene backbone, and is a good candidate for practical devices. Further study based on the concept described above is now in progress.

Acknowledgment. We thank Nihon Soda Co. for a generous gift of hexachlorocyclotriphosphazene.

Synthetic Studies in the Lysocellin Family of Polyether Antibiotics. The Total Synthesis of Ferensimycin B

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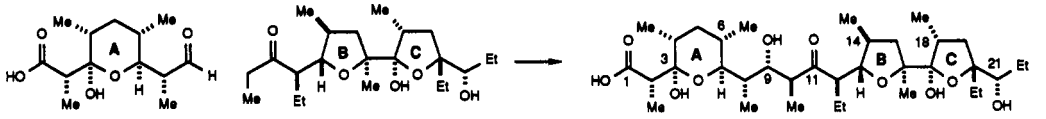
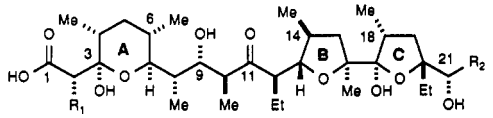
Abstract: A convergent asymmetric synthesis of the polyether antibiotic ferensimycin B has been completed. Chiral enolate bond constructions were employed to establish seven of the 16 stereocenters of the subunits **35** and **52**, which comprise the C_1–C_9 and C_{10}–C_{23} portions of ferensimycin B. The stereogenic centers at C_3, C_4, C_9, C_{10}, C_{16}, C_{17}, and C_{18} were incorporated through internal asymmetric induction, while those at C_{20} and C_{21} were established by using asymmetric epoxidation methodology. In this transformation, a vanadium-catalyzed internal epoxidation of a bis-homoallylic alcohol was employed to relay chirality from the C_{13} to the C_{16} oxygen-bearing stereocenter. A final aldol addition reaction on intermediates devoid of protecting groups united the fragments **52** and **35** to provide synthetic ferensimycin B, whose absolute configuration was found to be



52 **35** *Ferensimycin B*

the same as that of the closely related ionophore lysocellin. This synthesis thus establishes the absolute configuration of ferensimycin B.

Recent studies from this laboratory have described asymmetric syntheses of some of the principal representatives of the ionophore class of polyether antibiotics.[3] The present investigation describes the synthesis of ferensimycin B (**1a**), a member of the lysocellin family of ionophores. No prior synthesis activities have addressed this family of natural products.



Ferensimycin B **1a**: R_1 = Me; R_2 = Et

Ferensimycin A **1b**: R_1 = Me; R_2 = Me

Lysocellin **1c**: R_1 = H; R_2 = Et

In the construction of complex organic molecules, the synthesis plan frequently evolves from advances made in the synthesis of related structures that share some common architectural element. In this regard, ferensimycin shares common structural features with both lonomycin C (**2b**),[4] a target of current interest, and X-206 (**3b**),[5] a molecule whose synthesis has recently been realized.[3b] To illustrate this point, the insight gained in the construction of the γ- and δ-lactols found in X-206[3b] has proven to be instrumental in the design of the present ferensimycin synthesis. Similarly, in our ongoing efforts to develop a synthesis of lonomycin C,[6] the experience gained in the construction of the sensitive ring A, the carboxyl terminus, and, in particular, the potentially labile stereogenic center at C_2 of ferensimycin has proven to be invaluable in the ongoing development of a route to this latter

[†] Present address: Department of Chemistry, Duke University, Durham, NC.

(1) National Institutes of Health Postdoctoral Fellow.
(2) National Science Foundation Predoctoral Fellow, 1986–1989.
(3) (a) Calcimycin (A23187): Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–6791. (b) X-206: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. (c) Ionomycin: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.
(4) (a) Otake, N.; Koenuma, M.; Miyamae, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1975**, 4147–4150. (b) Riche, C.; Pascard-Billy, C. *J. Chem. Soc., Chem. Commun.* **1975**, 951–952.
(5) Blount, J. F.; Westley, J. W. *J. Chem. Soc., Chem. Commun.* **1975**, 533.
(6) Evans, D. A.; Sheppard, G. S. *J. Org. Chem.* **1990**, *55*, 5192–5194.

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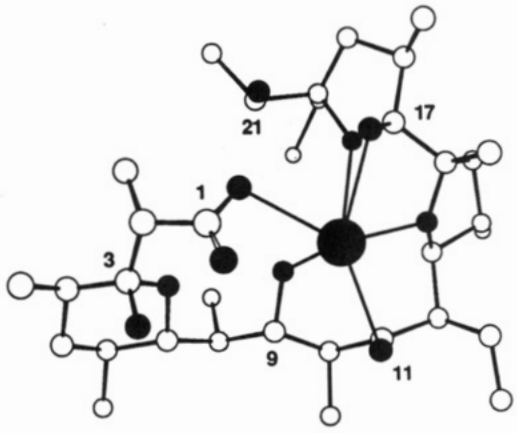
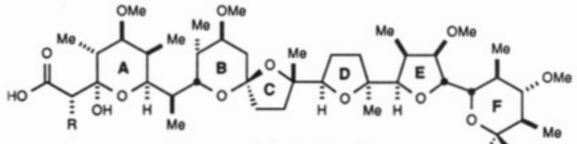
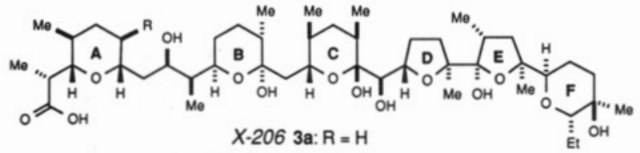


Figure 1. X-ray structure of ferensimycin A thallium(I) salt.

target structure. Thus, the current study has served as a bridge for the evolving methodology needed for the construction of complex ionophore natural products. The following discussion describes our efforts to develop a stereoselective synthesis of ferensimycin B.



Lonomycin A **2a**: R = H
Lonomycin C **2b**: R = Me



X-206 **3a**: R = H
Alborixin **3b**: R = Me

Background. Lysocellin (**1c**), the first member of this family of natural products, was obtained from cultures of *Streptomyces cacaoi* in 1975.[7] These studies established the relative and absolute configuration of the lysocellin silver salt by X-ray crystallography. Ferensimycins B (**1a**) and A (**1b**) were subsequently isolated from the fermentation broth of *Streptomyces* sp. No. 5057[8] and were found to exhibit antibacterial activity similar to lysocellin. In this study, the structures of the ferensimycins were deduced by NMR analysis, and the stereochemical assignments were made by analogy to the lysocellin structure. Independently, Westley and co-workers at Hoffmann-La Roche also isolated ferensimycin A and determined its structure by X-ray diffraction of the thallium(I) salt.[9] This group has also recently reported the X-ray structures of several additional lysocellin analogues.[10]

The metal-ligating sites in both lysocellin and the ferensimycins include the carboxyl terminus as well as the C_9, C_{11}, C_{13}, and both C_{17} oxygen substituents, as is evident from the X-ray structure of ferensimycin A (Figure 1). Additional stabilization of the metal complex is provided by internal hydrogen bonding between the carboxyl and the C_{21} hydroxyl moieties. Another hydrogen bond is also evident between the carboxyl and C_3 lactol functional groups. The inwardly turned oxygen functionality forms a well-defined coordination sphere for the ion, while the hydrocarbon backbone presents a hydrophobic exterior to the solvent. The ability of the ionophores to complex and transport metal ions in nonpolar media is the basis of their antibiotic activity.

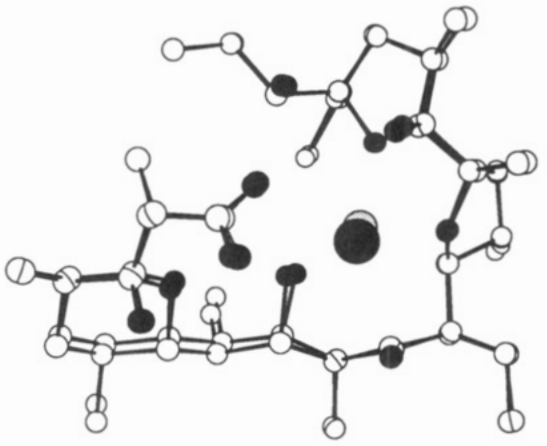
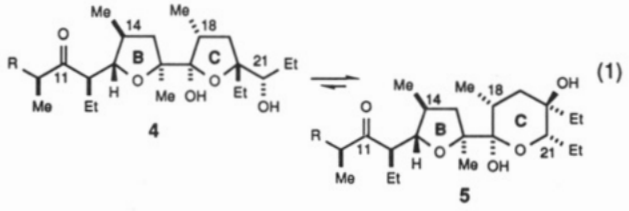


Figure 2. Superposition of ferensimycin–thallium(I) and lysocellin–silver(I) complexes.

Although the X-ray structure for ferensimycin B is not available, the nearly exact superposition (Figure 2) of the X-ray structures of the ferensimycin A thallium(I) salt and the silver(I) salt of lysocellin clearly illustrates the remarkable structural homology that is probably shared by all members of this family. In this comparison it is noteworthy that it is the position of the metal ion, rather than the conformation of the ligand, that adjusts to the alteration in the size of the ion.

Degradation Studies. In conjunction with the development of a synthesis of either lysocellin or the ferensimycins, we needed to define conditions for dealing with the sensitive functionality present in these targets. Unfortunately, no degradation or analogue synthesis activities have been reported for the ferensimycins, although selected transformations have been documented for lysocellin. Most significantly, although the metal carboxylate complexes of lysocellin are quite stable, the free ligand as its carboxylic acid reportedly undergoes successive decarboxylation as well as ring-chain tautomerization of the ring-C lactol portion of the structure (eq 1); however, these transformations have not been rigorously documented in the literature with either experimental detail or spectroscopic data.[7b]



(1)

4 **5**

Otake and co-workers have examined several important lysocellin transformations.[11] This study reports that **4** (R = H) can be prepared through alkali-induced retro-aldol cleavage of lysocellin in analogy with the related degradation reported for lasalocid,[12] and that the analogous isomerization to **5** (R = H) can be effected in refluxing methanol in the presence of catalytic quantities of acetic acid. For several reasons, we felt that the structure of **5** (R = H) was not completely secure. First, in the mass spectrometric analysis of both isomers, a parent ion for the anticipated structure was not observed for either entity, and the structural assignment for **5** (R = H) was extrapolated from the M–H_2O ion fragment. We felt that the spectroscopic data was also consistent with internal ketal **6**. Secondly, if the structure of the ring-C ring-chain tautomer were **5** as claimed, then it is somewhat surprising that lactol methyl ethers such as **7** were not

(7) (a) Otake, N.; Koenuma, M.; Kinashi, H.; Sato, S.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1975**, 92–93. (b) Koenuma, M.; Kinashi, H.; Otake, N.; Sato, S.; Saito, Y. *Acta Crystallogr., Sect. B* **1976**, *32*, 1267–1269. (c) Ebata, E.; Kasahara, H.; Sekine, K.; Inoue, Y. *J. Antibiot.* **1975**, *28*, 118–121.

(8) Kusakabe, Y.; Mizuno, T.; Kawabata, S.; Tanji, S.; Seino, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1119–1129.

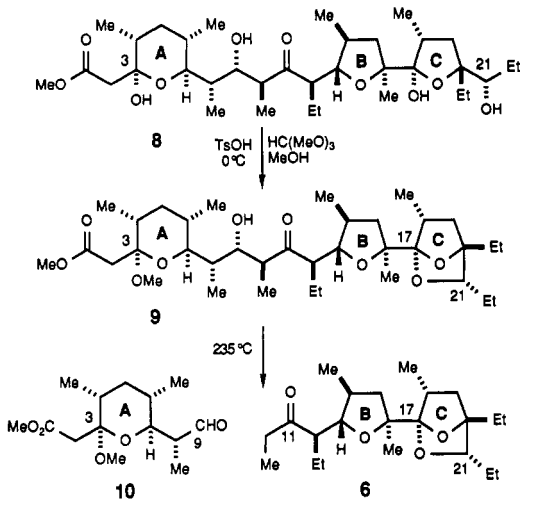
(9) Private communication from John W. Westley. The authors wish to thank Dr. Westley for supplying the X-ray coordinates for ferensimycin A.

(10) Westley, J. W.; Liu, C.-M.; Blount, J. F.; Todaro, L.; Sello, L. H.; Troupe, N. *J. Antibiot.* **1986**, *39*, 1704–1711.

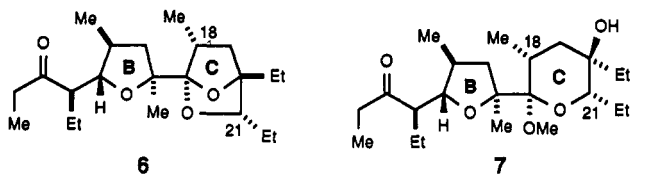
(11) Koenuma, M.; Otake, N. *J. Antibiot.* **1977**, *30*, 819–828.

(12) Westley, J. W.; Evans, R. H., Jr.; Williams, T.; Stempel, A. *J. Chem. Soc., Chem. Commun.* **1970**, 71–72.

Scheme I



produced under the conditions of the isomerization (vide infra). Due to the fact that structures such as **6** and **7** appeared to be attractive intermediates in the synthesis plan, a resolution of the issues raised by the Otake study[11] was undertaken.



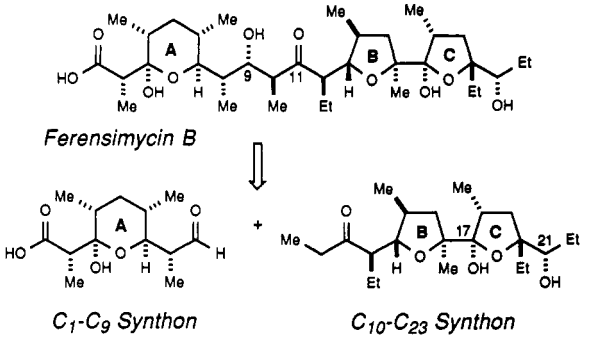
Since intermediates **6** and **7**, which are common to both lysocellin and ferensimycin B, might be produced through retro-aldol cleavage of either structure, we elected to degrade an available sample of lysocellin.[13] Transformation of the lysocellin sodium salt, via the free acid, to the derived methyl ester **8** was carried out with diazomethane according to literature precedent.[11] Attempted protection of the lactol functionality at C_3 and C_{17} (MeOH, $CH(OMe)_3$, TsOH) resulted in the formation of **9** (46% from **1c**), where the C_3 lactol was derivatized as expected while the C_{21} hydroxyl cyclized on to the C_{17} lactol center to form the ring-C bicyclic ketal. Subsequent pyrolytic cleavage (235 °C, 25 Torr, 30 min)[14] of **9** afforded the illustrated retro-aldol fragments **10** and **6**, in 87% and 63% yields, respectively (Scheme I).[15]

On the basis of these results, we are no longer confident that the acid-catalyzed ring-C tautomerization reported by Otake is taking place with either lysocellin methyl ester **8** or the ethyl ketone **4** (R = H) (eq 1). We speculate that the compound claimed to be **5** (R = H) might well be the bicyclic ketal **6**.[16] It is noteworthy that Westley and co-workers have recently isolated several ionophores obviously related to lysocellin that possess this ring-C bicyclic ketal structure.[10]

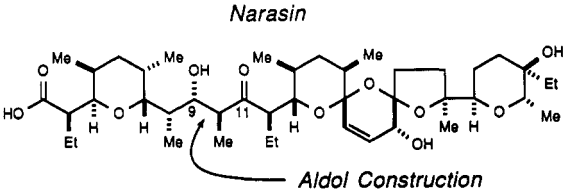
Synthesis Plan

The ferensimycins are more challenging synthesis targets than lysocellin due to the presence of the inherently labile C_2 methyl-bearing stereocenter. In view of our parallel interest in developing a synthesis of lonomycin C, we therefore selected ferensimycin B as the primary objective with lysocellin as a secondary target in the event that complications arose in the synthesis of the more complex structure. The C_9–C_{10} aldol disconnection of

Scheme II



ferensimycin B conveniently divides the molecule into subunits of comparable complexity (Scheme II). At the outset, we felt that bicyclic ketal **6** would be an attractive intermediate since the lactol and hydroxyl functionalities present in the structure were conveniently masked. In the anticipated aldol assembly of these fragments, an important stereochemical precedent may be found in the elegant synthesis of narasin by Kishi and co-workers.[17] In this polyether, similarly configured in the C_1–C_{12} region, an aldol addition was employed to generate the C_9–C_{10} bond. Although the anti arrangement at C_9 and C_{10} differs from that which would be predicted on the basis of the generally accepted chair transition state for the aldol reaction of the presumed *Z* enolate, high anti stereoselectivity was observed when the free acid was employed as the aldehyde component. On the other hand, the corresponding C_1 ester derivative afforded a mixture of narasin diastereomers. These data suggest that additional organizational features, including substrate chelation, may contribute to the stereochemical course of the reaction. Presumably, metal ligation via a transition state different from the traditional Zimmerman–Traxler model[18] is responsible for the desired anti stereochemistry.



Accordingly, the strategy for the aldol assemblage of ferensimycin B was adopted wherein the maximum number of ionophore ligation sites (Figure 1) might be left available for metal ion organization during the aldol reaction. Given the postulate that these ionophores are designed with "optimized configurations" as a result of evolutionary pressure,[19] we anticipated that the correct aldol adduct might be obtained through selection of the correct organizing metal enolate combined with reacting partners possessing the correct available ligation sites.

In addition to the expectation of achieving kinetic control in an appropriately configured aldol union of the fragments, we also anticipated that the desired configuration at the C_{10} methyl-bearing stereocenter might be established by thermodynamic equilibration of the undesired syn aldol diastereomer having the desired C_9 hydroxyl-bearing stereocenter. Still has shown that some of the unnatural isomers of lasalocid can be equilibrated to the desired configuration in the presence of an appropriate metal ion.[19] We felt that this equilibration procedure might also be applicable to ferensimycin B, since both of these ionophores are selective for divalent cations. On the basis of the Still precedent, the challenges associated with the design of the desired aldol union are thus reduced to the establishment of the appropriate C_9 hy-

(13) We wish to express our gratitude to Professor Noboru Otake, Institute of Applied Microbiology, University of Tokyo, for supplying us with authentic samples of both ferensimycin B and lysocellin.

(14) Westley, J. W.; Evans, R. H., Jr.; Williams, T.; Stempel, A. *J. Org. Chem.* **1973**, *38*, 3431–3433.

(15) The experimental details of this series of transformations may be found in the supplementary material.

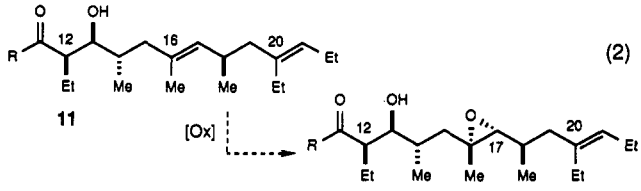
(16) We corresponded with Professor Otake to get a sample of the material that he assigned as **5** (R = H). Unfortunately, his material had decomposed.

(17) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. *IUPAC Frontiers of Chemistry*; Laidler, K. L., Ed.; Pergamon Press: Oxford, 1982; pp 287–304.

(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

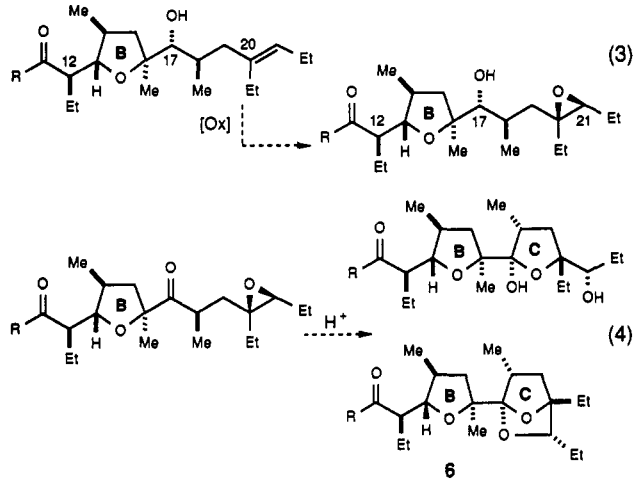
(19) Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, *28*, 2817–2820.

droxyl-bearing stereocenter in the aldol step.



(2)

The C_{10}–C_{23} Subunit. The initial approach to the C_{10}–C_{23} fragment was modeled after the ionophore's proposed biosynthesis according to the Cane, Celmer, Westley Model.[20] The asymmetric synthesis of the illustrated diene precursor **11** using chiral enolate methodology would be followed by iterative directed vanadium bis-homoallylic alcohol epoxidations (eqs 2 and 3), according to the precedent established by Kishi and co-workers.[21] The completion of this fragment would rely on the illustrated acid-catalyzed ring closure to either the lactol or bicyclic ketal **6** (eq 4). Although **6** had been prepared in the microscale degradation of lysocellin (vide supra), its utility as a viable intermediate in the synthesis plan had not been examined.



(3)

(4)

6

The successful synthesis of the C_{10}–C_{23} fragment, as the bicyclic ketal **6**, is outlined in Scheme III.[15] The backbone of this synthon was assembled through consecutive alkylation[22] reactions to produce **12** and **13** in good overall yields. In staging the second alkylation, the procedure of Landauer and Rydon was employed to construct the labile allylic iodide, which was utilized in the subsequent alkylation without additional purification.[23] This method was found to afford minimal olefin isomerization (E:Z ≈ 95:5), although attempted chromatographic purification of this iodide resulted in extensive decomposition. The subsequent aldol addition[24] was carried out under normal conditions to afford an 82% yield of the aldol adduct **11a** contaminated by less than 4% of an unidentified isomer that was removed at a later stage in the synthesis. Extensive studies on the directed epoxidation of **11a** with anhydrous *tert*-butyl hydroperoxide and vanadyl acetylacetonate[25] (0.1 equiv) established that the anticipated epoxidation proceeded stereoselectively with the desired sense of asymmetric induction.[26] The liability associated with this oxidation was revealed in attempts to drive the reaction to completion without incurring either overoxidation or premature epoxy alcohol cyclization. In the route that was chosen for development, **11a** was transformed to the derived ethyl ketone **11b** via the Weinreb amide[27,28] in good overall yield.

