120386-82-5; **22**, 120386-61-0; **23**, 120386-62-1; **24**, 120386-63-2; **25**, 120386-64-3; **26**, 120386-65-4; **27**, 120386-66-5; **28**, 120386-68-7; **29**, 120386-70-1; **30b**, 120411-20-3; **31**, 120411-17-8; **32**, 120411-19-0; **34**, 120544-84-5; BPTI, 9087-70-1; Dbf, 132-64-9; Scm-Cl, 26555-40-8; Dnp-F, 70-34-8; Scm-S-Dbf-OH, 101697-58-9; Z-Ala-O-Dbf-S-Scm, 101697-56-7; Z-Gly-Gly-OH, 2566-19-0; H-Ala-OBu-*t*·HCl, 13404-22-3; Z-Gly-Gly-Ala-OBu-*t*, 120386-71-2; H-Gly-Gly-Ala-OBu-*t*, 120386-72-3; Boc-Cys(Acm)-OH, 19746-37-3; Boc-Cys(Acm)-Gly-Gly-Ala-OBu-*t*, 120386-73-4; Boc-Cys(Scm)-Gly-Gly-Ala-OBu-*t*, 120411-21-4; Z-Arg(Pmc)-OH, 112160-32-4; Z-Arg(Pmc)-OSu, 120386-74-5; H-Asn-OH, 70-47-3; Z-Arg(Pmc)-Asn-OH, 120386-75-6; H-Arg(Pmc)-Asn-OH, 120386-76-7; Bpoc-Lys(Boc)-OH, 47766-94-9; Bpoc-Lys(Boc)-OSu, 120386-77-8; Bpoc-Lys(Boc)-Arg(Pmc)-Asn-OH, 120386-78-9; Bpoc-Lys(Boc)-Arg(Pmc)-Asn-OH·DCHA, 120386-79-0; H-Arg(Pmc)-OH, 112160-37-9; Boc-Cys(Acm)-OSu, 19746-38-4; Boc-Cys(Acm)-Arg(Pmc)-OH, 120411-22-5; Boc-Tyr-OH, 3978-80-1; Boc-Tyr(Dnp)-OH, 120386-80-3; Z-Cys(Trit)-OH·DEA, 53308-88-6; Z-Cys(Scm)-OH, 53907-19-0; Z-Cys(Scm)-OH·CHA, 120386-81-4; H-Cys(Boc-Cys(Acm)-Met-Arg(Pmc)-Thr(*t*-Bu)-O-Dbf-S)-Gly-Gly-Ala-OH, 120386-83-6; Boc-Cys(Acm)-Met-Arg(Pmc)-Thr(*t*-Bu)-Cys(HO-Dbf-S)-Gly-Gly-Ala-OH, 120411-23-6; H-Cys(Boc-Cys(Acm)-Arg(Pmc)-Ala-Lys(Boc)-Arg(Pmc)-Asn-Asn-Phe-Lys(Boc)-Ser(*t*-Bu)-Ala-Blu(OBu-*t*)-Asp(OBu-*t*)-O-Dbf-S)-Met-Arg-Thr-Cys(Dnp)-Gly-Gly-Ala-OH, 120474-54-6; Boc-Cys(Acm)-Gln-Thr(*t*-Bu)-Phe-Val-Tyr(Dnp)-Gly-Gly-O-Dbf-SH, 120411-14-5; H-Cys(Boc-Cys(Acm)-Gln-Thr(*t*-Bu)-Phe-Val-Tyr(Dnp)-Gly-Gly-O-Dbf-S)-Arg-Ala-Lys-Arg-Asn-Asn-Phe-Lys-Ser-Ala-Glu-Asp-Cys(Dnp)-Met-Arg-Thr-Cys(Dnp)-Gly-Gly-Ala-OH, 120474-55-7; Boc-Cys(Acm)-Gln-Thr(*t*-Bu)-Phe-Val-Tyr(Dnp)-Gly-Gly-Cys(Dnp)-Arg-Ala-Lys-Arg-Asn-Asn-Phe-Lys-Ser-Ala-Glu-Asp-Cys(Dnp)-Met-Arg-Thr-Cys(Dnp)-Gly-Gly-Ala-OH, 120474-53-5; Boc-C(Acm)-(38-50)-C(Dnp)-(51-54)-C(Dnp)-(55-58)-OH, 120474-52-4.

Synthesis of Bryostatins. 1. Construction of the C(1)–C(16) Fragment†

Mary A. Blanchette, Michael S. Malamas, Michael H. Nantz, John C. Roberts, Peter Somfai, David C. Whritenour, and Satoru Masamune*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Masanori Kageyama and Tadashi Tamura

Kao Institute for Fundamental Research, 2606 Akabane, Ichikaimachi, Tochigi 321-34, Japan

Received March 27, 1989

The synthesis of fragment AB [C(1)–C(16)] of bryostatin 1 is described. Two aldol coupling reactions involving (i) chiral fragment A [C(1)–C(10)] with achiral B [C(11)–C(16)] and (ii) chiral fragment A1 [C(7)–C(10)] with achiral A2 [C(6)–C(1)] constitute crucial steps in which an external chiral boron reagent is used to control stereoselectivity in the creation of a new stereogenic center. This type of double asymmetric synthesis, although rarely precedented, provides a powerful means of stereocontrol over the fragment assembly.

Two decades ago, Pettit et al. found that extracts from the invertebrate colonial filter-feeder *Bugula neritina* were active against the murine P388 lymphocytic leukemia.[1] Subsequent efforts directed toward the isolation of the bioactive constituents have yielded 13 bryostatins of known structure, all but one of which differ only in their C(7) and C(20) substituents.[2] Whereas bryostatin 1 (**1**),[2a] the most abundant bryostatin, contains C(7) acetate and C(20) octadienoate substituents, there are various other ester derivatives, as well as three C(20)-deoxy bryostatins. Because of their attractive stereostructural features, anticancer properties, and relative scarcity, we have chosen **1** as a synthetic target. As depicted in Scheme I, a logical (and straightforward) retrosynthesis of **1** begins with the dissection of the lactonic linkage and the C(16)–C(17) double bond to provide the two major fragments AB [C(1)–C(16)] and CD [C(17)–C(27)]. The AB fragment can be further disassembled into fragments A [C(1)–C(10)] and B [C(11)–C(16)] and finally into A1 [C(7)–C(10)] and A2 [C(1)–C(6)]. In the coupling of A1 and A2, a stereogenic center is created at C(7) of A, and in the coupling of A and B, at C(11) of AB. Thus, these reactions are concerned with a fundamental, general problem of convergent synthesis, which involves the stereoselective assembly of two fragments (at least one of which is chiral) with concomitant creation of a new stereogenic center or centers.[3]

Stereogenic centers embedded in fragments generally correspond directly to those of a target molecule. When a center (or centers) is/are created in the coupling of two fragments, e.g. an enolate and an aldehyde, the product ratio heavily depends on the diastereoselectivities[3a] of the two reactants. The stereoselection attained in such a coupling, once a choice of fragments has been made, is therefore predetermined and normally unpredictable in both magnitude and sense. Thus, the fragment-coupling step often constitutes the least stereoselective step in the total synthesis, and, traditionally, such a reaction is performed with anticipated resignation to the ensuing product mixture with subsequent efforts directed toward separation of the congeners.[4] One approach to this problem, however, is externally altering (or ideally overpowering) the diastereofacial selectivities of the reactants. The use of enolates

† This paper is dedicated to Professor Frederick D. Greene in appreciation of his 27 years of service as Editor of *The Journal of Organic Chemistry*.

(1) Pettit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature (London)* **1970**, *227*, 962.

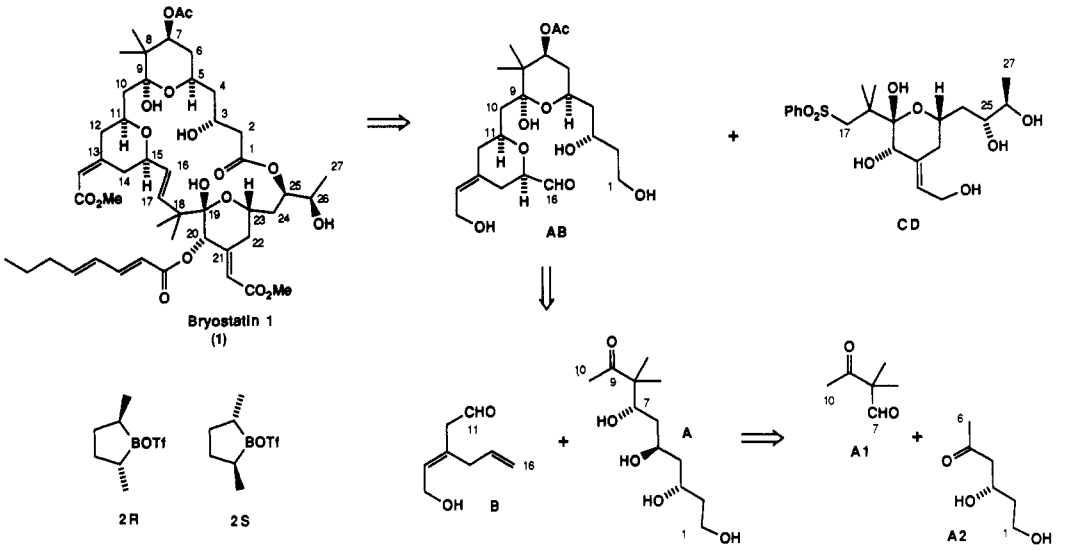
(2) (a) Pettit, G. T.; Herald, C. L.; Doubec, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (b) Pettit, G. R.; Kamano, Y.; Herald, C. L. *J. Org. Chem.* **1987**, *52*, 2854 and references cited therein.

(3) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Masamune, S. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Verlagsgesellschaft mbH: Weinheim, 1987; pp 49–71. As discussed in these references, the process of fragment assembly should be distinguished from one whereby stereogenic centers are created on a chiral substrate by a homochiral reagent or catalyst, as has been executed on numerous occasions in recent years.

