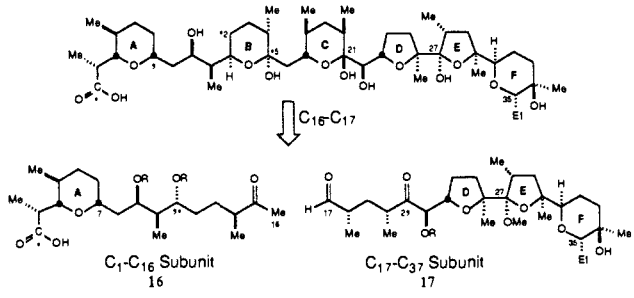
J. Am. Chem. Soc. **1988**, *110*, 2506–2526

Total Synthesis of the Polyether Antibiotic X-206

David A. Evans,* Steven L. Bender,[1] and Joel Morris

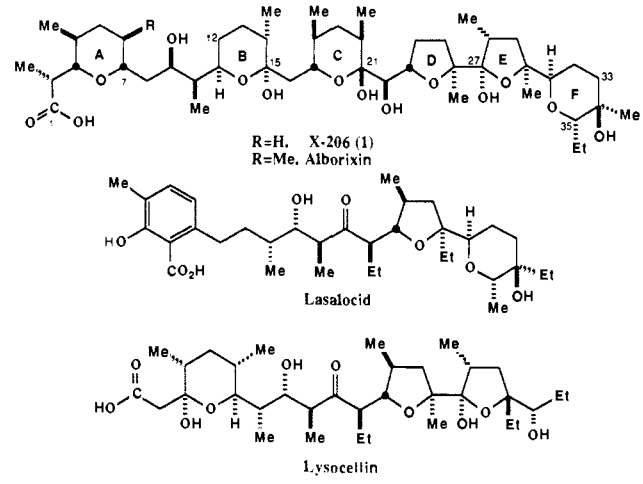
Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received September 8, 1987*

Abstract: A convergent asymmetric synthesis of the polyether antibiotic X-206 has been achieved through the synthesis and coupling of the C_1–C_{16} and C_{17}–C_{37} synthons **16** and **17**, respectively. All absolute stereochemical relationships within the molecule were controlled by application of recent methodological advances in asymmetric synthesis. In the synthesis of subunit **16**, both the alkylation and aldol reactions of chiral imide-derived enolates were utilized to establish the five stereogenic centers at C_2–C_4 and C_9–C_{10}, while the stereochemistry at C_{14} was indirectly controlled by the Sharpless asymmetric epoxidation. The C_7 and C_{11} stereocenters, which are situated at the two assemblage points for **16**, were established through internal asymmetric induction. The synthesis of the more complex C_{17}–C_{37} subunit **17** followed a similar strategy for absolute stereocontrol. Chiral enolate methodology was employed to define the stereogenic centers at C_{18}, C_{22}, and C_{23} while asymmetric epoxidation was used to create the oxygen-bearing centers at C_{30}–C_{31} and C_{34}–C_{35}. The remaining three stereogenic centers at C_{20}, C_{26}, and C_{28} were controlled by internal asymmetric induction. The successful construction of this synthon relied upon the development of an efficient assemblage reaction in which three fragments comprising the entire carbon framework of **17** were united in



a single operation. The final coupling of the two halves was achieved by a nonstereoselective aldol reaction. In supporting studies, the selective manipulation and degradation of the natural product were also investigated.

The remarkable structural complexity and diversity of the polyether antibiotics continues to challenge synthetic organic chemists nearly a decade after the landmark synthesis of lasalocid A was reported by Kishi and co-workers.[2,3] Along with the macrolide antibiotics,[4] the polyethers have served as the focal point for dramatic advances in acyclic stereocontrol, which currently plays a central role in organic synthesis. Much of our insight into those factors that control acyclic stereoselectivity for such basic processes as electrophilic additions to olefins (e.g., hydroboration,[5] epoxidation,[6] and halocyclization[7]) the Claisen rearrangement,[8] and carbonyl addition reactions[9] can be attributed to studies directed toward polyether antibiotics synthesis. In this paper we provide additional examples of such stereoselective reactions in conjunction with the first total synthesis of the polyether antibiotic X-206 (**1**).



The polyether antibiotic X-206 occupies a position of some historical significance as one of the first three polyether ionophores to be discovered almost 30 years ago.[10] The structure of this large ionophore (MW 870) remained undefined until 1975. In 1971 Westley and Blount reported a crystal structure of the silver salt of X-206, which subsequently proved to be flawed.[11] These authors later amended the initially reported structure to that shown

(1) Taken from the Ph.D. Thesis of S. L. Bender, Harvard University, 1986.

(2) Nakata, T.; Schmid, G.; Vranescic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935.

(3) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982.

(4) *Macrolide Antibiotics*; Omura, S., Ed.; Academic: Orlando, Florida, 1984.

(5) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259–260.

(6) (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741–2744. (b) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343–4346. (c) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347–4351. (d) Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229–4232.

(7) (a) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *102*, 260–262. (b) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.

(8) (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48–61. (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Ritzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988–2006. (c) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285. (d) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294.

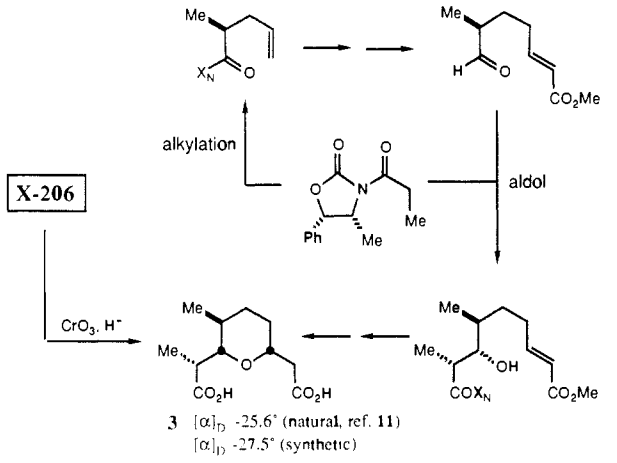
(9) (a) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745–2748. (b) Still, W. C; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031–1034. (c) Collum, D. B.; Still, W. C.; McDonald, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 2117–2120.

(10) Berger, J.; Rachlin, A. I.; Scott, W. E.; Sternbach, L. H.; Goldberg, M. W. *J. Am. Chem. Soc.* **1951**, *73*, 5295–5298.

(11) Blount, J. F.; Westley, J. W. *J. Chem. Soc., Chem. Commun.* **1971**, 927.

0002-7863/88/1510-2506$01.50/0

Scheme I



3 $[\alpha]_D$ -25.6° (natural, ref. 11)
$[\alpha]_D$ -27.5° (synthetic)

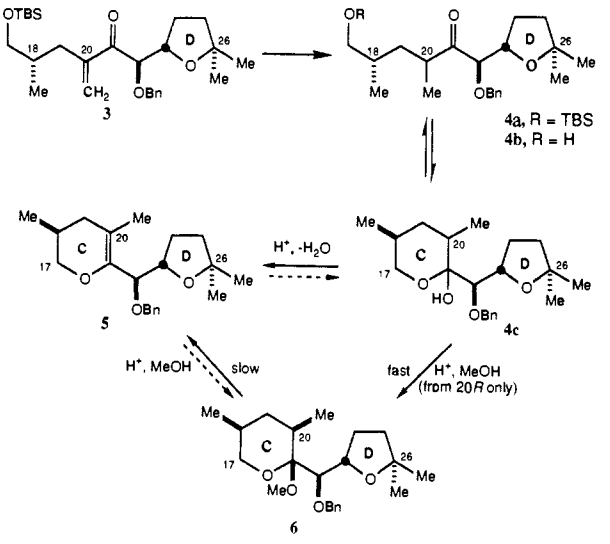
above on the basis of an X-ray analysis of the free-acid hydrate.[12] The 37-carbon backbone of X-206 and of closely related alborixin[13] is biosynthesized from 18 acetate/propionate units and, to date, remains the largest among the polyethers. Although the D, E, and F rings closely resemble the corresponding subunits of lysocellin and lasalocid, several structural features distinguish X-206 from other members of the class. For example, X-206 possesses three lactol functions that are not only crucial components of the hydrogen bond network but also provide three of the six metal ion binding sites.[11]

Clearly, a viable synthesis strategy must address the special features of X-206 in addition to providing general solutions to the structural problems that are common to the polyethers as a class. As a consequence of the stimulus provided by these stereochemically complex targets, chiral enolate methodology was developed in conjunction with a general program in ionophore and macrolide synthesis.[14] With highly stereoselective aldol and alkylation reactions, as well as other reactions such as Sharpless asymmetric epoxidation,[15] at our disposal, we elected to develop an approach to the synthesis of X-206 that would rely *exclusively* on asymmetric synthesis to resolve all absolute stereochemical issues. The selection of this boundary condition for the synthesis plan represented a significant departure from all previous syntheses of polyether antibiotics,[16] all of which have utilized classical resolution and/or the "chiral pool" to establish absolute stereochemistry.

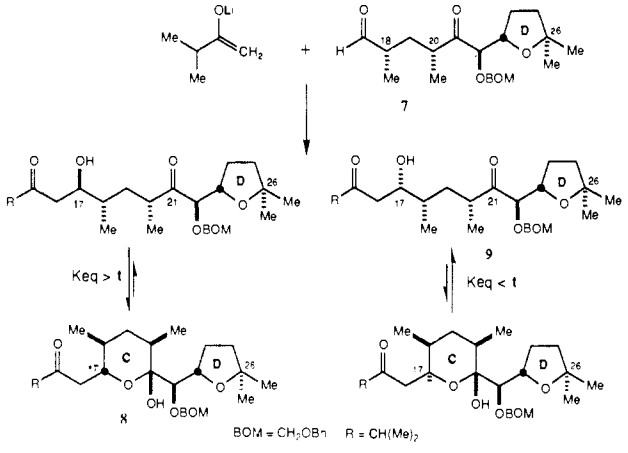
Preliminary Studies

Determination of the Absolute Configuration of X-206. In the original Westley–Blount structure of X-206, an absolute configuration, based on anomalous dispersion, was reported.[11] Since the errors in this structure invalidate the anomalous dispersion analysis, the subsequent report of the "correct" structure,[12] without separate experimental determination of the absolute configuration, secured the relative, but not the absolute, configuration of X-206. Therefore, it appeared necessary to unambiguously establish the absolute stereochemistry of X-206 through the asymmetric synthesis of a known degradation product, the diacid 2.[11] The synthesis of **2** is briefly outlined in Scheme I. The agreement between the optical rotations of the synthetic and the natural samples of **2** confirms the configuration of X-206 as that shown.[17]

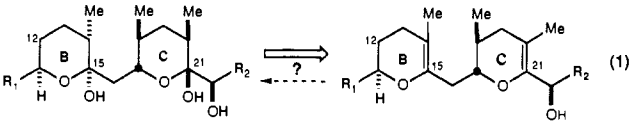
Scheme II



Scheme III



Model Studies on the C-Ring Lactol. Six of the 22 stereocenters in X-206 occur as the thermodynamically controlled anomeric carbons of the lactol rings (C_{15}, C_{21}, C_{27}) or as their adjacent epimerizable methyl-bearing centers (C_{14}, C_{20}, C_{28}). These six stereocenters are, in principle, derivable from the "prochiral" dihydropyran or dihydrofuran precursors, as is illustrated below for rings B and C (eq 1). Model studies were conducted to address the utility of such hydration reactions.[18]



(1)

In order to explore this approach for the elaboration of ring C, the synthesis of the dihydropyran **5** was undertaken (Scheme II). As previously reported, the ketone **4a** was prepared as a 2:1 mixture of 20*R*:20*S* diastereomers by the hydrogenation of the α,β-unsaturated ketone **3**.[19] In one aspect of our original plan, we entertained the possibility of controlling the C_{20} stereocenter by the acid-catalyzed equilibration of cyclic lactols through the intermediacy of a common dihydropyran species. To test this idea,

(12) Blount, J. F.; Westley, J. W. *J. Chem. Soc., Chem. Commun.* **1975**, 533.

(13) (a) Gachon, P.; Farges, C.; Kergomand, A. *J. Antibiot.* **1976**, *29*, 603–610. (b) Alleaume, M.; Busetta, B.; Farges, C.; Gachon, P.; Kergomand, A.; Staroln, T. *J. Chem. Soc., Chem. Commun.* **1975**, 411–412. (c) Seto, H.; Mizune, T.; Otake, N.; Gachon, P.; Kergomand, A.; Westley, J. W. *J. Antibiot.* **1979**, *32*, 970–971.

(14) For reviews, see: Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. D. A. Evans, Proceedings of The Robert A. Welch Foundation Conferences on Chemical Research. XXXVII. Stereospecificity in Chemistry and Biochemistry; Houston, TX, 1983; pp 13–49.

(15) For a review, see: Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, FL, 1985; Vol. 5, Chapter 7.

(16) (a) Calcimycin, lasalocid, and monensin: see ref 3, Vol. 2, Chapter 1. X-14547A: (b) Nicolaou, K. C.; Paphatjis, D. P.; Claremon, D. A.; Dolle, R. E., III *J. Am. Chem. Soc.* **1981**, *103*, 6967–6969. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630–633. (d) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429–3432.

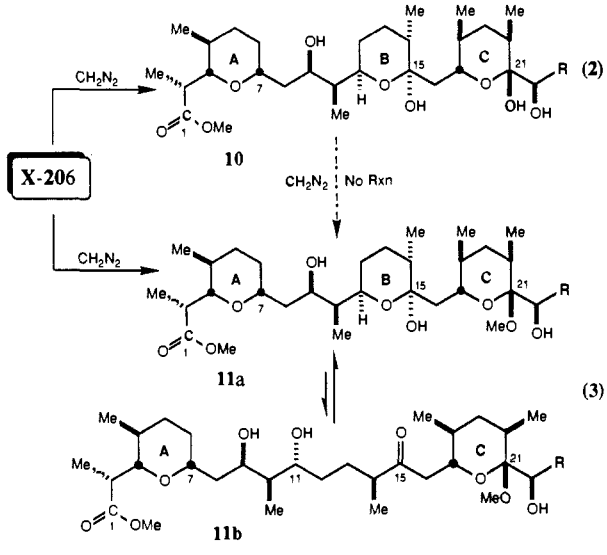
(17) Samples of X-206 and of diacid **2** were generously provided by Dr. J. W. Westley of Hoffman-La Roche.

(18) For the sake of clarity, the carbon numbering in the X-206 structure will be employed in the discussion of both model systems and synthetic intermediates.

(19) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799–803.

4a was desilylated to a mixture of the hydroxy ketone **4b** and the lactol **4c**, which was cleanly dehydrated to a single dihydropyran **5**. *Surprisingly, this dihydropyran resisted all attempts to effect the acid-catalyzed addition of water, methanol, or other nucleophiles.* In fact, treatment of the methyl ketal **6** with a range of acids *in methanol* resulted in the slow, but complete, conversion to the dihydropyran **5**. These results suggested that the ring-C dihydropyran, and by analogy the ring-B dihydropyran, should actually be *avoided* as intermediates throughout the synthesis. As a consequence, we elected to explicitly (i.e., kinetically) control the C_{14}, C_{20}, and C_{28} methyl-bearing stereocenters so as to avoid the "dangers" of dihydropyran and dihydrofuran species. A somewhat different aspect of the behavior of the ring-C lactol was revealed by the addition of the enolate of methyl isopropyl ketone to the keto aldehyde **7** (Scheme III). Analysis of the aldol products by ^{1}H NMR spectroscopy indicated that diastereomer **8**, possessing the natural configuration at C_{17}, exists principally in the lactol form, while diastereomer **9** is found entirely as the hydroxy ketone tautomer. This difference presumably arises as a consequence of the unfavorable axial disposition of the C_{17} side chain in the lactol tautomer of **9**. These and related studies clearly illustrate the impact of stereochemistry on the ring–chain tautomerism in structures such as X-206.

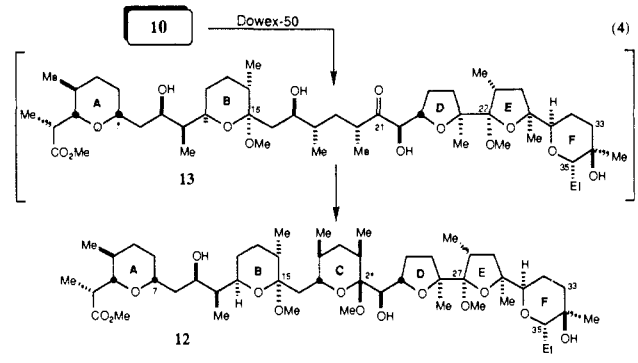
Derivatization and Degradation of X-206. From the preceding discussion, it is apparent that the lactol functions will assume a prominent role in the synthesis of X-206. In addition to the synthetic investigations, studies on the derivatization and degradation of X-206 provided a number of unexpected results pertaining to the lactol functionality. For example, the attempted esterification of X-206 with diazomethane was found to yield not only the anticipated methyl ester **10** but also a more polar byproduct (eq 2). The structure of this new derivative was assigned



as the ring-C methyl ketal **11** on the basis of the following observations. The ^{1}H NMR spectrum revealed the presence of a methyl ether in addition to a methyl ester. Mild acid hydrolysis (2:1 THF/0.2 N HCl, 25 °C, 3.5 h) of **11** to **10** established that the ether linkage was located at an anomeric center of one of the lactols. Finally, no reaction occurred upon treatment of **11** with lead tetraacetate, a reaction that proceeds readily on the methyl ester **10**. This implies that the vicinal diol unit at C_{21}–C_{22} was no longer available as the site for cleavage, which implicates the C_{21} anomeric hydroxyl as a site of methylation. From a mechanistic standpoint, the regioselective methylation can be rationalized by invoking competitive attack by the carboxylate and the C_{21} hydroxyl on the intermediate methyldiazonium ion. The proximity of these groups in the free-acid hydrate is well-supported by the X-ray crystal structure, which indicates that these two functional groups are well within hydrogen-bonding range. Additional support for this mechanism is provided by the observation that the methyl ester **10** does not react with diazomethane, which establishes that hydroxyl methylation precedes esterification in the pathway leading to **11**. It should be noted that an analogous methyl transfer has been reported in the reaction of lasalocid with diazomethane.[20]

Remarkably, etherification of the C_{21} hydroxyl exerts a profound influence on the tautomeric composition of the ring-B lactol. Whereas no evidence of the hydroxy ketone tautomer was observed for the methyl ester **10**, according to both ^{1}H and ^{13}C NMR analysis **11** clearly exists as a mixture of the lactol **11a** and the associated hydroxy ketone tautomer **11b**.[21] In fact, the rate of interconversion was sufficiently slow to allow chromatographic separation (silica gel) of these two ring–chain tautomers. The resulting chromatographic fractions appeared to be quite stable as monitored by TLC analysis; however, rapid equilibration of **11a** and **11b** was observed upon concentration of solutions of the individual constituents or the addition of acetic acid (eq 3). The kinetic barrier to tautomerization may possibly be derived from the presence of a hydrogen bond(s), which must be broken in the process of interconversion. Among the many lactols (hydroxy ketones) that have been prepared during the course of this work, **11** is unique in this respect.

From a preparative standpoint, the side reaction leading to **11** was inconsequential since treatment of the reaction mixture with aqueous hydrochloric acid in THF afforded the desired methyl ester **10** in high yield. Since our prior experience (vide supra) had indicated that the lactol functions are prone to acid-catalyzed dehydration, we examined whether anomeric alcoholysis reactions could be effected. Treatment of **10** with Dowex-50 resin in methanol/methyl orthoformate (0 °C, 2 h) led cleanly to the tris(methyl ketal) **12** as an amorphous solid (eq 4). When this

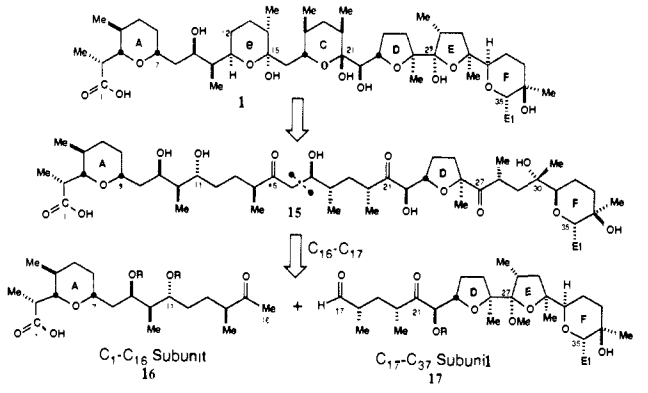


reaction was monitored by TLC, a distinct sequence of events was observed: **10** was rapidly consumed to give the anticipated tris(ketal) **12**, along with a more polar intermediate, which was slowly converted to **12**. Quenching the reaction after partial conversion, followed by chromatographic purification, provided a sample of the polar intermediate, which was identified as the bis(methyl ketal) **13** on the basis of its ^{1}H and ^{13}C NMR spectral characteristics and its chemical behavior. In the ^{1}H NMR spectrum of **13**, three methoxy singlets (methyl ester plus two methyl ketals) and a one-proton multiplet at 2.95 ppm indicated that two lactol rings are ketalized and that one exists as the hydroxy ketone tautomer. The ^{13}C NMR spectrum confirmed this conclusion with only two ketal carbons observable at 102 and 110 ppm, while a resonance at 214 ppm provided unambiguous evidence of a ketone carbonyl. In contrast to monoketal **11a,b**, the bis(ketal) **13** was rapidly cleaved by lead tetraacetate at the C_{21}–C_{22} bond to give the expected fragments.

Once again, remote functionalization exerts a pronounced effect on the equilibrium between lactol and hydroxy ketone tautomers. The slow rate of conversion of **13** to **12** is consistent with ketalization proceeding through a small equilibrium concentration of the lactol tautomer. In addition, the monoketal **11** was rapidly converted to **12** under the same conditions, with no evidence of **13** as an intermediate. Finally, the assertion that the ketalizaiton

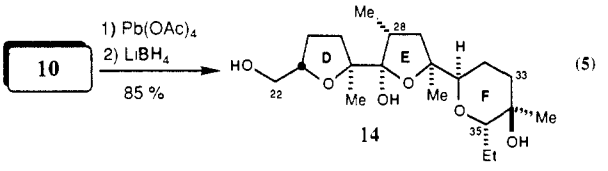
(20) Westley, J. W. *J. Med. Chem.* **1973**, *16*, 397–403.
(21) ^{1}H and ^{13}C NMR (deuteriochloroform) indicates a ~70:30 lactol/hydroxy ketone mixture at equilibrium. In deuteriobenzene, the lactol comprises at least 90% of the mixture.

Scheme IV



occurs without epimerization or any other structural change was verified by hydrolysis of **12** to **10**. It is interesting that, according to TLC analysis, the monoketal **11** was a major intermediate in this transformation.

In addition to its utility in structure elucidation, the lead tetraacetate cleavage reaction is useful for preparative-scale degradation of X-206. Treatment of the methyl ester **10** with lead tetraacetate resulted in rapid cleavage of the C_{21}–C_{22} bond (eq 5). Immediate reduction of the unpurified product mixture with



(5)

lithium borohydride permitted the isolation of the crystalline C_{22}–C_{37} fragment **14** (mp 118–119 °C) in 85% yield. During the development of the synthesis of the C_{17}–C_{37} subunit, **14** was employed as a model in important ketalization and hydrolysis experiments; these will be presented in conjunction with the synthesis of this subunit (vide infra). In conclusion, the studies described in the preceding paragraphs provide invaluable insight into the behavior of the lactol functions, which contributed to the eventual design of the synthesis of X-206 that is presented below.

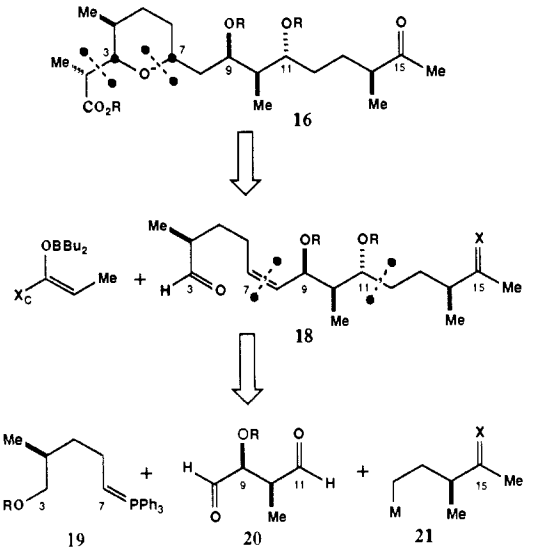
Retrosynthetic Analysis

The synthesis plan developed for X-206 was guided by the constraints imposed by the structure as well as by our reliance on asymmetric synthesis. With regard to structural elements, examination of the hypothetical hydroxy ketone tautomer of X-206 (**15**) reveals a β-hydroxy ketone moiety near the center of the molecule. An aldol disconnection of the C_{16}–C_{17} bond then affords two subunits, **16** and **17**, of nearly equal size, hereafter referred to as the left half and the right half, respectively (Scheme IV). The left half (**16**) may be further dissected in a straightforward manner (Scheme V). The illustrated analysis hinges on the identification of two syn aldol relationships at C_1–C_3 and C_9–C_{11}, which are readily accessible with chiral imide enolate methodology. Although the disconnections illustrated in Scheme IV are not tied to a strict ordering, the preliminary excision of C_1–C_2 from the carboxyl terminus is predicated on the desirability of introducing the carboxylate function late in the synthesis.

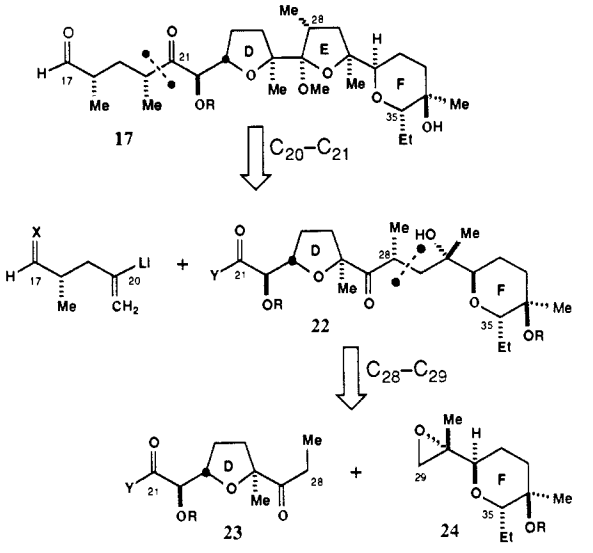
A consequence of this operation is that an important stereochemical issue at C_7 associated with the formation of ring A arises as a potential problem. The aldehyde **18** is further dissected by application of a Wittig transform at C_7–C_8 and a disconnection at C_{11}–C_{12} that corresponds to the addition of an organometallic to an aldehyde in the synthetic direction. The resulting fragments **19**–**21**, each of which contains only one or two stereogenic centers, were envisioned to be readily available through asymmetric synthesis.

In contrast to the left half, the disposition of functionality and the stereocenters in the right half (**17**) greatly complicated the task of locating suitable sites for disconnection. Therefore, the synthesis plan relied less upon the identification of reliable bond

Scheme V



Scheme VI

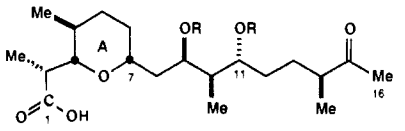


disconnections and more upon the accessibility of the fragments produced. For example, it was recognized that an asymmetric aldol reaction could easily provide the structural array at C_{21}–C_{23}, which suggested that disconnection at the C_{20}–C_{21} bond would be desirable (Scheme VI). Previously mentioned model studies verified that this approach was effective for the construction of the C_{17}–C_{26} segment of X-206.[19] The success of the route relied upon an unexpectedly stereoselective hydrogenation reaction to establish the C_{20} methyl-bearing stereocenter. These model studies identified as a subgoal the C_{21}–C_{37} synthon **22**, which in turn might be logically constructed from the ketone **23** and the epoxide **24**. Despite the disconcerting lack of experimental precedent for this coupling reaction, in which the C_{28} stereocenter must also be properly defined, the simplicity of the fragments **23** and **24** provided the motivation to explore this approach to the synthesis of the right half of X-206.