Vanadium-catalyzed epoxidation of **11b** afforded the cyclized adduct **15**, via the intermediacy of epoxy alcohol **14**, in 70% yield after chromatographic purification. From **15**, two oxidation sequences were then evaluated. The vanadium-catalyzed epoxidation of **15**, although appealing, proved to be impractical since the intervening epoxyalcohol cyclization could not be effectively suppressed. Alternatively, **15** was oxidized to the derived ketone and the remaining double bond was epoxidized with *m*-chloroperbenzoic acid to give the epoxy ketones **17** and **18**. These diastereomers were cyclized with PPTS (MeOH, 0 °C) to give a separable mixture of the desired bicyclic ketal **6** along with its diastereomer **19** (**6**:**19** = 1:1.5). The stereochemical assignments of each of these diastereomeric ketals were unambiguously determined by NMR spectroscopy. Finally, the bicyclic ketal **6** proved to be identical with the degradation product derived from lysocellin (Scheme I).

Despite the appeal of this biomimetic route, it ultimately proved to be impractical. First, the vanadium-catalyzed epoxidation of **15** could not be effectively executed without the intervention of the epoxy alcohol cyclization. Secondly, epoxidation to form **17** and **18** proceeded with poor selectivity, and the products spontaneously cyclized to provide the bicyclic ketals **6** and **19**. Most importantly, all attempts to reopen the bicyclic ketal **6** to a more suitably protected lactol ether with a multitude of reagents failed. Thus, the optimistic projection that the bicyclic ketal **6** might be a useful intermediate proved to be false. In retrospect, this exercise underscored the importance of designing a route to this synthon that would avoid the use of acid-labile protecting groups whose removal might result in irreversible internal ketal formation.

The alternate, successful approach to the C_{10}–C_{23} fragment is illustrated in Scheme IV. Examination of **4** as its ring-opened tautomer reveals an enolate-derived disconnection of the C_{18}–C_{19} bond to give the illustrated ring-B synthon **20** along with epoxy alcohol **21**. The major concern with this disconnection was that appropriate control of the C_{18} methyl-bearing stereocenter must be addressed in the assemblage process. Our optimism for anticipating the desired stereochemical outcome of this reaction was based on a related transformation developed in the synthesis of the polyether antibiotic X-206 (Scheme V).[3b] To date, we have accumulated insufficient data to fully identify the stereochemical control elements associated with the latter bond construction since such reactions are double stereodifferentiating in nature.[29]

Two additional issues were raised by the projected assemblage of subunits **20** and **21**. The first was the problem of carbonyl differentiation, while the second dealt with the intrinsically low reactivity of epoxide electrophiles in enolate bond constructions. In addressing the first of these issues, we chose to exploit the analogy provided above (Scheme V) wherein the latent C_{11} carbonyl group was protected as its tetrahedral hydroxamate intermediate.[28] In this instance we were able to effect hydrazone metalation and subsequent epoxide alkylation in a transformation that requires careful control of the reaction parameters.[3b]

In analogy with the previous approach to this fragment (Scheme III), chiral enolate and hydroxyl directed epoxidation reactions were employed in the construction of the ring-B synthon **20** (Scheme VI). The synthesis began with a Johnson[30] ortho ester

(20) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594–3600.

(21) (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935. (b) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2741–2744.

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

(23) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224–2234.

(24) 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 ref 31.

(25) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63–74.

(26) Mathre, D. J. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1985.

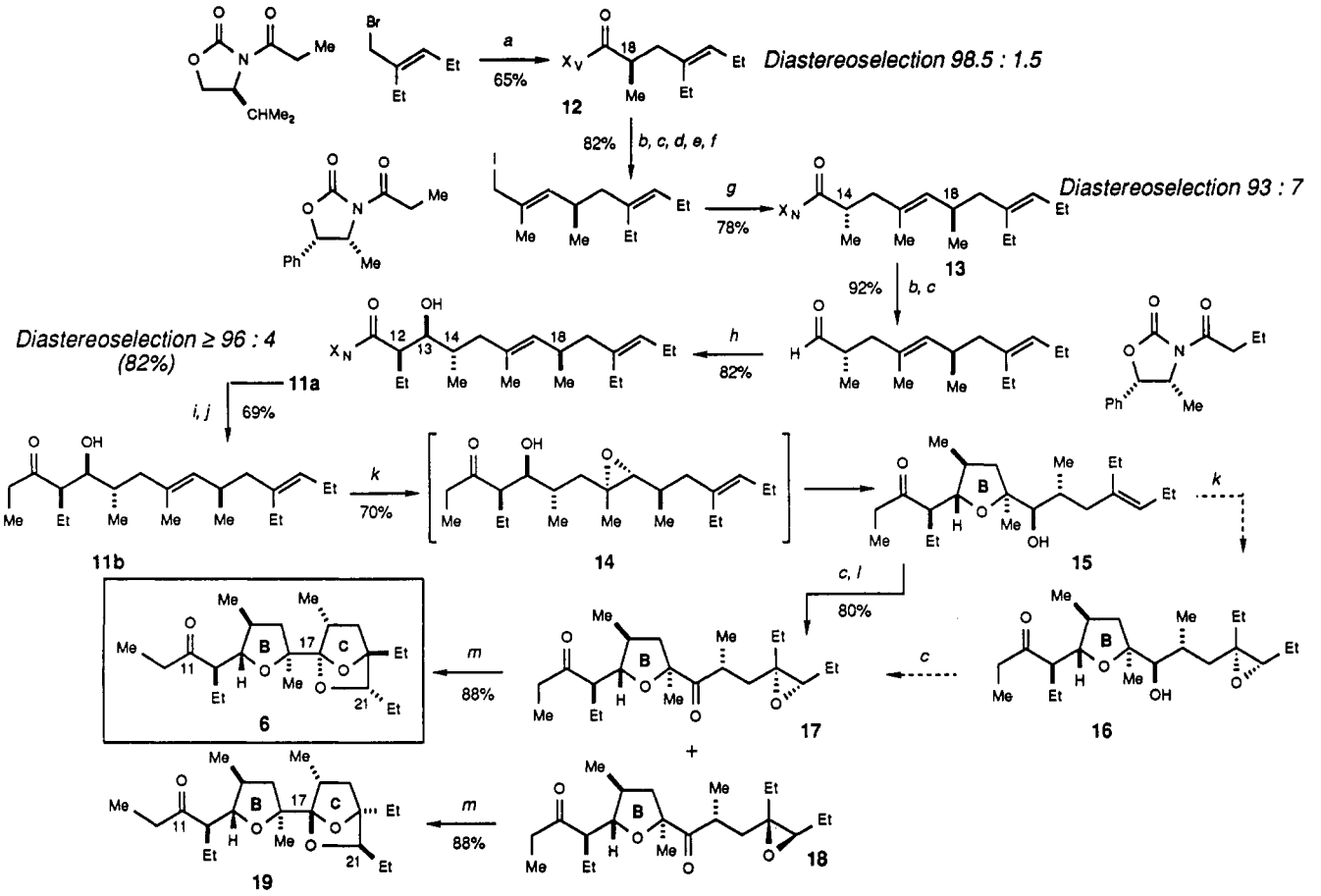
(27) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993. For precise details for carrying out related transformations, see ref 3b.

(28) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3819. (b) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676–678.

(29) For a relevant example of asymmetric induction in the reaction of a chiral epoxide with metal enolates, see: Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245–4248.

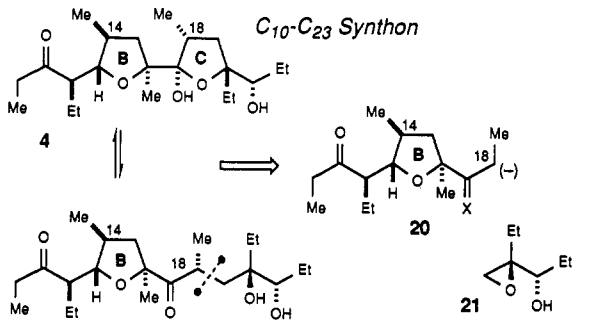
(30) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.

Scheme III



[a] LDA, 2 equiv of R-Br, −35 °C, 18 h. [b] $LiAlH_4$, 0 °C, 3 h. [c] $(COCl)_2$, Et_3N, DMSO. [d] $EtO_2CC(Me)=PPh_3$, CH_2Cl_2, 40 °C, 12 h. [e] DIBAL, CH_2Cl_2, −78 to −20 °C, 2 h. [f] $(PhO)_3PMe^+I^-$, DMF, 20 °C, 20 min. [g] NaHMDS, 3 equiv of enolate/equiv of R-I, −30 °C, 4 h. [h] Bu_2BOTf, Et_3N, 1.2 equiv of enolate per equiv of RCHO, −78 → 0 °C, 2.5 h. [i] MeONHMe-HCl, Me_3Al, CH_2Cl_2. [j] EtMgBr, THF, 0 °C, 18 h. [k] $VO(acac)_2$, TBHP, NaOAc, 25 °C, 1.5 h. [l] *m*-DPBA, 0 °C, 4 h. [m] PPTS, MeOH, 0 °C.

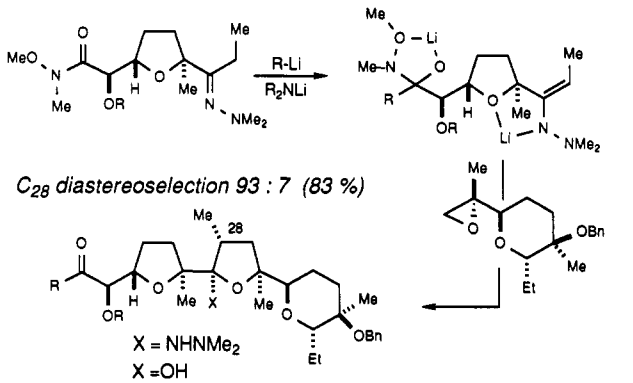
Scheme IV



Claisen rearrangement on 2-methyl-1-penten-3-ol to give ester **22a**, which was saponified to afford the derived acid in 71% overall yield. Acylation of the lithium salt of phenylalanine-derived oxazolidinone **23**[31] with the mixed pivaloyl anhydride derived from **22b** provided imide **22c** as a crystalline solid, mp 144.5–145.5 °C. Subsequent methylation of the enolate derived from this substrate secured the C_{14} methyl-bearing stereocenter. This enolate was generated by consecutive treatment of **22c** with sodium hexamethyldisilazide (NaHMDS) and methyl iodide (2.5 h, −78 °C) to furnish α-methylcarboximide **24** as a 91/9 mixture of diastereomers as determined by capillary GC analysis. The major diastereomer was obtained in 82% yield after preparative HPLC purification.

Reductive removal of the chiral auxiliary with lithium aluminum hydride followed by Swern[32] oxidation of the resulting alcohol **25a** afforded the labile aldehyde **25b** in a combined yield of 82%. This aldehyde was immediately employed in the subsequent aldol reaction with imide **26**, resulting in the construction of the C_{12} and C_{13} stereocenters. The boron aldol addition[24] between butyrate imide **26** and aldehyde **25b** provided aldol adduct **27** (84% yield, mp 151–153 °C) in greater than 99% diastereomeric purity as determined by capillary GC analysis. This series of reactions completed the necessary bimolecular asymmetric bond constructions required for the ring-B synthon.

Scheme V

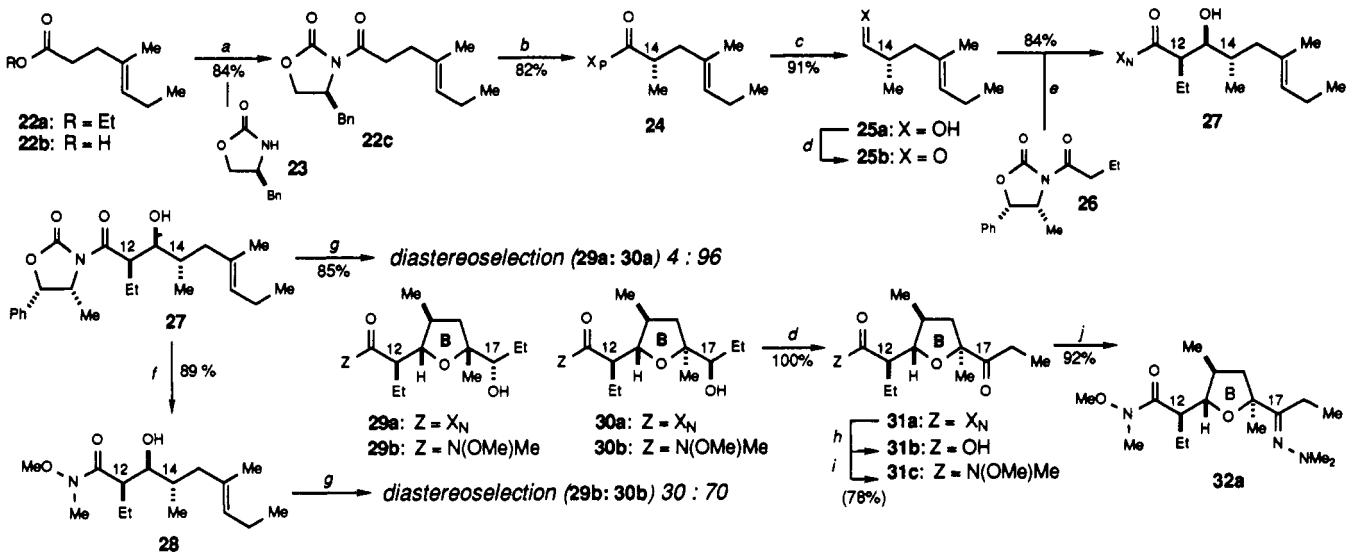


At this juncture, the option of elaborating the C_{11} terminus to the requisite ethyl ketone, either before or after the vanadium-catalyzed epoxidation sequence, was considered. Although amide

(31) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 83–91.

(32) Omura, K.; Swern, D. A. *Tetrahedron* **1978**, *34*, 1651–1660.

Scheme VI



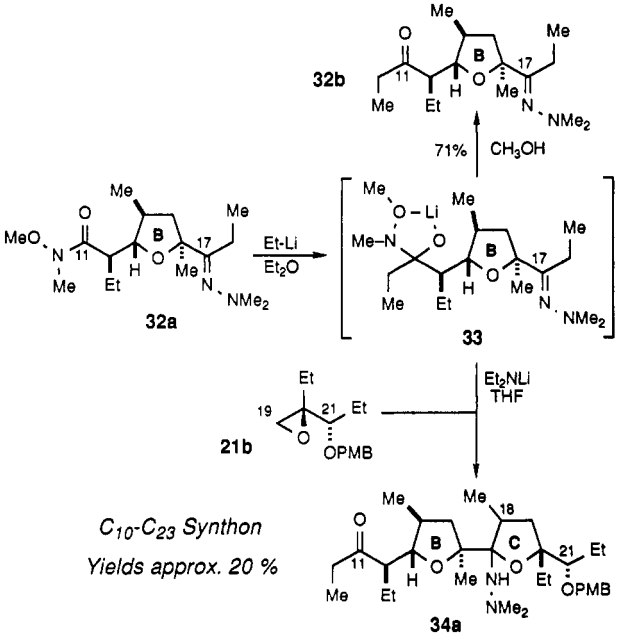
[a] Me_3CCOCl, Et_3N, Li-**23**. [b] NaHMDS, MeI, −78 °C, 2.5 h. [c] $LiAlH_4$, THF, 0 °C, 3.5 h. [d] $(COCl)_2$, Et_3N, DMSO. [e] Bu_2BOTf, Et_3N, 1.5 equiv of enolate/equiv of RCHO, −78 → 0 °C. [f] MeONHMe-HCl, Me_3Al, THF. [g] $VO(acac)_2$, TBHP, PhH, 25 °C, 11 h; HOAc, 45 min, 25 °C. [h] LiOH, H_2O_2, THF-H_2O, 0 → 25 °C, 4 h. [i] MeONHMe-HCl, CH_2Cl_2, DMAP, $Me_2CHN{=}C{=}NCHMe_2$. [j] Me_2NNH_2, TMSCl, 25 °C, 36 h.

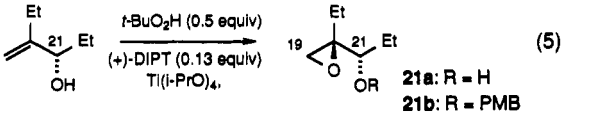
28 could have been transformed to the derived ethyl ketone prior to the epoxidation sequence without disrupting the diastereoselectivity of the oxidation (see Scheme III, **11a** → **11b** → **15**), subsequent functional group incompatibility in the hydrazone enolate/epoxide coupling ruled out this course of action. The epoxidation of bis-homoallylic alcohol **27** and subsequent acid-catalyzed ring opening of the intermediate epoxide afforded the diastereomeric tetrahydrofurans **30a** and **29a** in a 94:6 ratio (Scheme VI), from which the major diastereomer **30a** (mp 219–220 °C) was obtained in 85% yield after chromatography. The stereochemical assignment of the major product diastereomer was based on ample literature precedent[20,33] and was eventually confirmed by correlation with degradation product **6**. The hydroxamic acid derivative **28** was also prepared[27] (89%) in direct analogy to the related reaction of imide **11a** (Scheme III) and epoxidized in a similar manner but with substantially lower stereoselectivity.[21] We speculate that **28**, with its more basic carbonyl oxygen, might be functioning as a bidentate chelate during epoxidation and that, for unanticipated reasons, this chelation is deleterious to the vanadate-directed oxidation diastereoselectivity.

A subsequent Swern oxidation of **30a** provided the ring-B synthon **31a** (100%, mp 191–193 °C), which was then transformed to the hydroxamic acid derivative **31c**. Earlier studies had indicated that neither the direct transamination according to the Weinreb procedure[27] nor basic hydrolysis of imide **31a** was a viable option due to a competing reaction at the endocyclic carbonyl of the chiral auxiliary. Fortunately, the basic hydroperoxide-mediated hydrolysis[34] procedure subsequently introduced by us effected the desired hydrolysis in 86% yield. The *N*-methoxy-*N*-methylamide **31c** was then formed from the acid **31b** through the carbodiimide-derived mixed anhydride in 91% yield. Treatment of ketone **31c** with excess *N*,*N*-dimethylhydrazine in the presence of trimethylsilyl chloride afforded the hydrazone **32a** in 92% yield as a single diastereomer to complete the synthesis of the ring-B synthon.

The other coupling partner, epoxide **21a** (eq 5), was obtained from a Sharpless kinetic resolution[35] of 2-ethyl-1-penten-3-ol in 76% yield (90% ee) after purification by preparative HPLC. The derived *p*-methoxybenzyl ether **21b** was prepared in the usual fashion by alkylation of the sodium salt of **21a** with *p*-methoxybenzyl chloride (NaH, 1.4 equiv of R–Br, THF–DMF, 0 °C, 4 h, 86%).

Scheme VII





(5)

With the components **32a** and **21** in hand, we focused on their coupling (Scheme VII). As illustrated, the stable tetrahedral intermediate produced upon addition of ethyllithium to the C_{11} *N*-methoxy-*N*-methylamide moiety was intended to conveniently mask the incipient ketone during the subsequent bond construction with epoxide **21**.

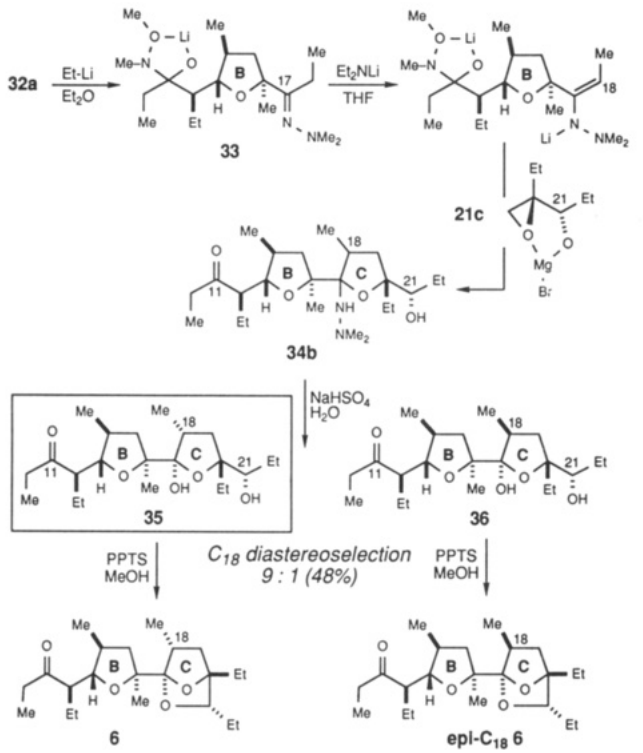
In accord with precedent, formation of the stable tetrahedral intermediate through the addition of ethyllithium to **32a** was followed by deprotonation of the C_{17} hydrazone with LDA. However, alkylation of the metalloenamine with epoxide **21** af-

(33) A closely related epoxidation was employed in the synthesis of X-206, *ref* 3b.