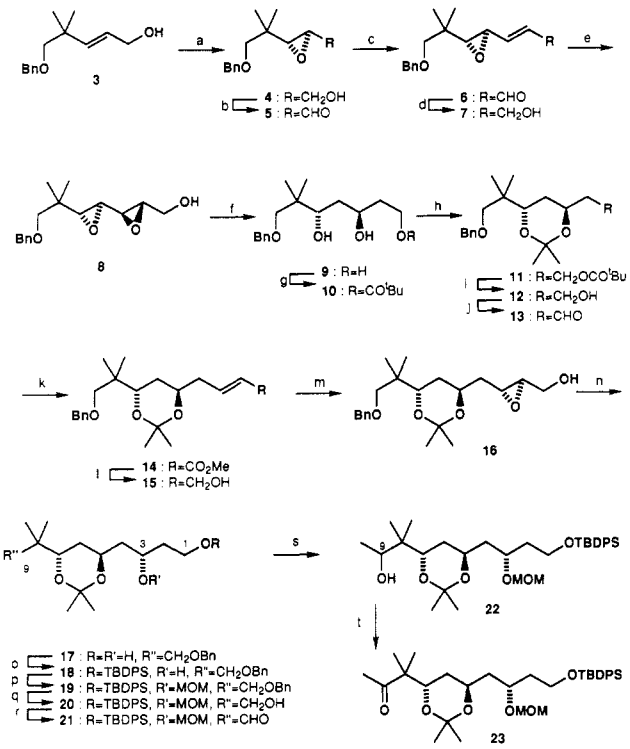
(4) For instance, see: (a) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1986**, *27*, 4741. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

0022-3263/89/1954-2817$01.50/0

Scheme I

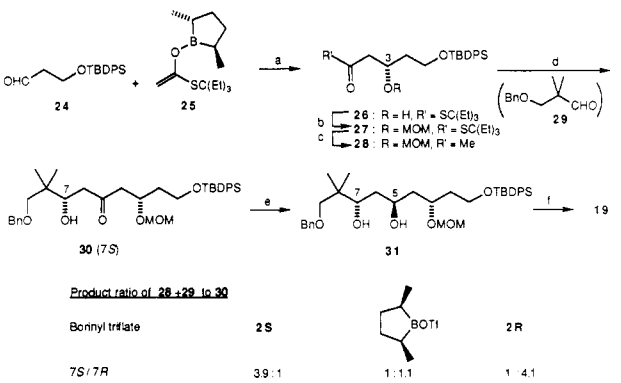


Scheme II[a]



[a] (a) (−)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (85%); (b) $(COCl)_2$, DMSO, CH_2Cl_2; (c) $Ph_3PCHCHO$, benzene; (d) $NaBH_4$, MeOH (61%, three steps); (e) (+)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (80%); (f) Red-Al, THF; (g) tBuCOCl, pyridine, CH_2Cl_2 (55%, two steps); (h) $(CH_3)_2C(OMe)_2$, PPTS (94%); (i) DIBAL, Et_2O (95%); (j) $(COCl)_2$, DMSO, CH_2Cl_2; (k) $(EtO)_2P(O)CH_2CO_2Me$, NaH, toluene (88%, two steps); (l) DIBAL, Et_2O (87%); (m) (−)-DET, $Ti(iPrO)_4$, TBHP, CH_2Cl_2 (80%); (n) Red-Al, THF; (o) TBDPS–Cl, imidazole, DMF (86%, two steps); (p) MOMBr, iPr_2EtN (85%); (q) W-2 RaNi, EtOH (88%); (r) $(COCl)_2$, DMSO, CH_2Cl_2; (s) MeLi, THF; (t) $(COCl)_2$, DMSO, CH_2Cl_1 (93%, three steps).

Scheme III[a]



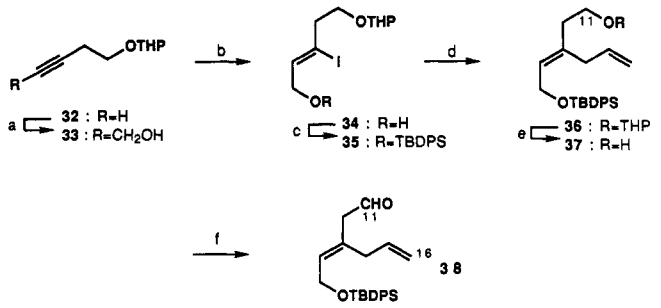
[a] (a) Pentane (79%, 89% ee); (b) $(MeO)_2CH_2$, P_2O_5, $CHCl_3$ (91%); (c) $LiCuMe_2$, Et_2O (91%); (d) (i) iPr_2EtN, **2R**, pentane–Et_2O; (ii) **29** (87%); (e) $Me_4NBH(OAc)_3$, AcOH–MeCN (86%); (f) $(CH_3)_2C(OMe)_2$, PPTS, CH_2Cl_2 (98%).

derived from chiral ketones and a chiral boron reagent, e.g. (*R,R*)- or (*S,S*)-2,5-*trans*-dimethylborolanyl trifluoromethanesulfonate (**2R** and **2S**),[5] instead of an achiral boron reagent such as diethylboryl trifluoromethanesulfonate[6] exemplifies this approach. The stereochemical course of the coupling reaction may be analyzed in terms of the diastereofacial selectivity of (i) the chiral ligands attached to boron and (ii) the chiral fragment or fragments. The external chiral reagent is thus designed and selected to serve as the major controlling factor, directing the stereochemical outcome predictably. This paper highlights our initial efforts directed toward solving this important problem.[7]

Synthesis of Fragment A [C(1)–C(10)]. Comparison of our two syntheses of the A fragment, outlined in Schemes II and III, demonstrates the relative simplicity of Scheme III, which adopts a convergent, fragment-coupling approach. Our original route (Scheme II) utilizes Red-Al (Aldrich) ring opening of epoxy alcohols to provide 1,3-diols, a method available at the onset of this project.[8] This reaction sequence proceeds uneventfully and does not require much explanation. The epoxidation of allylic alcohol **3**[9] affords **4** (85%, 92% ee), which, after oxidation

(5) Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.
(6) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559.
(7) For articles related to this subject, see: (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (b) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229.
(8) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.
(9) Allylic alcohol **3** was prepared from aldehyde **29** in two steps (see ref 15).

Scheme IV[a]



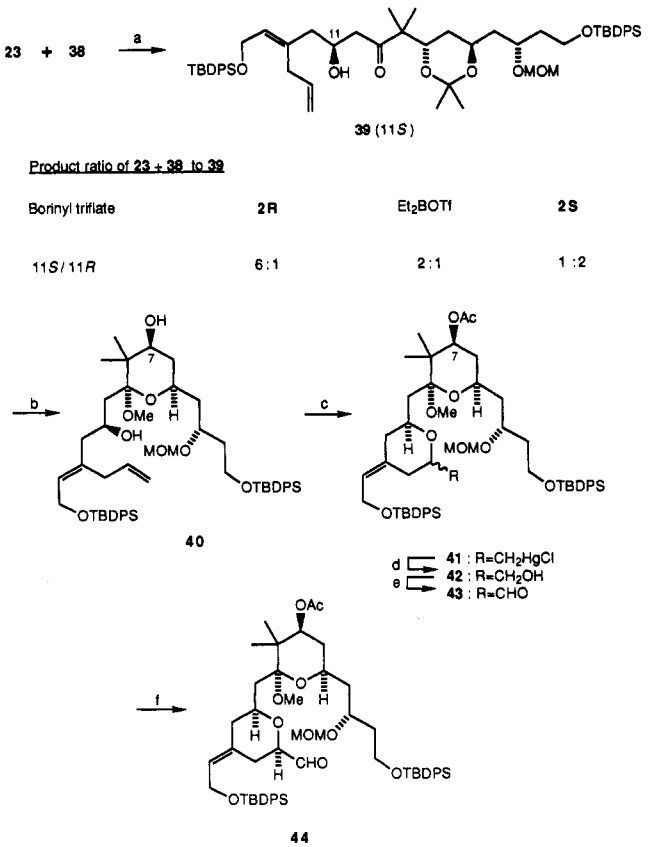
[a] (a) BuLi, HCOH(g), THF (89%); (b) Red-Al, THF, then I_2 (90%); (c) TBDPS-Cl, iPr_2EtN, imidazole, CH_2Cl_2 (95%); (d) allylMgBr, CuI, Et_2O (77%); (e) EtOH, PPTS (92%); (f) $(Py)_2CrO_3$, CH_2Cl_2.

to aldehyde **5**, formylolefination, and reduction, is converted to allylic alcohol **7** (61%, three steps). The following epoxidation affords bisepoxide **8** (80%, >98% de). Directed double ring opening by treatment with Red-Al followed by hydroxyl group differentiation leads to alcohol **12** (50%, four steps). An analogous sequence of Swern oxidation, Horner–Emmons olefination, reduction, epoxidation, and ring opening yields diol **17** (65%, five steps). Subsequent protection of the C(1) and C(3) alcohols,[10] and deprotection of the C(9) alcohol, affords **20** (64%, three steps), which is subsequently converted to fully protected fragment A, methyl ketone **23** (71%, three steps).

Although each step of Scheme II proceeds smoothly to afford a product of *secured* stereochemical assignment (which served the purpose of confirming the stereochemistry of **19** obtained through the route shown in Scheme III), the sequence is obviously too lengthy. This drawback has been remedied by the application of our recent stereoselective aldol methodology utilizing external chiral reagent control. This convergent synthesis, with less than half the steps, begins with aldehyde **24**,[11] which is converted to thioester **26** (79%, 89% ee) with our homochiral acetate equivalent: boron enolate reagent **25**.[5] Although treatment of **26** with methoxymethyl bromide under standard conditions affords only low yields of MOM ether **27** (40–50%),[12] the less utilized procedure with dimethoxymethane and P_2O_5 completes this task satisfactorily (91%).[13] Conversion to methyl ketone **28** ensues upon treatment with lithium dimethylcuprate (94%).[14]

In the subsequent coupling reaction, external chiral reagent **2S** (Scheme I), selective for the desired stereochemistry, is utilized. Thus the boron enolate derived from **2S** and **28** is condensed with aldehyde **29**,[15] providing **30** (87%) as an inseparable mixture of diastereomers. Directed reduction of this mixture with the Saksena–Evans reagent $[Me_4NBH(OAc)_3]$[16] leads to **31** (86%) as a 3.9:1 mixture of separable diastereomers. Consistent with our intuition that this product ratio reflects the ratio obtained

Scheme V[a]



[a] (a) **2R**, iPr_2EtN, pentane (86%); (b) MeOH, PPTS (84%); (c) (i) $Hg(OAc)_2$, THF–MeOH, then KCl; (ii) AcCl, pyridine, CH_2Cl_2 (80–90%, two steps); (d) $NaBH_4$, O_2, DMF (70–80%); (e) $(COCl)_2$, DMSO, CH_2Cl_2 (85%); (f) Al_2O_3 (3% H_2O), CH_2Cl_2.

in the aldol reaction is that the use of an achiral reagent (*meso*-2,5-dimethylboranyl triflate)[17] and subsequent reduction affords **31** as a 1:1.1 ratio of diastereomers. Similarly, the use of **2R**, selective for the undesired diastereomer, leads to a 1:4.1 ratio. In these coupling reactions, ketone **28** happens to behave like an achiral methyl ketone and the **30**(7*S*)/**30**(7*R*) ratios in the matched and mismatched reactions simply reflect the diastereofacial selectivity of the chiral reagent **2R** or **2S** (apparent single asymmetric synthesis). The synthesis of **19** was completed by acetonide formation on diol **31** (98%), and the C(7) and C(5) stereochemistry was confirmed by comparison with compound **19**, prepared via the route described earlier in Scheme II.

Synthesis of Fragment B [C(11)–C(16)]. The B fragment is synthesized in a straightforward manner as outlined in Scheme IV. Thus, one-carbon extension on THP ether **32**[18] affords alcohol **33** (89%). Application of Corey's trisubstituted olefin synthesis provides **36** (74%, three steps) via iodides **34**[19,20] and **35**. Subsequent C(11) alcohol deprotection followed by Collins oxidation affords aldehyde **38**, fully protected fragment B, which is used without purification.