Synthesis of the Left Half (16)

As detailed below, the left half (**16**) was efficiently constructed from relatively simple fragments, which in turn were prepared in a concise manner by employing asymmetric synthesis methodology to establish all the stereocenters. The fragments were assembled with stereoselective bond constructions for which stereochemical precedent was available from studies on rather simple substrates.

Asymmetric Synthesis of the C_3–C_7 Fragment 30. The alkylation of the sodium enolate derived from imide **25** with allyl iodide,



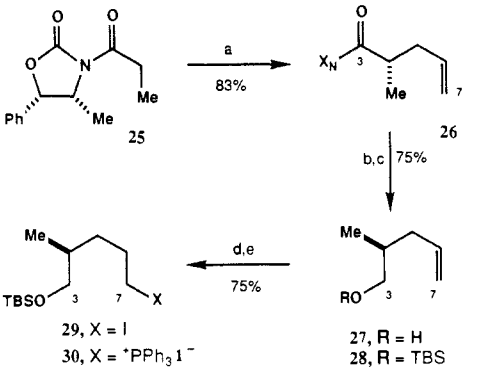
C_1-C_{16} Subunit
16

according to the established procedure, provided the imide **26** in >99% diastereomeric purity after recrystallization (Scheme VII).[22] Reduction of **26** with $LiAlH_4$ in THF afforded the alcohol **27**, which was protected as its *tert*-butyldimethylsilyl (TBS) ether **28**. After conversion of **28** to the terminal iodide **29** by successive hydrozirconation and iodination,[23] treatment with triphenylphosphine afforded an 83% yield of the crystalline phosphonium salt **30** (mp 138.5–140 °C). The five-step sequence from **25** to **30** proceeded in an overall yield of 47% and was amenable to a multigram scale-up.

Asymmetric Synthesis of the C_8–C_{11} Fragment 34. The C_9 and C_{10} strereocenters in this fragment were established through the aldol reaction of the boron enolate derived from imide **31** with cinnamaldehyde.[24] Capillary GC analysis revealed that only traces of undesired diastereomers were present in the unpurified reaction mixture, from which the aldol adduct **32** (mp 121–122 °C) was isolated by recrystallization in 93% yield (Scheme VIII). Subsequent treatment of **32** with the aluminum amide reagent derived from *N,O*-dimethylhydroxylamine hydrochloride and $AlMe_3$, according to the procedure of Weinreb,[25] effected the desired transamination of **32** to the *N*-methoxy-*N*-methylamide **33**. Protection of the hydroxyl group of **33** as its benzyloxymethyl (BOM) ether afforded **34** in 94% overall yield from **32**.[26] For several reasons, the hydroxy amide **33** represents a nearly ideal synthon for the dialdehyde **20** (see Scheme V). Not only is **33** available in either absolute configuration by the efficient aldol–transamination sequence, but the stability of **33** to either acidic or basic conditions permits the use of virtually any protecting group for the hydroxyl function.[27] Finally, either terminus can be unmasked to provide the aldehyde function in a single, high-yielding step under nonepimerizing conditions.

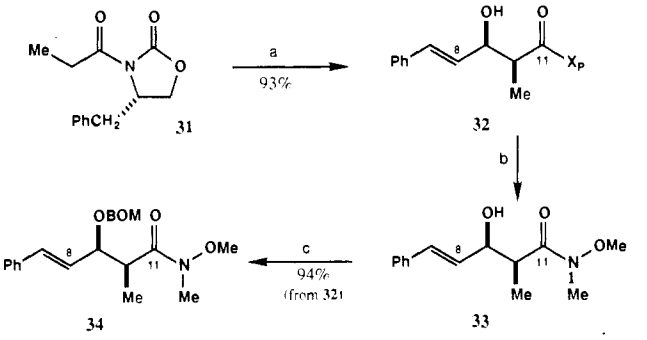
Asymmetric Synthesis of the C_{12}–C_{16} Fragment 39. As illustrated in the synthesis plan (Scheme V), the organometallic reagent **21** comprises the final fragment for the left half (**16**). Results obtained in model studies indicated that the C_{11}–C_{12} bond construction would require this reagent in excess. Accordingly, to synthesize the precursor bromide **39**, an approach based upon asymmetric epoxidation was selected from among several alternatives for reasons of both practicality and economy (Scheme IX). Sharpless asymmetric epoxidation of tiglic alcohol with the (+)-diethyl tartrate catalyst afforded epoxy alcohol **35**, which posesses the requisite absolute configuration.[15] Unfortunately, the water solubility of low-molecular-weight epoxy alcohols results in poor yields when literature isolation procedures are employed.[15] As a remedy for this situation, a simple nonaqueous isolation procedure was developed, as follows. The epoxidation is conducted in the usual way, with the exception that the amount of the catalyst is generally reduced (i.e., 0.2 equiv of $Ti(O\text{-}i\text{-}Pr)_4$/0.28 equiv of tartrate ester) to simplify product isolation.[28] At the completion

Scheme VII[a]



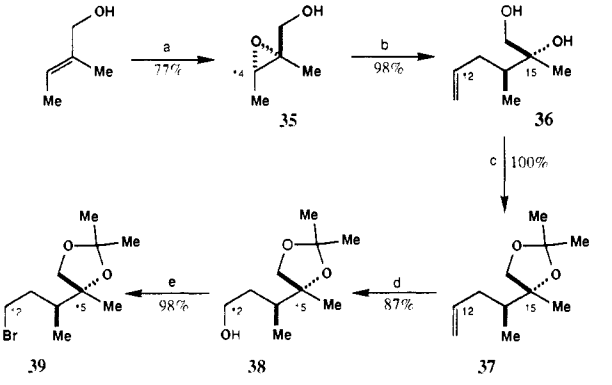
[a] (a) NaHMDS, THF, allyl iodide, −78 °C; (b) $LiAlH_4$, THF, −78 to −20 °C, (**26** → **27**, 82%); (c) TBSCl, Et_3N, DMAP, CH_2Cl_2, 25 °C (**27** → **28**, 92%); (d) Cp_2ZrHCl, PhH, 25 °C, 9 h; I_2, (**28** → **29**, 90%); (e) Ph_3P, MeCN, 50 °C, 14 h, (**29** → **30**, 83%).

Scheme VIII[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2; PhCH=CHCHO; H_2O_2; (b) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2; (c) $BnOCH_2Cl$, *i*-Pr_2EtN, THF, 25 °C, 38 h.

Scheme IX[a]



[a] (a) $Ti(O\text{-}i\text{-}Pr)_4$, (+)-DET, TBHP, CH_2Cl_2, −20 °C; (b) CH_2=C-HCH_2MgCl, THF, −20 °C; (c) $(MeO)_2CMe_2$, Dowex-50 H^+, 25 °C, 1.5 h; (d) O_3, EtOH, −78 °C; Me_2S, $NaBH_4$, −40 to 25 °C; (e) Ph_3P, CBr_4, Et_2O, 25 °C.

of the reaction, triethanolamine is added to neutralize the Lewis acidity of the titanium.[29] The cold reaction solution is then rapidly filtered through a pad of silica gel and eluted with ether. The titanium and the triethanolamine are retained on the silica gel, while the filtrate contains only the desired epoxy alcohol and recovered tartrate ester. Concentration and Kugelrohr distillation (or chromatography) of the residue provides the epoxy alcohol product in high purity and yield. With this procedure, the epoxy alcohol **35** was isolated in 77% yield and ca. 94% ee (Scheme IX).[30]

(22) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739. (b) Mathre, D. J. Ph.D. Dissertation, California Institute of Technology, 1985.

(23) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116.

(24) Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(25) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.

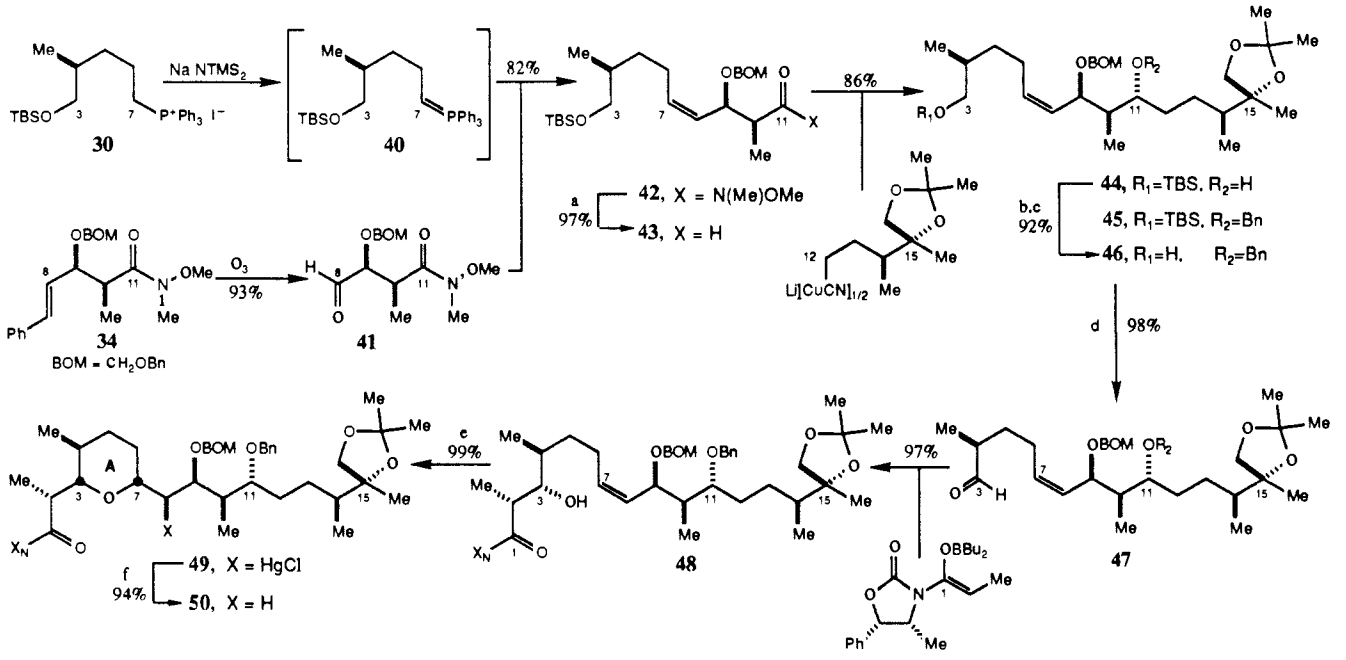
(26) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260–6261.

(27) In contrast to the corresponding esters and imides, β-hydroxy amides such as **33** can be converted to their sodium aldolates and alkylated without retroaldolization occurring.

(28) Recently, Sharpless and co-workers have found that addition of molecular sieves allows more general use of *catalytic* asymmetric epoxidation: (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922–1925. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

(29) In the case of crotyl alcohol, the omission of the triethanolamine does not noticeably affect the yield of epoxy alcohol. However, more sensitive epoxy alcohols (see ref 15) may benefit from sequestering the titanium with triethanolamine. Since no adverse affects have been observed from its presence, triethanolamine is added routinely as a preventive measure.

Scheme X[a]



[a] (a) DIBAL, THF, −78 to −50 °C; (b) KH, catalytic EtOH, THF, 25 °C; BnBr, (**44** → **45**, 94%); (c) *n*-$Bu_4N^+F^-$, THF, 25 °C, 1.25 h. (**45** → **46**, 98%); (d) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, −78 to −40 °C; (e) $Hg(OAc)_2$, CH_2Cl_2, 25 °C; (f) *n*-Bu_3SnH, PhMe, 25–55 °C.

Extension of this procedure to the epoxidation of crotyl alcohol ((*E*)-2-buten-1-ol), for which the literature yield is only 45%,[31,32] resulted in an improvement in yield to 70–75% without loss of enantioselectivity.

The establishment of the C_{14} methyl-bearing stereocenter was achieved by the reaction of epoxide **35** with allylmagnesium chloride in THF.[33] As expected, the ring-opening reaction was highly regioselective, affording the diol **36** as a single stereoisomer, as evidenced by capillary GC analysis. After conversion of the diol **36** to the acetonide **37**, ozonolysis followed by a reductive workup (Me_2S, $NaBH_4$) provided the primary alcohol **38** in 87% overall yield. Treatment of **38** with Ph_3P and CBr_4 afforded the target bromide **39**.[34] This five-step synthesis of **39**, which satisfies the criterion of practicality, proceeds with an overall yield of 64%.

Assemblage of the Left Half. With syntheses of the three chiral fragments **30**, **34**, and **39** available, attention was directed toward the coupling of these fragments to assemble the left half of X-206 (Scheme X). The C_7–C_8 bond was selected as the first coupling site, primarily on the basis of rather subtle issues such as reaction stoichiometry and isomer separability. Ozonolysis of **34** afforded the aldehyde **41**, which was immediately coupled with the phosphorane **40** under "salt-free" conditions ($NaN(SiMe_3)_2$, toluene).[35] A 92:8 mixture of *Z*/*E* olefin isomers was obtained, from which the desired *Z* isomer **42** was isolated by chromatography in 82% yield. Reduction of the amide **42** to the aldehyde **43** proceeded cleanly with DIBAL in THF.[25] Numerous related reductions have been carried out in this laboratory with great success. In no instance has any epimerization of the stereocenter α to the resultant aldehyde function been detected. With respect to the second coupling reaction wherein the C_{11} stereocenter is established, the desired 11*R* isomer **44** was envisioned to result from a "chelation-controlled" addition process mediated by the C_9 β-alkoxy group. Among the various organometallics that participate in such addition reactions,[36] for practical reasons the organocuprates appeared to be the reagents of choice.[37,38] Operationally the success of this reaction depends upon the generation of the cuprate derived from **39** uncontaminated by any of the more reactive organolithium species. Control experiments demonstrated that the organolithium reagent derived from **39**, upon reaction with aldehyde **43**, afforded principally the *undesired* 11*S* diastereomer (11*R*:11*S* = 1:2).

Recourse to the higher order cuprates developed by Lipshutz and co-workers provided a reproducible and effective solution to the problem.[39] Addition of the aldehyde **43** to 1.5 equiv of the cuprate derived from **39** cleanly afforded the 11*R* alcohol **44** in 86% isolated yield. HPLC analysis of the unpurified reaction mixture indicated a reaction diastereoselectivity of 98:2 for the addition process. The configuration at the newly formed C_{11} stereocenter was assigned in analogy with literature precedent.[37] Protection of the C_{11} hydroxyl as its benzyl ether was followed by removal of the silyl ether protecting group at the C_3 terminus. Swern oxidation of the alcohol **46** afforded the aldehyde **47**,[40] which underwent a clean aldol reaction with 1.75 equiv of the boron enolate derived from imide **25**.[24] The aldol adduct **48** was isolated in 97% yield (based on the aldehyde **47**) as a single diastereomer according to 300-MHz ^1H NMR analysis.

The aldol reaction concluded the assemblage of the carbon backbone of the left half, and attention was then directed to the elaboration of ring A. In the development of the synthesis plan,

(30) The enantiomeric excess was determined by 300-MHz ^1H NMR analysis of the Mosher ester: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

(31) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464–466.

(32) Since the original report (ref 31), other workers have had similar difficulties with crotyl alcohol in the asymmetric epoxidation reaction: (a) Parry, R. J.; Mizusawa, A. E.; Chiu, I. C.; Naidu, M. V.; Ricciardone, M. *J. Am. Chem. Soc.* **1985**, *107*, 2512–2521 (32% yield). (b) Harris, R. N., III; Sundararaman, P.; Djerassi, C. *J. Am. Chem. Soc.* **1983**, *105*, 2408–2413 ("low yields"). (c) Helbig, W. *Liebigs Ann. Chem.* **1984**, 1165–1169 (no yield given). (d) Kobayashi, Y.; Kitano, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1984**, 1329–1330 (no yield given).

(33) Felkin, H.; Frajerman, C.; Roussi, G. *Bull. Soc. Chim. Fr.* **1970**, 3704–3710.

(34) (a) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86–90. (b) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891–3898.

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

(36) For a recent review of chelation control in addition reactions of α- and β-alkoxy carbonyl compounds, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

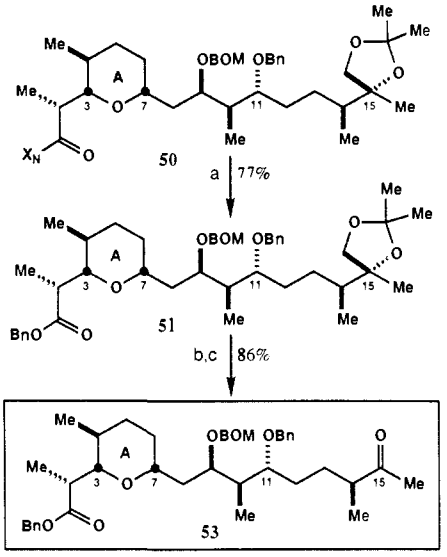
(37) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035–1038.

(38) For a discussion of cuprate stability, see: Bertz, S. H.; Dabbagh, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1030–1032.

(39) For reviews, see: (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (b) Lipshutz, B. H. *Synthesis* **1987**, 325–341.

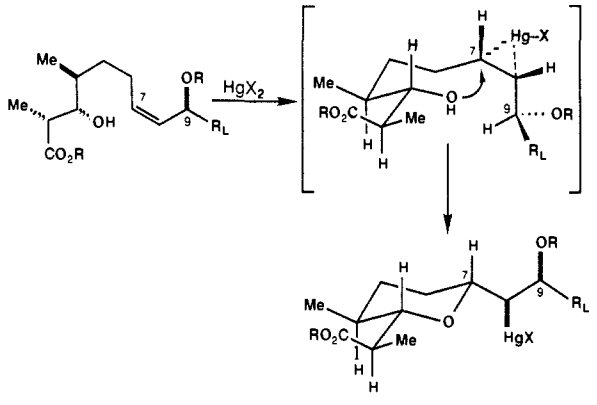
(40) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

Scheme XI[a]



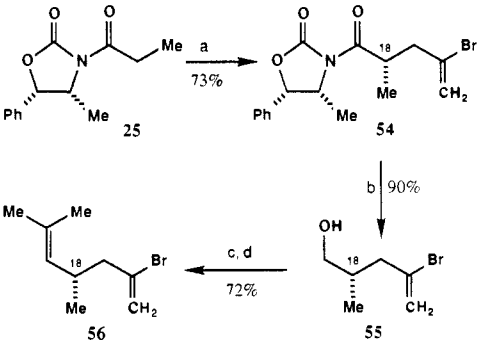
[a] (a) BnOLi, THF, 0 °C; (b) 1 M aqueous H_2SO_4, THF/EtOH, 50 °C, 5 h, (**51** → **52**, 90%); (c) $NaIO_4$, acetone/H_2O, (**52** → **53**, 95%).

analysis of steric and conformational effects suggested that a *Z* olefin substrate, such as **48**, should undergo a mercury(II)-mediated cyclization to form ring A with the desired C_7 stereochemistry. If one makes the reasonable assumption that mercuronium ions are intermediates in these reactions,[41] the formation of the mercuronium ion illustrated in eq 6 should be favored on the basis of both steric and stereoelectronic considerations.[42,43]



Irrespective of whether the mercuronium ion formation or the heterocyclization is the rate-determining step in this reaction, we had projected that the oxymercuration would proceed in the desired fashion (eq 6).[44] In the event, treatment of the aldol adduct **48** with $Hg(OAc)_2$ in CH_2Cl_2, followed by an aqueous NaCl wash, led to the isolation of a single chloromercurial **49** in quantitative yield. The desired axial disposition of the C_7 proton was clearly

Scheme XII[a]



[a] (a) LDA, 2,3-dibromopropene, THF, −35 °C; (b) $LiAlH_4$, THF, −78 to 0 °C; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −65 °C; Et_3N, −70 to −10 °C; (d) Ph_3P^+-*i*-PrI^-, *n*-BuLi, THF, −78 to 25 °C.

indicated by ^1H NMR decoupling experiments: irradiation of the C_8 proton at 2.59 ppm resulted in the collapse of the C_7 broad triplet into a broad doublet with an axial–axial coupling constant of 9 Hz.

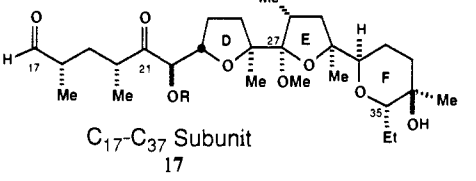
Although the mercury-mediated cyclization of **48** had proceeded according to our expectations, demercuration of the chloromercurial **49** proved to be surprisingly troublesome. In preliminary studies, repeated attempts to demercurate a chloromercurial (or the precursor acetoxymercurial) similar to **49** under a variety of literature conditions resulted in complete decomposition. It was finally discovered that *n*-Bu_3SnH cleanly effected the desired reduction.[45] After optimization, demercuration of **49** by this procedure afforded **50** in 94% isolated yield (Scheme X).

From **50**, three straightforward functional group manipulations completed the synthesis of the left half (Scheme XI). Excision of the chiral auxiliary was achieved by treatment of **50** with lithium benzyl oxide in THF (77%). Acidic hydrolysis of the acetonide **51** required rather vigorous conditions; however, the diol **52** was obtained in 90% yield under optimized conditions. Finally, oxidative cleavage of the glycol function in **52** with $NaIO_4$ proceeded uneventfully to give the target methyl ketone **53** (95%).

Regarding stereochemistry, each of the eight stereogenic centers in the C_1–C_{16} subunit **53** was installed with a stereoselectivity of at least 97%. Of these eight stereocenters, six were incorporated in a predictable manner through "reagent control". The other two centers (C_7 and C_{11}), located at the sites of fragment coupling, were established through internal asymmetric induction. From the outset, the degree of convergency that is explicit in this approach more than compensated for the increased risk associated with employing "substrate control" for these two stereocenters. In retrospect, the very high level of stereoselectivity obtained in the construction of each of the stereocenters *exceeds* the stereoselectivity observed in the Wittig reaction (*Z*:*E* = 92:8) that was employed for the C_7–C_8 bond construction. Evidently, acyclic stereocontrol is beginning to reach a level of sophistication wherein other problems, such as functional group manipulation and olefin stereoselectivity, may become the more significant obstacles in the synthesis of stereochemically complex molecules.

Synthesis of the Right Half (17)

Whereas the synthesis of the left half described above generally proceeded according to the original plan, the synthesis of the right half (**17**) evolved through the exploration of various tactical, as well as experimental, alternatives. In large part, the difficulties



C_{17}-C_{37} Subunit
17

(41) Pasto, D. J.; Gontar, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6902–6908.

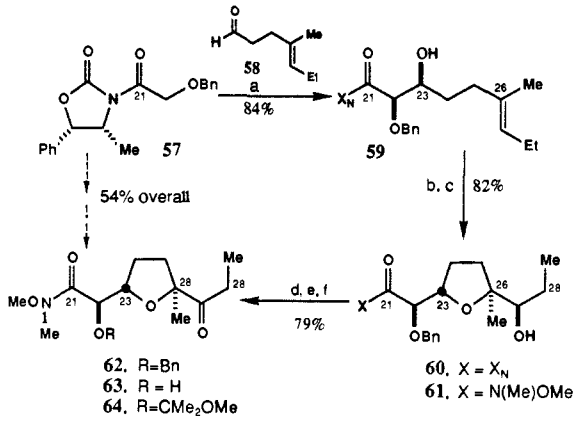
(42) For example, see: (a) Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, *40*, 2297–2302. (b) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274–1280. (c) Giese, B.; Bartmann, D. *Tetrahedron Lett.* **1985**, *26*, 1197–1200. (d) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825. (e) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489. (f) Midland, M. M.; Halterman, R. L. *J. Org. Chem.* **1981**, *46*, 1227–1229.

(43) For example, see: (a) Kahn, S. D.; Pau, C. F.; Chamberlain, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650–663. (b) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666–671. (c) Chamberlain, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672–677. (d) Houk, K. N.; Rondan, N. G.; Yun-Dong, W.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257–2274. (e) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166.

(44) In supporting studies designed to determine the source(s) of asymmetric induction, a series of substrates related to **48** underwent stereoselective oxymercuration reactions such that the rate-determining step was established to be cyclization. For complete details, see ref 1.

(45) Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611–6624.

Scheme XIII[a]



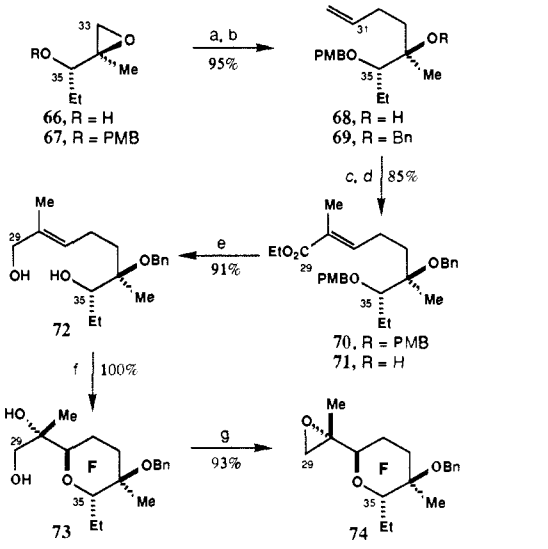
[a](a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2; **58**; H_2O_2; (b) TBHP, catalytic $VO(acac)_2$, CH_2Cl_2, (**59** → **60**, 89%); (c) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2, 0 °C, (**60** → **61**, 92%); (d) aqueous H_2CrO_4, Et_2O, (**61** → **62**, 91%); (e) 1 atm of H_2, 5% Pd/C, catalytic $HClO_4$, EtOH, (**62** → **63**, 97%); (f) CH_2=C(Me)OMe, catalytic PPTS, CH_2Cl_2, 0 °C, 20 min, (**63** → **64**, 90%).

were caused by the density of both functionality and stereogenic centers, which not only precluded a linear approach but also complicated the selection of reasonable disconnection points. The bond disconnection at C_{20}–C_{21}, illustrated in Scheme VI, was selected after model studies established that the C_{20} stereocenter could be defined by hydrogenation of an enone intermediate.[19] The speculative nature of the second bond construction at C_{28}–C_{29} and of the attendant stereochemical issue at C_{28} constituted one of the major uncertainties at the outset of the synthesis. The following discussion describes the studies leading to the resolution of these uncertainties and the successful synthesis of the right half.

Asymmetric Synthesis of the C_{17}–C_{20} Fragment 56. The C_{18} stereocenter was secured by alkylation of the lithium enolate of imide **25** with 2,3-dibromopropene (Scheme XII).[22] The reaction diastereoselectivity, as determined by analysis of the unpurified product, was 98:2. Purification by chromatography provided a 73% yield of the crystalline imide **54**, mp 59–60 °C, contaminated with <1% of its diastereomer. Reduction of **54** with $LiAlH_4$ provided the alcohol **55**, which was oxidized according to the method of Swern.[40] The resultant aldehyde was treated with isopropylidenetriphenylphosphorane to give the vinyl bromide **56** in good overall yield. In the first approach to this synthon, direct protection of the alcohol **55** was undertaken, rather than the two-step sequence described above. In the development of this route, the oxidative step was deferred until immediately prior to the aldol coupling of the two halves. It was found, however, that the final intermediates were far too labile to permit the efficient unmasking of the C_{17} aldehyde function from the derived protected alcohol. For this reason, a double bond was selected as the ideal C_{17} carbonyl synthon.

