Total Synthesis of the Cytotoxic Macrocycle (+)-Hitachimycin

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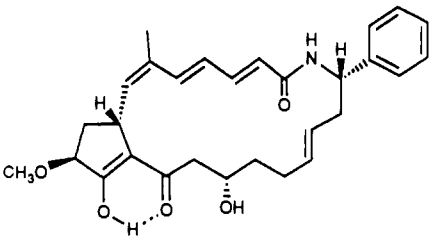
Abstract: The first total synthesis of the antitumor antibiotic (+)-hitachimycin (a.k.a. stubomycin) (**1**) has been achieved in 22 steps and 1.1% overall yield. The cornerstone of the synthetic strategy was a highly stereoselective three-component coupling of (−)-5-methoxycyclopentenone (**4**) with a zincate derived from vinyl iodide **3a** and aldehyde (−)-**51**.

The macrocyclic antitumor antibiotic (+)-hitachimycin (a.k.a. stubomycin) (**1**) was independently isolated by the Ōmura[1] and Umezawa[2] groups in the early 1980s. Umezawa and co-workers subsequently documented the cytotoxic activity of **1** against Ehrlich ascites carcinoma, P388 lymphocytic leukemia, and HeLa S_3 cells.[1-4] Initial structure elucidation studies by Ōmura et al.



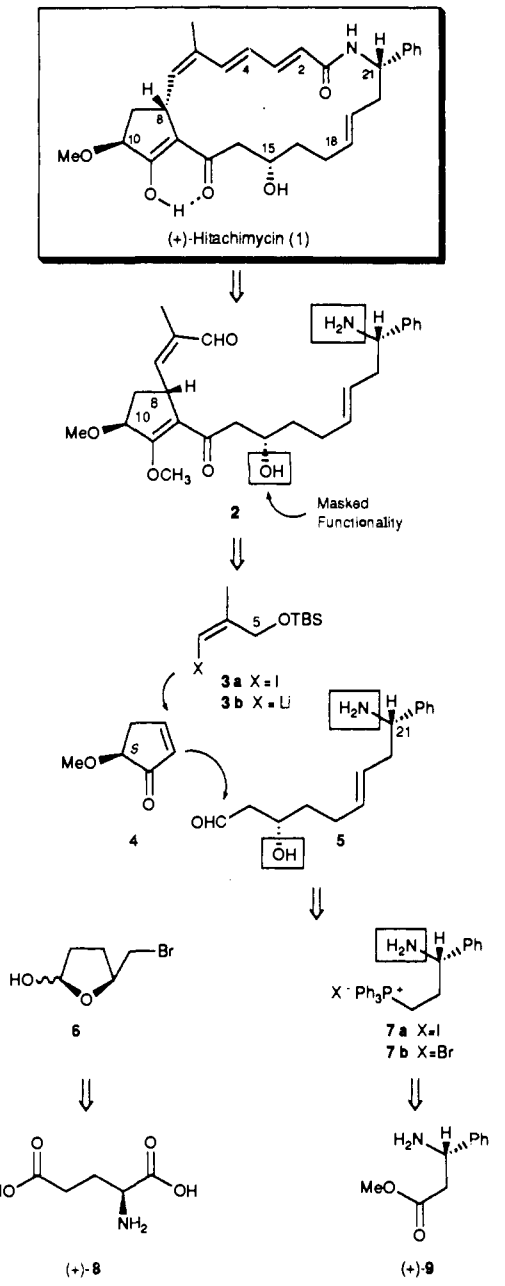
(+)-Hitachimycin (1)
(a.k.a. Stubomycin)

revealed the novel architecture of **1**, but the configurations at two stereocenters remained undefined. As a prelude to a synthetic venture, we determined the complete relative and absolute stereochemistry as well as the crystal and solution conformations of **1**.[5] Herein we report full details of experiments culminating in the first (and to date only) total synthesis of (+)-hitachimycin.[6]

Synthetic Plan. From the retrosynthetic perspective, the hitachimycin structure embodies several challenging features. Of particular concern was the instability of the carbonyl-conjugated (*E,E,Z*) triene unit, which dictated installation late in the synthetic sequence. Racemization at C(8) and C(10) as well as β-elimination of the C(15) hydroxyl also loomed as potential pitfalls. These factors influenced the approach outlined in Scheme I, wherein removal of the triene unit served as the initial disconnection.

Importantly, the first retron (**2**) manifests a trans disposition of the C(10) methoxy and C(8) alkenyl substituents, an arrangement which invites disconnection into three subunits. The latter could be assembled synthetically via a one-step, three-component coupling, a strategy first exploited by Stork and Isobe[7] and more recently popularized by Noyori.[8,9] Model studies in our laboratory suggested that the requisite trans orientation of

Scheme I. Retrosynthetic Analysis



(1) Ōmura, S.; Nakagawa, A.; Tanaka, Y. In *Trends in Antibiotic Research*; Umezawa, H., Ed.; Japan Antibiotics Research Association: Tokyo, 1982; pp 135-145.
(2) Umezawa, I.; Takeshima, H.; Komiyama, K.; Koh, Y.; Yamamoto, H.; Kawaguchi, M. *J. Antibiot.* **1981**, *34*, 259.
(3) Komiyama, K.; Edanami, K.; Yamamoto, H.; Umezawa, I. *J. Antibiot.* **1982**, *35*, 703.
(4) For recent studies on the biological activity of hitachimycin analogs, see: (a) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Nakagawa, A.; Ōmura, S. *J. Antibiot.* **1988**, *41*, 614. (b) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Zhi-Bo, Y.; Nakagawa, A.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 718. (c) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Zhi-Bo, Y.; Nakagawa, A.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 1114.
(5) Smith, A. B., III; Wood, J. L.; Rizzo, C. J.; Furst, G. T.; Carroll, P. J.; Donohue, J.; Ōmura, S. *J. Am. Chem. Soc.*, preceding article in this issue.
(6) For a preliminary communication, see: Smith, A. B., III; Rano, T. A.; Chida, N.; Sulikowski, G. A. *J. Org. Chem.* **1990**, *55*, 1136.
(7) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

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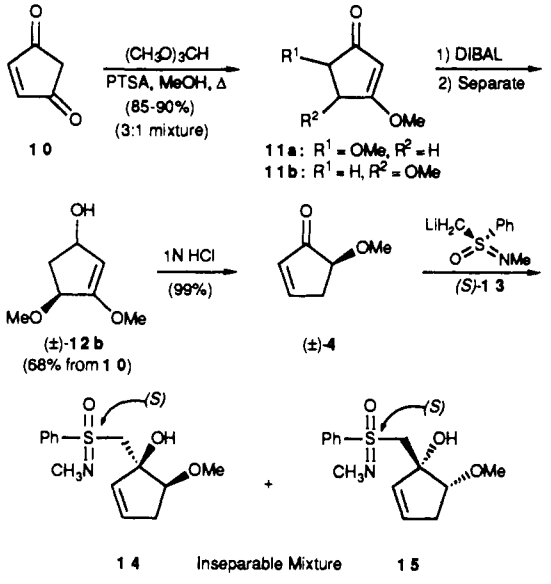
the nucleophile and the methoxy group could in fact be established via a 1,4-addition;[10] this maneuver thus emerged as the cornerstone of our synthetic plan.

Vinyl iodide **3a** and (*S*)-5-methoxycyclopentenone (**4**),[11] two of the three components which would ultimately make up the C(5–21) segment of (+)-**1**, were anticipated to be readily available. Aldehyde **5**, the third key fragment, was envisioned to arise via Wittig–Schlosser olefination of bromo lactol **6** with the ylide generated from phosphonium salt **7**, followed by chain extension of the resultant epoxide. In the execution of this scheme, the selection of appropriate protective groups proved to be unexpectedly difficult (vide infra). Scalemic **6** and **7** would in turn derive from (*S*)-(+)-glutamic acid (**8**) and (*S*)-(+)-β-phenyl-β-alanine methyl ester (**9**), respectively.[12] As neither the pool of chiral substrates nor asymmetric synthesis seemed to offer a convenient route to scalemic 5-methoxycyclopentenone (**4**), a resolution of this component was envisioned.

Preparation of (−)-4 via a Johnson Sulfoximine Resolution. The synthesis of (±)-**4** was based on a preparation of 5-ethoxy-2-cyclopentenone reported by DePuy and co-workers in 1962.[13,14] Treatment of 2-cyclopentene-1,4-dione (**10**) with trimethyl orthoformate in acidic methanol quantitatively furnished the desired vinylogous ester **11b** and the regioisomer **11a** as a 3:1 mixture (Scheme II). Much to our surprise, the products proved to be

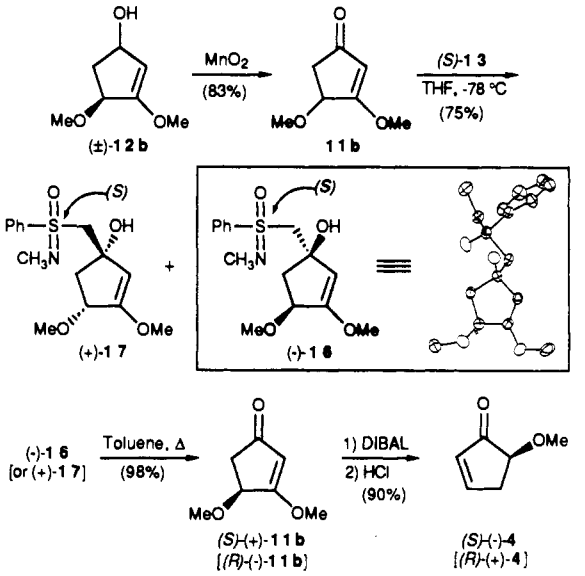
Scheme II



inseparable by flash column chromatography or spinning band distillation. However, 1,2-reduction of the mixture with DIBAL proceeded with high facial selectivity (ca. 10:1), affording two chromatographically separable alcohols in 68 and 23% yields, respectively. Subsequent treatment of the major product (**12b**) with 1 M HCl then cleanly generated (±)-**4** (99%).

With multigram quantities of (±)-**4** in hand, we turned next to the Johnson sulfoximine resolution protocol.[15] Although lithiated (*S*)-sulfoximine **13** added readily to **4** in a 1,2 fashion (Scheme II), the resultant diastereomers defied chromatographic separation. Undaunted, we revisited vinylogous ester **11b**, now readily available uncontaminated by **11a** via manganese dioxide oxidation of **12b** (Scheme III). Highly stereoselective addition

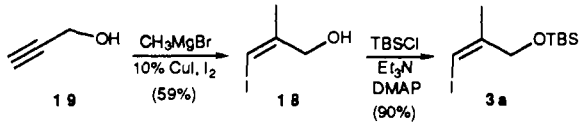
Scheme III



of **13** to **11b** (i.e., anti to the methoxyl) generated the readily separable diastereomeric alcohols (−)-**16** and (+)-**17**. Subsequent crystallization of the more polar diastereomer from diethyl ether provided crystals suitable for X-ray analysis, which in turn led to unambiguous assignment of the (*S,S*) configuration of (−)-**16**. To complete the resolution, **16** was subjected to thermolysis in toluene at reflux, affording (*S*)-(+)-**11b** in 98% yield. Likewise, the (*S,R*) diastereomer **17** provided (*R*)-(−)-**11b** in 85% yield. DIBAL reductions of (*S*)-(+)- and (*R*)-(−)-**11b** followed by treatment with 1 M HCl then provided (*S*)-(−)- and (*R*)-(+)-**4**, respectively. The enantiomeric purities (>95% ee) were readily established via ^{1}H NMR analysis employing the shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium(III) [Eu(hfc)$_3$].

Construction of Vinyl Iodide 3a. We next focused attention on alkenyl iodide **3a**. Here Duboudin's procedure was utilized for the preparation of the known iodo alcohol **18** from propargyl alcohol (**19**) (Scheme IV).[16] Protection with TBSCl then afforded **3a** as a distillable oil.

Scheme IV



Synthesis of the C(13–21) Aldehyde 5. The third subunit required for the tricomponent coupling, aldehyde **5**, presented a considerable synthetic challenge. In particular, control of the olefin geometry and selection of a nitrogen protecting group emerged as critical issues. As outlined in Scheme I, the proposed Wittig–Schlosser protocol required the preparation of bromo lactol **6** and a suitably protected phosphonium halide **7**. The resiliency of sulfonamides under basic conditions and the potential for

(8) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299. (c) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718. (d) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785.

(9) For a review of enolate trapping in conjunction with organocopper conjugate additions, see: Taylor, R. J. K. *Synthesis* **1985**, 364.

(10) (a) Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Tetrahedron Lett.* **1988**, *29*, 439. (b) Smith, A. B., III; Trumper, P. K. *Tetrahedron Lett.* **1988**, *29*, 443.

(11) Wilson, S. R.; Chen, H.-T. *Bioorg. Chem.* **1980**, *9*, 212.

(12) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459. Also see: Pietsch, H. *Tetrahedron Lett.* **1972**, 2789. Kawahara, S.; Kawakami, H. *Yakugaku Zasshi* **1961**, *81*, 1063.

(13) DePuy, C. H.; Thurn, R. D.; Isaks, M. *J. Org. Chem.* **1962**, *27*, 744.

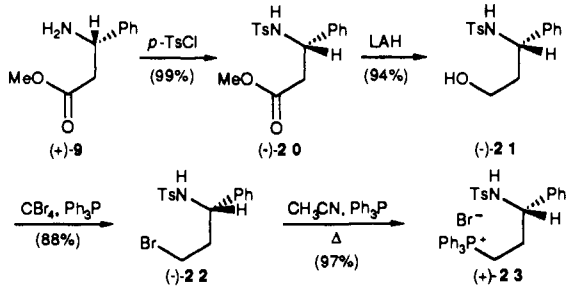
(14) (a) Of the three previously reported preparations[11,13,14b] of 5-methoxycyclopentenone, only that reported by DePuy provides the correct regioisomer. Goliasch and Wilson employed initial α-bromination of cyclopentenone followed by silver-mediated solvolysis with MeOH. As DePuy noted[14c] and we confirm, this approach provides 4-methoxycyclopentenone. (b) Hafner, K.; Goliasch, K. *Chem. Ber.* **1961**, *94*, 2909. (c) DePuy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. *J. Org. Chem.* **1964**, *29*, 3503. DePuy, C. H.; Isaks, M.; Eilers, K. L. *Chem. Ind. (London)* **1961**, 429.

(15) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 1 and references cited therein.

(16) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227.

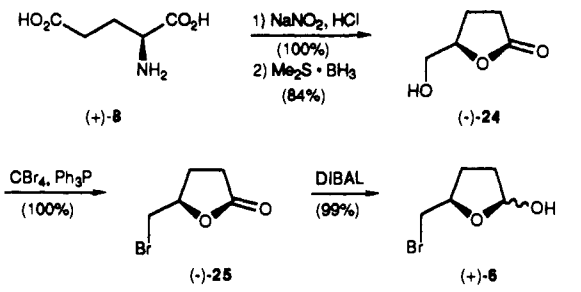
cleavage via dissolving metal reduction led to our initial choice of the *p*-tolylsulfonyl protecting group. Thus, (+)-β-phenyl-β-alanine methyl ester (**9**)[12] was transformed to (−)-**20** with *p*-toluenesulfonyl chloride (Scheme V). Following $LiAlH_4$ reduction to alcohol (−)-**21** and treatment of the latter with CBr_4/Ph_3P, exposure of the resultant bromide [(−)-**22**] to Ph_3P in hot CH_3CN provided the *N*-tolylsulfonyl phosphonium salt (+)-**23** as a hygroscopic amorphous solid in 79% overall yield for the four steps.

Scheme V



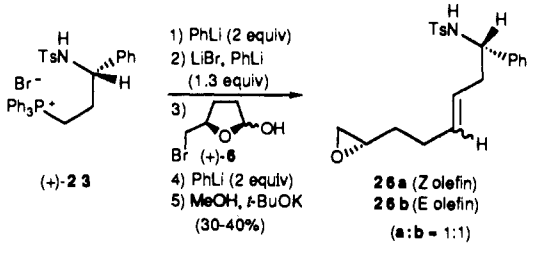
With ample quantities of (+)-**23** in hand, we turned to the preparation of bromo lactol **6**. As reported by Červinka and Hub, diazotization[17a] of (*S*)-(+)-glutmamic acid (**8**) and borane reduction[17b] readily furnished hydroxy lactone (−)-**24** in 84% yield (Scheme VI). Conversion to bromide (−)-**25**[18] followed by DIBAL reduction to the requisite lactol [(+)-**6**] then set the stage for a detailed study of the Wittig–Schlosser process.

Scheme VI



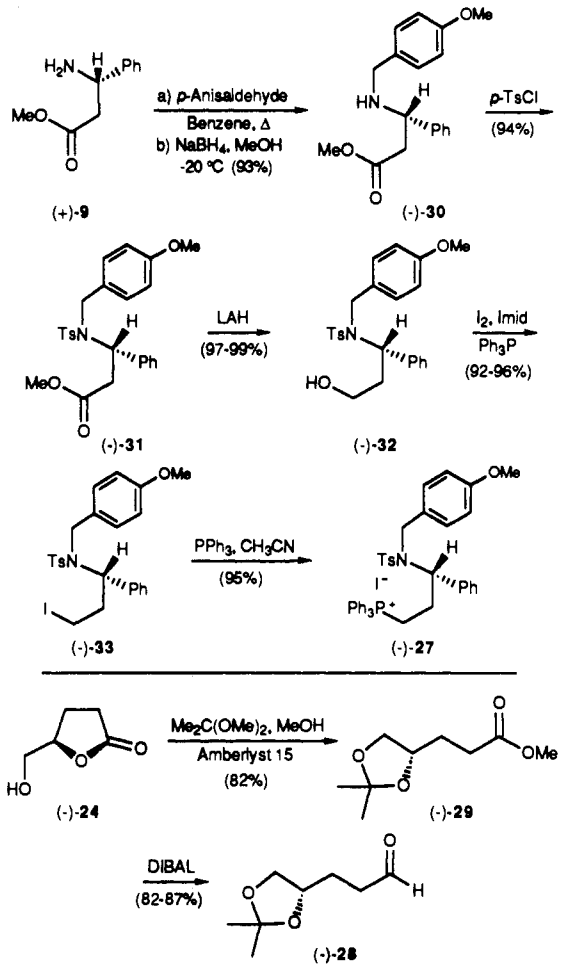
Initially, the coupling of (+)-**6** with (+)-**23** appeared promising (Scheme VII). Generation of the dianion of (+)-**23** followed by addition of phenyllithium (1.3 equiv, to deprotonate the lactol), LiBr, and (+)-**6** apparently afforded the intermediate betaine. Putative generation of the betaine ylide[19] with phenyllithium (2 equiv) and quenching with methanol and potassium *tert*-butoxide afforded a 1:1 mixture of the expected epoxy olefins **26a** and **26b** in 30–40% yields. Although we were pleased by the successful generation of **26b**, the reaction proved both capricious and unresponsive to optimization. Modification of the substrates seemed to offer the best recourse.