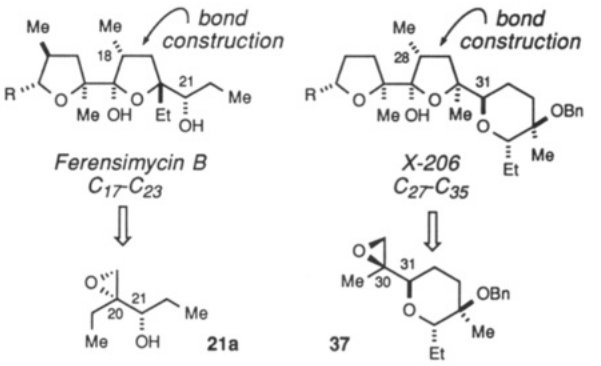
(34) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

(35) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

Scheme VIII



Scheme IX



forded only low yields of the desired C_{10}–C_{23} synthon **34a**.[15] After further investigation, several factors were found to influence the outcome of the overall process. The addition of ethyllithium to the amide **32a** was found to be solvent dependent. In diethyl ether, ethyl ketone **32b** derived from the quenching of intermediate **33** was produced in 71% yield (−78 °C, 15 min). On the other hand, the same reaction in THF suffered from the formation of multiple products arising from the apparent premature breakdown of the tetrahedral intermediate **33**. However, THF was required in the subsequent bond construction to maintain a homogeneous reaction mixture and effect hydrazone metalation[36] and alkylation with epoxide **21**. The desired bond construction was also plagued by the low reactivity of epoxide **21b** toward nucleophilic ring opening. For example, the reaction between the PMB-protected epoxide **21b** and the lithiated hydrazone was sufficiently slow enough (1–2 days, 0 °C) to preclude isolation of the adduct in good yield due to extensive decomposition of the individual components. Ultimately, conversion of the epoxide synthon into its magnesium alkoxide **21c** with ethylmagnesium bromide prior to its addition to the metalloenamine activated the epoxide toward ring opening (Scheme VIII). This procedure resulted in a substantial reaction-rate enhancement with complete consumption of the starting material occurring within 4 h at 0 °C. An analogous intramolecular Lewis acid epoxide activation has been reported by Marshall.[37]

The hydrazinyltetrahydrofurans **34b** (Scheme VIII) successfully produced upon introduction of these modifications were sufficiently labile so that effective purification was precluded. Consequently, the mixture was immediately treated with a biphasic solution of aqueous sodium bisulfate and pentane/dichloromethane (3:1 v/v) for 15 min to produce the stable lactol diastereomers. Chromatographic purification afforded diastereomers **35** and **36** in a 90:10 ratio in 48% combined yield. The only side products isolated were the related bicyclic ketals **6** and the derived C_{18} ketal diastereomer in a combined yield of 11%. The minimal amount of bicyclic ketal observed during this reaction was attributed to the short exposure time to acid and the biphasic conditions used for hydrolysis of the intermediate hydrazinyltetrahydrofurans. The ratio of diastereomers **35** and **36** was determined by conversion of the mixture to the bicyclic ketals **6** and *epi*-C_{18} **6** under nonequilibrating conditions (PPTS, MeOH, 25 °C) followed by analysis of the mixture by capillary GC. In analogous experiments carried out during the X-206 synthesis,[3b] it had been shown that ketal formation and hydrazinyl lactol hydrolysis under these conditions did not result in any measurable diastereomer equilibration. We thus speculate that the C_{18} stereocenter generated in this coupling reaction is established through the kinetically controlled alkylation of the lithiated hydrazone.

The stereochemical assignment for the C_{18}–C_{23} portion of the aldol precursor **35** was established by both homonuclear decoupling and NOE experiments on the bicyclic ketal **6**. The spectroscopic properties, optical rotation, and capillary GC retention time of synthetic **6** were compared and found to be identical with those samples obtained by degradation of natural lysocellin and with the bicyclic ketal obtained from the previously described synthesis (Scheme III). The synthesis of hydroxy lactol **35** was thus completed in 12 steps, during which eight stereogenic centers were created in an overall yield of 21%.

The metalloenamine–epoxide annelation reactions utilized in this (Scheme VIII) and the X-206 synthesis (Scheme V) provide important analogies for the synthesis of other ionophore natural products. The stereochemical aspects of these reactions are of special interest (Scheme IX). It is evident from the relevant portions of X-206 and ferensimycin B that both the C_{18} and the corresponding C_{28} stereocenters have the same absolute configuration, yet opposite relative stereochemistry with respect to the epoxide-derived stereocenters (C_{20} and C_{21} in ferensimycin B, and C_{30} and C_{31} in X-206). Although the origin of the stereoselection in the coupling process is not obvious, these experiments suggest that the control elements present in the metalloenamine are

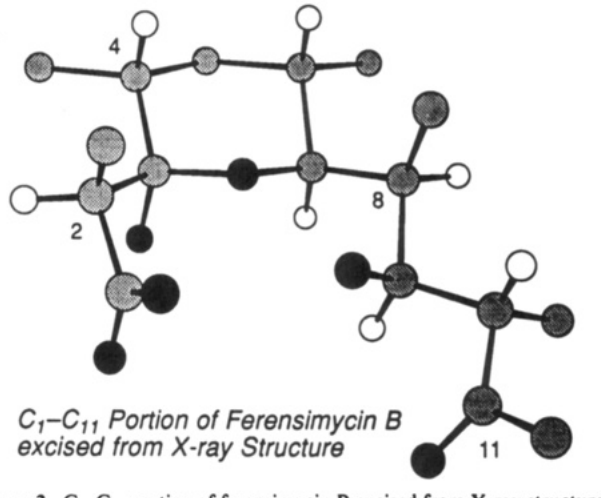
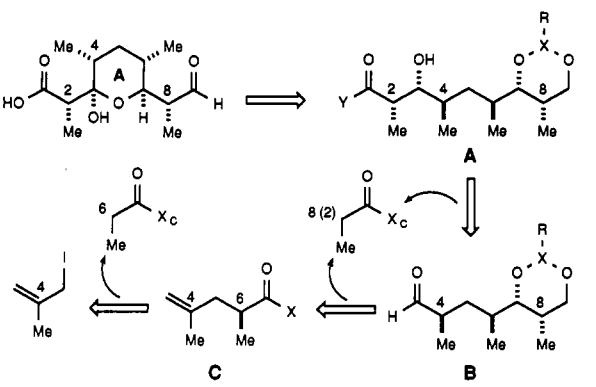


Figure 3. C_1–C_{11} portion of ferensimycin B excised from X-ray structure.

(36) For other synthetic applications of dimethylhydrazones, see: (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11–14. (b) Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078–2082. (c) Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Van Duyne, G. *J. Am. Chem. Soc.* **1984**, *106*, 4865–4869. (d) Jung, M. E.; Shaw, T. J. *Tetrahedron Lett.* **1977**, *18*, 3305–3308.

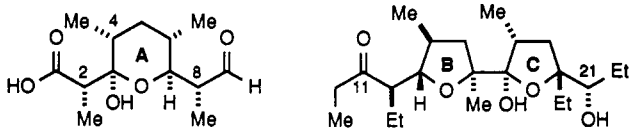
(37) Marshall, J. A.; Andrews, R. C. *J. Org. Chem.* **1985**, *50*, 1602–1606.

Scheme X



dominant to those of the epoxide in dictating the stereochemical outcome in these reactions.

The C_1–C_9 Subunit. The C_1–C_9 ferensimycin fragment contains a masked β-keto acid whose predisposition toward decarboxylation as the free acid has been documented.[7b,11] This intrinsic lability represents one of several challenges to be addressed in the synthesis of this portion of the molecule. The other principal issue to be



C_1-C_9 Synthon *C_{10}-C_{23} Synthon*

acknowledged is that of the stereochemistry of the C_2 methyl-bearing stereocenter. Inspection of the A ring of the ferensimycin–thallium(I) complex reveals that, given the orientation of the carboxyl ligand in the complex, the C_2 methyl group adopts the thermodynamically preferred configuration (Figure 3) to avoid the destabilizing syn pentane interaction with the C_4 methyl group.[38] One might further speculate that the undesired ferensimycin C_2 diastereomer might be an inferior chelating ligand due to the improper alignment of the carboxyl ligand, which should be expected to occupy the conformational space previously occupied by the methyl substituent. This line of reasoning suggests that thermodynamic considerations could be employed to establish this stereocenter, possibly under conditions where carboxyl chelation, but not decarboxylation, might be orchestrated. On the other hand, the compelling argument for attempting to establish the C_2 center under kinetically controlled conditions hinges on the resultant diastereomeric purity of synthetic intermediates incorporating this portion of the ionophore. We took the position that the latter course of action would be preferred if possible, with an equilibration strategy being a legitimate alternative in the event of a failure to achieve kinetic stereochemical control at C_2.

The chiral propionate enolate bond constructions used to establish the majority of the stereocenters in this ferensimycin synthon are illustrated in Scheme X.[39] It was our intention to establish the required stereochemical relationship at C_2 through the aldol bond construction evident in precursor A. In the elaboration of this intermediate, we hoped that a mild oxidation of the C_3 hydroxyl moiety might be designed to provide the desired β-keto acid derivative without loss of the C_2 stereocenter. The anticipated lability of this intermediate β-keto ester placed constraints on the type of 1,3-diol protecting group that could be selected for this reaction sequence.

The synthesis was initiated with the alkylation of the norephedrine-derived lithium enolate derived from **38** and methallyl iodide (2 equiv, −78 → −40 °C) to give a 96/4 mixture of diastereomers, from which **39** was isolated as a low-melting solid (mp 42–44 °C) in 73% yield after chromatography (Scheme XI). The auxiliary was then reductively removed with lithium aluminum hydride (85%) and the resulting alcohol **40a** oxidized by the method of Parikh and Doering (pyr-SO_3)[40] to afford aldehyde **40b** in 87% yield, which was employed immediately in the next step. An aldol reaction between **40b** and the boron enolate derived from **38** afforded the expected adduct **41** in 86% yield as a single crystalline diastereomer, mp 110–111 °C. Reduction of **41** with lithium borohydride proceeded in 90% yield to provide the derived diol **42a**, which was protected as the α-naphthylidene acetal **42b** (82%) when a benzene solution of the diol with 1-naphthaldehyde was treated with a catalytic amount of trichloroacetic acid in the presence of 4-Å molecular sieves.[41] The selection of this acetal protecting group was made with the hope of conferring crystallinity on subsequent intermediates containing this moiety.

On the basis of prior work from our laboratory, we were optimistic that the hydroboration of olefin **42b** would proceed selectively to establish the C_4 stereocenter with the desired sense of asymmetric induction.[42] Treatment of **42b** with thexylborane (Scheme XI) followed by an oxidative workup produced a mixture of alcohols, **43a** and its C_4 epimer, in a ratio of 84:16 as determined by capillary GC analysis. After chromatographic separation, the desired isomer was isolated in 79% yield. Since other diol-protected substrates afforded the same sense of asymmetric induction in this reaction, the assignment of the C_4 stereochemical relationship in **43a** was made by analogy.

The remainder of the carbon skeleton was assembled through a final aldol reaction between the boron enolate derived from **43c** and aldehyde **43b** to provide the crystalline adduct **44**, mp 131–133 °C, as a single diastereomer (Scheme XII). In concluding the elaboration of the synthon, a Parikh–Doering oxidation[40] of the C_3 alcohol moiety in **44** provided the desired β-keto imide **45**, mp 120–121 °C, in excellent yield with no evidence of epimerization at the C_2 methyl-bearing stereocenter. As we have demonstrated in several previous studies,[43] such dicarbonyl substrates exhibit surprisingly high barriers to enolization due to the presence of allylic strain interactions between the chiral auxiliary and the C_2 substituents, preventing the obligatory alignment of the C_1 carbonyl and α hydrogen. The A-ring lactol was then assembled when the acetal protecting group was removed by catalytic hydrogenation to provide the crystalline intermediate **46a**, mp 125.5–126.5 °C, which was transformed under mild conditions (MeOH, $CH(OMe)_3$, $ClCH_2CO_2H$, 25 °C) to the derived lactol methyl ether **46b**.[15] Strict control over ketalization conditions is required for this reaction since irreversible dehydration effectively destroys the intermediate. Experience gained in our successful synthesis of X-206[3b] provided to be invaluable in developing the proper conditions for carrying out these transformations.

Despite the efficiency of the route to **46b**, we were completely thwarted in all attempts to remove the imide auxiliary from this intermediate due to competing attack of nucleophiles at the oxazolidinone carbonyl. This obstacle befell the project prior to the development of the basic peroxide procedure for effecting such transformations.[34] In the absence of an effective method for revealing the carboxyl moiety, we elected to remove the chiral auxiliary at an earlier point in the synthesis where steric hindrance in the vicinity of the carboxyl terminus was less acute. Accordingly, the aldol adduct **44** was silylated[44] to suppress the competing retro-aldol process, and the derived imide **47** was subjected to transesterification with lithium benzyl oxide (THF, −20 °C)[22] to

(38) It is noteworthy that syn pentane interactions dictate virtually all acyclic dihedral angle relationships in this region of the molecule.

(39) For a preliminary account of this study, see: Evans, D. A.; Polniaszek, P. *Tetrahedron Lett.* **1986**, *27*, 5683–5686.

(40) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

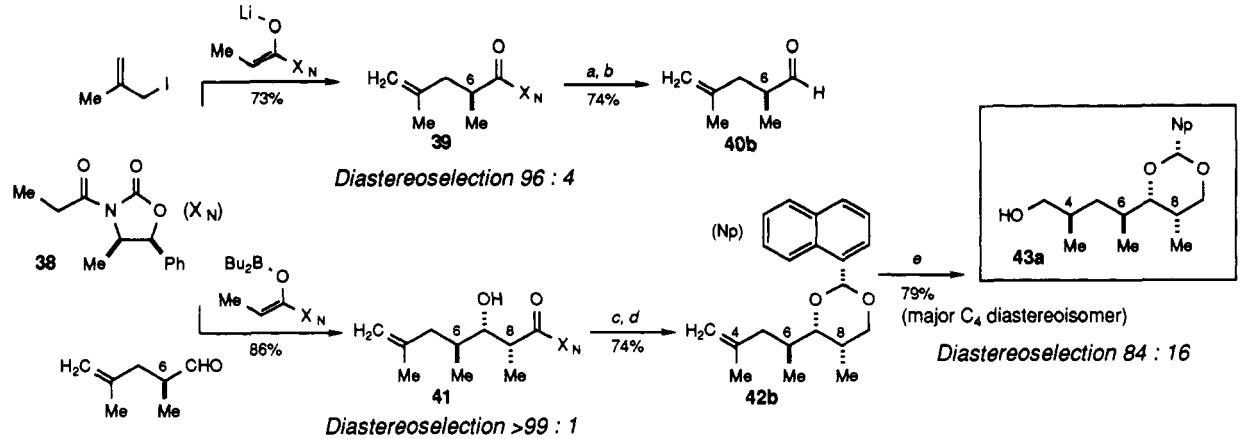
(41) Meskens, F. A. J. *Synthesis* **1981**, 501–522.

(42) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807–810. Our own analysis for the sense of asymmetric induction for this reaction has subsequently been supported by others: Houk, K. N.; Rondan, N. G.; Wu, Y-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257–2274.

(43) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. N.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.

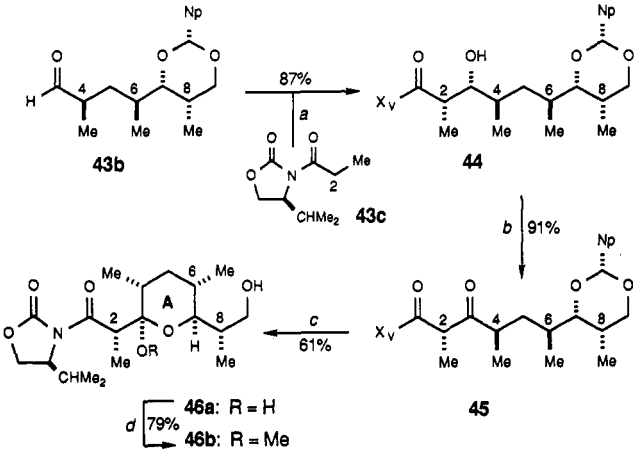
(44) Nicosia, S.; Galli, G. *Anal. Biochem.* **1974**, *61*, 192–199.

Scheme XI



[a] $LiAlH_4$, Et_2O, 0 → 25 °C, 3.5 h. [b] DMSO, SO_3–Pyr, Et_3N. [c] $LiBH_4$, THF, −30 → 0 °C, 4 h. [d] 1-Naphthaldehyde, 2 equiv, CCl_3COOH, benzene, 25 °C, 12 h. [e] Thexylborane, THF, −10 °C, 5 h; H_2O_2, $NaHCO_3$.

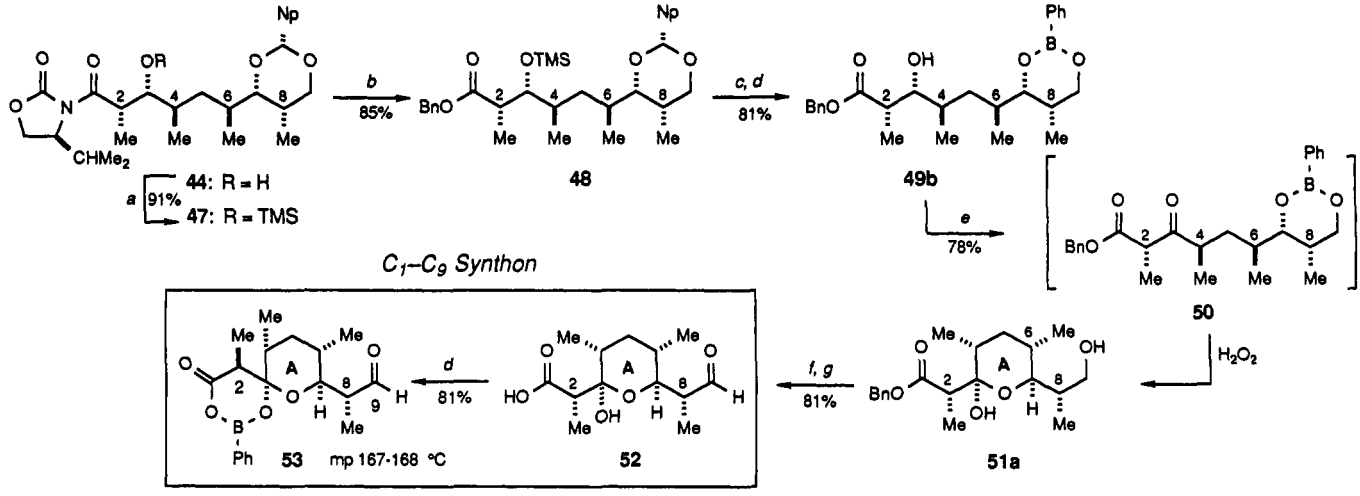
Scheme XII



[a] Bu_2BOTf, Et_3N, CH_2Cl_2. [b] DMSO, SO_3–Pyr, Et_3N. [c] Pd/C, H_2, $(COOH)_2$, EtOAc, 0 °C. [d] $ClCH_2CO_2H$, MeOH, $CH(OMe)_3$, 25 °C.

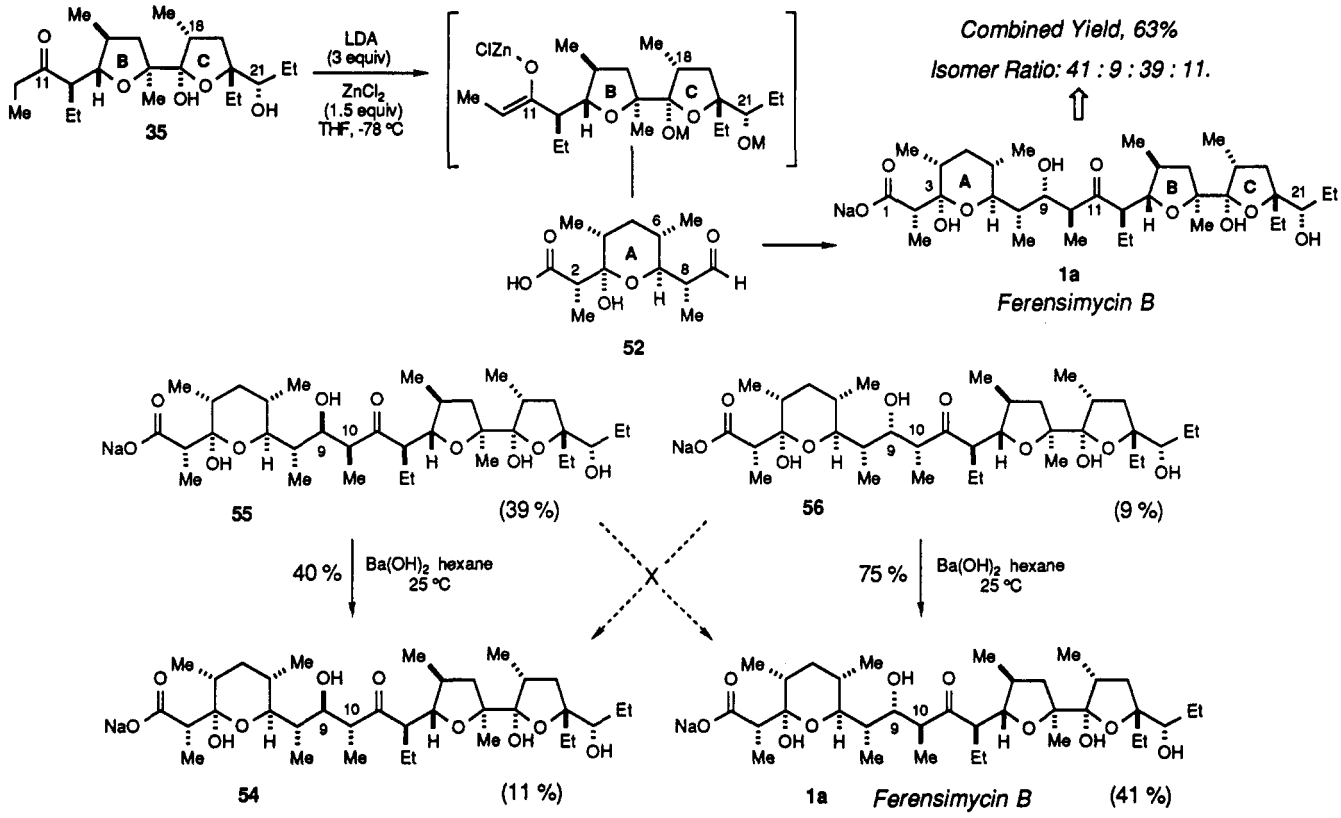
provide the benzyl ester **48** in 85% yield (Scheme XIII). This transesterification procedure, which was unsuccessful for **46b**, was realized for this less sterically hindered substrate. The remaining obstacles to the completion of the synthesis included the oxidation of the C_3 hydroxyl moiety and subsequent removal of the diol protecting group. Due to the perceived lability of β-keto esters such as **50** toward racemization, we elected to exchange the acetal protecting group for the more labile C_7–C_9 diol-masked phenylboronate.[45] Accordingly, the naphthylidene acetal was hydrolyzed with 2:1 THF–1 M sulfuric acid to give the intermediate triol ester **49a** (81% yield), which was then transformed to the phenylboronate ester **49b** with phenylboronic acid in benzene at room temperature. The boronate ester, thus formed in high yield, was readily purified by extractive isolation. Swern oxidation of **49b**, wherein diisopropylethylamine was used in place of triethylamine to suppress racemization, provided the highly sensitive β-keto ester **50**, which was not purified but deprotected directly with aqueous peroxide to give the ring-A lactol **51a** in 78% yield after chromatography (Scheme XIII). It was gratifying to note that analysis of the unpurified reaction mixture showed no evidence of epimerization at C_2 during this series of transformations. In this reaction sequence, the phenylboronate ester proved to be an ideal 1,3-diol protecting group as it was stable to the Swern oxidation and yet was readily hydrolyzed under mild conditions. Oxidation of **51a** with pyridine–SO_3 complex[40] afforded the derived aldehyde **51b**, which was subjected to benzyl ester hydrogenolysis to give the unstable acid **52**. In exploring derivatives of **52** that might be suitable for the final aldol coupling, we also prepared the boronic ester **53** as a crystalline solid, mp 167–168 °C. Having completed the synthesis of the C_1–C_9 fragment (16 steps, 10% yield), we addressed the aldol union of the two ferensimycin synthons.

