two strong bands appeared at 1490 and 1030 cm^{-1}, which correspond to similarly strong absorptions at 1530 cm^{-1} and at 1019 and 994 cm^{-1} in neutral hexafluorobenzene. The infrared spectrum of $C_6F_5CF_3AsF_6$ was too complex to allow absorption due to the cation to be distinguished from those due to decomposition products. Intense fluorescence and thermal instability of the monocyclic cations prevented the recording of their Raman spectra even at very low temperatures. The Raman spectrum of $C_{10}F_8AsF_6$ was obtained by employing a Teflon rotating sample cell with a sapphire window. While the majority of vibrational modes in the cation are shifted only slightly in frequency from those in the neutral molecule, the relative intensities of some IR absorptions and Raman lines are greatly changed. In addition, the most intense feature in the Raman spectrum of $C_{10}F_8AsF_6$ (the band at 420 cm^{-1}) has no observed counterpart in $C_{10}F_8$. The absence in the Raman spectrum of $\nu_1(AsF_6^-)$ (which is ordinarily a strong band) hints at absorption enhancement of the cation Raman spectrum. On the whole, however, the overall framework of the molecule appears to be altered little by ionization. Moreover, the mutual exclusion of the IR and Raman activity appears to hold for the $C_{10}F_8^+$ ion (see Table I). Therefore, it is likely that the cation is at least approximately centrosymmetric in its lattice site. It may retain the D_{2h} symmetry of the parent molecule.

Magnetic Susceptibility and ESR Spectra. The magnetic susceptibility of $C_6F_6AsF_6$ (Table II) obeys the Curie law down to 3.8 K. The low effective moment of 1.3 μ_B is probably due, at least in part, to decomposition of the pressure- and temperature-sensitive compound during manipulation to the degradation products which are diamagnetic. A higher moment was obtained for the more stable $C_{10}F_8AsF_6$, which also exhibits Curie law behavior over the range 74 to 5.8 K. For that salt μ (eff) = 1.68 μ_B.

ESR spectra of dilute solutions of $C_6F_6Sb_2F_{11}$ in SbF_5 at 77 K consist of a septet (J = 20 Hz) centered at g = 2.003, in agreement with results reported by Bazhin et al.[1] for solutions of C_6F_6 in superacid media. ESR spectra of $C_{10}F_8AsF_6$ in anhydrous HF or SbF_5 at 4 K were unresolved, symmetrical resonances with g = 2.004.

X-ray Diffraction. The Debye–Scherrer X-ray powder pattern of $C_6F_6AsF_6$ is given in Table III. Single crystals of $C_6F_6AsF_6$ were grown as described above. Due to thermal degradation and resultant fragmentation of these crystals, it proved impossible to collect sufficient high-quality diffractometer data for a complete structure determination. Precession photographs did, however, establish the identity of the crystals and the bulk powder from which they were prepared. The data are consistent with a rhombohedral unit cell: a = 6.60 (1) Å, α = 106.0 (1)°, v = 246.1 Å, Z = 1. Efforts to grow single crystals of $C_{10}F_8AsF_6$ were unsuccessful. The powder diffraction pattern, however, has been indexed (Table IV) on the basis of a tetragonal unit cell: (293 K) a_0 = 8.30 (1) Å, c_0 = 18.76 (1) Å, V = 1292 Å^3; (213 K) a_0 = 8.26 (1) Å, c_0 = 18.57 (3) Å, V = 1267 Å^3. Since AsF_6^- has an effective volume of ~105 Å^3 and the effective packing volume of $C_{10}F_8$ in its crystal[40] is 226 Å, the anticipated formula unit volume for the 1:1 salt is ~330 Å^3. The observed unit cell volume is therefore consistent with four formula units. Moreover, the dimensions of the unit cell indicate that the $C_{10}F_8^+$ species may be aligned with its long molecular axis[41] (~9.6 Å) parallel to C. (The c_0 dimension is consistent with the molecules being arranged head to tail on a fourfold axis 4_2.) The X-ray powder data for $C_{10}F_8ReF_6$ have not been fully indexed and are given in Table V. Similarity of the low-angle d spacings with the data for $C_{10}F_8AsF_6$ suggests a close structural relationship, but the salts are not isomorphous.

Acknowledgment. The authors thank Professor J. C. Tatlow and Dr. R. Stephens of the University of Birmingham, U.K., for infrared spectra of the 1,3- and 1,4-C_6F_8 dienes which were helpful particularly in the early stages of this study. Professor R. Chambers and his co-workers, of the University of Durham, U.K., provided various samples of perfluoro aromatics essential to the research. Lessons in Frontier orbital theory and detailed discussion of the course of the $Ar^+ + F^-$ interaction were provided by our colleague Professor Andrew Streitwieser, Jr., to whom we are greatly indebted. One of us (N.B.) thanks the Warden and Fellows of All Souls College, Oxford, for the Visiting Fellowship, during the tenure of which this manuscript was first drafted. The work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Science Division of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

Registry No. O_2SbF_6, 12361-66-9; $O_2Sb_2F_{11}$, 12592-38-0; $C_{10}F_8AsF_6$, 71715-93-0; AsF_5, 7784-36-3; $NOAsF_6$, 18535-07-4; C_6F_8, 775-51-9; $C_6F_7CF_3$, 27943-60-8; $C_{10}F_6O_2$, 1024-60-8; C_6F_6, 392-56-3; CsF, 13400-13-0; octafluorotoluene, 434-64-0; octafluoronaphthalene, 313-72-4; iridium hexafluoride, 7783-75-7; hexafluorobenzene hexafluoroiridate(V), 102781-69-1; dioxygenyl hexafluoroarsenate, 12370-43-3; hexafluorobenzene hexafluoroarsenate(V), 53863-36-8; octafluorotoluene hexafluoroarsenate(V), 76097-35-3; hexafluorobenzene·$Sb_2F_{11}^-$, 54189-38-7; hexafluorobenzene·SbF_6^-, 54532-41-1; octafluoronaphthalene hexafluororhenate(V), 102747-22-8; rhenium hexafluoride, 10049-17-9; nitric oxide, 10102-43-9; 1,2,3,3,4,6,6-heptafluoro-5-(trifluoromethyl)-1,4-cyclohexadiene, 31665-17-5; hexadiene, 31665-17-5; CsF, 13400-13-0.

(40) Del Pra, A. *Acta Crystallogr.* **1972**, *B28*, 3438–3439.
(41) Potenza, J.; Mastropaolo, D. *Acta Crystallogr.* **1975**, *B31*, 2527–2529.

L-Aspartic Acid in Acyclic Stereoselective Synthesis. Synthetic Studies on Amphotericin B

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Abstract: The development of a potentially general approach to the synthesis of polyketide nature products is presented that features the use of L-aspartic acid as a synthetic equivalent to an asymmetric 1,3-dicarbonyl fragment. Illustrations of the manner in which the rational application of covalent, chelation, and stereoelectronic control can be used to afford products of complementary stereochemistries are given. Thiol ester **9** has been featured as a particularly valuable synthetic intermediate for the preparation of a variety of structural units found in propionate-derived compounds. This methodology has been utilized in a synthesis of the C21–C37 fragment (**35**) of amphotericin B.

The polyene macrolide class of antibiotics have attracted considerable attention for their potent fungicidal properties.[1,2] While the skeletal features of most of the compounds in this group have been determined, a complete structural description has been

(1) For reviews on the chemistry and biology of the polyene macrolide antibiotics, see: (a) Hamilton-Miller, J. M. T. *Bacteriol. Rev.* **1973**, *37*, 166. (b) Tereshin, I. M. *Polyene Antibiotics-Present and Future*; University of Tokyo: Tokyo, Japan, 1976. (c) Hammond, S. M. *Prog. Med. Chem.* **1977**, *14*, 105.

(2) For discussions on the treatment of systemic fungal infections, see: (a) Hermans, P. E.; Keys, T. F. *Mayo Clin. Proc.* **1983**, *58*, 223. (b) Medoff, G.; Brajtburg, J.; Kobayashi, G. S. *Ann. Rev. Pharmacol. Toxicol.* **1983**, *23*, 303.

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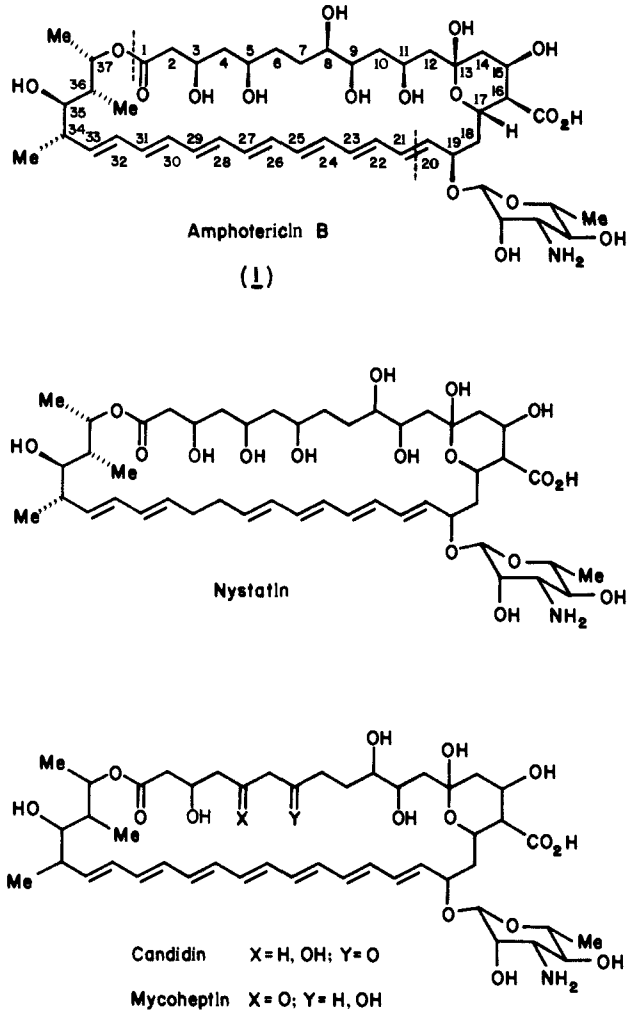


Figure 1.