Asymmetric Synthesis of the C_{21}–C_{28} Fragment 64. Aldol reaction of the imide **57** and the aldehyde **58** afforded the adduct **59** in 84% yield, thereby establishing both the C_{22} and C_{23} stereocenters (Scheme XIII).[24] The remote C_{26} stereocenter was then efficiently established through the hydroxyl-directed epoxidation protocol developed by Kishi and co-workers for their lasalocid synthesis.[6a] Thus, vanadium(V)-catalyzed epoxidation of the bishomoallylic alcohol **59** was followed by in situ cyclization to give a 95:5 mixture of diastereomeric products, from which the major diastereomer **60** was isolated in 89% yield after chromatography. Transamination of **60** with the aluminum amide reagent from *N,O*-dimethylhydroxylamine hydrochloride and $AlMe_3$ yielded the amide **61** (92%),[25] which was readily oxidized to ketone **62** (91%). In anticipation of the rather delicate reactions to be employed in the latter stages of the synthesis, the benzyl protecting group employed for the C_{22} hydroxyl moiety was efficiently exchanged for the more labile methoxyisopropyl (MOP) mixed ketal. From the above route, the target amide **64** was obtained in only six steps from the imide **57** with an overall yield of 54%.

Scheme XIV[a]



[a](a) CH_2=$CHCH_2MgCl$, THF, 25 °C, (**67** → **68**, 100%); (b) KH, BnBr, THF, 25 °C, (**68** → **69**, 95%); (c) O_3, −78 °C; Ph_3P, 25 °C; Ph_3P=C(Me)CO_2Et, 25 °C, (**69** → **70**, 85%); (d) DDQ, CH_2Cl_2/H_2O, (**70** → **71**, 91%); (e) DIBAL, CH_2Cl_2, −78 to 0 °C; (f) TBHP, Ti(O-*i*-Pr)$_4$, (+)-DET, CH_2Cl_2, −20 °C; (g) TsCl, pyr, 25 °C; K_2CO_3, MeOH, 0 °C.

Asymmetric Synthesis of the C_{29}–C_{37} Fragment 74. The four stereocenters in this fragment were efficiently established through a twofold application of the asymmetric epoxidation reaction. Racemic 2-methyl-1-penten-3-ol was subjected to asymmetric epoxidation with 0.5 equiv of *tert*-butyl hydroperoxide (Scheme XIV). Due to the favorable relative rates for this structural type of secondary allylic alcohol in the kinetic resolution process,[46] the epoxy alcohol **66** was obtained in good yield (based on the theoretical maximum of 50%) and high optical purity.[47] Once again, the yield of this water-soluble epoxy alcohol was improved by use of the nonaqueous isolation procedure developed for the synthesis of **35** (vide supra). After protection of the hydroxyl function as its *p*-methoxybenzyl (PMB) ether **67** (90%), the epoxide ring was regiospecifically opened with allylmagnesium chloride in quantitative yield. The resulting tertiary alcohol **68** was benzylated and then ozonolyzed to give an aldehyde; the carbon framework was completed by Wittig reaction with (carbethoxyethylidene)-triphenylphosphorane. Chromatographic separation of the resulting 94:6 mixture of *E* and *Z* olefin isomers provided the ester **70** in >98% isomeric purity (85% yield from **69**).

Oxidative cleavage of the PMB ether in **70** provided the hydroxy ester **71** (91%),[48] which was reduced with diisobutylaluminum hydride to the diol **72**, thus setting up the substrate for the second asymmetric epoxidation, which was carried out under the standard conditions with (+)-diethyl tartrate as the chiral ligand.[15] During the course of this reaction, the intermediate epoxide underwent intramolecular attack by the C_{35} hydroxyl group to give the tetrahydropyran **73** accompanied by small amounts of a diastereomer (vide infra).[49] After selective tosylation of the unpurified mixture at the primary hydroxyl, treatment with K_2CO_3/methanol cleanly effected ring closure to provide a 40:1 diastereomeric mixture of epoxides. The small amount of the unwanted diastereomer contaminant was readily removed by chromatography, and the crystalline epoxide **74**, mp 48.5–49.5 °C, was isolated in 85% overall yield from **70**. The excellent yields and the exper-

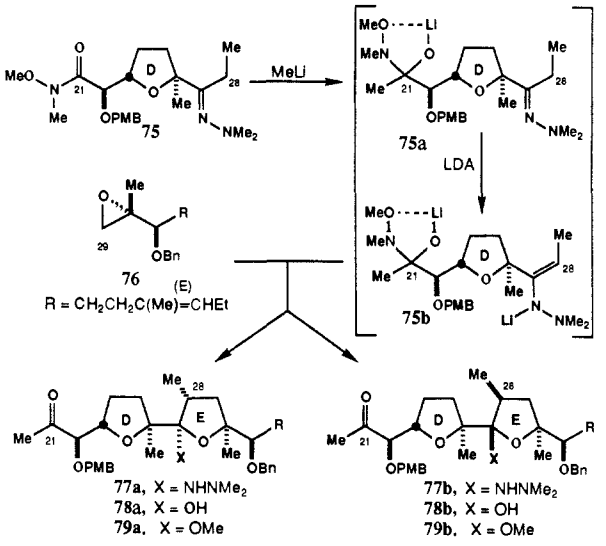
(46) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.

(47) The precise extent of conversion (in the vicinity of 50%) has a significant effect on the enantiomeric excess of **66**. Thus, the measured optical purity varied slightly between reactions (but always >92% ee).

(48) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.

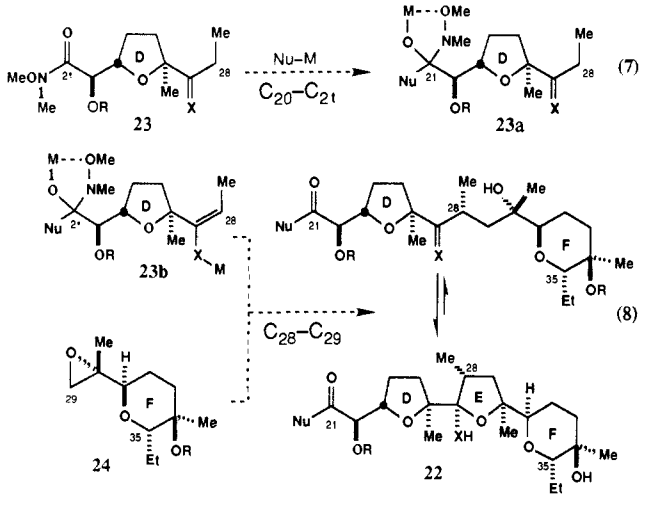
(49) A similar cyclization has been reported in the preparation of *C*-glycosyl compounds through asymmetric epoxidation: Reed, L. A., III; Ito, Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 6468–6470.

Scheme XV



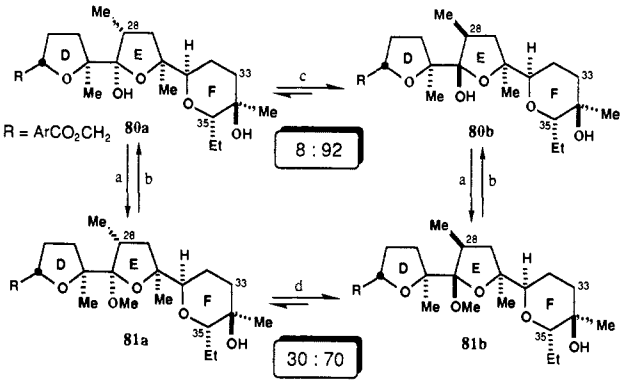
imental ease of many of the steps in this sequence compensate for the greater length (11 steps) of this route compared to the syntheses of the other fragments. A direct consequence of the iterative application of the asymmetric epoxidation reaction is that the epoxide **74** is generated in high enantiomeric purity (>99.9%). The essential ingredient for attaining this level of enantiomeric purity is the equally high "enantiofacial" selectivity observed in the second epoxidation *for both* **72** *and its enantiomer*.[50,51] Nearly all of the enantiomer contaminant in **72** is therefore converted into the diastereomeric impurity, which is ultimately removed in the purification of **74**.

Assemblage of the Right Half. The two connective operations that are required for the assemblage of this subunit from the fragments are illustrated below. According to this plan, the ring-D fragment **23** is required to provide both an electrophilic acyl center at C_{21} (eq 7) and an nucleophilic site, through enolization, at C_{28} (eq 8). Because of the ambivalent character of the C_{21}–C_{28}



fragment, the compatibility of functional groups during the coupling reactions became problematic, particularly as ketone enolates have proven to be quite unreactive toward epoxides.[52]

Scheme XVI[a]



[a] (a) PPTS, MeOH, $(MeO)_3CH$, 0 °C; (b) 0.2 N aqueous HCl, THF, 25 °C; (c) CSA, H_2O/CH_2Cl_2, 25 °C; (d) CSA, MeOH/CH_2Cl_2, 25 °C.

This reactivity issue could be remedied by employing the more nucleophilic, metalated Schiff base,[53] for example, **23** (X = NR),[54] but only if the electrophilicity of the C_{21} carbonyl was masked. Upon the realization that *the stable tetrahedral intermediate that results from the addition of an organolithium to a N-methoxy-N-methylamide can serve as a protecitve group* (*eq 8*), we investigated the in situ hydrazone metalation and epoxide coupling of the adduct resulting from the C_{20}–C_{21} bond construction. The crucial set of model studies that affirmed the viability of this assemblage plan is illustrated in Scheme XV.

Treatment of the hydrazone **75** with methyllithium in THF afforded the stable tetrahedral intermediate **75a**.[55] After metalation of this intermediate with lithium diisopropylamide (LDA), reaction with epoxide **76** effected the second-bond construction.[56] The readily separable C_{28} diastereomers **77a** and **77b** were isolated in 27% and 44% yields, respectively (vide infra); however, assignment of the configuration at C_{28} was not possible by routine spectroscopic analysis of these two isomers. With regard to the C_{27} stereocenter, consideration of conformational effects in five-membered rings suggests that the ring-E anomeric center is thermodynamically controlled such that, in either C_{28} configuration, the large ring-D substituent disposes itself in a trans 1,2-relationship to the C_{28} methyl group. Treatment of **77a** and **77b** individually with aqueous HCl in THF provided the lactols **78a** and **78b**, with no crossover detectable by TLC or ^1H NMR spectroscopy. In order to determine whether equilibration at C_{28} might occur under more vigorous conditions, the lactols were subjected to camphorsulfonic acid (CSA) in moist dichloromethane. Under these conditions, rapid interconversion does take place to give an equilibrium mixture of **78a** and **78b**, in which the lactol derived from the "major" hydrazino lactol (i.e., the product isolated in 44% yield) strongly predominated. The thermodynamically favored lactol was converted, without epimerization at C_{28}, to the corresponding methyl ketal with pyridinium tosylate (PPTS) in methanol. The configuration of this methyl ketal was tentatively assigned by ^1H NMR NOE studies as the *undesired* C_{28} stereoisomer **79b**.

In parallel experiments, equilibration and ketalization studies on the degradation product **14** independently addressed the C_{28} stereochemical issue. The triol **14** was first converted to its *p*-methoxybenzoyl ester **80a** to facilitate analysis (Scheme XVI). Under the standard conditions (CSA, moist CH_2Cl_2, 25 °C, 1 h), **80a** was rapidly equilibrated with the diastereomeric lactol **80b**, affording a **80a**/**80b** ratio of 8:92. *These indications that the desired* C_{28} *R stereochemistry is the less stable of the two*

(50) For a discussion of similar stereochemical consequences in another example of twofold asymmetric epoxidation, see: Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312–5313.

(51) Sharpless and co-workers have established that existing chirality at a remote location, as in **72**, has essentially no impact on the "diastereoselectivity" of the epoxidation: Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, Florida, 1985; Vol. 5, Chapter 8.

(52) To our knowledge, only a single example of a ketone enolate–epoxide reaction has been reported: Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165. Attempts to generalize this reaction were unsuccessful (S. L. Schreiber, personal communication).

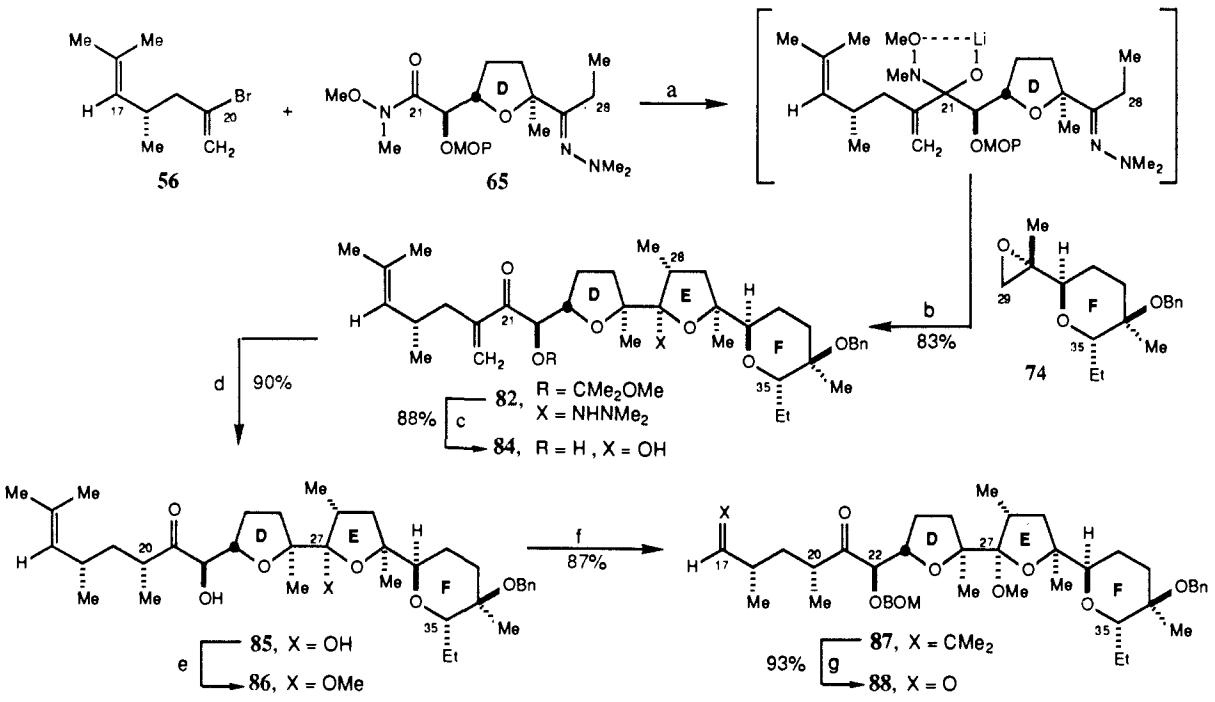
(53) In addition to providing a more reactive enolate equivalent, the Schiff base also possesses greatly decreased electrophilicity, thus protecting the C_{27} carbonyl during the C_{20}–C_{21} bond construction.

(54) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11–14.

(55) Exposure of the tetrahedral intermediate to excess LDA for several hours at 0 °C caused only slight decomposition, as judged by TLC.

(56) The epoxide **76** was prepared by asymmetric epoxidation in an early, unsuccessful approach to **74**.

Scheme XVII[a]



[a] (a) 2 equiv *t*-BuLi, **56**, Et_2O, −78 °C; **65**, −78 to 0 °C; (b) LDA, 0 °C; **74**, 0 °C; (c) 1 N aqueous $NaHSO_4$, 25% CH_2Cl_2/pentane; (d) 1 atm of H_2, $(Ph_3P)_3RhCl$, PhMe, 25 °C; (e) PPTS, $(MeO)_3CH$, MeOH, 0 °C; (f) $BnOCH_2Br$, H^+ sponge, MeCN, 25–45 °C; (g) O_3, $MeOH/CH_2Cl_2$, −78 °C.

diastereomeric possibilities appeared to eliminate the feasibility of employing thermodynamic control to establish the requisite stereochemistry at C_{28}.

In order to acquire more information on the equilibration process, the amount of epimerization occurring during ketalization and deketalization was evaluated quantitatively. Treatment of the lactols **80a** and **80b** with PPTS in methanol at 0 °C afforded the corresponding methyl ketals **81a** and **81b** with <1% cross-contamination according to HPLC analysis. Similarly, hydrolysis of the ketals back to the lactols proceeded without epimerization with 0.2 N aqueous hydrochloric acid in THF (25 °C, 30 min). Evidently, the intermediate oxonium ion traps the participating solvent significantly faster than it loses the C_{28} proton to give the dihydrofuran. The methyl ketals also equilibrate readily (CSA, 10% $MeOH/CH_2Cl_2$, 25 °C, 2 h), although the preference for the unnatural 28*S* isomer is decreased to 70:30.

The preceding studies implied that the C_{28}–C_{29} bond construction (eq 8), although successful in the model study, threatened the synthesis by providing the *undesired* C_{28} stereochemistry. Fortunately, the first attempt to improve the kinetic ratio in this coupling reaction proved auspicious. In diethyl ether (rather than THF) as solvent, the reaction of **75b** with epoxide **76** proceeded with an inverted kinetic selectivity to give a 4:1 mixture of **77a** and **77b**, respectively (Scheme XV). In spite of the notorious fallibility of such model studies, the coupling strategy for the right half of X-206 was pursued on the basis of the provided analogies. We were gratified to find that the application of this sequence to the actual system was achieved without difficulty (Scheme XVII). Under optimal conditions, an 83% isolated yield (based on the epoxide **74**) of the desired **82** was obtained, along with 6% of the C_{28} epimer **83**.[57]

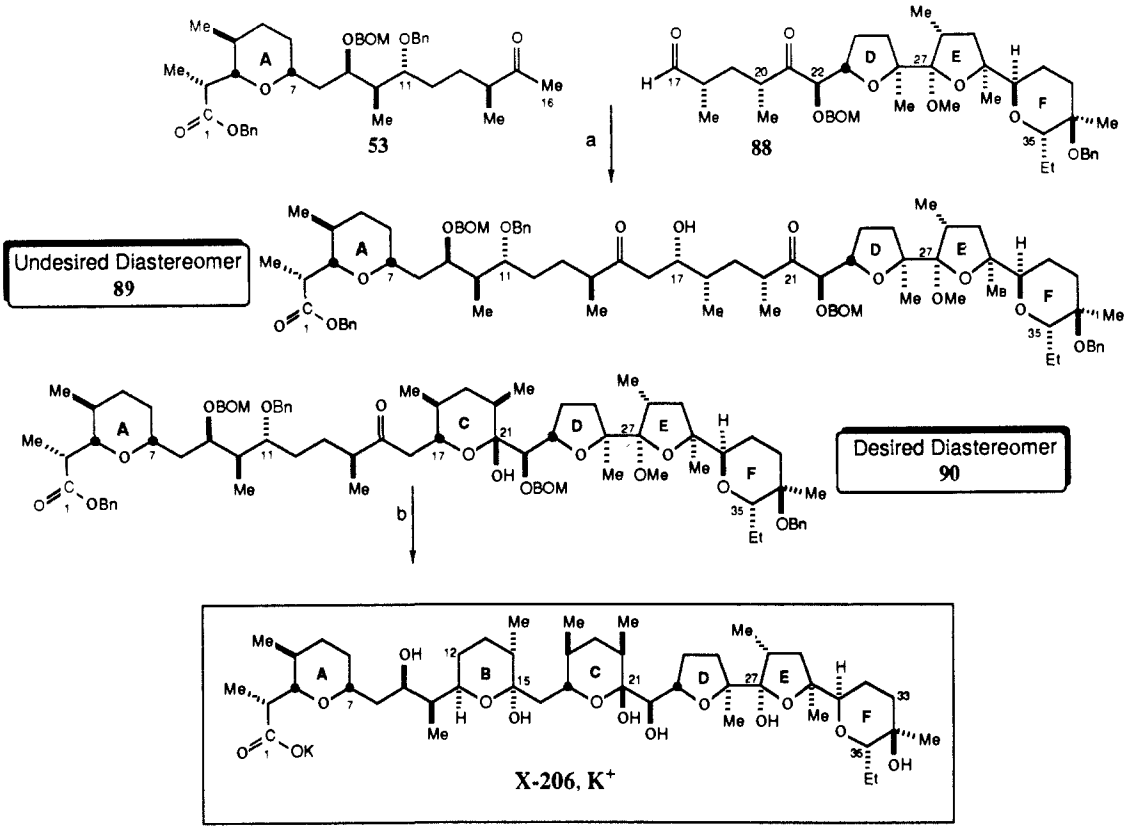
From the enone **82**, all that remains to complete the synthesis of the right half is the establishment of the C_{20} stereocenter and some protecting group manipulations. Exposure of **82** to aqueous acid in a two-phase system effected both the hydrolysis of the hydrazinolactol and the removal of the acid-labile C_{22} methoxyisopropyl protecting group. Hydrogenation of enone **84** with Wilkinson's catalyst proceeded in complete analogy to our previously reported model system to give a 93:7 mixture of C_{20} diastereomers.[19] The desired diastereomer **85** was isolated in 90% yield and in high diastereomeric purity by chromatography. Ring E was ketalized under nonepimerizing conditions (PPTS, methanol, 0 °C) to yield **86**, which was treated with benzyl bromomethyl ether and 1,8-bis(dimethylamino)naphthalene in acetonitrile to give **87** in 87% overall yield from **85**.[19] Finally, the utility of the isopropylidene moiety as a masked aldehyde equivalent was demonstrated by the clean ozonolysis of **87** to the target keto aldehyde **88** in 93% yield.

The synthesis of **88** required 17 steps from 2-methyl-1-penten-3-ol with an overall yield of 25%, which compares favorably with the synthesis of the left half **53** (17 steps, 17% overall yield). Unquestionably, the effectiveness of this route stems from the consolidation of the assemblage process into a single reaction. The 11 stereocenters in the right half were all incorporated with high stereoselectivity: seven of these were established through asymmetric synthesis with at least 96% stereoselectivity, while the other four were controlled by internal asymmetric induction with a minimum stereoselectivity of 93%. As was the case for for the C_1–C_{16} subunit **53**, no significant problems were encountered in preparing ample quantities of the C_{17}–C_{37} subunit **88**.

Aldol Coupling of the C_1–C_{16} and C_{17}–C_{37} Subunits. With efficient syntheses of both **53** and **88** secured, the aldol coupling of the two subunits was undertaken. In the initial studies, the principal objective was to obtain and characterize both diastereomeric aldol adducts. Accordingly, the kinetic aldol addition reaction of the lithium enolate of ketone **53** (LDA, ether, −78 °C) with a slight excess of aldehyde **88** was investigated. After optimization of the isolation protocol, the two diastereomeric aldol adducts **89** and **90** were obtained in yields of 47% and 41%, respectively (Scheme XVIII). As had been anticipated, the two isomers were readily separable as a result of the differences in the tautomeric composition of ring C (vide infra) and were readily identified by ^1H NMR spectroscopy. The stereochemical outcome of this reaction (55:45) slightly favored the *undesired* diastereomer **89**, a fact consistent with a small diastereofacial bias imposed on the aldehyde by the α-stereocenter in accord with Cram's rule.[58]

(57) Even though the stereochemical outcome of the coupling sequence in ether was satisfactory, the reaction was also conducted in THF in order to confirm the solvent effect observed in the model study. Surprisingly, the strong selectivity for **83** persisted, but the chemical yield was somewhat lower due to side reactions.

Scheme XVIII[a]



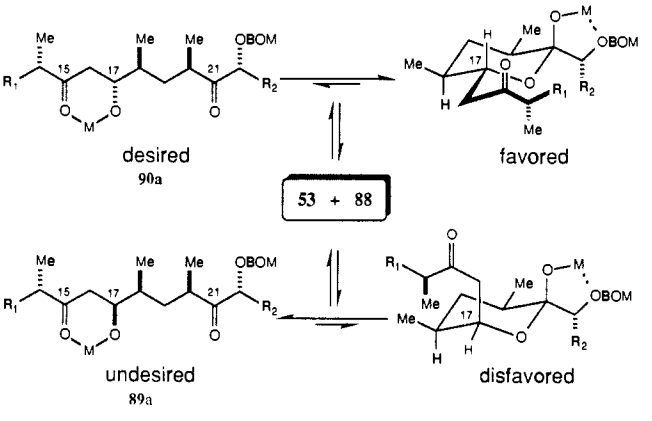
[a](a) LDA, **53**, Et_2O, −78 °C, 5 min; **88**, −78 °C, 5 min; (b) 1 atm of H_2, 10% Pd/C, 0.01 N $HClO_4$ in 80% aqueous THF, 25 °C.

For comparison with X-206, the desired diastereomer **90** was carried forward by catalytic hydrogenolysis of all of the benzyl protecting groups. Under the acidic conditions (ca. 0.01 N perchloric acid) necessary to effect complete hydrogenolysis of the benzyl ethers in **90**, the ring-E methyl ketal at C_{28} was also hydrolyzed. When the deprotection was complete, TLC analysis in several solvent systems revealed a single product which coeluted with natural X-206. Synthetic X-206 was isolated in 94% yield as fine white needles by slow evaporation of an ether/hexane solution of the potassium salt. The synthetic material was identical in all respects (TLC, ^1H and ^{13}C NMR, IR, $[\alpha]_D$, and melting point) with the potassium salt of natural X-206. In particular, the 500-MHz ^1H NMR spectra of the potassium complexes of synthetic and natural X-206 in deuteriobenzene are very well resolved and completely superimposable.

Although the aldol reaction described in the preceding paragraph permitted the completion of the synthesis, the low kinetic stereoselectivity led us to consider more selective aldol variants. In certain instances, the presence of oxygen functionality in the vicinity of the bond construction may be exploited to enhance reaction stereoselectivity[59,60] through metal chelate organization.[36] Unfortunately, the lack of such functionality on the aldol substrates **53** and **88** suggested that a survey of different enolate counterions, in hopes of optimizing chelation, would be fruitless.

An alternative approach to attaining C_{17} stereocontrol might rely upon the selection of a reversible rather than a kinetic aldol

Scheme XIX



reaction. For this strategy to succeed, the metal aldolate **89a** must be less stable than the desired diastereomeric aldolate **90a**. The relative stabilities of these intermediates can be estimated by analysis of the ring–chain tautomers illustrated below (Scheme XIX). From the preceding studies (see Scheme III), it has been substantiated that the configuration at C_{17} dictates whether the lactol or hydroxy ketone tautomer is the predominant species in solution. The reasonable assumption that the hydroxy ketone tautomer of **90**, which is present at equilibrium as a minor component, is essentially equal in energy to **89** leads to the conclusion that **90** is thermodynamically more stable than **89**. Extension of these principles to the corresponding aldolates **89a** and **90a** suggests that good stereoselectivity for **90** should occur in the aldol reaction under equilibrating conditions. In order to test this concept, the model aldol adducts **8** and **9** (Scheme III) were examined.