Synthesis of Fragment AB [C(1)–C(16)]. The completion of the AB portion of bryostatin 1, outlined in

(10) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(11) Aldehyde **24** was prepared from *cis*-3-hexen-1-ol in two steps, and its use has been described on one previous occasion: Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.
(12) (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 782. (b) Stork, G.; Takahashi, T. *Ibid.* **1977**, *99*, 1275.
(13) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1976**, 276.
(14) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.
(15) The preparation of aldehyde **29** from 2,2-dimethyl-1,3-propanediol in two or three steps has been described several times; for example, see: Yeh, C.-L.; Dawson, M.; Hemler, M. E.; Lands, W. E. M. *Tetrahedron Lett.* **1977**, 4257.
(16) (a) Saksena, A. K.; Mangiaraeina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Evans, D. A.; Chapman, K. T. ibid. **1986**, *27*, 5939. (c) Evans, D. A.; Dimare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476.
(17) Kim, B.-M. Ph.D. Thesis, MIT, 1987.
(18) The preparation of THP ether **32** has been described previously, for example, see: Jones, E. R. K.; Shen, T. J.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1950**, 230.
(19) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
(20) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595–4597.

Scheme V, begins with the crucial step of coupling fragments A and B. Reaction of **38** with the enolate derived from **23** and **2R** provides ketol **39** as a mixture of inseparable diastereomers. The first pyran cyclization, which ensues upon deacetonization in methanol, affords methyl acetal **40** (84%) as a 6:1 ratio of separable diastereomers. Again, consistent with our notion that this product ratio reflects the ratio obtained in the aldol condensation are the results that (i) the use of an achiral reagent (diethylboryl triflate)[6] and subsequent pyran formation affords **40** as a 2:1 ratio of diastereomers and (ii) similarly the use of **2S** leads to a 1:2 ratio.[21] Note that the desired stereochemistry is obtained by the complimentary selectivities of **38** and **2R** (a matched case).[3a] Furthermore, the above ratios of diastereomers observed for both the matched and mismatched pairs are in accord with the approximate multiplicativity rules of double asymmetric synthesis.[3a]

The synthesis of the AB fragment was completed by a second pyran formation on methyl acetal **40**. This stereorandom cyclization is triggered by treatment with $Hg(OAc)_2$ to afford an organomercurial intermediate, which, after acetylation of the C(7) alcohol, yields **41** (85%).[22] Oxidative demercuration leads to alcohol **42** (75%), and Swern oxidation affords aldehyde **43** (85%) as a 1:1 equatorial–axial mixture. Subsequent equilibration to a 9:1 equatorial–axial mixture of aldehydes is effected with Al_2O_3, thereby concluding the synthesis of **44**, the AB fragment.[23]

Experimental Section

Boiling points and melting points are uncorrected. Reactions were run in oven-dried glassware under Ar or N_2. All homogeneous liquid reagents other than chlorodiphenyl*tert*-butylsilane were distilled under N_2 before use. Amines, CH_2Cl_2, DMF, DMSO, MeCN, pyridine, and benzene were distilled from CaH_2 under N_2. Ether and THF were likewise distilled from $LiAlH_4$, $CHCl_3$ from P_2O_5, and AcOH from CrO_3. Column chromatography was performed with 230–400 mesh silical gel (Merck), and preparative TLC was performed with UNIPLATE thin-layer chromatography plates (Analtech). ^1H NMR spectra were recorded at 250 MHz on a Bruker WM 250 spectrometer or at 300 MHz on a Varian XL-300 spectrometer (as indicated), and ^{13}C NMR spectra were recorded at 75.4 MHz on a Varian XL-300. IR spectra were recorded on a Perkin-Elmer 283B spectrometer. Optical rotations were recorded at ambient temperature on an Autopol III polarimeter. Mass spectra were obtained by using a Finnigan MAT 8200 spectrometer.

Experimental Procedures for Scheme II: Fragment A via Sharpless Epoxidation. Allylic Alcohol 3 (via aldehyde 29). A magnetically stirred solution of 2,2-dimethyl-1,3-propanediol (85 g, 0.81 mol), benzaldehyde (73 g, 0.69 mol), and *p*-TsOH (10 mg) dissolved in benzene (0.2 L) was heated at reflux temperature for 14 h. After 12 mL of water was collected by means of a Dean–Stark apparatus, the solution was cooled to 25 °C and extracted with 10% NaOH(aq) and then water. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by Kugelrohr distillation (123–127 °C, 4.0 mm) to yield 124 g (91%) of the benzylidine acetal as an oil, which crystallized upon standing to a white solid: mp 29–30 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.28 (s, 3 H), 3.58 (d, J = 11.3 Hz, 1 H), 3.72 (d, J = 11.3 Hz, 1 H), 4.49 (s, 1 H), 7.33 (m, 5 H); MS (m/z) $[M]^+$ 191, 107, 105.

To a magnetically stirred solution of this benzylidene acetal (140 g, 0.72 mol) dissolved in THF (0.8 L) was added dropwise BH_3·THF (1 M, 800 mL, 0.8 mol). The colorless solution was heated at reflux temperature for 72 h, after which it was allowed to cool to room temperature before being quenched by the dropwise addition of methanol (0.5 L). The solution was concentrated in vacuo, and the residual oil was dissolved in ether. The ethereal solution was extracted with 0.1 N HCl and brine. The aqueous extracts were back-extracted with ether, and the combined organic phase was then dried over $MgSO_4$. Upon filtration and concentration in vacuo, the residual oil was purified by fractional distillation (123–126 °C, 2.5 mm) to give 132 g (94%) of the alcohol: IR (neat) 3450, 3020, 2980, 2870, 1075 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 6 H), 2.87 (s, 1 H), 3.31 (s, 2 H), 3.43 (s, 2 H), 4.50 (s, 2 H), 7.32 (m, 5 H); HRMS $[M]^+$ calcd 194.1307, found 194.1306.

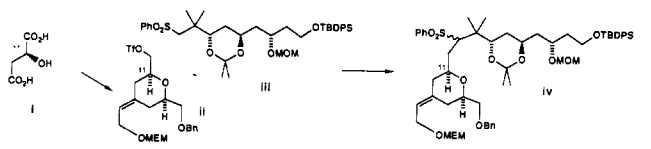
A solution of this alcohol (21 g, 108 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise to a rapidly stirred solution of PCC (34 g, 158 mmol) dissolved in CH_2Cl_2 (0.2 L). The initially bright orange solution immediately turned black. Five reactions were set up simultaneously in this fashion and were allowed to proceed at 25 °C. An additional 4.5 g of PCC was added to each reaction after 8 h to ensure complete reaction. After an additional 3 h each reaction was diluted with ether (150 mL). The organic phase was decanted, and the remaining gummy black residue was washed with ether (3 × 75 mL). The combined organic extract was filtered through a column of florisil and concentrated in vacuo to afford 101 g of crude material. Purification by Kugelrohr distillation (78–83 °C, 2.5mm) gave 86.2 g (82%) of **29**: IR (neat) 2980, 1730, 1450, 1100, 890, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 6 H), 3.41 (s, 2 H), 4.46 (s, 2 H), 7.28 (m, 5 H), 9.52 (s, 1 H).

Triethyl phosphonoacetate (132 mL, 664 mmol) was added dropwise to a magnetically stirred 0 °C slurry of sodium hydride (80% dispersion in mineral oil, 19.6 g, 610 mmol) suspended in toluene (1.2 L). To the resulting clear solution was added a solution of aldehyde **29** (86 g, 447 mmol) dissolved in THF (0.1 L). The reaction was stirred at 0 °C for 1 h, whereupon it was allowed to warm to ambient temperature and stir for an additional 6 h. The reaction was quenched by addition of saturated NaCl(aq), and the organic phase was separated. The aqueous phase was extracted with ether, and the combined organic phases were concentrated in vacuo. Flash SiO_2 chromatography (10:1 hexane/ethyl acetate) on the residual yellow oil gave 104 g (89%) of the unsaturated methyl ester: IR (neat) 2960, 2860, 1715, 1645, 1450, 1360, 1270, 1170, 1090, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 6 H), 1.27 (t, J = 7.1 Hz, 3 H), 3.24 (s, 2 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.49 (s, 2 H), 5.80 (d, J = 16 Hz, 1 H), 7.01 (d, J = 16 Hz, 1 H), 7.29 (m, 5 H); MS (m/z) $[M]^+$ 262, 176, 141, 91.

To a solution of this unsaturated methyl ester (104 g, 396 mmol) dissolved in ether (1.5 L) at −78 °C was added dropwise DIBAL (25% solution in toluene, 672 mL, 1 mol). The reaction mixture was stirred overnight at 25 °C and subsequently quenched by the addition of methanol (0.7 L). The precipitated salts were dissolved with 1.0 N HCl(aq) (0.3 L), and the organic phase was separated. The aqueous phase was extracted with ether and then ethyl acetate. The combined oranic extracts were concentrated in vacuo to afford 84 g of a light yellow oil readily purified by Kugelrohr distillation (124–132 °C, 0.2 mm) to give 69 g (79%) of **3**: IR (neat) 3380, 3010, 2960, 2860, 1450, 1355, 1080, 1020, 965, 725, 675 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.60 (br s, 1 H), 3.21 (s, 2 H), 4.08 (d, J = 5.3 Hz, 2 H), 4.48 (s, 2 H), 5.60 (dt, J = 16, 5.3 Hz, 1 H), 5.75 (d, J = 16 Hz, 1 H), 7.29 (m, 5 H); HRMS $[M]^+$ calcd 220.1463, found 220.1463.

Epoxy Alcohol 4. To a mechanically stirred mixture of CH_2Cl_2 (1.5 L) and activated powdered 4-Å molecular sieves (40 g) was added titanium(IV) isopropoxide (30 mL, 100 mmol). After the mixture was cooled to −40 °C, (−)-diethyl D-tartrate (23 mL, 134

(21) Additional confirmation of the C(11) stereochemistry has been made. In brief, the route outlined below starting from i led to iv with the unambiguously assigned stereochemistry at C(11) (the same as that of i). Both **44** and iv were transformed to an identical derivative. The synthetic route from i to iv is superceded by that described in the text and is therefore not elaborated on.



(22) Whitesides, G. M.; Hill, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 870.

(23) A preliminary account of this work was presented at the Seventh IUPAC Conference on Organic Synthesis held in Nancy, France (July 4–7, 1988): Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587.

mmol) was added, and the resultant mixture was stirred for 15 min. A solution of **3** (112 g, 510 mmol) in CH_2Cl_2 (0.1 L) was then added, and stirring was continued for 30 min prior to the addition of anhydrous *tert*-butyl hydroperoxide (4.0 M in toluene, 330 mL, 1.32 mol). The reaction mixture was allowed to warm to 0 °C over 8 h, whereupon it was poured into a 6-L Erlenmeyer flask containing a 0 °C mixture of ether (2 L), ferrous sulfate (165 g, 590 mmol), and tartaric acid (66 g, 440 mmol) dissolved in water (670 mL). Upon vigorous mixing the aqueous layer turned dark brown. The mixture was stirred at 25 °C for 1 h, after which the layers were separated. The aqueous layer was extracted with ether and ethyl acetate. The combined organic extract was concentrated in vacuo to afford a yellow oil, which was dissolved in ether (1.1 L) and added with vigorous mechanical stirring to a 0 °C solution of NaOH (s) (17 g, 425 mmol) in saturated NaCl(aq) (0.4 L). After 2.5 h, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extract was concentrated in vacuo, and the residual oil was purified by SiO_2 flash chromatography (5:1 hexane/ethyl acetate) to give 102 g (85%) of **4**: $[\alpha]^{24}_D$ +8.38° (*c* 2.50, $CHCl_3$); IR (neat) 3425, 2960, 2860, 1450, 1360, 1160, 1040, 890, 728, 688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 6 H), 1.70 (br s, 1 H), 2.92 (d, J = 2.3 Hz, 1 H), 3.09 (m, 1 H), 3.22 (A of AB d, J = 8.7 Hz, 1 H), 3.27 (B of AB d, J = 8.7 Hz, 1 H), 3.55 (dd, J = 12, 6.3 Hz, 1 H), 3.85 (dd, J = 12, 2.2 Hz, 1 H), 4.51 (s, 2 H), 7.32 (m, 5 H); MS (*m/z*) $[M - H_2O]^+$ 218, 187, 107, 91.