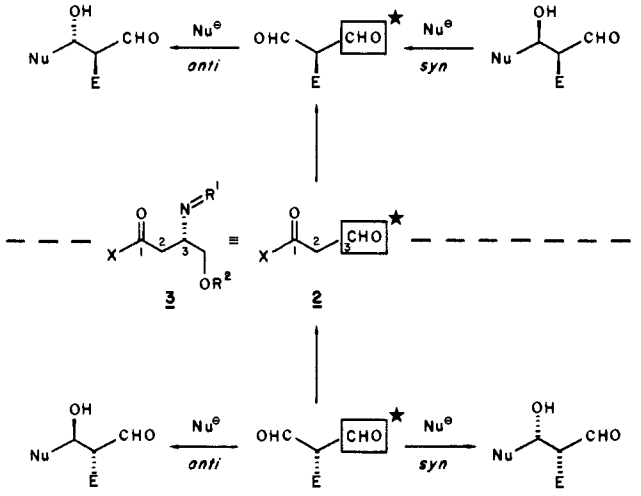


Figure 2.

solved only for amphotericin B (1) through X-ray analysis[3] (Figure 1). In order to gain structural insights to the antifungal activity of the polyene macrolide antibiotics, we have initiated efforts to develop a practical synthetic strategy to this class of compounds with an initial target of amphotericin B.[4,5]

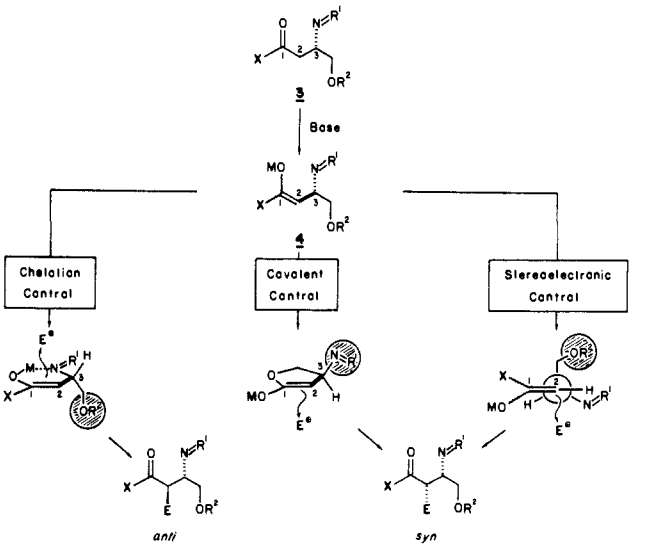


Figure 3.

The basis of our approach lies in the stereocontrolled elaboration of an asymmetric β-dicarbonyl equivalent of the general type **2** (Figure 2).[6] This key intermediate may be functionally realized through a protected amino alcohol **3**, which, in turn, is derivable from L-aspartic acid. It was anticipated that key intermediate **2** would allow synthetic entry to all possible stereoisomeric polyketide precursors through suitable asymmetric elaboration of positions C1 and C2 and by taking advantage of its inherent symmetry.

With this in mind, we analyzed the general problem of kinetic stereoselection in the manner depicted (Figure 3). As a pertinent illustration, the alkylation of asymmetric enolate **4** derived from key intermediate **3** will be considered. Under kinetically controlled conditions, the conformation of the bonds linking the resident stereocenter (C3) to the site of reactivity must be suitably biased in the transition state to render the diastereomeric faces of the π-system of unequal reactivity. This critical control over the C2–C3 bond (darkened) may be exercised by three mechanisms: internal chelation with a metal center (*chelation control*),[7] covalent bonding to form a cyclic intermediate which is subsequently cleaved to an acyclic product (*covalent control*), and selective orbital interactions between the allylic stereocenter and the adjacent π-system in the transition state (*stereoelectric control*).[8] In the present case, these processes promise to be stereocomplementary, thereby allowing alkylation favoring either the syn or anti products from a common intermediate.

We report herein on the results of our efforts to reduce to practice our synthetic strategy to the polyene macrolide antibiotics, including a demonstration of all of the three methods of stereoselection discussed. These results have been applied to the synthesis of the C21–C37 half of amphotericin B, in which the

(3) (a) Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873. (b) Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560.

(4) For preliminary studies, see: McGarvey, G. J.; Hiner, R. N.; Matsubara, Y.; Oh, T. *Tetrahedron Lett.* **1983**, 2733.

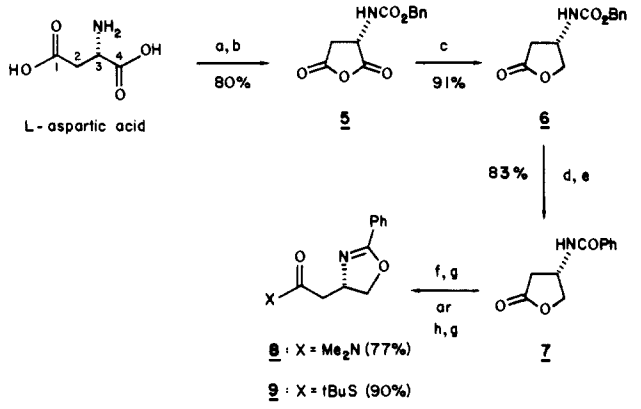
(5) For other synthetic efforts addressing the polyene macrolide antibiotics, see: (a) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, 2847. (b) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, 4991. (c) Hirama, M.; Vie, M. *Tetrahedron Lett.* **1982**, 5307. (d) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (f) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (g) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (h) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (i) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, j. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2843. (j) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (k) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183. (l) Boschell, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 5239.

(6) For an interesting alternative chiral β-dicarbonyl synthon, see: Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

(7) For a recent comprehensive review treating such asymmetric alkylations, see: Evans, D. A. *Asymmetric Synthesis*; Morrisn, J. D., Ed.; Academic: Orlando, FL, 1984; Vol. 3B, pp 1–110.

(8) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435 and references cited therein.

Scheme I[a]



[a] (a) $ClCO_2Bn$, K_2CO_3, H_2O, room temperature; (b) Ac_2O, AcOH, room temperature; (c) $NaBH_4$, THF, 0 °C; (d) HBr, AcOH, room temperature; (e) ClCOPh, pyr, CH_2Cl_2, 0 °C; (f) Me_2NH, EtOH, room temperature; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C → room temperature; (h) *t*-$BuSAlMe_2$, CH_2Cl_2, 0 °C → room temperature.

propionate-derived region (C33–C37) likely finds correspondence with other members of this class of compounds (see Figure 1).

Results and Discussion

Preparation of Key Intermediates. The initial task of converting L-aspartic acid to a key intermediate of the type **3** requires selective reduction of the α-amino carboxyl group to an alcohol in the presence of a chemically similar β-amino carboxyl functionality. After numerous unsuccessful attempts to direct the reduction of a variety of acyclic derivatives, the selective reduction of protected anhydride **5** was explored (Scheme I).[4] Treatment with $NaBH_4$ resulted in regiospecific reduction in the desired sense to afford lactone **6**. This regiocontrol parallels that which has been observed for the reduction of the analogous anhydride derived from (*S*)-malic acid[9] and provides a valuable method for adjusting the oxidation states of these similar carboxylic acids.

The desired β-amino carbonyl species **7**, **8**, and **9** were prepared by standard protecting-group interconversion at the amine followed by lactone ring opening with either Me_2NH or *t*-$BuSAlMe_2$[10] with subsequent protection of the vicinal amino alcohol through dehydration to the 2-phenyloxazoline. The enantiomeric purities of these compounds were confirmed by comparison with the corresponding racemic modifications through ^1H NMR analysis using a chiral shift reagent.[11] Of practical note, the intermediates in Scheme I are all conveniently purified by simple recrystallizations, thereby allowing the required intermediates to be readily prepared on a large scale.

Stereoselective Methylations of β-Amino Enolates[12] Derived from Compounds 7, 8, and 9. A survey of the available data addressing the alkylation of chiral enolates reveals only a handful of studies examining the diastereoselectivity of asymmetric β-heteroatom enolates.[12] Good levels of diastereofacial selection have been observed in the alkylations of enolate dianions derived from β-hydroxy esters and lactones.[13] On the other hand, enolates derived from α-sulfinyl esters show low levels of stereocontrol in such alkylation reactions, in contrast to their highly selective participation in aldol condensations.[14] In a study examining an asymmetric β-amino enolate, the dianion of di-*tert*-butyl L-*N*-formylaspartate exhibited excellent stereoselectivity but was accompanied by more than 20% alkylation at the nitrogen-bearing carbon.[15]

With the elimination of this undesirable competing alkylation in our substrates through the selective reduction of L-aspartic acid

Covalent Control

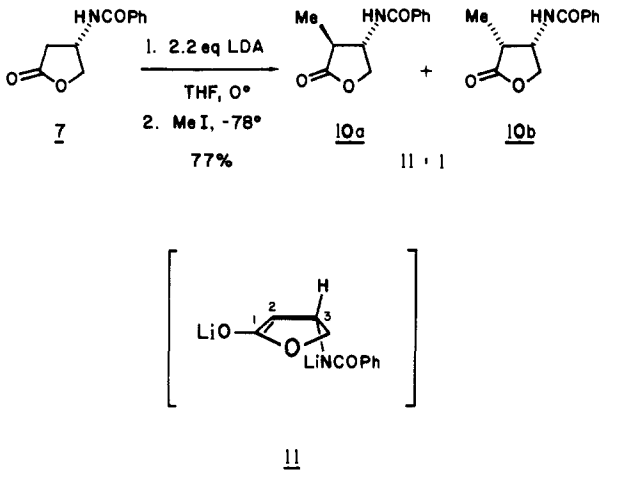
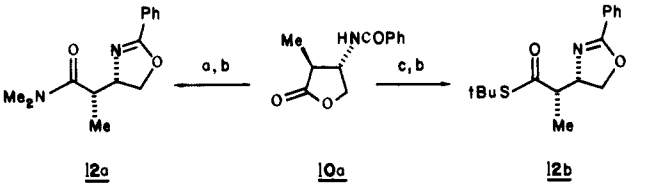


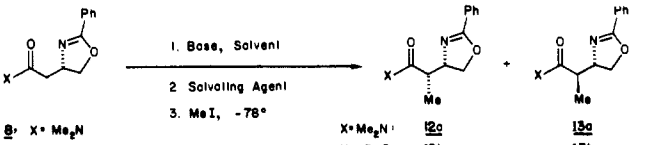
Figure 4.

Scheme II[a]



[a] (a) Me_2NH, THF, 0 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C → room temperature; (c) *t*-$BuSAlMe_2$, CH_2Cl_2, 0 °C → room temperature.

Table I. Stereoselective Methylation of Acyclic β-Amino Enolates



entry	X	base/solvent	solvating agent[a]	12:13[b]	yield[c]
1	Me_2N	$LiNEt_2$/THF		16:84	85%
2	Me_2N	$LiNEt_2$/THF	HMPA	33:67	80%
3	*t*-BuS	$LiNEt_2$/THF			NR
4	*t*-BuS	$LiNEt_2$/THF	HMPA	62:38	93%
5	*t*-BuS	$LiNEt_2$/THF	12-crown-4	62:38	54%
6	*t*-BuS	$NaN(Me_3Si)_2$/THF		5:95	92%
7	*t*-BuS	$NaN(Me_3Si)_2$/THF	HMPA	86:14	98%
8	*t*-BuS	$NaN(Me_3Si)_2$/THF	18-crown-6	82:18	78%
9	*t*-BuS	$NaN(Me_3Si)_2$/DMF		50:50	87%
10	*t*-BuS	KH/THF		24:76	86%
11	*t*-BuS	$NaN(Me_3Si)_2$/THF–HMPA		90:10	78%

[a] Added subsequent to enolate formation. [b] Determined by ^1H NMR integration and capillary GC. [c] After chromatographic purification.