Scheme VII



The N-diprotected phosphonium iodide **27** and preformed aldehyde **28** were envisioned as tactically superior surrogates for **23** and **6**, respectively (Scheme VIII). Preparation of **27** began with reductive amination of *p*-anisaldehyde with (+)-**9**. Sulfonylation of (−)-**30** gave (−)-**31**, whereupon $LiAlH_4$ reduction afforded primary alcohol (−)-**32**. Iodination and treatment with triphenylphosphine in acetonitrile at reflux then afforded the desired phosphonium salt (−)-**27** in 75% overall yield for the six steps. The known aldehyde [(−)-**28**][20] was readily prepared via treatment of hydroxy lactone (−)-**24** with 2,2-dimethoxypropane in acidic methanol followed by DIBAL reduction of the resultant ester (−)-**29**.[21]

Scheme VIII

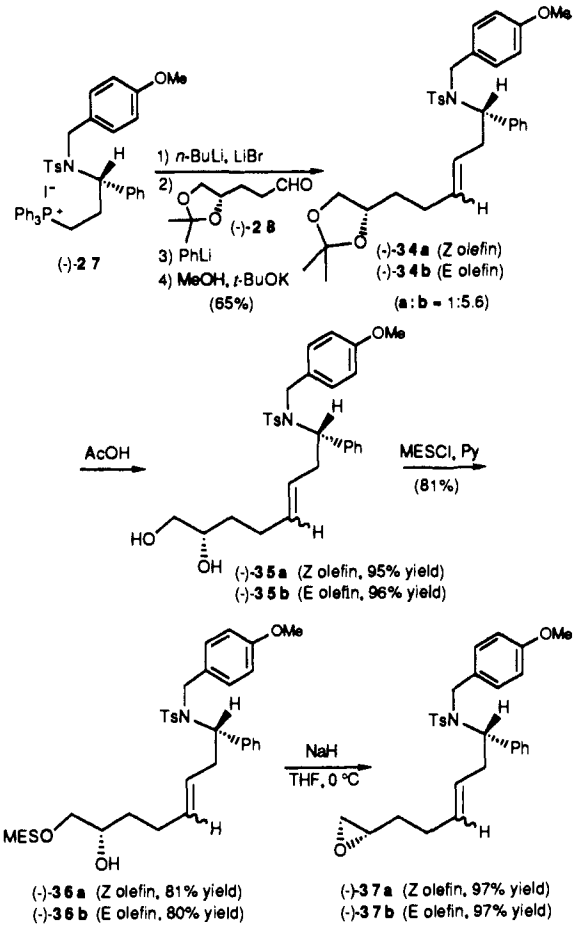


The coupling of (−)-**27** with (−)-**28** via the standard Wittig–Schlosser protocol provided olefins (−)-**34a** and (−)-**34b** with significantly improved efficiency (60–65% yields) and stereoselectivity (1:5.6 *Z*:*E* ratio) (Scheme IX). Importantly, the isomers were separable by flash chromatography on silver nitrate-impregnated silica gel.[22] Moreover, **34a** and **34b** readily furnished the corresponding epoxides (−)-**37a** and (−)-**37b**. Following acetonide cleavage, the resultant diols (−)-**35a** and (−)-**35b** underwent selective mesitylene sulfonation of the primary hydroxyl, affording (−)-**36a** and (−)-**36b**. Base treatment then generated the desired oxiranes.

To our delight, the trans epoxy olefin **37b** proved to be crystalline, whereas the cis isomer **37a** was not. Subsequent studies revealed that a 1:1 mixture of **37a** and **37b** could be readily separated by crystallization. X-ray analysis unambiguously established both the relative stereochemistry at C(15) and C(21) as well as the (*E*) olefin geometry in (−)-**37b** (Figure 1). By circumventing the cumbersome $AgNO_3/SiO_2$ chromatography,

(17) (a) Červinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2927. (b) Also see: Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.
(18) Castro, B. R. *Org. React.* **1983**, *29*, 1–162.
(19) Schlosser, M.; Tuong, H. B.; Schaub, B. *Tetrahedron Lett.* **1985**, *26*, 311 and references cited therein.
(20) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749.
(21) Larcheveque, M.; Lalande, J. *Tetrahedron* **1984**, *40*, 1061.
(22) deVries, G. *Chem. Ind.* **1962**, 1049 and references cited therein.

Scheme IX



crystallization promised to facilitate preparative sequences enormously. Nonetheless, the multistep elaboration of **34b** to **37b** and the technical complexity of the Wittig–Schlosser protocol still represented significant drawbacks.

In an effort to eliminate the latter problems, we considered the use of bromo lactol **6** in a conventional Wittig reaction (Scheme X). We recognized that this tactic would most likely result in a mixture of olefin isomers. However, the simplicity of the transformation, coupled with the potential for radical-induced equilibration of the *E*/*Z* mixture followed by crystallization of **37b**, rendered this alternative particularly attractive. In the event, the monoanions of (+)-**6** and (−)-**27** were generated separately; addition of the former to the ylide solution then afforded (−)-**37a** and (−)-**37b** (1:1 ratio) in 66% yield after flash chromatography. To rectify the lack of stereoselectivity, a benzene solution of the purified mixture (0.08 M) and diphenyl disulfide (3.0 mol %) was irradiated at 0 °C with a Hanovia medium-pressure mercury lamp.[23] The resultant 4:1 mixture of (*E*) and (*Z*) isomers **37b** and **37a** was recovered in 96% yield, whereupon crystallization provided the desired trans epoxy olefin (−)-**37b** in 57–63% yield (38–42% overall yield for the two steps).

Turning to the homologation step (Scheme X), **37b** underwent regiocontrolled ring opening upon exposure to 2-lithio-1,3-dithiane, affording (−)-**38b** in 82–85% yields. Hydroxyl protection with *tert*-butyldiphenylsilyl chloride (BPSCl) then provided (−)-**39b**. In similar fashion, **37a** sequentially furnished (−)-**38a** and (−)-**39a**. Final unmasking of the requisite aldehyde via dithiane hydrolysis was anticipated to be straightforward (vide infra).

Initial Coupling Studies. A Revised Protection Strategy. With scalemic dithianes (−)-**39a** and (−)-**39b** in hand, we began to explore the coupling of the fragments, focusing initially on the 1,4-addition of vinyl iodide **3a** to **4** (Scheme XI). Treatment of

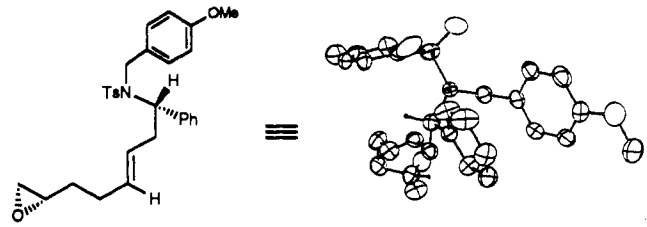
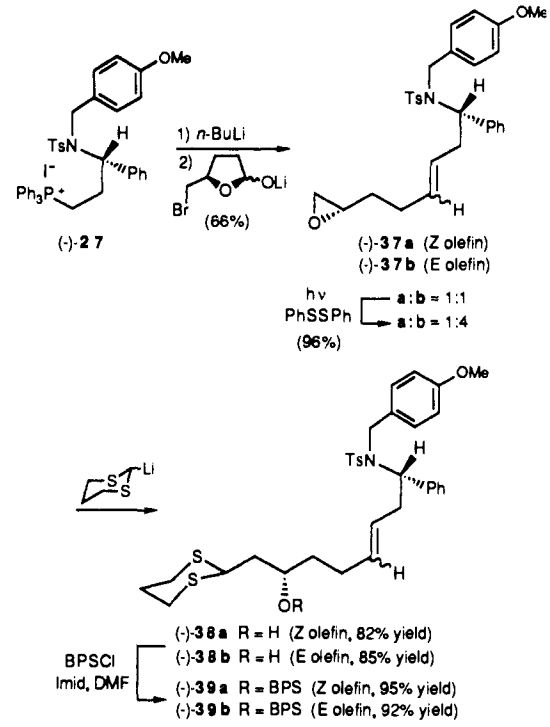
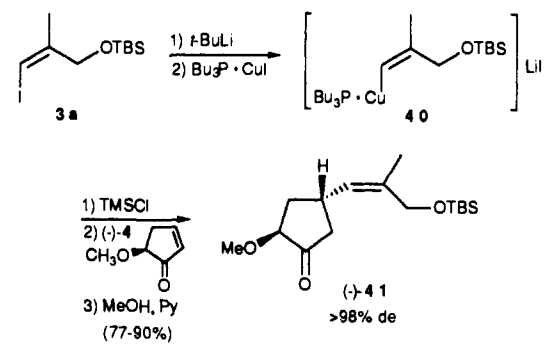


Figure 1. ORTEP drawing of (*E*) epoxy olefin **37b**.

Scheme X



Scheme XI



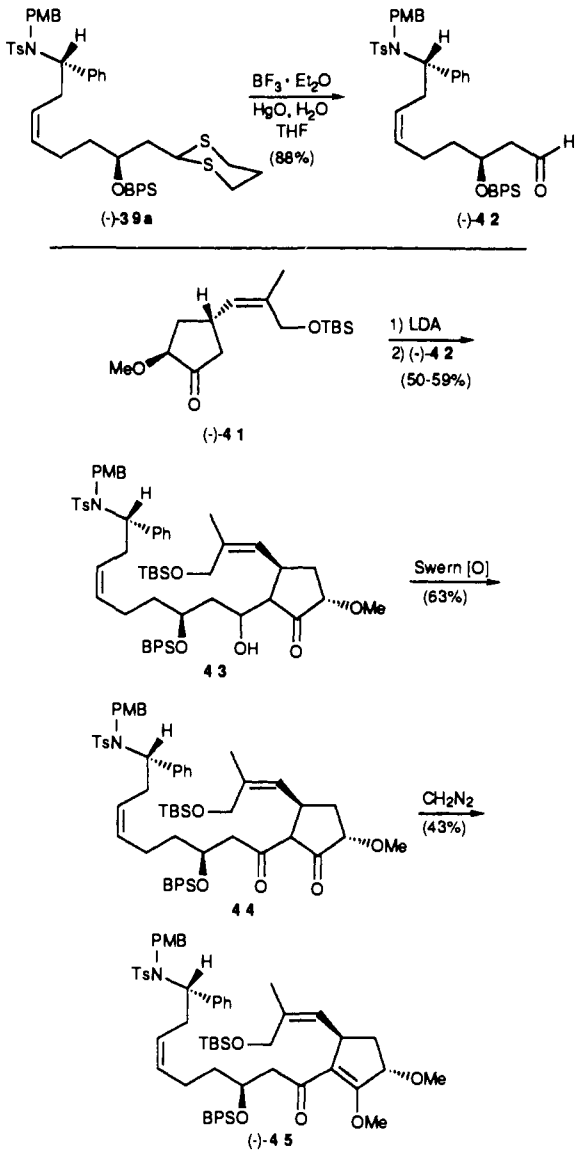
the former with *tert*-butyllithium followed by addition of the copper(I) iodide·tributylphosphine complex exploited by Noyori[24] provided organocopper reagent **40**.[25] Addition of TMSCl[26] followed by rapid introduction of (−)-**4** and hydrolysis then furnished the desired trans 1,4-adduct (−)-**41** in high yield with excellent diastereoselectivity (ca. 20:1). Unfortunately, other experiments suggested that the inclusion of TMSCl was critical. In turn, the generation of an intermediate silyl enol ether via this protocol appeared to preclude the tricomponent coupling tactic. Accordingly, we sought to develop a two-step procedure whereby the aldehyde subunit would be incorporated in a subsequent aldol reaction.[27]

(23) Thalmann, A.; Oeryle, K.; Gerlach, H. *Org. Synth.* **1984**, *63*, 192 and references cited therein.

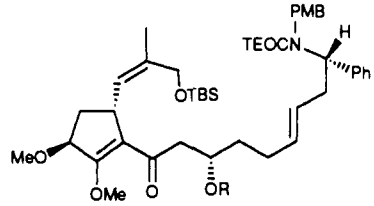
(24) Noyori, M.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.
(25) Copper(I) iodide was purified via the method of Kauffman: Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1984**, *22*, 101.
(26) Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, *26*, 6015.

To conserve valuable forefront materials, we elected to employ (*Z*)-dithiane (−)-**39a** for the exploratory chemistry (Scheme XII). Hydrolysis of **39a** to the corresponding aldehyde (−)-**42** proceeded smoothly under conditions developed by Vedejs and Fuchs.[28] Kinetic deprotonation of ketone (−)-**41** with LDA at −78 °C and addition of aldehyde **42** then afforded β-hydroxy ketone **43**. Swern oxidation to vinylogous acid **44** and treatment of the latter with diazomethane[29] furnished vinylogous methyl ester (−)-**45**.[30]

Scheme XII



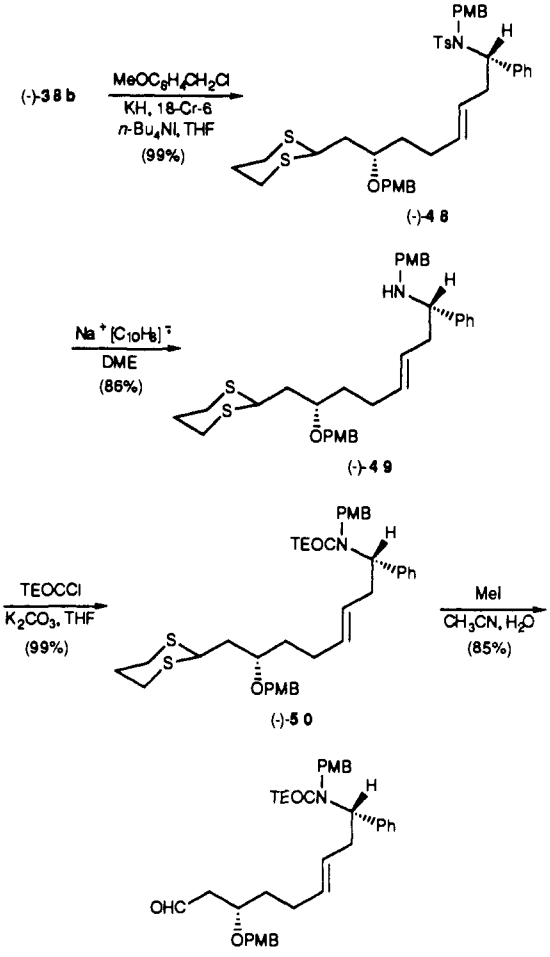
Notwithstanding the modest efficiency of the three-step preparation of **45** (ca. 16%), sufficient material was available for further investigation. Much to our chagrin, all attempts to remove the sulfonamide protecting group in **44** and **45** proved fruitless, as dissolving metal reduction invariably led to destruction of the starting material.[31] After a thorough reevaluation of our protection strategy, we opted to install a fluoride-labile moiety on nitrogen; the [β-(trimethylsilyl)ethoxy]carbonyl group devised by Carpino appeared ideal.[32] The prospect of an advanced intermediate (i.e., **46**) masked with three fluoride-sensitive functions dictated that one or both of the hydroxyl protecting groups would likewise have to be altered. We reasoned that the *tert*-butyldiphenylsilyl ether (BPS) could be replaced by *p*-methoxybenzyl (cf., **47**), setting the stage for N,O-bisdeprotection in the concluding phase of the synthesis. The allylic silyl ether could then be retained, subjected to selective cleavage, or removed together with the TEOC group (vide infra).



46 R = BPS
47 R = PMB

To implement the revised scheme, the secondary hydroxyl of dithiane (−)-**38b** was alkylated with *p*-methoxybenzyl chloride to afford (−)-**48** (Scheme XIII). Sodium naphthalenide reduction of the latter then provided the secondary amine (−)-**49** in 85% yield for the two steps. Acylation of the nitrogen with TEOCCl[33] afforded urethane (−)-**50** (99% yield) as a mixture of rotamers. Hydrolysis with excess methyl iodide[34] in aqueous acetonitrile then furnished the newly targeted aldehyde (−)-**51** (85%). Importantly,

Scheme XIII



(27) Previous work from these laboratories[27a] established that vinylogous acids (i.e., 1,3-diketones) can be constructed via aldol addition followed by Swern[39] or Collins[27b] oxidation of the resultant β-hydroxy ketones: (a) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567. (b) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

(28) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

(29) Garbisch, E. W. *J. Am. Chem. Soc.* **1963**, *85*, 1696.

(30) The endo- or exocyclic disposition of the olefinic bond could not be unequivocally determined. For hitachimycin (**1**) this point is moot since hydrolysis of the vinylogous ester will ultimately furnish the vinylogous acid moiety of **1**.

(31) Numerous dissolving metal reductions employing both sodium naphthalenide and sodium amalgam were attempted with both **44** and **45**.

(32) Carpino, L. A.; Tsao, J.-H. *J. Chem. Soc., Chem. Commun.* **1978**, 358.

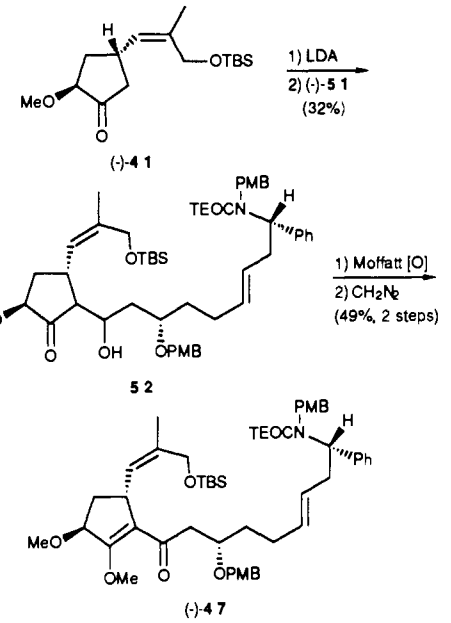
(33) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

(34) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.

(−)-**51** was prepared in 13 steps and 18.2% overall yield from the known (*S*)-(+)-β-phenyl-β-alanine methyl ester (**9**), for an average yield per step of ca. 88%!

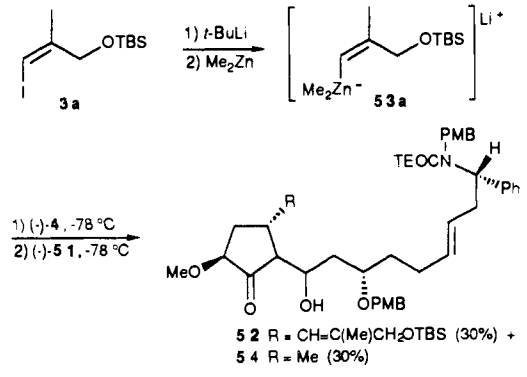
By analogy with the sulfonamide series, kinetic deprotonation of 1,4-adduct (−)-**41** (LDA) and addition to aldehyde (−)-**51** provided the desired aldol **52** in 32% yield (Scheme XIV). Moffatt oxidation and diazomethane etherification then furnished vinylogous ester (−)-**47** (49%). At this juncture we were poised to install the triene moiety, but we confronted a serious material shortage. In an attempt to improve the efficiency of the conversion of **41** to **47** (i.e., 16% yield for two steps), we elected to reconsider the feasibility of the tricomponent coupling tactic.