Scheme XIII



[a] TMS–imidazole, DMAP, CH_2Cl_2. [b] LiOBn, THF, −20 °C. [c] 2:1 THF 1 M H_2SO_4, 45 °C. [d] $PhB(OH)_2$, PhH, 25 °C, 12 h. [e] $(ClCO)_2$, DMSO, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, −50 °C; H_2O_2. [f] DMSO, SO_3–Pyr, Et_3N. [g] Pd/C H_2, EtOAc.

Scheme XIV



Aldol Coupling of the C_1–C_9 and C_{10}–C_{23} Fragments. It was our intention to take advantage of the inherent metal-ligating properties of the molecule, either kinetically or thermodynamically, to obtain the desired anti relationship between the newly created centers formed in the final aldol construction. In analogy with the favorable selectivity observed in the Kishi narasin synthesis,[17] the carboxylic acid portion of the C_1–C_9 fragment **52** was left unprotected for this reaction. This simplification in the protection strategy extended to the C_3 lactol functionality as well. Due to the lability of the C_{10}–C_{23} synthon **35** (Scheme VIII), particularly toward the acidic conditions that may be required in a deprotection scheme, a similar decision was made to avoid the use of protecting groups in this fragment. The liability in this course of action resided in the reactivity of the fragments to be joined; nevertheless, the advantages of this approach were evident. Most importantly, it was hoped that the requisite ligation sites present in the ionophore might provide the necessary organization to bias the course of the aldol reaction under either kinetic or thermodynamic conditions. As a final practical issue, this strategy facilitated the immediate correlation of reaction products with authentic material.

After considerable experimentation (vide infra), we found that reaction of 3 equiv of the zinc enolate[46] trianion (LDA, $ZnCl_2$, THF, −78 °C) derived from ketone **35** with 1 equiv of aldehyde provided four adducts in a combined yield of 63% based on aldehyde (Scheme XIV). Excess enolate employed for deprotonation of the acid and lactol portions of the aldehyde was readily recovered. The distribution of the four aldol diastereomers was 41:11:39:9, corresponding to the desired threo Cram adduct **1a** (41%), along with the threo-anti Cram isomer **54** (11%), the erythro-anti Cram isomer **55** (39%), and the erythro Cram adducts **56** (9%). After isolation of the individual adducts, the two syn diastereomers were subjected to barium hydroxide equilibration (10 equiv $Ba(OH)_2 \cdot 8H_2O$, hexane, 25 °C, 8 h).[19] Under these conditions, adduct **55** underwent C_{10} methyl epimerization to the threo-anti Cram product **54** in 40% yield. This equilibration was accompanied by the formation of insignificant quantities of the C_9 alcohol diastereomers **56** and **1a**. In a similar fashion, the erythro Cram adduct **56** was epimerized to ferensimycin B (**1a**) in 75% yield, again with insignificant crossover to isomers **54** and **55**. Stereochemical assignments for all four of the aldol diastereomers were based on C_9–C_{10} vicinal proton coupling constants in combination with these equilibration experiments.

Since no crossover from one C_9 diastereomer manifold to the other occurred in these experiments, the mechanism of equilibration is concluded to be C_{10} enolization–ketonization rather than retroaldol–realdol isomerization. A portion of the X-ray structure of ferensimycin A (Figure 4) clearly illustrates that the C_{10} methyl group in the natural product is in the thermodynamically preferred configuration. By inspection, the contiguous stereocenters in this region of the molecule are all oriented to avoid the unfavorable syn pentane interaction between the C_8 and C_{10} methyl groups. Our belief that the C_{10} *epi*-methyl compound could be equilibrated to the natural configuration was accordingly realized.

Since the ratio of the product diastereomers formed in the initial coupling exhibited no time dependence under the reaction conditions employed, the zinc enolate derived from **35** exhibited the desired (and predicted) kinetic bias (4:1) for the stereochemistry of the natural product at the C_{10} stereocenter. One probable structure for this enolate is provided in Figure 5. It is interesting to note that the low selectivity in the aldol union came from the lack of π-facial discrimination in the addition to aldehyde coupling partner **52**. Although it is not generally appreciated, the addition of *Z* enolates to chiral α-substituted aldehydes exhibits a preference for the "anti-Felkin" carbonyl diastereoface. This important point was predicted by us some years ago,[47] and cases documenting this unusual reversal of reactivity have slowly emerged.[48] The present aldol reaction appears to be another case that highlights this stereochemical issue.

As in the syntheses of lasalocid[21b,49] and narasin,[17] where similar aldol bond constructions had been chosen, considerable experimentation was necessary to find conditions that would give a reasonable yield of the aldol adduct with the desired threo Cram stereochemistry. Other reaction conditions, such as variations in

(45) Ferrier, R. J. *Methods Carbohydr. Chem.* **1972**, *6*, 419–426.

(46) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.

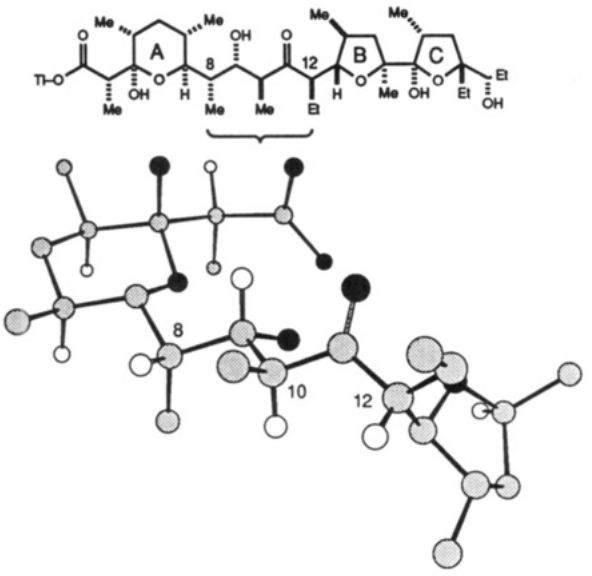


Figure 4. Ferensimycin A partial X-ray structure showing C_8–C_{12} conformation.

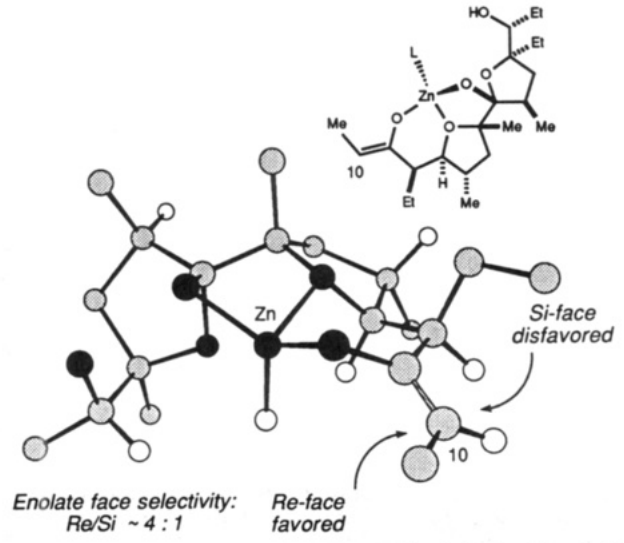


Figure 5. Projected conformation (Chem 3D) of the C_{10}–C_{23} zinc(II) enolate.

metal counterion, solvent, and temperature, were employed in an attempt to optimize both the selectivity and chemical yield of this transformation. When the reaction was carried out either at 0 °C or in less polar solvents (diethyl ether, benzene), decreased selectivity was observed. Although the lithium enolate was slightly more selective (**1a**:**54**:**55**:**56** = 43:16:26:15), neither the lithium nor the magnesium enolates afforded a higher yield of the natural product. In separate experiments, protection of the carboxylic acid moiety in the aldehyde **52** as the benzyl ester, masking both the acid and C_3 lactol portions as the phenylboronate ester **53**, or protection of the C_{21} hydroxyl group as *tert*-butyldimethylsilyl ether failed to enhance overall selectivity and conversion. Under optimized conditions for this transformation (zinc enolate trianion with both partners totally unprotected), the combined yield of synthetic ferensimycin B after equilibration of adduct **58** was 30%.

(47) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1–115. See the discussion on pp 105–106. The analysis also correctly predicted that *E* enolates would behave as "normal" nucleophiles.

(48) A recent manuscript that addresses the issue of aldehyde diastereoface selectivity versus enolate geometry will appear shortly: Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.

(49) (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006. (b) Still, W. C.; Kempf, D.; Hauck, P. *Tetrahedron Lett.* **1986**, *27*, 2727–2730.

Avoidance of any protecting-group manipulations on the acid-sensitive natural product greatly increased the efficiency of this bond construction. Synthetic ferensimycin B sodium salt was found to be identical with an authentic sample of the natural product in all respects (mp, $[\alpha]_D$, IR, ^{1}H NMR, ^{13}C NMR, MS, TLC). With the completion of this synthesis, the absolute configuration of this natural product has been established.

Conclusion

This study represents the first endeavor to synthesize any member of the lysocellin family of polyether antibiotics. The experience gained in both the synthesis of the constituent parts of the structure and their assemblage should provide useful analogies for dealing with similar architectural problems in other polyether target structures. As an example, our ongoing synthesis of lonomycin has relied heavily on the experience gained in the present study.[6] In the present investigation, it is evident that local control of absolute stereochemical relationships is becoming more predictable. On the other hand, the key aldol assemblage reactions that join large fragments with predictable stereocontrol still lack the guidance of refined models and reaction methodology. These latter reactions represent some of the continuing challenges in reaction design in this area of natural product synthesis.

Experimental Section

General. Nuclear magnetic resonance spectra (NMR) were recorded as solutions in the indicated solvents on Bruker AM-250, AM-300, and AM-500 spectrometers. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane, $CDCl_3$, or C_6D_6 as an internal standard. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. Capillary GLC analyses were determined on an HP 5880A gas chromatograph equipped with a DB-1 or DB-5 (J & W Associates) fused silica capillary column. Preparative HPLC was performed on a Waters Prep LC 50 instrument with silica gel (PrepPak) columns.

Flash chromatography was performed with EM Reagents silica gel 60 (230–400 mesh) and the indicated solvent systems. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone ketyl. Toluene and benzene were distilled from sodium metal. Dichloromethane, pyridine, diethylamine, diisopropylamine, triethylamine, methyl iodide, chlorotrimethylsilane, and oxalyl chloride were distilled from calcium hydride. Dimethyl sulfoxide was distilled under reduced pressure and stored over activated 4-Å molecular sieves. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen in flame-dried glassware.

Ethyl (*E*)-4-Methylhept-4-enoate (22a). A solution of 25.7 g (257 mmol) of 2-methyl-1-penten-3-ol, 189 mL (1.03 mol) of ethyl orthoacetate, and 2.25 mL (31.0 mmol) of propionic acid was heated to 138 °C with removal of the ethanol formed by distillation. After 40 mL of ethanol had been collected, the solution was allowed to cool to ambient temperature, whereupon 24 mL of 3.5% aqueous acetic acid was added in one portion. After the mixture was stirred for 30 min at 25 °C, the volatiles were removed in vacuo, and the residue was purified by fractional distillation (91 °C, 1 mmHg) to afford 35.1 g (81%) of ester **22a** as a colorless liquid: IR (CH_2Cl_2) 2970, 2940, 2880, 1735, 1460, 1375, 1345, 1110, 1060, 1035, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10 (t, 1 H, J = 7.1 Hz, C_{17}-H), 4.05 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.33 (t, 2 H, J = 8.2 Hz, both C_{14}-H), 2.22 (t, 2 H, J = 7.5 Hz, both C_{15}-H), 1.90 (dq, 2 H, J = 7.5 and 7.5 Hz, both C_{18}-H), 1.54 (s, 3 H, C_{16}-CH_3), 1.20 (t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 0.86 (t, 3 H, J = 7.5 Hz, C_{18}-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 173.3, 132.6, 127.2, 60.0, 34.6, 33.2, 21.0, 15.6, 14.1, 14.0. Anal. Calcd for $C_{10}H_{17}O_2$: C, 70.97; H, 10.12. Found: C, 71.05; H, 10.14.

(*E*)-4-Methyl-4-heptenoic Acid (22b). A solution of 35.1 g (208 mmol) of ester **22a** in 639 mL of methanol and 426 mL of 2.0 M aqueous KOH (20 mmol) was stirred at 0 °C for 2 h, warmed to room temperature, and then stirred an additional 8 h. The methanol was removed in vacuo, and the resulting aqueous solution was washed with CH_2Cl_2 (2 × 500 mL). The aqueous phase was acidified to pH 1 at 0 °C by gradual addition of solid sodium hydrogen sulfate. The cloudy solution was extracted with CH_2Cl_2 (3 × 500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield 25.81 g (88%) of **22b** as a yellow liquid, which was used without further purification: IR (CH_2Cl_2) 2800–3300 (br), 1715 (br), 1430 (br), 1300, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.15 (br s, 1 H, CO_2H), 5.20 (t, 1 H, J = 7.7 Hz,

C_{17}-H), 2.45 (t, 2 H, J = 7.5 Hz, both C_{14}-H), 2.35 (t, 2 H, J = 7.7 Hz, both C_{15}-H), 2.00 (dq, 2 H, J = 7.6 and 7.6 Hz, both C_{18}-H), 1.65 (s, 3 H, C_{16}-CH_3), 0.95 (t, 3 H, J = 7.6 Hz, C_{18}-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 179.8, 132.2, 127.4, 34.2, 33.0, 21.1, 15.5, 14.0.

(4*S*)-3-[(*E*)-4-Methyl-1-oxohept-4-enyl]-4-(phenylmethyl)oxazolidin-2-one (22c). To a mechanically stirred solution of 14.92 g (105.8 mmol) of acid **22b** in 592 mL of diethyl ether at room temperature was added 15.12 mL (107.8 mmol) of triethylamine in one portion. After the solution was cooled to −78 °C, 13.36 mL (108.5 mmol) of trimethylacetyl chloride was added dropwise. The white suspension was gradually warmed to 0 °C, and after 1 h was recooled to −78 °C. In a separate flask, a solution of 18.73 g (105.8 mmol) of (4*S*)-4-(phenylmethyl)-2-oxazolidinone (**23**)[31] in 159 mL of THF at −78 °C was treated with 70.1 mL (106 mmol) of 1.51 M *n*-butyllithium in hexane and stirred for 15 min. The resulting solution was added via cannula to the white suspension containing the mixed anhydride. After 15 min at −78 °C, the suspension was warmed to 0 °C and stirred an additional 1 h. The reaction was quenched by rapid transfer via cannula to 750 mL of 1 M aqueous ammonium chloride. The volatiles were removed in vacuo, and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 750 mL). The combined organic extracts were washed successively with 750 mL of 1 M aqueous hydrochloric acid and 750 mL of saturated aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by chromatography (10 cm × 21 cm, 15% ethyl acetate/hexane) afforded 26.7 g (84%) of **22c** as a white crystalline solid: mp 144.5–145.5 °C; $[\alpha]_D$ +67.3° (*c* 3.95, CH_2Cl_2); IR (CH_2Cl_2) 3060, 2970, 2930, 1785, 1705, 1385, 1355, 1215, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.35 (m, 5 H, ArH), 5.20 (t, 1 H, J = 6.6 Hz, C_{17}-H), 4.65–4.70 (m, 1 H, N-C*H*), 4.12–4.22 (m, 2 H, O-CH_2), 3.30 (dd, 1 H, J = 13.3 and 3.2 Hz, one Ph-C*H*), 3.01–3.09 (m, 2 H, both C_{14}-H), 2.75 (dd, 1 H, J = 13.4 and 9.7 Hz, one Ph-C*H*), 2.31–2.40 (m, 2 H, both C_{15}-H), 2.00 (dq, 2 H, J = 7.5 and 7.5 Hz, both C_{18}-H), 1.65 (s, 3 H, C_{16}-CH_3), 0.91 (t, 3 H, J = 7.6 Hz, C_{18}-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 172.8, 153.2, 135.2, 132.5, 129.2, 128.7, 127.3, 127.1, 66.0, 54.9, 37.8, 34.1, 33.9, 21.0, 15.6, 14.0. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.87; H, 7.61; N, 4.66.

(4*S*)-3-[(2*S*)-(*E*)-2,4-Dimethyl-1-oxohept-4-enyl]-4-(phenylmethyl)-oxazolidin-2-one (24). To a solution of 105 mL (105 mmol) of 1.0 M sodium hexamethyldisilazide in THF diluted with an additional 102 mL of THF at −78 °C was slowly added via an addition funnel a solution of 26.53 g (88.43 mmol) of imide **22c** in 40 mL of THF. After the mixture was stirred for 2 h at −78 °C, 27.52 mL (442.1 mmol) of iodomethane was added rapidly via an addition funnel. After 2.5 h, the reaction was quenched by the addition of 200 mL of saturated aqueous ammonium chloride. The volatiles were removed in vacuo in a hood, and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 200 mL of 10% aqueous sodium bisulfate and 200 mL of saturated aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Capillary GLC analysis (DB-1, 200 °C, 15 psi, t_r **24** = 5.71 min, t_r C_{14} *epi*-**24** = 5.98 min) of the unpurified material indicated a 91:9 ratio of diastereomers. Preparative HPLC (10% ethyl acetate/hexane; two recycles) afforded 1.80 g (7.6% yield) of the minor isomer and 22.66 g (82% yield) of the major isomer **24** as a colorless oil: $[\alpha]_D$ +77.8° (*c* 3.15, CH_2Cl_2); IR (CH_2Cl_2) 2980, 2940, 2780, 1785, 1705, 1460, 1385, 1350, 1295, 1240, 1210, 1105, 1020, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.35 (m, 5 H, ArH), 5.20 (t, 1 H, J = 7.5 Hz, C_{17}-H), 4.60–4.70 (m, 1 H, N-C*H*), 4.20 (d, 2 H, J = 4.9 Hz, both O-C*H*), 4.00 (ddq, 1 H, J = 6.7, 6.7, and 6.7 Hz, C_{14}-H), 3.30 (dd, 1 H, J = 13.3 and 3.2 Hz, one Ph-C*H*), 2.80 (dd, 1 H, J = 13.3 and 9.8 Hz, one Ph-C*H*), 2.42 (dd, 1 H, J = 13.2 and 6.7 Hz, one C_{15}-H), 2.04 (dd, 1 H, J = 13.3 and 8.0 Hz, one C_{15}-H), 1.95–2.00 (m, 2 H, both C_{18}-H), 1.60 (s, 3 H, C_{16}-CH_3), 1.20 (d, 3 H, J = 6.9 Hz, C_{14}-CH_3), 0.92 (t, 3 H, J = 9.5 Hz, C_{18}-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 177.1, 153.0, 135.4, 131.5, 129.4, 129.1, 128.8, 127.2, 65.9, 55.3, 43.5, 37.9, 35.8, 27.0, 21.2, 16.7, 15.7, 14.1. Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.50; H, 7.70; N, 4.39.

(2*S*)-(*E*)-2,4-Dimethyl-4-hepten-1-ol (25a). To a solution of 22.5 g (71.7 mmol) of imide **24** in 350 mL of diethyl ether at 0 °C was added 75 mL (75 mmol) of 1.0 M lithium aluminum hydride in THF over 1 h. After 3.5 h at 0 °C, the reaction was quenched by sequential dropwise addition of 2.7 mL of water, 2.7 mL of 15% aqueous sodium hydroxide, and 8.1 mL of water. Anhydrous Na_2SO_4 was added to the suspension, which was then filtered and rinsed with anhydrous ether (3 × 150 mL). Careful removal of the solvent in vacuo (<25 °C) afforded a mixture of the oxazolidinone and alcohol **25a**. Kugelrohr distillation (oven temperature 145–155 °C, 16 mmHg) of the residue afforded 9.2 g (91% yield) of alcohol **25a** as a colorless liquid: $[\alpha]_D$ −5.7° (*c* 3.6, CH_2Cl_2); IR (thin film) 3350 (br), 2870, 2830, 2780, 1460, 1380, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (t, 1 H, J = 5.9 Hz, C_{15}-H), 3.50 (dd, 1 H, J = 10.6 and 5.7 Hz, one C_{13}-H), 3.42 (dd, 1 H, J = 10.6 and 5.9 Hz, one C_{13}-H), 1.95–2.10 (m, 3 H, both C_{18}-H and one C_{15}-H), 1.70–1.85 (m, 3 H, one C_{15}-H, C_{14}-H, and OH), 1.6 (s, 3 H, C_{16}-CH_3), 0.93 (t, 3 H, J = 7.5 Hz, C_{18}-CH_3), 0.87 (d, 3 H, J = 6.4 Hz, C_{14}-CH_3); ^{13}C ($CDCl_3$, 65 MHz) δ 133.0, 128.3, 68.5, 44.2, 33.6, 21.1, 16.6, 15.7, 14.2; TLC R_f 0.22 (20% ethyl acetate/hexane).