(9) Barton, D. H. R.; Benechie, M.; Khoung-Huu, F.; Potier, P.; Reyma-Pinedo, V. *Tetrahedron Lett.* **1982**, 651.
(10) Hatch, R. P.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 3960.
(11) The racemate of **9** was prepared from DL-aspartic acid and subsequently compared with optically active **9** by using tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium(III) to shift the ^1H NMR spectrum. None of the enantiomeric compound could be detected in **9**.
(12) By this nomenclature, "β-" refers to the position of the substituent or center relative to the carbonyl carbon from which enolization takes place.
(13) For β-hydroxy esters, see: (a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2829. (c) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. (d) Fráter, G. *Helv. Chim. Acta* **1980**, *63*, 1383. (e) Zuger, M.; Weller, Th.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. (f) Fráter, G. *Tetrahedron Lett.* **1981**, 425. (g) Wasmuth, D.; Arigoni, D.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 344. (h) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928. (i) Bajwa, J. S.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 1114. For β-hydroxy lactones, see: Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319. (k) Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, 3055.
(14) Solladié, G. *Synthesis* **1981**, 185.
(15) Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.

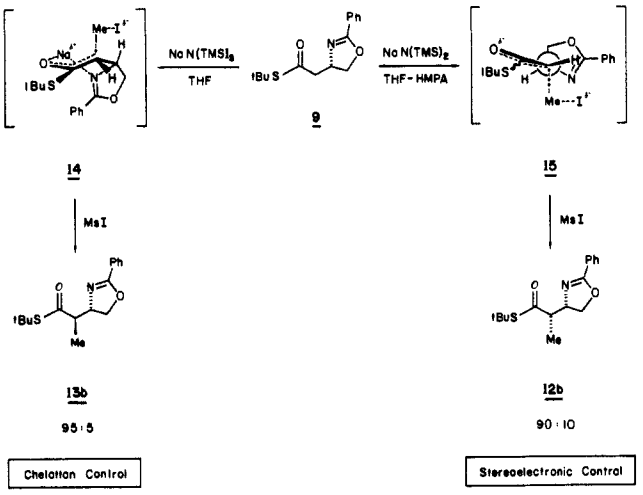


Figure 5.

described above, we set out to explore the asymmetric methylation of the enolates derived from compounds **7**, **8**, and **9**. The potential of covalent control (vide supra) was initially examined as a means of imposing diastereoselectivity upon the enolate.[4] Toward this end, lactone **7** was doubly deprotonated and then quenched with excess MeI to afford the diastereomeric alkylation products **10a** and **10b** in a ratio of 11:1, respectively (Figure 4).[16] Selection in favor of the trans isomer **10a** is consistent with alkylation from the more accessible face of dianion **11** and proceeds in levels comparable to those reported for the dianions of analogous β-hydroxy-γ-butyrolactones.[13j,k] The methylated lactone may be subjected to the ring-opening/dehydration conditions used previously (Scheme I) to cleanly provide the syn-methylated amide **12a** or thiol ester **12b** (Scheme II).

We next compared these products with those resulting from methylation of the acyclic enolates derived from compounds **8** and **9**. A summary of this study is given in Table I. While the lithium enolate of amide **8** was observed to undergo smooth methylation favoring **13a** (entry 1), the corresponding enolate of thiol ester **9** was found to be unreactive under the same conditions (entry 3). Introduction of HMPA subsequent to enolization served to reduce the selectivity of the amide methylation (entry 2) but enhanced the reactivity of the thiol ester sufficiently such that complete methylation is realized with, however, modest selection for isomer **12b** (entry 4). If the more reactive sodium enolate of **9** is generated by using $NaN(SiMe_3)_2$, clean methylation at low temperatures is observed in the absence of activating agents with a strong preference for isomer **13b** (entry 6). Use of a more polar solvent or a more ionic metal served to diminish the diastereofacial selectivity of this enolate (entries 9 and 10). However, addition of potent solvating agents to the preformed sodium enolate altered the selectivity decidedly in favor of **12b** (entries 7 and 8). This trend could be maximized by simply conducting the deprotonation in the presence of HMPA (entry 11).

Selection of the anti isomer **13**, which is optimized by entry 6, most reasonably results from chelation control enforcement of a transition state resembling **14** (Figure 5). This result finds analogy with other studies treating β-heteroatom enolates.[13-15] When the chelate is disrupted through highly ionizing conditions, diastereofacial selection becomes governed by stereoelectronic control. Transition state **15** emerges as the preferred geometry when stereoelectronic stabilization is balanced against steric effects, using the rationale we previously described.[8] Methylation antiperiplanar to the substituent interacting with the enolate π-system (CH_2OR) generates the syn isomer **12b**. Thus, by the simple expedient of controlling the ionic character of the reaction medium, conformational control may be exercised in the transition state, thereby affording access to stereocomplementary alkylation products from a common intermediate, **9**.

(16) The ratio of isomeric products was determined by capillary GC and ^1H NMR integration.

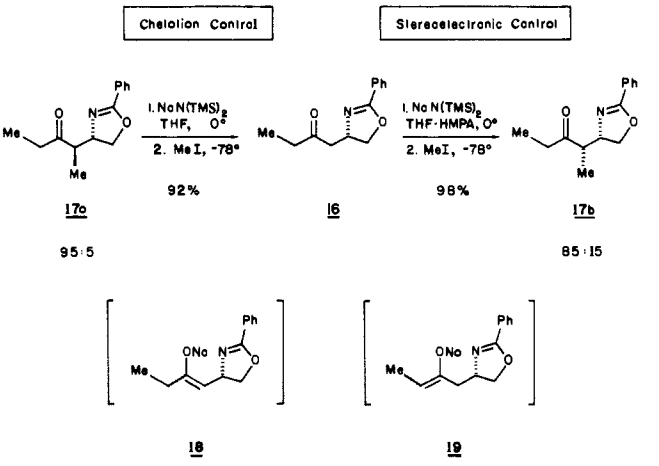


Figure 6.

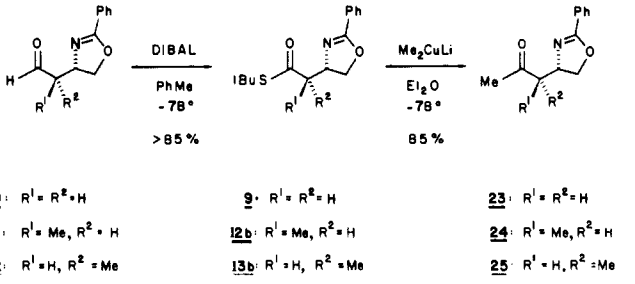


Figure 7.

That similar stereoelectronically controlled syn alkylation could not be achieved with amide **8** was attributed to the relative instability of its enolate compared with that of the thiol ester, favoring stabilization through chelation. This contention was supported by methylation reactions carried out on ethyl ketone **16** (vide infra). By application of the same conditions used for the thiol ester **9**, identical trends in diastereoselection were observed, presumably as a result of the intervention of the same stereocontrolling features noted before (Figure 6). It is noteworthy that these alkylations are indicative of regiospecific enolization toward the nitrogen-bearing carbon (**18**) rather than via kinetic deprotonation at the more accessible position (**19**). A preliminary survey of a variety of deportonating conditions using lithium amide bases indicates that this regioselection is general and was significantly perturbed only through the use of lithium 2,2,4,4-tetramethylpiperidide (50:50 mixture of enolates corresponding to **18**:**19**).[17] The structural effects governing the kinetic and thermodynamic acidities in this example are presently unclear and await further investigation.

Stereoselective Elaboration of Compounds 9, 12b, and 13b. Having accomplished the first phase of our general synthetic strategy (see Figure 2), selective elaboration of the thiol ester functionality was examined. Clean reduction of compounds **9**, **12b**, and **13b** to the corresponding aldehydes could be realized through treatment with diisobutylaluminum hydride (DIBAL) at low temperature in toluene (Figure 7). No epimerization of the adjacent stereocenter accompanied this transformation. These thiol esters could also be conveniently converted to methyl ketones **23**–**25** by using Me_2CuLi,[18] again in high yield without detectable epimerization. The utility of this ketone synthesis is expanded by the observation that Grignard reagents are efficiently acylated by these thiol esters in the presence of Cu(I) salts.[18] For example, ethyl ketone **16** was prepared from thiol ester **9** in 90% yield through treatment with excess $C_2H_5MgBr/CuBr\cdot DMS$ in THF at −23 °C. With routine access available to a variety of aldehydes

(17) This is based on ^1H NMR analysis of the enolates after trapping with Me_3SiCl or t-$BuMe_2SiCl$.

(18) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654.

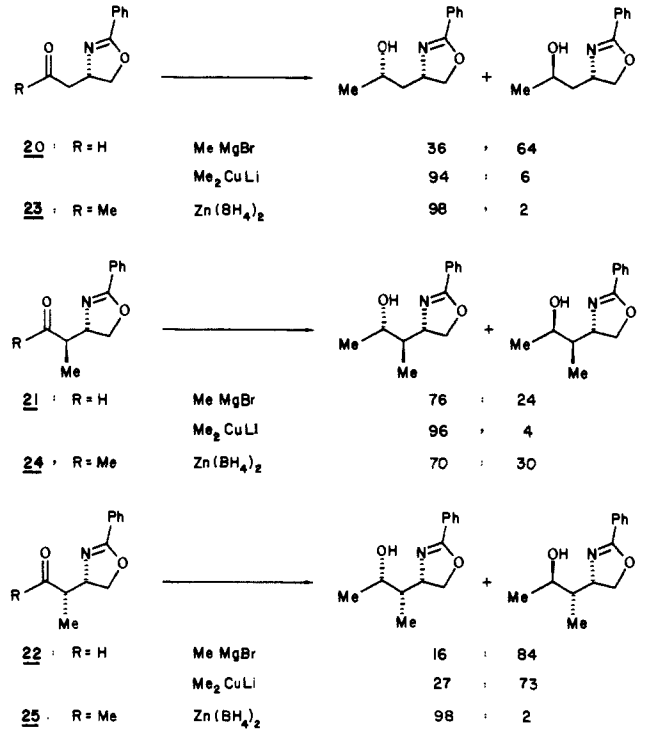


Figure 8.