Aldehyde 5. To a mechanically stirred solution of oxalyl chloride (42 mL, 475 mmol) in CH_2Cl_2 (1.2 L) at −78 °C was added dropwise, over 30 min, DMSO (67 mL, 951 mmol). Upon complete addition, **4** (56.2 g, 238 mmol) dissolved in CH_2Cl_2 (150 mL) was added dropwise over 40 min. The initially clear solution became white and cloudy after stirring for 1.5 h. Triethylamine (170 mL, 1.19 mol) was then added dropwise while the reaction temperature was maintained at −78 °C. Upon complete addition, the reaction mixture was warmed slowly to −10 °C over 2.5 h and then quenched by addition of water (100 mL). The organic layer was separated and washed several times with water and then with saturated NaCl(aq). The combined aqueous washes were back-extracted with CH_2Cl_2. The organic extracts were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was filtered through a plug of SiO_2 (10:1 hexane/ethyl acetate) to give **5** as a yellow oil (57 g), which was used in the next step without further purification: IR (neat) 3422, 2960, 2860, 1723, 1450, 1360, 1172, 1090, 845, 725, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (s, 3 H), 0.88 (s, 3 H), 3.21 (m, 4 H), 4.44 (s, 2 H), 7.27 (m, 5 H), 8.96 (d, J = 6.1 Hz, 1 H).

Unsaturated Aldehyde 6. A solution of crude **5** (57 g) in THF (100 mL) was added with vigorous overhead mechanical stirring to a 0 °C slurry of (formylmethylene) triphenylphosphorane (91 g, 300 mmol) in benzene (1.6 L). The resultant slurry was stirred for 12 h at 0 °C, whereupon the suspended solids were filtered. The filtrate was concentrated in vacuo to a yellow oil containing white solids (triphenylphosphine oxide). The oil was triturated with 2:1 hexane/ethyl acetate (8 × 50 mL), and the extracts were combined and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (12:1 hexane/ethyl acetate) to give 34.2 g (55%, two steps) of **6**: IR (neat) 2960, 2860, 1725, 1688, 1450, 1360, 1175, 1085, 850, 728, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.94 (s, 3 H), 2.86 (d, J = 1.9 Hz, 1 H), 3.16 (A of AB, J = 8.8 Hz, 1 H), 3.20 (B of AB, J = 8.8 Hz, 1 H), 3.45 (dd, J = 6.7, 2.0 Hz, 1 H), 4.43 (s, 2 H), 6.27 (dd, J = 16, 6.7 Hz, 1 H), 6.45 (dd, J = 16, 6.0 Hz, 1 H), 7.27 (m, 5 H), 9.48 (d, J = 7.4 Hz, *E*-C*H*O).

Allylic Alcohol 7. To a magnetically stirred solution of **6** (34.2 g, 131 mmol) in methanol (0.6 L) at −50 °C was added portionwise sodium borohydride (7.9 g, 208 mmol). The resultant white suspension was stirred at −20 °C for 6 h, whereupon the reaction was quenched by dropwise addition of water (15 mL). The methanol was removed in vacuo, and the residual oil was dissolved in ether (300 mL). The organic solution was washed with water and saturated NaCl(aq) and dried over $MgSO_4$. After filtration and concentration in vacuo, the crude oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to afford 30.5 g (93%) of **7**: $[\alpha]^{24}_D$ +0.90° (*c* 1.7, $CHCl_3$); IR (neat) 3410, 2960, 2860, 1450, 1360, 1201, 1085, 1015, 960, 880, 728, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 0.93 (s, 3 H), 1.30 (br s, 1 H), 2.60 (d, J = 2.3 Hz, 1 H), 3.26 (m, 3 H), 4.18 (t, J = 4.5 Hz, 2 H), 4.49 (s, 3 H), 5.48 (dd, J = 15, 7.6 Hz, 1 H), 6.95 (dt, J = 16, 5.2 Hz, 1 H), 7.32 (m, 5 H); MS (*m/z*) $[M]^+$ 262, 245, 107, 91.

Bisepoxide 8. To a mechanically stirred suspension of powdered 4-Å molecular sieves (25 g) in CH_2Cl_2 (0.8 L) at −40 °C was added titanium(IV) isopropoxide (14.5 mL, 49 mmol) followed by addition of (+)-diethyl L-tartrate (11 mL, 64 mmol). After the mixture was stirred 15 min, a solution of **7** (64 g, 244 mmol) in CH_2Cl_2 (80 mL) was added, and stirring was continued for 30 min prior to the addition of anhydrous *tert*-butyl hydroperoxide (4.0 M solution in toluene, 120 mL, 480 mmol). The reaction mixture was warmed to 0 °C over 12 h and subsequently poured into a 3-L Erlenmeyer flask containing ether (1 L) and saturated Na_2SO_4(aq) (130 mL). The resultant solution was stirred vigorously for 2 h, whereupon the solids were filtered and triturated with hot ethyl acetate (2 × 350 mL). The combined organic phases were concentrated in vacuo, and the residual oil was dissolved in ether (1.5 L). The ether solution was then added with rapid mechanical stirring to a 0 °C solution of NaOH(s) (20 g, 0.5 mol) in saturated NaCl(aq) (0.6 L). After 2 h the aqueous layer was separated and extracted with ether and then ethyl acetate. The combined organic phases were concentrated in vacuo, and the residual oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to give 54.5 g (80%) of **8**: IR (neat) 3445, 2960, 2860, 1450, 1360, 1090, 1220, 890, 728, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 0.89 (s, 3 H), 1.94 (t, J = 5.6 Hz, 1 H), 2.86 (d, J = 2.3 Hz, 1 H), 2.96 (m, 1 H), 3.04 (d, J = 3.6 Hz, 2 H), 3.28 (A of AB d, J = 8.8 Hz, 1 H), 3.32 (B of AB d, J = 8.8 Hz, 1 H), 3.60 (m, 1 H), 3.85 (dd, J = 11, 3.6 Hz, 1 H), 4.49 (s, 2 H), 7.30 (m, 5 H).

Triol 9. To a −40 °C solution of **8** (25.5 g, 92 mmol) in THF (750 mL) was added Red-Al (3.5 M solution in toluene, 130 mL, 455 mmol) dropwise over 1 h. The reaction was allowed to warm to ambient temperature and stirred for 2 days. The reaction was quenched by slow cannulation of the reaction mixture into a saturated solution of Rochelle's salt (aq) (1 L) with vigorous mixing. Ether (500 mL) was added upon complete cannulation, and after the mixture was stirred for an additional 30 min, the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$. After filtration, the solvents were removed in vacuo to afford 25 g of the crude **9** as a viscous oil, which was used in the next step without further purification. A small sample was purified by SiO_2 chromatography (9:1 $CHCl_3$/MeOH) for analytical purposes: **IR** ($CHCl_3$) 3485, 2880, 1465, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 0.85 (s, 3 H), 1.50 (m, 2 H), 1.75 (m, 1 H), 2.68 (br s, 3-O*H*), 3.30 (A of AB d, J = 7.6 Hz, 1 H), 3.37 (B of AB d, J = 7.6 Hz, 1 H), 3.82 (m, 3 H), 4.12 (m, 1 H), 4.47 (AB apparent singlet, 2 H), 7.27 (m, 5 H); MS (*m/z*) $[M]^+$ 282, 174, 108, 101, 91.

Pivalate Ester 10. To a magnetically stirred 0 °C solution of crude **9** (25 g) in CH_2Cl_2 (650 mL) was added pyridine (14.2 mL, 177 mmol) followed by dropwise addition of pivaloyl chloride (21.7 mL, 177 mmol). After being stirred for 4 h, the reaction mixture was diluted with ether (0.8 L) and subsequently washed with saturated $CuSO_4$(aq) (3 × 100 mL). The combined aqueous washes were back-extracted with ethyl acetate (3 × 100 mL). The combined organic extract was then dried over $MgSO_4$, filtered, and concentrated in vacuo to a light yellow oil. Hexane (100 mL) was added, and the solution was cooled to 0 °C, whereupon crystallization occurred. The crystals were collected by suction filtration and dried in vacuo to give 18.3 g (55%, two steps) of **10**: mp 77 °C; $[\alpha]^{24}_D$ −8.9° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3480, 2960, 2870, 1720, 1285, 1160, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 0.92 (s, 3 H), 1.20 (s, 9 H), 1.50 (m, 2 H), 1.82 (m, 2 H), 2.90 (m, 1 H), 3.35 (dd, J = 16, 8.8 Hz, 2 H), 3.60 (m, 1 H), 3.80 (m, 1 H), 3.90 (m, 1 H), 4.25 (m, 1 H), 4.33 (m, 1 H), 4.98 (A of AB d, J = 12 Hz, 1 H), 5.00 (B of AB d, J = 12 Hz, 1 H), 7.35 (m, 5 H); HRMS $[M]^+$ calcd 366.2406, found 366.2405.

Acetonide 11. To a magnetically stirred 24 °C solution of **10** (18.3g, 50 mmol) in CH_2Cl_2 (300 mL) was added 2,2-dimethoxypropane (55 mL, 500 mmol) and *p*-TsOH (100 mg, 0.64 mmol). The reaction was complete after 2 h (as indicated by TLC) and subsequently quenched by washing with saturated $NaHCO_3$(aq) followed by saturated NaCl(aq). The organic phase was then dried

over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (4:1 hexane/ethyl acetate) to yield 19.2 g (94%) of **11**: $[\alpha]^{24}_D$ −8.48° (*c* 4.00, $CHCl_3$); IR (neat) 2960, 2860, 1730, 1475, 1450, 1380, 1280, 1220, 1160, 1090, 920, 880, 725, 687 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.19 (s, 9 H), 1.27 (s, 3 H), 1.29 (s, 3 H), 1.40 (m, 1 H), 1.75 (m, 3 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.81 (dd, *J* = 9.9, 6.3 Hz, 2 H), 4.13 (t, *J* = 6.4 Hz, 2 H), 4.49 (A of AB d, *J* = 13 Hz, 1 H), 4.45 (B of AB d, *J* = 13 Hz, 1 H), 7.32 (m, 5 H); MS (*m/z*) $[M - C_4H_9]^+$ 349, 265, 185, 91.