(2*S*)-(*E*)-2,4-Dimethyl-4-hepten-1-al (25b). To a solution of 9.20 mL (105 mmol) of oxalyl chloride in 487 mL of CH_2Cl_2 at −78 °C was slowly added a solution of 15.0 mL (211 mmol) of dimethyl sulfoxide in 100 mL of CH_2Cl_2. After the mixture was stirred for 15 min at −78 °C, a solution of 8.79 g (61.9 mmol) of alcohol **25a** in 100 mL of CH_2Cl_2 was added dropwise. The reaction was stirred for 1 h before 43 mL (310 mmol) of triethylamine was added in one portion, and the reaction mixture was stirred for an additional 3 h at −78 °C. The reaction was warmed to −55 °C, diluted with 300 mL of hexane, and warmed to room temperature. The mixture was partitioned between 500 mL of 0.5 M aqueous sodium bisulfate and an additional 500 mL of hexane. The layers were separated, and the aqueous phase was extracted with 9:1 (v/v) hexane/CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed with 2 L of saturated aqueous sodium bicarbonate and 2 L of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo (<25 °C). Purification by filtration through silica gel (4 cm × 18 cm, 5% ethyl acetate/hexane) afforded 7.82 g of labile aldehyde **25b** as a yellow oil, which was used immediately in the subsequent aldol reaction. TLC R_f 0.58 (20% ethyl acetate/hexane).

(4*R*,5*S*)-3-(1-Oxobutyl)-4-methyl-5-phenyl-2-oxazolidinone (26). A mechanically stirred solution of 20.0 g (0.113 mol) of (4*R*,5*S*)-norephedrine 2-oxazolidinone[50] (0.28 M in THF) was metalated with 80 mL (1.55 M in hexane, 0.124 mol) of *n*-butyllithium, and acylated according to our published procedure[50] with 22.0 mL (21.3 g, 0.135 mol) of butanoic anhydride to give 30 g (108% mass balance) of unpurified product. The title compound was isolated by recrystallization from pentane/diethyl ether to afford 24.3 g (87%) of **26** as a white crystalline solid: mp 55.5–56 °C; IR (CH_2Cl_2) 2970, 2940, 2880, 1785, 1705, 1385, 1370, 1350, 1235, 1220, 1200, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 6.83 (s, 5 H, aromatic H's), 5.62 (d, 1 H, J = 7.2 Hz, C_5-H), 4.73 (qn, 1 H, J = 6.8 Hz, C_4-H), 2.93 (t, 1 H, J = 7.5 Hz, $C_{2'}$-*H*), 2.90 (t, 1 H, J = 6.9 Hz, $C_{2'}$-*H*), 1.68 (m, 2 H, $C_{3'}$-H_2), 0.98 (t, 3 H, J = 7.0 Hz, $C_{4'}$-H_3), 0.88 (d, 3 H, J = 6.8 Hz, C_4-CH_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 172.9, 153.0, 133.5, 128.7, 125.7, 79.0, 54.7, 37.4, 17.8, 14.6, 13.6; specific rotation $[\alpha]_{589}$ +40.4° (*c* 4.9, CH_2Cl_2). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.20; H, 7.12.

(4*S*)-3-[(2*R*,3*S*,4*S*)-(*E*)-2-Ethyl-3-hydroxy-4,6-dimethyl-1-oxonon-6-enyl]-4-methyl-5-phenyl-2-oxazolidinone (27). To a solution of 392 mg (1.58 mmol) of (4*R*,5*S*)-3-(1-oxobutyl)-4-methyl-5-phenyloxazolidin-2-one (**26**) in 1.5 mL of CH_2Cl_2 at −78 °C was added 0.40 mL (1.6 mmol) of di-*n*-butylboron triflate dropwise, followed by 0.25 mL (1.8 mmol) of triethylamine in one portion. The solution was stirred for 1 h at −78 °C and for 30 min at 0 °C, recooled to −78 °C, and then a solution of 145 mg (1.04 mmol) of aldehyde **25b** in 2 mL of CH_2Cl_2 was added dropwise. The reaction was stirred for 30 min at −78 °C and then at −25 °C for 12 h. The reaction was quenched at 0 °C by the sequential addition of 1.44 mL of pH 7 aqueous phosphate buffer, 4 mL of methanol, and 1.44 mL of 1:1 (v/v) 30% aqueous hydrogen peroxide:methanol, and stirred at 0 °C for 1.5 h. The reaction was diluted with 5 mL of water, and the methan was removed in vacuo. The resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with 15 mL of saturated aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. An aliquot of the unpurified material was silylated (Et_2NTMS, DMAP, CH_2Cl_2, room temperature, 30 min) and capillary GLC analysis (DB-1, 220 °C, 15 psi, t_r **27** = 8.53 min) of the resulting silyl ether indicated a 99.6:0.4 ratio of diastereomers. Removal of the excess butyrate imide was accomplished by chromatography on silica gel (3 cm × 21 cm, 10% to 20% ethyl acetate/hexane) to afford 335 mg (84% yield) of aldol adduct **27** as a white crystalline solid: mp 151–153 °C; $[\alpha]_D$ −1.7° (*c* 2.1, CH_2Cl_2); IR (thin film) 3520 (br), 2965, 2940, 2880, 1785, 1700, 1460, 1350 (br), 1200 (br), 1120 cm^{-1}; ^1H ($CDCl_3$, 250 MHz) δ 7.20–7.40 (m, 5 H, ArH), 5.60 (d, 1 H, J = 7.2 Hz, Ph-C*H*), 5.10 (t, 1 H, J = 7.0 Hz, C_{17}-H), 4.80 (dq, 1 H, J = 6.8 and 6.8 Hz, N-C*H*), 4.10 (dt, 1 H, J = 10.2 and 3.8 Hz, C_{12}H), 3.46–3.54 (m, 1 H, C_{13}-H), 2.60 (br s, 1 H, OH), 2.40 (br d, 1 H, J = 11.2 Hz, one C_{15}-H), 1.60–2.00 (m, 6 H), 1.50 (s, 3 H, C_{16}-CH_3), 0.80–0.90 (m, 9 H), 0.78 (d, 3 H, J = 6.4 Hz, N-CH-CH_3); ^{13}C ($CDCl_3$, 65 MHz) δ 176.7, 152.9, 133.5, 133.3, 129.0, 128.9, 128.8, 125.9, 79.0, 77.7, 55.3, 46.8, 43.4, 34.8, 25.5, 21.4, 19.6, 16.0, 15.8, 14.7, 14.5, 11.8; TLC R_f 0.24 (20% ethyl acetate/hexane). Anal. Calcd for $C_{23}H_{33}NO_4$:

(50) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835.

C, 71.29; H, 8.58. Found: C, 70.89; H, 8.64.

[3(2*R*,2(2*S*,3*S*,5*S*,5(1*R*))),4*R*,4*R*]-3-[2-(5-(1-Hydroxypropyl)-3,5-dimethyltetrahydro-2-furanyl)-1-oxobutyl]-4-methyl-5-phenyl-2-oxazolidinone (30a). To a blue-green suspension of 723 mg (1.87 mmol) of aldol adduct **27** and 120 mg (0.30 mmol) of $VO(acac)_2$ in benzene at 0 °C was added 1.21 mL (3.6 mmol) of 3.0 M *tert*-butyl hydroperoxide in isooctane, which had been stirring over activat4d crushed 3-Å molecular sieves for 10 min, resulting in a deep-red solution. After 1 hr at 0 °C and 11 h at room temperature, the reaction was quenched with 1.0 mL of glacial acetic acid and 26 mL of dimethyl sulfide. After stirring for 45 min at room temperature, the solution was diluted with 15 mL of CH_2Cl_2, washed with 1 M aqueous hydrochloric acid (2 × 50 mL) and 50 mL of 10% aqueous sodium bicarbonate, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was filtered through silica gel (10 g, 40% ethyl acetate/hexane) to furnish the unpurified product as a 94/6 mixture of C_{16}–C_{17} diastereomers as determined by capillary GLC analysis (DB-1, 220 °C, 15 psi, t_r **30a** = 8.73 min, t_r **29a** = 8.12 min). The diastereomers were separated by chromatography on silica gel (4 cm × 21 cm column, 20% ethyl acetate/hexane) to afford 638 mg (85% yield) of **30a** as a white crystalline solid: mp 219–220 °C; $[\alpha]_D$ −7.5° (*c* 1.7, MeOH); IR (CH_2Cl_2) 3570 (br), 2970, 2940, 2880, 1785, 1700, 1460, 1345 (br), 1225, 1195, 1120, 1035, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5 H, ArH), 5.60 (d, 1 H, *J* = 7.2 Hz, Ph-C*H*), 4.80 (dq, 1 H, *J* = 6.7 and 6.7 Hz, N-C*H*), 4.20 (ddd, 1 H, *J* = 10.0, 5.9, and 3.9 Hz, C_{12}-H), 3.70 (dd, 1 H, *J* = 9.3 and 6.1 Hz, C_{13}-H), 3.40 (br d, 1 H, *J* = 10.1 Hz, C_{17}-H), 2.50 (br s, 1 H, OH), 2.31–2.39 (m, 1 H, C_{14}-H), 1.75–1.95 (m, 3 H), 1.70 (dd, 1 H, *J* = 12.0 and 6.9 Hz, one C_{15}-H), 1.47–1.53 (m, 1 H, one C_{18}-H), 1.21–1.29 (m, 1 H, one C_{18}-H), 1.10 (s, 3 H, C_{16}-CH_3), 1.03 (t, 3 H, *J* = 7.5 Hz, C_{12}-CH_2CH_3), 1.04 (d, 3 H, *J* = 6.3 Hz, C_{14}-CH_3), 0.92 (t, 3 H, *J* = 7.4 Hz, C_{18}-CH_3), 0.91 (d, 3 H, *J* = 6.5 Hz, N-CH-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 174.4, 152.9, 133.3, 128.7, 125.6, 86.9, 84.9, 78.6, 78.1, 55.2, 48.5, 40.1, 36.8, 24.5, 24.2, 22.1, 17.1, 14.5, 11.7, 11.3. Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.56; H, 8.35; N, 3.49.

[3(2*R*,2(2*S*,3*S*,5*S*)),4*R*,5*R*]-3-[2-(5-(1-Oxopropyl)-3,5-dimethyltetrahydro-2-furanyl)-1-oxobutyl]-4-methyl-5-phenyl-2-oxazolidinone (31a). To a solution of 2.55 mL (29.2 mmol) of oxalyl chloride in 124 mL of CH_2Cl_2 at −78 °C was slowly added a solution of 4.1 mL (58 mmol) of dimethyl sulfoxide in 27 mL of CH_2Cl_2. After the mixture was stirred for 30 min at −78 °C, a solution of 6.78 g (16.9 mmol of the alcohol **30a** in 27 mL of CH_2Cl_2 was added dropwise. The solution was stirred for 1 h at −78 °C before 11.7 mL (83.9 mmol) of triethylamine was added in one portion. After stirring for 1 h at −78 °C and 1.5 h at 0 °C, the reaction was diluted with 200 mL of hexane and partitioned between 200 mL of 0.5 M aqueous sodium bisulfate and an additional 200 mL of hexane. The aqueous phase was separated and extracted with 9:1 (v/v) hexane:CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed successively with 1.5 L of 0.5 M aqueous sodium hydrogen sulfate, 1.5 L of saturated aqueous sodium bicarbonate, and 1.5 L of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (4 cm × 18 cm, 15% ethyl acetate/hexane) afforded 6.84 g (100%) of an oil that by capillary GLC analysis (DB-1, 220 °C, 10 psi, t_r **31a** = 10.12 min) indicated a diastereomeric purity of 99%. Preparation of an analytical sample by recrystallization from hexane/ethyl acetate provided ketone **31a** as a white crystalline solid: mp 191–193 °C; $[\alpha]_D$ −14.3° (*c* 2.05, CH_2Cl_2); IR (CH_2Cl_2) 2980, 2940, 2880, 1785, 1700, 1460, 1380, 1370, 1345, 1230, 1200, 1120, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5 H, ArH), 5.63 (d, 1 H, *J* = 7.2 Hz, Ph-C*H*), 4.80 (dq, 1 H, *J* = 6.7 and 6.7 Hz, N-C*H*), 4.10–4.20 (m, 1 H, C_{12}-H), 3.73 (dd, 1 H, *J* = 7.5 and 7.5 Hz, C_{13}-H), 2.60–2.80 (m, 2 H, both C_{18}-H), 2.23 (dq, 1 H, *J* = 7.6 and 7.6 Hz, C_{14}-H), 1.80–2.05 (m, 4 H), 1.30 (s, 3 H, C_{16}-CH_3), 1.03 (t, 3 H, *J* = 7.2 Hz, C_{12}-CH_2CH_3), 0.97 (d, 3 H, *J* = 6.8 Hz, C_{14}-CH_3), 0.95 (t, 3 H, *J* = 7.5 Hz, C_{18}-CH_3), 0.91 (d, 3 H, *J* = 6.5 Hz, N-CH-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 215.76, 174.0, 152.8, 133.3, 128.8, 128.7, 125.6, 87.5, 86.9, 78.6, 55.1, 48.1, 43.7, 36.8, 29.4, 25.1, 22.3, 17.5, 14.5, 11.4, 7.6. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.88; H, 7.82; N, 3.53.

(α*R*,2*S*,3*S*,5*S*)-5-(1-Oxopropyl)-3,5-dimethyl-α-ethyltetrahydro-2-furanacetic Acid (31b). To a solution of 7.0 g (18 mmol) of imide **31a** in 262 mL of THF (reagent grade) and 87 mL of deionized water at 0 °C was added 11.9 mL (105 mmol) of 30% aqueous hydrogen peroxide followed by 1.47 g (35.0 mmol) of lithium hydroxide monohydrate. The reaction was stirred at 0 °C for 1 h and at room temperature for an additional 3 h. The reaction was quenched at 0 °C by the addition of 100 mL of 1.5 M aqueous sodium sulfite. After the solution was stirred for 20 min, the THF was removed in vacuo and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL). The aqueous extract was acidified to pH 2 with 1 M aqueous hydrochloric acid and extracted with ethyl acetate (3 × 400 mL). The combined organic extracts were washed with 1 L of aqueous saturated sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 3.65 g (86% yield) of acid **31b** as an opaque white oil: $[\alpha]_D$ −12.5° (*c* 2.35, CH_2Cl_2); IR (CH_2Cl_2) 2900–3200 (br), 1750, 1715, 1465, 1385, 1370, 1110, 1045, 980, 950 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.60 (dd, 1 H, *J* = 7.4 and 7.4 Hz, C_{13}-H), 2.48–2.68 (m, 2 H, both C_{18}-H), 2.35–2.41 (m, 1 H, C_{12}-H), 2.10 (dq, 1 H, *J* = 7.7 and 7.7 Hz, C_{14}-H), 1.93 (dd, 1 H, *J* = 12.9 and 7.8 Hz, one C_{15}-H), 1.78 (dd, 1 H, *J* = 12.9 and 7.7 Hz, one C_{15}-H), 1.66–1.74 (m, 2 H, C_{12}-CH_2CH_3), 1.24 (s, 3 H, C_{16}-CH_3), 0.94 (t, 3 H, *J* = 7.2 Hz, C_{12}-CH_2CH_3), 0.91 (t, 3 H, *J* = 7.7 Hz, C_{18}-CH_3), 0.87 (d, 3 H, *J* = 7.6 Hz, C_{14}-CH_3); ^{13}C ($CDCl_3$, 63 MHz) δ 212.0, 179.3, 87.5, 86.6, 51.9, 43.7, 36.9, 29.5, 25.2, 21.8, 17.2, 12.0, 7.7.

(α*R*,2*S*,3*S*,5*S*)-1-(1-Oxopropyl)-*N*-methoxy-*N*,3,5-trimethyl-α-ethyltetrahydro-2-furanacetamide (31c). To a solution of 5.6 g (57 mmol) of *N*-methoxy-*N*-methylamine hydrochloride in 130 mL of CH_2Cl_2 at room temperature were added sequentially 12 mL (86 mmol) of triethylamine, a solution of 3.45 g (14.3 mmol) of acid **31b** in 10 mL of CH_2Cl_2, 3.5 g (29 mmol) of 4-(*N*,*N*-dimethylamino)pyridine, and 4.5 mL (29 mmol) of 1,3-diisopropylcarbodiimide. After stirring for 24 h at room temperature, the reaction was partitioned between 150 mL each of water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford a mixture of **31c** and diisopropylurea. Chromatography on silica gel (3 cm × 18 cm, 20% ethyl acetate/hexane) afforded 3.71 g (91% yield) of amide **31c** as a colorless oil: $[\alpha]_D$ −8.1° (*c* 0.70, CH_2Cl_2); IR (thin film) 2980, 2940, 2880, 1720, 1660, 1460, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.65 (s, 3 H, OCH_3), 3.50 (dd, 1 H, *J* = 7.9 and 7.9 Hz, C_{13}-H), 3.13 (br s, 3 H, N-CH_3), 2.92–2.98 (m, 1 H, C_{12}-H), 2.56–2.64 (m, 2 H, both C_{18}-H), 2.15 (br dq, 1 H, *J* = 7.5 and 7.5 Hz, C_{14}-H), 1.87 (dd, 1 H, *J* = 12.8 and 7.8 Hz, one C_{15}-H), 1.69–1.81 (m, 3 H, one C_{15}-H and both C_{12}-CH_2CH_3), 1.21 (s, 3 H, C_{16}-CH_3), 0.96 (t, 3 H, *J* = 7.3 Hz, C_{12}-CH_2CH_3), 0.84 (t, 3 H, *J* = 7.5 Hz, C_{18}-CH_3), 0.83 (d, 3 H, *J* = 7.5 Hz, C_{14}-CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 216, 174, 127.8, 87.4, 86.8, 61.1, 47.0, 43.8, 36.7, 29.1, 24.9, 22.8, 17.0, 11.7, 7.3. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54. Found: C, 63.20; H, 9.60.

(α*R*,2*S*,3*S*,5*S*)-5-[1-(*N*,*N*-Dimethylhydrazono)propyl]-*N*-methoxy-*N*,3,5-trimethyl-α-ethyltetrahydro-2-furanacetamide (32a). To a solution of 2.31 g (8.13 mmol) of ketone **31c** in 26.7 mL (340 mmol) of *N*,*N*-dimethylhydrazine at 0 °C was added 1.75 mL (13.8 mmol) of chlorotrimethylsilane dropwise. After 15 min, the reaction was warmed to room temperature and stirred for 36 h. The excess hydrazine was evaporated under a stream of nitrogen, and the residue was partitioned between 25 mL of pH 7 aqueous phosphate buffer and 25 mL of CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extracts were washed with 100 mL of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 2.62 g of a thick yellow liquid. Capillary GLC analysis (DB-1, 165 °C, 10 psi, t_r **32a** = 5.74 min) showed a mixture composed of 3.5% of unreacted starting ketone **31c**, 3% of a minor diastereomer, and 93.5% of the diastereomerically pure hydrazone **32a** (92% yield): $[\alpha]_D$ −40.1° (*c* 2.2, CH_2Cl_2); IR (CH_2Cl_2) 2985, 2940, 2880, 1655, 1465, 1385 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.78 (dd, 1 H, *J* = 7.9 and 7.9 Hz, C_{13}-H), 3.15 (br s, 3 H, N-CH_3), 2.89 (s, 3 H, OCH_3), 2.69 (dq, 1 H, *J* = 11.8 and 7.5 Hz, one C_{18}-H), 2.48 (dq, 1 H, *J* = 11.8 and 7.5 Hz, one C_{18}-H), 2.38 (s, 6 H, N-$N(CH_3)_2$), 2.28–2.38 (m, 3 H), 2.08–2.12 (m, 1 H, one C_{12}-CH_2CH_3), 2.00–2.04 (m, 1 H, one $C_{12}CH_2CH_3$), 1.96–2.00 (m, 1 H, one C_{15}-H), 1.47 (s, 3 H, C_{16}-CH_3), 1.30 (t, 3 H, *J* = 7.5 Hz, C_{18}-CH_3), 1.00 (d, 3 H, *J* = 6.2 Hz, C_{14}-CH_3), 0.97 (t, 3 H, *J* = 7.4 Hz, C_{12}-CH_2CH_3); ^{13}C ($CDCl_3$, 75 MHz) δ 178.5, 87.0, 84.2, 61.3, 47.6, 46.1, 37.3, 32.5, 28.4, 23.3, 20.8, 17.3, 12.6, 12.14; TLC R_f = 0.16 (30% ethyl acetate/hexane); exact mass calcd for $C_{17}H_{33}N_3O_3$ (M^+) 327.2515, found 327.2521.

(2*R*,α*S*)-α-Ethyl-2-ethyloxiranemethanol (21a). To a solution of 18.3 g (160 mmol) of 2-ethyl-1-penten-3-ol and 2.4 g of powdered and activated 3-Å molecular sieves in 144 mL of CH_2Cl_2 at −20 °C were added 20.8 mL (21 mmol) of 1.0 M (+)-diisopropyl tartrate in CH_2Cl_2 and 4.8 mL (25 mmol) of titanium tetraisopropoxide. After the catalyst was aged for 15 min at −20 °C, the solution was cooled to −30 °C and 25.6 mL (77 mmol) of 3.0 M *tert*-butyl hydroperoxide in isooctane was slowly added. The reaction was stirred at −20 °C for 28 h, and then 38.6 mL (39 mmol) of 1.0 M triethanolamine in CH_2Cl_2 was added in one portion. After stirring for 30 min at 0 °C, the solution was rapidly filtered through 8 g of silica gel and the filtercake was washed with 40 mL of diethyl ether. The filtrate was concentrated in vacuo, and the residue purified by preparative HPLC (15% ethyl acetate/hexane). The resolved allylic alcohol (7.79 g, 86%) eluted first, followed by 7.97 g (76%) of epoxide

21a as a colorless liquid: $[\alpha]_D$ −8.1° (*c* 3.0, CH_3OH); IR (thin film) 3300–3600 (br), 2980, 2940, 2890, 1465, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.69 (br d, 1 H, *J* = 8.2 Hz, C_{21}-H), 2.87 (d, 1 H, *J* = 4.7 Hz, one C_{19}-H), 2.65 (d, 1 H, *J* = 4.7 Hz, one C_{19}-H), 2.29 (s, 1 H, OH), 1.60–1.85 (m, 3 H), 1.42 (ddq, 1 H, *J* = 7.2, 7.2, and 7.2 Hz, one C_{20}-CH_2CH_3), 1.01 (t, 3 H, *J* = 7.4 Hz, C_{21}-CH_2CH_3), 0.92 (t, 3 H, *J* = 7.5 Hz, C_{20}-CH_2CH_3); ^{13}C (63 MHz, $CDCl_3$) δ 71.2, 61.8, 48.2, 25.8, 23.8, 9.8, 7.9; TLC R_f = 0.37 (30% ethyl acetate/hexane). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.58; H, 10.90.