Scheme XIV



Effective Three-Component Coupling. Final Elaboration of (+)-Hitachimycin. As foreshadowed by our earlier experiments,[10] the addition of cuprate **40** to (−)-**4** in the absence of TMSCl followed by enolate trapping with aldehyde (−)-**51** provided the desired coupling product **52** in only 5% yield. Aware that the Noyori group recently had successfully employed zincates in conjugate addition/enolate trapping,[8d] we turned to organozinc nucleophiles. At the outset we explored the reactivity of **53a**

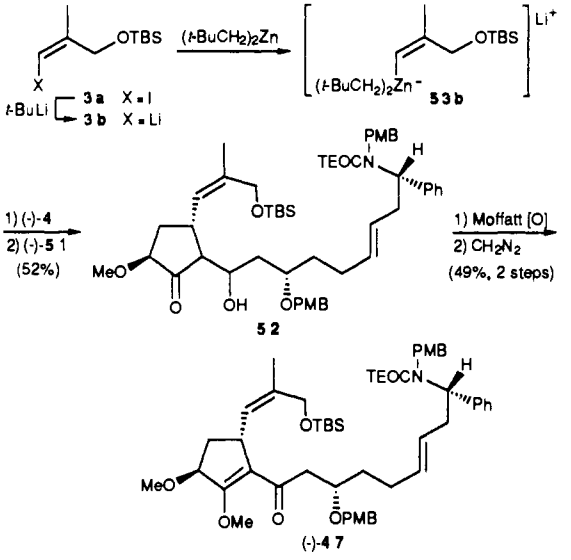
Scheme XV



(Scheme XV), prepared via sequential treatment of **3a** with *tert*-butyllithium and ethereal dimethylzinc.[35] Subsequent addition of (−)-**4** and then (−)-**51** at −78 °C did furnish the tricomponent adduct **52** in 30% yield; unfortunately, the desired product was accompanied by a significant quantity of the methyl congener **54**, as methyl transfer from **53a** presumably competed with delivery of the vinyl ligand.

Although the deleterious methyl transfer could be completely suppressed by using THF as cosolvent, a concomitant decrease in the yield of **52** to 26% also resulted. Fortunately, Tückmantel, Oshima, and Nozaki had reported[36] a detailed study of the rates of ligand transfer from zincates, revealing that the neopentyl group transferred much more slowly than either the *tert*-butyl or methyl ligand. We were delighted to discover that reaction of enone (−)-**4** with zincate **53b** (Scheme XVI), generated from equimolar amounts of vinyllithium **3b** and dineopenylzinc,[37] followed by enolate trapping with (−)-**51** afforded **52** in 52% yield.

Scheme XVI



Once the successful tricomponent coupling was achieved, the end game developed rapidly. Conversion of **52** to the corresponding vinylogous ester (−)-**47** (49% yield, Scheme XVI) and desilylation of the latter with tetra-*n*-butylammonium fluoride and acetic acid (TEOC and TBS groups, respectively; 75%, Scheme XVII) generated amino alcohol (−)-**55**. Interestingly, acidic removal of the TBS group was required to prevent racemization at C(10). Selective acylation of the secondary amine with phosphonate **56** via the Shioiri procedure (diethyl cyanophosphonate, DMF, 0 °C)[38] then gave (−)-**57** in 68% yield. After Swern oxidation[39] to aldehyde (−)-**58** (86%), deprotonation with lithium hexamethyldisilazide induced the critical Horner–Emmons macrocyclization, furnishing lactam (−)-**59** as a single isomer in 69% yield. Partial unmasking to (+)-**60** was effected via DDQ oxidation in wet CH_2Cl_2 followed by an acidic workup. Finally,

(35) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931.

(36) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581 and references cited therein.

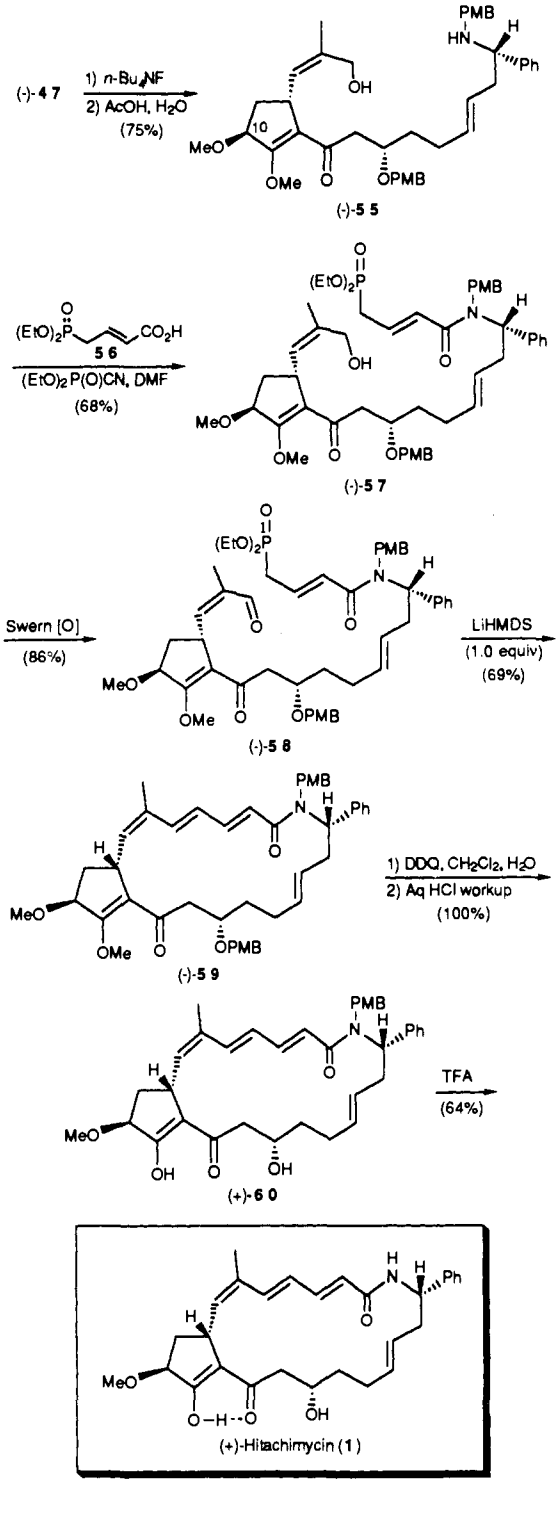
(37) Dineopentylzinc was prepared via an extension of a method previously described for dimethylzinc.[35] Also see: Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133 and ref 36.

(38) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.

(39) For a review of the Swern oxidation, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(40) **Materials and Methods.** Unless stated otherwise, reactions were carried out under an argon atmosphere in flame-dried glassware, and solvents were freshly distilled. Diethyl ether, THF, and DME were distilled from sodium/benzophenone. Benzene and methylene chloride were distilled from calcium hydride. Pyridine, diisopropylamine, and triethylamine were distilled from calcium hydride and stored over potassium hydroxide or sodium hydroxide. DMF from freshly opened bottles was stored over 4-Å molecular sieves and used without purification. Toluene and methanol were distilled from sodium. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Silica gel for flash chromatography (particle size 0.040–0.063 mm) was supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. Melting points are corrected unless otherwise noted. ^1H and ^{13}C chemical shifts are reported as δ values relative to tetramethylsilane. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center. Microanalyses were performed by Robertson Laboratories (Madison, NJ) or by Mr. S. T. Bella of the Rockefeller University Microanalytical Laboratory. Single-crystal X-ray analyses were performed by Dr. Patrick Carroll of the University of Pennsylvania.

Scheme XVII



exposure of (+)-**60** to neat, anhydrous trifluoroacetic acid at room temperature removed the *N*-PMB moiety, affording crystalline (+)-hitachimycin (**1**) in 64% yield after chromatography. Synthetic (+)-**1** (mp 236–240 °C) was identical in all respects with an authentic sample kindly provided by Professor Ōmura.

Experimental Section[40]

(±)-3,4-Dimethoxycyclopent-2-en-1-one (11b) and (±)-3,5-Dimethoxycyclopent-2-en-1-one (11a). A solution of 2-cyclopentene-1,4-dione (**10**) (36 g, 0.37 mol), trimethyl orthoformate (45 mL, 0.41 mol), and MeOH (700 mL) was heated at reflux for 2.5 h. After stirring for an additional 16 h at room temperature, the reaction mixture was concentrated in vacuo and the resultant oil dissolved in CH_2Cl_2 (200 mL). The solution was washed with saturated $NaHCO_3$ (2 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated in vacuo to yield a yellow oil. Distillation (bp 103.5–104.5 °C, 0.2 mmHg) gave a 3:1 mixture of **11b** and **11a** (44.2 g, 85% yield) as a colorless oil, which solidified upon refrigeration: IR ($CHCl_3$) 3010 (s), 2950 (s), 2840 (m), 1710 (s), 1610 (s), 1465 (m), 1450 (m), 1415 (m), 1380 (s), 1365 (s), 1290 (s), 1260 (s), 1200 (s), 1180 (s), 1110 (s), 1045 (m), 1000 (m), 985 (m), 945 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.39, 2.53 (diastereomers, dd, dd, J = 17.74, 2.29 Hz, J = 17.41, 2.91 Hz, 1 H), 2.71, 2.92 (diastereomers, dd, dd, J = 17.75, 6.44 Hz, J = 17.36, 6.84 Hz, 1 H), 3.47, 3.53 (diastereomers, s, s, 3 H), 3.87, 3.90 (diastereomers, s, s, 3 H), 3.99, 4.46 (diastereomers, dd, dd, J = 6.86, 2.94 Hz, J = 6.48, 2.33 Hz, 1 H), 5.30, 5.37 (diastereomers, s, s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.9, 41.0, 57.5, 57.7, 58.3, 58.8, 76.6, 78.7, 102.4, 105.5, 186.7, 187.6, 200.8, 202.4; mass spectrum (CI, NH_3) m/z 143.0724 [$(M + H)^+$, calcd for $C_7H_{11}O_3$ 143.0715].

Allylic Alcohols (±)-12a and (±)-12b. A solution of enones (±)-**11a** and (±)-**11b** (1:3 mixture, 4.6 g, 32.4 mmol) in CH_2Cl_2 (70 mL) was cooled to −78 °C and treated with DIBAL (1.0 M in hexanes, 43 mL, 43 mmol). The resultant mixture was stirred for 0.5 h at −78 °C and then quenched with MeOH (3 mL) and a saturated solution of Rochelle's salt (50 mL). After the mixture was stirred for 30 min at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc eluant) then afforded two compounds. The first to elute was alcohol (±)-**12a**, which upon standing at room temperature furnished 4-methoxycyclopent-2-en-1-one (834 mg, 23% yield) as a colorless oil: R_f 0.29 (1:1 hexanes/EtOAc); IR ($CHCl_3$) 3010 (s), 2940 (s), 2830 (m), 1725 (s), 1650 (m), 1465 (m), 1405 (m), 1360 (s), 1330 (m), 1300 (w), 1280 (m), 1105 (s), 1085 (s), 995 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.30 ($^1/_2$ ABX, J = 18.27, 2.20 Hz, 1 H), 2.69 ($^1/_2$ ABX, J = 18.27, 5.86 Hz, 1 H), 3.44 (s, 3 H), 4.61 (m, 1 H), 6.27 (dd, J = 5.78, 1.36 Hz, 1 H), 7.62 (dd, J = 5.78, 2.29 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.8, 160.7, 135.7, 78.5, 57.0, 41.0; mass spectrum (CI, NH_3) m/z 113.0603 [$(M + H)^+$, calcd for $C_6H_9O_2$ 113.0602].

The second compound to elute was alcohol (±)-**12b** (3.17 g, 68% yield), a colorless oil: R_f 0.18 (1:1 hexanes/EtOAc); IR ($CHCl_3$) 3580 (w), 3540–3140 (m), 3020 (s), 2980 (s), 2830 (m), 1650 (s), 1465 (m), 1455 (m), 1445 (m), 1380 (s), 1335 (m), 1280–1200 (s), 1090 (s), 1055 (s), 1015 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.66 (ddd, J = 14.34, 3.12, 3.12 Hz, 1 H), 2.62 (ddd, J = 7.24, 7.24, 4.35 Hz, 1 H), 3.41 (s, 3 H), 3.68 (s, 3 H), 4.08 (dd, J = 7.38, 3.35 Hz, 1 H), 4.59 (m, 1 H), 4.88 (d, J = 2.54 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.5, 101.9, 80.5, 71.2, 57.2, 56.8, 39.0; mass spectrum (CI, NH_3) m/z 144.0776 [M^+, calcd for $C_7H_{12}O_3$ 144.0786].

(±)-5-Methoxycyclopent-2-en-1-one (4). A solution of alcohol (±)-**12b** (2.65 g, 18.40 mmol) in Et_2O (15 mL) was treated with 1 M HCl (5 drops) and stirred at room temperature for 1 h. Anhydrous K_2CO_3 (100 mg) was then added, and the mixture was stirred for 0.5 h and filtered. The solvent was removed by distillation through a 9-in. Vigreux column using an 80 °C water bath. Flash chromatography (10:1 pentane/Et_2O eluant) then gave (±)-**4** (2.04 g, 99% yield) as a colorless oil: IR ($CHCl_3$) 3010 (m), 2940 (m), 2840 (m), 1725 (s), 1590 (m), 1450 (w), 1430 (w), 1345 (m), 1250 (m), 1180 (m), 1120 (s), 1030 (w), 1010 (w), 950 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.55 (comp m, 1 H), 3.03 (comp m, 1 H), 3.56 (s, 3 H), 3.88 (dd, J = 6.49, 2.75 Hz, 1 H), 6.20 (comp m, 1 H), 7.64 (comp m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.0, 57.8, 78.3, 132.3, 161.3, 206.8; mass spectrum (CI, NH_3) m/z 112.0524 [M^+, calcd for $C_6H_8O_2$ 112.0522].

(±)-3,4-Dimethoxycyclopent-2-en-1-one (11b). A mixture of alcohol (±)-**12b** (2.2 g, 15.3 mmol), MnO_2 (15 g, 160 mmol), and pentane (160 mL) was stirred for 60 h. Two additional 5-g portions of MnO_2 were added after 14 h and after 36 h. The suspension was then filtered, and the solid cake was washed with Et_2O (100 mL) and CH_2Cl_2 (100 mL). Concentration in vacuo and flash chromatography (1:1 hexanes/EtOAc eluant) afforded (±)-**11b** (1.81 g, 83% yield) as a colorless oil, which solidified upon standing: mp 40.5–43.0 °C; IR ($CHCl_3$) 3010 (m), 2940 (m), 2830 (m), 1735 (m), 1690 (s), 1610 (s), 1455 (m), 1445 (w), 1410 (m), 1385 (s), 1360 (m), 1330 (m), 1295 (m), 1260 (m), 1210 (s), 1175 (m), 1100 (m), 1040 (m), 985 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.41 ($^1/_2$ ABX, J = 17.76, 2.36 Hz, 1 H), 2.72 ($^1/_2$ ABX, J = 17.83, 6.51 Hz, 1 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 4.45 (dd, J = 6.47, 2.28 Hz, 1 H), 5.37 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 41.2, 57.7, 59.0, 76.9, 105.7, 186.9, 201.0; mass spectrum (CI, NH_3) m/z 142.0641 [M^+, calcd for $C_7H_{10}O_3$ 142.0630].

Sulfoximine Adducts (−)-16 and (+)-17. A solution of (*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (**13**) (2.15 g, 12.7 mmol) in THF (86 mL) was cooled to 0 °C, and *n*-BuLi (2.5 M in hexanes, 5.6 mL, 13.9 mmol) was added dropwise. The reaction was stirred at room temperature for

5 min and at 0 °C for 5 min and then was cooled to −78 °C. Following the addition of a solution of enone (±)-**11b** (1.8 g, 12.7 mmol) in THF (3.7 mL), the mixture was stirred for 0.5 h and poured into saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (3 × 75 mL), and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc eluant) afforded two products. The first compound to elute was the (*S,R*) diastereomer (+)-**17** (1.52 g, 38% yield), a colorless oil: R_f 0.52 (EtOAc); $[\alpha]^{25}_D$ +15.4° (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3560–3110 (br m), 2950 (m), 2840 (m), 1655 (s), 1453 (s), 1385 (m), 1250 (s), 1160 (s), 1120 (s), 1090 (s), 1045 (m), 1025 (m), 885 (w), 860 (w), 830 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.00 (dd, *J* = 14.2, 4.5 Hz, 1 H), 2.20 (dd, *J* = 14.2, 7.4 Hz, 1 H), 2.65 (s, 3 H), 3.06 (d, *J* = 13.5 Hz, 1 H), 3.36 (s, 3 H), 3.58 (d, *J* = 13.6 Hz, 1 H), 3.71 (s, 3 H), 4.14 (dd, *J* = 7.3, 4.4 Hz, 1 H), 5.37 (s, 1 H), 7.50 (comp m, 3 H), 7.87 (m, 2 H); mass spectrum (CI, NH_3) *m/z* 312.1283 [$(M + H)^+$, calcd for $C_{15}H_{22}O_4NS$ 312.1264]. Anal. Calcd for $C_{15}H_{21}O_4NS$: C, 57.86; H, 6.79; O, 20.57; N, 4.50. Found: C, 57.53; H, 6.95; O, 20.92; N, 4.37.

The second compound to elute was the (*S,S*) diastereomer (−)-**16** (1.46 g, 37% yield), which recrystallized from Et_2O as colorless needles: mp 98.5–99.0 °C; R_f 0.38 (EtOAc); $[\alpha]^{25}_D$ −16.4° (*c* 0.29, $CHCl_3$); IR ($CHCl_3$) 3560–3120 (br w), 3010 (m), 2940 (w), 2820 (w), 1650 (s), 1450 (m), 1380 (m), 1245 (m), 1170 (m), 1150 (s), 1080 (m), 1040 (m), 880 (w), 850 (w), 690 (w), 570 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.15 (dd, *J* = 14.24, 4.10 Hz, 1 H), 2.66 (s, 3 H), 3.02 (d, *J* = 13.66 Hz, 1 H), 3.16 (dd, *J* = 14.22, 7.38 Hz, 1 H), 3.41 (s, 3 H), 3.55 (d, *J* = 13.55 Hz, 1 H), 3.60 (s, 3 H), 4.22 (dd, *J* = 7.32, 4.10 Hz, 1 H), 4.69 (s, 1 H), 7.57–7.65 (comp m, 3 H), 7.88 (dd, *J* = 7.97, 0.09 Hz, 2 H); mass spectrum (CI, NH_3) *m/z* 312.1268 [$(M + H)^+$, calcd for $C_{15}H_{22}O_4NS$ 312.1264]. Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.79; O, 20.57; N, 4.50. Found: C, 57.81; H, 6.90; O, 20.77; N, 4.49.

(*S*)-(+)-3,4-Dimethoxycyclopent-2-en-1-one (11b). A solution of (*S,S*)-sulfoximine adduct (−)-**16** (760 mg, 2.53 mmol) in toluene was heated at reflux for 8 h. The reaction mixture was then cooled and concentrated in vacuo. Flash chromatography (EtOAc eluant) yielded (+)-**11b** (353 mg, 98% yield) as a colorless solid: mp 40.5–43.0 °C; $[\alpha]^{25}_D$ +37.6° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2940 (m), 2830 (m), 1735 (m), 1690 (s), 1610 (s), 1455 (m), 1445 (w), 1410 (m), 1385 (s), 1360 (m), 1330 (m), 1295 (m), 1260 (m), 1210 (s), 1175 (m), 1100 (m), 1040 (m), 985 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.41 (dd, *J* = 17.8, 2.36 Hz, 1 H), 2.72 (dd, *J* = 17.8, 6.51 Hz, 1 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 4.45 (dd, *J* = 6.47, 2.28 Hz, 1 H), 5.37 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 41.2, 57.7, 59.0, 76.9, 105.7, 186.9, 201.0; mass spectrum (CI, NH_3) *m/z* 142.0641 [M^+, calcd for $C_7H_{10}O_3$ 142.0630].