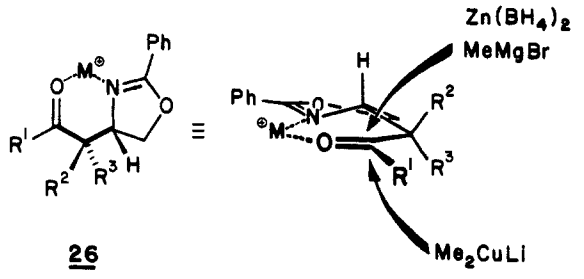


Figure 9.

and ketones, a systematic study of the stereoselective elaboration of these carbonyl species was undertaken.

We chose to compare the methylation of aldehydes **20–22** with the reduction of ketones **23–25** under reaction conditions expected to promote chelation control. The results of this survey are given in Figure 8. Several general features of these asymmetric transformations warrant discussion. The reactions of compounds **20** and **23** display relatively high levels of 1,3-asymmetric induction in comparison with simple β-alkoxy and β-amino carbonyl compounds.[19] This we attribute to the lack of conformational flexibility in chelate **26**, which unambiguously fixes the relationship between the asymmetric center and the prochiral center under nucleophilic attack (Figure 9). This rigid array favors attack by relatively small reagents [$Zn(BH_4)_2$ and MeMgBr] in an axial sense, while the bulkier cuprate reagent avoids a destabilizing 1,3-interaction with the axial hydrogen at C3 and approaches from the opposite face.[20]

In the reactions of compounds **21**, **22**, **24**, and **25**, this C3 directing effect is superimposed upon the stronger 1,2-directing effects of the C2 substituent.[21] Consequently, the reactions of MeMgBr and $Zn(BH_4)_2$ with **21** and **24**, respectively, show modest selectivities as a result of the conflicting effects of the neighboring stereocenters. Stereoselection increases for the corresponding reactions on compounds **22** and **25** since 1,2- and 1,3-induction now reinforce each other. An analogous pattern is observed for the reaction of Me_2CuLi upon the opposite diastereoface of aldehydes **21** and **22**.

From the results of these studies, it is apparent that most of the stereorelations in Figure 2 are available through suitable matching of substrates and reagents. For those stereochemistries not directly available, advantage may be taken of the inherent symmetry of chiral intermediate **9**. The utility of this strategy for asymmetric acyclic synthesis is further enhanced by the ease with which the minor isomer may be removed through simple chromatographic purification, allowing one to proceed with diastereomerically pure materials.

Synthesis of the C21–C37 Half of Amphotericin B. With these background studies in hand, we sought to exploit key intermediate **9** in a chiral synthesis of the C33–C37 propionate fragment of amphotericin B.[22] The polyene macrolide **1** readily lends itself to retrosynthetic simplification to two approximately equal halves by the disconnections indicated by the dotted lines in Figure 1. The polyene fragment **27**, in turn, may be reasonably assembled through fusion of the propionate and olefinic segments at the C32–C33 bond (dotted line in **27**, Figure 10). This plan requires the asymmetric preparation of the C33–C37 aldehyde with differentiation of the C35 and C37 alcohols to accommodate later stages of the synthesis. Of the several approaches one can envision germinating from thiol ester **9**, the strategy we chose to implement is summarized in Figure 10.

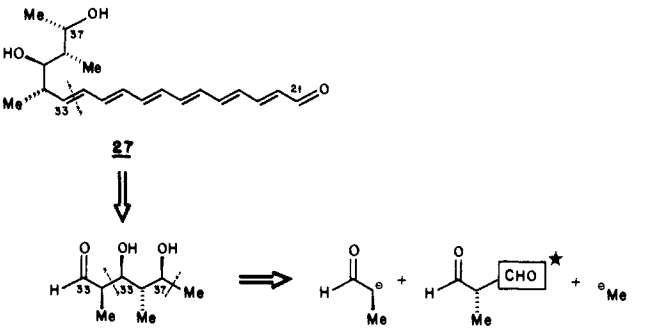
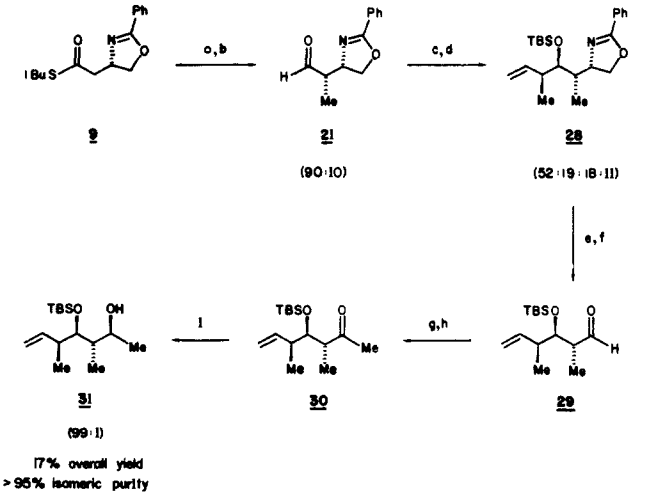


Figure 10.

Scheme III[a]



[a] (a) $NaN(Me_3Si)_2$, THF-HMPA, 0 °C; MeI, −78 °C; (b) DIBAL, PhMe, −78 °C; (c) $Li[Me_6AlCH_2CH{=}CHCH_3]$, Et_2O, −78 °C; (d) *t*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2; (e) DIBAL, PhMe, 0 °C; (f) $NaIO_4$, Et_2O/H_2O; (g) MeMgBr, THF, −78 °C; (h) PCC, CH_2Cl_2, room temperature; (i) L-Selectride, THF, −100 °C.

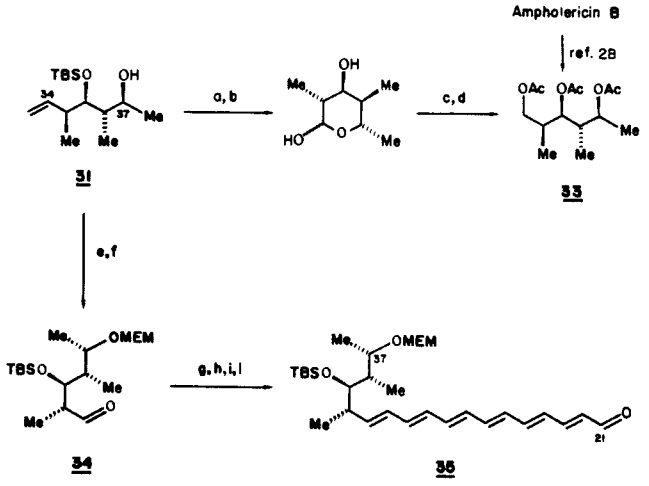
(19) For some pertinent examples, see: (a) Fougvey, C.; Jacques, J.; Angiolini, L.; Tramontini, M. *Tetrahedron* **1974**, *30*, 2801. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, 1035. (c) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (d) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

(20) This explanation neglects the potential influence of ligands associated with the chelating metal which, of course, may have relevance.

(21) For recent examples of 1,2-stereodirection overcoming 1,3-effects, see: (a) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. *Tetrahedron* **1984**, *40*, 2225. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 566. See also ref 23a.

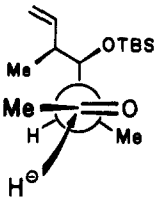
(22) For previous syntheses of this fragment, see ref 5b and 5l.

Scheme IV[a]



[a] (a) HCl, MeOH, room temperature; (b) O_3, MeOH, −78 °C; PtO_2, H_2; (c) $LiAlH_4$, THF, −78 °C → room temperature; (d) Ac_2O, pyr, room temperature; (e) MEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, room temperature; (f) O_3, MeOH, −78 °C, DMS, room temperature; (g), LiCH=CHCH=CHOEt, THF, −78 → 0 °C; (h) MsCl, Et_3N, CH_2Cl_2, −43 °C; (i) repeat step (g), then TsOH (catalyst) H_2O/THF, 0 °C.

Aldehyde **21** was prepared by the methods previously discussed (Scheme III). The C33–C34 carbons were to be appended through a syn-selective aldol-type process. When initial attempts using enolate anions of a variety of propionate species gave discouraging selection for the desired isomer, the application of allylic organometallics was explored. It was found that the required product (**28**) could be realized through condensation with a crotylaluminate species derived from crotyllithium.[23] This method proved to be a practical solution to this problem despite its modest stereoselectivity (52% of the desired isomer) since the requisite material (**28**) could be easily obtained in isomerically pure form through simple flash chromatography (silica gel) of the protected product mixture in a respectable 30% overall yield from thiol ester **9**. The next step required libration of the aldehyde presently residing in protected form as an oxazoline. The heterocycle was cleanly reduced to a benzylamino alcohol through treatment with DIBAL at 0 °C[24] and then directly cleaved to aldehyde **29** with $NaIO_4$. Methylation of this aldehyde under a variety of conditions failed to afford the necessary isomer (**31**) in satisfactory levels of selectivity. This problem was circumvented by reducing the corresponding methyl ketone (**30**, 61% overall yield from **28**) with L-Selectride at low temperature to result in a single stereoisomer in almost quantitative yield. This stereoselectivity may be best rationalized through *stereoelectronic control* via a Felkin–Ahn transition state resembling **32**.[25]



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The stereochemically pure monoprotected diol **31** was converted by routine methods to triacetate **33**, which was found to be identical with material derived by degradation of amphotericin B[28] (Scheme IV). Assured of the stereochemical identity of our synthetic material, we moved to complete the synthesis of the C21–C37 half of the polyene macrolide. Protection of the free alcohol as a MEM ether was followed by exposure of the C34 aldehyde through ozonolytic cleavage (**34**, 95% overall yield). When several approaches employing Wittig-type methodology proved inefficient, alternative methods of olefination were explored.[26] An acceptable solution was realized through an iterative application of the Wollenberg reagent for the preparation of dienals.[27] By use of this methodology, hexaenylaldehyde **35** was obtained in good overall yield (48% from **34**) as a single stereoisomer, as judged by chromatographic, ^1H NMR, and ^{13}C NMR analyses. The all trans geometry was inferred from coupling constant data in the vinylic region of the ^{1} NMR spectrum. These absorbances were completely resolved in the dienyl and tetraenyl precursors and possessed J values in the range 9–16 Hz. Those resonances that were resolvable in the hexaenyl product **35** were also indicative of the trans geometry (10–15.5 Hz). With this route to compound **35** in hand, we now have access to sufficient quantities of synthetic material to complete our studies toward the total synthesis of amphotericin B.

Summary and Conclusions

L-Aspartic acid has been converted to a chiral thiol ester (**9**) which has been demonstrated to serve as a versatile intermediate for asymmetric synthesis. Complementary kinetic stereoselection was realized by exercising covalent, chelation, and stereoelectronic control over the formation of critical bonds in the transition state, leading to diastereofacial discrimination of prochiral carbons. In the application of chelation control, amplified stereoselection has been achieved through suppression of conformational mobility in the intervening chelate by incorporating a rigid, bicyclic array in the complex. Finally, the utility of our asymmetric 1,3-dicarbonyl equivalent has been demonstrated in a synthesis of the C21–C37 half of amphotericin B. Further exploitation of thiol ester **9** in asymmetric synthesis, as well as the development of new stereoselective transformations based upon the stereocontrolling features uncovered in this investigation, is now in progress.