[2*S*-[2α[2′*R,3′*S**,5′*S*(*R**)],4α,5β(*S**)]]-4-[5′-Ethyl-5′-(1-hydroxypropyl)octahydro-2′-hydroxy-2,3′,4-trimethyl[2,2′-bifuran]-5-yl]-3-hexanone (35b).** To a solution of 71 mg (0.22 mmol) of hydrazone **32** in 0.3 mL of ether at −78 °C was added a suspension of ethyllithium in 1 mL of diethyl ether. The ethyllithium suspension was prepared by evaporation at room temperature of the benzene from 3 mL of a 0.73 M solution of ethyllithium[51] in benzene followed by addition of 1 mL of anhydrous diethyl ether to the resulting white crystalline solid (minimum exposure time to ether is necessary to avoid decomposition). The reaction was stirred for 15 min at −78 °C. Thin-layer chromatography at this point showed complete disappearance of the slow-moving amide hydrazone **32a** (R_f = 0.16, 30% ethyl acetate/hexane) and the appearance of the much faster moving ethyl ketone hydrazone **32b** (R_f = 0.47, 30% ethyl acetate/hexane) along with a trace of base-line material.[52]

After the addition of 0.3 mL of THF, 0.31 mL (0.33 mmol) of 1.05 M lithium diethylamide in tetrahydrofuran/diethyl ether was added. The lithium diethylamide solution was prepared by addition of 0.90 mL (1.6 mmol) of 1.7 M methyllithium in diethyl ether to a solution of 0.17 mL (0.12 g, 1.6 mmol) of diethylamine in 0.5 mL of THF at −20 °C. The reaction was warmed to 0 °C and stirred for 20 min before one portion of the magnesium alkoxide of epoxy alcohol **21a** in THF was added. Two portions of magnesium alkoxide were prepared in two separate flasks by addition of 0.65 mL of 2.0 M ethylmagnesium bromide in THF to each of two solutions of 168 mg (1.32 mmol) of epoxide **21a** and 0.10 mL (0.57 mmol) of hexamethylphosphoramide in 0.3 mL of THF at −78 °C, followed by rapid warming to 0 °C and stirring until evolution of ethane subsided. After the reaction was stirred at 0 °C for 2 h, thin layer chromatography analysis of the reaction mixture showed the presence of excess epoxide **21a** (R_f = 0.37, 30% ethyl acetate/hexane), unreacted ethyl ketone hydrazone **32b** (R_f = 0.47, 30% ethyl acetate/hexane), and the product hydrazinol lactols **34b** (R_f = 0.29, 30% ethyl acetate/hexane). At this point, the second portion of magnesium alkoxide, prepared as described above, was added.[53] After another 2 h at 0 °C, thin layer chromatography analysis indicated the absence of any intermediate ethyl ketone hydrazone **32b** and only the presence of the excess epoxide **21a**, the product hydrazinol lactols **34b**, and traces of faster moving spots (R_f > 0.5, 30% ethyl acetate/hexane) consisting of traces of diethyl diketone and ca. 10% of bicyclic ketals **6** and *epi*-**6**. The reaction was quenched by transferring the mixture via cannula to a rapidly stirring solution of 20 mL of saturated aqueous ammonium chloride. The aqueous phase was extracted with ether (3 × 25 mL), and the combined ethereal extracts were washed with 100 mL of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the labile hydrazinol lactols **34** as a pale yellow oil. The unpurified oil was immediately hydrolyzed to the lactols **35** and **36**.

Hydrolysis. To a rapidly stirred solution of 256 mg of the unpurified hydrazinol lactols **34** contaminated with unreacted epoxide **21a** in 15 mL of 3:1 (v/v) pentane/CH_2Cl_2 at room temperature was added 9 mL of 10% aqueous sodium bisulfate. The resulting biphasic mixture was stirred for 15 min. The layers were separated, and the organic phase was washed with 25 mL of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were washed with 50 mL of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Thin layer chromatography analysis of the combined residues indicated five components were present: bicyclic ketals **6** and *epi*-**6** as the fastest moving components (R_f > 0.7, 30% ethyl acetate/hexane), the desired lactols **35** and **36** (R_f = 0.45, 30% ethyl acetate/hexane), the epoxide **21a** (R_f = 0.37, 30% ethyl acetate/hexane) or a derivative thereof, traces of diethyl diketone (R_f = 0.47, 30% ethyl acetate/hexane), and a more polar component (R_f < 0.3) tentatively assigned the structure arising from ethyllithium addition to the epoxide (based on low-resolution mass spectral analysis). The residue was purified by chromatography (2 cm × 18 cm, 10% ethyl acetate/hexane) to afford 9 mg of the bicyclic ketals **6** and *epi*-**6** and 40 mg (48%) of the lactols **35** and **36** as a mixture of C_{17}–C_{18} diastereomers. To determine a diastereomeric ratio, an aliquot of the unpurified mixture of lactols **35** and **36** was converted to bicyclic ketals **6** and *epi*-**6** (vide infra). The ratio of lactols **35** and **36** was found to be 90:10 by capillary GLC analysis (DB-1, 190 °C, 5 psi, t_r **6** = 5.07, t_r *epi*-**6** = 5.18 min) of their respective bicyclic ketals. The lactols **35** and **36** were separated by chromatography (2 cm × 18 cm, 10% ethyl acetate/hexane) to afford **35** as a colorless oil: $[\alpha]_D$ −14.3° (*c* 1.2, CH_2Cl_2); IR (CH_2Cl_2) 3500 (br), 2980, 2940, 2880, 1710, 1465, 1380, 1055, 1035, 985 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.71 (dd, 1 H, *J* = 9.75 and 5.4 Hz, C_{13}-H), 3.59 (br dd, 2 H, *J* = 10.1 and 2.2 Hz, C_{21}-H and C_{21}-OH), 2.62–2.69 (m, 1 H, C_{12}-H), 2.56 (dq, 1 H, *J* = 18.2 and 7.3 Hz, one C_{10}-H), 2.37 (dq, 1 H, *J* = 18.2 and 7.3 Hz, one C_{10}-H), 2.10–2.20 (m, 2 H, C_{14}-H and C_{18}-H), 2.05 (dd, 1 H, *J* = 12.0 and 12.0 Hz, one C_{15}-H), 1.98 (dd, 1 H, *J* = 11.8 and 11.8 Hz, one C_{18}-H), 1.70–1.80 (m, 2 H, one C_{12}-CH_2CH_3 and one C_{19}-H), 1.45–1.60 (m, 4 H, both C_{20}-CH_2CH_3, one C_{12}-CH_2CH_3, and one C_{15}-H), 1.35–1.45 (m, 1 H, one C_{22}-H), 1.15–1.20 (m, 1 H, one C_{22}-H), 1.14 (s, 3 H, C_{16}-CH_3), 1.01 (t, 3 H, *J* = 7.1 Hz, C_{10}-CH_3), 1.03 (d, 3 H, *J* = 6.3 Hz, C_{18}-CH_3), 1.00 (t, 3 H, *J* = 7.3 Hz, C_{22}-CH_3), 0.93 (d, 3 H, *J* = 6.3 Hz, C_{14}-CH_3), 0.89 (t, 3 H, *J* = 7.4 Hz, C_{20}-CH_2CH_3), 0.82 (t, 3 H, *J* = 7.4 Hz, C_{12}-CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.2, 107.8, 88.2, 86.9, 85.0, 73.1, 57.4, 42.5, 38.1, 37.5, 37.3, 36.6, 30.4, 24.8, 24.6, 21.0, 16.2, 14.0, 12.5, 10.9, 7.5, 7.4; TLC R_f 0.45 (30% ethyl acetate:hexane). Anal. Calcd for $C_{22}H_{40}O_5$: C, 68.71; H, 10.48. Found: C, 68.72; H, 10.45.

[1*R*-[1α,1[2*S(*R**),3*S**,5*S**],3β,4α,6β]]-4-[5-(3,4-Diethyl-6-methyl-2,7-dioxabicyclo[2.2.1]hept-1-yl)tetrahydro-3,5-dimethyl-2-furanyl]-3-hexanone (6).** To a solution of 10 mg (0.026 mmol) of lactol **35** in 2.5 mL of methanol at room temperature was added 4 mg (cat) of pyridinium *p*-toluenesulfonate. After 2 h, the reaction was quenched by addition of 2 mL of 5% aqueous sodium bicarbonate and extracted with 3:1 (v/v) pentane/CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 50 mL of saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford 7 mg (73% yield) of the bicyclic ketal **6** as a colorless oil in 99% diastereomeric purity as determined by capillary GLC analysis; $[\alpha]_D$ −20.8° (*c* 0.12, CH_2Cl_2); IR (CH_2Cl_2) 2880–3000, 1710, 1460, 1375, 1120, 1065, 1030, 955, 940 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.90 (dd, 1 H, *J* = 9.4 and 5.6 Hz, C_{13}-H), 3.50 (ddd, 1 H, *J* = 9.6, 3.6, and 1.7 Hz, C_{21}-H), 2.54 (ddd, 1 H, *J* = 10.2, 5.6, and 3.6 Hz, C_{12}-H), 2.48 (dq, 1 H, *J* = 18.1 and 7.2 Hz, one C_{10}-H), 2.41–2.48 (m, 1 H, C_{18}-H), 2.28 (dd, 1 H, *J* = 12.3 and 10.3 Hz, one C_{15}-H), 2.17 (dq, 1 H, *J* = 18.2 and 7.2 Hz, one C_{10}-H), 2.00–2.05 (m, 1 H, C_{14}-H), 1.88–1.95 (m, 1 H, one C_{12}-CH_2CH_3), 1.80 (dd, 1 H, *J* = 12.3 and 8.4 Hz, one C_{15}-H), 1.67 (ddd, 1 H, *J* = 11.7, 11.7, and 1.8 Hz, exo C_{19}-H), 1.40–1.57 (m, 4 H, one C_{12}-CH_2CH_3, one C_{22}-H, and both C_{20}-CH_2CH_3), 1.35 (s, 3 H, C_{16}-CH_3), 1.31 (d, 3 H, *J* = 6.9 Hz, C_{18}-CH_3), 1.13–1.27 (m, 2 H, one C_{22}-H, and endo C_{19}-H), 1.05 (t, 3 H, *J* = 7.2 Hz, C_{10}-CH_3), 0.96 (t, 3 H, *J* = 7.4 Hz, C_{22}-CH_3), 0.92 (d, 3 H, *J* = 6.4 Hz, C_{14}-CH_3), 0.87 (t, 3 H, *J* = 7.4 Hz, C_{20}-CH_2CH_3), 0.79 (t, 3 H, *J* = 7.4 Hz, C_{12}-CH_2CH_3); ^{13}C NMR (C_6D_6, 75 MHz) δ 211.5, 112.6, 88.2, 86.8, 82.,0, 57.8, 43.8, 39.4, 37.3, 36.5, 35.8, 30.1, 25.0, 24.6, 23.5, 21.3, 16.5, 15.4, 12.6, 11.6, 8.3, 7.6; exact mass calcd for $C_{22}H_{39}O_4$(M + 1) 367.2848, found 367.2848.

(4*R*,5*S*)-3-[1-Oxo-2-(phenylmethoxy)ethyl]-4-methyl-5-phenyl-2-oxazolidinone (38). A solution of 2.90 g (16.4 mmol) of (4*R*,5*S*)-norephedrine 2-oxazolidinone[50] (0.25 M in THF) was metalated with 10.5 mL (1.57 M in hexane, 16.5 mmol) of *n*-butyllithium and acylated with 3.00 g (16.2 mmol) of (phenylmethoxy)acetal chloride according to the general acylation procedure[50] to give 5.72 g (109% mass balance) of crude product. The title compound was isolated by flash chromatography (3 × 30 cm column, 8:2 hexanes/ethyl acetate) to afford 4.61 g (87%) of the *N*-propionyloxazolidinone as a white crystalline solid: mp 99–100 °C; IR ($CDCl_3$) 3040, 3000, 2930, 1785, 1725, 1380, 1350, 1260, 1220, 1205, 1150, 1125 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.33 (s, 10 H, aromatic H's), 5.68 (d, 1 H, *J* = 7.2 Hz, C_5-*H*), 4.75 (qn, 1 H, *J* = 6.8 Hz, C_4-*H*), 4.71 (s, 2 H, C_2-H_2), 4.66 (s, 2 H, OCH_2Ph), 0.93 (d, 3 H, *J* = 6.8 Hz, C_4-H_3); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 169.8, 152.9, 137.2, 133.0, 128.8, 128.7, 128.4, 128.0, 125.6, 79.9, 73.4, 69.7, 54.4, 14.5; $[\alpha]_{589}$ +16.2° (*c* 2.47, CH_2Cl_2). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89. Found: C, 70.06; H, 5.97.

(4*R*,5*S*)-3-[(2*S*)-1-Oxo-2,4-dimethylpent-4-enyl]-4-methyl-5-phenyloxazolidin-2-one (39). To a solution of 3.00 mL (21.5 mmol) of diisopropylamine in 45 mL of THF at −78 °C was added 13.5 mL (21.2 mmol) of 1.57 M *n*-butyllithium in hexane. After 30 min, a solution of 4.67 g (21.0 mmol) of propionate imide **38** in 5 mL of tetrahydrofuran

(51) Ethyllithium was stored in benzene and, prior to use, required the evaporation of benzene and addition of ether. Storage of ethyllithium in ether results in rapid decomposition (<1 day).

(52) On occasions when TLC indicated that the starting material was still present, another aliquot of ethyllithium in ether was added until no starting material remained.

(53) Several experiments in which the amount of epoxide was varied indicated that the best results were obtained when a total of >5 equiv of epoxide was used and added as described above in two portions with a period of 2 h between additions.

was added dropwise. After an additional 30 min, 7.28 g (40.0 mmol) of methallyl iodide was added neat, and the mixture was stirred for 1 h at −78 °C, 2 h at −40 °C, and then for 15 min at −20 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride. The volatiles were removed in vacuo and the aqueous layer extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a yellow oil. Capillary GLC analysis (DB-5, 200 °C, 15 psi, t_r **39** = 2.64 min, t_r C_6 *epi*-**39** = 2.30 min) of the residue showed a 96:4 ratio of diastereomers. Chromatography on silica gel (MPLC, Merck Lobar C column, 5% ethyl acetate/hexane) afforded 4.18 g (73%) of the alkylation product **39** as a white solid, which was >99% diastereomerically pure by GLC analysis: mp 42–44 °C; $[\alpha]_D$ +33.7° (*c* 5.9, CH_2Cl_2); IR (CH_2Cl_2) 3062, 2998, 1780, 1700, 1342, 1195, 1120, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.45 (m, 3 H, ArH), 7.28–7.33 (m, 2 H, ArH), 5.66 (d, 1 H, *J* = 7.4 Hz, Ph-C*H*), 4.70–4.85 (m, 3 H, N-C*H* and both C_3-H), 4.05 (tq, 1 H, *J* = 7.0 Hz, C_6-H), 2.52 (dd, 1 H, *J* = 14.0 and 7.0 Hz, one C_5-H), 2.04 (dd, 1 H, *J* = 14.0 and 7.8 Hz, one C_5-H), 1.77 (s, 3 H, C_4-CH_3), 1.17 (d, 3 H, *J* = 6.7 Hz, C_6-CH_3), 0.86 (d, 3 H, *J* = 6.5 Hz, N-CH-CH_3); ^{13}C NMR ($CDCl_3$) δ 176.7, 152.7, 142.9, 133.4, 128.7, 125.6, 112.3, 78.7, 54.8, 41.7, 35.6, 22.3, 16.8, 14.5; TLC R_f 0.52 (50% ethyl acetate/hexane). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37. Found: C, 70.94; H, 7.26.

(2*S*)-2,4-Dimethylpent-4-en-1-ol (40a). To a well-stirred suspension of 2.23 g (58.8 mmol) of lithium aluminum hydride in 120 mL of diethyl ether at 0 °C was added dropwise a solution of 16.91 g (58.92 mmol) of imide **39** in 25 mL of diethyl ether. The ice bath was removed and the mixture allowed to warm to room temperature. After stirring for 30 min, the reaction was quenched by sequential addition of 2.2 mL of water, 2.2 mL of 15% aqueous sodium hydroxide, and 6.6 mL of water. The mixture was filtered, and the filtrate was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by atmospheric fractional distillation. Kugelrohr distillation of the remaining residue (73 °C, 18 mmHg) afforded 5.10 g of the alcohol **40a** as a colorless oil. The nondistilled residue was dissolved in warm ether and the oxazolidinone partially precipitated by the addition of petroleum ether. Filtration followed by concentration and distillation as above afforded an additional 568 mg of product for a combined yield of 85%: $[\alpha]_D$ −3.9° (*c* 4.1, CH_2Cl_2); IR ($CHCl_3$) 3645, 3400 (br), 3090, 2940, 1649, 1453, 1375, 1123, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (s, 1 H, one C_3-H), 4.71 (s, 1 H, one C_3-H), 3.50 (dd, 1 H, *J* = 8.7 and 5.7 Hz, one C_7-H), 3.42 (dd, 1 H, *J* = 8.7 and 5.7 Hz, one C_7-H), 2.64 (br s, 1 H, OH), 2.09–2.18 (m, 1 H, one C_5-H), 1.81–1.91 (m, 2 H, one C_5-H and C_6-H), 1.73 (s, 3 H, C_4-CH_3), 0.89 (d, 3 H, *J* = 6.5 Hz, C_6-CH_3); ^{13}C NMR ($CDCl_3$) δ 144.3, 111.7, 68.0, 42.2, 33.6, 22.2, 16.6; TLC R_f 0.44 (50% ethyl acetate/hexane). Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.58; H, 12.10.

(2*S*)-2,4-Dimethylpent-4-en-1-al (40b). To a solution of 2.66 g (23.3 mmol) of alcohol **40a** and 22.7 mL (163 mmol) of triethylamine in 50 mL of dimethyl sulfoxide at 25 °C was slowly added a solution of 11.11 g (69.87 mmol) of pyridine sulfur trioxide complex in 50 mL of dimethyl sulfoxide. After 15 min, the reaction was quenched by partitioning between 250 mL of diethyl ether and 150 mL of water. After the aqueous layer was discarded, the cloudly ethereal layer was washed twice with 50 mL of saturated aqueous cupric sulfate, once with 25 mL of water, dried over anhydrous magnesium sulfate, filtered, and concentrated by atmospheric fractional distillation. Kugelrohr distillation of the remaining liquid (90 °C, 140 mmHg) afforded 2.21 g (87%) of aldehyde **40b**: IR ($CHCl_3$) 2985, 2955, 1715, 1460, 1383, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.64 (d, 1 H, *J* = 2.0 Hz, C_7-H), 4.80 (s, 1 H, one C_3-H), 4.71 (s, 1 H, one C_3-H), 2.65–1.80 (m, 3 H, C_6-H and both C_5-H), 1.72 (s, 3 H, C_4-CH_3), 1.05 (d, 3 H, *J* = 6.5 Hz, C_6-CH_3); TLC R_f 0.66 (50% ethyl acetate/hexane).

(4*R*,5*S*)-3-[(2*R*,3*S*,4*S*)-1-Oxo-2,4,6-trimethyl-3-hydroxyhept-6-enyl]-4-methyl-5-phenyloxazolidin-2-one (41). To a solution of 1.75 g (7.51 mmol) of propionate imide **38** in 20 mL of CH_2Cl_2 at −78 °C was added 2.02 mL (8.25 mmol) of di-*n*-butylboryl triflate.[54] The dry ice bath was subsequently removed until the triflate solubilized. After the solution was recooled to −78 °C, 1.25 mL (8.92 mmol) of triethylamine was added dropwise. After 1 h, 0.98 mL (7.5 mmol) of aldehyde **40b** was added neat in one portion. The solution was stirred for 30 min at −78 °C, 1 h at 0 °C, and then quenched by the addition of 7 mL of pH 7 aqueous phosphate buffer. After enough methanol was added to make the solution homogeneous, a solution containing 7 mL of 30% aqueous hydrogen peroxide in 7 mL of methanol was slowly added, and the mixture stirred at 0 °C for 1 h. The volatiles were removed in vacuo, and the remaining aqueous slurry was extracted twice with 100 mL of diethyl ether. The combined ethereal layers were washed with 5% aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a white solid. Capillary GLC analysis of an unpurified, silylated sample ($TMSNEt_2$, DMAP, CH_2Cl_2) showed >99.5% of the desired diastereomer (DB-5, 225 °C, 10 psi, t_r = 7.22 min). Purification by chromatography on silica gel (MPLC, Merck Lobar C column, gradient of 20 to 30% ethyl acetate/hexane) afforded 2.22 g (86%) of imide **41** as a white crystalline solid: mp 110–111 °C; $[\alpha]_D$ +17.0° (*c* 2.6, CH_2Cl_2); IR (CH_2Cl_2) 3695, 3550, 3060, 2980, 1785, 1685, 1346, 1198, 892 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.47 (m, 3 H, ArH), 7.29–7.34 (m, 2 H, ArH), 5.68 (d, 1 H, *J* = 7.2, Ph-C*H*), 4.76–4.84 (m, 2 H, N-C*H* and one C_3-H), 4.72 (s, 1 H, one C_3-H), 3.98 (qd, 1 H, *J* = 7.3 and 2.5 Hz, C_8-H), 3.76 (dd, 1 H, *J* = 8.0 and 2.5 Hz, C_7-H), 3.00 (br s, 1 H, OH), 2.61 (m, 1 H, one C_5-H), 1.74–1.80 (m, 2 H, C_6-H and one C_5-H), 1.73 (s, 3 H, C_4-CH_3), 1.24 (d, 3 H, *J* = 6.9 Hz, C_8-CH_3), 0.90 (d, 3 H, *J* = 7.0 Hz, C_6-CH_3), 0.86 (d, 3 H, *J* = 6.1 Hz, N-CH-CH_3); ^{13}C NMR (CCl_4) δ 176.8, 151.6, 144.1, 133.6, 128.4, 125.4, 111.9, 78.4, 75.3, 54.3, 41.6, 39.7, 33.7, 22.2, 15.0, 14.2, 9.4; TLC R_f 0.41 (50% ethyl acetate/hexane). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88. Found: C, 69.36; H, 7.75.