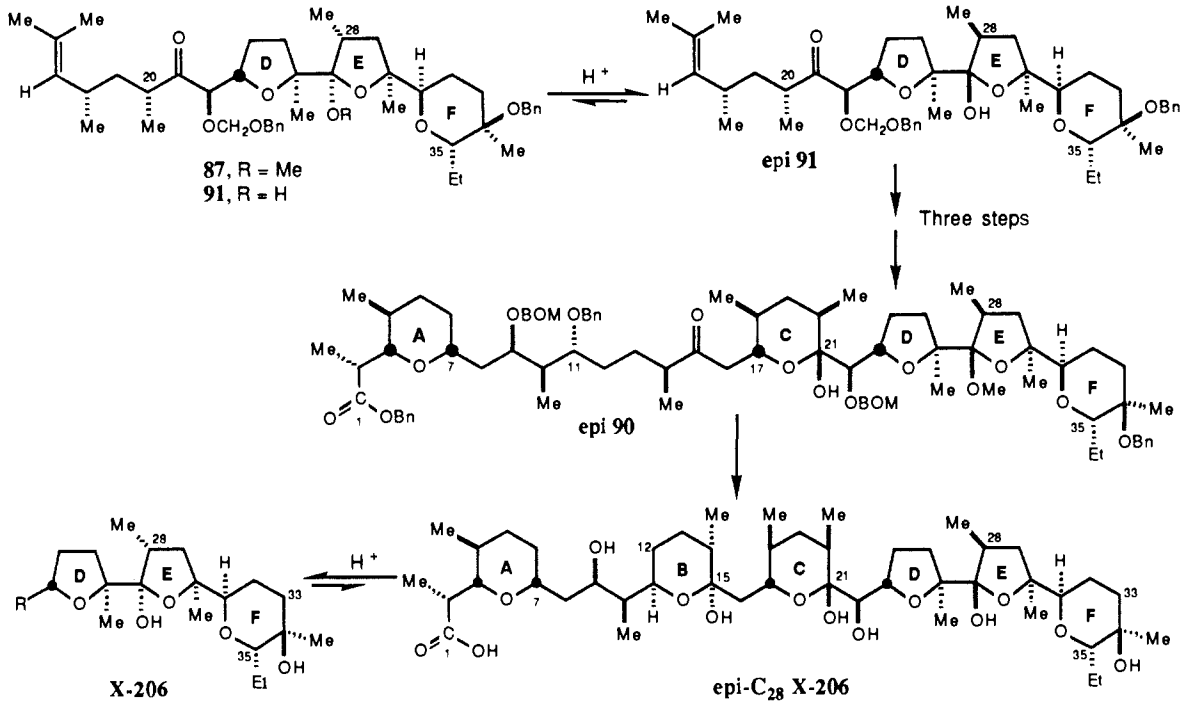
Under a variety of reaction conditions, we were unable to observe any interconversion of **8** and **9**. This approach thus fails as a consequence of the reluctance of the aldolates to undergo retroaldolization. The available experimental evidence indicates that the retroaldol reaction is strongly accelerated by structural

(58) For applications of Cram's rule, see: Eliel, E. L. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, Florida, 1983; Vol. 2, Chapter 5.

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

(60) For some examples in total syntheses, see: (a) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262–263 (monensin). (b) Lewis, M. D. Ph.D. Dissertation, Harvard University, 1983 (narasin). (c) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528–5531 (rifamycin S). (d) Masamune, S.; Hirama, J.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *104*, 1568–1571 (6-deoxyerythronolide B).

Scheme XX



features that destabilize, either sterically or electronically, the aldolate relative to the enolate and aldehyde components.[61] In this regard, aldol adducts derived from ethyl ketones appear to be significantly more labile that those derived from methyl ketones.[62] In terms of these factors, the final aldol condensation in the X-206 synthesis is a worst-case scenario, since the aldolates completely lack any such activating features. Shortly after the completion of this project, Masamune and co-workers[63] disclosed that enolates derived from chiral boron triflate reagents that possess C_2 symmetry undergo highly stereoselective aldol addition reactions; the applicability of this reagent to the final coupling reaction is obvious. It is clear that the convergent syntheses based on aldol coupling reactions stand to benefit from this and future developments of this type.

Ionophore Tertiary Structure and Rational Stereocontrol. In principle, during the evolution of a synthesis plan for a "large" structure such as X-206, one should both acknowledge and exploit the molecule's tertiary structure, which might be imposed by both noncovalent interactions and other associative phenomena such as metal ion ligation. In practice, relying upon these structural properties is highly risky, for at least two reasons. First, these kinds of noncovalent interactions cannot yet be quantitatively evaluated as a function of medium, and secondly, a pathway to the "stabilized" structure may not be kinetically accessible relative to undesired pathways (e.g., C_{17} stereocontrol via aldol reversibility). During the course of the X-206 synthesis, we speculated that the "unnatural" *S* configuration of the C_{28} methyl-bearing stereogenic center would greatly diminish the stability of the complexed ionophore, since the attendant inversion of configuration at C_{27} prevents access to the required conformation for complete ligation and hydrogen bonding.[64] *This analysis leads directly to the prediction that epi-C_{27}/C_{28} X-206 will be less stable than X-206, despite the strong thermodynamic preference for the unnatural configuration at C_{28} in partial structures* (see Scheme XVI, **80**, **81**). In order to confirm this hypothesis, we carried out an unambiguous synthesis of *epi*-C_{27}/C_{28} X-206, which was readily achieved as follows. The advanced intermediate **87** was subjected to the standard equilibration conditions to give the expected mixture of C_{28} lactol diastereomers, from which *epi*-**91** was isolated by chromatography in 78% yield (Scheme XX). Reketalization of *epi*-**91** afforded *epi*-**87**, which was ozonolyzed and combined with the lithium enolate of **53** to give *epi*-**89** and *epi*-**90** in direct analogy to the terminal steps in the synthesis (Scheme XVIII). When *epi*-**90** was subjected to hydrogenolysis, two products were obtained according to TLC analysis, wherein the minor product at higher R_f coeluted with X-206. Analysis of the mixture by 500-MHz ^{1}H NMR confirmed that the minor component (ca. 25% of the mixture) was indeed X-206, while the major component appeared to be *epi*-C_{27}/C_{28} X-206 on the basis of a multiplet at 2.7 ppm for the C_{28} proton that is highly characteristic of the 28*S* configuration. Obviously, partial epimerization at C_{28} occurred under the mildly acidic conditions of deprotection. Finally, exposure of the mixture to the standard equilibration conditions resulted in the smooth and complete (>95%) conversion of *epi*-C_{27}/C_{28} X-206 to X-206. In retrospect, this set of experiments clearly demonstrates that one could have relied upon the tertiary structure of the target to establish both of the C_{27} and C_{28} stereogenic centers. Future synthesis planning in this area will no doubt be in a position to take greater advantage of such noncovalent interactions.

Experimental Section

General Methods. Melting points are uncorrected. Combustion analyses were performed by Spang Microanalytical Laboratory (Eagle Harbor, MI), Galbraith Laboratories, Inc. (Knoxville, TN), or Lawrence Henling (California Institute of Technology Microanalytical Laboratory). Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh). Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium metal/benzophenone ketyl. Toluene and benzene were distilled from sodium metal. Dichloromethane, pyridine, diisopropylethylamine, triethylamine, diisopropylamine, and acetonitrile were distilled from calcium hydride. Dimethylformamide (DMF) was distilled under reduced pressure from calcium hydride and stored over activated 5-Å molecular sieves under an argon atmosphere. Reagent grade anhydrous dimethyl sulfoxide was stored over activated 4-Å molecular sieves under argon. Chloroform was passed through a column of

(61) For a discussion of the factors pertaining to reversibility in the aldol condensation, see: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, Florida, 1983; Vol. 3, Chapter 2, pp 161–165.

(62) For example, Still and co-workers have recently reported the application of reversible aldol methodology in controlling the C_{11} and C_{12} stereochemistry in lasalocid: Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett.* **1987**, *28*, 2817–2820.

(63) Masamune, S.; Sato, T.; Kim, B.-M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281.

(64) According to the X-ray structures (ref 11 and 12), the free acid of X-206 forms a complex with water that is virtually identical with the structure of the metal complexes.

activity I basic alumina immediately before use as a solvent for optical rotation measurements. Anhydrous *tert*-butyl hydroperoxide (TBHP) in benzene or toluene was prepared according to the method of Sharpless.[65] Benzyl bromide was filtered through alumina before use. Tri-*n*-butyltin hydride was prepared according to the literature method[66] and stored in a Schlenk flask at −20 °C under argon. Commercial *N,O*-dimethylhydroxylamine (Aldrich) was recrystallized from 2-propanol. Benzyl chloromethyl ether, obtained from Aldrich Chemical Co., was stored at −20 °C under argon and was monitored periodically by ^{1}H NMR analysis for indications of decomposition. Titanium tetraisopropoxide was distilled in vacuo and stored under argon. Tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) was obtained from Aldrich (Gold Label grade). Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with use of flame-dried glassware.

For brevity, experimental details for the preparation of intermediates **28**, **29**, **37**, **38**, **45**, **46**, **62–64**, **69**, **71**, and **72** were not incorporated in the following section. Full details for these procedures and complete characterization of the compounds can be found in ref 1.

X-206, Methyl Ester (10). To a solution of 300 mg (0.337 mmol) of X-206 monohydrate (**1**) in 5 mL of ether was added ethereal diazomethane until nitrogen evolution ceased and the yellow color persisted. After an additional 10 min, the solution was concentrated, and the residue was purified by chromatography (40 g of silica gel). Elution with 300 mL of 30% EtOAc/CH_2Cl_2 gave 86 mg (29%) of the methyl ester **10** as an amorphous solid. Continued elution with EtOAc eluted the mono(methyl ketal) **11** in two distinct bands (see text). The first band provided 35 mg of **11** while the second band afforded 150 mg of **11**: the total yield of **11** was 185 mg (61%), as an amorphous solid.

Data for X-206, methyl ester **10**: mp 80–90 °C; $[\alpha]_D$ + 10.7° (*c* 3.0, $CHCl_3$); IR ($CHCl_3$) 3400 (br), 2950 (br), 1735, 1465, 1390, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.23 (d, 1 H, *J* = 1.3 Hz, OH), 5.70 (d, 1 H, *J* = 1.5 Hz, OH), 5.39 (br s, 1 H, OH), 4.41 (dd, 1 H, *J* = 10.1 and 5.6 Hz, C_{23}-H), 4.34 (br d, 1 H, *J* = 9.8 Hz, C_9-H), 4.16 (t, 1 H, *J* = 9.6 Hz, C_{17}-H), 3.79 (ddd, 1 H, *J* = 11, 10, and 2 Hz, C_{11}-H), 3.69 (s, 3 H, OCH_3), 3.48–3.54 (m overlapping dd, 2 H, *J* = 9.9 and 3.5 Hz, C_3-H (dd) and C_7-H), 3.40 (dd, 1 H, *J* = 11.5 and 3.4 Hz, C_{35}-H), 3.36 (d, 1 H, *J* = 12.1 Hz, C_{22}-H), 3.31–3.35 (m, 1 H, C_{31}-H), 2.96 (s, 1 H, OH), 2.81 (br s, 1 H, OH), 2.79 (br s, 2 H, H_2O?), 2.66 (qd, 1 H, *J* = 7.1 and 3.5 Hz, C_2-H), 2.45 (d, 1 H, *J* = 12.1 Hz, C_{22}-OH), 2.30 (dd, 1 H, *J* = 12.3 and 8.9 Hz, one of C_{29}-H), 2.02–2.28 (m, 4 H), 1.1–1.9 (m, 26 H), 1.06, 1.22, and 1.34 (3 s, 9 H, 3 CCH_3), 1.12 (d, 3 H, *J* = 7.1 Hz, $CHCH_3$), 1.07 (d, 3 H, *J* = 6.7 Hz, $CHCH_3$), 0.96 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3), 0.89 and 0.90 (overlapping d, 6 H, *J* = 6.6 Hz, 2 $CHCH_3$), 0.80–0.83 (m, 9 H, 3 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 108.6, 99.0, 97.6, 90.5, 84.1, 83.3, 82.7, 77.2, 76.7, 72.8, 72.1, 71.6, 69.6, 69.3, 67.8, 51.5, 43.6, 43.1, 41.8, 41.0, 40.2, 39.8, 39.1, 37.0, 35.5, 33.7, 32.9, 32.8, 32.5, 31.9, 31.6, 30.2 (2), 27.7, 25.1 (2), 24.1, 21.3, 20.0, 17.7, 17.2, 16.4, 16.3, 15.2, 10.5, 9.7, 8.8; TLC R_f 0.34 (30% EtOAc/CH_2Cl_2). Anal. Calcd for $C_{48}H_{84}O_{14}$: C, 65.13; H, 9.57. Calcd for $C_{48}H_{84}O_{14}$·0.5H_2O: C, 64.45; H, 9.58. Found: C, 64.43; H, 9.36.

Data for X-206, methyl ester, mono(methyl ether) **11**: $[\alpha]_D$ +24.8° (*c* 3.0, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 2950 (br), 1735, 1460, 1385, 1050 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 6.71 (s, 1 H, OH), 5.69 (s, 1 H, OH), 4.51 (q, 1 H, *J* = 5 Hz, C_{22}-H), 4.20–4.29 (m, 2 H), 4.14 (t, 1 H, *J* = 10 Hz), 3.84 (s, 3 H, CO_2CH_3), 3.55 (s, 3 H, OCH_3), 3.28–3.60 (m, 6 H), 2.82 (br s, 1 H, OH), 2.25–2.57 (m, 5 H), 1.2–2.1 (m, 30 H), 1.35 and 1.52 (2 s, 6 H, 2 CCH_3), 1.10–1.18 (m, 9 H, 3 $CHCH_3$), 0.99–1.05 (m, 9 H, 2 $CHCH_3$ and CCH_3), 0.91 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 0.70 (d, 3 H, *J* = 6.2 Hz, $CHCH_3$), 0.54 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$); ^{13}C NMR (C_6D_6, 75 MHz) δ 174.7, 108.8, 102.4, 98.4, 89.7, 84.3, 83.8, 82.3, 79.8, 78.2, 75.8, 73.4, 72.4, 71.2, 70.5, 69.2, 52.0, 51.5, 43.62, 43.57, 41.9, 41.7, 41.1, 40.2, 39.3, 36.7, 35.4, 35.3, 33.3, 32.9, 32.7, 32.1, 31.9, 30.1, 29.4, 27.9, 25.4, 25.3, 24.5, 21.8, 20.3, 18.0, 17.2, 17.1, 16.7, 15.0, 10.7, 10.2, 9.3; TLC R_f 0.66 (**11a**) and 0.21 (**11b**) (70% EtOAc/hexane). Anal. Calcd for $C_{49}H_{86}O_{14}$: C, 65.45; H, 9.64. Found: C, 65.38; H, 9.56.

X-206, Methyl Ester, Tris(methyl ketal) (12). To a solution of 100 mg (0.113 mmol) of X-206 methyl ester (**10**) in 3 mL of 10% trimethyl orthoformate/methanol at 0 °C was added 50 mg of Dowex-50X 12–200 acidic resin. The mixture was stirred for 2 h at 0 °C, and then the solution was decanted and partitioned between 25% CH_2Cl_2/pentane and dilute pH 7 phosphate buffer. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (15 g of silica gel, 35% EtOAc/hexane) yielded 84 mg (80%) of the tris(methyl ketal) **12** as an amorphous solid: $[\alpha]_D$ +4.8° (*c* 3.0, $CHCl_3$); IR ($CHCl_3$) 3500 (br), 2950 (br), 1735. 1460, 1380, 1100, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.05–4.10 (m, 1 H, C_{23}-H), 3.98–4.03 (m, 1 H, C_9-H), 3.74 (dd, 1 H, *J* = 6.6 and 3.1 Hz, C_{22}-H), 3.64 (s, 3 H, CO_2CH_3), 3.59–3.63 (m, 1 H), 3.45–3.53 (m, 3 H), 3.41 (dd, 1 H, *J* = 12 and 3 Hz), 3.23, 3.36, and 3.39 (3 s, 9 H, 3 OCH_3), 2.79 (s, 1 H, OH), 2.68 (qd, 1 H, *J* = 7.1 and 3.0 Hz, C_2-H), 2.44 (d, 1 H. *J* = 6.6 Hz, C_{22}-OH), 2.30–2.38 (m, 2 H), 2.15 (td, 1 H, *J* = 12 and 8 Hz), 1.2–1.9 (m, 40 H), 1.24 and 1.30 (2 s, 6 H, 2 CCH_3), 1.12 (d, 3 H, *J* = 7.1 Hz, $CHCH_3$), 1.07 (s overlapping d, 6 H, CCH_3 and $CHCH_3$), 0.99 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3), 0.95 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 0.80–0.86 (m, 12 H, 4 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 110.0, 101.4, 100.2, 87.7, 84.0, 83.6, 82.9, 80.1, 78.1, 73.3, 72.4, 72.2, 71.0, 69.6, 69.5, 51.5, 50.6, 48.1, 47.2, 43.5, 43.3, 41.4, 40.4. 39.0, 38.2, 37.3, 35.6, 35.4, 34.7, 32.7, 31.91, 31.86, 31.4, 29.6. 29.2, 27.8, 24.9, 24.7, 22.3, 20.9, 19.9, 18.4, 17.2, 17.1, 16.3, 15.0, 10.7, 10.3, 9.0; TLC R_f 0.35 (35% EtOAc/hexane). Anal. Calcd for $C_{51}H_{90}O_{14}$: C, 66.06; H, 9.78. Found: C, 65.93; H, 9.80.

Hydrolysis of the Tris(methyl ketal) 12 to X-206, Methyl Ester (10). A solution of 250 mg (0.27 mmol) of the tris(methyl ketal) **12** in 15 mL of 2:1 THF/0.2 N aqueous HCl was stirred at 25 °C for 3.5 h, at which time 1 mL of 2 M pH 7 phosphate buffer was added. The mixture was partitioned between 25% CH_2Cl_2/pentane and water. The organic layer was dried over Na_2SO_4 and concentrated to give 235 mg (98%) of the methyl ester of X-206 (**10**) as a solid foam: TLC and ^{1}H NMR analysis indicated a high degree of purity.

[2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*R*,5*R*,6*S*))]-5-[5-(6-Ethyl-5-hydroxy-5-methyltetrahydropyran-2-yl)-2-hydroxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydro-2-furanmethanol (14). To a solution of 110 mg (0.25 mmol) of lead tetraacetate in 2 mL of toluene was added 177 mg (0.20 mmol) of X-206 methyl ester (**10**) in one portion. After 10 min, 5 drops of ethylene glycol was added to consume the excess lead tetraacetate. The mixture was partitioned between pH 7 phosphate buffer and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with brine, diluted with hexane, dried over Na_2SO_4, and concentrated. The residue was immediately dissolved in 4 mL of THF and cooled to −78 °C, and 0.25 mL (0.50 mmol) of 2.0 M $LiBH_4$ in THF was added. The solution was stirred for 15 min at −78 °C, 0.4 mL of acetone was added, and the cooling bath was removed. After 10 min, 5 mL of pH 7 phosphate buffer was added, and the mixture was partitioned between brine and EtOAc. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (15 g of silica gel, 10% *i*-PrOH/CH_2Cl_2). Several byproducts (presumably derived from the C_1–C_{21} fragment) eluted first, followed by 63 mg (85%) of the triol **14** as a white solid. An analytical sample was recrystallized from hexane: mp 118–119 °C; $[\alpha]_{435}$ −32.1°, $[\alpha]_D$ −16.7° (*c* 1.10, CH_2Cl_2); IR ($CHCl_3$) 3550 (br), 2980, 2950, 2880, 1460, 1375, 1100, 1050, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16–4.20 (m, 1 H, C_{23}-H), 3.74 (ddd, 1 H, *J* = 11.7, 6.0, and 3.0 Hz, one of C_{22}-H), 3.49 (ddd, 1 H, *J* = 11.7, 6.9, and 5.1 Hz, one of C_{22}-H), 3.43 (dd, 1 H, *J* = 11.4 and 3.6 Hz, C_{35}-H), 3.27–3.34 (m, 1 H, C_{31}-H), 3.22 (d, 1 H, *J* = 1.0 Hz, C_{27}-OH), 2.80 (br s, 1 H, C_{35}-OH), 2.15–2.35 (m, 3 H), 2.15 (t, 1 H, *J* = 6.5 Hz, C_{22}-OH), 1.35–1.95 (m, 10 H), 1.26 and 1.33 (2 s, 6 H, 2 CCH_3), 1.08 (d, 3 H, $CHCH_3$), 1.07 (s, 3 H, CCH_3), 1.00 (t, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 108.4, 87.9, 84.0, 83.0, 81.5, 71.6, 69.5, 64.7, 42.7, 38.2, 33.3, 31.3, 27.9, 24.9, 24.8, 24.4, 21.1, 19.9, 14.7, 10.5; TLC R_f 0.26 (10% *i*-PrOH/CH_2Cl_2). Anal. Calcd for $C_{20}H_{36}O_6$: C, 64.49; H, 9.74. Found: C, 64.46; H, 9.73.

[2*S*]-2-Methyl-4-penten-1-ol (27). In a three-necked, 250-mL flask, equipped with a dropping funnel and septa, a solution of 13.66 g (50.00 mmol) of the imide **26**[22] in 100 mL of THF was stirred and cooled at −78 °C as 50.0 mL (50.0 mmol) of 1.0 M $LiAlH_4$ in THF was added from the dropping funnel at a rate to maintain the internal temperature below −70 °C. The total time of addition was 40 min. The reaction mixture was stirred for 1 h at −78 °C and then at −78 to −20 °C over a 2-h period. The reaction was quenched by dropwise addition of 20 mL of 9:1 THF/water (*caution*: vigorous evolution of hydrogen gas), followed by 2 mL of 3 N sodium hydroxide and then 6 mL of water. The mixture was stirred vigorously for 10 min, and then 50 mL of hexane and 10 g of anhydrous magnesium sulfate were added. The mixture was filtered through Celite, and the filter cake was washed well with ether. The filtrate was concentrated in vacuo at aspirator pressure with a bath temperature of 10 °C to a volume of ca. 150 mL. The remainder of the solvent was removed by distillation at atmospheric pressure. The residue was dissolved in 50 mL of 1:1 ether/pentane, and a precipitate formed. The mixture was cooled to 0 °C, the supernatant was decanted, and the precipitate was washed with 2 × 20 mL of 1:1 ether/pentane. The solid was dried in vacuo to give 4.70 g (55%) of 4(*R*)-methyl-5(*R*)-phenyl-2-oxazolidinone. The combined supernatants were concentrated in va-

(65) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607–3608.

(66) Kuivila, H. G. *Synthesis* **1970**, 499–509.

cuo, and Kugelrohr distillation (oven temperature 110–130 °C, 25 mmHg) of the residue gave 4.12 g (82%) of the alcohol **27**: $[\alpha]_D$ −2.3° (*c* 1.0, $CHCl_3$); IR (thin film) 3350 (br), 3080, 2960, 2920, 2880, 1645, 1460, 1440, 1045, 995, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80 (ddt, 1 H, *J* = 17.0, 10.0, and 7.0 Hz, =C*H*CH_2), 4.98–5.08 (m, 2 H, =CH_2), 3.47 (apparent qd [ABX], 2 H, *J* = 10.6 and 6.2 Hz, CH_2OH), 2.13–2.24 (m, 1 H, one of CH_2CH=), 2.07 (br s, 1 H, OH), 1.87–1.98 (m, 1 H, one of CH_2CH=), 1.73 (octet, 1 H, *J* = 6.6 Hz, C*H*CH_3), 0.92 (d, 3 H, *J* = 6.8 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 136.9, 115.9, 67.7, 37.8, 35.6, 16.3; TLC R_f 0.36 (35% EtOAc/hexane). Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.86; H, 12.11.

[(4*S*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-methylpentyl]triphenylphosphonium Iodide (30). To a solution of 554 mg (1.62 mmol) of the unpurified iodide **29** in 2.5 mL of dry MeCN were added 0.02 mL of *i*-Pr_2EtN and 550 mg (2.1 mmol) of Ph_3P. The solution was stirred at 50 °C for 14 h in the dark. After the mixture was cooled to room temperature, ca. 5 mL of toluene was added, and the solvent was evaporated under reduced pressure. The gummy residue was triturated with 2 × 10 mL of hexane to give a pale orange solid. Recrystallization from 10 mL of EtOAc afforded 810 mg (83%) of the phosphonium salt **30** as white prisms: mp 138.5–141 °C; $[\alpha]_D$ +1.0° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) 2960, 1445, 1120, 840, 690, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68–7.87 (m, 15 H, Ar H), 3.47–3.77 (m, 2 H, CH_2P), 3.30–3.39 (m, 2 H, CH_2O), 1.42–1.84 (m, 5 H), 0.82 (s, 9 H, C(CH_3)$_3$), 0.80 (d, 3 H, *J* = 6.6 Hz, CHCH_3), −0.036 and −0.042 (2 s, 6 H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.0 (d, J_{CP} = 3 Hz), 133.4 (d, J_{CP} = 10 Hz), 130.4 (d, J_{CP} = 12 Hz), 118.0 (d, J_{CP} = 86 Hz), 67.6, 35.1, 34.1 (d, J_{CP} = 14 Hz), 25.7, 23.4 (d, J_{CP} = 50 Hz), 20.2 (d, J_{CP} = 4 Hz), 18.0, 16.4, −5.6. Anal. Calcd for $C_{30}H_{42}IOPSi$: C, 59.60; H, 7.00. Found: C, 59.73; H, 7.03.

[3(2*S*,3*R*,4*E*),4*S*]-3-(3-Hydroxy-2-methyl-1-oxo-5-phenyl-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (32). To a solution of 4.665 g (20.0 mmol) of the imide **31** in 50 mL of CH_2Cl_2 at −78 °C was added 3.33 mL (2.42 g, 24.0 mmol) of Et_3N, followed by 5.53 mL (6.03 g, 22.0 mmol) of Bu_2BOTf. The solution was stirred for 1 h at −78 °C and for 15 min at 0 °C. After the solution was recooled to −78 °C, 2.77 mL (2.91 g, 22.0 mmol) of cinnamaldehyde was added in one portion. The yellow solution was stirred for 30 min at −78 °C, 15 min at −78 to 0 °C, and 30 min at 0 °C and then quenched with 100 mL of 1 M NaOAc in 90% methanol/water. After 5 min, 10 mL of 30% aqueous H_2O_2 was added dropwise (*caution*: initial reaction is highly exothermic). After being stirred an additional 15 min at 10–15 °C, the mixture was partitioned between 400 mL of water and 250 mL of hexane. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from CH_2Cl_2/hexane to give 6.47 g (89%) of fine white needles. The mother liquors were concentrated, and the residue was purified by chromatography (50 g of silica gel, 40% EtOAc/hexane) to give 0.32 g of additional product. The total yield was 6.79 g (93%) of aldol adduct **32**: mp 121–122 °C; $[\alpha]_D$ +78.6° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3600 (sh), 3540 (br), 3040, 3020, 1785, 1690, 1390, 1240, 970, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.42 (m, 10 H, Ar H), 6.67 (dd, 1 H, *J* = 15.9 and 1.0 Hz, PhC*H*=), 6.22 (dd, 1 H, *J* = 15.9 and 5.9 Hz, =C*H*CH), 4.63–4.75 (m, 2 H, C*H*OH and NC*H*), 4.10–4.20 (m, 2 H, CH_2O), 3.99 (qd, 1 H, *J* = 7.0 and 3.8 Hz, C*H*C=O), 3.25 (dd, 1 H, *J* = 13.4 and 3.3 Hz, one of PhCH_2), 2.98 (d, 1 H, *J* = 2.8 Hz, OHe, 2.80 (dd, 1 H, *J* = 13.4 and 9.4 Hz, one of PhCH_2), 1.31 (d, 3 H, *J* = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3, 153.1, 136.8, 135.2, 131.5, 129.4, 129.1, 128.9, 128.5, 127.7. 127.4, 126.5, 73.0, 66.2, 55.2, 43.2, 37.9, 11.6; TLC R_f 0.30 (40% EtOAc/hexane). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34. Found: C, 72.34; H, 6.40.