Experimental Section

3(*S*)-[(Carbobenzyloxy)amino]-γ-butyrolactone (6). *N*-(Carbobenzyloxy)-L-aspartic anhydride (**5**) was prepared from *N*-(carbobenzyloxy)-L-aspartic acid[29] by the method of Lutz and co-workers[30] in 80% overall yield from L-aspartic acid. To a stirred slurry of 19.20 g (0.50 mol) of sodium borohydride in THF (700 mL) at 0 °C was added 125 g (0.50 mol) of anhydride **5** in THF (800 mL) over a period of 3 h. After stirring at room temperature for 1 h, the reaction mixture was carefully acidified to pH 2 with 6 N HCl and then concentrated to approximately one-fourth the volume under reduced pressure (water aspirator). The result was diluted with water and extracted with four portions of ether, and then the combined organic extracts were concentrated under reduced pressure to a heterogeneous residue. The yellow residue was taken up in benzene (500 mL) containing *p*-TsOH (500 mg), and then water was azeotropically removed by using a Dean-Stark apparatus. After the mixture refluxed for 5 h, the benzene was removed by distillation at atmospheric pressure to afford a viscous orange residue which gave white crystals upon trituration with ether. The white solids were collected by filtration (77.5 g), and the filtrate was concentrated under reduced pressured and triturated with ether to afford a second crop of white crystals (29.6 g, 91% combined): R_f 0.67 (silica gel, ethyl acetate); mp 103–104 °C; $[\alpha]^{20}_D$ −54.9° (*c* 2.27, $CHCl_3$); IR ($CHCl_3$) 3430, 1783, 1720, 1505 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.42 (d of d, 1 H, J = 18.0, 4.2 Hz, C(O)CH-*H*), 2.80 (d of d, 1 H, J = 18.0, 7.2 Hz, C(O)CH-*H*), 4.35 (br m, 3 H, CHN and OCH_2), 5.06 (s, 2 H, $PhCH_2$), 5.30 (br m, 1 H, NH), 7.30 (s, 5 H, C_6H_5). Anal. Calcd for

(23) The reagent derived from crotylmagnesium bromide resulted in inferior selectivity. For reviews on crotylmetal reagents including the species used in this study, see: (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(24) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053.

(25) (a) Cherēst, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(26) For a summary of these olefination studies, see: Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1985**, 4981.

(27) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717.

(28) Cope, A. C.; Axen, U.; Burrows, E. P.; Weinlich, J. *J. Am. Chem. Soc.* **1966**, *88*, 4228.

(29) Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.

(30) Lutz, W. B.; Ressler, C.; Nettleton, D. E., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 167.

$C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.31; H, 5.62; N, 5.91.

3(*S*)-Amino-γ-butyrolactone Hydrobromide. Through a stirred solution of 24.05 g (102 mmol) of lactone **6** in glacial acetic acid (185 mL) at room temperature was bubbled 5 equiv of anhydrous HBr. The milky suspension was treated with 20 mL of ether, stirred an additional 2 h, then cooled to −5 °C, and filtered. The slightly off-white solids retrieved were sequentially washed with ether and anhydrous acetone to afford 15.72 g of product. The filtrate was concentrated under reduced pressure and similarly cooled, filtered, and washed to yield a second crop (750 mg) of product (88% combined): mp 198–201 °C; $[\alpha]^{20}_D$ −42.6° (*c* 1.08, H_2O); ^1H NMR (Me_2SO-d_6, 90 MHz) δ 2.50 (d of d, 1 H, *J* = 17.5, 3.0 Hz, C(O)CH-*H*), 3.00 (d of d, 1 H, = 17.5, 8.4 Hz, C(O)CH-*H*), 4.25 (d of d, 1 H, J = 2.5 Hz, OCH-*H*), 4.49 (d of d, 1 H, *J* = 11.4, 6.0 Hz, OCH-*H*), 8.30 (br s, 3 H, NH_3). Anal. Calcd for $C_4H_8BrNO_2$: C, 26.40; H, 4.43; N, 7.70. Found: C, 26.49; H, 4.45; N, 7.65.

3(*S*)-(Benzoylamino)-γ-butyrolactone (7). To a stirred suspension of 9.01 g (49.5 mmol) of the amino-γ-butyrolactone hydrobromide in CH_2Cl_2 (100 mL) at 0 °C was added 7.20 mL (62 mmol) of benzoyl chloride and 14.0 mL (173 mmol) of pyridine. Within 1 h, the mixture became homogeneous and bright yellow, at which point it was stoppered and stored in a refrigerator (−2 °C) for 48 h. The cold, orange solution was then carefully poured into 100 mL of 0.5 N HCl and thoroughly agitated, the layers were separated, and the aqueous phase was extracted twice with fresh CH_2Cl_2. The combined organic extracts were washed once with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting orange solids were collected and washed twice with ether to afford 9.51 g (94%) of slightly colored product: R_f 0.65 (silica gel, ethyl acetate); mp 123.5–126 °C; $[\alpha]^{20}_D$ −97.0° (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 3430, 1776, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.25 (d of d, 1 H, *J* = 18.0, 3.0 Hz, C(O)-CH-*H*), 2.93 (d of d, 1 H, *J* = 18.0, 7.2 Hz, C(O)CH-*H*), 4.30 (d of d, 1 H, *J* = 9.6, 2.9 Hz, OCH-*H*), 4.55 (d of d, 1 H, *J* = 9.6, 6.0 Hz, OCH-*H*), 4.90 (m, 1 H, CHN), 7.40 (m, 4 H, meta and para C_6H_5, NH), 7.76 (m, 2 H, ortho C_6H_5). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.70; H, 5.43; N, 6.81.

2-Phenyl-4(*S*)-[2-(*N*,*N*-dimethylamino)-2-oxoethyl]-2-oxazoline (8). To a stirred suspension of 152 mg (0.75 mmol) of lactone **7** in ethanol (4 mL) at 0 °C was added 1.0 mL (15 mmol) of anhydrous dimethylamine. The reaction vessel was sealed and stirred for 6.5 h at 0 °C, at which time the reaction mixture was conentrated to a yellow oil under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL), cooled to 0 °C, and then treated with 0.37 mL (2.7 mmol) of triethylamine and 0.10 mL (1.3 mmol) of methanesulfonyl chloride. After 30 min at 0 °C, the mixture was stirred at room temperature for 12 h and then poured into 5 mL of saturated aqueous $NaHCO_3$. Following separation, the aqueous layer was saturated with NaCl and extracted 3 times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated to a yellow oil which was purified by radial chromatography (silica gel, 12.5% methanol/hexanes) to afford 165 mg (95%) of product as a white solid: R_f 0.39 (silica gel, 28% acetone in ethyl acetate); mp 86.5–89 °C; $[\alpha]^{20}_D$ +47.0° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.24 (d of d, 1 H, *J* = 9.6, 16.5 Hz, C(O)-CH-*H*), 2.93 (s, 3 H, CH_3N), 2.98 (s, 3 H, CH_3N), 3.14 (d of d, 1 H, *J* = 3.6, 16.5 Hz, C(O)CH-*H*), 4.10 (m, 1 H, CHN), 4.70 (m, 2 H, OCH_2), 7.40 (m, 3 H, meta and para C_6H_5), 7.92 (m, 2 H, ortho C_6H_5). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.10; H, 6.96; N, 12.04.

2-Phenyl-4(*S*)-[2-((2-methyl-2-propyl)thio)-2-oxoethyl]-2-oxazoline (9). To a stirred solution of 37.6 mL (75.2 mmol) of a 2.0 M solution of trimethylaluminum in toluene in CH_2Cl_2 (20 mL) at 0 °C was added 8.7 mL (76 mmol) of 2-methyl-2-propanethiol. After the mixture stirred 5 min at 0 °C and then 10 min at room temperature, 5.14 g (25.03 mmol) of lactone **7** in CH_2Cl_2 (65 mL) was introduced. This mixture was stirred 12 h at room temperature, cooled to −78 °C, sequentially treated with 100 mL of ether and 150 mL of 1 N HCl, and then stirred vigorously as the mixture gradually warmed to room temperature. Following separation of the layers, the aqueous phase was extracted with four portions of ether, and then the combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to a brown oil. The oil was dissolved in CH_2Cl_2 (130 mL) at 0 °C and then treated with 10.9 mL (78.2 mmol) of triethylamine and 3.00 mL (37.9 mmol) of methanesulfonyl chloride. After stirring 2 h at 0 °C and 12 h at room temperature, the reaction mixture was poured into 100 mL of 0.5 N HCl. Following separation, the aqueous phase was washed 3 times with CH_2Cl_2, and then the organic phases were combined, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). The result was concentrated under reduced pressure to yield a brown oil which was purified by flash chromatography (silica gel, 9% ethyl acetate in hexanes) to afford 6.28 g (90%) of pure product as a slightly yellow crystalline solid: R_f 0.59 (silica gel, 35% ethyl acetate in cyclohexane); mp 41.9–43.5 °C; $[\alpha]^{20}_D$ +32.7° (*c* 2.17, $CHCl_3$); IR (CCl_4) 2940, 1677, 1645, 1244, 860 cm^{-1}; ^1H NMR (CCl_4, 360 MHz) δ 1.43 (s, 9 H, *t*-C_4H_9S), 2.50 (d of d, 1 H, *J* = 9.0, 15.0 Hz, C(O)CH-*H*), 3.08 (d of d, 1 H, *J* = 3.9, 15.0 Hz, C(O)CH-*H*), 4.03 (m, 1 H, CHN), 4.48 (m, 2 H, OCH_2), 7.33 (m, 3 H, meta and para C_6H_5), 7.88 (m, 2 H, ortho C_6H_5). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 64.95; H, 6.91; N, 5.01; S, 11.56.