(*R*)-(−)-3,4-Dimethoxycyclopent-2-en-1-one (11b). Thermolysis of the (*S,R*)-sulfoximine adduct (+)-**17** (3.08 g, 9.916 mmol) as described above for **16** provided (−)-**11b** (641 mg, 85% yield), identical to (+)-**11b** in all respects except optical rotation: $[\alpha]^{25}_D$ −34.3° (*c* 0.28, $CHCl_3$).

(*S*)-(−)-5-Methoxycyclopent-2-en-1-one (4). A solution of (*S*)-3,4-dimethoxycyclopentenone (+)-**11b** (123 mg, 0.865 mmol) in CH_2Cl_2 (4 mL) was cooled to −78 °C, and DIBAL (1.0 M in hexanes, 0.95 mL, 0.95 mmol) was added dropwise. The mixture was stirred for 0.5 h at −78 °C and then quenched with MeOH (5 drops) and a saturated solution of Rochelle's salt (5 mL). After the mixture was stirred for 30 min at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and treated with 1 M HCl (3 drops) for 1 h. Anhydrous K_2CO_3 (500 mg) was then added, and the mixture was stirred and filtered. The solvent was removed by careful distillation through a 9-in. Vigreux column using an 80 °C water bath. Flash chromatography (3:1 pentane/Et_2O eluant) provided (−)-**4** (87 mg, 90% yield) as a colorless oil: $[\alpha]^{25}_D$ −73.0° (*c* 0.03, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2940 (m), 2840 (m), 1725 (s), 1590 (m), 1450 (w), 1430 (w), 1345 (m), 1250 (m), 1180 (m), 1120 (s), 1030 (w), 1010 (w), 950 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.55 (comp m, 1 H), 3.03 (comp m, 1 H), 3.56 (s, 3 H), 3.88 (dd, *J* = 6.49, 2.75 Hz, 1 H), 6.20 (comp m, 1 H), 7.64 (comp m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 35.0, 57.8, 78.3, 132.3, 161.3, 206.8; mass spectrum (CI, NH_3) *m/z* 112.0524 [M^+, calcd for $C_6H_8O_2$ 112.0522].

For determination of the enantiomeric purity of (−)-**4**, samples of (±)-**4** and (−)-**4** (ca. 10 mg each) were prepared for ^1H NMR analysis. The sample of racemic ketone was treated with a solution of tris[3-(heptafluoropropyl)-*d*-camphorato]europium(III) (20 μL, 0.162 mg/mL). The ^1H spectrum then showed two distinct methoxy signals of equal intensity. Following treatment of the sample of (−)-**4** with 30 μL of the shift reagent solution, only one methoxy resonance was resolved. Accordingly, an enantiomeric purity of >95% was assigned to (−)-**4**.

(*R*)-(+)-5-Methoxycyclopent-2-en-1-one (4). Reduction–elimination of (*R*)-3,4-dimethoxycyclopentenone (−)-**11b** as described for (+)-**11b** provided (+)-**4**, identical to (−)-**4** in all respects except optical rotation: $[\alpha]^{25}_D$ +79.5° (*c* 0.33, $CHCl_3$).

Vinyl Iodide 3a. A solution of 1-iodo-2-methyl-*cis*-propen-3-ol (**18**)[16] (7.5 g, 37.9 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated with Et_3N (10.0 mL, 74 mmol), *tert*-butyldimethylsilyl chloride (6.1 g, 40.7 mmol), and 4-(dimethylamino)pyridine (a few crystals). The ice bath was removed, and TEA·HCl began to precipitate as the reaction warmed to ambient temperature. After 2 h, the mixture was diluted with Et_2O (400 mL) and washed with water, saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Distillation (bp 62–64 °C, 1.1 mmHg) provided 10.6 g (90% yield) of **3a** as a colorless oil, which could be stored in a desiccator at 0 °C (over anhydrous K_2CO_3) for over a year without noticeable decomposition: IR ($CHCl_3$) 3020 (w), 2970 (s), 2940 (s), 2900 (m), 2870 (m), 1610 (w), 1480 (m), 1470 (m), 1450 (w), 1395 (w), 1380 (w), 1370 (w), 1290 (m), 1260 (m), 1210 (m), 1145 (m), 1120–1060 (m), 1020 (m), 1010 (w), 840 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.88 (d, *J* = 1.4 Hz, 3 H), 4.22 (d, *J* = 0.7 Hz, 2 H), 5.83 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 5.2, 18.2, 21.4, 25.9, 68.6, 72.5, 100.0, 146.7, 166.0, 207.2; mass spectrum (CI, NH_3) *m/z* 313.0512 [$(M + H)^+$, calcd for $C_{10}H_{21}IOSi$ 313.0484].

Sulfonamide (−)-20. A solution of ester (+)-**9**[12] (12.5 g, 69.8 mmol) in CH_2Cl_2 (450 mL) was treated with anhydrous K_2CO_3 (1 g, excess) and *p*-toluenesulfonyl chloride (20 g, 105 mmol). After 0.5 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was then washed three times with saturated K_2CO_3 solution, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (30% EtOAc/hexanes eluant) gave (−)-**20** (23.12 g, 99% yield) as a crystalline solid: mp 104–106 °C; $[\alpha]^{27}_D$ −53.6° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3370 (w), 3280 (w), 3030 (m), 2960 (w), 1740 (s), 1601 (w), 1500 (w), 1440 (m), 1335 (s), 1165 (s), 1095 (m), 810 (m), 700 (m), 670 (m), 550 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 2.81 (ABX, J_{AB} = 16.0 Hz, $J_{AX} = J_{BX}$ = 6.1 Hz, $\Delta\nu_{AB}$ = 49.4 Hz, 2 H), 3.56 (s, 3 H), 4.72 (ddd, $J_1 = J_2 = J_3$ = 6.2 Hz, 1 H), 5.66 (d, *J* = 7.6 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.18–7.21 (m, 5 H), 7.60 (d, *J* = 8.3 Hz, 2 H); mass spectrum (CI, NH_3) *m/z* 334.1143 [$(M + H)^+$, calcd for $C_{17}H_{20}NO_4S$ 334.1108]. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74. Found: C, 61.54; H, 5.77.

Alcohol (−)-21. A suspension of lithium aluminum hydride (2.3 g, 243 mmol) in Et_2O (200 mL) was cooled to 0 °C, and a solution of sulfonamide (−)-**20** (23.12 g, 69.35 mmol) in a mixture of THF and Et_2O (2.5:1, 70 mL) was added dropwise. The ice bath was removed and the mixture stirred at ambient temperature. After 0.5 h, the reaction was carefully quenched with 2 N HCl. Stirring was continued for 5 h, leading to precipitation of a white solid. The latter was removed by filtration and the resultant solution extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo, furnishing (−)-**21** (19.94 g, 94% yield) as a crystalline solid. One recrystallization (EtOAc/hexanes) provided 19.46 g (92%) of colorless needles: mp 140–141 °C; $[\alpha]^{27}_D$ −95.0° (*c* 0.02, $CHCl_3$); IR ($CHCl_3$) 3620–3460 (m), 3360 (m), 3330–3140 (m), 3030 (m), 2960 (m), 2920 (m), 2880 (m), 1605 (m), 1500 (m), 1460 (m), 1440–1400 (m), 1380–1290 (s), 1250–1220 (m), 1165 (s), 1095 (m), 1070 (m), 1050 (m), 810 (m), 700 (m), 670 (m), 590–540 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.89–1.99 (comp m, 3 H), 2.37 (s, 3 H), 3.63–3.66 (m, 1 H), 3.80–3.82 (m, 1 H), 4.53 (ddd, *J* = 8.3, 5.1, 5.1 Hz, 1 H), 5.37 (d, *J* = 7.3 Hz, 1 H), 7.00–7.02 (m, 2 H), 7.14–7.17 (m, 5 H), 7.57 (d, *J* = 8.3 Hz, 2 H); mass spectrum (CI, NH_3) *m/z* 306.1142 [$(M + H)^+$, calcd for $C_{16}H_{20}NO_3S$ 306.1164]. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27. Found: C, 62.86; H, 6.29.

Bromide (−)-22. A solution of alcohol (−)-**21** (3.12 g, 10.2 mmol) in THF (50 mL) was cooled to 0 °C under a $CaSO_4$ drying tube, and triphenylphosphine (4 g, 15.3 mmol) and CBr_4 (5 g, 15.3 mmol) were added. The ice bath was removed and the mixture stirred for 13 h. Following concentration in vacuo, the residual oil was dissolved in a minimum of $CHCl_3$ and purified by flash chromatography (10% EtOAc/hexanes and then 50% EtOAc/hexanes eluant), affording (−)-**22** (3.28 g, 88% yield) as a crystalline solid. One recrystallization (CH_2Cl_2/hexanes) provided 2.92 g (78%) of colorless plates: mp 112–113 °C; $[\alpha]^{22}_D$ −9.0 °C (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 3360 (w), 3320–3180 (w), 3020 (w), 2980–2880 (w), 1600 (w), 1490 (w), 1460–1400 (w), 1390–1300 (m), 1285 (w), 1160 (s), 1090 (m), 1050 (w), 950 (w), 805 (m), 695 (m), 650 (m), 550 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.18–2.23 (m, 1 H), 2.35–2.39 (m, 1 H), 2.37 (s, 3 H), 3.12–3.17 (ddd, *J* = 10.3, 7.6, 6.1 Hz, 1 H), 4.49 (ddd, $J_1 = J_2 = J_3$ = 7.4 Hz, 1 H), 5.13 (d, *J* = 7.8 Hz, 1 H), 7.00–7.02 (m, 2 H), 7.14 (d, *J* = 8.1 Hz, 2 H), 7.16–7.18 (m, 3 H), 7.58 (d, *J* = 8.3 Hz, 2 H). Anal. Calcd for $C_{16}H_{18}BrNO_2S$: C, 52.18; H, 4.93. Found: C, 52.37; H, 4.88.

Phosphonium Bromide (+)-23. A mixture of bromide (−)-**22** (6.48 g, 17.6 mmol), triphenylphosphine (6.9 g, 26 mmol), and CH_3CN (35 mL)

was heated at reflux for 4 days. After concentration in vacuo, trituration of the remaining oil with Et_2O furnished a powdery solid. The powder was filtered, washed well with Et_2O, and dried over P_2O_5 (high vacuum, 56 °C) to give (+)-**23** (10.82 g, 97% yield): mp 248–251 °C; $[\alpha]^{27}_D$ +26.7° (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 3070 (m), 3010 (m), 2990–2800 (s), 2775 (m), 1600 (w), 1590 (w), 1485 (w), 1440 (s), 1330 (m), 1250–1210 (m), 1160 (s), 1115 (s), 1095 (m), 1080–1030 (w), 810 (w), 730–670 (s), 650 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.91–2.08 (m, 1 H), 2.23 (s, 3 H), 2.45–2.74 (m, 1 H), 3.43–3.68 (m, 1 H), 3.79–3.98 (m, 1 H), 4.66 (ddd, J = 9.2, 9.2, 4.2 Hz, 1 H), 6.95 (d, J = 7.7 Hz, 2 H), 7.25 (m, 3 H), 7.58 (d, J = 7.7 Hz, 2 H), 7.61–7.83 (comp m, 17 H), 8.88 (d, J = 10.1 Hz, 1 H); mass spectrum (CI, NH_3) m/z 550.2000 [$(M - Br)^+$, calcd for $C_{34}H_{33}NO_2PS$ 550.1973].

(*S*)-(−)-5-(Bromomethyl)-γ-butyrolactone (25). A solution of alcohol (−)-**24**[17b] (3.28 g, 28.2 mmol) in THF (100 mL) was cooled to 0 °C, and triphenylphosphine (11.1 g, 42.5 mmol) was added. Upon dissolution of the latter, CBr_4 (14.0 g, 42.5 mmol) was introduced and the ice bath removed. After 2 h, triphenylphosphine oxide began to precipitate; shortly thereafter, the reaction was complete as indicated by TLC analysis. The mixture was diluted with Et_2O and filtered through Celite. Flash chromatography (25% EtOAc/hexanes eluant) gave (−)-**25** (5.12 g, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ −2.7° (*c* 0.69, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2960 (w), 1785 (s), 1455 (w), 1435 (w), 1415 (m), 1350 (w), 1335 (m), 1165 (s), 1020 (m), 980 (m), 910 (m), 880 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.08–2.17 (m, 1 H), 2.41–2.49 (m, 1 H), 2.57 (ddd, J = 17.4, 9.8, 8.3 Hz, 1 H), 2.66 (ddd, J = 17.4, 10.5, 5.4 Hz, 1 H), 3.54 (dd, J = 11.0, 5.6 Hz, 1 H), 3.58 (dd, J = 11.0, 4.7 Hz, 1 H), 4.73–4.78 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 28.3, 34.0, 77.8, 176.1; mass spectrum (CI, NH_3) m/z 177.9629 [$(M + H)^+$, calcd for $C_5H_7O_2Br$ 177.9630].

(*S*)-(+)-5-(Bromomethyl)-γ-butyrolactol (6). A solution of lactone (−)-**25** (6.58 g, 36.76 mmol) in CH_2Cl_2 (100 mL) was cooled to −78 °C, and DIBAL (1.0 M in hexanes, 40.3 mL) was added dropwise over 20 min. The reaction was stirred for 0.5 h at −78 °C and then quenched by dropwise addition of methanol (ca. 2 mL). Following introduction of a saturated solution of Rochelle's salt (100 mL), the ice bath was removed and stirring continued until the resulting emulsion separated. The mixture was extracted with Et_2O, and the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (30% EtOAc/hexanes eluant) provided (+)-**6** (6.23 g, 94% yield). NMR analysis revealed a 1:1 mixture of α/β anomers accompanied by ca. 5% of the hydroxy aldehyde: IR ($CHCl_3$) 3700 (m), 3650–3160 (broad m), 3020 (m), 3000 (m), 2960 (m), 2880 (m), 1720 (w), 1465 (m), 1445 (m), 1425 (m), 1355 (m), 1280–1180 (s), 1100–1000 (s), 980 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.70–2.35 (diastereomers, comp m, 4 H), 2.80, 2.83 (diastereomers, d, d, J = 2.2 Hz, J = 3.3 Hz, 1 H), 3.41, 3.46, 3.55 (diastereomers, d, J = 5.4 Hz, 2 H, $^1/_2$ ABX, J_{AB} = 10.1 Hz, J_{AX} = 6.4 Hz, 1 H, $^1/_2$ ABX, J_{BA} = 10.1 Hz, J_{BX} = 5.8 Hz, 1 H), 4.34, 4.49 (diastereomers, ddd, J = 13.4, 6.6, 6.6 Hz, 1 H, dddd, J = 7.5, 5.5, 5.5, 5.5 Hz, 1 H), 5.57, 5.63 (diastereomers, m, m, 1 H); mass spectrum (CI, NH_3) m/z 180.9872 [$(M + H)^+$, calcd for $C_5H_{10}BrO_2$ 180.9864]. Anal. Calcd for $C_5H_9BrO_2$: C, 33.17; H, 5.01. Found: C, 33.11; H, 4.91.

Epoxides 26a and 26b. A suspension of phosphonium bromide (+)-**23** (3.51 g, 5.57 mmol) and lithium bromide (5.0 g, 37.4 mmol, 10.6 equiv) in THF (100 mL) at ambient temperature was treated with phenyllithium (1.8 M in 70:30 cyclohexane/ether, 11.9 mL, 11.7 mmol). The resultant yellow homogeneous solution was stirred at ambient temperature for 30 min, cooled to −78 °C, and diluted with Et_2O (ca. 90 mL). An additional equivalent of PhLi (1.8 M, 5.7 mL, 5.6 mmol) was added, followed by a solution of lactol (+)-**6** (1 g, 5.57 mmol) in THF (6 mL). The light yellow solution was then warmed to −35 °C for 30 min. PhLi (14.0 mL, 13.7 mmol, 2.5 equiv) was added, and stirring was continued for 45 min as the reaction turned dark orange. The mixture was allowed to warm to −10 °C and then quickly cooled to −78 °C and quenched with MeOH (0.34 mL, 8.35 mmol). Potassium *tert*-butoxide (937 mg, 8.35 mmol) was added, the ice bath was removed, and the reaction mixture was stirred for 1 h at ambient temperature. Saturated NH_4Cl solution was then added and the mixture extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexanes eluant) gave 0.72 g (35% yield) of a 1:1 mixture of **26a** (*Z*) and **26b** (*E*), as determined by integration of the benzylic protons in the ^1H NMR spectrum. The olefins were separated by flash chromatography employing 10% $AgNO_3$-impregnated SiO_2 (25% EtOAc/hexanes eluant):[22] IR (mixture, $CHCl_3$) 3380 (m), 3360–3140 (m), 3020 (s), 2940 (s), 2780 (m), 1605 (m), 1500 (m), 1460 (m), 1430 (m), 1415 (m), 1410 (s), 1375–1320 (s), 1295 (m), 1250–1210 (s), 1160 (s), 1100 (s), 1060 (m), 950 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) (*E*) isomer δ 1.34–1.48 (m, 1 H), 1.59–1.75 (m, 1 H), 2.06–2.14 (dd, J = 13.9, 6.9 Hz, 2 H), 2.35 (s, 3 H), 2.35–2.43 (m, 2 H), 2.46 (dd, J = 4.8, 2.7 Hz, 1 H), 2.74 (dd, J = 4.8, 4.2 Hz, 1 H), 2.84 (m, 1 H), 4.40 (ddd, $J_1 = J_2 = J_3$ = 6.6 Hz, 1 H), 5.07–5.19 (m, 1 H), 5.40–5.53 (m, 2 H), 7.03–7.19 (comp m, 7 H), 7.55 (d, J = 8.3 Hz, 2 H), (*Z*) isomer δ 1.39–1.64 (comp m, 2 H), 2.12 (dd, J = 14.9, 5.8 Hz, 2 H), 2.37 (s, 3 H), 2.40–2.62 (m, 3 H), 2.75 (dd, $J_1 = J_2$ = 3.7 Hz, 1 H), 2.86 (m, 1 H), 4.34 (ddd, $J_1 = J_2 = J_3$ = 6.8 Hz, 1 H), 5.03 (d, J = 6.7 Hz, 1 H), 5.12–5.23 (m, 1 H), 5.43–5.55 (m, 1 H), 7.03–7.22 (m, 7 H), 7.55 (d, J = 7.9 Hz, 2 H); mass spectrum (CI, NH_3) m/z 372.1597 [$(M + H)^+$, calcd for $C_{21}H_{26}NO_3S$ 372.1635].