(2*S*,3*R*,4*E*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-5-phenyl-4-pentenamide (33). To a suspension of 4.88 g (50.0 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 100 mL of CH_2Cl_2 at 0 °C was added 25 mL (50 mmol) of 2.0 M $AlMe_3$ in toluene over a 5-min period (*caution*: vigorous gas evolution). After the addition was complete, the cooling bath was removed, and the clear solution was stirred for 30 min at room temperature. The solution was recooled to −15 °C, and a solution of 9.14 g (25.00 mmol) the imide **32** in 40 mL (plus a 10 mL rinse) of CH_2Cl_2 was added via cannula. The cloudy reaction mixture was stirred at 0–10 °C, at which temperature gas evolved steadily and the mixture slowly cleared. After 30 min, the clear solution was cooled to −10 °C and allowed to warm slowly overnight (12 h). The solution was then cannulated into 150 mL of 1 M aqueous tartaric acid, and the mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. A majority (2.65 g, 60% recovery) of the byproduct 4-(*S*)-(phenylmethyl)-2-oxazolidinone was removed by crystallization from ca. 100 mL of 30% EtOAc/hexane. Concentration of the supernatant gave a mixture of the amide **33** and the oxazolidinone, which was used in the next step without purification. In a smaller scale (2.00 mmol) reaction, purification of the mixture by chromatography (50% EtOAc/hexane) gave spectroscopically pure **33** in 92% yield: $[\alpha]_D$ +37.0° (*c* 2.0, $CHCl_3$); IR (thin film) 3400, 2980, 2940, 1650, 1460, 1390, 990, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 50 °C) δ 7.16–7.30 (m, 5 H, Ar H), 6.68 (dd, 1 H, *J* = 16.0 and 1.3 Hz, PhC*H*=), 6.19 (dd, 1 H, *J* = 16.0 and 5.6 Hz, CHC*H*=), 4.57–4.60 (m, 1 H, C*H*OH), 3.70 (s, 3 H, OCH_3), 3.65 (br s, 1 H, OH), 3.19 (s, 3 H, NCH_3), 3.04 (qd, 1 H, *J* = 7.0 and 3.6 Hz, C*H*CH$_3$), 1.22 (d, 3 H, *J* = 7.0 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1 (br), 136.8, 130.6, 129.4, 28.3, 127.3, 126.2, 72.5, 61.3, 39.9, 31.9 (br), 11.0; mass spectrum (EI, 70 eV), *m/e* (relative intensity) 249 (2, M^+), 218 (5), 189 (15), 143 (19), 133 (100); TLC R_f 0.24 (50% EtOAc/hexane); exact mass calcd for $C_{14}H_{19}NO_3$ 249.13648, found 249.13629.

(2*S*,3*R*,4*E*)-*N*-Methoxy-*N*,2-dimethyl-5-phenyl-3-[(phenylmethoxy)methoxy]-4-pentenamide (34). To a solution of the unpurified amide **33**/oxazolidinone mixture from above (theoretical yield, 25.0 mmol) in 30 mL of THF were added 7.7 mL (5.7 g, 44 mmol) of *i*-Pr_2EtN, 5.2 mL (5.9 g, 37.5 mmol) of benzyl chloromethyl ether, and 0.92 g (2.5 mmol) of $Bu_4N^+I^-$. After 38 h at room temperature, 1 mL of methanol was added to consume the excess alkylating agent. After an additional hour, the reaction mixture was partitioned between 300 mL of water and 300 mL of 75% EtOAc/hexane. The organic layer was washed with 0.5 N aqueous $NaHSO_4$, pH 7 phosphate buffer, and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by chromatography (400 g of silica gel, 35% to 40% EtOAc/hexane), gave 8.71 g (94% for two steps) of the amide **34** as a nearly colorless syrup: $[\alpha]_D$ −139.1° (*c* 2.50, $CHCl_3$); IR (thin film) 3070, 2990, 2930, 1665, 1460, 1390, 1030, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 50 °C) δ 7.18–7.38 (m, 10 H, Ar H), 6.57 (d, 1 H, *J* = 16.0 Hz, PhC*H*=), 6.18 (dd, 1 H, *J* = 16.0 and 8.0 Hz, CHC*H*=), 4.75 and 4.84 (AB quartet, 2 H, *J* = 6.8 Hz, OCH_2O), 4.56 and 4.71 (AB quartet, 2 H, *J* = 11.9 Hz, PhCH_2O), 4.40 (t, 1 H, *J* = 8.0 Hz, C*H*CH=), 3.66 (s, 3 H, OCH_3), 3.25 (quintet, 1 H, *J* = 7.3 Hz, C*H*CH$_3$), 3.09 (s, 3 H, NCH_3), 1.29 (d, 3 H, *J* = 6.8 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 175.1, 138.1, 136.8, 133.7, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.0, 126.7, 92.4, 79.3, 69.8, 61.4, 41.0, 32.4, 14.2; TLC R_f 0.28 (35% EtOAc/hexane). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37. Found: C, 71.39; H, 7.29.

(2*S*,3*S*)-2,3-Dimethyloxiranemethanol (35). To a solution of 2.57 g (29.8 mmol) of (*E*)-2-methyl-2-buten-1-ol in 100 mL of CH_2Cl_2 at −20 °C were added 1.43 mL (1.72 g, 8.35 mmol) of (+)-diethyl tartrate and 1.77 mL (1.69 g, 6.00 mmol) of Ti(O-*i*-Pr)$_4$. After 15 min, the solution was cooled to −30 °C, and 8.2 mL of 4.0 M TBHP in benzene was added in one portion. The solution was stirred at −40 to −30 °C for 30 min and then placed in a −20 °C freezer. After 10 h at −20 °C, Me_2S (3.6 mL) was added, and the reaction mixture was kept at −20 °C an additional 5 h. Then, 9 mL of 1.0 M triethanolamine in CH_2Cl_2 was added, and the solution was stirred 30 min at 0 °C. The solution was filtered through 75 g of silica gel in a sintered-glass funnel and eluted with 500 mL of ether. Concentration of the filtrate and Kugelrohr distillation (oven temperature 120 °C, 5 mmHg) of the residue gave 2.33 g (77%) of the epoxy alcohol **35** as a colorless oil: $[\alpha]_D$ −22.2° (*c* 3.0, CH_2Cl_2); IR (thin film) 3420 (br), 3000, 2970, 2930, 2880, 1460, 1380, 1030, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 and 3.55 (AB quartet, 2 H, *J* = 12.3 Hz, CH_2OH), 3.16 (q, 1 H, *J* = 6.6 Hz, C*H*CH$_3$), 2.64 (br s, 1 H, OH), 1.32 (d, 3 H, *J* = 6.6 Hz, CHCH_3), 1.29 (s, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$) δ 65.5, 60.9, 55.9, 13.8, 13.4; TLC R_f 0.31 (diethyl ether).

(2*R*,3*S*)-2,3-Dimethyl-5-hexene-1,2-diol (36). A solution of 2.04 g (20.0 mmol) of the epoxide **35** in 25 mL of THF was stirred and cooled in a dry ice/acetone bath as 25 mL (50 mmol) of 2.0 M allylmagnesium chloride in THF was added at a rate to maintain the reaction temperature at −20 °C. When the addition was complete, the cooling bath was removed, and the reaction was allowed to warm to room temperature. After 90 min, the solution was recooled to 0 °C, added to 125 mL of 1:1 brine/1 N $NaHSO_4$, and extracted with 100 mL of EtOAc. The organic layer was washed with 50 mL of brine, and the combined aqueous layers were extracted with 2 × 50 mL 10% *i*-PrOH/CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give 2.81 g (98%) of the diol **36** of sufficient purity for the next reaction. An analytical sample was prepared from a smaller scale reaction by chromatography and Kugelrohr distillation (oven temperature 100 °C, 0.2 mmHg): $[\alpha]_D$ +14.7° (*c* 3.0, $CHCl_3$); IR (thin film) 3400 (br), 3080, 2980, 2940, 2880, 1645, 1460, 1380, 1040, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.71–5.86 (m, 1 H, C*H*=CH$_2$), 4.98–5.09 (m, 2 H, CH=CH_2), 3.59 (dd, 1 H, *J* = 10.9 and 5.1 Hz, one of CH_2OH), 3.46 (dd, 1 H, *J* = 10.9 and 6.2 Hz, one of CH_2OH), 2.22–2.34 (m, 1 H, one of =CHCH_2), 1.99 (m, 1 H, *J* = 5.8 Hz, CH$_2$O*H*), 1.94 (s, 1 H, CO*H*), 1.68–1.83 (m, 2 H), 1.12 (s, 3 H, CCH_3), 0.95 (d, 3 H, *J* = 6.5 Hz,

$CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 115.8, 75.0, 68.0, 39.6, 36.3, 20.2, 13.4; TLC R_f 0.22 (60% EtOAc/hexane).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.53; H, 11.09.

[4*R*,4(1*S*)]-4-(3-Bromo-1-methylpropyl)-2,2,4-trimethyl-1,3-dioxolane (39). To a solution of 2.260 g (12.00 mmol) of the alcohol **38** and 0.33 mL (0.32 g, 3.0 mmol) of 2,6-lutidine in 30 mL of ether were added 3.93 g (15.0 mmol) of Ph_3P and 4.81 g (14.5 mmol) of CBr_4. Within a few seconds, a precipitate began to form. The mixture was stirred 11 h at room temperature, diluted with 50 mL of pentane, and filtered. The filter cake was washed with 50 mL of 1:1 pentane/ether. The filtrate was concentrated, and the residue was purified by chromatography (150 g of silica gel, 10% EtOAc/hexane) to give 2.950 g (98%) of the bromide **39** as a colorless oil: $[\alpha]_D$ −43.5° (*c* 3.0, CH_2Cl_2); IR (thin film) 2990, 2940, 2880, 1455, 1380, 1370, 1255, 1210, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.70 and 3.85 (AB quartet, 2 H, *J* = 8.5 Hz, CH_2O), 3.53 (ddd, 1 H, *J* = 9.5, 7.7, and 4.5 Hz, one of CH_2Br), 3.35 (ddd, 1 H, *J* = 9.5, 8.5, and 7.0 Hz, one of CH_2Br), 1.78–1.97 (m, 2 H), 1.55–1.68 (m, 1 H), 1.37 and 1.41 (2 s, 6 H, $C(CH_3)_2$), 1.21 (s, 3 H, CCH_3), 0.98 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 109.2, 83.4, 73.1, 40.2, 36.0, 31.9, 27.3, 26.8, 21.8, 13.8; TLC R_f 0.30 (10% EtOAc/hexane). Anal. Calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C, 49.83; H, 7.62.

(2*S*,4*S*)-*N*-Methoxy-*N*,2-dimethyl-4-oxo-3-[(phenylmethoxy)methoxy]butanamide (41). A solution of 1.109 g (3.00 mmol) of the amide **34** in 15 mL of methanol containing 3 drops of pyridine and a little Sudan III indicator dye was stirred and cooled at −78 °C as O_3 was bubbled through until the indicator decolorized. Immediately, 3 mL of Me_2S was added, and the solution was allowed to warm to room temperature. After 4 h, 10 mL of toluene was added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography (50 g of silica gel, 65% EtOAc/hexane, high flow rate) to give 845 mg (95%) of the aldehyde **41** with a purity of >90% by ^1H NMR analysis: IR (thin film) 2950, 2900, 1785 (w), 1730, 1660, 1460, 1390, 1180, 1115, 1045, 1000, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.82 (d, 2 H, *J* = 1.0 Hz, *H*C=O), 7.27–7.39 (m, 5 H, Ar H), 4.87 and 4.89 (AB quartet, 2 H, *J* = 7.1 Hz, OCH_2O), 4.63 and 4.69 (AB quartet, 2 H, *J* = 11.9 Hz, $PhCH_2O$), 4.10 (dd, 1 H, *J* = 6.0 and 1.0 Hz, O=CHC*H*), 3.71 (s, 3 H, OCH_3), 3.32–3.43 (br m, 1 H, C*H*CH_3), 3.19 (s, 3 H, NCH_3), 1.28 (d, 3 H, *J* = 7.1 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.4, 174.1 (br and w), 137.3, 128.4, 127.8, 127.7, 95.0, 82.6, 70.1, 61.4, 39.6, 32.2 (br), 13.5; TLC R_f 0.25 (60% EtOAc/hexane).

(2*S*,3*R*,4*Z*,8*S*)-*N*-Methoxy-9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-*N*,2,8-trimethyl-3-[(phenylmethoxy)methoxy]-4-nonenamide (42). To a suspension of 1.451 g (2.40 mmol) of the phosphonium salt **30** in 20 mL of toluene at 25 °C was added 3.00 mL (3.00 mmol) of 1.0 M $NaN(SiMe_3)_2$ in THF dropwise. The bright orange mixture was stirred at 25 °C for 15 min and then cooled to −78 °C. A solution of 828 mg (2.80 mmol) of the aldehyde **41** in 5 mL of toluene was cooled to ca. −70 °C and then added rapidly via cannula to the ylide **40**. The resulting peach-colored mixture was stirred 45 min at −78 to −20 °C, 30 min at 0 °C, and 15 min at 0 °C to room temperature. The reaction was quenched with 10 mL of 1 N pH 7 phosphate buffer and partitioned between 100 mL of 25% CH_2Cl_2/pentane and 100 mL of water. The organic layer was washed with 50 mL of water and brine, and the aqueous layers were extracted with 50 mL of 25% CH_2Cl_2/pentane. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography (150 g of silica gel, 17% EtOAc/hexane) gave 859 mg (72%) of enriched *Z* isomer **42** (*Z*:*E* = 98:2 by HPLC analysis), followed by 196 mg (17%) of a 68:32 mixture of *Z* and *E* olefin isomers. Total yield was 1.055 g (89%), and the *Z*/*E* stereoselectivity of the reaction was calculated to be 92:8. The mixed fractions were combined with mixed fractions from previous reactions to give 440 mg of a 52:48 *Z*/*E* mixture, which was chromatographed (90 g silica gel, 15% EtOAc/hexane) to yield an additional 190 mg (83% recovery) of **42**: $[\alpha]_D$ −84.8° (*c* 1.5, $CHCl_3$); IR (thin film) 2960, 2940, 2890, 2860, 1670, 1465, 1385, 1255, 1100, 1040, 1030, 880, 775 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz, 50 °C) δ 7.07–7.35 (m, 5 H, Ar H), 5.63 (dt, 1 H, *J* = 11.0 and 6.9 Hz, C_7-H), 5.44 (ddt, 1 H, *J* = 11.0, 9.4, and 1.5 Hz, C_8-H), 4.90 (t, 1 H, *J* = 9.0 Hz, C_9-H), 4.86 (d, 1 H, *J* = 6.7 Hz, one of OCH_2O), 4.72 (d, 1 H, *J* = 12.1 Hz, one of OCH_2Ph), 4.67 (d, 1 H, *J* = 6.7 Hz, one of OCH_2O), 4.48 (d, 1 H, *J* = 12.1 Hz, one of OCH_2O), 3.41 (apparent qd [ABX], 2 H, J_{AB} = 9.7 Hz, J_{AX} = 5.5 Hz, J_{BX} = 6.0 Hz, C_3-H_2), 3.18–3.29 (m, 1 H, C*H*C=O), 3.20 (s, 3 H, OCH_3), 2.90 (s, 3 H, NCH_3), 2.17–2.42 (m, 2 H, C_6-H_2), 1.50–1.70 (m, 2 H), 1.43 (d, 3 H, *J* = 6.8 Hz, O=CCHC*H*$_3$), 1.12–1.28 (m, 1 H), 0.97 (s, 9 H, $C(CH_3)_3$), 0.93 (d, 3 H, *J* = 6.6 Hz, CH_2CHCH_3), 0.05 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (C_6D_6, 75 MHz, 50 °C) δ 175.3, 139.0, 135.8, 128.5, 128.4, 127.6, 92.0, 73.4, 69.7, 68.5, 61.0, 41.2, 36.0, 33.6, 32.3, 26.2, 25.8, 18.5, 16.9, 14.4, −5.2; TLC R_f 0.25 (20% EtOAc/hexane). Anal. Calcd for $C_{27}H_{47}NO_5Si$: C, 65.68; H, 9.59. Found: C, 65.89; H, 9.57.

(2*S*,3*R*,4*Z*,8*S*)-2,8-Dimethyl-9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-[(phenylmethoxy)methoxy]-4-nonenal (43). A solution of 1.481 g (3.00 mmol) of the amide **42** in 24 mL of THF was stirred and cooled at −78 °C as 6.0 mL (6.0 mmol) of 1.0 M DIBAL in toluene was added slowly. The solution was stirred an additional 30 min at −78 °C and 30 min at −78 to −50 °C. The excess hydride was consumed by addition of 0.25 mL of acetone, and after 5 min the solution was added via cannula to a vigorously stirred mixture of 60 mL of 0.5 M tartaric acid and 60 mL of hexane. After 30 min, the layers were separated, and the organic layer was washed with 25 mL each of water and brine. The aqueous layers were extracted with 50 mL of 25% CH_2Cl_2/pentane, and the combined organic layers were dried (Na_2SO_4) and concentrated. Chromatography (80 g of silica gel, CH_2Cl_2, high flow rate) yielded 1.263 g (97%) of the aldehyde **43** as a clear oil: IR (thin film) 2960, 2940, 1730, 1260, 1100, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.77 (d, 1 H, *J* = 1.2 Hz, O=C*H*), 7.24–7.37 (m, 5 H, Ar H), 5.72 (dt, 1 H, *J* = 10.9 and 7.5 Hz, C_7-H), 5.30 (ddt, 1 H, *J* = 10.9, 9.7, and 1.6 Hz, C_8-H), 4.84 (dd, 1 H, *J* = 9.7 and 4.9 Hz, C_9-H), 4.76 (d, 1 H, *J* = 6.9 Hz, one of OCH_2O), 4.64–4.69 (m, 2 H, one of OCH_2O and one of $PhCH_2O$), 4.51 (d, 1 H, *J* = 11.9 Hz, one of $PhCH_2O$), 3.39 (d, 2 H, *J* = 5.9 Hz, C_3-H_2), 2.49–2.59 (m, 1 H, C_{10}-H), 2.00–2.26 (m, 2 H, C_6-H_2), 1.42–1.64 (m, 2 H), 1.13 (d overlapping m, 3 H, *J* = 7.0 Hz, $CHCH_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.86 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 0.02 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.5, 138.0, 136.4, 128.4, 127.8, 127.6, 126.0, 91.6, 70.9, 69.7, 68.0, 51.1, 35.5, 33.2, 25.9, 25.4, 18.3, 16.6, 8.9, −5.4; TLC R_f 0.33 (CH_2Cl_2).

[2*S*,2(4*R*),5*R*,6*R*,7*R*,8*Z*,12*S*]-6,12-Dimethyl-13-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-7-[(phenylmethoxy)methoxy]-8-tridecen-5-ol (44). To a solution of 7.45 mL (12.0 mmol) of 1.6 M *t*-BuLi in pentane in 20 mL of ether at −78 °C was added dropwise a solution of 1.51 g (6.00 mmol) of the bromide **39** in 5 mL of ether. The solution was stirred for 15 min at −78 °C and for 15 min at −78 to −50 °C. After the mixture was recooled to −78 °C, 261 mg (2.9 mmol) of CuCN was added in one portion under a flow of argon, and the resulting mixture was warmed to 0 °C for exactly 10 min to form a pale yellow solution to the cuprate. The solution was cooled to −78 °C (small amount of precipitate forms), and a solution of 834 mg (1.92 mmol) of freshly prepared aldehyde **43** in 5 mL of ether was added via cannula, giving a deep orange solution. After 15 min at −78 °C and 15 min at −78 to −20 °C, 10 mL of 0.5 N NH_4Cl in 3 N aqueous NH_3 was added. The mixture was added to 100 mL of ether and 50 mL of 0.5 N NH_4Cl in 3 N aqueous NH_3, and air was bubbled through the vigorously stirred mixture for 20 min. The layers were separated, and the organic layer was washed with water and brine. The aqueous layers were extracted once with 25% CH_2Cl_2/pentane, and the combined organic layers were dried over Na_2SO_4 and concentrated. Chromatography of the residue (125 g of silica gel, 15–25% EtOAc/hexane) gave 997 mg (86%) of the alcohol **44** as a colorless syrup: $[\alpha]_D$ −56.5° (*c* 3.0, CH_2Cl_2); IR (thin film) 3500 (br), 2960, 2940, 2890, 2865, 1465, 1380, 1260, 1210, 1100, 1030, 840, 780 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.06–7.32 (m, 5 H, Ar H), 5.58 (dt, 1 H, *J* = 11.0 Hz, one of OCH_2O), 4.62 (d, 1 H, *J* = 12.0 Hz, one of $PhCH_2O$), 4.51 (d, 1 H, *J* = 6.7 Hz, one of OCH_2O), 4.35 (d, 1 H, *J* = 12.0 Hz, one of $PhCH_2O$), 3.80 (d, 1 H, *J* = 8.3 Hz, one of CCH_2O), 3.63 (d overlapping br m, 2 H, one of CCH_2O and $C1_1$-H), 3.36 (br d, 2 H, *J* = 5.3 Hz, C_3-H_2), 3.18 (d, 1 H, *J* = 4.4 Hz, OH), 2.05–2.27 (m, 2 H, C_6-H_2), 1.26–1.80 (m, 9 H), 1.43 and 1.37 (2 s, 6 H, $C(CH_3)_2$), 1.14 (s, 3 H, CCH_3), 1.07 (d, 3 H, *J* = 6.7 Hz, $CHCH_3$), 1.00 (d, 3 H, *J* = 7.0 Hz, $CHCH_3$), 0.97 (s, 9 H, $C(CH_3)_3$), 0.88, (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 0.05 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (C_6D_6, 75 MHz) δ 138.5, 135.0, 128.6, 127.9, 127.8, 109.0, 92.1, 84.4, 74.2, 73.3, 70.0, 68.2, 44.0, 43.0, 35.8, 34.1, 33.6, 29.6, 28.0, 27.3, 26.2, 25.7, 21.0, 18.5, 16.9, 14.8, 12.1, −5.2; TLC R_f 0.24 (20% EtOAc/hexane). Anal. Calcd for $C_{35}H_{62}O_6Si$: C, 69.26; H, 10.30. Found: C, 69.08; H, 10.07.

[2*S*,5*Z*,7*R*,8*R*,9*R*,12*S*,12(4*R*)]-2,8-Dimethyl-12-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-9-(phenylmethoxy)-7-[(phenylmethoxy)methoxy]-5-tridecenal (47). To a solution of 0.217 mL (318 mg, 2.50 mmol) of oxalyl chloride in 15 mL of CH_2Cl_2 at −78 °C was added 0.35 mL (0.39 g, 5.0 mmol) of dimethyl sulfoxide dropwise. After 10 min, a solution of 1.166 g (2.00 mmol) of the alcohol **46** in 4 mL (plus a 1-mL rinse) of CH_2Cl_2 was added via cannula slowly such that the reaction temperature remained below −65 °C. After 15 min at −78 °C, 1.39 mL (1.01 g, 10.0 mmol) of Et_3N was added in one portion. The reaction was allowed to slowly warm from −78 to −40 °C over a period of 1 h, and the resulting mixture was partitioned between 100 mL of hexane and 50 mL of 0.5 N aqueous $NaHSO_4$. The organic layer was washed with additional aqueous $NaHSO_4$, water, and brine, dried over Na_2SO_4, and concen-

trated. Chromatography (50 g of silica gel, 20% EtOAc/hexane, high flow rate) of the residue gave 1.135 g (98%) of the aldehyde **47** as a thick oil: IR (thin film) 2980, 2940, 2880, 2710 (w), 1725, 1455, 1380, 1210, 1100, 1040, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.53 (d, 1H, J = 1.5 Hz, O=C*H*), 7.22–7.34 (m, 10 H, Ar H), 5.59 (dt, 1 H, J = 11.0 and 7.3 Hz, C_7-H), 5.37 (br dd, 1 H, J = 11.0 and 9.5 Hz, C_8-H), 4.74 (d, 1 H, J = 6.9 Hz, one of OCH_2O), 4.48–4.55 (m, 3 H, C_9-H and one each of different $PhCH_2O$), 4.42 (d, 1 H, J = 11.4 Hz, one of $PhCH_2O$), 3.67 and 3.78 (AB quartet, 2 H, CCH_2O), 3.37–3.44 (m, 1 H, C_{11}-H), 1.25–2.30 (m, 10 H), 1.33 and 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.12 (s, 3 H, CCH_3), 1.00 (d, 6 H, J = 7.0 Hz, 2 $CHCH_3$), 0.94 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 0.77–0.92 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.2, 139.0, 138.1, 132.7, 130.0, 128.34, 128.26, 127.74, 127.71, 127.6, 127.4, 108.9, 92.0, 84.2, 80.3, 73.7, 72.1, 71.2, 69.6, 45.8, 42.2, 41.4, 30.4, 28.9, 28.4, 27.5, 27.0, 25.3, 20.8, 14.4, 13.3, 10.2; TLC R_f 0.28 (15% EtOAc/hexane).

[(3(2*R*,3*S*,4*S*,7*Z*,8*R*,9*R*,10*R*,14*S*,14(4*R*)),4*R*,5*R*]-3-[3-Hydroxy-2,4,10-trimethyl-14-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-oxo-11-(phenylmethoxy)-9-[(phenylmethoxy)methoxy]-7-pentadecenyl]-4-methyl-5-phenyl-2-oxazolidinone (48). To a solution of 816 mg (3.50 mmol) of the imide **25** and 0.56 mL (0.40 g, 4.0 mmol) of Et_3N in 15 mL of CH_2Cl_2 at −78 °C was added 0.80 mL (0.88 g, 3.2 mmol) of di-*n*-butylboron triflate. The solution was stirred for 0.5 h at −78 to −50 °C and then for 1 h at 0 °C. After the mixture was recooled to −78 °C, a solution of 1.135 g (1.96 mmol) of freshly prepared aldehyde **47** in 3 mL (plus a 1-mL rinse) of CH_2Cl_2 was added. The reaction was allowed to slowly warm from −78 to 0 °C over a 2-h period and then was added to a solution of 3 g of NaOAc in 50 mL of methanol at 0 °C, to which 4 mL of 30% aqueous H_2O_2 was added. After being stirred 0.5 h at 0 °C to room temperature, the mixture was partitioned between 150 mL of water and 100 mL of hexane. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Chromatography of the residue (150 g of silica gel, 30% EtOAc/hexane) afforded 1.540 g (97%) of the aldol adduct **48** as a thick resin after thorough removal of residual solvent at 70 °C and 0.2 mmHg: $[\alpha]_D$ −46.5° (*c* 2.0, CH_2Cl_2); IR (thin film) 3500 (br), 2980, 2940, 2880, 1785, 1700, 1455, 1370, 1200, 1060, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.46 (m, 15 H, Ar H), 5.62–5.72 (m, 2 H, C_7-H and PhC*H*CH), 5.30 (t, 1 H, J = 10.4 Hz, C_8-H), 4.68–4.79 (m, 3 H, one of OCH_2O, one of $PhCH_2O$, and NC*H*), 4.64 (d, 1 H, J = 6.9 Hz, one of OCH_2O), 4.49–4.56 (m, 3 H, one each of two different $PhCH_2O$ and C_8-H), 4.40 (d, 1 H, J = 11.5 Hz, one of $PhCH_2O$), 3.92 (qd, 1 H, J = 7.0 and 2.2 Hz, C_2-H), 3.66 and 3.79 (AB quartet, 2 H, J = 8.3 Hz, CCH_2O), 3.60 (ddd, 1 H, J = 9.1, 3.4, and 2.2 Hz, C_3-H), 3.38–3.43 (m, 1 H, C_{11}-H), 3.10 (d, 1 H, J = 3.4 Hz, OH), 2.24–2.40 (m, 1 H, one of C_6H), 1.89–2.01 (m, 2 H), 1.2–1.6 (m, 6 H), 1.33 and 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.17 (d, 3 H, J = 7.0 Hz, $CHCH_3$), 1.12 (s, 3 H, CCH_3), 0.84, 0.88, 0.94, and 1.01 (4 d, 12 H, J = 7 Hz, 4 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.6, 152.4, 139.0, 138.1, 134.5, 133.2, 128.8, 128.7, 128.5, 128.3, 128.2, 127.7, 127.5, 127.4, 125.6, 108.9, 91.6, 84.2, 80.2, 78.9, 75.1, 73.7, 72.2, 71.1, 69.4, 54.8, 42.2, 41.0, 39.6, 35.6, 32.9, 28.7, 28.6, 27.5, 26.9, 25.1, 20.6, 15.4, 14.3 (2), 10.2, 9.5; TLC R_f 0.21 (30% EtOAc/hexane). Anal. Calcd for $C_{49}H_{67}NO_9$: C, 72.30; H, 8.30. Found: C, 72.33; H, 8.24.