2(*S*)-Methyl-3(*S*)-(benzoylamino)-γ-butyrolactone (10a)/2(*R*)-Methyl-3(*S*)-(benzoylamino)-γ-butyrolactone (10b). To a stirred solution of 3.0 mmol of LDA in THF (3 mL) at −78 °C was added 150 mg (0.73 mmol) of lactone **7** in THF (2.5 mL). After 1 h, the reaction mixture was transferred via cannula to a chilled (−78 °C) solution of 1.3 mL (21 mmol) of methyl iodide in THF (16 mL) and maintained at −78 °C for an additional 2 h. The reaction was quenched with 0.16 mL (2.8 mmol) of acetic acid in THF (4.0 mL), and the mixture was allowed to warm to room temperature before 20 mL of saturated aqueous $NaHCO_3$ was added. Following separation of the layers, the aqueous phase was extracted 3 times with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. This solution was filtered through a short plug of silica gel and then concentrated under reduced pressure to afford 126 mg (77%) of products as a white solid [R_f 0.77, 0.67 (silica gel, ethyl acetate)]. The ratio of **10a**:**10b** was determined to be 11:1 by comparison of the integrated values for the methyl resonances for the isomers in the ^1H NMR spectrum (**10a**, δ 1.42; **10b**, δ 1.28). Purified **10a** was obtained through selective precipitation by treating an ethyl acetate solution of the mixture with petroleum ether: R_f 0.77 (silica gel, ethyl acetate).[31]

2-Phenyl-4(*S*)-[3-(*N*,*N*-dimethylamino)-3-oxo-2(*S*)-propyl]-2-oxazoline (12a)/2-Phenyl-4(*S*)-[3-(*N*,*N*-dimethylamino)-3-oxo-2(*R*)-propyl]-2-oxazoline (13a). Table I. Entry 1. To a stirred solution of 0.15 mL (1.4 mmol) of diethylamine in THF (0.5 mL) at 0 °C was added 0.69 mL (1.3 mmol) of a 1.95 M solution of *n*-butyllithium in hexane. After stirring 15 min at 0 °C, the mixture was cooled to −78 °C, a solution of 114 mg (0.49 mmol) of amide **8** in THF (1.5 mL) was introduced, and the mixture was stirred an additional 10 min at −78 °C. In a dropwise fashion, 0.11 mL (1.7 mmol) of methyl iodide was added and the result kept at −78 °C for 1 h, after which 0.5 mL of methanol and 3 mL of saturated aqueous NH_4Cl were sequentially introduced. After warming to room temperature, the mixture was diluted with ethyl acetate (10 mL), from which the aqueous phase was separated and extracted with three portions of ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford yellow solids which were purified by radial chromatography (silica gel, ethyl acetate) to give, in order of elution, 6 mg (5%) of unchanged starting material, 17 mg (14%) of isomer **12a**, and 86 mg (71%) of isomer **13a**. Isomer **13a** was obtained as a white solid, R_f 0.19 (silica gel, ethyl acetate),[31] while isomer **12a** was isolated as a colorless oil, R_f 0.36 (silica gel, ethyl acetate).[31]

2-Phenyl-4(*S*)-[3-((2-methyl-2-propyl)thio)-3-oxo-2(*S*)-propyl]-2-oxazoline (13b). Table I. Entry 6. To a stirred solution of 1.40 g (7.56 mmol) of sodium hexamethyldisilazide in THF (20 mL) at 0 °C was added 1.00 g (3.60 mmol) of thiol ester **9** in THF (10 mL) in a dropwise fashion. After 15 min, the solution was cooled to −78 °C and 1.15 mL (18.5 mmol) of methyl iodide was added. The reaction mixture was stirred 3 h at −78 °C, then quenched with 20 mL of saturated aqueous NH_4Cl, and allowed to warm to room temperature. The mixture was partitioned between water and ether, the layers were separated, and the aqueous layer was extracted twice with ether. The combined organic phases were washed sequentially with saturated aqueous sodium sulfite and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to afford 968 mg (92%) of product as a colorless oil which solidified upon standing. The product was found to be a greater than 95% pure 95:5 mixture of diastereomers **13b**:**12b** by gas chromatographic and ^1H NMR analyses (retention times: major 29.95, minor 28.04 at 160 °C): R_f 0.38 (major isomer, silica gel, 20% ether in hexanes).[31]

2-Phenyl-4(*S*)-[3-((2-methyl-2-propyl)thio)-3-oxo-2(*R*)-propyl]-2-oxazoline (12b). Table I. Entry 11. To a stirred solution of 1.36 g (7.40 mmol) of sodium hexamethyldisilazide in THF (10 mL) and 5.20 mL (29.6 mmol) of hexamethylphosphoric triamide at 0 °C was added 1.02 g (3.70 mmol) of thiol ester **9** in THF (10 mL) in a dropwise manner. After 15 min, the solution was cooled to −78 °C and 1.15 mL (18.5 mmol) of methyl iodide was added. The reaction was stirred 3 h at −78 °C, then quenched with 20 mL of saturated aqueous NH_4Cl, and allowed to warm to room temperature. The mixture was partitioned between water and ether, the layers were separated, and the aqueous layer was extracted 3 times with ether. The combined organic phases were washed

(31) The spectral and analytical data for this compound are given in the supplementary material.

sequentially with saturated aqueous sodium sulfite and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow oil. This residue was purified by flash chromatography (silica gel, 20% ether in hexanes) to result in 850 mg (79%) of product as a slightly yellow oil which was found to be a 90:10 mixture of diastereomers **12b**:**13b** by ^1H NMR and gas chromatographic analyses (retention times: major 29.95, minor 28.04 at 160 °C): R_f 0.39 (major isomer, silica gel, 20% ether in hexanes).[31]

2-Phenyl-4(*S*)-(2-oxobutyl)-2-oxazoline (16). To a mixture of 2.13 g (10.4 mmol) of CuBr·DMS in THF (40 mL) at −78 °C was added 13.3 mL (10 mmol) of a 0.75 M solution of ethylmagnesium bromide in ether. After the mixture stirred 10 min at −78 °C, a solution of 1.07 g (3.85 mmol) of thiol ester **9** in THF (10 mL) was added in dropwise fashion. The reaction mixture was stored at −23 °C for 4 h, quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and then partitioned with 100 mL of ether. Following separation, the organic phase was washed with portions of a 1:1 mixture of saturated aqueous NH_4Cl/concentrated aqueous NH_4OH until no blue coloration of the aqueous phase could be detected. The organic layer was washed once with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow oil. Evaporative distillation (160–180 °C, 0.75 mmHg) gave 754 mg (90%) of product as a waxy white solid: R_f 0.20 (silica gel, 50% ether in hexanes).[31]

2-Phenyl-4(*S*)-(3-oxo-2(*R*)-pentyl)-2-oxazoline (17a). To a stirred solution of 71 mg (0.39 mmol) of sodium hexamethyldisilazide in THF (1.0 mL) at 0 °C was added a solution of 40 mg (0.18 mmol) of ethyl ketone **16** in THF (1.0 mL). After 15 min, the result was chilled to −78 °C and 0.10 mL (1.6 mmol) of methyl iodide was introduced and the solution maintained at −78 °C for 30 h at which time saturated aqueous NH_4Cl was introduced and the mixture allowed to warm to room temperature. The solution was partitioned between water and ether, the aqueous layer was extracted with two portions of fresh ether, and the combined organic phases were washed successively with saturated aqueous sodium sulfite and saturated aqueous NaCl. After drying ($MgSO_4$), the solution was concentrated under reduced pressure to afford the crude product as a 95:5 mixture of diastereomers **17a**:**17b** contaminated with 8% of the starting ketone **16**, as judged by ^1H NMR and gas chromatographic analysis (retention times: major 30.0, minor 28.0 min; SE-30, 10 m × $^1/_8$ in., 160 °C). Flash chromatography (silica gel, 50% ether in hexanes) afforded 32 mg (85%) of pure product **17a** as a colorless oil: R_f = 0.29 (silica gel, 50% ether in hexanes).[31]

2-Phenyl-4(*S*)-(3-oxo-2(*S*)-pentyl)-2-oxazoline (17b). In a manner completely analogous to the procedure affording diastereomer **17a**, 37 mg (0.17 mmol) of ethyl ketone **16** was deprotonated in the presence of 0.23 mL (1.43 mmol) of hexamethylphosphoric triamide and the resulting enolate alkylated with methyl iodide. Following workup, the crude product (100% yield) was found to be a 15:85 mixture of diastereomers **17a**:**17b** in at least 98% purity, as judged by ^{1} NMR and gas chromatographic analyses (retention times: major 28.0, minor 30.0; SE-30, 10 m × $^1/_8$ in., 160 °C). Flash chromatography (silica gel, 50% ether in hexanes) afforded 30 mg (83%) of pure product **17b** as a colorless oil: R_f 0.38 (silica gel, 50% ether in hexanes).[31]

General Procedure for the Reduction of Thiol Esters 8, 12b, and 13b to Aldehydes 20, 21, and 22. To a 0.1 M solution of the thiol ester in toluene at −78 °C was added 3.5 equiv of DIBAL (1.0 M in toluene) and the result maintained at −78 °C for 5 h. At this time, 10.5 equiv of acetic acid as a 1.0 M solution in anhydrous ether was carefully introduced, and the mixture was allowed to warm to room temperature and was then partitioned between ether and water. The separated aqueous phase was acidified to pH 4 (congo red indicator) with 1.0 N aqueous HCl and extracted twice with fresh ether. The combined layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford the product as an oil (>85% yield) in greater than 95% purity as judged by ^1H NMR spectroscopy. **2-Phenyl-4(*S*)-(2-oxoethyl)-2-oxazoline (20)**: R_f 0.28 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3-oxo-2(*R*)-propyl)-2-oxazoline (21)**: R_f 0.28 (silica gel, 50% ether in hexanes).[31] **2-Phenyl-4(*S*)-(3-oxo-2-(*S*)-propyl)-2-oxazoline (22)**: R_f 0.30 (silica gel, 50% ether in hexanes).[31]

General Procedure for the Conversion of Thiol Esters 8, 12b, and 13b to Methyl Ketones 23, 24, and 25. A 0.25 M solution of lithium dimethylcuprate in ether was prepared at 0 °C by treating a slurry of 3 equiv of CuBr·DMS in ether with 6 equiv of methyllithium (0.85 M in ether). The mixture was chilled to −78 °C, and a 0.2 M solution of the thiol ester (1 equiv) in ether was added dropwise and kept at −78 °C for an additional 2 h, at which time excess saturated aqueous NH_4Cl was introduced and the result allowed to warm to room temperature. The mixture was diluted to about twice its volume with ether and sequentially extracted with portions of a 1:1 mixture of saturated aqueous NH_4Cl/concentrated aqueous NH_4OH until the absence of blue color in the aqueous phase. The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow residue which was purified by flash chromatography (silica gel, 33% ether in dichloromethane) to afford the product as a colorless oil (85% yields). **2-Phenyl-4(*S*)-(2-oxopropyl)-2-xazoline (23)**: R_f 0.40 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3-oxo-2-(*R*)-butyl)-2-oxazoline (24)**: R_f 0.50 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3-oxo-2(*S*)-butyl)-2-oxazoline (25)**: R_f 0.58 (silica gel, 33% ether in dichloromethane).[31]