Aldehyde (−)-28. A solution of ester (−)-**29**[21] (41.1 g, 0.218 mol) in CH_2Cl_2 (400 mL) was cooled to −78 °C, and DIBAL (1.0 M in hexanes, 229 mL) was added dropwise. Stirring was continued for 7 min, and the reaction was then quenched with MeOH (40 mL). After 5 min, the mixture was warmed to ambient temperature and treated with a saturated solution of Rochelle's salt (400 mL). Et_2O (ca. 400 mL) was added, and the mixture was vigorously stirred until the resulting emulsion separated. The mixture was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Distillation (bp 42 °C, 2 mmHg) furnished (−)-**28** (28.4 g, 82% yield) as an oil. Data not previously reported include the following:[20] $[\alpha]^{25}_D$ −2.2° (*c* 3.46, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 1.40 (s, 3 H), 1.81–1.89 (m, 1 H), 1.90–1.94 (m, 1 H), 2.56–2.61 (comp m, 2 h), 3.55 (dd, J = 8.0, 6.8 Hz, 1 H), 4.05 (dd, J = 8.0, 6.1 Hz, 1 H), 4.10–4.15 (m, 1 H), 9.81 (dd, $J_1 = J_2$ = 1.5 Hz, 1 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 25.3, 25.7, 26.6, 39.7, 68.8, 74.6, 108.8, 201.4.

***p*-Methoxybenzylamine (−)-30.** A mixture of ester (+)-**9**[12] (4.0 g, 22.3 mmol), *p*-anisaldehyde (3.2 mL, 28 mmol), and benzene (50 mL) was heated at reflux under a Dean–Stark apparatus for ca. 24 h. The reaction mixture was then filtered through a pad of anhydrous $MgSO_4$ and the filtrate concentrated in vacuo. The residue was taken up in methanol (45 mL) and the solution cooled to −20 °C. Sodium borohydride (1.6 g, 44 mmol) was added portionwise, and the mixture was stirred at −20 °C until the initially formed imine (R_f ca. 0.7, 50% EtOAc/hexanes) was consumed (ca. 1 h). After careful quenching with saturated NH_4Cl solution, the mixture was concentrated in vacuo. The resultant oil was dissolved in H_2O, and the solution was extracted with EtOAc. The organic layer was then washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (4% MeOH/$CHCl_3$ eluant) provided (−)-**30** (6.2 g, 93% yield) as a colorless oil: R_f 0.35 (40% EtOAc/hexanes); $[\alpha]^{20}_D$ −32° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3330 (w), 3070 (m), 3040 (m), 3020 (m), 2960 (m), 2940 (m), 2920 (m), 2840 (m), 1735 (s), 1620 (s), 1590 (m), 1520 (s), 1500 (m), 1470 (s), 1460 (s), 1440 (s), 1365 (m), 1345 (m), 1305 (s), 1250 (s), 1200 (s), 1175 (s), 1105 (m), 1035 (s), 820 (m), 700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.60–1.90 (br s, 1 H), 2.63 (dd, J = 15.7, 5.1 Hz, 1 H), 2.73 (dd, J = 15.7, 8.5 Hz, 1 H), 3.53 (AB q, J_{AB} = 14.1 Hz, $\Delta\nu_{AB}$ = 52.8 Hz, 2 H), 3.63 (s, 3 H), 3.79 (s, 3 H), 4.1 (dd, J = 8.8, 5.1 Hz, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 7.28 (m, 1 H), 7.35 (d, J = 4.2 Hz, 4 H); mass spectrum (CI, NH_3) m/z 300.1607 [$(M + H)^+$, calcd for $C_{18}H_{22}NO_3$ 300.1599].

***p*-Toluenesulfonamide (−)-31.** A solution of amine (−)-**30** (3.42 g, 11.3 mmol) in pyridine (9 mL) and CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (6.5 g, 34 mmol) followed by a few crystals of 4-(dimethylamino)pyridine. The ice bath was removed, and the reaction was stirred at ambient temperature for 72 h. The mixture was then poured into Et_2O (ca. 100 mL) and washed with H_2O (3 × 15 mL). The organic phase was washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Pyridine was removed by repeated azeotropic distillation with toluene in vacuo. The residual oil was crystallized (Et_2O/hexane) to provide (−)-**31** (4.85 g, 94% yield) as colorless needles: mp 78–79 °C; $[\alpha]^{22}_D$ −49.7° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3030 (w), 2960 (w), 2840 (w), 1740 (s), 1610 (m), 1600 (w), 1590 (w), 1530 (s), 1495 (w), 1465 (m), 1440 (m), 1340 (m), 1310 (m), 1250 (s), 1180 (s), 1160 (s), 1090 (m), 1030 (m), 885 (m), 810 (m), 700 (m), 655 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 2.79 (d, J = 1.6 Hz, 1 H), 2.81 (s, 1 H), 3.50 (s, 3 H), 4.09 (AB q, J_{AB} = 15.4 Hz, $\Delta\nu_{AB}$ = 395.6 Hz, 2 H), 5.42 (dd, J = 8.1, 7.6 Hz, 1 H), 6.75 (d, J = 7.0 Hz, 2 H), 6.83 (d, J = 7.1 Hz, 2 H), 7.00 (d, J = 9.6 Hz, 2 H), 7.15–7.21 (m, 3 H), 7.27 (d, J = 8.0 Hz, 2 H), 7.65 (d, J = 8.3 Hz, 2 H); mass spectrum (CI, NH_3) m/z 454.1605 [$(M + H)^+$, calcd for $C_{25}H_{28}NO_5S$ 454.1688]. Anal. Calcd for $C_{25}H_{27}NO_5S$: C, 66.12; H, 6.00. Found: C, 66.47; H, 6.06.

Alcohol (−)-32. A solution of (−)-**31** (49.0 g, 108 mmol) in THF (215 mL) was cooled to 0 °C, and ethereal $LiAlH_4$ (1.0 M, 81 mL, 3 equiv) was added dropwise. The ice bath was removed and stirring continued for 1 h. The reaction was again cooled to 0 °C and carefully acidified with 2 N HCl. Following extraction with EtOAc, the organic solution was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Recrystallization (Et_2O/hexanes) of the resultant solid gave (−)-**32** (44.3 g, 97% yield) as a colorless

powder: mp 75–77 °C; $[\alpha]^{21}_D$ −79.9° (*c* 3.54, $CHCl_3$); IR ($CHCl_3$) 3640–3280 (w), 3060 (w), 3020 (m), 3000 (m), 2950 (m), 2880 (m), 2840 (*m*), 1615 (m), 1600 (m), 1585 (m), 1515 (s), 1495 (m), 1465 (m), 1450 (m), 1440 (m), 1340–1310 (m), 1305 (m), 1250 (m), 1180 (m), 1160 (s), 1115 (m), 1090 (m), 1055 (m), 1035 (m), 890 (m), 810 (m), 700 (m), 650 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (ddt, J = 14.3, 10.6, 3.8 Hz, 1 H), 1.86 (ddd, J = 19.0, 9.5, 4.8 Hz, 1 H), 2.45 (s, 3 H), 2.84 (dd, J = 8.7, 5.2 Hz, 1 H), 3.47 (ddd, J = 16.3, 8.3, 4.0 Hz, 1 H), 3.80 (s, 3 H), 3.81–3.83 (m, 1 H), 4.10 (AB q, J_{AB} = 15.2 Hz, $\Delta\nu_{AB}$ = 502.7 Hz, 2 H), 5.16 (dd, J = 11.1, 4.5 Hz, 1 H), 6.76 (d, J = 7.0 Hz, 2 H), 6.79 (d, J = 8.7 Hz, 2 H), 7.10 (d, J = 8.4 Hz, 2 H), 7.17 (apparent t, J = 7.8 Hz, 2 H), 7.21–7.26 (m, 1 H), 7.30 (d, J = 6.0 Hz, 2 H), 7.67 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 34.9, 47.4, 55.2, 57.4, 58.2, 113.6, 127.1, 128.0, 128.3, 128.6, 129.4, 129.6, 129.7, 137.5, 138.4, 143.4, 159.0; mass spectrum (CI, NH_3) m/z 426.1709 [$(M + H)^+$, calcd for $C_{24}H_{28}NO_4S$, 426.1739]. Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.74; H, 6.39. Found: C, 67.85; H, 6.41.

Iodide (−)-33. A solution of alcohol (−)-**32** (43.8 g, 102.9 mmol) in Et_2O (167 mL) and CH_3CN (100 mL) was cooled to 0 °C and treated with triphenylphosphine (35.0 g, 133 mmol) and imidazole (9.1 g, 133 mmol). Upon dissolution, iodine (35.6 g, 144 mmol) was added in portions over 15 min. The ice bath was removed and stirring was continued for ca. 15 min. The mixture was then poured into a separatory funnel containing Et_2O (2 L) and washed with saturated $Na_2S_2O_3$ solution (2 × 100 mL), aqueous $CuSO_4$ (100 mL), water (100 mL), and brine (2 × 100 mL). The solution was dried briefly ($MgSO_4$), filtered, and concentrated in vacuo. Most of the triphenylphosphine oxide was separated via addition of Et_2O followed by filtration at 0 °C. The resultant oil was passed through a short plug of SiO_2 to remove the residual triphenylphosphine oxide (80% Et_2O/petroleum ether eluant). Concentration in vacuo afforded (−)-**33** (53 g, 96% yield) as a light yellow syrup: $[\alpha]^{23}_D$ −23.8° (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) 3080 (w), 3030 (m), 3010 (m), 2960 (m), 2930 (m), 1615 (m), 1601 (m), 1590 (m), 1520 (s), 1500 (m), 1465 (m), 1455 (m), 1445 (m), 1350–1335 (s), 1310 (m), 1250 (s), 1180 (s), 1160 (s), 1090 (m), 1035 (m), 940 (w), 910 (m), 895 (m), 885 (m), 840 (m), 815 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (dd, J = 15.0, 7.6 Hz, 2 H), 2.25 (s, 3 H), 2.92 (dd, J = 17.5, 7.7 Hz, 1 H), 3.10 (ddd, J = 9.9, 6.8, 6.8 Hz, 1 H), 3.81 (s, 3 H), 4.14 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 384.2 Hz, 2 H), 5.03 (dd, J_1 = J_2 = 7.6 Hz, 1 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.89 (d, J = 7.4 Hz, 2 H), 7.08 (d, J = 8.5 Hz, 2 H), 7.20–7.28 (m, 5 H), 7.65 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.1, 21.1, 35.9, 47.5, 54.8, 61.3, 113.4, 126.7, 127.8, 128.0, 128.1, 128.9, 129.1, 129.2, 135.6, 137.6, 142.8, 158.6; mass spectrum (CI, NH_3) m/z 536.0721 [$(M + H)^+$, calcd for $C_{24}H_{26}NO_3S$ 536.0756].

Phosphonium Iodide (−)-27. A solution of iodide (−)-**33** (125 g, 0.233 mol) in CH_3CN (233 mL) was treated with recrystallized triphenylphosphine (55 g, 0.21 mol) and heated at reflux for 48 h. Two more portions of triphenylphosphine (3 g, 11 mmol each) were then added; the mixture was heated for an additional 24 h after each addition. Following concentration in vacuo, the residue was dissolved in $CHCl_3$ (1 L), and the solution was divided into five 200-mL portions. Each was boiled with Norite (ca. 1 g), filtered, and concentrated in vacuo, and the resultant foam was triturated with Et_2O until a powdery solid was obtained. Drying over P_2O_5 (high vacuum, room temperature) for several days furnished (−)-**27** (177 g, 95% yield) as a hygroscopic white solid: mp 106–109 °C; $[\alpha]^{23}_D$ −36.9° (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 3050 (w), 3030 (w), 3000 (m), 2980–2880 (s), 1610 (m), 1600 (m), 1590 (m), 1510 (s), 1500 (m), 1490 (m), 1445 (s), 1350–1320 (s), 1310 (m), 1250–1215 (m), 1180 (m), 1160 (s), 1110 (m), 1035 (m), 995 (m), 985 (m), 840 (m), 810 (m), 690 (s), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.05–2.09 (m, 1 H), 2.35–2.41 (m, 1 H), 2.40 (s, 3 H), 3.24 (m, 1 H), 3.50 (ddd, J = 24.3, 11.8, 8.5 Hz, 1 H), 3.80 (s, 3 H), 4.18 (AB q, J_{AB} = 5.2 Hz, $\Delta\nu_{AB}$ = 286.1 Hz, 2 H), 5.10 (dd, J_1 = J_2 = 7.5 Hz, 2 H), 6.75 (d, J = 6.6 Hz, 2 H), 6.79 (d, J = 7.5 Hz, 2 H), 7.16–7.23 (m, 5 H), 7.26 (d, J = 8.2 Hz, 2 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.61–7.65 (m, 6 H), 7.66–7.72 (m, 6 H), 7.81–7.84 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 20.9, 21.4, 25.9, 49.2, 55.3, 61.6, 61.9, 113.9, 116.6, 117.9, 127.1, 128.6, 129.1, 130.1, 130.4, 130.6, 133.2, 133.3, 133.4, 135.2, 137.4, 143.3, 159.0. Anal. Calcd for $C_{42}H_{42}INO_3PS$: C, 63.17; H, 5.30. Found: C, 62.98; H, 5.16.

Acetonides (−)-34a and (−)-34b. After drying for 12 h (70 °C, 0.5 mmHg), phosphonium iodide (−)-**27** (4.83 g, 6.04 mmol) and LiBr (1.05 g, 12.1 mmol) were suspended in THF (4 mL) and then cooled to −78 °C. *n*-Butyllithium (2.93 mL, 6.69 mmol) was added, and the reaction was warmed to 0 °C and then stirred for 45 min as the blood-red color of the ylide developed. A solution of aldehyde (−)-**28** (868.6 mg, 5.45 mmol) in THF (1.0 mL) was introduced, and the resulting mixture was stirred for ca. 12 min; TLC analysis then indicated complete consumption of the aldehyde. Phenyllithium (1.8 M in cyclohexane/Et_2O 70:30, 3.90 mL, 6.68 mmol) and Et_2O (10 mL) were added, and the mixture was stirred at −23 °C for 1 h. The resulting blood-red solution was cooled to −78 °C and quenched with MeOH (0.58 mL, 14.5 mmol). Following introduction of potassium *tert*-butoxide (825 mg, 7.37 mmol), the cold bath was removed and the mixture warmed to ambient temperature. Saturated NH_4Cl solution was then added and the mixture extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexanes eluant) furnished a 1:5.6 mixture of **34a** and **34b** (2.07 g, 58% yield). The isomers were separated via flash chromatography on $AgNO_3$-impregnated SiO_2 (35% Et_2O/hexanes eluant). (*E*) isomer (−)-**34b**: $[\alpha]^{27}_D$ −17.4° (*c* 1.26, $CHCl_3$); IR ($CHCl_3$) 3140–3000 (m), 2940 (m), 2880 (m), 2850 (m), 1620 (m), 1605 (m), 1590 (m), 1520 (w), 1500 (m), 1460 (m), 1390 (m), 1380 (m), 1360–1320 (w), 1310 (m), 1280–1210 (w), 1180 (m), 1160 (w), 1050 (m), 975 (m), 900 (m), 840 (m), 820 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (s, 3 H), 1.37 (s, 3 H), 1.39–1.46 (m, 1 H), 1.55–1.62 (m, 1 H), 1.86–1.95 (comp m, 2 H), 2.41–2.53 (comp m, 2 H), 2.43 (s, 3 H), 3.41 (m, 1 H), 3.78 (s, 3 H), 3.91 (ddd, J = 12.6, 5.8, 2.4 Hz, 2 H), 4.13 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 277.4 Hz, 2 H), 4.97 (dd, J = 9.4, 6.4 Hz, 1 H), 5.13–5.18 (m, 1 H), 5.27–5.33 (m, 1 H), 6.73 (d, J = 8.7 Hz, 2 H), 6.96–6.98 (m, 2 H), 7.01 (d, J = 8.6 Hz, 2 H), 7.17–7.26 (m, 5 H), 7.61 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 25.5, 26.7, 28.4, 32.9, 35.5, 47.6, 55.0, 61.1, 75.2, 108.3, 113.4, 126.7, 127.1, 127.6, 127.9, 128.1, 128.7, 129.2, 129.5, 132.1, 137.4, 138.5, 142.6, 158.8; mass spectrum (CI, NH_3) m/z 550.2615 [$(M + H)^+$, calcd for $C_{32}H_{40}NO_5S$ 550.2627]. Anal. Calcd for $C_{32}H_{39}NO_5S$: C, 69.92; H, 7.15. Found: C, 70.17; H, 7.11.

(*Z*) isomer (−)-**34a**: $[\alpha]^{20}_D$ −18.6° (*c* 1.43, $CHCl_3$): IR ($CHCl_3$) 3140–3000 (m), 2940 (m), 2880 (m), 2850 (m), 1620 (m), 1605 (m), 1690 (m), 1520 (w), 1500 (m), 1460 (m), 1390 (m), 1380 (m), 1360–1320 (s), 1280–1210 (s), 1180 (m), 1160 (s), 1050 (m), 940 (w), 900 (s), 840 (m), 820 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20–1.51 (m, 1 H), 1.35 (s, 3 H), 1.41 (s, 3 H), 1.57–1.70 (m, 1 H), 1.92–2.06 (comp m, 2 H), 2.42 (s, 3 H), 2.54 (ddd, J_1 = J_2 = J_3 = 7.2 Hz, 2 H), 3.43–3.52 (m, 1 H), 3.77 (s, 3 H), 3.97–4.09 (comp m, 2 H), 4.15 (AB q, J_{AB} = 15.6 Hz, $\Delta\nu_{AB}$ = 144.4 Hz, 2 H), 4.94 (dd, J_1 = J_2 = 8.0 Hz, 1 H), 5.08–5.18 (m, 1 H), 5.22–5.32 (m, 1 H), 6.74 (d, J = 8.6 Hz, 2 H), 6.92–7.01 (m, 2 H), 7.03 (d, J = 8.6 Hz, 2 H), 7.14–7.22 (m, 5 H), 7.61 (d, J = 8.3 Hz, 2 H); mass spectrum (field desorption) m/z 549.2530 [M^+, calcd for $C_{32}H_{39}NO_5S$ 549.2250].

Diol (−)-35b. (*E*) olefin (−)-**34b** (42.2 g, 76.9 mmol) was dissolved in a 4:1 mixture of glacial acetic acid and water (700 mL) containing THF (30 mL), and the mixture was stirred at ambient temperature for 1 h. Following concentration in vacuo, two portions of toluene were added and evaporated. Flash chromatography (50% EtOAc/hexanes → 100% EtOAc, gradient elution) afforded (−)-**35b** (37.8 g, 96% yield) as a colorless oil: $[\alpha]^{23}_D$ −33.6° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3660–3200 (m), 3070 (m), 3030 (m), 3020 (m), 3000–2910 (s), 2880 (m), 2870 (m), 1620 (m), 1605 (m), 1590 (m), 1520 (s), 1500 (m), 1470–1440 (m), 1405 (m), 1390 (m), 1370 (m), 1360–1320 (s), 1310 (s), 1360–1340 (s), 1180 (s), 1160 (s), 1100 (s), 1040 (s), 980 (m), 915 (m), 895 (s), 835 (m), 815 (s), 700 (s), 660 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.36–1.42 (comp m, 2 H), 1.90–2.08 (m, 2 H), 2.30–2.57 (m, 4 H), 3.35 ($^1/_2$ ABX, J_{AB} = 11.0 Hz, J_{AX} = 7.6 Hz, 1 H), 3.57 ($^1/_2$ ABX, J_{BA} = 11.1 Hz, J_{BX} = 3.1 Hz, 1 H), 3.63–3.67 (m, 1 H), 3.77 (s, 3 H), 4.11 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 150.1 Hz, 2 H), 5.00 (dd, J_1 = J_2 = 6.8 Hz, 1 H), 5.24–5.27 (m, 2 H), 6.72 (d, J = 8.7 Hz, 2 H), 6.92–6.96 (m, 2 H), 7.01 (d, J = 8.7 Hz, 2 H), 7.16–7.25 (m, 5 H), 7.59 (d, J = 8.3 Hz, 2 H); mass spectrum (field desorption) m/z 510.2300 [$(M + H)^+$, calcd for $C_{29}H_{36}NO_5S$ 510.2310].