Alcohol 12. To a solution of **11** (19.2g, 42 mmol) in ether (0.6L) at −78 °C was added DIBAL (1 M solution in hexane, 95 mL, 95 mmol) dropwise. After 1 h, the reaction was quenched by the dropwise addition of methanol (150 mL) and warmed to 25 °C over 1 h, whereupon white salts precipitated. The salts were filtered through a Buchner funnel and washed with a 1:1:1 mixture of hexane/ethyl acetate/methanol. The combined organic phases were concentrated in vacuo to afford a colorless oil, which was purified by SiO_2 flash chromatography (8:1 hexane/ethyl acetate) to give 14.4 g (95%) of **12**: $[\alpha]^{24}_D$ −28.44° (*c* 2.7, $CHCl_3$); IR (neat) 3425, 2960, 2860, 1450, 1370, 1215, 1090, 960, 725, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.30 (s, 3 H), 1.33 (s, 3 H), 1.39 (m, 1 H), 1.74 (m, 3 H), 2.59 (t, *J* = 4.9 Hz, 1 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.80 (m, 3 H), 3.95 (m, 1 H), 4.46 (A of AB d, *J* = 12 Hz, 1 H), 4.50 (B of AB d, *J* = 12 Hz, 1 H), 7.33 (m, 5 H); MS (*m/z*) $[M - CH_3]^+$ 307, 266, 159, 92, 91.

Aldehyde 13. Dimethyl sulfoxide (9 mL, 129 mmol) was added dropwise to a solution of oxalyl chloride (5.50 mL, 64.5 mmol) in CH_2Cl_2 (250 mL) at −78 °C. Upon complete addition, a solution of **12** (10.4g, 32.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and stirring was continued at −78 °C. After 1 h, triethylamine (23 mL, 161 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction solution was then poured into water (50 mL), and the layers were separated. The organic layer was washed with additional water and saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield crude **13**. Partial purification was accomplished by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 10.5 g of a yellow oil, which was used in the next step without further purification: IR ($CHCl_3$) 2880, 1735, 1520, 1370, 1250, 1170, 1090, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 0.83 (s, 3 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.36 (ddd, *J* = 12, 9.7, 6.2 Hz, 1 H), 1.82 (ddd, *J* = 12, 9.6, 5.8 Hz, 1 H), 2.39 (ddd, *J* = 16, 4.2, 2.5 Hz, 1 H), 2.52 (ddd, *J* = 13, 11, 2.5 Hz, 1 H), 3.09 (d, *J* = 9.0 Hz, 1 H), 3.23 (d, *J* = 8.9 Hz, 1 H), 3.76 (dd, *J* = 9.6, 6.2 Hz, 1 H), 4.18 (m, 1 H), 4.35 (A of AB d, *J* = 12 Hz, 1 H), 4.41 (B of AB d, *J* = 12 Hz, 1 H), 7.26 (m, 5 H), 9.67 (t, *J* = 3.6 Hz, 1 H).

Unsaturated Methyl Ester 14. Triethyl phosphonoacetate (9 mL, 49 mmol) was added dropwise to a 0 °C slurry of sodium hydride (80% dispersion in mineral oil, 1.2 g, 45.9 mmol) suspended in toluene (250 mL). After the mixture was stirred for 1 h, crude **13** (10.5 g) dissolved in THF (50 mL) was added dropwise over 30 min. Stirring was continued at 0 °C for 10 h, whereupon the reaction was quenched with water. The organic layer was separated and washed with additional water and saturated NaCl(aq). The combined aqueous washes were back-extracted with ether, and the combined organic extracts were concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (20:1 hexane/ethyl acetate) to yield 10.9 g (88%, two steps) of **14**: IR (neat) 2965, 2860, 1718, 1648, 1450, 1375, 1215, 1085, 960, 730, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.29 (t, *J* = 6.8 Hz, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.80 (m, 3 H), 2.37 (m, 2 H), 3.15 (d, *J* = 8.6 Hz, 1 H), 3.29 (d, 8.5 Hz, 1 H), 3.83 (m, 2 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 4.45 (A of AB d, *J* = 12 Hz, 1 H), 4.49 (B of AB d, *J* = 12 Hz, 1 H), 5.88 (d, *J* = 16 Hz, 1 H), 6.93 (dt, *J* = 16, 6.9 Hz, 1 H), 7.33 (m, 5 H); HRMS $[M - CH_3]^+$ calcd 375.2171, found 375.2169.

Allylic Alcohol 15. To a solution of **14** (10.1 g, 26 mmol) in ether (0.6 L) at −78 °C was added DIBAL (1 M solution in hexane, 64 mL, 64 mmol). The reaction was quenched after 2 h at −78 °C by dropwise addition of water (20 mL). The precipitated salts were filtered and washed several times with ethyl acetate. All filtrates were combined and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (8:1 hexane/ethyl acetate) to afford 7.8 g (87%) of **15**: $[\alpha]^{24}_D$ −30.11° (*c* 0.445, $CHCl_3$): IR (neat) 3380, 2940, 2860, 1450, 1370, 1220, 1080, 995, 720, 680 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.73 (m, 2 H), 2.25 (m, 2 H), 3.16 (d, *J* = 8.7 Hz, 1 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.83 (m, 2 H), 4.11 (t, *J* = 7.0 Hz, 2 H), 4.45 (A of AB d, *J* = 12 Hz, 1 H), 4.51 (B of AB d, *J* = 12 Hz, 1 H), 5.71 (m, 1 H), 7.33 (m, 5 H); MS (*m/z*) $[M]^+$ 348, 333, 185, 127, 111, 91, 59, 43.

Epoxy Alcohol 16. To a suspension of powdered 4-Å molecular sieves (3 g) in CH_2Cl_2 at −40 °C was added titanium(IV) isopropoxide (1.1 mL, 3.4 mmol) followed by addition of (−)-diethyl D-tartrate (0.8 mL, 4.2 mmol). After the mixture was stirred for 15 min, a solution of **15** (8 g, 23 mmol) in CH_2Cl_2 (20 mL) was added, and stirring was continued for 30 min prior to addition of *tert*-butyl hydroperoxide (3.8 M solution in toluene, 9.2 mL, 35 mmol). The reaction mixture was warmed to 0 °C over 7 h and then quenched by pouring into a 1-L Erlenmeyer flask containing a mixture of ether (0.3 L) and saturated Na_2SO_4(aq) (9 mL). After mixture was stirred vigorously for 1 h, the precipitated titanium salts were filtered and washed with additional ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 6.7 g (80%) of **16**: $[\alpha]^{24}_D$ −9.43° (*c* 0.53, $CHCl_3$): IR (neat) 3420, 2980, 2860, 1450, 1375, 1220, 1180, 1080, 895, 720, 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.90 (s, 3 H), 1.30 (s, 6 H), 1.35 (m, 1 H), 1.65 (m, 1 H), 1.83 (m, 2 H), 2.95 (m, 1 H), 3.08 (m, 1 H), 3.16 (d, *J* = 8.6 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.62 (m, 1 H), 3.78–3.95 (m, 3 H), 4.46 (A of AB d, *J* = 12 Hz, 1 H), 4.50 (B of AB d, *J* = 12 Hz, 1 H), 7.32 (m, 5 H); HRMS $[M - CH_3]^+$ calcd 349.2015, found 349.2011.

Diol 17. To a solution of **16** (6.7g, 18.8 mmol) in THF (300 mL) at −40 °C was added dropwise Red-Al (3.4 M solution in toluene, 21.4 mL, 75 mmol). The reaction temperature was maintained at −23° to −20 °C for 72 h, whereupon the reaction was quenched by addition of water (10 mL). Ether (100 mL) was added, and the quenched solution was vigorously stirred for 2 h before the precipitated salts were filtered. The filtrate was concentrated in vacuo to give 5.1 g of crude **17**, a pale yellow oil which was used in the next step without further purification. A small sample was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) for analytical purposes: IR ($CHCl_3$) 3490, 2800, 2760, 1390, 1215, 1095, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3 H), 0.82 (s, 3 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.46 (m, 2 H), 1.62 (m, 7 H), 3.08 (d, *J* = 9.0 Hz, 1 H), 3.22 (d, *J* = 8.0 Hz, 1 H), 3.77 (m, 2 H), 4.03 (m, 2 H), 4.37 (A of AB d, *J* = 12 Hz, 1 H), 4.41 (B of AB d, *J* = 12 Hz, 1 H), 7.26 (m, 5 H).

Silyl Ether 18. To a solution of crude **17** (5.1 g) in DMF (150 mL) at room temperature was added imidazole (2.3 g, 33 mmol) and chlorodiphenyl*tert*-butylsilane (5.9 mL, 23 mmol). After being stirred for 5 h, the reaction mixture was diluted with ether and washed with water and then saturated NaCl(aq). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (10:1 hexane/ethyl acetate) to afford 9.6 g (86%, two steps) of **18**: $[\alpha]^{24}_D$ −11.96° (*c* 1.53, $CHCl_3$); IR (neat) 3515, 2980, 2860, 1460, 1440, 1380, 1220, 1090, 730, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (s, 3 H), 0.89 (s, 3 H), 1.04 (s, 9 H), 1.28 (s, 3 H), 1.32 (s, 3 H), 1.38 (m, 1 H), 1.62–1.75 (m, 5 H), 3.15 (d, *J* = 8.7 Hz, 1 H), 3.30 (d, *J* = 8.6 Hz, 1 H), 3.35 (d, *J* = 3.5 Hz, 1 H), 3.84 (m, 3 H), 4.06 (m, 2 H), 4.43 (A of AB d, *J* = 13 Hz, 1 H), 4.49 (B of AB d, *J* = 13 Hz, 1 H), 7.3–7.4 (m, 11 H), 7.70 (m, 4 H); MS (*m/z*) $[M]^+$ 590, 255, 199, 91.

Methoxymethyl Ether 19. To a solution of **18** (7.2 g, 12 mmol) in diisopropylamine (25 mL) at 0 °C was added portionwise over 1.5 h (bromomethyl)methyl ether (5 mL, 60 mmol). The reaction was allowed to warm to ambient temperature and stirred for 15 h, whereupon CH_2Cl_2 (250 mL) was added. The resultant mixture was then washed with pH 7 phosphate buffer, and the organic layer was removed and dried over $MgSO_4$. After filtration and concentration in vacuo, the residual material (containing the amine) was filtered through SiO_2 (3:1 hexane/ethyl acetate) to yield 10.6 g of crude product. Further purification was accomplished by SiO_2 flash chromatography (30:1 hexane/ethyl acetate)

to give 6.82 g (85%) of **19**: $[\alpha]^{24}_D$ −12.75° (*c* 0.80, $CHCl_3$); IR (neat) 3068, 2960, 2860, 1470, 1430, 1380, 1220, 1100, 1035, 910, 815, 720, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.89 (s, 3 H), 1.04 (s, 9 H), 1.28 (s, 3 H), 1.29 (s, 3 H), 1.30 (m, 2 H), 1.60 (m, 2 H), 1.80 (, 2 H), 3.14 (d, *J* = 8.5 Hz, 1 H), 3.30 (m, 4 H), 3.35 (d, *J* = 6.8 Hz, 1 H), 3.7–3.85 (m, 4 H), 4.45 (m, 2 H), 4.65 (m, 2 H), 7.3–7.45 (m, 11 H), 7.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, decoupled) δ 19.7, 20.6, 24.3, 24.8, 26.9, 33.5, 37.7, 38.5, 42.2, 55.5, 60.4, 63.9, 69.5, 73.2, 73.3, 76.7, 96.7, 100.2, 127.3, 127.6, 128.2, 129.5, 134.0, 135.6; MS (*m/z*) $[M - CH_3]^+$ 633, 255, 199, 91, 45.