[2*R*,2(2*S*,3*S*,6*R*,6(1*S*,2*R*,3*R*,4*R*,7*S*,7(4*R*))),4*R*,5*R*]-3-[2-[6-[1-(Chloromercurio)-3-methyl-7-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-4-(phenylmethoxy)-2-[(phenylmethoxy)methoxy]octyl]-3-methyltetrahydro-2-pyranyl]-1-oxopropyl]-4-methyl-5-phenyl-2-oxazolidinone (49). A mixture of 1.540 g (1.89 mmol) of the aldol adduct **48** and 0.96 g (3.0 mmol) of $Hg(OAc)_2$ in 15 mL of CH_2Cl_2 was stirred at room temperature for 20 h, and then 10 mL of brine was added. After 15 min, the mixture was partitioned between 75 mL of hexane and 50 mL of brine. The organic layer was washed with an additional 50 mL of brine and dried over Na_2SO_4. Concentration afforded 1.973 g (99%) of the chloromercurial **49** as a solid foam of high purity by TLC and ^1H NMR analysis: IR (thin film, moistened with $CHCl_3$) 2980, 2940, 2880, 1780, 1710, 1460, 1370, 1350, 1240, 1200, 1060, 790, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.19–7.40 (m, 15 H, Ar H), 5.50 (d, 1 H, J = 6.9 Hz, PhC*H*CH), 5.00 (quintet, 1 H, J = 6.9 Hz, NC*H*), 4.75 (s, 2 H, OCH_2O), 4.60 and 4.63 (AB quartet, 2 H, J = 12.0 Hz, $PhCH_2O$), 4.43 and 4.49 (AB quartet, 2 H, J = 11.5 Hz, $PhCH_2O$), 4.06 (dd, 1 H, J = 4.3 and 3.0 Hz, C_9-H), 3.99 (qd, 1 H, J = 7.0 and 3.0 Hz, C_2-H), 3.67 and 3.78 (AB quartet, 2 H, J = 8.4 Hz, CCH_2O), 3.56 (br t, 1 H, $J \cong$ 8.5 Hz, C_7-H), 3.49 (dd, 1 H, J = 9.8 and 3.0 Hz, C_3-H), 3.32–3.36 (m, 1 H, C_{11}-H), 2.59 (dd, 1 H, J = 8.3 and 2.8 Hz, C_8-H), 1.66–1.80 (m, 4 H), 1.45–1.58 (m, 2 H), 1.35–1.42 (m, 1 H), 1.34 and 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.16 (d, 3 *H*, J = 7.0 Hz, $CHCH_3$), 1.14 (s, 3 H, CCH_3), 1.03–1.09 (m, 2 H), 0.85, 0.87, 0.94, and 0.98 (4 d, 12 H, J = 7 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 153.0, 138.5, 137.5, 133.5, 128.55, 128.47, 127.9, 127.8, 127.6, 125.6, 109.0, 95.5, 84.1, 82.9, 81.1, 80.0, 79.2, 78.9, 73.5, 71.3, 70.3, 67.9, 55.4, 42.9, 40.6, 33.2, 32.2, 28.9, 27.9, 27.5, 27.0, 21.1, 16.2, 14.4, 14.1, 11.6, 9.5; TLC R_f 0.23 (20% EtOAc/hexane).

[3(2*R*,2(2*S*,3*S*,6*R*,6(2*R*,3*R*,4*R*,7*S*,7(4*R*)))),4*R*,5*R*]-3-[2-[6-[3-Methyl-7-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-4-(phenylmethoxy)-2-[(phenylmethoxy)methoxy]octyl]-3-methyl-2-tetrahydropyranyl]-1-oxopropyl]-4-methyl-5-phenyl-2-oxazolidinone (50). To a solution of 1.973 g (1.88 mmol) of the chloromercurial **49** and 25 mg of AIBN in 4 mL of toluene was added 1.25 mL (1.37 g, 4.7 mmol) of *n*-Bu_3SnH in one portion. Mercury began to precipitate within a few seconds, and the mixture was stirred at room temperature for 1 h and then at 55 °C for 1 h. The oil bath was removed, and 1 mL of CCl_4 was added to consume the excess hydride reagent. After 1 h, the reaction solution was decanted from the precipitated mercury, diluted with 150 mL of 25% CH_2Cl_2/pentane, and washed well with 2 × 50 mL of 5% aqueous KF. The organic layer was dried over Na_2SO_4 and then filtered through 50 g of silica gel, with 30% EtOAc/hexane as eluant, in order to remove the tin byproducts. Concentration of the filtrate and chromatography of the residue (150 g of silica gel, 15% EtOAc/hexane) gave 1.443 g (94%) of the imide **50** as a hard glass after drying at 80 °C (0.1 mmHg) in a Kugelrohr apparatus for 1 h: $[\alpha]_D$ +20.3° (*c* 1.5, $CHCl_3$); IR (thin film) 2980, 2940, 2880, 1785, 1715, 1455, 1350, 1240, 1200, 1045, 1030, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14–7.40 (m, 15 H, Ar H), 5.51 (d, 1 H, J = 6.9 Hz, PhC*H*O), 4.75 and 4.77 (AB quartet, 2 H, J = 6.7 Hz, OCH_2O), 4.57–4.67 (m, 3 H, $PhCH_2O$ and NC*H*), 4.46 and 4.52 (AB quartet, 2 H, J = 11.5 Hz, $PhCH_2O$), 3.92–4.06 (m, 2 H, C_9-H and C_2-H), 3.65 and 3.75 (AB quartet, 2 H, J = 8.4 Hz, CCH_2O), 3.28–3.49 (m, 3 H, C_3-H, C_7-H, and C_{11}-H), 1.1–2.0 (m, 12 H), 1.32 and 1.39 (2 s, 6 H, $C(CH_3)_2$), 1.15 (d, 3 H, J = 6.9 Hz, $CHCH_3$), 1.08 (s, 3 H, CCH_3), 0.81–1.02 (m, 10 H, 3 $CHCH_3$ and C*H*), 0.76 (d, 3 H, J = 6.5 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.4, 153.0, 139.0, 138.1, 133.5, 128.52, 128.47, 128.3, 127.8, 127.6, 127.5, 127.4, 125.6, 108.9, 95.0, 84.2, 82.9, 80.8, 78.9, 76.0, 75.4, 73.6, 71.5, 69.9, 55.4, 42.2, 40.9, 40.3, 40.0, 32.8, 32.7, 32.1, 29.3, 27.8, 27.5, 27.0, 20.7, 17.0, 14.3, 14.1, 9.8, 9.6; TLC R_f 0.33 (20% EtOAc/hexane). Anal. Calcd for $C_{49}H_{67}NO_9$: C, 72.30; H, 8.30. Found: C, 72.19; H, 8.40.

[α*R*,2*S*,3*S*,6*R*,6(2*R*,3*R*,4*R*,7*S*,7(4*R*))]-6-[3-Methyl-7-(2,2,4-trimethyl-1,3-dioxolan-2-yl)-4-(phenylmethoxy)-2-[(phenylmethoxy)methoxy]octyl]-α,3-dimethyltetrahydro-2-pyranylacetic Acid, Benzyl Ester (51). To a solution of 0.263 mL (275 mg, 2.5 mmol) of BnOH in 4 mL of THF at −20 °C was added 1.0 mL (1.9 mmol) of 1.9 M *n*-BuLi in hexane. After 5 min, this solution was added via cannula to a solution of 862 mg (1.059 mmol) of the imide **50** in 8 mL of THF at −78 °C. The reaction was stirred 3 h at −30 to 0 °C and 6 h at 0 °C and then quenched with saturated aqueous NH_4Cl. The mixture was partitioned between 25% CH_2Cl_2/pentane and water. The organic layer was dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (75 g of silica gel, 15% EtOAc/hexane) afforded 611 mg (77%) of the benzyl ester **51** as a colorless syrup: $[\alpha]_D$ +7.9° (*c* 1.5, $CHCl_3$); IR (thin film) 2940, 2880, 1745, 1455, 1380, 1210, 1050, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.38 (m, 15 H, Ar H), 5.01 and 5.17 (AB quartet, 2 H, J = 12.6 Hz, CO_2CH_2Ph), 4.69 and 4.71 (AB quartet, 2 H, J = 6.8 Hz, OCH_2O), 4.55 and 4.59 (AB quartet, 2 H, J = 12.0 Hz, $PhCH_2O$), 4.44 and 4.45 (narrow AB quartet, 2 H, J = 11.6 Hz, $PhCH_2O$), 3.97 (td, 1 H, J = 6.3 and 2.9 Hz, C_9-H), 3.67 and 3.76 (AB quartet, 2 H, J = 8.4 Hz, CCH_2O), 3.47 (dd, 1 H, J = 9.9 and 3.4 Hz, C_3-H, 3.30–3.44 (m, 2 H, C_7-H and C_{11}-H), 2.69 (qd, 1 H, J = 7.1 and 3.4 Hz, C_2-H), 1.1–1.9 (m, 13 H), 1.33 and 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.14 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.12 (s, 3 H, CCH_3), 0.76, 0.88, and 0.93 (3d, 9 H, J = 7 Hz, 3 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 139.2, 138.2, 136.6, 128.4, 128.3, 128.2, 127.81, 127.76, 127.7, 127.6, 127.4, 127.3, 108.9, 95.0, 84.3, 83.4, 80.9, 76.1, 75.3, 73.7, 71.1, 69.8, 65.9, 42.3, 41.8, 40.3, 40.0, 32.8, 32.3, 31.8, 29.0, 27.8, 27.5, 27.0, 20.7, 17.1, 14.3, 9.7, 9.4; TLC R_f 0.22 (15% EtOAc/hexane). Anal. Calcd for $C_{46}H_{64}O_8$: C, 74.16; H, 8.66. Found: C, 74.25; H, 8.70.

[α*R*,2*S*,3*S*,6*R*,6(2*R*,3*R*,4*R*,7*S*,7(4*R*))]-6-[8,9-Dihydroxy-3,7,8-trimethyl-4-(phenylmethoxy)-2-[(phenylmethoxy)methoxy]nonyl]-α,3-dimethyltetrahydro-2-pyranylacetic Acid, Benzyl Ester (52). A solution of 670 mg (0.90 mmol) of the benzyl ester **51** in 12 mL of 8:3:1 THF/1 M aqueous H_2SO_4/ethanol was heated at 50 °C for 5 h. The reaction mixture was cooled to room temperature and partitioned between 50 mL of 0.2 N aqueous $NaHCO_3$ and 75 mL of CH_2Cl_2. The aqueous layer was extracted twice with 20-mL portions of CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by chromatography (60 g of silica gel, 55% EtOAc/hexane) afforded 570 mg (90%) of the diol **52** as a viscous syrup: $[\alpha]_D$ +12.1° (*c* 1.5, $CHCl_3$); IR (thin film) 3450 (br), 2970, 1740, 1455, 1380, 1045, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.38 (m, 15 H, Ar H), 4.99 and 5.19 (AB quartet, 2 H, J = 12.6 Hz, CO_2CH_2Ph), 4.68 and 4.71 (AB quartet, 2 H, J = 6.8 Hz, OCH_2O), 4.54 and 4.60 (AB quartet, 2 H, J = 11.9 Hz, $PhCH_2O$), 4.44 (s, 2 H, $PhCH_2O$), 4.00

(td, 1 H, J = 6.4 and 2.9 Hz, C_9-H), 3.54 (dd, 1 H, J = 10.9 and 4.8 Hz, one of CH_2OH), 3.30–3.49 (m, 4 H, one of CH_2OH, C_3-H, C_7-H, and C_{11}-H), 2.68 (qd, 1 H, J = 7.0 and 3.5 Hz, C_2-H), 2.18 (t, 1 H, J = 5.8 Hz, CH_2OH), 2.13 (s, 1 H, COH), 1.1–1.9 (m, 13 H), 1.13 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.04 (s, 3 H, CCH_3), 0.76, 0.87, and 0.91 (3 d, 9 H, J = 7 Hz, 3 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 139.2, 138.2, 136.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 94.9, 83.4, 80.7, 75.9, 75.3, 75.1, 71.0, 69.7, 68.2, 66.0, 41.8, 40.5, 40.0, 39.8, 32.8, 32.2, 31.7, 28.8, 26.3, 20.1, 17.1, 13.8, 9.7, 9.4; TLC R_f 0.20 (50% EtOAc/hexane). Anal. Calcd for $C_{43}H_{60}O_8$: C, 73.26; H, 8.58. Found: C, 73.33; H, 8.77.

[αR,2S,3S,6R,6(2R,3R,4R,7S,7(4R))]-6-[3,7-Dimethyl-8-oxo-4-(phenylmethoxy)-2-[(phenylmethoxy)methoxy]nonyl]-α,3-dimethyltetrahydro-2-pyranylacetic Acid, Benzyl Ester (53). To a solution of 570 mg (0.808 mmol) of the diol **52** in 15 mL of acetone was added a solution of 340 mg (1.6 mmol) of $NaIO_4$ in 5 mL of water. The mixture was stirred for 5 h at room temperature and then partitioned between 100 mL of water and 100 mL of hexane. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by chromatography (50 g of silica gel, 20% EtOAc/hexane) afforded 517 mg (95%) of the ketone **53** as a colorless oil: $[\alpha]_D$ +23.5° (c 2.0, $CHCl_3$); IR (thin film) 2940, 1745, 1715, 1500, 1455, 1380, 1175, 1040, 1030, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.37 (m, 15 H, Ar H), 5.01 and 5.16 (AB quartet, 2 H, J = 12.6 Hz, CO_2CH_2Ph), 4.68 and 4.70 (AB quartet, 2 H, OCH_2O), 4.54 and 4.59 (AB quartet, 2 H, J = 11.9 Hz, $PhCH_2O$), 4.43 (s, 2 H, $PhCH_2O$), 3.98 (td, 1 H, J = 6.4 and 2.8 Hz, C_9-H), 3.30–3.50 (m, 3 H, C_3-H, C_7-H, and C_{11}-H), 2.68 (qd, 1 H, J = 7.0 and 3.3 Hz, C_2HH), 2.43 (sextet, 1 H, J = 6.6 Hz, C_{14}-H), 2.08 (s, 3 H, $O{=}CH_3$), 1.2–1.9 (m, 11 H), 0.76, 0.86, 1.05, and 1.14 (4 d, 12 H, J = 7 Hz, 4 $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.2, 174.5, 139.2, 138.2, 136.6, 128.4, 128.3, 128.2, 127.82, 127.78, 127.61, 127.59, 127.4, 127.2, 95.0, 83.4, 80.2, 76.0, 75.2, 70.9, 69.8, 65.9, 47.3, 41.8, 40.0, 39.9, 32.8, 32.3, 31.8, 27.7, 27.6, 17.1, 16.3, 9.54, 9.46; TLC R_f 0.22 (20% EtOAc/hexane). Anal. Calcd for $C_{42}H_{56}O_7$: C, 74.97; H, 8.39. Found: C, 75.23; H, 8.29.

[3(2S),4R,5R]-3-(4-Bromo-2-methyl-1-oxo-4-pentenyl)-4-methyl-5-phenyl-2-oxazolidinone (54). To a solution of 12.6 mL (9.1 g, 90 mmol) of i-Pr_2NH in 50 mL of THF at −78 °C was added 47.0 mL (80 mmol) of 1.7 M n-BuLi in hexane. After 30 min at ca. −70 °C, a solution of 17.50 g (75.00 mmol) of the imide **25** in 20 mL of THF was added via cannula over a 20-min period such that the internal temperature remained below −65 °C. After 40 min at −78 °C, 57.5 g (290.0 mmol) of 2,3-dibromopropene was added via cannula over a 10-min period. The solution was gradually warmed from −78 to −35 °C over 5 h and then stirred at −35 °C for 10 h and at −15 °C for 1 h. The reaction was quenched with 50 mL of saturated aqueous NH_4Cl, and the solution was partitioned between water and 25% CH_2Cl_2/pentane. The organic layer was washed with 0.5 N aqueous HCl and brine, dried over Na_2SO_4, and concentrated. The excess dibromopropene was removed by rotoevaporation at 1 Torr, and the residue was purified by chromatography (550 g of silica gel, 2:1 CH_2Cl_2/hexane) to give 17.30 g of the imide **54**, along with some mixed fractions (ca. 3 g). The mixed fractions were rechromatographed to give an additional 1.72 g of product. Total yield of the imide **54** was 19.02 g (72%) as a white solid. An analytical sample was recrystallized from hexane: mp 59–60 °C; $[\alpha]_D$ +42.0° (c 2.1, $CHCl_3$); IR ($CHCl_3$) 3020,2980, 1875,1695, 1630, 1455, 1340, 1240, 1190, 1120, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.47 (m, 5 H, Ar H), 5.68 (d, 1 H, J = 7.4 Hz, $PhCH$), 5.64 (m, 1 H, one of $=CH_2$), 5.46 (d, 1 H, J = 1.6 Hz, one of $=CH_2$), 4.78 (quintet, 1 H, J = 6.9 Hz, NCH), 4.21 (sextet, 1 H, J = 7.0 Hz, $O{=}CCH$), 2.96 (ddd, 1 H, J = 14.7, 7.3, and 0.8 Hz,one of CH_2), 2.52 (ddd, 1 H, J = 14.7, 6.9, and 1.0 Hz, one of CH_2), 1.24 (d, 3 H, J = 6.9 Hz, $O{=}CCHCH_3$), 0.89 (d, 3 H, J = 6.9 Hz, $NCHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 152.3, 133.2, 130.9, 129.5, 128.4, 125.5, 118.6, 78.5, 54.6, 44.3, 36.4, 16.6, 14.3; TLC R_f 0.30 (20% EtOAc/hexane). Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15. Found: C, 54.28; H, 5.14.

(2S)-4-Bromo-2-methyl-4-penten-2-ol (55). Reduction of the imide **54** (7.047 g, 20.00 mmol), according to the procedure given for the reduction of **26**, afforded 3.224 g (90%) of the alcohol **55**: $[\alpha]_D$ −8.1° (c 3.0, $CHCl_3$); IR (thin film) 3350 (br), 2965, 2935, 2880, 1630, 1155, 1040, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.60 (q, 1 H, J = 1.2 Hz, one of $=CH_2$), 5.45 (d, 1 H, J = 1.5 Hz, one of $=CH_2$), 3.54 (t, 2 H, J = 5.5 Hz, CH_2OH), 2.58 (ddd, 1 H, J = 14.1, 5.9, and 1.0 Hz, one of $=CCH_2$), 2.23 (ddd, 1 H, J = 14.1, 8.1, and 0.7 Hz, one of $=CCH_2$), 2.01–2.15 (m, 1 H, $CHCH_3$), 1.47 (t, 1 H, J = 5.5 Hz, OH), 0.95 (d, 3 H, J = 6.8 Hz, $CHCH_3$); TLC R_f 0.33 (35% EtOAc/hexane). Anal. Calcd for $C_6H_{11}BrO$: C, 40.25; H, 6.19. Found: C, 40.25; H, 6.15.

(4S)-2-Bromo-4,6-dimethyl-1,5-heptadiene (56). To a solution of 1.96 mL (2.86 g, 22.5 mmol) of oxalyl chloride in 100 mL of CH_2Cl_2 at −78 °C was added 3.19 mL (3.51 g, 45.0 mmol) of dimethyl sulfoxide dropwise. After 10 min, a solution of 2.69 g (15.0 mmol) of the alcohol **55** in 10 mL of CH_2Cl_2 was dried over a 3 min period via cannula. The mixture was stirred at −65 °C for 20 min and then recooled to −78 °C, and 10.4 mL (7.57 g, 75.0 mmol) of Et_3N was added. The resulting mixture was stirred at −70 to −10 °C for 1.5 h and then partitioned between pentane and water. The organic layer was washed with 1 N aqueous $NaHSO_4$ and brine and dried over Na_2SO_4. Concentration in vacuo (aspirator vacuum, 30 °C) afforded 2.88 g (108% mass balance) of the crude aldehyde **55** as a golden oil, which was used immediately in the next step as follows. To a suspension of 7.32 g (19.0 mmol) of isopropyltriphenylphosphonium iodide in 75 mL of THF at 0 °C was added 7.0 mL (18.0 mmol) of 2.58 M n-BuLi in hexane dropwise. The mixture was stirred for 15 min at 0 °C and 15 min at room temperature to give a deep red solution of the ylide containing a small amount of undissolved phosphonium salt. The reaction was cooled to −78 °C, and a solution of the unpurified aldehyde (2.88 g) in 10 mL of THF was added via cannula. The light orange mixture was warmed to 0 °C for 30 min and then stirred at room temperature for 30 min. The excess ylide was quenched by dropwise addition of acetic acid until the color dissipated, and the mixture was concentrated in vacuo to ca. 40 mL. After dilution with 100 mL of pentane, the solids were removed by filtration, and the filtrate was concentrated in vacuo (aspirator vacuum). Chromatography (150 g of silica gel, pentane) afforded 2.20 g (72% for two steps) of the product **56** as a colorless, mobile oil; $[\alpha]_D$ +20.6° (c 2.5, $CHCl_3$); IR (thin film) 2970, 2930, 2870, 1630, 1450, 1380, 1190, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.50 (d, 1 H, J = 1.1 Hz, one of $=CH_2$), 5.38 (d, 1 H, J = 1.5 Hz, one of $=CH_2$), 4.88 (apparent doublet of quintets, 1 H, J = 9.2 and 1.4 Hz, $=CHCH$), 2.70–2.83 (m, 1 H, $CHCH_3$), 2.23–2.40 (m, 2 H, $CHCH_2$), 1.66 and 1.68 (2 d, 6 H, J = 1.3 Hz, $=C(CH_3)_2$), 0.93 (d, 3 H, J = 6.7 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.6, 131.3, 129.4, 117.3, 77.4, 77.0, 76.6, 49.2, 31.0, 25.6, 20.0, 18.0. Anal. Calcd for $C_9H_{15}Br$: C, 53.22; H, 7.44. Found: C, 53.30; H, 7.33.

[3(2R,3S,6E),4R,5R]-3-[3-Hydroxy-1-oxo-2-(phenylmethoxy)-6-nonenyl]-4-methyl-5-phenyl-2-oxazolidinone (59). To a solution of 1.627 g (5.00 mmol) of the imide **57** in 20 mL of CH_2Cl_2 at −78 °C were added 0.83 mL (0.61 g, 6.0 mmol) of Et_3N and 1.38 mL (1.51 g, 5.50 mmol) of n-Bu_2BOTf. The solution was stirred for 1 h at −78 °C and for 45 min at 0 °C and recooled to −78 °C, and 0.99 mL (0.82 g, 6.5 mmol) of (E)-4-methyl-4-heptenal (**58**) was added in one portion. After 1 h at −78 °C and 1 h at −78 to −45 °C, 30 mL of MeOH and 10 mL of 0.5 M pH 7 phosphate buffer were added, and the resulting mixture was stirred vigorously in an ice bath as 5 mL of 30% aqueous H_2O_2 was added dropwise. After 20 min at 0 °C to room temperature the reaction mixture was partitioned between water and 25% CH_2Cl_2/hexane. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography (125 g of silica gel, 4–8% acetone/CH_2Cl_2). First to elute was 0.185 g (11%) of the starting imide **57**, followed by 1.906 g (84%) of the aldol adduct **59** as a thick gum: $[\alpha]_D$ +59.1° (c 3.1, $CHCl_3$); IR (thin film) 3500 (br), 2980, 2950, 2870, 1780, 1710, 1495, 1455, 1360 (br), 1200, 1150, 1120, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.47 (m, 10 H, Ar H), 5.71 (d, 1 H, J = 7.0 Hz, $CHCHPh$), 5.12–5.20 (m, 2 H, $CHC{=}O$ and $=CH$), 4.70–4.82 (m, 2 H, NCH and one of $PhCH_2$), 4.49 (d, 1 H, J = 11.4 Hz, one of $PhCH_2$), 3.88–3.97 (m, 1 H, $CHOH$), 1.93–2.21 (m, 5 H, OH and $CH_2C{=}CCH_2$), 1.70–1.81 (m, 2 H, CH_2CHOH), 1.59 (s, 3 H, $=CCH_3$), 0.87–0.98 (m, 6 H, $CHCH_3$ and CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 152.9, 137.2, 133.7, 133.0, 128.7, 128.6, 128.4, 128.3, 128.0, 126.8, 125.6, 79.8, 79.7, 73.0, 72.3, 55.4, 35.3, 32.4, 21.1, 15.7, 14.24, 14.17; TLC R_f 0.18 (30% EtOAc/hexane). Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37. Found: C, 71.58; H, 7.39.

[3(2R,2(2S,5S,5(1R))),4R,5R]-3-[2-[5-(1-Hydroxypropyl)-5-methyltetrahydro-2-furanyl]-1-oxo-2-(phenylmethoxy)ethyl]-4-methyl-5-phenyl-2-oxazolidinone (60). To a solution of 1.882 g (4.17 mmol) of the aldol adduct **59** in 20 mL of CH_2Cl_2 at 0 °C were added 56 mg (0.21 mmol) of $VO(acac)_2$ and 2.15 mL (8.3 mmol) of 3.85 M TBHP in benzene. The resulting dark red solution was stirred for 3 h at 0 °C and for 1 h at room temperature. Since TLC analysis indicated a small amount of starting material remained, an additional 22 mg of $VO(acac)_2$ was added. The reaction mixture was stirred for 1 h at room temperature, and then 10 mL of saturated aqueous Na_2SO_3 was added. The mixture was stirred vigorously for 10 min and then partitioned between 25% CH_2Cl_2/pentane and 1% aqueous $NaHCO_3$. The organic layer was washed with 0.2 N aqueous $NaHSO_4$ and 1 N pH 7 phosphate buffer, dried over Na_2SO_4, and concentrated. ^1H NMR analysis of the unpurified product indicated a diastereomer ratio of 95:5, based on the integration of the respective C_{22}-H doublets at 5.40 ppm (major) and at 5.13 ppm (minor). The product was purified by chromatography (150 g of silica gel, 4–7% acetone/CH_2Cl_2). The minor diastereomer eluted first,

followed by 1.730 g (89%) of the imide **60** as a thick syrup: $[\alpha]_D$ +20.7° (*c* 3.0, $CHCl_3$); IR (thin film) 3200 (br), 2980, 2880, 1780, 1710, 1455, 1350 (br), 1200, 1120, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.46 (m, 10 H, Ar H), 5.64 (d, 1 H, *J* = 7.0 Hz, PhC*H*CH), 5.40 (d, 1 H, *J* = 4.9 Hz, O=CC*H*), 4.56–4.78 (m, 3 H, NC*H* and PhCH_2O), 4.36–4.43 (m, 1 H, O=CCHC*H*), 3.43 (br d, 1 H, *J* = 10 Hz, C*H*OH), 2.28 (br s, 1 H, O*H*), 1.99–2.13 (m, 3 H), 1.40–1.63 (m, 2 H), 1.18–1.32 (m, 1 H), 1.17 (s, 3 H, CCH_3), 1.02 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3), 0.84 (d, 3 H, *J* = 7.0 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 152.9, 137.6, 133.0, 128.8, 128.7, 128.3, 128.1, 127.8, 125.6, 87.5, 80.1, 79.4, 78.9, 78.2, 73.2, 55.3, 30.8, 27.8, 24.6, 23.6, 14.3, 11.2; TLC R_f 0.24 (5% acetone/CH_2Cl_2); TLC R_f for minor diastereomer 0.34 (5% acetone/CH_2Cl_2). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11. Found: C, 69.15; H, 7.24.