Diol (−)-35a. The (*Z*) olefin diol (−)-**35a** was prepared as described above for (−)-**35b**: $[\alpha]^{22}_D$ −7.3° (*c* 1.42, $CHCl_3$); IR ($CHCl_3$) 3360–3200 (m), 3070 (m), 3030 (m), 3020 (m), 2995–2920 (m), 2880 (m), 2870 (m), 1620 (m), 1605 (m), 1590 (m), 1520 (s), 1500 (m), 1470–1440 (m), 1405 (m), 1390 (m), 1370 (m), 1360–1320 (s), 1360–1340 (m), 1310 (m), 1160 (s), 1100 (m), 1040 (m), 940 (w), 900 (m), 835 (m), 815 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.36–1.46 (m, 2 H), 1.95–2.21 (comp m, 2 H), 2.39 (s, 3 H), 2.44–2.68 (comp m, 2 H), 3.05–3.28 (comp m, 2 H), 3.41 ($^1/_2$ ABX, J_{AB} = 11.0 Hz, J_{AX} = 7.3 Hz, 1 H), 3.58–3.71 (comp m, 2 H), 3.75 (s, 3 H), 4.14 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 156.8 Hz, 2 H), 4.90 (dd, J = 9.6, 6.2 Hz, 1 H), 5.08–5.15 (m, 1 H), 5.23–5.33 (m, 1 H), 6.73 (d, J = 8.7 Hz, 2 H), 6.76–6.98 (comp m, 2 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.14–7.27 (comp m, 5 H), 7.59 (d, J = 8.2 Hz, 2 H); mass spectrum (field desorption) m/z 510.2290 [$(M + H)^+$, calcd for $C_{29}H_{36}NO_5S$ 510.2310].

Mesitylene Sulfonate (−)-36b. Diol (−)-**35b** (14.6 g, 28.57 mmol) was azeotropically dried three times by dissolution in benzene (40 mL portions) and concentrated in vacuo and then dried further over P_2O_5 at high vacuum for 72 h. The sample was then dissolved in pyridine (286 mL).

Solid mesitylenesulfonyl chloride (6.56 g, 30 mmol) was added in three equal portions over a 10-h period; the reaction was cooled to −50 °C before each addition and then stirred at ambient temperature. After 48 h, the reaction mixture was quenched with cold water (~70 mL) and concentrated in vacuo. The dark-colored residue was dissolved in water, and the solution was extracted alternately with Et_2O and EtOAc several times. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (20 → 30% EtOAc/hexanes gradient elution) afforded (−)-**36b** (11.8 g) as a colorless syrup, accompanied by diol **35a** (3.84 g). Resubmission of the diol to the above protocol then gave a total of 16.0 g (80% overall yield) of **36b**: $[\alpha]^{25}_D$ −20.1° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3360 (w), 3620–3300 (w), 3030 (m), 2950 (m), 2840 (w), 1630 (m), 1620 (m), 1590 (w), 1580 (w), 1520 (m), 1500 (m), 1480–1420 (m), 1410 (m), 1360 (m), 1340 (m), 1310 (m), 1250 (m), 1190 (m), 1180 (s), 1160 (s), 1090 (m), 1055 (m), 1035 (m), 980 (m), 890 (m), 815 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39–1.41 (m, 2 H), 1.95–1.98 (m, 2 H), 2.16 (d, *J* = 4.7 Hz, 1 H), 2.31 (s, 3 H), 2.43 (s, 3 H), 2.44–2.48 (m, 2 H), 2.62 (s, 6 H), 3.75–3.77 (comp m, 2 H), 3.78 (s, 3 H), 3.88 (m, 1 H), 4.11 (AB q, J_{AB} = 15.4 Hz, $\Delta\nu_{AB}$ = 303.2 Hz, 2 H), 4.97 (dd, $J_1 = J_2$ = 7.8 Hz, 1 H), 5.21 (m, 2 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.92–6.94 (m, 2 H), 6.97 (s, 3 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 7.18–7.26 (m, 6 H), 7.59 (d, *J* = 8.2 Hz, 2 H); mass spectrum (CI, NH_3) *m/z* 692.2730 [$(M + H)^+$, calcd for $C_{38}H_{46}NO_7S_2$ 692.2725].

Mesitylene Sulfonate (−)-36a. The (*Z*) olefin mesitylene sulfonate (−)-**36a** was prepared as described above for (−)-**36b**: $[\alpha]^{20}_D$ −7.3° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3660 (w), 3630–3280 (m), 3030 (m), 3020 (m), 2860 (m), 2480 (m), 1615 (m), 1610 (m), 1590 (m), 1570 (w), 1520 (s), 1500 (m), 1465 (m), 1455 (m), 1445 (m), 1410 (m), 1360 (s), 1335 (s), 1310 (s), 1250 (s), 1190 (s), 1180 (s), 1160 (s), 1120 (m), 1090 (m), 1060 (m), 1040 (s), 970 (m), 950 (m), 895 (s), 840–800 (s), 700 (m), 660 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43–1.48 (comp m, 2 H), 1.75 (m, 1 H), 1.92–2.25 (comp m, 2 H), 2.29 (s, 3 H), 2.43 (s, 3 H), 2.40–2.75 (comp m, 2 H), 2.63 (s, 6 H), 3.77 (s, 3 H), 3.78–3.95 (comp m, 3 H), 4.17 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 140.0 Hz, 2 H), 4.88 (dd, *J* = 9.9, 5.9 Hz, 1 H), 5.09–5.35 (comp m, 2 H), 6.77 (d, *J* = 9.5 Hz, 2 H), 6.87–6.96 (m, 2 H), 6.99 (s, 1 H), 7.05 (d, *J* = 7.5 Hz, 2 H), 7.15–7.30 (comp m, 6 H), 7.60 (d, *J* = 9.0 Hz, 2 H); mass spectrum (field desorption) *m/z* 691.2680 (M^+, calcd for $C_{38}H_{45}NO_7S_2$ 691.2650).

Epoxide (−)-37b from Mesitylene Sulfonate (−)-36b. A solution of (−)-**36b** (16.0 g, 23.12 mmol) in THF (140 mL) was cooled to 0 °C, and sodium hydride (743 mg, 30 mmol) was added in one portion, followed by a few lumps of 18-crown-6. The ice bath was removed and stirring continued for 3 h. The reaction mixture was then cooled to 0 °C, carefully quenched with saturated NH_4Cl solution (50 mL), and filtered through a small pad of SiO_2 (EtOAc eluant). The resultant solution was concentrated in vacuo, and the residual oil was dissolved in Et_2O. The ethereal solution was washed alternately with water and saturated $NaHCO_3$ solution (three portions each), washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily crude product was passed through a short column of SiO_2 (20 → 60% EtOAc/hexanes gradient elution), affording a colorless oil. Crystallization from Et_2O/pentane gave (−)-**37b** (11.0 g, 97% yield) as colorless needles: mp 62–65 °C (uncorrected); $[\alpha]^{25}_D$ −29.2° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3120–3030 (m), 3020 (m), 2960 (m), 2840 (m), 1620 (m), 1605 (m), 1590 (m), 1520 (s), 1500 (m), 1460 (m), 1445 (m), 1390 (m), 1370 (m), 1335 (s), 1310 (s), 1250 (s), 1180 (s), 1160 (s), 1095 (m), 970 (m), 895 (m), 835 (m), 815 (m), 700 (m), 640 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45–1.49 (comp m, 2 H), 1.63–2.03 (comp m, 2 H), 2.39 (dd, *J* = 5.0, 2.7 Hz, 1 H), 2.43 (s, 3 H), 2.44–2.53 (comp m, 2 H), 2.66 (dd, *J* = 5.0, 4.1 Hz, 1 H), 2.77 (m, 1 H), 3.77 (s, 3 H), 4.13 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 271.0 Hz, 2 H), 4.99 (dd, *J* = 9.3, 6.5 Hz, 1 H), 5.16–5.22 (m, 1 H), 5.31–5.36 (m, 1 H), 6.73 (d, *J* = 8.7 Hz, 2 H), 6.96–6.99 (m, 2 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 7.17–7.21 (m, 3 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.61 (d, *J* = 8.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 28.8, 32.1, 35.6, 47.0, 47.6, 51.7, 55.2, 61.3, 113.5, 127.0, 127.2, 127.7, 128.1, 128.9, 129.2, 129.6, 129.7, 132.1, 137.4, 138.5, 142.9, 158.9. Anal. Calcd for $C_{29}H_{33}NO_4S$: C, 70.85; H, 6.77. Found: C, 70.65; H, 6.81.

Epoxide (−)-37a from Mesitylene Sulfonate (−)-36a. The (*Z*) olefin epoxide (−)-**37a** was prepared as described above for (−)-**37b** and isolated as a colorless oil: $[\alpha]^{25}_D$ −27.6° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 3070–3020 (m), 3010 (m), 2940 (m), 2840 (w), 1620 (m), 1605 (m), 1590 (w), 1520 (s), 1500 (m), 1460 (m), 1445 (m), 1340 (s), 1310 (m), 1250 (s), 1180 (m), 1165 (s), 1095 (m), 1040 (m), 940 (m), 905 (m), 895 (m), 835 (m), 815 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.46–1.56 (comp m, 2 H), 2.03–2.13 (m, 2 H), 2.42 (s, 3 H), 2.45 (dd, *J* = 5.0, 2.7 Hz, 1 H), 2.55 (apparent t, *J* = 7.4 Hz, 2 H), 2.73 (dd, *J* = 4.9, 3.1 Hz, 1 H), 2.88 (comp m, 1 H), 3.77 (s, 3 H), 4.16 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 145.8 Hz, 2 H), 4.94 (dd, $J_1 = J_2$ = 8.3 Hz, 1 H), 5.12–5.19 (m, 1 H), 5.25–5.33 (m, 1 H), 6.75 (m, 2 H), 6.92–6.95 (m, 2 H), 7.04 (d, *J* = 8.6 Hz, 2 H), 7.16–7.22 (comp m, 5 H), 7.61 (d, *J* = 8.6 Hz, 2 H); mass spectrum (CI, NH_3) *m/z* 492.2193 [$(M + H)^+$, calcd for $C_{29}H_{34}NO_4S$ 492.2209]. Anal. Calcd for $C_{29}H_{33}NO_4S$: C, 70.85; H, 6.77. Found: C, 71.03; H, 6.86.

Epoxides (−)-37a and (−)-37b from (−)-27 and (+)-6. Phosphonium iodide (−)-**27** (11.76 g, 14.72 mmol) was dissolved in a minimum of CH_2Cl_2, benzene was added, and the solution was concentrated in vacuo. The resultant foam was dried further under high vacuum for 30 min and then dissolved in THF (30 mL). The solution was cooled to 0 °C. Dropwise addition of *n*-butyllithium (2.5 M in hexane, 6.47 mL, 16.2 mmol) gave a blood-red solution, which was stirred at 0 °C for 70 min. During this period, a solution of LDA was prepared by adding *n*-butyllithium (6.47 mL, 16.2 mmol) to a solution of *i*-Pr_2NH (2.26 mL, 16.2 mmol) in THF (10 mL) at 0 °C. The resultant solution was stirred for 15 min and then transferred via a cannula to a cold (0 °C) solution of lactol **6** (2.93 g, 16.2 mmol) in THF (5 mL). This mixture was stirred for 10 min at 0 °C and then transferred by cannula to the ylide solution. As the whole was stirred for 1 h at 0 °C, the red color of the ylide slowly faded and triphenylphosphine oxide precipitated. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexanes eluant) gave a 1:1 mixture of (−)-**37a** and (−)-**37b** (4.78 g, 66% yield), as determined by integration of the benzyl AB quartets in the ^1H NMR spectrum.

Equilibration of Epoxy Olefins (−)-37a and (−)-37b. A 1:1 mixture of (−)-**37a** and (−)-**37b** (3.23 g, 6.57 mmol) was diluted with benzene (82 mL) to a concentration of ca. 0.08 M, and the solution was transferred to a Pyrex jacket. Diphenyl disulfide (43 mg, 0.197 mmol, 3 mol %) was added, and the solution was then degassed with argon for 30–40 min, cooled to 0 °C, and irradiated for 3 h with a 450-W medium-pressure Hanovia mercury lamp suspended in a water-cooled quartz immersion well. Concentration in vacuo gave a slightly yellowish syrup, which was dissolved in EtOAc and decolorized with Norite. Filtration, concentration in vacuo, and flash chromatography (10 → 30% EtOAc/hexanes, gradient elution) furnished a 4:1 mixture of **37b** and **37a** (3.12 g, 96% yield). Crystallization from Et_2O/pentane with several seed crystals gave pure (*E*) isomer (−)-**37b** (1.88 g, 57.8% yield). Concentration of the mother liquors furnished a ca. 1:1 mixture of isomers which could be reequilibrated.

Dithiane (−)-38b. A solution of 1,3-dithiane (7.86 g, 65.4 mmol) in THF (degassed with argon, 65 mL) was cooled to −45 °C, and *n*-butyllithium (hexane, 26.2 mL, 65.4 mmol) was added dropwise over 15 min. The resultant solution was stirred at −23 °C for 80 min and then added via a cannula to a solution of epoxide (−)-**37b** (10.72 g, 21.80 mmol) in degassed THF (22 mL) at 0 °C. The ice bath was removed, and the reaction was stirred for 5 min as a dark green color developed. Upon quenching with saturated NH_4Cl solution, the color dissipated. The mixture was filtered through a pad of $MgSO_4$, and the solids were washed well with EtOAc. Concentration in vacuo and flash chromatography (10 → 35% EtOAc/hexanes, gradient elution) afforded (−)-**38b** (11.3 g, 85% yield) as a colorless syrup: $[\alpha]^{25}_D$ −14.6° (*c* 6.11, $CHCl_3$); IR ($CHCl_3$) 3620–3320 (w), 3080 (w), 3040 (m), 3020 (m), 2960 (m), 2940 (m), 2850 (w), 1620 (m), 1605 (m), 1590 (w), 1520 (s), 1500 (m), 1470 (m), 1455 (m), 1435 (m), 1355–1315 (s), 1310 (m), 1280 (m), 1250 (s), 1180 (m), 1160 (s), 1090 (m), 1030 (m), 970 (m), 910 (m), 895 (m) 830 (m), 810 (m), 700 (m), 660 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38–1.43 (m, 2 H), 1.79–1.82 (comp m, 2 H), 1.83–1.91 (comp m, 1 H), 1.95–2.00 (comp m, 3 H), 2.04–2.13 (comp m, 1 H), 2.42 (s, 3 H), 2.45–2.52 (comp m, 2 H), 2.82–2.94 (comp m, 4 H), 3.77 (s, 3 H), 3.81–3.85 (m, 1 H), 4.11 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 256.5 Hz, 2 H), 4.20 (dd, *J* = 8.2, 5.9 Hz, 1 H), 4.99 (dd, *J* = 8.5, 7.1 Hz, 1 H), 5.18–5.23 (m, 1 H), 5.29–5.37 (m, 1 H), 6.72 (d, *J* = 8.7 Hz, 2 H), 6.97–7.00 (comp m, 4 H), 7.17–7.21 (comp m, 3 H), 7.24 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 25.6, 28.4, 29.7, 30.0, 35.3, 36.4, 42.4, 43.7, 47.3, 54.9, 61.0, 67.5, 113.2, 126.5, 126.9, 127.5, 127.9, 128.5, 129.2, 129.5, 132.4, 137.3, 138.2, 142.7, 158.5; mass spectrum (CI, NH_3) *m/z* 612.2374 [$(M + H)^+$, calcd for $C_{33}H_{42}NO_4S$ 612.2276].

Dithiane (−)-38a. The (*Z*) olefin dithiane (−)-**38a** was prepared in 82% yield as described above for (−)-**38b**: $[\alpha]^{20}_D$ −6.8° (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 3660 (w), 3610–3300 (w), 3060 (w), 3020 (m), 3000 (m), 2950 (m), 2910 (m), 2840 (m), 1615 (m), 1600 (m), 1590 (w), 1515 (s), 1495 (m), 1455 (m), 1445 (m), 1435 (m), 1350–1320 (s), 1310 (m), 1260–1230 (s), 1175 (m), 1160 (s), 1110 (m), 1090 (m), 935 (m), 910 (m), 890 (m), 830 (m), 810 (m), 700 (m), 655 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.39–1.49 (m, 2 H), 1.77–2.28 (comp m, 7 H), 2.42 (s, 3 H), 2.47–2.65 (comp m, 2 H), 2.79–3.01 (comp m, 4 H), 3.78 (s, 3 H), 3.81–3.98 (m, 1 H), 4.14 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 148.8 Hz, 2 H),

4.28 (dd, J = 7.9, 6.4 Hz, 1 H), 4.91 (dd, J = 9.5, 6.6 Hz, 1 H), 5.07–5.19 (m, 1 H), 5.25–5.38 (m, 1 H), 6.77 (d, J = 8.5 Hz, 2 H), 6.90–6.99 (comp m, 2 H), 7.02 (d, J = 9.0 Hz, 2 H), 7.15–7.25 (comp m, 5 H), 7.64 (d, J = 8.5 Hz, 2 H); mass spectrum (CI, NH_3) m/z 612.2317 [$(M + H)^+$, calcd for $C_{33}H_{42}NO_4S$ 612.2276].

Silyl Ether (−)-39b. A solution of dithiane (−)-**38b** (2.57 g, 4.21 mmol) in DMF (13 mL) was treated with imidazole (630 mg, 9.26 mmol), *tert*-butyldiphenylsilyl chloride (1.4 mL, 5.47 mmol), and 4-pyrrolidinopyridine (a few crystals). The reaction was stirred for 18 h and then poured into a separatory funnel containing Et_2O (250 mL). The ether layer was washed three times with water, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (10 → 20% EtOAc/hexanes, gradient elution) provided (−)-**39b** (3.30 g, 92% yield) as a colorless amorphous solid: $[\alpha]^{20}_D$ −3.6° (c 0.70, $CHCl_3$); IR ($CHCl_3$) 3070 (w), 3030 (w), 3000 (m), 2960 (m), 2940 (m), 2910 (m), 2860 (w), 1600 (w), 1585 (w), 1510 (m), 1495 (w), 1470 (w), 1460 (w), 1450 (w), 1440 (w), 1430 (m), 1330 (m), 1300 (m), 1250 (m), 1180 (m), 1160 (m), 1110–1080 (m), 1040 (m), 970 (w), 910 (s), 890 (m), 820 (m), 700 (s), 655 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.28–1.42 (comp m, 2 H), 1.62–1.86 (comp m, 5 H), 1.97–2.03 (m, 1 H), 2.31–2.46 (comp m, 2 H), 2.41 (s, 3 H), 2.52–2.58 (m, 1 H), 2.63–2.71 (comp m, 3 H), 3.70 (s, 3 H), 3.92–3.96 (m, 1 H), 4.00 (dd, J = 14.3, 5.2, 1 H), 4.10 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 241.7 Hz, 2 H), 4.91–5.03 (comp m, 3 H), 6.71 (d, J = 8.7 Hz, 2 H), 6.95–6.99 (m, 4 H), 7.15–7.19 (m, 3 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.32–7.41 (comp m, 6 H), 7.60 (d, J = 8.3 Hz, 2 H), 7.61–7.67 (comp m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.5, 25.8, 27.0, 27.6, 29.8, 30.3, 35.5, 36.4, 42.0, 43.9, 47.5, 55.2, 61.2, 69.5, 113.4, 126.3, 127.2, 127.4, 127.6, 128.1, 128.8, 129.4, 129.5, 129.6, 132.5, 134.0, 135.9, 137.4, 138.5, 142.8, 158.8. Anal. Calcd for $C_{49}H_{59}NO_4SSi$: C, 69.22; H, 6.99; N, 1.65. Found: C, 69.18; H, 7.05; N, 1.54.