Alcohol 20. To a solution of **19** (2.8 g, 4.3 mmol) in absolute ethanol (20 mL) at 25 °C was added freshly neutralized W-2 Raney nickel, prepared by washing 6 mL of a pH 10, 50% slurry of Raney nickel (Aldrich) with 300 mL of water and 250 mL of absolute ethanol. The reaction mixture was heated at 50 °C for 4 h and subsequently filtered. The residual solids were washed with hot methanol, and the combined filtrate was concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (6:1 hexane/ethyl acetate) to give 2.1 g (88%) of **20**: $[\alpha]^{24}_D$ −14.0° (*c* 1.31, $CHCl_3$); IR ($CHCl_3$) 3500, 2937, 2883, 1460, 1423, 1374, 1201 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.86 (s, 3 H), 1.03 (s, 9 H), 1.32 (s, 6 H), 1.42 (m, 1 H), 1.62 (t, *J* = 6.7 Hz, 2 H), 1.79 (m, 3 H), 2.95 (s, 1-O*H*), 3.30 (s, 3 H), 3.35 (dd, *J* = 10, 4.9 Hz, 1 H), 3.54 (dd, *J* = 10, 4.7 Hz, 1 H), 3.72 (m, 3 H), 3.91 (m, 2 H), 4.61 (A of AB d, *J* = 6.6 Hz, 1 H), 4.65 (B of AB d, *J* = 6.6 Hz, 1 H), 7.37 (m, 6 H), 7.66 (m, 4 H).

Aldehyde 21. DMSO (1.1 mL, 14.2 mmol) was added dropwise to a solution of oxalyl chloride (0.7 mL, 8 mmol) in CH_2Cl_2 at −78 °C. After 5 min, a solution of **20** (2.1 g, 3.8 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h, whereupon triethylamine (2.5 mL, 18 mmol) was added. The resultant mixture was allowed to warm to 0 °C over 3 h and was subsequently quenched with water (20 mL). The organic layer was separated and washed with additional water and then saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford crude **21** (2.1 g), which was used in the next step without purification. A small sample was purified by SiO_2 chromatography (10:1 hexane/ethyl acetate) for analytical purposes: $[\alpha]^{24}_D$ −14.80° (*c* 1.28, $CHCl_3$); IR ($CHCl_3$) 2936, 2880, 2860, 1742, 1460, 1421, 1380, 1200, 1090, 815 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.04 (s, 9 H), 1.30 (s, 6 H), 1.46 (m, 1 H), 1.74 (m, 5 H), 3.30 (s, 3 H), 3.70 (t, *J* = 5.3 Hz, 2 H), 3.91 (m, 3 H), 4.62 (m, 2 H), 7.28 (m, 6 H), 7.66 (m, 4 H), 9.56 (s, 1 H).

Alcohol 22. To a solution of **21** (2.1g, 3.6 mmol) in THF (20 mL) at −78 °C was added MeLi (1.42 M in ether, 3.2 mL, 4.5 mmol) dropwise. After 25 min, the reaction was quenched by pouring into saturated $NaHCO_3$(aq) (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residual oil was purified by SiO_2 flash chromatography (3:1 hexane/ethyl acetate) to give 2.0 g (95%) of **22** as a ca. 2:1 mixture of diasteriomers: IR (neat) 3500, 2880, 1430, 1380, 1210, 1180 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ (diastereochemical shift when different is given in brackets) 0.67 [0.82] (s, 3 H), 0.90 [0.88] (s, 3 H), 1.05 (s, 9 H), 1.07 [1.10] (s, 3 H), 1.35 [1.38] (s, 6 H), 1.6–2.0 (m, 7 H), 3.32 (s, 3 H), 3.6–4.0 (m, 6 H), 4.63 (m, 2 H), 7.38 (m, 6 H), 7.66 (m, 4 H).

Ketone 23, Fragment A. DMSO (0.70 mL, 9.9 mmol) was added dropwise to a solution of oxalyl chloride (0.43 mL, 4.9 mmol) in CH_2Cl_2 (25 mL) at −78 °C. After 5 min, a solution of **22** (1.4g, 2.4 mmol) in CH_2Cl (5 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h, whereupon triethylamine (1.7 mL, 12 mmol) was added. The resultant mixture was allowed to warm to −30 °C over 4 h and subsequently quenched with water. The organic layer was separated and washed with additional water and then saturated NaCl(aq). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product. Purification was accomplished by SiO_2 flash chromatography (7:1 hexane/ethyl acetate) to give 1.28 g (92%) of **23**: $[\alpha]^{24}_D$ −60.0° (*c* 0.44, $CHCl_3$); IR (neat) 2936, 1708, 1430, 1382, 1226, 1172, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.28 (s, 6 H), 1.43 (m, 2 H), 1.68 (m, 2 H), 1.78 (m, 2 H), 2.15 (s, 3 H), 3.29 (s, 3 H), 3.72 (m, 2 H) 3.87 (m, 2 H), 3.96 (dd, *J* = 9, 7 Hz, 1 H), 4.59 (A of AB d, *J* = 6 Hz, 1 H), 4.63 (B of AB d, *J* = 6 Hz, 1 H), 7.39 (m, 6 H), 7.67 (m, 4 H); HRMS $[M - CH_3]^+$ calcd 555.3138, found 555.3141.

Experimental Procedures for Scheme III: Fragment A via Aldol Methodology. Aldehyde 24. A solution of CH_2Cl_2 (50 mL), *cis*-3-hexen-1-ol (1.0 g, 10 mmol), *N,N*-diisopropylamine (2.7 mL, 15 mmol), catalytic imidazole, and chlorodiphenyl*tert*-butylsilane (2.8 mL, 11 mmol) was stirred at room temperature for 40 h. The reaction mixture was poured into 3:1 hexane/ethyl acetate (200 mL) and washed with saturated $NaHCO_3$(aq) and saturated NaCl(aq). After drying over $MgSO_4$, filtration and concentration in vacuo led to 3.8 g of the crude silyl ether, which was used directly in the next step without purification. A small sample was purified by SiO_2 chromatography (15:1 hexane/ethyl acetate) for analytical purposes: IR (neat) 3100–2720, 1580, 1100–1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 8 Hz, 3 H), 1.02 (s, 9 H), 1.96 (m, 2 H), 2.28 (q, *J* = 7 Hz, 2 H), 3.62 (t, *J* = 8 Hz, 2 H), 5.36 (m, 2 H), 7.37 (m, 6 H), 7.64 (m, 4 H); MS (*m/z*) $[M]^+$ 338, 282, 281.

A stirred solution of this silyl ether (3.8 g, <10 mmol) in 4:1 CH_2Cl_2/MeOH (70 mL) was cooled to −78 °C and subjected to a steady flow of ozone. When the solution remained blue without additional ozone, dimethyl sulfide (3.0 mL, 41 mmol) was added and the cooling bath was removed. After 30 min, triethylamine (3.0 mL, 22 mmol) was added, and the reaction mixture was heated at reflux for 20 min. Phosphate buffer (200 mL, pH 7) was added and the aqueous layer was extracted with 4:1 hexane/ethyl acetate. After drying over $MgSO_4$, filtration, and concentration in vacuo, SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 2.9 g (87% two steps) of **24**: IR (neat) 3020–2800, 2720, 1740, 1130–1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 2.61 (dt, *J* = 7, 2 Hz, 2 H), 4.02 (t, *J* = 6 Hz, 2 H), 7.40 (m, 6 H), 7.64 (m, 4 H), 9.82 (t, *J* = 3 Hz, 1 H).

Thioester 26. A stirred solution of (*S*)-[3-(3-ethylpentyl)] ethanethioate (87 mg, 0.50 mmol) in pentane (3.0 mL) was cooled to −78 °C. After rapid addition of diisopropylethylamine (107 μL, 0.60 mmol), **2R** (127 μL, 0.60 mmol) was added dropwise. After 30 min the solution was warmed to 0 °C and stirred for 1 h to insure the formation of enolate **25**. Upon cooling to −78 °C, a solution of aldehyde **24** (200 mg, 0.65 mmol) in pentane (0.4 mL) was added dropwise. After 1 h the reaction mixture was warmed to room temperature for 10 min and subsequently quenched by addition of excess *N,N*-dimethylethanolamine. The mixture was diluted with saturated NH_4Cl(aq), extracted with ether, washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (8:1 hexane/ethyl acetate) gave 191 mg of **26** (79%, 89% ee [determined by use of $Eu(hfc)_3$ on the corresponding acetate derivative and corrected for the % ee of the reagent]): IR (neat) 3530–3300, 3000–2810, 1670, 1120–1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 9 H), 1.03 (s, 9 H), 1.77 (m, 2 H), 1.76 (q, *J* = 8 Hz, 6 H), 2.65 (m, 2 H), 3.40 (d, *J* = 4 Hz, 2 H), 3.81 (m, 2 H), 4.28 (m, 1 H), 7.38 (m, 6 H), 7.65 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 429.1919, found 429.1918.

Methoxymethyl Ether 27. A solution of dimethoxymethane (2.2 mL, 24 mmol) and **26** (200 mg, 0.44 mmol) in $CHCl_3$ (3.6 mL) at 0 °C was added to a slurry of P_2O_5 (1 g, 7 mmol) in $CHCl_3$ (3.6 mL) and stirred at 0 °C. After 1.5 h the reaction was complete by TLC and was quenched by addition of saturated Na_2CO_3(aq), extracted with ether, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude oil was purified by preparative TLC (10:1 hexane/ethyl acetate) to obtain 196 mg (91%) of **27**: IR 2980–2810, 1670, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7 Hz, 9 H), 1.04 (s, 9 H), 1.77 (q, *J* = 7 Hz, 6 H), 1.78 (m, 2 H), 2.63 (dd, *J* = 14, 7 Hz, 1 H), 2.77 (dd, *J* = 14, 7 Hz, 1 H), 3.27 (s, 3 H), 3.72 (m, 2 H), 4.20 (m, 1 H), 4.59 (A of AB d, *J* = 7 Hz, 1 H), 4.61 (B of AB, *J* = 7 Hz, 1 H), 7.38 (m, 6 H), 7.62 (m, 4 H); MS (*m/z*) $[M]^+$ 530, 473, 472.

Ketone 28. At 0 °C, DMS·CuBr (250 mg, 1.2 mmol) was stirred in ether (5.0 mL), and MeLi (1.7 M in ether, 1.4 mL, 2.4 mmol) was added dropwise. The reaction vessel was cooled to −78 °C, and a solution of **27** (196 mg, 0.37 mmol) was added dropwise in ether (0.5 mL). The reaction mixture was warmed −15 °C and stirred for 1 h. After quenching with saturated NH_4Cl(aq) and extracting with ether, the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (8:1 hexane/ethyl acetate) led to 145 mg (94%) of **28**: IR

2980–2820, 1710, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.85 m, 2 H), 2.12 (s, 3 H), 2.55 (dd, J = 14, 7 Hz, 1 H), 2.74 (dd, J = 14, 7 Hz, 1 H), 3.25 (s, 3 H), 3.72 (m, 2 H), 4.22 (m, 1 H), 4.58 (AB apparent singlet, 2 H), 7.37 (m, 6 H), 7.63 (m, 4 H); HRMS $[M - CH_3]^+$ calcd 399.1992, found 399.1989.