General Procedure for Methylating Compounds 20, 21, and 22 with Lithium Dimethylcuprate. A 0.30 M solution of lithium dimethylcuprate in ether was prepared at 0 °C by treating a slurry of 4 equiv of CuBr·DMS in ether with 8 equiv of methyllithium (0.85 M in ether). After the mixture cooled to −78 °C, a 0.25 M solution of the aldehyde (1 equiv) in ether was added dropwise, and the result was maintained at −78 °C for 3 h and then allowed to warm to 0 °C before being quenched with an excess of a 1:1 mixture of saturated aqueous NH_4Cl/concentrated aqueous NH_4OH. After any remaining solids were dissolved with additional concentrated aqueous NH_4OH, the mixture was extracted with three portions of ether, and then the combined ether extracts were washed sequentially with concentrated aqueous NH_4OH and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to afford the product as a colorless oil in yields in excess of 85%. The product was analyzed by ^1H NMR spectroscopy and gas chromatography to assay its diastereomeric composition and then separated into its pure components by radial chromatography (silica gel, 33% hexane in ether), as greater than 98% of the mass of the crude oil obtained directly from the reaction. **2-Phenyl-4(*S*)-(2(*S*)-hydroxypropyl)-2-oxazoline**: R_f 0.30 (silica gel, 53% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(2(*R*)-hydroxypropyl)-2-oxazoline**: R_f 0.20 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3(*S*)-hydroxy-2(*R*)-butyl)-2-oxazoline**: R_f 0.37 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3(*R*)-hydroxy-2(*R*)-butyl)-2-oxazoline**: R_f 0.22 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3(*S*)-hydroxy-2(*S*)-butyl)-2-oxazoline**: R_f 0.40 (silica gel, 33% ether in dichloromethane).[31] **2-Phenyl-4(*S*)-(3-(*R*)-hydroxy-2(*S*)-butyl)-2-oxazoline**: R_f 0.30 (silica gel, 33% ether in dichloromethane).[31]

General Procedure for Methylating Compounds 20, 21, and 22 with Methylmagnesium Bromide. To a 0.50 M solution of methylmagnesium bromide (4 equiv) in ether at −78 °C was added a 0.25 M solution of the aldehyde (1 equiv) in ether. After 3 h at −78 °C, the reaction was quenched by addition of excess saturated $NaHCO_3$, and the mixture was allowed to warm to 0 °C and then partitioned between ether and water. The aqueous layer was separated and extracted with three portions of fresh ether, and then the combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting oil was passed through a short column of silica gel (33% ether in dichloromethane) to afford the colorless products which were examined by ^1H NMR spectroscopy and gas chromatography to determine the ratio of diastereomers. These isomers were resolved by radial chromatography to give purified yields of the methylation products as colorless oils in excess of 80%.

General Procedure for the Reduction of Compounds 23, 24, and 25 with Zinc Borohydride. To a 0.1 M solution of the methyl ketone (1 equiv) in ether at −78 °C was added a 0.5 M solution of zinc borohydride (2.5 equiv) in DME over a 30-min period. After the result was maintained at −78 °C for 2 h, the reaction was quenched with excess acetone, warmed to room temperature, and then partitioned between dichloromethane and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with three portions of dichloromethane, and the combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), and then concentrated under reduced pressure. The resulting oil was examined by ^1H NMR spectroscopy and gas chromatography to determine the ratio of diastereomeric products. Purification of the crude products by radial chromatography (silica gel, 50% ether in hexanes) gave the pure alcohols as colorless oils in yields greater than 85%.

2-Phenyl-4(*S*)-[4(*S*)-methyl-3(*R*)-hydroxyhex-5-en-2(*S*)-yl]-2-oxazoline. To a solution of 4.18 mL (13.9 mmol) of tri-*n*-butylcrotyltin in ether (40 mL) at 0 °C was added 5.65 mL (13.3 mmol) of a 2.36 M solution of *n*-butyllithium in hexanes. The result was stirred at room temperature for 5 h, then the solution was cooled to −78 °C, 5.56 mL (13.3 mmol) of a 2.4 M solution of trimethylaluminum in toluene was introduced, and the mixture was warmed to 0 °C. After 15 min, the solution was chilled to −78 °C, a solution of 1.11 g (5.56 mmol) of aldehyde **21** in ether (15 mL) was added over 30 min, and the resulting mixture was maintained at −78 °C for 8 h. After the mixture warmed to 0 °C, the reaction was quenched with excess methanol and then partitioned between water and ether. The aqueous layer was separated and extracted 4 times with fresh ether, and then the organic phases were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and

concentrated under reduced pressure. The resulting oil was partially purified by radial chromatography (silica gel, 50% ether in hexane) into two components, the more mobile component (814 mg, colorless oil) containing predominantly the desired stereoisomer, while the slower moving fraction (410 mg, colorless oil) contained a small amount of starting aldehyde and unwanted stereoisomers. The major component was taken on in the next step without further purification.

2-Phenyl-4(*S*)-4(*S*)-methyl-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]hex-5-en-2(*S*)-yl)-2-oxazoline (28). To a solution of the major component from the crotyl anion condensation and 0.67 mL (4.8 mmol) of triethylamine in dichloromethane (50 mL) at 0 °C was added 0.83 mL (3.6 mmol) of (*tert*-butyldimethylsilyl) trifluoromethanesulfonate. After 1 h, the reaction mixture was vigorously shaken with an equal volume of saturated aqueous $NaHCO_3$ and the derived aqueous layer extracted 3 times with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to an oil which was filtered through a short column of silica gel (10% ether in hexane). Following removal of solvents in vacuo, the residue was purified by radial chromatography (silica gel, 10% ether in hexane) to afford 681 mg (37% from **21**) of a major component as a colorless oil which was found to be greater than 98% pure **28** by ^1H NMR and gas chromatographic analyses (retention time: 20.70 at 190 °C): R_f 0.34 (silica gel, 10% ether in hexanes).[31]

2(*S*)-(Benzylamino)-3(*S*)-methyl-4(*R*)-[(*tert*-butyldimethylsilyl)-oxy]-5(*S*)-methylhept-6-en-1-ol. To a solution of 207 mg (0.55 mmol) of oxazoline **28** in toluene (20 mL) at 0 °C was added 2.95 mL (2.77 mmol) of a 0.94 M solution of DIBAL in hexane. After 1 h, the solution was cooled to −78 °C, 2.0 mL of methanol was carefully introduced, and the result was warmed to 0 °C and partitioned between ether and water. The aqueous layer was extracted with four portions of ether, and the combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, ether) to remove contamination by desilylated material to afford 171 mg (81%) of the desired product as a colorless oil: R_f 0.46 (silica gel, ether).[31]

2(*R*)-Methyl-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4(*S*)-methylhex-5-enal (29). To a solution of 353 mg (0.93 mmol) of the benzylamino alcohol in absolute ethanol (20 mL) and water (10 mL) at room temperature was added a solution of 998 mg (5.0 mmol) of $NaIO_4$ in water (10 mL) over 5 min. After 5 h, the reaction mixture was partitioned between water and dichloromethane, the layers were separated, and the aqueous layer was acidified to pH 4 (congo red) with 0.5 N aqueous HCl and then extracted 4 times with fresh dichloromethane. The combined organic layers were washed once with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford the desired product contaminated only by a trace (>3%) of starting material. This mixture was generally taken on without further purification. An analytically pure sample of the aldehyde (colorless oil) could be obtained by flash chromatography (silica gel, 5% ether in hexane, 81% yield): R_f 0.55 (silica gel, 10% ether in hexanes).[31]

3(*S*)-Methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methylhept-6-en-2(*S*)-ol and 3(*S*)-Methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methylhept-6-en-2(*R*)-ol. To a vigorously stirred solution of 1.18 mL (4.0 mmol) of 3.4 M solution of methylmagnesium bromide in ether in THF (10 mL) at −78 °C was added a solution of 224 mg (0.93 mmol) of aldehyde **29** in THF (5.0 mL). After 2 h, the reaction mixture was warmed to 0 °C where it was kept for 30 min before the reaction was quenched with excess saturated aqueous NH_4Cl. Sufficient water was added to dissolve any remaining solids, and the result was extracted with four portions of ether. The combined ether extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography (silica gel, 10% ether in hexane) to yield 227 mg (89% from the benzylamino alcohol) of pure product as a colorless oil: major diastereomer, R_f 0.30 (silica gel, 10% ether in hexanes); minor diastereomer, R_f 0.25 (silica gel, 10% ether in hexanes).[31]

3(*R*)-Methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methylhept-6-en-2-one (30). To a stirred suspension of 279 mg (1.29 mmol) of pyridinium chlorochromate and 20 mg (0.24 mmol) of sodium acetate in dichloromethane (5.0 mL) at room temperature was rapidly added a solution of 141 mg (0.52 mmol) of the alcohols in 3.0 mL of dichloromethane. After 12 h, the mixture was poured into 100 mL of ether, the result was filtered through a short column of Florisil, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 5% ether in hexane) to afford 110 mg (85%) of the pure product as a colorless oil: R_f 0.59 (silica gel, 20% ether in hexanes).[31]

3(*S*)-Methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methylhept-6-en-2(*S*)-ol (31). To a solution of 169 mg (0.63 mmol) of ketone **30** in THF (25 mL) at −100 °C was added 1.5 mL (1.57 mmol) of a 1.0 M solution of L-Selectride in THF. After 1 h, the reaction mixture was allowed to warm slowly to 0 °C and then was treated with 2.0 mL of 15% aqueous NaOH and 1.0 mL of 30% aqueous H_2O_2. After stirring 30 min, the mixture was partitioned between water and ether, the phases were separated, and the aqueous layer was extracted with three portions of ether. The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure to give 170 mg (~100%) of product as a colorless oil that was greater than 95% pure by ^1H NMR and gas chromatographic analyses: R_f 0.25 (silica gel, 10% ether in hexanes).[31]

3(*S*)-Methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methyl-6-(*S*)-[(methoxyethoxymethyl)oxy]hept-1-ene. To a solution of 170 mg (0.62 mmol) of alcohol **31** in dichloromethane (1.0 mL) at room temperature were added 0.22 mL (1.25 mmol) of diisopropylethylamine and 0.11 mL (0.94 mmol) of methoxyethoxymethyl chloride. After 48 h, the reaction mixture was partitioned between water and dichloromethane, the aqueous layer was extracted with three portions of fresh dichloromethane, and the combined organic phases were washed with saturated aqueous NaCl and dried (Na_2SO_4). Concentration under reduced pressure afforded a red residue which was purified by flash chromatography (silica gel, 20% ether in hexane) to give 218 mg (96% from **30**) of the product as a colorless oil which was determined to be greater than 99% diastereomerically pure by gas chromatographic analysis (retention times: major 15.73, 99.1%; minor 16.51, 0.9%, at 160 °C): R_f 0.22 (silica gel, 10% ether in hexanes).[31]

2(*R*)-Methyl-3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-4(*S*)-methyl-5-(*S*)-hydroxyhexanal as a Mixture of the Corresponding Lactols. Through a solution of 61 mg (0.22 mmol) of olefin **31** in methanol (10 mL) at −78 °C was bubbled ozone until the persistence of a blue cast to the reaction mixture. After the reaction mixture was purged of ozone by a stream of nitrogen, 5 mg (0.02 mmol) of platinum oxide was introduced, and the result was allowed to slowly (~1 h) warm to room temperature under an atmosphere of hydrogen. Filtration and concentration under reduced pressure afforded 58 mg (95%) of a colorless oil judged to be greater than 95% of the desired materials by ^1H NMR spectroscopy. The crude product was used in subsequent reactions without purification: R_f 0.62, 0.70 (silica gel, 50% ether in hexanes).[31]

2(*S*)-Methyl-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]-4(*S*)-methyl-5-(*S*)-hydroxyhexan-1-ol. To a stirred suspension of 20 mg (0.53 mmol) of lithium aluminum hydride in THF (2.0 mL) at −78 °C was added a solution of 28 mg (0.10 mmol) of the lactols in THF (1.0 mL). The reaction mixture was allowed to warm to room temperature and vigorously stirred an additional 2 h before cooling to 0 °C. The reaction was then carefully quenched with excess water. The reaction mixture was partitioned between 0.5 N aqueous HCl and ethyl acetate, the aqueous layer was extracted 4 times with fresh ethyl acetate, and the combined organic phases were dried ($MgSO_4$). Concentration under reduced pressure gave 18 mg (~63%) of a colorless oil which was used immediately without purification in subsequent reactions: R_f 0.30 (silica gel, ether).