Silyl Ether (−)-39a. The (Z) olefin silyl ether (−)-**39a** was prepared in 95% yield as described above for (−)-**39b** and isolated as a colorless oil: $[\alpha]^{20}_D$ −8.5° (c 1.47, $CHCl_3$); IR ($CHCl_3$) 3070 (m), 3030 (m), 3010 (m), 2970 (m), 2940 (m), 2910 (m), 2870 (m), 1620 (m), 1600 (w), 1590 (w), 1520 (m), 1500 (m), 1475 (m), 1465 (m), 1445 (m), 1430 (m), 1365 (m), 1340 (m), 1310 (m), 1260 (s), 1180 (m), 1160 (s), 1110 (s), 1090 (s), 1050 (m), 935 (m), 890 (m), 820 (m), 700 (s), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.39–1.48 (m, 2 H), 1.78–2.10 (comp m, 6 H), 2.41 (s, 3 H), 2.41–2.50 (comp m, 2 H), 2.52–2.76 (comp m, 4 H), 3.76 (s, 3 H), 3.99–4.11 (comp m, 2 H), 4.12 (AB q, J_{AB} = 15.6 Hz, $\Delta\nu_{AB}$ = 108.5 Hz, 2 H), 4.92–5.02 (comp m, 3 H), 6.72 (d, J = 8.7 Hz, 2 H), 6.91–6.99 (m, 4 H), 7.15–7.25 (m, 5 H), 7.30–7.41 (m, 6 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.66–7.67 (m, 4 H); mass spectrum (field desorption) m/z 850.3520 [$(M + H)^+$, calcd for $C_{49}H_{60}NO_4SSi$ 850.3450].

Ketone (−)-41. Et_2O (2.7 mL) was cooled to −78 °C, and *tert*-butyllithium (1.7 M in pentane, 2.3 mL, 3.96 mmol) was added. A solution of vinyl iodide **3a** (618 mg, 2.0 mmol) in Et_2O (4.5 mL) was then introduced dropwise, and the reaction mixture was stirred for 2 h at −78 °C. A solution of copper(I) iodide·tri-*n*-butylphosphine complex (777 mg, 2.0 mmol) in Et_2O (2.7 mL) was cooled to 0 °C and treated with *n*-Bu_3P (0.49 mL, 2.0 mmol). The resultant mixture was stirred for 1 h and added to the vinyl anion solution via a cannula, and the whole was stirred for an additional 1 h. Trimethylsilyl chloride (1.2 mL, 9.9 mmol) was then added, followed immediately by a solution of (−)-**4** (111.1 mg, 0.99 mmol) in Et_2O (3 mL). The resulting bright yellow solution was stirred for 1 min and then quenched with a mixture of MeOH (1.7 mL) and pyridine (0.8 mL). The cold bath was removed and some saturated NH_4Cl solution added. The mixture was stirred until two phases separated (in some experiments, a few drops of water were added to dissolve the salts). Following extraction with Et_2O, the organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Traces of pyridine were azeotropically removed with hexane in vacuo. The residual oil was then dissolved in MeOH, and the solution was stirred at ambient temperature until TLC analysis indicated complete hydrolysis of the TMS enol ether (R_f 0.5, 10% EtOAc/hexanes). Concentration in vacuo and flash chromatography (6% EtOAc/hexanes eluant) afforded (−)-**41** (229 mg, 77% yield) as a colorless oil: R_f 0.3 (10% EtOAc/hexanes); $[\alpha]^{23}_D$ −52.1° (c 1.76, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2960 (s), 2940 (s), 2910 (m), 2870 (m), 2740 (m), 1750 (s), 1470 (m), 1440 (w), 1405 (w), 1395 (w), 1380 (w), 1365 (w), 1260 (m), 1210 (m), 1115 (m), 1090 (s), 1010 (m), 960 (m), 840 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.87 (s, 9 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.77 (ddd, J = 13.8, 8.3, 6.5 Hz, 1 H), 1.89 (dd, J = 19.0, 8.1 Hz, 1 H), 2.02–2.08 (comp m, 1 H), 2.46 (ddd, J = 19.0, 8.1, 1.4 Hz, 1 H), 3.30 (comp m, 1 H), 3.42 (s, 3 H), 3.55 (dd, J = 5.8, 4.6 Hz, 1 H), 4.15 (AB q, J_{AB} = 9.6 Hz, $\Delta\nu_{AB}$ = 9.7 Hz, 2 H), 5.09 (dd, J = 9.4, 1.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.3, 18.3, 21.1, 25.9, 31.2, 37.5, 43.3, 57.8, 62.0, 80.7, 129.1, 136.5, 214.9; mass spectrum (CI, NH_3) m/z 298.1964 [M^+, calcd for $C_{16}H_3O_3Si$ 298.1956].

Aldehyde (−)-42. A solution of (Z) olefin dithiane (−)-**39a** (459.5 mg, 0.54 mmol) in 15% aqueous THF (4.6 mL) was treated with red HgO (234 mg, 1.08 mmol) followed by $BF_3{\cdot}Et_2O$ (0.26 mL, 2.2 mmol). The bright orange color gradually faded. After 5 h, the mixture was diluted with Et_2O and filtered. The filtrate was washed twice with saturated $NaHCO_3$ and twice with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (15% EtOAc/hexanes eluant) furnished (−)-**42** (362 mg, 88% yield) as a colorless oil: $[\alpha]^{25}_D$ −9.5° (c 0.50, $CHCl_3$); IR ($CHCl_3$) 3080 (m), 3040 (m), 3020 (m), 2970 (s), 2940 (s), 2870 (m), 1725 (s), 1620 (m), 1605 (m), 1590 (m), 1520 (s), 1500 (m), 1470 (m), 1455 (m), 1435 (m), 1430 (m), 1390 (m), 1370 (m), 1335 (s), 1310 (m), 1250 (s), 1180 (m), 1160 (s), 1090 (s), 1040 (m), 935 (m), 900 (m), 820 (m), 700 (s), 660 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.43–1.57 (m, 2 H), 1.82–1.92 (m, 2 H), 2.41 (s, 3 H), 2.46–2.51 (m, 4 H), 3.75 (s, 3 H), 4.10 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 148.6 Hz, 2 H), 4.18 (m, 1 H), 4.87 (dd, J = 8.3, 7.6 Hz, 1 H), 4.97–5.04 (comp m, 2 H), 6.71 (d, J = 8.7 Hz, 2 H), 6.85–6.89 (m, 2 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.14–7.25 (comp m, 6 H), 7.31–7.44 (comp m, 6 H), 7.57 (d, J = 8.3 Hz, 2 H), 7.62–7.66 (m, 3 H), 9.69 (dd, $J_1 = J_2$ = 2.5 Hz, 1 H); mass spectrum (field desorption) m/z 760.3530 [$(M + H)^+$, calcd for $C_{46}H_{54}NO_5SSi$ 760.3490].

Alcohols 43. Lithium diisopropylamide was prepared by adding *n*-butyllithium (2.5 M in hexane, 0.72 mL, 1.7 mmol) to a solution of diisopropylamine (0.24 mL, 1.7 mmol) in THF (2 mL) at 0 °C. The reaction was stirred for 15 min at 0 °C and cooled to −78 °C. A solution of ketone (−)-**41** (466 mg, 1.56 mmol) in THF (2 mL) was precooled to −78 °C and then transferred via a cannula to the LDA solution. The resultant mixture was stirred for 90 min and then added dropwise by cannula to a cold (−78 °C) solution of aldehyde (−)-**42** (817 mg, 1.07 mmol) in THF (3 mL). The reaction was stirred for 40 min, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (15% EtOAc/hexanes eluant) gave unreacted ketone **41** (235 mg, 50% yield) and a mixture of diastereomeric aldols **43** (643 mg, 56% yield) as a colorless oil: IR ($CHCl_3$) 3700–3400 (w), 3080 (w), 3010 (m), 2970 (s), 2940 (s), 2910 (m), 2870 (m), 1745 (m), 1620 (m), 1605 (w), 1595 (w), 1520 (m), 1500 (w), 1475 (m), 1465 (m), 1430 (m), 1335 (m), 1310 (m), 1255 (m), 1210 (m), 1180 (m), 1160 (s), 1115 (s), 1095–1050 (s), 840 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04, 0.05, 0.06, 0.07 (diastereomers s, s, s, s, 6 H), 0.85, 0.87, 0.88, 0.89 (diastereomers, s, s, s, s, 9 H), 0.91, 0.99, 1.00, 1.03 (diastereomers, s, s, s, s, 9 H), 1.30–2.14 (comp m, 10 H), 1.76 (d, J = 1.0 Hz, 3 H), 2.30–2.49 (m, 2 H), 2.39 (s, 3 H), 2.85 (d, J = 4.4 Hz, 1 H), 2.93 (d, J = 4.4 Hz, 1 H), 3.20–3.55 (m, 1 H), 3.39, 3.40, 3.41 (diastereomers, s, s, s, 3 H), 3.48–3.65 (m, 1 H), 3.73 (s, 3 H), 3.70–3.95 (m, 2 H), 4.09–4.38 (m, 3 H), 4.82–4.96 (m, 3 H), 5.10 (d, J = 9.6 Hz, 1 H), 5.15 (d, J = 9.6 Hz, 1 H), 6.65–6.74 (m, 4 H), 6.85–6.99 (m, 4 H), 7.11–7.23 (m, 6 H), 7.51–7.58 (m, 2 H), 7.62–7.71 (m, 3 H); mass spectrum (field desorption) m/z 1058.550 [$(M + H)^+$, calcd for $C_{62}H_{84}NO_8SSi$ 1058.545].

1,3-Diketone 44. A solution of oxalyl chloride (16.4 μL, 0.189 mmol) in CH_2Cl_2 (0.30 mL) was cooled to −65 °C, and a solution of DMSO (26.8 μL, 0.38 mmol) in CH_2Cl_2 (0.10 mL) was introduced. After 2 min, a solution of aldol **43** (182.0 mg, 0.172 mmol) in CH_2Cl_2 (ca. 0.2–0.5 mL, including syringe and flask washings) was added dropwise. The reaction was stirred for 15 min and then treated dropwise with Et_3N (120 μL, 0.86 mmol). The mixture was stirred for an additional 5 min, warmed to ambient temperature, diluted with water, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexanes eluant) furnished **44** (115 mg, 63% yield) as a colorless oil. The product was characterized as the vinylogous ester derivative (−)-**45**.

Vinylogous Ester (−)-45. Diazomethane (ca. 6 mmol) was generated by adding *N*-methyl-*N*-nitrosourea (640 mg, 6.2 mmol) to a vigorously stirred mixture of 50% KOH (1 mL) and Et_2O (5 mL) at 0 °C. Portions of the ethereal solution (ca. 1.5–3 mL total) were then added dropwise via a flame-polished pipet to a stirred solution of vinylogous acid **44** (97 mg, 0.092 mmol) in Et_2O (3 mL) at ambient temperature. After ca. 15 min, TLC analysis indicated complete reaction of the "streaky" vinylogous acid with formation of a less polar product. $MgSO_4$ was added, and the mixture was stirred until the yellow color of CH_2N_2 dissipated. Filtration, concentration in vacuo, and flash chromatography (12–15% EtOAc/hexanes eluant) afforded (−)-**45** (42 mg, 43% yield) as a colorless oil: $[\alpha]^{22}_D$ −48.2° (c 0.25, $CHCl_3$); IR ($CHCl_3$) 3070 (w), 3020 (m), 2970 (s), 2940 (s), 2870 (m), 1735 (m), 1650 (w), 1620 (m), 1520 (m), 1470 (m), 1430 (m), 1395 (m), 1380 (m), 1360 (m), 1340 (m), 1310 (m), 1250 (s), 1210 (s), 1160 (s), 1110 (s), 1090 (s), 1050 (m), 1010 (m), 940 (w), 895 (w), 835 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06

(d, J = 2.9 Hz, 6 H), 0.90 (s, 9 H), 1.00 (s, 9 H), 1.36–1.41 (m, 2 H), 1.63 (s, 3 H), 1.73 (ddd, J = 13.9, 7.6, 4.3 Hz, 1 H), 1.85–1.98 (comp m, 2 H), 2.02 (ddd, J = 13.8, 8.3, 3.9 Hz, 1 H), 2.40 (s, 3 H), 2.45–2.53 (m, 2 H), 2.79 ($^1/_2$ ABX, J_{AB} = 16.3 Hz, J_{AX} = 6.8 Hz, 1 H), 2.99 ($^1/_2$ ABX, J_{BA} = 16.2 Hz, J_{AX} = 5.8 Hz, 1 H), 3.28 (s, 3 H), 3.74 (s, 3 H), 3.74–3.77 (m, 1 H), 3.80 (s, 3 H), 4.13 (AB q, J_{AB} = 15.3 Hz, $\Delta\nu_{AB}$ = 171.7 Hz, 2 H), 4.23 (AB q, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 222.6 Hz, 2 H), 4.32–4.36 (m, 1 H), 4.66 (dd, J = 7.3, 3.8 Hz, 1 H), 4.76 (d, J = 9.7 Hz, 1 H), 4.93 (dd, J = 9.3, 6.8 Hz, 1 H), 4.96–5.08 (comp m, 2 H), 6.68 (d, J = 8.6 Hz, 2 H), 6.93–6.97 (m, 4 H), 7.15–7.20 (comp m, 5 H), 7.29–7.38 (comp m, 6 H), 7.55 (d, J = 8.1 Hz, 2 H), 7.63–7.68 (comp m, 4 H); mass spectrum (field desorption) m/z 1069.5300 [(M + H)$^+$, calcd for $C_{63}H_{83}NO_8SSi$ 1069.5380].

***p*-Methoxybenzyl Ether (−)-48.** A solution of dithiane (−)-**38b** (26.9 g, 43.9 mmol) in THF (300 mL) was cooled to 0 °C and treated with potassium hydride (35% dispersion in mineral oil, 7.5 g, 66 mmol). The ice bath was removed and the mixture stirred for 15 min. After recooling to 0 °C, dropwise addition of 4-methoxybenzyl chloride (8.9 mL, 66 mmol) was followed by introduction of tetrabutylammonium iodide (1.2 g, 3.3 mmol, 5 mol %) and 18-crown-6 (872 mg, 3.3 mmol, 5 mol %). The reaction was allowed to warm to ambient temperature while stirring for 20 min. Finally, the mixture was again cooled to 0 °C and quenched with saturated NH_4Cl solution. After concentration in vacuo, the residue was dissolved in water and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (25% EtOAc/hexanes eluant) gave (−)-**48** (31.9 g, 99% yield) as a colorless syrup: $[\alpha]^{23}_D$ −9.0° (c 3.12, $CHCl_3$); IR ($CHCl_3$) 3060 (m), 3010 (m), 3005 (m), 2940 (m), 2910 (m), 2860 (m), 2840 (m), 1620 (s), 1590 (m), 1520 (s), 1500 (m), 1470 (m), 1455 (m), 1425 (m), 1340 (s), 1310 (s), 1250 (s), 1180 (s), 1160 (s), 1090 (s), 1040 (s), 970 (m), 900 (m), 895 (m), 830 (m), 820 (m), 700 (m), 660 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$) δ 1.41–1.55 (comp m, 2 H), 1.77 (ddd, J = 13.8, 9.4, 4.4 Hz, 1 H), 1.81–1.94 (comp m, 4 H), 2.06–2.14 (m, 1 H), 2.42 (s, 3 H), 2.43–2.58 (comp m, 2 H), 2.79–2.89 (comp m, 4 H), 3.56–3.62 (m, 1 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.01 (dd, J = 8.9, 5.5 Hz, 1 H), 4.13 (AB q, J_{AB} = 15.5 Hz, $\Delta\nu_{AB}$ = 244.0 Hz, 2 H), 4.34 (s, 2 H), 4.99 (dd, J = 9.5, 6.2 Hz, 1 H), 5.12–5.19 (m, 1 H), 5.29–5.37 (m, 1 H), 6.71 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.99–7.02 (m, 4 H), 7.17–7.25 (comp m, 7 H), 7.61 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 25.9, 28.1, 30.1, 30.4, 33.6, 35.6, 40.1, 43.9, 47.6, 55.2, 61.4, 71.0, 74.7, 113.4, 113.7, 126.6, 127.2, 127.7, 128.1, 128.9, 129.3, 129.4, 129.6, 130.8, 132.7, 137.4, 138.5, 142.9, 158.8; mass spectrum (FAB, NBA matrix) m/z 732.2910 [(M + H)$^+$, calcd for $C_{41}H_{50}NO_5S_3$ 732.2850]. Anal. Calcd for $C_{41}H_{49}NO_5S_3$: C, 67.27; H, 6.75. Found: C, 67.08; H, 6.61.

Secondary Amine (−)-49. A solution of *p*-toluenesulfonamide (−)-**48** (31.9 g, 43.6 mmol) in 1,2-dimethoxyethane (870 mL) was cooled to −78 °C, and a solution of sodium naphthalenide (1 M in DME, ca. 125 mL, 125 mmol) was added dropwise over 30 min. The dark green color of the radical anion faded during the addition but persisted upon its completion. The mixture was stirred at −78 °C for ca. 40 min and then quenched with water, which caused complete decolorization. Following concentration in vacuo, the residue was diluted with water and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (15:4:1 hexanes/Et_2O/TEA eluant) furnished (−)-**49** (21.7 g, 86% yield) as a colorless oil: $[\alpha]^{26}_D$ −11.6° (c 3.28, $CHCl_3$); IR ($CHCl_3$) 3060 (w), 3040 (w), 3020 (m), 2960 (m), 2930 (m), 2880 (m), 1620 (m), 1595 (w), 1520 (s), 1475 (m), 1460 (m), 1450 (m), 1430 (m), 1360 (w), 1310 (m), 1260 (s), 1180 (m), 1080 (m), 1045 (m), 980 (w), 915 (w), 830 (m), 710 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48–1.64 (comp m, 2 H), 1.65–1.78 (br m, 1 H), 1.79–1.85 (comp m, 2 H), 1.95 (ddd, J = 14.1, 5.4, 4.6 Hz, 1 H), 2.01–2.12 (comp m, 3 H), 2.28–2.38 (comp m, 2 H), 2.74–2.88 (comp m, 4 H), 3.51 (AB q, J_{AB} = 13.1 Hz, $\Delta\nu_{AB}$ = 72.2 Hz, 2 H), 3.61–3.64 (m, 1 H), 3.65–3.69 (m, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.12 (dd, J = 9.0, 5.3 Hz, 1 H), 4.42 (AB q, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 12.8 Hz, 2 H), 5.28–5.35 (m, 1 H), 5.41–5.47 (m, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H), 7.21–7.24 (m, 1 H), 7.25 (d, J = 8.5 Hz, 2 H), 7.27–7.35 (comp m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 28.1, 30.0, 30.4, 33.8, 40.1, 41.8, 43.9, 50.7, 55.2, 61.8, 71.0, 74.7, 113.6, 126.8, 127.1, 127.2, 128.2, 128.5, 129.2, 129.4, 130.7, 132.7, 132.9, 143.9, 158.4, 159.0; mass spectrum (FAB, NBA matrix) m/z 578.2800 [(M + H)$^+$, calcd for $C_{33}H_{44}NO_3S_2$ 578.2760].