[α*R*,2*S*,5*S*,5(1*R*)]-5-(1-Hydroxypropyl)-*N*-methoxy-*N*,5-dimethyl-α-(phenylmethoxy)tetrahydro-2-furanacetamide (61). To a stirred suspension of 1.08 g (11.1 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 15 mL of CH_2Cl_2 at 0 °C was slowly added 5.55 mL (11.1 mmol) of 2.0 M $AlMe_3$ in toluene (*caution*: gas evolution). After the addition was complete, the clear solution was stirred at room temperature for 15 min and then recooled to −10 °C, and a solution of 1.730 g (3.70 mmol) of the imide **60** in 15 mL of CH_2Cl_2 was added. The solution was stirred for 1 h at −10 to 0 °C, 2 h at 0 °C, and 0.5 h at room temperature and then added to 100 mL of ice-cold 0.5 N aqueous HCl and 50 mL of CH_2Cl_2. After the mixture was stirred vigorously for 5 min, the layers were separated, and the aqueous layer was extracted with 2 × 25 mL of CH_2Cl_2. The combined organic layers were washed with dilute aqueous HCl and pH 7 phosphate buffer, dried over Na_2SO_4, and concentrated. The residue was dissolved in ca. 10 mL of ether, and most of the 4-(*R*)-methyl-5(*R*)-phenyl-2-oxazolidinone was precipitated by cooling and addition of pentane. The supernatant was decanted, and the solid was washed with 50% ether/pentane. The combined supernatants were concentrated to give the product contaminated with some residual oxazolidinone (in larger scale reactions, this material was used directly in the next step). The residue was purified by chromatography (150 g of silica gel, 10–20% acetone/CH_2Cl_2). The oxazolidinone eluted first, followed by 1.193 g (92%) of the amide **61** as a syrup: $[\alpha]_D$ +17.8° (*c* 2.0, $CHCl_3$); IR (thin film) 3480 (br), 2970, 2940, 2875, 1660, 1455, 1100, 990, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.40 (7, 5 H, Ar H), 4.73 and 4.57 (AB quartet, 2 H, *J* = 12.1 Hz, PhCH_2O), 4.31–4.41 (m, 2 H, O=CC*HCH*), 3.56 (s, 3 H, OCH_3), 3.42 (dt, 1 H, *J* = 10.0 and 2.3 Hz, C*H*OH), 3.19 (s, 3 H, (NCH_3), 2.28 (br s, 1 H, OH), 1.90–2.10 (m, 3 H), 1.42–1.58 (m, 2 H), 1.18–1.34 (m, 1 H), 1.12 (s, 3 H, CCH_3), 1.02 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3); TLC R_f 0.21 in 10% acetone/CH_2Cl_2). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32. Found: C, 64.63; H, 8.48.

[α*R*,2*S*,5*S*]-*N*-Methoxy-α-(1-methoxy-1-methylethyl)-*N*,5-dimethyl-5-[1-(dimethylhydrazino)propyl]tetrahydro-2-furanacetamide (65). To a solution of 1.494 g (4.51 mmol) of the ketone **64** in 15 mL of Me_2NNH_2 at 0 °C was added 1.14 mL (0.98 g, 9.0 mmol) of Me_3SiCl dropwise. After the addition was complete, the ice bath was removed, and the reaction was stirred for 20 h at room temperature. Most of the excess Me_2NNH_2 was then removed by warming to ca. 40 °C under an argon stream (*caution*: this operation must be conducted in an efficient hood since Me_2NNH_2 is a suspected carcinogen). The residue (ca. 6–7 mL) was partitioned between 75% EtOAc/hexane and water. The organic layer was washed with water and with 0.5 N pH 7 phosphate buffer, and the aqueous layers were extracted once with 75% EtOAc hexane. The combined organic layers were dried over Na_2SO_4 and concentrated to give 1.645 g (98%) of the hydrazone **65**. An analytical sample was purified by chromatography (EtOAc): $[\alpha]_D$ −44.2° (*c* 2.5, $CHCl_3$); IR (thin film) 2985, 2955, 2860, 2775 (w), 1675, 1215, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.83 (br s, 1 H, O=CC*H*O), 4.10 (br q, 1 H, *J* = 7 Hz, OC*HCH*$_2$), 3.81 (br s, 3 H, NOCH_3), 3.23 (s, 3 H, COCH_3), 3.20 (br s, 3 H, NCH_3), 2.31–2.52 (m, 3 H), 2.38 (s, 6 H, N(CH_3)$_2$), 1.68–2.09 (m, 3 H), 1.35 and 1.43 (2 s, 6 H, C(CH_3)$_2$), 1.34 (s, 3 H, CCH_3), 1.14 (t, 3 H, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.9, 101.3, 86.5, 80.6, 69.9 (br), 67.8, 60.8, 49.2, 47.6, 36.2, 27.0, 26.6, 25.0, 24.8, 20.7, 12.3; TLC R_f = 0.26 (EtOAc). Anal. Calcd for $C_{18}H_{35}N_3O_5$: C, 57.89; H, 9.45. Found: C, 57.71; H, 9.59.

(2*R*,α*S*)-α-Ethyl-2-methyloxiranemethanol (66). To a solution of 5.01 g (50.0 mmol) of 2-methyl-1-penten-3-ol in 50 mL of CH_2Cl_2 at −20 °C were added 6.5 mL (6.5 mmol) of 1.0 M (+)-diisopropyl tartrate in CH_2Cl_2 and 1.49 mL (1.42 g, 5.0 mmol) of Ti(O-*i*-Pr)$_4$. After 15 min at −20 °C, the solution was cooled to −30 °C, and 6.25 mL (25.0 mmol) of 4.00 M TBHP in benzene was added over a 2-min period. The reaction was kept at −20 °C for 33 h, and then 7.5 mL (7.5 mmol) of 1 M triethanolamine in CH_2Cl_2 was added. After being stirred for 30 min at 0 °C, the solution was rapidly filtered through ca. 40 g of silica gel in a sintered-glass funnel, eluting with 200 mL of ether. The filtrate was concentrated in vacuo (aspirator vacuum, bath temperature 20 °C), and the residue was chromatographed (120 g of silica gel, 40–70% ether/pentane). The resolved allylic alcohol (2.28 g, 91%) eluted first, followed by the epoxide **66** as a mixture with diisopropyl tartrate. Kugelrohr distillation (oven temperature 100 °C, 10 mmHg) of the mixture afforded 2.37 g (82%) of the epoxy alcohol **65**: $[\alpha]_D$ +5.9° (*c* 3.5, $CHCl_3$); IR (thin film) 3450 (br), 2970, 2940, 2880, 1460, 1070, 980, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.56–3.60 (m, 1 H, C*H*OH), 2.91 (dd, 1 H, *J* = 4.8 and 0.6 Hz, one of CH_2O), 2.61 (d, 1 H, *J* = 4.8 Hz, one of CH_2O), 2.24 (t, 1 H, *J* = 1.6 Hz, OH), 1.62–1.74 (m, 1 H), 1.35–1.51 (m, 1 H), 1.34 (d, 3 H, *J* = 0.4 Hz, CCH_3), 1.02 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3); TLC R_f 0.30 (60% diethyl ether/pentane). Anal. Calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.93; H, 10.46.

[2*R*,2(1*S*)]-2-[1-[(4-Methoxyphenyl)methoxy]propyl]-2-methyloxirane (67). A dry flask was charged with 250 mg (6.25 mmol) of a 60% dispersion of NaH in oil, and the oil was removed by washing twice with 5 mL of THF. The oil-free NaH was then suspended in 10 mL of DMF. After the mixture was cooled to 0 °C, 1.01 mL (1.10 g, 7.00 mmol) of 4-methoxybenzyl chloride was added, followed by a solution of 581 mg (5.00 mmol) of the epoxy alcohol **66** in 5 mL of THF. The mixture was stirred vigorously for 4 h at 0 °C and then partitioned between 0.02 N pH 7 phosphate buffer and 25% CH_2Cl_2/pentane. The organic layer was washed twice with water and then with brine, dried over Na_2SO_4, and concentrated. Purification by chromatography (150 g of silica gel, 10% EtOAc/hexane) yielded 1.060 g (90%) of the epoxide **67** as a colorless oil: $[\alpha]_D$ −28.6° (*c* 2.5, $CHCl_3$); IR (thin film) 2970, 2940, 2880, 1610, 1510, 1250, 1080, 1040, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (d, 2 H, *J* = 8.7 Hz, Ar H), 6.88 (d, 1 H, *J* = 8.7 Hz, Ar H), 4.39 and 4.61 (AB quartet, 2 H, *J* = 11.2 Hz, Ar CH_2), 3.80 (s, 3 H, OCH_3), 2.92 (dd, 1 H, *J* = 8.5 and 4.2 Hz, OC*H*CH$_2$), 2.64 and 2.73 (AB quartet, 2 H, *J* = 5.1 Hz, OCH_2C), 1.52–1.74 (m, 2 H, CHCH_2), 1.31 (s, 3 H, CCH_3), 0.98 (t, 3 H, *J* = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 159.0, 130.6, 129.0, 128.9, 113.5, 82.6, 71.5, 56.6, 54.9, 53.2, 24.5, 16.1, 10.1; TLC R_f 0.27 (15% EtOAc/hexane). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.17; H, 8.56.

(3*S*,4*R*)-3-[(4-Methoxyphenyl)methoxy]-4-methyl-7-octen-4-ol (68). To a solution of 2.102 g (8.89 mmol) of the epoxide **67** in 25 mL of THF was added 6.7 mL (13.4 mmol) of 2.0 M allylmagnesium chloride in THF. After 16 h at room temperature, the solution was partitioned between saturated aqueous NH_4Cl and 25% CH_2Cl_2/pentane. The organic layer was dried over Na_2SO_4 and concentrated to give 2.477 g (100%) of analytically pure alcohol **68**: $[\alpha]_D$ +1.8° (*c* 3.0, $CHCl_3$); IR (thin film) 3550 (br), 3450 (br), 2840–3000, 1640, 1625, 1515, 1250, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, 2 H, *J* = 8.7 Hz, Ar H), 6.89 (d, 2 H, *J* = 8.7 Hz, Ar H), 5.84 (m, 1 H, C*H*=CH$_2$), 5.02 (dq, 1 H, *J* = 17.1 and 1.8 Hz, one of CH=CH_2), 4.94 (dq, 1 H, *J* = 10.2 and 1.2 Hz, one of CH=CH_2), 4.52 and 4.67 (AB quartet, 2 H, *J* = 10.8 Hz, Ar CH_2O), 3.81 (s, 3 H, OCH_3), 3.17 (dd, 1 H, *J* = 3.8 and 8,1 Hz, CH_2CHO), 2.01–2.29 (m, 2 H, =CHCH_2), 2.15 (s, 1 H, O*H*), 1.41–1.71 (m, 4 H), 1.17 (s, 3 H, CCH_3), 1.06 (t, 3 H, *J* = 7.4 Hz, CH_2CH_3); TLC R_f 0.29 (20% EtOAc/hexane). Anal. Calcd for $C_{16}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.25; H, 9.33.

(2*E*,6*R*,7*S*)-7-[(4-Methoxyphenyl)methoxy]-2,6-dimethyl-6-(phenylmethoxy)-2-nonenoic Acid, Ethyl Ester (70). A solution of 4.95 g (13.43 mmol) of the olefin **69** in 100 mL of methanol containing 5 drops of pyridine and a small amount of Sudan III dye was stirred vigorously at −78 °C as ozone was bubbled through. As soon as the dye faded, 0.5 mL of tetramethylethylene was added, and the dry ice bath was removed. When the temperature had risen to −40 °C, a solution of 4.40 g (16.8 mmol) of Ph_3P in 15 mL of CH_2Cl_2 was added. The solution was stirred at room temperature for 1 h, and then the solvents were removed in vacuo. The residue was dissolved in 120 mL of CH_2Cl_2 at 0 °C, and 6.60 g (18.2 mmol) of (carbethoxyethylidene)triphenylphosphorane was added. After 15 min, the ice bath was removed. The reaction was stirred at room temperature for 15 h, and then an additional 1.00 g of the phosphorane was added. After an additional 6 h, the solution was concentrated, and the residue was triturated with 10% CH_2Cl_2/hexane. The solid was dissolved in 25 mL of CH_2Cl_2, diluted with 75 mL of hexane, and then concentrated in vacuo at 0 °C to ca. 50 mL. The precipitate (Ph_3P=O) was removed by filtration and washed with 10% CH_2Cl_2/hexane. Concentration of the combined supernatant and filtrate gave the crude ester as a 94:6 mixture of *E* and *Z* isomers according to capillary GC analysis. Purification by chromatography (400 g of silica gel, 10–15% EtOAc/hexane) gave 5.18 g (85% for two steps) of the ester **70** of >98% purity by GC analysis: $[\alpha]_D$ +29.1° (*c* 2.5, $CHCl_3$); IR (thin film) 2980, 2875, 1710, 1650, 1610, 1515, 1250, 1100, 1040, 825, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23–7.35 (m, 7 H, Ar H), 6.87 (d, 2 H, *J* = 8.7 Hz, Ar H), 6.76 (tq, 1 H, *J* = 7.4 and 1.3 Hz, =C*H*), 4.58 (s, 2 H, Ar CH_2O), 4.42 and 4.52 (AB quartet, 2 H, *J* = 11.4 Hz, Ar CH_2O) 4.18 (q, 2 H, *J* = 7.1 Hz, OCH_2CH$_3$), 3.80 (s, 3 H,

OCH_3), 3.39 (dd, 1 H, J = 8.8 and 3.0 Hz, CHO), 2.27 (br q, 2 H, J = 8 Hz, $=CHCH_2$), 1.50–1.96 (m, 4 H), 1.80 (d, 3 H, J = 1.3 Hz, $=CCH_3$), 1.28 (t, 3 H, J = 7.1 Hz, OCH_2CH_3), 1.25 (s, 3 H, CCH_3), 1.06 (t, 3 H, J = 7.5 Hz, $CHCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 159.1, 142.3, 139.5, 131.1, 129.0, 128.2, 127.6, 127.0, 113.7, 84.6, 79.7, 73.9, 63.6, 60.3, 55.2, 34.2, 23.5, 22.8, 19.2, 14.2, 12.2, 12.0; TLC R_f 0.32 (15% EtOAc/hexane); TLC R_f for Z isomer 0.40 (15% EtOAc/hexane). Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.43. Found: C, 73.74; H, 8.41.

[2*S*,3*R*,6*R*,6(2*S*)]-2-Ethyl-6-(1,2-dihydroxy-1-methylethyl)-3-methyl-3-(phenylmethoxy)tetrahydropyran (73). To a solution of 5.05 g (17.27 mmol) of the allylic alcohol **72** in 150 mL of CH_2Cl_2 at −20 °C were added 5.66 mL (5.40 g, 19.0 mmol) of Ti(O-*i*-Pr)$_4$ and 11.7 mL (23.4 mmol) of 2.0 M (+)-diethyl tartrate in CH_2Cl_2. After 15 min, the solution was cooled to −35 °C, and 8.0 mL (24 mmol) of 3.0 M TBHP in toluene was added slowly. The solution was stirred at −30 °C for 1 h and then kept at −20 °C for 10 h. The reaction was poured into 200 mL of water containing 20 g of tartaric acid and 20 g of $FeSO_4$, and the mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in 100 mL of ether and stirred vigorously with 100 mL of 1 N aqueous NaOH for 1 h. The mixture was diluted with 100 mL of ether, and the layers were separated. The organic layer was washed with 1 N pH 7 buffer, and the aqueous layers were extracted with 100 mL of 25% CH_2Cl_2/pentane. The combined organic layers were dried over Na_2SO_4 and concentrated to give 5.35 g (100%) of the diol **73** of high purity by TLC and ^1H NMR analysis. Analysis by capillary GC (DB-1, 175 °C) indicated a diastereomer ratio of 97.5:2.5. An analytical sample was purified by chromatography (4% *i*-PrOH/CH_2Cl_2): $[\alpha]_D$ −18.1° (*c* 2.5, $CHCl_3$); IR (thin film) 3420 (br), 2975, 2940, 2875, 1500, 1460, 1385, 1115, 1055, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22–7.39 (m, 5 H, Ar H), 4.39 and 4.46 (AB quartet, 2 H, J = 11.0 Hz, $PhCH_2O$), 3.88 (dd, 1 H, J = 11.2 and 2.3 Hz, one of CH_2OH), 3.77–3.84 (m, 1 H, $CHCH_2CH_3$), 3.55 (dd, 1 H, J = 12.0 and 2.7 Hz, $CHCH_2CH_2$), 3.38 (t, 1 H, J = 10.6 Hz, one of CH_2OH), 3.22 (d, 1 H, J = 0.5 Hz, COH), 2.96 (dd, 1 H, J = 9.9 and 2.2 Hz, CH_2OH), 1.58–1.96 (m, 4 H), 1.32–1.46 (m, 2 H), 1.14 (s, 3 H, CCH_3), 1.09 (d, 3 H, J = 0.5 Hz, CCH_3), 1.02 (t, 3 H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5, 128.2, 127.2, 127.1, 79.5, 74.2, 74.1, 73.25, 67.7, 63.1, 29.6, 21.5, 21.2, 20.5, 20.1, 10.2; TLC R_f 0.27 (60% EtOAc/hexane). Anal. Calcd for $C_{18}H_{28}O_3$: C, 70.10; H, 9.15. Found: C, 69.93; H, 9.15.

[6*R*,6(1*S*),3*R*,2*S*]-2-Ethyl-3-methyl-6-(2-methyloxiran-2-yl)-3-(phenylmethoxy)tetrahydropyran (74). The unpurified diol **73** from above (5.35 g, 17.3 mmol) was dissolved in 20 mL of dry pyridine at 0 °C and 4.8 g (25.0 mmol) of tosyl chloride was added in one portion. The solution was allowed to warm to room temperature, and, after 14 h, 3 mL of water was added to consume the excess tosyl chloride. After 30 min, the reaction was partitioned between 75% EtOAc/hexane and 1 N aqueous $NaHSO_4$. The organic layer was washed with 1 N $NaHSO_4$, 1 N pH 7 phosphate buffer, and brine and dried over Na_2SO_4. Concentration in vacuo gave the crude tosylate, which was immediately dissolved in 80 mL of methanol. This solution was cooled to 0 °C, and 5.0 g of anhydrous K_2CO_3 was added. The mixture was stirred vigorously for 1 h at 0 °C and then partitioned between 25% CH_2Cl_2/pentane and 0.2 N pH 7 phosphate buffer. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the crude epoxide as a 97.5:2.5 mixture of diastereomers according to capillary GC analysis (Dwax-4, 215 °C). Recrystallization from 50 mL of hexane gave a pale yellow solid containing traces of polar impurities but free of minor diastereomer. This material (ca. 3 g) was further purified by chromatography (100 g of silica gel, 20% EtOAc/hexane). The mother liquors from the recrystallization were enriched in the minor diastereomer, and upon chromatography (200 g of silica gel, 10–15% EtOAc/hexane) the minor diastereomer (ca. 100 mg) eluted first, followed by **74**. The product fractions from the chromatographies were combined to give 4.65 g (93%) of the epoxide **74** as an oil that solidified upon standing. An analytical sample was recrystallized from pentane: mp 48.5–49.5 °C; $[\alpha]_D$ −28.3° (*c* 2.0, $CHCl_3$); IR (thin film of original oil) 2970, 2940, 2880, 1455, 1380, 1115, 1060, 1030, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.42 (m, 5 H, Ar H), 4.40 and 4.52 (AB quartet, 2 H, J = 11.1 Hz, $PhCH_2O$), 3.80 (dd, 1 H, J = 11.3 and 3.3 Hz, $CHCH_2CH_3$), 3.32 (dd, 1 H, J = 10.0 and 3.4 Hz, $CHCH_2CH_2$), 2.61 and 2.73 (AB quartet, 2 H, J = 5.0 Hz, CH_2O), 1.82–1.98 (m, 2 H), 1.58–1.75 (m, 2 H), 1.42–1.55 (m, 2 H), 1.38 (s, 3 H, $BnOCCH_3$), 1.15 (s, 3 H, OCH_2CCH_3), 1.00 (t, 3 H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.7, 128.1, 127.3, 127.0, 78.4, 74.1, 71.7, 62.9, 57.8, 52.7, 30.3, 22.0, 20.9, 20.8, 17.1, 10.5; TLC R_f 0.25 (10% EtOAc/hexane); TLC R_f for minor diastereomer 0.35 (10% EtOAc/hexane). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.54; H, 9.19.

4-Methoxybenzoic Acid, [1(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*)))]-[5-[5-(2-Ethyl-3-hydroxy-3-methyltetrahydropyran-6-yl)-2-hydroxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]methyl Ester (80a). To a solution of 75 mg (0.20 mmol) of triol **14** in 2 mL of CH_2Cl_2 at room temperature were added 69 μL (50 mg, 0.50 mmol) of Et_3N, 41 μL (51 mg, 0.30 mmol) of 4-methoxybenzoyl chloride, and ca. 5 mg of DMAP. The solution was stirred for 1 h, and then the reaction mixture was partitioned between 75% EtOAc/hexane and pH 7 phosphate buffer. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by chromatography (15 g of silica gel, 50% EtOAc/hexane) gave 97 mg (96%) of the ester **80a**: IR (thin film) 3500 (br), 2980, 2950, 1715, 1610, 1515, 1260, 1170, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, 2 H, J = 9.0 Hz, Ar H), 6.93 (d, 2 H, J = 9.0 Hz, Ar H), 4.22–4.42 (m, 3 H, C_{22}-H_2 and C_{23}-H), 3.87 (s, H, OCH_3), 3.41 (dd, 1 H, J = 11.4 and 3.5 Hz, C_{35}-H), 3.30 (br d, 1 H, J = ca. 8 Hz, C_{31}-H), 3.12 (d, 1 H, J = 0.6 Hz, C_{27}-OH), 2.77 (br s, 1 H, C_{34}-OH), 2.02–2.42 (m, 3 H), 1.3–1.9 (m, 10 H), 1.28 and 1.33 (2 s, 6 H, 2 CCH_3), 1.09 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 1.07 (s, 3 H, CCH_3), 0.98 (t, 3 H, J = 7.4 Hz, CH_2CH_3); TLC R_f 0.21 (30% EtOAc/CH_2Cl_2). Anal. Calcd for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36. Found: C, 66.52; H, 8.52.

4-Methoxybenzoic Acid, [1(2*S*,5*S*,5(2*S*,3*S*,5*S*,5(2*S*,3*R*,6*R*)))]-[5-[5-(2-Ethyl-3-hydroxy-3-methyltetrahydropyran-5-yl)-2-hydroxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]methyl Ester (80b). A solution of 86 mg (0.17 mmol) of the ester **80a** and 7 mg of CSA in 10 mL of water-saturated CH_2Cl_2 was stirred for 1 h at 25 °C. The reaction was diluted with 40 mL of CH_2Cl_2 and washed with pH 7 phosphate buffer. The organic layer was dried over Na_2SO_4 and concentrated. HPLC analysis (40% EtOAc/isooctane, 2 mL/min flow rate) of the unpurified reaction mixture from a smaller scale equilibration indicated that ratio of **80a** (t_r 5.7 min) to **80b** (t_r 7.0 min) was 8:92 at equilibrium. Recrystallization of the residue from 3 mL of hexane gave 74 mg (86%) of the ester **80b** as white needles: mp 133–134 °C; IR ($CHCl_3$) 3580, 3400 (br), 2980, 1710, 1610, 1510, 1280, 1260, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, 2 H, J = 9.0 Hz, Ar H), 6.91 (d, 2 H, J = 9.0 Hz, Ar H), 4.22–4.42 (m, 3 H, C_{22}-H_2 and C_{23}-H), 3.94 (s, 1 H, C_{27}-OH), 3.86 (s, 3 H, OCH_3), 3.53 (dd, 1 H, J = 12.0 and 3.3 Hz, C_{35}-H), 3.36 (dd, 1 H, J = 10.2 and 4.6 Hz, C_{31}-H), 2.60–2.75 (m, 2 H, C_{28}-H and C_{34}-OH), 2.46 (dt, 1 H, J = 11.8 and 8.8 Hz), 2.00–2.10 (m, 1 H), 1.95 (t, 1 H, J = 12.1 Hz, one of C_{29}-H), 1.60–1.83 (m, 7 H), 1.38–1.52 (m, 3 H), 1.09, 1.14, and 1.31 (3 s, 9 H, 3 CCH_3), 1.08 (d, 3 H, J = 6.4 Hz, $CHCH_3$), 1.02 (t, 3 H, J = 7.4 Hz, CH_2CH_3); TLC R_f 0.29 (30% EtOAc/CH_2Cl_2). Anal. Calcd for $C_{28}H_{42}O_8$: C, 66.38; H, 8.36. Found: C, 66.03; H, 8.53.

[1*R*,1(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*))),5*S*]-1-[5-[5-[2-Ethyl-3-methyl-3-(phenylmethoxy)tetrahydropyran-2-yl]-3,5-dimethyl-2-(2,2-dimethylhydrazino)tetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]-1-(2-methoxy-2-methylethoxy)-5,7-dimethyl-3-methylene-6-octen-2-one (82). To a solution of 1.24 mL (2.9 mmol) of 2.35 M *t*-BuLi in pentane in 4 mL of ether at −78 °C was added 288 μL (305 mg, 1.50 mmol) of the vinyl bromide **56** dropwise over a 5-min period. After 5 min at −78 °C and 15 min at −78 to −40 °C, a solution of 487 mg (1.30 mmol) of the hydrazone **65** in 2 mL (plus a 1-mL rinse) of ether was added via cannula. The solution was stirred 30 min at −40 to 0 °C, and then 2.0 mL of a 1 M solution of LDA (from 0.62 mL of *i*-Pr_2NH and 1.55 mL of 2.58 M *n*-BuLi in hexane in 1.85 mL of ether at 0 °C) was added. After 3 h at 0 °C, 290 mg (1.00 mmol) of the epoxide **74** was added to the yellow solution under a flow of argon. Within a few seconds, a gummy yellow precipitate formed but then mostly redissolved over a 30-min period. The mixture was stirred for a total of 2.5 h at 0 °C, and then 5 mL of 10% AcOH/MeOH was added. The mixture was partitioned between 50 mL of 25% CH_2Cl_2/pentane and 50 mL of 0.5 N pH 7 phosphate buffer, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on triethylamine-deactivated silica gel (80 g of silica gel, 15% EtOAc/hexane). First to elute was 42 mg (6%) of the diastereomer **83**, followed by 602 mg (83%) of the title compound **82** as a thick syrup: $[\alpha]_D$ + 26.9° (*c* 2.0, $CHCl_3$); IR (thin film) 2800–3000, 1670, 1455, 1375, 1210, 1110, 1060, 1020, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10–7.43 (m, 5 H, Ar H), 6.38 (s, 1 H, one of $=CH_2$), 5.86 (s, 1 H, one of $=CH_2$), 4.88 (br d, 1 H, J = 9 Hz, $=CHCH$), 4.73 (d, 1 H, J = 6.2 Hz, C_{22}-H), 4.37 and 4.51 (AB quartet, 2 H, J = 11.0 Hz, $PhCH_2O$), 4.16 (br q, 1 H, J = 7 Hz, C_{23}-H), 3.77 (dd, 1 H, J = 11.1 and 2.7 Hz, C_{35}-H), 3.38 (br d, 1 H, J = 10.3 Hz, C_{31}-H), 3.21 (s, 3 H, OCH_3), 2.0–2.6 m, 6 H), 2.50–2.60 (m, 1 H, C_{28}-H), 2.40 (s, 6 H, $N(CH_3)_2$), 2.03–2.28 (m, 3 H), 1.0–1.9 (m, 12 H), 1.64 (d, 3 H, J = 1.0 Hz, one of $=C(CH_3)_2$), 1.60 (d, 3 H, J = 1.2 Hz, one of $=C(CH_3)_2$), 1.38 and 1.39 (2 s, 6 H, $OC(CH_3)_2$), 1.11, 1.17, and 1.20 (3 s, 9 H, 3

CCH_3), 1.08 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 0.99 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 0.88 (d, 3 H, J = 6.7 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.1, 146.3, 139.9, 130.9, 130.3, 128.1 (2), 127.4, 127.0, 103.5, 101.2, 88.0, 82.4, 81.5, 78.8, 76.3, 74.4, 71.0, 63.0, 50.8 (br), 49.3, 47.3, 45.0, 39.4, 37.4, 33.5, 31.2, 30.5, 28.0, 25.8, 25.7, 25.6, 24.7, 22.0, 20.9, 20.8, 20.7, 20.1, 17.9, 16.8, 10.6; TLC R_f 0.23 (20% EtOAc/hexane). Anal. Calcd for $C_{43}H_{70}N_2O_7$: C, 71.04; H, 9.70. Found: C, 71.09; H, 9.79.