(2*S*,3*S*,4*S*)-2,4,6-Trimethyl-1,3-dihydroxyhept-7-ene (42a). To a solution of 3.42 g (9.91 mmol) of aldol adduct **41** in 35 mL of THF at −30 °C was added dropwise 5.40 mL (10.9 mmol) of a 2.0 M solution of lithium borohydride in THF. The solution was stirred at −30 °C for 1 h, warmed to −11 °C, and gradually allowed to warm to 0 °C over a period of 4 h. The reaction mixture was quenched with excess saturated aqueous ammonium chloride, the volatiles were removed in vacuo (10 torr, 25 °C), and the aqueous layer was extracted with CH_2Cl_2 (5 × 40 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and the residue was purified by chromatography on silica gel (5 cm × 20 cm, 45% ethyl acetate/hexane) to afford 1.53 g (90%) of diol **42a** as an oil: $[\alpha]_D$ −3.8° (*c* 2.5, CH_2Cl_2); IR (thin film) 3400 (br), 2975, 2940, 2880, 1645, 1455, 1375, 1030, 970, 885, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1 H, one C_3-H), 4.75 (s, 1 H, one C_3-H), 3.69–3.81 (m, 2 H, both C_9-H), 3.53–3.59 (m, 1 H, C_7-H), 2.43–2.56 (m, 3 H, includes both OH's), 1.68–1.89 (m, 3 H), 1.74 (s, 3 H, C_4-CH_3), 0.97 (d, 3 H, *J* = 7.1 Hz), 0.79 (d, 3 H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 111.5, 77.7, 66.8, 42.2, 36.1, 34.1, 22.0, 15.1; TLC R_f 0.30 (50% ethyl acetate/hexane). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 69.72; H, 11.58.

[4-(1*S*)-2*R*,4*S*,5*S*]-2-(1-Naphthyl)-4-(1,3-dimethylbut-4-enyl)-5-methyl-1,3-dioxane (42b). A mixture of 78 mg (0.45 mmol) of diol **9**, 0.12 mL (0.88 mmol) of 1-naphthaldehyde, 28 mg (0.17 mmol) of trichloroacetic acid, and 200 mg of 3-Å molecular sieves in 2 mL of benzene was stirred for 12 h at room temperature. The reaction was quenched by adding 0.2 mL of triethylamine, filtered, dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (Merck Lobar C, 5% ethyl acetate/hexane) to afford 116 mg (82%) of **42b** as an oil: $[\alpha]_D$ −0.35° (*c* 1.7, CH_2Cl_2); IR (thin film) 3080, 2990, 2940, 2860, 1645, 1600, 1510, 1460, 1380, 1335, 1240, 1155, 1120, 1110, 1025, 1000, 885, 790, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 1 H, ArH), 7.80–7.86 (m, 3 H, ArH), 7.44–7.53 (m, 3 H, ArH), 6.04 (s, 1 H, acetal-H), 4.74 (s, 1 H, one C_3-H), 4.68 (s, 1 H, one C_3-H), 4.19 (dd, 1 H, *J* = 11.1 and 2.1 Hz, one C_9-H), 4.11 (dd, 1 H, *J* = 11.7 and 0.8 Hz, one C_9-H), 3.60 (dd, 1 H, *J* = 9.7 and 2.0 Hz, C_7-H), 2.63–2.68 (m, 1 H), 1.66–1.89 (m, 3 H), 1.64 (s, 3 H, C_4-CH_3), 1.23 (d, 3 H, *J* = 6.9 Hz), 0.80 (d, 3 H, *J* = 6.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 133.9, 133.6, 130.4, 129.0, 128.3, 125.8, 125.3, 125.0, 123.9, 123.6, 111.6, 100.0, 84.8, 74.1, 41.5, 32.3, 30.2, 22.2, 13.4, 11.1; TLC R_f 0.65 (50% ethyl acetate/hexane). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.29; H, 8.39. Found: C, 81.38; H 8.40.

[4-(1*S*,3*R*)-2*R*,4*S*,5*S*]-2-(1-Naphthyl)-4-(1,3-dimethyl-4-hydroxybutyl)-5-methyl-1,3-dioxane (43a) and [4-(1*S*,3*S*)-2*R*,4*S*,5*S*]-2-(1-Naphthyl)-4-(1,3-dimethyl-4-hydroxybutyl)-5-methyl-1,3-dioxane, Minor Isomer (C_4-*epi* 43a). A 0.5 M solution of thexylborane was generated by adding dropwise 7.0 mL (7.0 mmol) of a of 1 M solution of tetramethylethylene in THF to 7.0 mL (7.0 mmol) of a 1 M solution of borane in THF at −10 °C and stirring the solution at −10 °C for 2.5 h. To a separate flask containing 924 mg (2.98 mmol) of the naphthylidene acetal **42b** in 12 mL of THF at −10 °C was added 12.0 mL (6.00 mmol) of the cold thexylborane solution. After stirring for 5 hr at −10 °C, the reaction was quenched by careful sequential addition of 8 mL of 5% aqueous sodium bicarbonate, 30 mL of methanol, and 8 mL of 30% aqueous hydrogen peroxide. After the solution was stirred at 0 °C for

(54) Commercial preparations of di-*n*-butylboryl triflate (Aldrich) has not proven to be reliable in the execution of these aldol reactions. It is strongly recommended that this reagent be prepared according to the advertised procedure: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

an additional hour, the volatiles were removed in vacuo, and the residue extracted with diethyl ether (4 × 50 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (MPLC, Merck, Lobar B, two columns in series, 20% ethyl acetate/hexane) to afford 772 mg (79%) of the major desired diastereoisomer **43a** as an oil, followed by 118 mg (12%) of the minor diastereoisomer C_4-*epi* **43a**. Major isomer **43a**: $[\alpha]_D$ +12.7° (*c* 3.45, CH_2Cl_2); IR (thin film) 3450 (br), 2960, 2940, 2870, 1735, 1600, 1510, 1465, 1380, 1335, 1240, 1170, 1120, 1020, 1000, 800, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.12 (m, 1 H, ArH), 7.79–7.84 (m, 3 H, ArH), 7.24–7.53 (m, 3 H, ArH), 6.05 (s, 1 H, acetal-H), 4.18 (dd, 1 H, *J* = 11.2 and 2.4 Hz, one C_9-H), 4.10 (dd, 1 H, *J* = 11.2 and 1.4 Hz, one C_9-H), 3.59 (dd, 1 H, *J* = 9.9 and 2.1 Hz, C_7-H), 3.29 (dd, 1 H, *J* = 10.9 and 4.5 Hz, one C_3-H), 3.21 (dd, 1 H, *J* = 10.8 and 6.0 Hz, one C_3-H), 1.63–1.84 (m, 5 H, includes OH), 1.21 (d, 3 H, *J* = 6.9 Hz), 0.87–0.99 (m, 1 H), 0.87 (d, 6 H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8, 133.6, 130.4, 129.1, 128.4, 125.7, 125.3, 125.0, 123.8, 123.6, 100.1, 85.5, 74.1, 67.1, 37.6, 33.4, 32.2, 30.1, 18.3, 15.2, 10.9; TLC R_f 0.59 (50% ethyl acetate/hexane). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.83; H, 8.54. Found: C, 76.82; H, 8.60.

Minor isomer C_4-*epi* **43a**: $[\alpha]_D$ +4.01° (*c* 2.23, CH_2Cl_2); IR ($CHCl_3$) 3010, 2960, 2940, 2860, 1510, 1460, 1380, 1330, 1220, 1160, 1115, 1025, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.13 (m, 1 H, ArH), 7.82–7.84 (m, 3 H, ArH), 7.45–7.51 (m, 3 H, ArH), 4.13 (dd, 1 H, *J* = 11.2 and 2.0 Hz, one C_9-H), 4.05 (dd, 1 H, *J* = 11.3 and 0.3 Hz, one C_9-H), 3.52 (dd, 1 H, *J* = 9.9 and 1.8 Hz, C_7-H), 3.28 (dd, 1 H, *J* = 10.3 and 6.2 Hz, one C_3-H), 3.24 (dd, 1 H, *J* = 10.2 and 5.9 Hz, one C_3-H), 2.04 (br s, 1 H, OH), 1.52–1.79 (m, 4 H), 1.19 (d, 3 H, *J* = 6.83 Hz), 1.04–1.13 (m, 1 H), 0.79 (d, 3 H, *J* = 6.7 Hz), 0.72 (d, 3 H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 133.6, 130.4, 129.0, 128.3, 125.6, 125.2, 125.0, 123.9, 123.6, 100.1, 85.2, 74.1, 68.7, 36.3, 33.0, 31.3, 30.1, 15.8, 14.1, 11.0; TLC R_f 0.51 (50% ethyl acetate/hexane); exact mass calcd for $C_{21}H_{28}O_3$ (M^+) 328.2038, found 328.2033.

[4-(1*S*,3*R*)-2*R*,4*S*,5*S*]-2-(1-Naphthyl)-4-(1,3-dimethyl-4-oxobutyl)-5-methyl-1,3-dioxane (43b). To a solution of 0.045 mL (0.51 mmol) of oxalyl chloride in 1 mL of CH_2Cl_2 at −78 °C was added a solution of 0.10 mL (1.4 mmol) of dimethyl sulfoxide in 2 mL of CH_2Cl_2. After 30 min, a solution of 152 mg (0.463 mmol) of alcohol **43a** in 2 mL of CH_2Cl_2 was added. After an additional 30 min, 0.25 mL (1.8 mmol) of trietylamine was added at −78 °C, and the reaction mixture was allowed to warm to room temperature. Water was added and the mixture extracted with pentane (3 × 15 mL). The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Flash chromatography of the residue on silica gel (2 cm × 15 cm, 15% ethyl acetate/hexane) afforded 143 mg (95%) of aldehyde **43b** as a clear oil: $[\alpha]_D$ +40.8° (*c* 2.45, CH_2Cl_2); IR (thin film) 2980, 2940, 2860, 1730, 1515, 1465, 1390, 1340, 1245, 1170, 1115, 1000, 800, 775, 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.36 (d, 1 H, *J* = 2.9 Hz, C_3-H), 8.08–8.12 (m, 1 H, ArH), 7.80–7.84 (m, 3 H, ArH), 7.41–7.52 (m, 3 H, ArH), 6.00 (s, 1 H, acetal-H), 4.15 (dd, 1 H, *J* = 11.2 and 2.3 Hz, one C_9-H), 4.06 (dd, 1 H, *J* = 11.2 and 1.3 Hz, one C_9-H), 3.60 (dd, 1 H, *J* = 9.9 and 2.1 Hz, C_7-H), 2.41–2.58 (m, 1 H), 2.13–2.26 (m, 1 H), 1.64–1.81 (m, 2 H), 1.18 (d, 3 H, *J* = 6.9 Hz), 1.07–1.20 (m, 1 H), 1.01 (d, 3 H, *J* = 6.9 Hz), 0.85 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 205.1, 133.8, 133.6, 130.4, 129.0, 128.3, 125.8, 125.0, 123.8, 123.6, 100.1, 85.0, 74.0, 44.2, 35.1, 32.3, 30.1, 14.8, 14.6, 10.9; TLC R_f 0.42 (25% ethyl acetate/hexane). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.30; H, 7.98. Found: C, 77.19; H, 7.87.

(4*S*)-3-(1-Oxopropyl)-4-(1-methylethyl)-2-oxazolidinone (43c). A mechanically stirred solution of 115 g (0.891 mol) of (*S*)-valine-derived 2-oxazolidinone[50] (0.9 M in THF) was metalated with 550 mL (1.76 M in hexane, 0.968 mol) of *n*-butyllithium and acylated with 100 mL (107 g, 1.18 mol) of propanoyl chloride according to the general acylation procedure[50] to give 180 g of unpurified product. The title compound was isolated by molecular distillation (Kugelrohr, 100 °C, 0.01 mm) to afford 153 g (93%) of **43c** as a colorless liquid: $[\alpha]_{589}$ = +92° (*c* 0.38, CH_2Cl_2); IR (neat) 2970, 2880, 1785, 1705, 1385, 1370, 1245, 1210, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.6–4.1 (m, 3 H, C_4-*H*, C_5-H_2), 2.95 (q, 2 H, *J* = 7.6 Hz, C_2-H_2), 2.57–2.22 (m, 1 H, C_4-C*H*), 1.18 (t, 3 H, *J* = 7.6 Hz, C_3-H_3), 0.92 (overlapping d's, 6 H, $CH(CH_3)_2$). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.38; H, 8.30.

(4*S*)-3-[(2*S*,3*R*,4*R*,6*S*,7*S*,8*S*)-2,4,6,8-Tetramethyl-3-hydroxy-7,9-((*R*)-naphthylmethylenedioxy)-1-oxononanyl]-4-(1-methylethyl)-2-oxazolidinone (44). To a solution of 129 mg (0.697 mmol) of the valine-derived propionate imide in 2 mL of CH_2Cl_2 at −78 °C was added 0.19 mL (0.76 mmol) of di-*n*-butylboryl triflate.[54] The mixture was warmed briefly to dissolve the triflate, recooled to −78 °C, and 0.12 mL (0.86 mmol) of triethylamine was added. After the mixture was stirred at −78 °C for 1 h, a solution of 143 mg (0.438 mmol) of aldehyde **43b** in 2 mL of CH_2Cl_2 was added dropwise. The solution was stirred at −78 °C for 1 h, at 0 °C for 1 h, and then quenched by the sequential addition of 1 mL of pH 7 aqueous phosphate buffer, 3 mL of methanol, and 1 mL of 1:1 methanol:30% aqueous hydrogen peroxide. After stirring at 0 °C for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and the residue was chromatographed on silica gel (3 cm × 15 cm, 30% ethyl acetate/hexane) to afford 196 mg (87%) of aldol adduct **44** as white needles: mp 131–133 °C; $[\alpha]_D$ +20.9° (*c* 1.13, CH_2Cl_2); IR ($CHCl_3$) 3020, 3180, 1780, 1700, 1455, 1385, 1370, 1350, 1300, 1205, 1120, 1070, 1030, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 1 H, ArH), 7.78–7.82 (m, 3 H, ArH), 7.42–7.53 (m, 3 H, ArH), 6.03 (s, 1 H, acetal-H), 4.18 (dd, 1 H, *J* = 10.1 and 1.7 Hz, one C_9-H), 4.04–4.08 (m, 2 H, one C_9-H and N-C*H*), 3.96 (dd, 1 H, *J* = 9.1 and 2.7 Hz, one N-CH-C*H*-O), 3.81–3.87 (m, 2 H, C_2-H and one N-CH-C*H*-O), 3.64 (dd, 1 H, *J* = 9.7 and 1.5 Hz, C_7-H), 3.47 (dd, 1 H, *J* = 8.5 and 2.7 Hz, C_3-H), 2.60 (br s, 1 H, OH), 2.16–2.25 (m, 1 H, N-CH-C*H*-CH_3), 2.00–2.10 (m, 1 H, C_5-H), 1.89–1.99 (m, 1 H, C_6-H), 1.80–1.86 (m, 1 H, C_4-H), 1.72–1.79 (m, 1 H, C_8-H), 1.22 (d, 3 H, *J* = 6.8 Hz, C_8-CH_3), 0.97–1.06 (m, 1 H), 0.87–0.90 (m, 9 H), 0.73–0.77 (m, 6 H, both N-CH-CH-CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.8, 153.1, 133.9, 133.4, 130.3, 128.8, 128.1, 125.7, 125.2, 124.9, 123.8, 123.7, 100.1, 86.2, 75.8, 74.1, 62.7, 57.9, 39.4, 34.4, 32.1, 30.2, 27.9, 17.4, 16.8, 16.2, 14.2, 11.0, 9.8. Anal. Calcd for $C_{30}H_{41}NO_6$: C. 70.45; H, 8.02. Found: C, 70.57; H, 8.17.

(4*S*)-3-[(2*S*,3*R*,4*R*,6*S*,7*S*,8*S*)-2,4,6,8-Tetramethyl-3-[(trimethylsilyl)oxy]-7,9-((*R*)-naphthylmethylenedioxy)-1-nonanyl]-4-(1-methylethyl)-2-oxazolidinone (47). To a solution of 271 mg (0.530 mmol) of aldol adduct **44** in 4 mL of CH_2Cl_2 were added 0.13 mL (0.88 mmol) of (trimethylsilyl)imidazole and 20 mg (0.16 mmol) of (*N*,*N*-dimethylamino)pyridine. After stirring at room temperature for 5 h, the solution was concentrated in vacuo, and the resulting residue chromatographed on silica gel (3 cm × 15 cm, 15% ethyl acetate/hexane) to afford 281 mg (91%) of a clear oil: $[\alpha]_D$ +13.4° (*c* 0.91, CH_2Cl_2); IR ($CHCl_3$) 2980, 1780, 1700, 1470, 1390, 1260, 1220, 1120, 1080, 1005, 890, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 1 H, ArH), 7.73–7.84 (m, 3 H, ArH), 7.38–7.52 (m, 3 H, ArH), 5.98 (s, 1 H, acetal-H), 4.24 (dd, 1 H, *J* = 11.1 and 2.3 Hz, one C_9-H), 4.07 (d, 1 H, *J* = 11.1 and 0.8 Hz, one C_9-H), 3.88–3.97 (m, 1 H, C_2-H), 3.88 (dd, 1 H, *J* = 8.1 and 2.9 Hz, C_3-H), 3.63 (dd, 1 H, *J* = 9.8 and 2.0 Hz, C_7-H), 3.46 (dd, 1 H, *J* = 9.1 and 3.6 Hz, one N-CH-C*H*-O), 3.18–3.23 (m, 1 H, N-C*H*), 2.76 (t, 1 H, *J* = 8.8 Hz, one N-CH-C*H*-O), 1.84–2.09 (m, 3 H), 1.62–1.78 (m, 2 H), 1.21 (d, 3 H, *J* = 7.0 Hz), 1.08–1.13 (m, 1 H), 1.07 (d, 3 H, *J* = 6.6 Hz, C_2-CH_3), 1.03 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.8 Hz), 0.64 (d, 3 H, *J* = 6.9 Hz), 0.56 (d, 3 H, *J* = 7.0 Hz), 0.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 153.3, 134.1, 133.6, 130.5, 128.9, 128.3, 126.1, 125.5, 123.9, 123.8, 99.8, 86.9, 77.1, 74.4, 62.2, 57.8, 40.3, 37.1, 36.0, 31.3, 30.5, 27.5, 17.6, 17.4, 16.4, 15.3, 14.2, 11.2; TLC R_f 0.40 (25% ethyl acetate/hexane). Anal. Calcd for $C_{33}H_{49}NO_6Si$: C, 67.92; H, 8.40. Found: C, 67.88; H, 8.46.

Benzyl (2*S*,3*R*,6*S*,7*S*,8*S*)-2,4,6,8-Tetramethyl-3-[(trimethylsilyl)oxy]-7,9-((*R*)-naphthylmethylenedioxy)-1-nonanoate (48). To a solution of 0.14 mL (1.3 mmol) of benzyl alcohol in 0.7 mL of THF at 0 °C was added 0.45 mL (1.1 mmol) of 2.4 M *n*-butyllithium in hexane dropwise. After stirring at 0 °C for 20 min, the solution was cooled to −20 °C, and a solution of 147 mg (0.252 mmol) of silyl ether **47** in 0.6 mL of tetrahydrofuran was added dropwise. The resulting solution was stirred at −20 °C for 24 h, quenched with saturated aqueous bicarbonate, and extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (3 cm × 15 cm, 5% and then 10% ethyl acetate/hexane) to afford 119 mg (85%) of a clear oil: $[\alpha]_D$ −4.7° (*c* 2.3, CH_2Cl_2); IR (thin film) 3060, 2960, 2880, 2850, 1730, 1515, 1500, 1460, 1390, 1340, 1250, 1170, 1120, 1070, 1030, 1000, 890, 840, 800, 775, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (m, 1 H, ArH), 7.80–7.86 (m, 3 H, ArH), 7.37–7.54 (m, 3 H, ArH), 7.28–7.32 (m, 3 H, ArH), 7.14–7.19 (m, 2 H, ArH), 6.07 (s, 1 H, acetal-H), 4.78 (s, 2 H, benzylic), 4.23 (dd, 1 H, *J* = 11.0 and 1.9 Hz, one C_9-H), 4.11 (dd, 1 H, *J* = 11.2 and 0.8 Hz, one C_9-H), 3.77 (dd, 1 H, *J* = 6.0 and 4.8 Hz, C_3-H), 3.63 (dd, 1 H, *J* = 9.6 and 1.9 Hz, C_7-H), 2.63 (dq, 1 H, *J* = 6.7 Hz, C_2-H), 1.91–1.98 (m, 1 H), 1.73–1.88 (m, 3 H), 1.24 (d, 3 H, *J* = 6.9 Hz), 1.01 (d, 3 H, *J* = 7.0, C_2-CH_3), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.90–0.95 (m, 1 H), 0.90 (d, 3 H, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 136.0, 134.1, 133.6, 130.5, 128.9, 128.24, 128.19, 127.8, 125.8, 125.2, 124.9, 124.0, 123.8, 100.2, 85.9, 77.7, 76.4, 74.2, 65.6, 42.7, 37.1, 36.3, 32.7, 30.3, 17.8, 15.9, 12.6, 11.2, 0.4; TLC R_f 0.51 (25% ethyl acetate/hexane). Anal. Calcd for $C_{34}H_{46}O_5Si$: C, 72.47; H, 8.17. Found: C, 72.54; H, 8.29.