2(*S*)-Methyl-4(*S*)-methyl-1,3(*R*),5(*S*)-triacetoxyhexane (33). To a solution of 28 mg (0.10 mmol) of the monosilyl diol in methanol (2.0 mL) at room temperature was added two drops of 10% aqueous HCl. After 6 h, the reaction mixture was concentrated under reduced pressure to afford the crude triol which was dissolved in 1.0 mL of dichloromethane. To this solution at room temperature were added 0.12 mL (2.0 mmol) of pyridine, 0.07 mL (1.0 mmol) of acetic anhydride, and 1 mg of 4-(dimethylamino)pyridine. After 5 h, the dichloromethane was driven off at 50 °C, and the solution was maintained at that temperature until the reaction was judged completed (about 2 h) by thin-layer chromatography (silica gel, 50% ether in hexanes). The reaction mixture was then partitioned between water and dichloromethane, and the aqueous layer was made acidic with 10% aqueous HCl and then extracted with three portions of dichloromethane. The combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford a residue which was subjected to flash chromatography (silica gel, 20% ether in hexane) to give 29 mg (~100%) of the product as a colorless oil which was judged to be greater than 98% pure by ^1H NMR: R_f 0.59 (silica gel, 50% ether in hexanes).[31] This product was identical by TLC, IR, NMR, and capillary gas chromatographic analyses (retention time: 11.08 at 140 °C) with material obtained through degradation of amphotericin B.[28] Correlation of the optical rotations confirmed that both materials were of the same enantiomeric series.

2(*R*)-Methyl-3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-4(*S*)-methyl-5-(*S*)-[(methoxyethoxymethyl)oxy]hexanal (34). Through a solution of 109 mg (0.30 mmol) of the olefin in methanol (20 mL) at −78 °C was bubbled ozone until the persistence of a blue cast to the reaction mixture. The solution was swept of excess ozone by a stream of nitrogen, excess (1.0 mL) dimethyl sulfide was introduced, and the result was allowed to

warm to room temperature. After 8 h, the solution was concentrated under reduced pressure and the residue passed down a short column of silica gel (20% ether in hexanes) to afford 85 mg (78%) of the pure aldehyde as a colorless oil: R_f 0.30 (silica gel, 20% ether in hexanes).[31]

6(*S*)-Methyl-7(*R*)-[(*tert*-butyldimethylsilyl)oxy]-8(*S*)-methyl-9-(*S*)-[(methoxyethoxymethyl)oxy]deca-2,4-dienal. To a solution of 112 mg (0.29 mmol) of 1-(tri-*n*-butylstannyl)-4-ethoxybutadiene in THF (1.0 mL) at −48 °C was added 0.11 mL (0.27 mmol) of a 2.48 M solution of *n*-butyllithium in hexane. After 1 h, a solution of 49 mg (0.14 mmol) of aldehyde **34** in THF (1.0 mL) was introduced, the mixture was maintained at −78 °C an additional 10 min, and then the reaction was quenched with excess saturated aqueous $NaHCO_3$. The mixture was allowed to warm to 0 °C and partitioned between ether and water, and the separated aqueous layer was extracted with three portions of ether. The combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to a residue which was purified by flash chromatography (silica gel, gradient from 10% to 50% ether in hexane) to afford 52 mg (82%) of the intermediate hydroxydienyl ether [R_f 0.20, 0.27 (silica gel, 33% ether in hexane)]. This material was dissolved in 1.0 mL of dichloromethane, cooled to −43 °C, and then treated sequentially with 22 μL (0.16 mmol) of triethylamine and 10 μL (0.13 mmol) of methanesulfonyl chloride. After 30 min, 1.0 mL of aqueous acetic acid/sodium acetate buffer (pH 4.6) was introduced, and the reaction mixture was warmed to 0 °C, stirred an additional 15 min, and then partitioned between dichloromethane and water. The aqueous layer was extracted with two portions of dichloromethane, and then the combined organic extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). Concentration under reduced pressure afforded a residue which was purified by flash chromatography (silica gel, 20% ether in hexane) to yield 40 mg (72% from **34**) of pure dienal as a slightly yellow oil: R_f 0.38 (silica gel, 50% ether in hexanes).[31] ^1H and ^{13}C NMR spectra indicated that the product dienal was at least 95% isomerically pure.

10(*S*)-Methyl-11(*R*)-[(*tert*-butyldimethylsilyl)oxy]-12(*S*)-methyl-13(*S*)-[(methoxyethoxymethyl)oxy]tetradeca-2,4,6,8-tetraenal. To a solution of 114 mg (0.29 mmol) of 1-(tri-*n*-butylstannyl)-4-ethoxybutadiene in THF (1.0 mL) at −78 °C was added 0.12 mL (0.28 mmol) of a 2.25 M solution of *n*-butyllithium in hexane. After 1 h, a solution of 58 mg (0.14 mmol) of the dienal in THF (1.0 mL) was introduced, and the result was maintained at −78 °C for 3 h and then allowed to warm to 0 °C over a 30-min period. After an additional 30 min, the reaction was quenched by the addition of excess saturated aqueous NH_4Cl, and the result was partitioned between ether and water. The aqueous layer was extracted with three portions of ether, and the organic phases were combined, washed with saturated aqueous NaCl, and then dried ($MgSO_4$). Concentration under reduced pressure gave a yellow oil which was dissolved in 5.0 mL of THF and 2.0 mL of water. The resulting solution was cooled to 0 °C, and 5 mg of TsOH was added. After 1 h, the reaction mixture was partioned between ether and water, the aqueous layer was extracted with three portions of ether, and the combined organic phases were washed with saturated aqueous NaCl and then dried ($MgSO_4$). Concentration under reduced pressure afforded a yellow oil which was partially purified by flash chromatography (silica gel, gradient from 10% to 50% ether in hexane) to result in 59 mg of material which contains greater than 90% of the tetraenal, the remainder of the material being unreacted dienal, as judged by ^1H NMR spectroscopy (81% corrected yield). While this mixture was generally used without further purification in the next reaction, a pure sample of the tetraenal as a yellow oil could be obtained by radial chromatography (silica gel, 20% ether in hexane): R_f 0.41 (silica gel, 50% ether in hexanes).[31]

14(*S*)-Methyl-15(*R*)-[(*tert*-butyldimethylsilyl)oxy]-16(*S*)-methyl-17(*S*)-[(methoxyethoxymethyl)oxy]octadeca-2,4,6,8,10,12-hexaenal (35). In a manner analogous to that described for the preparation of the tetraenal, 49 mg of the semipurified tetraenal was elaborated to hexaenal **35**. Concentration of the dried organic phases obtained upon workup afforded 57 mg of a bright orange oil that was shown to be greater than 85% of the desired product in 95% isomeric purity through ^1H and ^{13}C NMR analyses. The only observable contaminant was the unreacted tetraenal. A pure sample of hexaenal **35** as an orange oil could be obtained by radial chromatography (silica gel, 20% ether in hexane): R_f 0.44 (silica gel, 50% ether in hexanes).[31]

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Registry No. 1, 1397-89-3; **5**, 4515-23-5; **6**, 87219-29-2; **7**, 87219-30-5; **8**, 87219-35-0; **9**, 102614-13-1; **10a**, 87219-33-8; **12a**, 87219-40-7; **12b**, 102614-15-3; **13a**, 87219-37-2; **13b**, 102614-14-2; **16**, 102614-16-4; **17a**, 102614-17-5; **17b**, 102614-18-6; **20**, 102614-19-7; **21**, 102614-20-0; **22**, 102614-21-1; **23**, 102614-22-2; **23** (alcohol) (isomer 1), 102614-25-5; **23** (alcohol) (isomer 2), 102614-26-6; **24**, 102614-23-3; **24** (alcohol) (isomer 1), 102614-27-7; **24** (alcohol) (isomer 2), 102680-17-1; **25**, 102614-24-4; **25** (alcohol) (isomer 1), 102680-18-2; **25** (alcohol) (isomer 2), 102680-19-3; **28**, 102614-29-9; **28** (desilylated), 102614-28-8; **29**, 102614-31-3; **30**, 102614-33-5; **31** (isomer 1), 102614-32-4; **31** (isomer 2), 102680-20-6; **31** (aldehyde) (lactol) (isomer 1), 102614-35-7; **31** (aldehyde) (lactol) (isomer 2), 102680-21-7; **33**, 85576-61-0; **33** (monosilylated diol), 102614-36-8; **33** (triol), 102614-37-9; **34**, 102614-38-0; **34** (hydroxy dienyl ether), 102614-39-1; **34** (dienal), 102629-99-2; **34** (tetraenal), 102614-40-4; **35**, 101664-53-3; 3(*S*)-amino-γ-butyrolactone hydrobromide, 102614-12-0; 2-methyl-2-propane thiol, 75-66-1; tributylcrotyltin, 31197-41-8; 2(*S*)-(benzylamino-3(*S*)-methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-(*S*)-methylhept-6-en-1-ol, 102614-30-2; 3(*S*)-methyl-4(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*S*)-methyl-6(*S*)-[(methoxyethoxymethyl)oxy]hept-1-ene, 102614-34-6; 1-(tri-*n*-butylstannyl)-4-ethoxy butadiene, 66876-05-9; L-aspartic acid, 56-84-8.

Supplementary Material Available: A description of general experimental procedures and the physical data for the indicated compounds (18 pages). Ordering information is given on any current masthead page.