Data for minor diastereomer **83**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.45 (m, 5 H, Ar H), 6.42 (s, 1 H, one of $=CH_2$), 5.86 (s, 1 H, one of $=CH_2$), 4.88 (br d, 1 H, $=CHCH$), 4.73 (d, 1 H, J = 6.4 Hz, C_{22}-H), 4.38 and 4.53 (AB quartet, 2 H, J = 11.0 Hz, $PhCH_2O$), 4.05 (br q, 1 H, J = 7 Hz, C_{23}-H), 3.76 (dd, 1 h, J = 11.0 and 2.8 Hz, C_{35}-H), 3.56 (dd, 1 H, J = 11.0 and 2.0 Hz, C_{31}-H), 3.21 (s, 3 H, OCH_3), 2.67–2.81 (m, 1 H, C_{28}-H), 2.50–2.63 (m, 1 H, C_{18}-H), 2.38 (s, 6 H, $N(CH_3)_2$), 1.7–2.3 (m, 10 H), 1.60 and 1.63 (2 d, 6 H, J = 1 Hz, $=C(CH_3)_2$), 1.12, 1.19, 1.23, and 1.36 (4 s, 12 H, CCH_3), 1.01–1.07 (m, 9 H, CCH_3, $CHCH_3$, and CH_2CH_3), 0.88 (d, 3 H, J = 6.7 Hz, $CHCH_3$); TLC R_f 0.38 (20% EtOAc/hexane).

[1*R*,1(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*))),5*S*]-1-[5-[5-[2-Ethyl-3-methyl-3-(phenylmethoxy)tetrahydropyran-2-yl]-2-hydroxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]-1-hydroxy-5,7-dimethyl-3-methylene-6-octen-2-one (84). A solution of 601 mg (0.82 mmol) of the hydrazine **82** in 25 mL of 25% CH_2Cl_2/pentane was stirred vigorously with 10 mL of 1 N aqueous $NaHSO_4$ for 7 h at room temperature. The mixture was partitioned between 100 mL of 25% CH_2Cl_2/pentane and 25 mL of 1 N pH 7 phosphate buffer. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (75 g of silica gel, 6–10% *tert*-butyl methyl ether/CH_2Cl_2). A small amount (20 mg) of an unidentified byproduct (not the C_{28} diastereomer) eluted first, followed by 447 mg (88%) of the hydroxy ketone **84** as a colorless gum: $[\alpha]_D$ −20.8° (*c* 2.5, hexane); IR (thin film) 3550 (br), 3480 (br), 2970, 2940, 2880, 1680, 1455, 1380, 1115, 1060, 980, 730, 700 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.45 (d, 2 H, J = 7.5 Hz, Ar H), 7.24 (t, 2 H, J = 7.5 Hz, Ar H), 7.12 (t, 1 H, J = 7.5 Hz, Ar H), 5.31 and 5.39 (2 s, 2 H, $=CH_2$), 4.93 (apparent doublet of quintet, 1 H, J = 9.2 and 1.3 Hz, $=CHCH$), 4.51 (dd, 1 H, J = 7.2 and 1.6 Hz, C_{22}-H), 4.45 (td, 1 H, J = 7.1 and 1.7 Hz, C_{23}-H), 4.20 and 4.37 (AB quartet, 2 H, J = 11.2 Hz, $PhCH_2O$), 3.94 (d, 1 H, J = 7.2 Hz, C_{22}-OH), 3.70 (dd, 1 H, J = 11 and 2 Hz, C_{35}-H), 3.28 (dd, 1 H, J = 11 and 2 Hz, C_{31}-H), 3.05 (s, 1 H, C_{27}-OH), 1.8–2.7 (m, 9 H), 0.9–1.7 (m, 13 H), 1.60 and 1.63 (2 d, 6 H, J = 1.2 Hz, $=CnCH_3)_2$), 1.29 and 1.46 (2 s, 6 H, 2 CCH_3), 1.10 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 0.92 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 0.84 (s, 3 H, CCH_3); ^{13}C NMR (C_6D_6, 75 MHz) δ 201.0, 145.3, 140.4, 131.1, 130.5, 127.3, 125.5, 108.5, 89.0, 83.8, 82.6, 78.4, 74.4, 74.0, 72.8, 63.2, 42.9, 39.5, 38.8, 33.6, 32.1, 30.6, 29.0, 25.7, 25.4, 24.2, 21.83, 21.76, 20.9, 20.8, 18.1, 14.9, 11.2; mass spectrum (EI), *m/e* (relative intensity) 594 (2, $M^+ - H_2O$), 239 (13), 197 (13), 151 (25), 91 (100); TLC R_f 0.21 (10% EtOAc/CH_2Cl_2); exact mass calcd for $C_{37}H_{54}O_6$ ($M^+ - H_2O$) 594.3920, found 594.3929.

[1*R*,1(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*))),3*R*,5*S*]-1-[5-[5-[2-Ethyl-3-methyl-3-(phenylmethoxy)tetrahydropyran-2-yl]-2-hydroxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]-1-hydroxy-3,5,7-trimethyl-6-octen-2-one (85). A solution of 374 mg (0.610 mmol) of the enone **84** and 5 μL of i-Pr_2EtN in 12 mL of toluene was stirred vigorously under 1 atm of hydrogen for 5 min, and then 85 mg (0.092 mmol) of $(Ph_3P)_3RhCl$ was added in one portion. The resulting orange solution was stirred for 4.5 h and then applied directly onto a column for chromatography (60 g of silica gel, 18% EtOAc/hexane). The desired 20*R* diastereomer **85** eluted first, followed by 46 mg (12%) of a 1:1 mixture of **85** and its C_{20} diastereomer. Chromatography of the mixed fractions and combination of product fractions from the chromatographies gave 336 mg (90%) of the ketone **85** with at least 98% diastereomeric purity at C_{20}: $[\alpha]_D$ −55.4° (*c* 2.0, hexane); IR (thin film) 3560 (br), 3480 (br), 2980, 2940, 2880, 1715, 1455, 1380, 1115, 1060, 980, 910, 730, 700 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.45 (d, 2 h, J = 7.5 Hz, Ar H), 7.24 (t, 2 H, J = 7.5 Hz, Ar H), 7.12 (t, 1 H, J = 7.5 Hz, Ar H), 4.78 (apparent doublet of quintets, 1 H, J = 9.6 and 1.3 Hz, $=CHCH$), 4.50 (ddd, 1 H, J = 8.2, 6.2, and 1.9 Hz, C_{23}-H), 4.20 and 4.37 (AB quartet, 2 H, J = 11.1 Hz, $PhCH_2O$), 4.07 (dd, 1 H, J = 6.2 and 1.9 Hz, C_{22}-H), 3.90 (d, 1 H, J = 6.2 Hz, C_{22}-OH), 3.70 (br d, 1 H, J = 11 Hz, C_{35}-H), 3.30 (dd, 1 H, J = 11.4 and 2.6 Hz, C_{31}-H), 2.95 (d, 1 H, J = 0.9 Hz, C_{27}-OH), 2.69 (hextet, 1 H, J = 6.8 Hz, C_{20}-H), 2.54 (dd, 1 H, J = 12.0 and 8.5 Hz, one of C_{29}-H), 2.12–2.47 (m, 4 H), 1.82–2.02 (m, 2 H), 1.1–1.8 (m, 9 H), 1.49 and 1.64 (2 d, 6 H, J = 1.2 Hz, $=C(CH_3)_2$), 1.27 and 1.47 (2 s, 6 H, 2 CCH_3), 1.10 and 1.14 (2 d, 6 H, J = 6.7 Hz, 2 $CHCH_3$), 1.01 (distorted t, 3 H, J = 7 Hz, CH_2CH_3), 0.84 (overlapping s and d, 6 H, CCH_3 and $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.8, 139.7, 131.2, 130.3, 128.1, 127.4, 127.0, 108.3, 88.3, 83.4, 80.1, 78.4, 76.7, 74.1, 72.2, 63.0, 42.5, 42.1, 39.9, 38.2, 33.1, 30.9, 30.2, 28.3, 25.7, 24.6, 24.0, 21.9, 21.6, 20.6, 17.9, 16.1, 14.4, 10.8; TLC R_f 0.30 (20% EtOAc/hexane). Anal. Calcd for $C_{37}H_{58}O_7$: C, 72.28; H, 9.51. Found: C, 72.17; H, 9.66.

[1*R*,1(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*))),3*R*,5*S*]-1-[5-[5-[2-Ethyl-3-methyl-3-(phenylmethoxy)tetrahydropyran-2-yl]-2-methoxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]-3,5,7-trimethyl-1-[(phenylmethoxy)methoxy]-6-octen-2-one (87). To a solution of 335 mg (0.545 mmol) of the lactol **85** in 5 mL of 10% trimethyl orthoformate/methanol at 0 °C was added 10 mg of PPTS. After 20 min, 0.10 mL of Et_3N was added, and the reaction was partitioned between 25% CH_2Cl_2/pentane and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated to give the methyl ketal **86** of high purity by TLC analysis. Without further purification, this material was dissolved in 4 mL of anhydrous MeCN, and 320 mg (1.5 mmol) of 1,8-bis(dimethylamino)naphthalene and 150 μL (220 mg, 1.1 mmol) of benzyl bromomethyl ether[67] were added consecutively. After ca. 15 min a precipitate began to form, and the mixture was stirred for 7 h at 25 °C and for 1 h at 45 °C. After the mixture was cooled to room temperature, 4 mL of ca. 0.2 M aqueous $NaHCO_3$ was added. The mixture was stirred for 10 min and then partitioned between 25% CH_2Cl_2/pentane and water. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by chromatography (60 g of silica gel, 14% EtOAc/hexane) provided 356 mg (87% from lactol **85**) of the ketone **87** as a colorless syrup: $[\alpha]_D$ −40.3° (*c* 2.0, hexane); IR (thin film) 2970, 2940, 2880, 1720, 1455, 1380, 1115, 1050 (br), 730, 695 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.47 (d, 2 H, J = 7.5 Hz, Ar H), 7.04–7.31 (m, 8 H, Ar H), 4.95 (apparent doublet of quintets, 1 H, J = 9.6 and 1.2 Hz, $=CHCH$), 4.76 and 4.78 (narrow AB quartet, 2 H, J = 6.9 Hz, OCH_2O), 4.48–4.68 (m, 4 H, C_{22}-H, C_{23}-H, and $PhCH_2O$), 4.22 and 4.37 (AB quartet, 2 H, J = 11.2 Hz, $PhCH_2O$), 3.71 (br d, 1 H, J = 11 Hz, C_{35}-H), 3.57 (s, 3 H, OCH_3), 3.44 (dd, 1 H, J = 11.5 and 2.3 Hz, C_{31}-H), 2.96–3.08 (m, 1 H, C_{20}-H), 2.60 (dd, 1 H, J = 12.0 and 8.5 Hz, one of C_{29}-H), 2.25–2.55 (m, 3 H), 1.1–2.1 (m, 12 H), 1.54 and 1.64 (2 d, 6 H, J = 1.1 Hz, $=C(CH_3)_2$), 1.31 and 1.40 (2 s, 2 CCH_3), 1.13 and 1.20 (2 d, 6 H, J = 6.6 Hz, 2 $CHCH_3$), 1.05 (distorted t, 3 H, J = 7 Hz, CH_2CH_3), 0.93 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 0.85 (s, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.5, 139.8, 137.8, 131.0, 130.3, 128.4, 128.1, 127.8, 127.4, 127.0, 109.8, 94.4, 88.5, 83.7, 81.7, 80.7, 78.5, 74.1, 71.8, 69.9, 63.0, 51.0, 42.9, 41.6, 40.4, 39.7, 34.7, 30.3, 30.2, 27.4, 25.7, 24.7, 23.0, 21.9, 21.8, 21.1, 20.6, 17.9, 14.8, 14.4, 10.8; TLC R_f 0.41 (20% EtOAc/hexane). Anal. Calcd for $C_{46}H_{68}O_8$: C, 73.76; H, 9.15. Found: C, 73.36; H, 9.11.

[2*S*,4*R*,6*R*,6(2*S*,5*S*,5(2*R*,3*R*,5*S*,5(2*S*,3*R*,6*R*)))]-6-[5-[5-[2-Ethyl-3-methyl-3-(phenylmethoxy)tetrahydropyran-2-yl]-2-methoxy-3,5-dimethyltetrahydrofuran-2-yl]-5-methyltetrahydrofuran-2-yl]-2,4-dimethyl-5-oxo-6-[(phenylmethoxy)methoxy]hexanal (88). Ozone was passed through a cooled (−78 °C) and stirred solution of 300 mg (0.400 mmol) of the olefin **87** in 16 mL of 3:1 methanol/CH_2Cl_2 containing 3 drops of pyridine and a small amount of Sudan III indicator until the dye faded, and then 0.20 mL of tetramethylethylene was immediately added. Without warming first, the solution was partitioned between 100 mL of water and 100 mL of hexane. The organic layer was washed with 2 × 50 mL of water, 2 × 25 mL of 0.1 N aqueous $FeSO_4$, and finally with 50 mL of water. The organic layer was dried over Na_2SO_4, and 5 μL of 2,6-lutidine was added before the solution was concentrated. The residue was immediately purified by chromatography (15 g of silica gel, 25% EtOAc/hexane, high flow rate) to give 268 mg (93%) of the aldehyde **88** as a pale yellow oil of high purity by ^1H NMR analysis at 500 MHz: IR (thin film) 2980, 2940, 2880, 2720 (w), 1730, 1460, 1380, 1050 (br), 735, 700 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 9.26 (d, 1 H, J = 2.0 Hz, O=CH), 7.46 (d, 2 H, J = 7.2 Hz, Ar H), 7.29 (d, 2 H, J = 7.3 Hz, Ar H), 7.25 (t, 2 H, J = 7.7 Hz, Ar H), 7.05–7.20 (m overlapping solvent peak, Ar H), 4.75 and 4.78 (AB quartet, 2 H, J = 6.8 Hz, OCH_2O), 4.62 (td, 1 H, J = 6.9 and 5.2 Hz, C_{23}-H), 4.50 and 4.59 (AB quartet, 2 H, J = 11.9 Hz, $PhCH_2O$), 4.38 (d, 1 H, J = 11.2 Hz, one of $PhCH_2O$), 4.36 (d, 1 H, J = 5.2 Hz, C_{22}-H), 4.23 (d, 1 H, J = 11.2 Hz, one of $PhCH_2O$), 3.72 (dd, 1 H, J = 11.0 and 2.6 Hz, C_{35}-H), 3.53 (s, 3 H, OCH_3), 3.45 (dd, 1 H, J = 12.4 and 2.7 Hz, C_{31}-H), 2.96–3.04 (m, 1 H, C_{20}-H), 2.59 (dd, 1 H, J = 12.1 and 8.4 Hz, one of C_{29}-H), 2.29–2.43 (m, 2 H), 2.17 (ddd, 1 H, J = 13.9, 8.8, and 5.2 Hz, one of C_{19}-H), 2.04–2.11 (m, 1 H, C_{18}-H), 1.87–1.97 (m, 3 H), 1.61–1.75 (m, 2 H), 1.56 (t, 1 H, J = 11.7 Hz, one of C_{29}-H), 1.40–1.54 (m, 2 H), 1.32 and 1.39 (2 s, 6 H, 2 CCH_3), 1.20–1.30 (m, 4 H), 1.13 (d, 3 H, J = 6.6 Hz, $CHCH_3$), 1.07 (d, 1 H, J = 6.8 hZ, $CHCH_3$), 1.05–1.13 (m, 4 H), 0.95–1.01 (m, 1 H), 0.89 (t, 3 H, J = 7.1 Hz,

(67) Prepared by D. J. Mathre using a modification of the procedure of Connor et al: Connor, D. S.; Klein, G. W.; Taylor, G. N. *Org. Synth.* **1972**, *52*, 17–19.

CH_2CH_3), 0.86 (s, 3 H, CCH_3), 0.72 (d, 3 H, J = 7.1 Hz, $CHCH_3$); TLC R_f 0.22 (20% EtOAc/hexane).

Aldol Reaction of Ketone 53 and Aldehyde 88. To a solution of 222 mg (0.330 mmol) of the methyl ketone **53** in 5 mL of ether at −78 °C was added via cannula a −78 °C solution of 0.36 mmol of LDA in ether (generated from 56 μL of i-Pr_2NH and 141 μL of 2.55 M n-BuLi in hexane in 2 mL of ether at −78 to 0 °C and then recooled to −78 °C). The solution was stirred for 5 min at −78 °C, and then a solution of 268 mg (0.37 mmol) of freshly prepared aldehyde **88** in 2 mL (plus a 1-mL rinse) of ether was added via cannula. After an additional 5 min at −78 °C, the reaction was quenched by addition of 100 μL of AcOH. Without warming, the mixture was partitioned between 50 mL of 25% CH_2Cl_2/pentane and 50 mL of 0.1 N pH 7 phosphate buffer. The organic layer was washed with brine, dried over (Na_2SO_4), and concentrated. The residue was purified by chromatography on 50 g of silica gel, with a stepwise gradient of 15% to 17.5% to 20% to 25% to 30% EtOAc/hexane as eluant. First to elute was a small amount of unreacted aldehyde **88**, followed by 176 mg (38%) of the desired aldol adduct **90**. Next to elute was 35 mg of mixed fractions containing **90** and an unidentified byproduct, followed by 218 mg (47%) of the epimeric aldol adduct **89**. Chromatography of the mixture provided an additional 11 mg of **90**, to give a total of 187 mg (41%) of the aldol adduct **90** as a colorless resin: $[\alpha]_D$ + 0.4°, $[\alpha]_{435}$ −3.7° (c 1.0, hexane); IR (thin film) 3400 (br), 2950 (br), 1740, 1715, 1500 (sharp), 1455, 1380, 1050 (v br), 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, [minor] refers to distinct peaks assignable to the minor ring C hydroxy ketone tautomer, which comprises ca. 20% of the equilibrium mixture in $CDCl_3$ at 25 °C) δ 7.20–7.40 (m, 25 H, Ar H), 5.28 (br s, 1 H, OH), 5.01 and 5.15 (AB quartet, 2 H, J = 12.6 Hz, CO_2CH_2Ph), 4.78 and 4.91 [minor] (AB quartet, J = 7.1 hZ, OCH_2O at C_{22}), 4.81 and 4.87 (AB quartet, 2 H, J = 7.1 Hz, OCH_2O at C_{22}), 4.66 and 4.68 (AB quartet, 2 H, J = 6.8 Hz, OCH_2O at C_9), 4.64 [minor] (s, $PhCH_2O$), 4.62 (s, 2 H, $PhCH_2O$), 4.53 and 4.58 (AB quartet, 2 H, J = 12.0 Hz, $PhCH_2O$), 4.48 (d, 1 H, J = 11.0 Hz, one of $PhCH_2O$), 4.27–4.42 (m, 4 H, $PhCH_2O$, C_{23}-H and one of $PhCH_2O$), 4.24 (td, 1 H, J = 9.1 and 3.0 Hz, C_{17}-H), 3.98 (td, 1 H, J = 6.4 and 2.7 Hz, C_9-H), 3.90 (d, 1 H, J = 5.7 Hz, C_{22}-H), 3.78 [minor] (dd, J = 11.4 and 3.2 Hz, C_{35}-H), 3.73 (dd, 1 H, J = 11.4 and 3.2 Hz, C_{35}-H), 3.30–3.48 (m, 4 H, C_3-H, C_7-H, C_{11}-H, and C_{31}-H), 3.34 (s, 3 H, OCH_3), 3.33 [minor] (s, OCH_3), 2.89–2.95 [minor] (symmetric m, C_{20}-H), 2.65–2.73 (m, 2 H, C_2-H and one of C_{16}-H), 2.53 (dd, 1 H, J= 16.6 and 3.0 Hz, one of C_{16}-H), 2.20–2.51 (m, 5 H), 1.97–2.14 (m, 2 H), 1.68–1.91 (m, 9 H), 0.9–1.6 (m, ca. 40 H), 0.86 (d, 3 H, J = 7.0 Hz, $CHCH_3$), 0.77 (d, 3 H, J = 5.8 Hz, $CHCH_3$), 0.76 (d, 3 H, J = 6.6 Hz, $CHCH_3$); TLC R_f 0.20 (20% EtOAc/hexane). Anal. Calcd for $C_{85}H_{118}O_{16}$: C, 73.14; H, 8.52. Found: C, 73.12; H, 8.64.

Data for aldol adduct **89**: IR (thin film) 3520 (br), 2950 (br), 1740, 1715, 1500 (sharp), 1460, 1380, 1050 (v br), 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.22–7.41 (m, 25 H, Ar H), 5.01 and 5.01 and 5.51 (AB quartet, 2 H, J = 12.6 Hz, $CO_2(CH_2Ph)$, 4.77 and 4.92 (AB quartet, 2 H, J = 7.0 Hz, OCH_2O at C_{22}), 4.66 and 4.69 (AB quartet, 2 H, J = 6.8 Hz, OCH_2O at C_9-H), 4.64 (apparent d [close AB quartet], 2 H, $\Delta\nu$ = 1.1 Hz, $PhCH_2O$), 4.53 and 4.58 (AB quartet, 2 H, J = 12.0 Hz, $PhCH_2O$), 4.50 (d, 1 H, J = 10.9 Hz, one of $PhCH_2O$), 4.42 (s, 2 H, $PhCH_2O$), 4.40 (apparent t, 1 H, J = 5.0 Hz, C_{23}-H), 4.37 (d, 1 H, J = 10.9 Hz, one of $PhCH_2O$), 4.32 (d, 1 H, J = 4.4 Hz, C_{22}-H), 3.93–4.00 (m, 2 H, C_9-H), 3.77 (dd, 1 H, J = 11.4 and 3.0 Hz, C_{35}-H), 3.46 (dd, 1 H, J = 9.9 and 3.5 Hz, C_3-H), 3.31–3.42 (m, 3 H, C_7-H, C_{11}-H, and C_{31}-H), 3.34 (s, 3 H, OCH_3), 2.94–3.02 (m, 2 H, C_{20}-H and OH), 2.68 (qd, 1 H, J = 7.1 and 3.5 Hz, C_2-H), 2.48 (dd, 1 H, J = 17.5 and 9.3 Hz, one of C_{16}-H), 2.37–2.44 (m, 3 H), 2.17–2.30 (m, 2 H), 1.69–1.96 (m, 10 H), 1.33–1.65 (m, 11 H), 1.18 and 1.26 (2 s, 6 H, 2 CCH_3), 1.14 (d, 3 H, J = 7.1 Hz, $CHCH_3$), 1.12 (s, 3 H, CCH_3), 1.07 (d, 3 H, J = 6.7 Hz, $CHCH_3$), 1.03 (d, 3 H, J = 7.0 Hz, $CHCH_3$), 0.98–1.01 (m [t overlapping 2 s], 9 H, 2 CCH_3 and CH_2CH_3), 0.84 and 0.85 (2 overlapping d, 6 H, J = 7 Hz, 2 $CHCH_3$), 0.76 (d, 3 H, J = 6.6 Hz, $CHCH_3$); TLC R_f 0.10 (20% EtOAc/hexane).

X-206, Potassium Salt (1). To a solution of 168 mg (0.120 mmol) of the aldol adduct **90** in 10 mL of 80% aqueous THF was added 40 mg of 10% Pd/C. The mixture was vigorously stirred for 3.5 h under 1 atm of hydrogen, and then 2 mL of 0.05 N aqueous $HClO_4$ was added. The mixture was stirred for 3 h more, and then an additional 40 mg of 10% Pd/C was added. After the mixture was stirred overnight (16 h) under 1 atm of hydrogen, the reaction was complete according to TLC analysis, and 1 mL of 0.2 N aqueous K_2CO_3 was added. The catalyst was removed by filtration through Celite, and the filtrate was partitioned between hexane and 0.2 N aqueous K_2CO_3. The organic layer was washed with water and with 0.2 N K_2CO_3 saturated with KCl. The organic layer was dried over anhydrous K_2CO_3 and concentrated, and the residue was dissolved in a small amount of ether/hexane. Slow evaporation of the solvent provided 102 mg (94%) of synthetic X-206, potassium salt as fine white needles: mp of Na^+ salt (from hexane) 185–188 °C (natural mp 187–190 °C); $[\alpha]_D$ +15.6°, $[\alpha]_{546}$ +18.5°, $[\alpha]_{435}$ +32.2° (c 0.73, $CHCl_3$) [natural $[\alpha]_D$ +16.1°, $[\alpha]_{546}$ +18.6°, $[\alpha]_{435}$ +33.2° (c 0.72, $CHCl_3$)]; IR ($CHCl_3$, 25 mg/mL) 3450, 3370 (br), 2980, 2940, 1570, 1460, 1400, 1385, 1105, 1040 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz)[68] δ 7.20 (s, 1 H, C_{21}-OH), 5.95 (s, 1 H, C_{27}-OH), 4.84 (dd, 1 H, J = 11.3 and 4.8 Hz, C_{23}-H), 4.66 (d, 1 H, J = 1.3 Hz, C_9-OH), 4.57 (dd, 1 H, J = 9.5 and 1.3 Hz, C_9-H), 4.29 (t, 1 H, J = 9.2 Hz, C_{17}-H), 3.96 (dd, 1 H, J = 11.7 Hz, C_{35}-H), 3.88 (dd, 1 H, J = 9.8 and 3.0 Hz, C_3-H), 3.68 (d, 1 H, J = 12.2 Hz, C_{22}-H) 3.60 (td, 1 H, J = 10.4 and 1.9 Hz, C_{11}-H), 3.52 (br t, 1 H, J = 10 Hz, C_7-H), 2.98 (dd, 1 H, J = 12.0 and 2.6 Hz, C_{31}-H), 2.81 (qd, 1 H, J = 7.0 and 3.0 Hz, C_2-H), 2.41–2.48 (m overlapping d, 2 H, J = 12.2 Hz, C_{22}-OH (d) and C_{14}-H (m)), 2.18–2.37 (m, 3 H), 1.96–2.05 (m, 2 H), 1.88 (t, 1 H, J = 11.9 Hz, one of C_{29}-H), 1.67–1.84 (m, 4 H), 0.91–1.53 (m, ca. 50 H), 0.64 (d, 3 H, J = 6.5 Hz, C_4HCH_3); ^{13}C NMR (C_6D_6, 75 MHz) δ 181.3, 109.2, 100.6, 99.0, 90.5, 87.1, 84.0, 83.3, 81.8, 79.7, 72.9, 72.1, 70.9, 70.4, 69.8, 68.0, 46.3, 43.7, 42.8, 41.7, 40.4, 39.6, 39.3, 36.0, 35.4, 34.7, 34.0, 33.1, 33.0, 32.0, 31.5, 31.0, 28.1, 27.5, 27.4, 27.3, 24.7, 20.5, 20.2, 18.2, 17.8, 17.0, 16.9, 16.6, 10.7, 10.6, 9.0; TLC R_f 0.32 (5% i-PrOH/CH_2Cl_2), 0.38 (50:50:1 EtOAc/hexane/AcOH).

Acknowledgment. We thank Dr. J. W. Westley, Hoffmann LaRoche, for kindly providing generous samples of X-206 as well as diacid **2**. Support from the National Science Foundation (predoctoral fellowship 1981–1984 for S.L.B.) and the National Institutes of Health is gratefully acknowledged. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

(68) Assignments follow those of Anteunis: Antenus, M. J. O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 931–947.