Benzyl (2*S*,3*R*,4*R*,6*S*,7*S*,8*S*)-2,4,6,8-Tetramethyl-3,7,9-trihydroxy-1-nonanoate (49a). A solution of 45 mg (0.080 mmol) of benzyl ester **48** in 6 mL of THF and 3 mL of 1 M aqueous sulfuric acid was stirred

at 45 °C for 32 h. The solution was cooled, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2 (3 × 25 mL). The extracts were dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and the residue was flash chromatographed on silica gel (2 cm × 15 cm, ethyl acetate) to afford 23 mg (81%) of a clear oil: $[\alpha]_D$ -13.3° (*c* 1.0, CH_2Cl_2); IR (thin film) 3420 (br), 1715, 1500, 1460, 1385, 1330, 1235, 1190, 1070, 1030, 975, 910, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (br s, 5 H, ArH), 5.14 (s, 2 H, benzylic), 3.66–3.82 (m, 4 H, both C_9-H, C_3-H, and OH), 3.54 (dd, 1 H, *J* = 9.4 and 1.5 Hz, C_7-H), 3.10 (br s, 1 H, OH), 2.69 (qd, 1 H, *J* = 7.2 and 1.2 Hz, C_2-H), 1.95–2.06 (m, 1 H, C_5-H), 1.93 (br s, 1 H, OH), 1.62–1.80 (m, 3 H), 1.18 (d, 3 H, *J* = 7.2, C_2-CH_3), 0.94 (d, 3 H, *J* = 7.0 Hz), 0.91–0.99 (m, 1 H), 0.85 (d, 3 H, *J* = 6.7 Hz), 0.82 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 135.7, 128.4, 128.1, 127.9, 80.0, 67.8, 66.3, 41.6, 39.8, 36.0, 35.9, 35.2, 18.3, 18.1, 9.5, 8.8; TLC R_f 0.38 (ethyl acetate). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.18; H, 9.09. Found: C, 68.26; H, 9.19.

Benzyl (2*S*,3*R*,4*R*,6*S*,7*S*,8*S*)-2,4,6,8-Tetramethyl-3,7,9-trihydroxy-7,9-(phenylborylenedioxy)-1-nonanoate (49b). A solution of 126 mg (0.358 mmol) of triol **49a** and 45 mg (0.37 mmol) of phenylboronic acid in 7.5 mL of benzene was stirred at room temperature for 12 h. The solution was diluted with 30 mL of 2:1 hexane/CH_2Cl_2 and washed with 5% aqueous bicarbonate (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to afford 158 mg (quantitative) of a clear oil: $[\alpha]_D$ -21.6° (*c* 0.55, CH_2Cl_2); IR ($CHCl_3$) 3500 (b), 2980, 2950, 1725, 1605, 1485, 1460, 1445, 1420, 1390, 1380, 1315, 1270, 1180, 1140, 1030, 980, 940, 700, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71–7.74 (m, 2 H, ArH), 7.18–7.35 (m, 8 H, ArH), 5.06 (s, 2 H, benzylic), 4.15 (dd, 1 H, *J* = 11.0 and 2.9 Hz, one C_9-H), 3.87 (dd, 1 H, *J* = 11.0 and 1.3 Hz, one C_9-H), 3.73 (dd, 1 H, *J* = 10.0 and 2.4 Hz, C_7-H), 3.70 (dd, 1 H, *J* = 11.0 and 2.5 Hz, C_3-H), (qd, 1 H, *J* = 7.1 and 3.2 Hz, C_2-H), 2.53 (br s, 1 H, OH), 2.14–2.24 (m, 1 H, one C_5-H), 1.93–2.04 (m, 2 H, C_4-H and C_8-H), 1.70–1.81 (m, 1 H, C_6-H), 1.19 (d, 3 H, *J* = 7.1 Hz, C_2-CH_3), 0.96–1.04 (m, 1 H, C_5-H), 0.93 (d, 3 H, *J* = 7.1 Hz), 0.88 (d, 3 H, *J* = 6.7 Hz), 0.82 (d, 3 H, *J* = 6.8 Hz, C_6-CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.1, 133.8, 130.4, 128.5, 128.1, 128.0, 127.4, 80.0, 76.7, 69.4, 66.3, 42.0, 39.2, 34.7, 34.0, 31.3, 17.3, 16.9, 10.0, 9.2. Anal. Calcd for $C_{26}H_{35}BO_5$: C, 71.23; H, 7.99. Found: C, 71.27; H, 8.07.

Benzyl (2*S*)-2-[(2*R*,3*R*,5*S*,6*S*)-2-Hydroxy-3,5-dimethyl-6-((1*S*)-1-methyl-2-hydroxyethyl)tetrahydropyran-2-yl]propanoate (51a). To a solution of 0.10 mL (1.1 mmol) of oxalyl chloride in 3 mL of CH_2Cl_2 at −50 °C was added 0.20 mL (2.8 mmol) of dimethyl sulfoxide in 20 mL CH_2Cl_2. After the mixture was stirred for 30 min at −50 °C, a solution of 209 mg (0.477 mmol) of alcohol **49b** in 2 mL of CH_2Cl_2 was added. After the solution was stirred at −50 °C for 1 h and then cooled to −78 °C, 0.42 mL (2.4 mmol) of diisopropylethylamine was added. The reaction mixture was stirred at −78 °C for 10 min, gradually warmed to 0 °C, stirred at 0 °C for 1 h, and then quenched with ice-cold water. Extractive workup with CH_2Cl_2 and concentration in vacuo afforded an oil, which was dissolved in 6 mL of ethyl acetate and treated with 1 mL of 30% aqueous hydrogen peroxide in 1 mL of water for 1 h. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Chromatography of the residue on silica gel (3 cm × 15 cm, stepwise gradient of 10% to 20% to 30% ethyl acetate/hexane) afforded 130 mg (78%) of lactol **51a** as a clear oil: $[\alpha]_D$ +42.4° (*c* 0.76, CH_2Cl_2); IR ($CHCl_3$) 3540 (br), 1750, 1700, 1460, 1390, 1280, 1185, 1155, 1100, 1085, 1050, 1015, 980, 910, 700, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 5 H, ArH), 5.24 (d, 1 H, *J* = 12.3 Hz, one benzylic-H), 5.12 (d, 1 H, *J* = 12.3 Hz, one benzylic-H), 4.82 (d, 1 H, *J* = 1.4 Hz, OH of lactol), 3.75 (dd, 1 H, *J* = 10.2 and 2.2 Hz, C_7-H), 3.56 (dd, 1 H, *J* = 10.6 and 3.7 Hz, one C_9-H), 3.39–3.51 (m, 1 H, one C_9-H), 2.85 (q, 1 H, *J* = 7.2 Hz, C_2-H), 2.17 (br s, 1 H, OH), 1.75–1.87 (m, 2 H), 1.52–1.63 (m, 1 H), 1.38–1.47 (m, 2 H), 1.23 (d, 3 H, *J* = 7.2 Hz, C_2-CH_3), 0.89 (d, 3 H, *J* = 7.0 Hz), 0.88 (d, 3 H, *J* = 6.7 Hz), 0.79 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) 175.0, 135.4, 128.5, 99.2, 67.3, 67.0, 46.3, 36.2, 35.0, 34.8, 32.1, 16.8, 15.7, 11.3, 9.1; TLC R_f 0.54 (50% ethyl acetate/hexane). Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.57; H, 8.57. Found: C, 68.48; H, 8.64.

Benzyl (2*S*)-2-[(2*R*,3*R*,5*S*,6*S*)-2-Hydroxy-3,5-dimethyl-6-((1*S*)-1-methyl-2-oxoethyl)tetrahydropyran-2-yl]propanoate (51b). To a solution of 130 mg (0.371 mmol) of alcohol **51a**, 0.26 mL (1.8 mmol) of triethylamine, and 2.5 mL of dimethyl sulfoxide in 3.5 mL of CH_2Cl_2 at 0 °C was added a solution of 295 mg (1.8 mmol) of pyridine sulfur trioxide complex in 2.5 mL of dimethyl sulfoxide. The solution was stirred for 30 min at 0 °C before it was quenched by the addition of water and extracted with 1,1,1-trichloroethane (3 × 25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, and the residue was chromatographed on silica gel (3 cm × 15 cm, 20% ethyl acetate/hexane) to afford 109 mg (85%) of an oil: $[\alpha]_D$ - 18.2° (*c* 0.56, CH_2Cl_2); IR ($CHCl_3$) 3450 (br), 2990, 2970, 2940, 2880, 1740, 1700, 1460, 1280, 1270, 1190, 1160, 1100, 1050, 1020, 990, 955 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.51 (s, 1 H, C_9-H), 7.37 (s, 5 H, ArH), 5.19 (s, 1 H, OH), 5.15 (d, 1 H, *J* = 12.7 Hz, one benzylic-H), 5.02 (d, 1 H, *J* = 12.7 Hz, one benzylic-H), 4.19 (dd, 1 H, *J* = 9.9 and 2.6 Hz, C_7-H), 2.79 (q, 1 H, *J* = 7.1 Hz, C_2-H), 2.45 (qd, 1 H, *J* = 6.9 and 2.6 Hz, C_8-H), 1.74–1.88 (m, 1 H, C_4-H), 1.52–1.69 (m, 1 H, C_6-H), 1.45–1.51 (m, 2 H, both C_5-H), 1.17 (d, 3 H, *J* = 7.1 Hz, C_2-CH_3), 1.04 (d, 3 H, *J* = 6.9 Hz, C_8-CH_3), 0.90 (d, 3 H, *J* = 6.8 Hz, C_4-CH_3), 0.85 (d, 3 H, *J* = 6.3 Hz, C_6-CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 204.0, 174.6, 135.4, 128.5, 128.3, 128.2, 99.4, 73.7, 67.0, 47.1, 46.2, 36.0, 34.8, 31.8, 16.7, 15.6, 10.9, 6.0; TLC R_f 0.45 (20% ethyl acetate/hexane). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.96; H, 8.04. Found: C, 68.82; H, 8.12.

(2*S*)-2-[(2*R*,3*R*,5*S*,6*S*)-2-Hydroxy-3,5-dimethyl-6-((1*S*)-1-methyl-2-oxoethyl)tetrahydropyran-2-yl]propanoic Acid (52). To a slurry of 47 mg of 10% palladium on carbon in 5 mL of ethyl acetate at 0 °C was added a solution of 98 mg (0.28 mmol) of aldehyde **52** in 2 mL of ethyl acetate. After stirring at 0 °C for 30 min under 1 atm of hydrogen, the mixture was filtered through Celite and the solvent removed in vacuo to afford 72 mg (100%) of the acid aldehyde **52** as a white solid: IR ($CHCl_3$) 3450 (br), 2990, 2960, 2940, 2886, 1720, 1465, 1400, 1280, 1185, 1160, 1130, 1095, 1045, 1020, 985, 950, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1 H, C_9-H), 5.70 (br s, 2 H), 4.20 (dd, 1 H, *J* = 10.3 and 2.7 Hz, C_7-H), 2.77 (q, 1 H, *J* = 7.1 Hz, C_2-H), 2.47 (qd, 1 H, *J* = 6.9 and 2.7 Hz, C_8-H), 1.73–1.87 (m, 1 H), 1.57–1.73 (m, 1 H), 1.46–1.54 (m, 2 H), 1.15 (d, 3 H, *J* = 7.1 Hz, C_2-CH_3), 1.06 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.7 Hz), 0.85 (d, 3 H, *J* = 6.5 Hz); TLC R_f 0.16 (10% methanol/chloroform).

Synthetic Ferensimycin B Sodium Salt (1a). To a solution of lithium diisopropylamide (0.995 mmol) in 0.5 mL of THF (generated from 663 μL of 1.50 M *n*-butyllithium in hexane and 167 μL of diisopropylamine at 0 °C) at −78 °C was added dropwise via syringe 109 mg (0.284 mmol) of ketone **35** in 1 mL of THF over 10 min (plus 1-mL rinse). After the mixture was stirred for 45 min at −78 °C, 667 μL (0.43 mmol) of a 0.63 M solution of zinc chloride in THF was added via syringe. After the homogeneous solution was stirred for 40 min at −78 °C, 23 mg (0.088 mmol) of aldehyde **52** in 1 mL of THF was added in one portion via syringe (plus 1-mL rinse). After the homogeneous solution was stirred for an additional 30 min at −78 °C, the reaction was quenched with excess saturated aqueous sodium bicarbonate. The reaction mixture was allowed to warm to room temperature and then shaken with 15 mL of CH_2Cl_2 in a separatory funnel for 5 min to form the sodium salts of the adducts. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (3 cm × 17 cm, stepwise gradient ranging from 2% to 50% methanol/chloroform). First to elute was unreacted ketone **35** (80.2 mg, 74%), followed by 15.0 mg of synthetic ferensimycin B sodium salt (**1a**, threo Cram), 4.0 mg of adduct **54** (threo-anti Cram), 14.4 mg of adduct **55** (erythro-anti Cram), and 3.5 mg of adduct **56** (erythro Cram). The combined yield was 63% based on aldehyde, in a ratio of 41:11:39:9. Ratios were determined from the weights of the isolated adducts. After epimerization (10 equiv $Ba(OH)_2 \cdot 8H_2O$, hexane, 25 °C, 8 h) of the erythro Cram adduct **56** to the desired threo Cram stereochemistry of the natural product in 75% yield, the combined yield of synthetic ferensimycin B sodium salt was 30%. Under similar conditions, the erythro-anti Cram adduct **55** was epimerized to threo-anti Cram adduct **54** in 40% yield.

Synthetic ferensimycin B sodium salt: mp 142–144 °C (natural mp 143–145 °C); $[\alpha]_D$ + 5.9° (*c* 0.49, $CHCl_3$) (natural $[\alpha]_D$ + 5.5° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3300 (br), 2980, 2940, 2880, 1740, 1715, 1585, 1460, 1380, 1250, 1110, 1050, 980 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 7.60 (br s, 1 H, OH), 6.69 (br s, 1 H, OH), 4.73 (s, 1 H, OH), 4.08 (s, 1 H, OH), 4.01 (apparent d, 1 H, J_{9-10} = 10.3 Hz, C_9-H), 3.93 (apparent d, 1 H, *J* = 10.2 Hz, C_{13}-H), 3.80 (dd, 1 H, *J* = 10.3 and 3.1 Hz, C_7-H or C_{21}-H), 3.63 (dd, 1 H, *J* = 8.8 Hz and 2.2 Hz, C_7-H or C_{21}-H), 2.70 (dq, 1 H, J_{9-10} = 10.1 Hz and *J* = 7.2 Hz, C_{10}-H), 2.62 (q, 1 H, *J* = 7.0 Hz, C_2-H), 2.44 (apparent d, 1 H, *J* = 10.8 Hz, C_{12}-H), 2.23–2.31 (m, 1 H, C_{14}-H), 1.20 (s, 3 H, C_{16}-CH_3), 1.06 (d, 6 H, *J* = 6.6 Hz, C_2-CH_3 and C_{14}-CH_3); ^{13}C NMR ($CHCl_3$, 63 MHz) δ 214.4, 181.4, 108.4, 100.1, 87.5, 86.5, 83.9, 80.4, 76.5, 70.9, 54.9, 47.3, 46.8, 42.8, 38.3, 38.2, 36.4, 35.0, 34.8, 32.5, 32.4, 31.0, 25.0, 24.1, 16.6, 15.8, 15.7, 15.4, 14.9, 12.9, 12.8, 12.6, 10.9, 7.1, 4.9; MS (FAB, *m*-nitrobenzyl alcohol) *m/z* 687 (M + Na), 665 (M + H); TLC R_f 0.42 (10% methanol/chloroform).

Adduct 54 sodium salt: oil; IR (CH_2Cl_2) 3360 (br), 2970, 2940, 2880, 1700, 1595, 1460, 1385, 1100, 1080, 1055, 1035, 980 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 3.90 (apparent d, 1 H, *J* = 10.2 Hz, C_7-H or C_{21}-H), 3.85 (apparent d, 1 H, *J* = 9.7 Hz, C_{13}-H), 3.61 (apparent d, 1 H, *J* = 8.5 Hz, C_7-H or C_{21}-H), 3.53 (dd, 1 H, J_{9-10} = 9.3 Hz and J_{8-9}

= 2.5 Hz, C_9-H), 2.83-2.94 (m, 2 H, C_{10}-H and C_{12}-H), 2.63 (q, 1 H, J = 7.1 Hz, C_2-H), 2.12-2.22 (m, 1 H, C_{14}-H), 1.22 (s, 3 H, C_{16}-CH_3), 1.06 (d, 3 H, J = 7.1 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.38 (10% methanol/chloroform).

Adduct 55 sodium salt: oil; IR (CH_2Cl_2) 3400 (br), 3060, 2980, 2940, 2880, 1710, 1580, 1470, 1420, 1380, 1155, 1105, 1050, 1035, 980, 900 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 4.06 (apparent d, 1 H, J_{8-9} = 6.9 Hz, C_9-H), 4.01 (apparent d, 1 H, J = 9.6 Hz, C_7-H or C_{21}-H), 3.71 (apparent d, 1 H, J = 9.5 Hz, C_{13}-H), 3.62 (apparent d, 1 H, J = 8.4 Hz, C_7-H or C_{21}-H), 2.77-2.80 (m, 1 H, C_{12}-H), 2.67-2.72 (m, 1 H, C_{10}-H), 2.54-2.59 (m, 1 H, C_2-H), 2.20-2.26 (m, 1 H, C_{14}-H), 1.22 (s, 3 H, C_{16}-CH_3), 1.16 (d, 3 H, J = 7.1 Hz, C_{10}-CH_3), 1.11 (d, 3 H, J = 7.1 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.32 (10% methanol/chloroform).

Adduct 56 sodium salt: oil; IR (CH_2Cl_2) 3400 (br), 3060, 2965, 2940, 2880, 1735, 1710, 1590, 1460, 1425, 1375, 1250, 1155, 1105, 1050, 980, 900 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 3.94 (apparent d, 1 H, J = 10.3 Hz, C_{13}-H), 3.91 (apparent d, 1 H, J_{9-10} = 4.7 Hz, C_9-H), 3.66 (apparent d, 1 H, J = 9.5 Hz, C_7-H or C_{21}-H), 3.58 (apparent d, 1 H, J = 8.4 Hz, C_7-H or C_{21}-H), 2.90-2.96 (m, 1 H, C_{10}-H), 2.65-2.75 (m, 2 H, C_2-H and C_{12}-H), 2.06-2.13 (m, 1 H, C_{14}-H), 1.21 (s, 3 H, C_{16}-CH_3), 1.14 (d, 3 H, J = 6.8 Hz, C_{10}-CH_3), 1.11 (d, 3 H, J = 7.2 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.28 (10% methanol/chloroform).

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Supplementary Material Available: Selected experimental procedures and spectral and analytical data for all reaction products are included (10 pages). Ordering information is given on any current masthead page.

Diene-Dienophile Hydrogen-Bonding Control of Diels-Alder Reactions with Dienes Bearing a Remote Stereogenic Center. Amplification of the Receptor Nature of Dienes by Conformational Tuning Leading to High Diastereofacial Discrimination

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Abstract: The Diels-Alder reactions of 1-(*O*-methylmandeloxy)butadiene and its analogues, bearing a remote stereogenic center, have been studied to elucidate the stereoselective control elements. Several model dienes (**5a-5f**) have been designed to enhance the facial selectivity at room temperature. The design concept of these dienes is based on our proposed perpendicular model (Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225-5228), which we used to rationalize the diastereofacial preference observed with diene **1**. Our approach to increasing the diastereoselectivity was to enhance the population of the preferred diene rotamer in the ground state as well as in the transition structure. From X-ray structures of the cycloadducts and the reversal of facial selectivity with dienes having a free hydroxy group at the chiral center, we conclude that diene-dienophile coordination through hydrogen bonding plays an important role in promoting chirality transfer. We postulate that facial selectivity is controlled by a balance of two competing forces (stereoelectronics vs hydrogen bonding) on the diene conformation in the transition structure. Conformational tuning at the stereogenic center helped in designing a diene (**5e**), which aims at maximizing the hydrogen-bonding interaction by decreasing the stereoelectronic preference. This diene exhibited high diastereoselectivity with an array of dienophiles at ca. 25 °C, without employing any external catalyst.

Asymmetric control is a challenging problem in organic chemistry.[1] Requirements to achieve enhanced face discrimination involve proper mechanistic understanding and identification of chiral control elements. Approaches to asymmetric induction include use of either covalently bound chiral auxiliary(ies) or of chiral Lewis acid catalysts. In both cases, propagation of chirality is achieved by blocking one prochiral face of a substrate through stereoelectronic contributions of the chiral center. Schematically, this can be categorized as a *repulsive interaction* approach as the incoming reactant preferentially approaches the least hindered substrate face in order to avoid steric congestion with stereogenic groups or ligands. In contrast, enzymes use *attractive interactions*, such as substrate binding through an array of conformationally well defined functionalities, to synthesize enantiomerically pure compounds efficiently under very mild reaction conditions.[2] A key to high asymmetric induction in those cases is the ability of the catalyst to bring the reacting substrates into close proximity.[3] Not surprisingly, in recent years, attempts have been made to design artificial enzymes,[4,5] which aim at binding two reacting species with a nonenzyme receptor to mimic enzyme catalysis.

Recently, during our mechanistic studies on asymmetric Diels-Alder reactions, we discovered such an *attractive interaction*, between the hydroxy group of a remote chiral template placed on a diene and the carbonyl groups of different dienophiles. As a result, high facial selectivity was achieved at ca. 25 °C without employing any external catalyst.[6] Except for allylic positions, the face-discriminating ability of unprotected heteroatom functionalities (such as oxygen or nitrogen atoms) present in chiral

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