Ketol 30. A solution of **28** (119 mg, 0.29 mmol) in ether (2.5 mL) and pentane (2.5 mL) was stirred at −78 °C. *N,N*-Diisopropylethylamine (0.20 mL, 0.66 mmol) was added rapidly, followed by dropwise addition of **2S** (73 μL, 0.33 mmol) (analogously, **2R** and *meso*-2,5-dimethylborolanyl triflate were used in their respective reactions). After 2 h, a solution of aldehyde **29** (66 mg, 0.35 mmol) was added dropwise in pentane (0.5 mL). After an additional hour the reaction was quenched by addition of excess *N,N*-dimethylethanolamine, warmed to 0 °C, and diluted with saturated NH_4Cl(aq). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. After preparative TLC (6:1 hexane/ethyl acetate), 152 mg (87%) of **29** was obtained: IR (neat) 3800–3300, 2990–2840, 1720, 1100–1070 cm^{-1}; ^1H NMR (300 MHz, CDL_3) δ 0.87 (s, 3 H), 0.94 (s, 3 H), 1.07 (s, 9 H), 1.79 (m, 2 H), 2.52 (m, 1 H) 2.60 (dd, J = 15, 6 Hz, 1 H), 2.80 (dd, J = 15, 7 Hz, 1 H), 3.28 (s, 3 H), 3.29 (m, 1 H), 3.42 (d, J = 5 Hz, 1 H), 3.74 (m, 2 H), 4.02 (m, 1 H), 4.30 (m, 1 H), 4.51 (s, 2 H), 4.60 (m, 2 H), 7.33 (m, 5 H), 7.40 (m, 6 H), 7.66 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 549.2672, found 549.2669.

Diol 31. To a solution of **30** (108 mg, 0.18 mmol) in MeCN (1.0 mL) at −78 °C was added a solution of $Me_4NB(OAc)_3H$ (230 mg, 0.90 mmol) in 1:1 MeCN/AcOH (2.0 mL). The reaction was maintained at −20 °C and stirred for 38 h. The mixture was diluted with ether and quenched with solid $NaHCO_3$. The organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (2:1 hexane/ethyl acetate) gave 77 mg of a major product and 16 mg of a minor product (86% combined): ^1H NMR (250 MHz, $CDCl_3$) (where the chemical shift differs in the minor diastereomer it appears in brackets) δ 0.92 [0.84] (s, 3 H), 0.94 [0.90] (s, 3 H), 1.06 [1.07] (s, 9 H), 1.2–1.7 (m, 6 H), 3.36 (m, 2 H), 3.38 [3.32] (s, 3 H), 3.45 [3.50] (OH, 1 H), 3.53 [3.62] (OH, 1 H) 3.76 (m, 2 H), 3.83 (m, 1 H), 4.07 (m, 1 H), 4.18 (m, 1 H), 4.48 (A of AB d, J = 8 Hz, 1 H), 4.51 (B of AB d, J = 8 Hz, 1 H), 4.63 (d, J = 6 Hz, 1 H), 4.69 (d, J = 6 Hz, 1 H), 7.32 (m, 5 H), 7.40 (m, 6 H), 7.67 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 551.2828, found 551.2830.

Fragment A. Intermediate 19 from Diol 31. To a solution of diol **31** (5*R*,7*S*) (72 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) was added 2,2-dimethoxypropane (12 μL, 0.10 mmol) and catalytic PPTS (2 mg). After 1.5 h the reaction was complete, and the mixture was diluted with ether. The organics were washed with saturated $CuSO_4$(aq), water, saturated $NaHCO_3$(aq), and saturated NaCl(aq) and dried over $MgSO_4$, filtered, and concentrated in vacuo. Preparative TLC (20:1 hexane/ethyl acetate) led to 72 mg (98%) of **19**, identical with authentic **19** (prepared as illustrated in Scheme II) as indicated by ^1H NMR, ^{13}C NMR, IR, MS, and $[\alpha]^{24}_D$ [cf. −12.64° (*c* 0.72, $CHCl_3$)].

Experimental Procedures for Scheme IV: Fragment B. Alcohol 33 via THP Ether 32. To a solution of 3-butyn-1-ol (3.1 g, 30 mmol) and DHP (2.4 g, 29 mmol) in CH_2Cl_2 (50 mL) was added catalytic PPTS (10 mg). After 3 h the reaction was complete by TLC, and the reaction mixture was diluted with ether and washed with 50% NaCl(aq). The aqueous washes were back-extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Short-path distillation (79–82 °C, 14 mm) afforded 4.8 g (89%) of **32**: IR (neat) 3290–3240, 2940–2820, 2100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.88 (m, 6 H), 1.96 (t, J = 2.3 Hz, 1 H), 2.48 (dt, J = 6.7, 2.3 Hz, 2 H), 3.50 (m, 2 H), 3.82 (m, 2 H), 4.63 (t, J = 3.9 Hz, 1 H).

To a solution of **32** (4.8 g, 31 mmol) in THF (100 mL) at −78 °C was added *n*-BuLi (1.4 M solution in hexanes, 25 mL, 36 mmol) dropwise. After 1 h at −30 °C, gaseous formaldehyde (excess) was bubbled through the solution for 30 min. The reaction mixture was quenched with saturated NH_4Cl(aq) and diluted with ether. The organic layer was separated, washed with saturated NaCl(aq), and concentrated in vacuo. Flash SiO_2 chromatography (2:1 hexane/ethyl acetate) led to 4.9 g (89%) of **33**: IR (neat) 3520–3200, 2920–2810, 2210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4–2.0 (m, 6 H), 2.50 (tt, J = 7, 3 Hz, 2 H), 3.50 (m, 2 H), 3.82 (m, 2 H), 4.22 (t, J = 2 Hz, 2 H), 4.61 (t, J = 5 Hz, 1 H); HRMS $[M - H]^+$ calcd 183.1021, found 183.1021.

Iodide 34. To ether (600 mL) was added Red-Al (3.4 M in toluene, 77 mL, 272 mmol). To this mechanically stirred solution maintained at 0 °C was added **33** (25 g, 136 mmol) in ether (50 mL), dropwise. After 1 h at room temperature, the reaction mixture was recooled to 0 °C and quenched by addition of ethyl acetate (13 mL, 133 mmol). After the mixture was cooled to −78 °C, iodine (50 g, 197 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched by slow addition of saturated Na_2SO_3(aq), and the organic layer was separated and successively washed with Na_2SO_3(aq), water, and saturated NaCl(aq). The resulting organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (2:1 hexane/ethyl acetate) gave 39.5 g (94%) of **34**: IR (neat) 3510–3180, 2980–2820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.4–1.8 (m, 6 H), 2.79 (dt, J = 6, 2 Hz, 2 H), 3.51 (m, 2 H), 3.83 (m, 2 H), 4.20 (t, J = 6 Hz, 2 H), 4.66 (t, J = 2 Hz, 1 H), 5.95 (t, J = 5 Hz, 1 H); MS (*m/z*) $[M]^+$ 312, 185, 85.

Silyl Ether 35. To a solution of **34** (12.0 g, 38.5 mmol) and imidazole (5.54 g, 82.0 mmol) in DMF (150 mL) at 0 °C was added chlorodiphenyl*tert*-butylsilane (10.5 mL, 40.5 mmol). After being stirred for 30 min at 0 °C and 5 min at room temperature, the reaction mixture was quenched with saturated NH_4Cl(aq), extracted with ether, washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 21 g (crude weight) of **35**, which was used in the next step without further purification. A small sample was purified by flash SiO_2 chromatography (12:1 hexane/ethyl acetate) for analytical purposes: IR (neat) 3100–2830, 1160–1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.4–1.8 (m, 6 H), 2.73 (dt, J = 2, 6 Hz, 2 H), 3.49 (m, 2 H), 3.80 (m, 2 H), 4.22 (dd, J = 2, 4 Hz, 2 H), 4.59 (t, J = 4 Hz, 1 H) 5.94 (t, J = 5 Hz, 1 H), 7.38 (m, 6 H), 7.65 (m, 4 H).

Bisolefin 36. To a solution of **35** (21 g, 38 mmol) in THF (100 mL) at −78 °C was added CuI (0.43 g, 2.3 mmol) and then allylmagnesium bromide (1.0 M ether solution, 53 mL, 53 mmol) dropwise. The mixture was allowed to warm to 0 °C over 2 h and was stirred for an additional 2 h, whereupon it was quenched with saturated NH_4Cl(aq). The mixture was extracted with ether and the combined organics were washed with saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (12:1 hexane/ethyl acetate) led to 14.6 g (82%, two steps) of **36**: IR (neat) 3080–2780, 1630, 1120–1000, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.4–1.7 (m, 6 H), 2.30 (dt, J = 7, 2 Hz, 2 H), 2.63 (d, J = 7 Hz, 2 H), 3.46 (m, 2 H), 3.83 (m, 2 H), 4.23 (d, J = 6 Hz, 2 H), 4.60 (t, J = 4 Hz, 1 H), 4.92 (m, 2 H), 5.54 (m, 2 H), 7.40 (m, 6 H), 7.68 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 407.2042, found 407.2044.

Alcohol 37. To a solution of **36** (14.6 g, 31.5 mmol) in ethanol (100 mL) was added PPTS (0.95 g, 3.8 mmol), and the mixture was maintained at 50 °C for 2 h. Upon cooling, the reaction mixture was quenched with saturated $NaHCO_3$(aq), and the ethanol was removed in vacuo. The resulting cloudy solution was diluted with ether, and the aqueous layer was removed. The ethereal solution was washed with saturated NaCl(aq), dried over $MgSO_4$, and concentrated in vacuo. Flash SiO_2 chromatography (4:1 hexane/ethyl acetate) led to 11.0 g (92%) of **37**: IR (neat) 3580–3200, 3080–2800, 1630, 1120–1000, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.42 (br s, 1 H), 2.24 (dt, J = 6, 2 Hz, 2 H), 2.61 (d, J = 6 Hz, 2 H), 3.64 (t, J = 6 Hz, 2 H), 4.26 (d, J = 6 Hz, 2 H), 4.93 (m, 2 H), 5.58 (m, 2 H), 7.41 (m, 6 H), 7.68 (m, 4 H); HRMS $[M - C_4H_9]^+$ calcd 323.1468, found 323.1465.

Aldehyde 38, Fragment B. To a solution of pyridine (6.6 mL, 82 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added CrO_3 (4.1 g, 41 mmol) in one portion. After stirring for 15 min at room temperature, a solution of **37** (2.4 g, 6.3 mmol) in CH_2Cl_2 (10 mL) was rapidly added. The mixture was stirred for 15 min at room temperature, diluted with ether, and washed with 5% NaOH(aq), 5% HCl(aq), water, and saturated $NaHCO_3$(aq). The ethereal solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting 2.4 g of crude **38** (>95% purity by ^1H NMR) was used in the next reaction without further purification (substantial decomposition occurs on SiO_2 chromatography): IR (neat)

3060–2800, 2730–2660, 1710, 1630, 1100–1000 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.03 (s, 9 H), 2.62 (nd, J = 6 Hz, 2 H), 3.01 (d, J = 2 Hz, 2 H), 4.26 (d, J = 6 Hz, 2 H), 4.93 nm, 2 H), 5.56 (m, 2 H), 7.40 (m, 6 H), 7.68 (m, 6 H), 9.54 (t, J = 2 Hz, 1 H).

Experimental Procedures for Scheme V: Completion of the AB Fragment. The AB Coupling: Ketol 39 from 23 (Fragment A) and 38 (Fragment B). To a solution of **23** (500 mg, 0.90 mmol) in ether (15 mL) at −78 °C was added diisopropylethylamine (0.62 mL, 3.6 mmol) followed by the dropwise addition of **2R** (225 mg, 0.90 mmol) (analogously, **1R** and diethylboryl triflate were used in their respective reactions). After stirring for 30 min, a solution of **38** (azeotroped with toluene, 500 mg, 1.3 mmol) in ether (2 mL) was added, and the resultant solution was stirred for an additional 1 h at −78 °C. The reaction was quenched by addition of *N,N*-dimethylethanolamine, warmed to 0 °C, and diluted with saturated NH_4(Cl(aq) and ether. The organic layer separated and successively washed with saturated NH_4Cl(aq) and saturated NaCl(aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash SiO_2 chromatography (4:1 hexane/ethyl acetate) yielded 718 mg (82%) of **39**: IR (neat) 3080–2800, 1695, 1420, 1130–1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 21 H), 1.12 (s, 3 H), 1.28 (s, 6 H), 1.3–1.9 (m, 8 H), 2.15 (m, J = 7 Hz, 2 H), 2.63 (m, 3 H), 3.00 [2.95: minor diastereomer] (d, J = 2 Hz, 1 H) 3.30 (s, 3 H), 3.7–4.0 (m, 6 H), 4.13 (m, 1 H), 4.23 (d, J = 5.9 Hz, 2 H), 4.60 (A of AB d, J = 6.6 Hz, 1 H), 4.63 (B of AB d, J = 6.7 Hz, 1 H), 4.92 (m, 2 H), 5.57 (m, 2 H), 7.39 (m, 12 H), 7.67 (m, 8 H); HRMS [M − OCH_3 − C_4H_9 − H]$^+$ calcd 859.4426, found 859.4422.

Methyl Acetal 40. To a stirring solution of **39** (963 mg, 1.06 mmol) in methanol (16 mL) and methyl orthoformate (2.3 mL) was added PPTS (25 mg, 0.10 mmol). After stirring for 2.5 h at ambient temperature, the mixture was quenched with aqueous $NaHCO_3$, extracted with ether, and washed with water and saturated NaCl(aq). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Analysis of the crude mixture (^1H NMR) revealed a 6:1 ratio of diastereomers. Flash SiO_2 chromatography (5:1 hexane/ethyl acetate) yielded 143 mg of the minor diastereomer contaminated with **40** and 638 mg of pure **40** (85% combined): IR (neat) 3600–3220, 3040–2810, 2220, 1700, 1140, 1000, 900, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (when data from the minor diastereomer differs, it appears in brackets) δ 0.89 (s, 3 H), 0.98 (s, 3 H), 1.04 (s, 18 H), 1.2–1.9 (m, 6 H), 2.03 (dd, J = 13, 6 Hz, 1 H), 2.28 [2.23] (dd, J = 13, 6 Hz, 1 H), 2.66 [2.67] (m, 1 H), 3.21 [3.20] (s, 3 H), 3.29 [3.30] (s, 3 H), 3.55 (br s, 1 H), 3.75 (t, J = 6.2 Hz, 2 H), 3.83 (m, 1 H), 3.91 (m, 1 H), 4.02 (m, 1 H), 4.17 [4.22] (m, 1 H), 4.22 (d, J = 6 [7] Hz, 2 H), 4.60 (A of AB d, J = 6.4 Hz, 1 H), 4.62 (B of AB, J = 6.2 Hz, 1 H), 4.91 (m, 2 H), 5.57 (m, 2 H), 7.38 (m, 12 H), 7.67 (m, 8 H); MS (m/z) [M − CH_3O − H]$^+$ 891, 877, 874, 873, 872, 835, 834, 833.

Organomercurial Chloride 41. To a solution of **40** (633 mg, 0.69 mmol) in THF (6.9 mL) and methanol (1.7 mL) at room temperature was added portionwise $Hg(OAc)_2$ (264 mg, 0.83 mmol). The colorless solution was stirred for 5 h, whereupon the reaction was quenched by addition of saturated KCl(aq). After the quenched reaction mixture was stirred for 30 min, water (4 mL) was added and the resultant mixture was extracted with ether. The combined organic extract was washed with saturated $NaHCO_3$(aq) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to afford the crude product, which was immediately acetylated without further purification. The crude organomercurial product was treated with AcCl (0.254 mL, 3.45 mmol) in CH_2Cl_2 (17 mL) and pyridine (0.86 mL) at 0 °C for 2 h. The reaction was quenched by addition of water, and the products were extracted with ether. The combined organic extract was washed with saturated $CuSO_4$(aq), water, and saturated NaCl(aq) and dried over $MgSO_4$. Filtration and concentration in vacuo afforded crude **41**, which was purified by flash SiO_2 chromatography (4:1 hexane/ethyl acetate) to yield 694 mg (84%) of **41** as a white foam: IR (CH_2Cl_2) 3020–2800, 1735, 1700, 1230, 1110–980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.04 (s, 21 H), 1.16–2.33 (m, 12 H), 2.03 (s, 3 H), 3.13 + 3.17 (s, 3 H), 3.28 + 3.30 (s, 3 H), 3.30 + 3.54 (m, 1 H), 3.76 (m, 4 H), 3.87 (m, 2 H), 4.18 (m, 3 H), 4.59 + 4.61 (AB apparent singlets, 2 H), 5.17 + 5.22 (m, 1 H), 5.40 + 5.48 (t, J = 7 Hz, 1 H), 7.43 (m, 12 H), 7.68 (m, 8 H); MS (m/z) [M − CH_3O]$^+$ 1168, 1148, 1145, 1141, 1111, 1061.

Alcohol 42. Through a solution of **41** (552 mg, 0.46 mmol) in CH_2Cl_2 (13 mL) was passed a steady stream of O_2 for 10 min from a compressed gas cylinder via a glass capillary tube (solution volume was maintained at >10 mL by replacing evaporated CH_2Cl_2). In a separate vessel, a slurry of $NaBH_4$ (160 mg, 4 mmol) was stirred in DMF (4 mL) and flushed with oxygen in a similar manner for 2–3 min. The borohydride solution was then slowly added to the organomercural chloride solution via cannula over a period of 5 min. Oxygen was passed through the reaction mixture for the next 1–2 h, whereupon the reaction was quenched by addition of saturated NH_4Cl(aq) and extracted with ether. The combined organic extract was washed with water and saturated $NaHCO_3$ and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the crude product was purified by flash SiO_2 chromatography (5:1 hexane/ethyl acetate) to give 365 mg (81%) of **42** as a 1:1 mixture of diastereomers: IR (CH_2Cl_2) 3600–3240, 3040–2810, 1740, 1700, 1140, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 + 0.94 (s, 3 H), 1.04 (s, 21 H), 1.2–2.3 (m, 10 H), 2.03 + 2.04 (s, 3 H), 3.14 + 3.18 (s, 3 H), 3.29 (s, 3 H), 3.3–3.6 (m, 2 H), 3.64 + 4.09 (m, 1 H), 3.73 (m, 3 H), 3.90 (m, 1 H), 4.19 (m, 2 H), 4.60 (AB apparent singlet, 2 H), 5.19 (m, 1 H), 5.44 + 5.47 (t, J = 7Hz, 1 H), 7.35–7.42 (m, 12 H), 7.66 (m, 8 H); HRMS [M − CH_3O − CH_3O]$^+$ calcd 916.4766, found 916.4770.

Aldehyde 44, the AB Fragment (via 43, its 1:1 diastereometric mixture). To a solution of oxalyl chloride (32 μL, 0.37 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DMSO (52 μL, 0.74 mmol). After 5 min, a solution of **42** (180 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After an additional 30 min at −78 °C, triethylamine (136 μL, 0.90 mmol) was added dropwise, and the mixture was warmed to ambient temperature, stirred for 30 min, and diluted with ether. The organic mixture was washed with 10% HCl(aq), water, and saturated $NaHCO_3$ (aq), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude **43**, which hydrates readily, was azeotroped with toluene and subjected to epimerization without further purification: ^1H NMR (250 MHz, $CDCl_3$) (chemical shifts for *cis*-**43** is presented with data for *trans*-**43** in brackets when different) δ 0.94 [0.93] (s, 3 H), 1.03 (s, 21 H), 2.04 [2.05] (s, 3 H), 1.62–2.12 (m, 8 H), 2.27 (d, J = 16 Hz, 1 H), 2.43 (d, J = 16 Hz, 1 H), 3.16 (m, 1 H), 3.19 (s, 3 H), 3.28 (s, 3 H), 3.44 (dd, J = 11, 2.7 Hz, 1 H), 3.58 (m, 1 H), 3.75 (t, J = 6.0 Hz, 2 H), 3.91 (m, 1 H), 4.21 (d, J = 6.6 Hz, 2 H), 4.59 (AB apparent singlet, 2 H), 5.19 (dd, J = 16, 5.4 Hz, 1 H), 5.47 [5.43] (t, J = 6.6 Hz, 1 H), 7.62–7.65 (m, 12 H), 7.67 (m, 8 H), 9.53 [9.62] (s, 1 H).

To a solution of dried aldehyde (180 mg, 0.18 mmol) in benzene (9 mL) was added active Al_2O_3 (Woelm B, 3% H_2O [Act. II], 1.8 g). The resulting slurry was stirred for 20 h at ambient temperature, filtered through Celite (washing with CH_2Cl_2 and ether), and concentrated in vacuo to yield 130 mg (74%) of **44** (*cis*-**43**) (9:1 cis/trans by ^1H NMR): ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 1.03 (s, 21 H), 2.04 (s, 3 H), 1.62–2.12 (m, 8 H), 2.27 (d, J = 16 Hz, 1 H), 2.43 (d, J = 16 Hz, 1 H), 3.16 (m, 1 H), 3.19 (s, 3 H), 3.28 (s, 3 H), 3.44 (dd, J = 11, 2.7 Hz, 1 H), 3.58 (m, 1 H), 3.75 (t, J = 6.0 Hz, 2 H), 3.91 (m, 1 H), 4.21 (d, J = 6.6 Hz, 2 H), 4.59 (apparent singlet, 2 H), 5.19 (dd, J = 16, 5.4 Hz, 1 H), 5.47 (t, J = 6.6 Hz, 1 H), 7.62–7.65 (m, 12 H), 7.67 (m, 8 H), 9.53 (s, 1 H).

Acknowledgment. This work was supported by the National Institutes of Health (Grants CA37804 and CA48175). M.H.N. and J.C.R. are NIH postdoctoral and predoctoral trainees (NCI T32-CA09112), respectively, and P.S. is a Swedish Natural Science Research Council postdoctoral fellow.

Supplementary Material Available: ^1H NMR spectra for compounds **3–28**, **30–42**, and **44** (39 pages). Ordering information is given on any current masthead page.