Urethane (−)-50. A solution of amine (−)-**49** (21.7 g, 37.6 mmol) in THF (187 mL) was cooled to 0 °C, and anhydrous K_2CO_3 (129 g, 0.94 mol) was added. The stirred slurry was treated with a solution of [2-(trimethylsilyl)ethoxy]carbonyl chloride (ca. 26 g, 144 mmol, 3.8 equiv) in toluene (13 mL) dropwise over 10 min. The ice bath was removed and the reaction was stirred overnight. The solids were filtered and washed well with Et_2O. Concentration in vacuo and flash chromatography (10 → 15% EtOAc/hexanes, gradient elution) gave (−)-**50** (27 g, 99% yield) as a colorless oil: $[\alpha]^{23}_D$ −32.9° (c 1.98, $CHCl_3$); IR ($CHCl_3$) 3090 (w), 3070 (w), 3020 (m), 3010 (s), 2960 (s), 2910 (s), 2860 (m), 2840 (m), 1685 (s), 1620 (s), 1590 (m), 1520 (s), 1465 (s), 1460 (s), 1450 (m), 1440 (m), 1420 (s), 1360 (m), 1310 (s), 1250 (s), 1180 (s), 1120 (m), 1090 (m), 1040 (m), 970 (m), 950 (m), 910 (m), 860 (s), 840 (s); ^{1}H NMR (500 MHz, DMSO-d_6, 115 °C) δ 0.02 (s, 9 H), 0.95 (dd, J_1 = J_2 = 8.1 Hz, 2 H), 1.49–1.58 (comp m, 2 H), 1.73–1.92 (comp m, 3 H), 1.94–1.98 (m, 2 H), 2.00–2.07 (comp m, 1 H), 2.61–2.71 (comp m, 2 H), 2.77–2.89 (comp m, 4 H), 3.58–3.63 (m, 1 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 4.11 (dd, J = 8.0, 5.8 Hz, 1 H), 4.16 (dd, J = 9.2, 7.7 Hz, 2 H), 4.25 (AB q, J_{AB} = 5.4 Hz, $\Delta\nu_{AB}$ = 45.1 Hz, 2 H), 4.39 (s, 2 H), 5.10 (dd, J_1 = J_2 = 7.7 Hz, 1 H), 5.23–5.31 (m, 1 H), 5.39–5.45 (m, 1 H), 6.76 (d, J = 8.6 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 7.01 (d, J = 8.6 Hz, 2 H), 7.20–7.34 (comp m, 7 H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C) δ 2.2, 16.9, 24.9, 26.9, 28.4, 28.6, 32.9, 33.9, 42.6, 46.8, 54.6, 59.4, 62.1, 69.5, 74.5, 113.0, 113.2, 126.1, 126.3, 127.2, 127.4, 127.5, 128.2, 128.3, 130.5, 131.5, 139.7, 155.7, 157.8, 158.4; mass spectrum (FAB, NBA matrix) m/z 722.3436 [(M + H)$^+$, calcd for $C_{40}H_{56}NO_5SSi$ 722.3317]. Anal. Calcd for $C_{40}H_{55}NO_5S_2Si$: C, 66.53; H, 7.67; N, 1.94. Found: C, 66.31; H, 7.48; N, 1.89.

Aldehyde (−)-51. At room temperature a solution of carbamate (−)-**50** (2.88 g, 3.99 mmol) in 20% aqueous CH_3CN (32 mL) was treated with MeI (12.4 mL, 199 mmol, filtered through 80–200 mesh, activity 1 neutral alumina). The biphasic mixture was stirred vigorously overnight. Excess MeI was then distilled off into a cold (−78 °C) receiver at aspirator pressure *in a hood with the sash fully closed*. The residue was dissolved in Et_2O, and the solution was washed with saturated $NaHCO_3$ solution and brine. The aqueous layers were extracted with Et_2O, and the combined ethereal solutions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (15% EtOAc/hexanes eluant) afforded (−)-**51** (2.16 g, 85% yield) as a colorless oil: $[\alpha]^{20}_D$ −43.8° (c 3.84, $CHCl_3$); IR ($CHCl_3$) 3040 (m), 3020 (m), 2960 (m), 2940 (m), 2920 (m), 2870 (m), 2860 (m), 1730 (m), 1685 (s), 1620 (m), 1590 (w), 1520 (s), 1460 (m), 1445 (m), 1415 (m), 1310 (m), 1260 (s), 1180 (m), 1110 (m), 1040 (m), 970 (w), 940 (w), 860 (m), 840 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, 115 °C) δ 0.02 (s, 9 H), 0.94 (dd, J_1 = J_2 = 8.2 Hz, 2 H), 1.47–1.64 (comp m, 2 H), 1.94–1.98 (m, 2 H), 2.54 (dd, J = 5.8, 2.4 Hz, 2 H), 2.61–2.67 (m, 2 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 3.83–3.88 (m, 1 H), 4.15 (dd, J = 8.3, 7.0 Hz, 2 H), 4.23 (AB q, J_{AB} = 15.7 Hz, $\Delta\nu_{AB}$ = 46.3 Hz, 2 H), 4.39 (AB q, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = 8.3 Hz, 2 H), 5.09 (dd, J_1 = J_2 = 7.8 Hz, 1 H), 5.24–5.31 (m, 1 H), 5.38–5.43 (m, 1 H), 6.75 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 7.19 (d, J = 8.6 Hz, 2 H), 7.20–7.30 (comp m, 5 H), 9.68 (dd, J_1 = J_2 = 2.6 Hz, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 1.5, 17.7, 28.1, 33.7, 34.5, 46.7, 48.1, 55.1, 59.4, 63.6, 70.8, 73.2, 113.3, 113.7, 127.1, 127.4, 128.2, 128.9, 129.3, 130.1, 131.1, 132.0, 139.65, 157.1, 158.3, 159.1, 201.5. Anal. Calcd for $C_{37}H_{49}NO_6Si$: C, 70.33; H, 7.82. Found: C, 70.09; H, 7.73.

Alcohols 52 via Aldol Coupling of (−)-41 with (−)-51. A solution of LDA (1.94 mmol) in THF (3 mL) was prepared as described above and cooled to −78 °C. A solution of ketone (−)-**41** (554 mg, 1.85 mmol) in THF (3.5 mL) was added dropwise, and the mixture was stirred for 90 min. A solution of aldehyde (−)-**51** (1.89 g, 1.94 mmol) in THF (7 mL) was then added. The reaction mixture was stirred for 5 min, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (1:1:4 Et_2O/CH_2Cl_2/hexanes eluant; performed twice) gave **52** (558 mg, 32% yield) as a mixture of diastereomers, isolated as a colorless oil. The IR and ^{1}H NMR spectra were identical with those described below.

Alcohols 52 and 54 via Dimethylzinc-Mediated Three-Component Coupling. A mixture of zinc bromide (451 mg, 2.00 mmol), MeI (0.25 mL, 4.00 mmol), Li wire (55.5 mg, 8.00 mmol), and Et_2O (8.0 mL) was sonicated at 0 → 25 °C for 1 h. The resultant clear, colorless ethereal solution of dimethylzinc (0.25 M) was employed in the three-component coupling reaction as described below for dineopentylzinc. Flash chromatography (1:1:4 Et_2O/CH_2Cl_2/hexanes eluant) gave aldol **52** (84 mg, 30% yield) as a mixture of diastereomers (R_f 0.31, 1:1:3 Et_2O/CH_2Cl_2/hexanes) followed by the methyl congener **54** (68 mg, 30% yield), also as a mixture of diastereomers (R_f 0.17, 1:1:3 Et_2O/CH_2Cl_2/hexanes). The spectra of **52** were identical with those described below. Data for **54**: IR ($CHCl_3$) 3460 (m), 3010 (m), 2970 (m), 2940 (m), 2870 (w), 2835 (w), 1735 (m), 1680 (s), 1615 (m), 1585 (w), 1515 (m), 1460 (m), 1405 (m), 1300 (m), 1250 (s), 1220 (s), 1170 (m), 1105 (w), 1080 (m), 1030 (m), 960 (m), 940 (w), 850 (m), 830 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) major diastereomer δ 0.04 (s, 9 H), 0.96–1.10 (m, 2 H), 1.18 (d, J = 6.7 Hz, 3 H), 1.46–1.78 (m, 4 H), 1.82–2.17 (m, 5 H), 2.32–2.54 (m, 1 H), 2.63 (br dd, J_1 = J_2 = 6.3 Hz, 2 H), 3.42 (s,

3 H), 3.52–3.71 (m, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 4.00–4.53 (m, 7 H), 5.20–5.43 (m, 3 H), 6.76 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.95–7.08 (m, 2 H), 7.24 (d, J = 8.6 Hz, 2 H), 7.26–7.38 (m, 5 H).

Alcohols 52 via Dineopentylzinc-Mediated Three-Component Coupling. A mixture of zinc bromide (451 mg, 2.00 mmol), neopentyl bromide (0.504 mL, 4.00 mmol), Li wire (55.5 mg, 8.00 mmol), and Et_2O (8.0 mL) was sonicated at 0 → 25 °C for 1 h. The resultant black suspension was used without purification; although dineopentylzinc could be purified by distillation (bp 50–55 °C, 3 mmHg), this proved to be unnecessary. A solution of vinyl iodide **3a** (94 mg, 0.3 mmol) in Et_2O (2.4 mL) was cooled to −78 °C, and *t*-BuLi (1.6 M in pentane, 0.375 mL, 0.60 mmol) was added. The mixture was stirred at −78 °C for 2 h, treated with dineopentylzinc (0.25 M in Et_2O, 1.2 mL, 0.30 mmol), and stirred for an additional 1.5 h. A solution of enone (−)-**4** (33.6 mg, 0.30 mmol) in Et_2O (2.0 mL) was then slowly added over 15 min. The resultant mixture was stirred at −78 °C for 1 h and treated with a solution of aldehyde (−)-**51** (190 mg, 0.30 mmol) in ether (3.5 mL). After 2.5 h at −78 °C, the reaction was quenched with saturated NH_4Cl solution. The mixture was then brought to ambient temperature, and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (1:1:4 Et_2O/CH_2Cl_2/hexanes eluant) afforded a mixture of diastereomeric aldols **52** (145 mg, 52% yield) as an oil: IR ($CHCl_3$) 3700–3300 (w), 3020 (w), 2970 (m), 2940 (m), 2860 (m), 1685 (m), 1615 (m), 1590 (w), 1520 (m), 1470 (m), 1415 (m), 1305 (m), 1255 (s), 1180 (m), 1080 (m), 1030 (m), 970 (m), 840 (m), 700 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.09 (s, 6 H), 0.89 (s, 9 H), 0.93–1.07 (br m, 2 H), 1.45–1.71 (m, 4 H), 1.75 (s, 3 H), 1.09–2.11 (comp m, 5 H), 2.53–2.62 (m, 2 H), 3.30–3.42 (m, 1 H), 3.41 (s, 3 H), 3.50–3.59 (m, 3 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.85–4.45 (comp m, 10 H), 5.11 (d, J = 9.6 Hz, 1 H), 5.20–5.44 (comp m, 2 H), 6.75 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.93–7.05 (m, 2 H), 7.21 (d, J = 8.6 Hz, 2 H), 7.23–7.48 (m, 5 H); mass spectrum (FAB, NBA matrix) m/z 952.5100 [$(M + Na)^+$, calcd for $C_{53}H_{79}NNaO_9Si_2$ 952.5190].

Vinylogous Ester (−)-47. A solution of **52** (4.01 g, 4.31 mmol) and pyridine (0.35 mL, 4.31 mmol) in DMSO (6.5 mL) and benzene (7.5 mL) was treated with trifluoroacetic acid (0.16 mL, 2.16 mmol) and DCC (2.67 g, 12.9 mmol). The mixture was stirred for 30 min at ambient temperature and then at 0 °C for 5 min. A large excess (ca. 52 mmol) of freshly prepared diazomethane (cf. preparation of (−)-**45**) was then added, and stirring was continued for 20 min. $MgSO_4$ was added, and argon was bubbled through the reaction mixture for ca. 15 min until the yellow color of CH_2N_2 dissipated. Filtration, concentration in vacuo, and flash chromatography (20% EtOAc/hexanes eluant) afforded (−)-**47** (1.95 g, 49% yield) as a colorless syrup: $[\alpha]^{25}_D$ −67.8° (c 5.10, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2970 (m), 2940 (m), 2870 (w), 1690 (m), 1620 (m), 1590 (w), 1520 (m), 1460 (m), 1420 (m), 1310 (m), 1260 (s), 1180 (m), 1090 (m), 1040 (m), 840 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 125 °C) δ 0.01 (s, 9 H), 0.80 (s, 6 H), 0.91 (s, 9 H), 0.90–0.96 (m, 2 H), 1.45–1.49 (m, 2 H), 1.60 (d, J = 1.2 Hz, 3 H), 1.70 (ddd, J = 12.0, 7.3, 4.6 Hz, 1 H), 1.91–1.97 (m, 2 H), 2.02 (ddd, J = 11.9, 8.2, 3.7 Hz, 1 H), 2.61–2.65 (m, 2 H), 2.79 (ABX, J_{AB} = 15.2 Hz, J_{AX} = 5.7 Hz, J_{BX} = 6.5 Hz, $\Delta\nu_{AB}$ = 69.1 Hz, 2 H), 3.26 (s, 3 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 3.76–3.84 (m, 2 H), 3.86 (s, 3 H), 4.10–4.40 (comp m, 8 H), 4.77–4.80 (ddd, J = 7.4, 3.6, 1.5 Hz, 1 H), 4.85 (dd, J = 9.6, 1.2 Hz, 1 H), 5.06 (dd, $J_1 = J_2$ = 7.7 Hz, 1 H), 5.24–5.28 (m, 1 H), 5.37–5.43 (m, 1 H), 6.73–6.76 (m, 2 H), 6.83–6.86 (m, 2 H), 6.98–7.00 (m, 2 H), 7.14–7.19 (m, 2 H), 7.20–7.29 (m, 5 H); mass spectrum FAB, NBA matrix) m/z 941.5300 (M^+, calcd for $C_{54}H_{79}NO_9Si_2$ 941.5290).

Amino Alcohol (−)-55. A solution of vinylogous ester (−)-**47** (260 mg, 0.276 mmol) in THF (1.5 mL) was cooled to 0 °C and treated dropwise with tetrabutylammonium fluoride (1 M in THF, 5.5 mL, 5.5 mmol). After 15 min, 75% aqueous acetic acid (13 mL) was added, and the mixture was stirred at 0–5 °C in a refrigerator overnight. After dilution with EtOAc, the mixture was washed with saturated $NaHCO_3$ solution, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with half-saturated brine and then with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (20% acetone/benzene eluant) gave (−)-**55** (142 mg, 75% yield) as a colorless syrup: $[\alpha]^{17}_D$ −88° (c 2.7, $CHCl_3$); IR ($CHCl_3$) 3660 (w), 3600–3100 (m), 3020 (s), 2980 (s), 2860 (m), 1680–1580 (s), 1520 (s), 1450 (s), 1400 (s), 1350 (s), 1310 (s), 1260–1210 (s), 1180 (s), 1085 (s), 1040 (s), 1010 (s), 980 (s), 960 (m), 830 (m), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43–1.58 (comp m, 2 H), 1.72–1.79 (m, 1 H), 1.73 (d, J = 1.3 Hz, 3 H), 1.97–2.19 (comp m, 4 H), 2.28–2.32 (m, 2 H), 2.94 (ABX, J_{AB} = 15.9 Hz, $J_{AX} = J_{BX}$ = 6.2 Hz, $\Delta\nu_{AB}$ = 95.7 Hz, 2 H), 3.31 (s, 3 H), 3.44 (d, J = 13.1 Hz, 1 H), 3.58–3.63 (comp m, 2 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 3.87–3.92 (m, 1 H), 3.94 (s, 3 H), 4.02–4.06 (m, 1 H), 4.32 (d, J = 11.8 Hz, 1 H), 4.41 (d, J = 11.8 Hz, 1 H), 4.57 (d, J = 10.9 Hz, 1 H), 4.73 (m, 1 H), 4.77 (d, J = 10.9 Hz, 1 H), 5.24–5.28 (m, 1 H), 5.39–5.45 (m, 1 H), 6.81–6.87 (comp m, 4 H), 7.15 (d, J = 8.6 Hz, 2 H), 7.21 (d, J = 8.6 Hz, 2 H), 7.22–7.25 (m, 1 H), 7.30–7.34 (comp m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 28.3, 33.3, 34.7, 37.8, 41.8, 47.8, 50.6, 54.8, 55.1, 55.2, 57.3, 61.7, 71.0, 74.8, 80.5, 113.5, 113.6, 120.4, 126.8, 126.8, 127.3, 128.2, 129.1, 129.2, 130.5, 130.8, 132.6, 133.1, 135.6, 143.9, 158.4, 159.0, 165.1, 197.4; mass spectrum (FAB, NBA matrix) m/z 684.3860 [$(M + H)^+$, calcd for $C_{42}H_{54}NO_7$ 684.3900].

Phosphonate (−)-57. A solution of amino alcohol (−)-**55** (348 mg, 0.509 mmol) and diethyl 3-phosphonocrotonic acid (**56**) (111 mg, 0.500 mmol, 0.98 equiv) in DMF (4.5 mL) was cooled to 0 °C and treated with diethyl cyanophosphonate (76 μL, 0.500 mmol) and Et_3N (70 μL, 0.500 mmol). After stirring at 0 °C for 30 min, the reaction mixture was diluted with EtOAc and washed with 0.5 N hydrochloric acid. The aqueous layer was extracted with EtOAc, and the combined organic solutions were washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (30% acetone/benzene eluant) gave (−)-**57** (308 mg, 68% yield) as a colorless syrup: $[\alpha]^{18}_D$ −143.7° (c 0.325, $CHCl_3$); IR ($CHCl_3$) 3660 (w), 3580–3200 (w), 3010 (m), 2940 (m), 2840 (w), 1735 (w), 1660 (m), 1620 (s), 1520 (m), 1470 (m), 1400 (m), 1350 (m), 1300 (m), 1250 (s), 1180 (m), 1030 (s), 975 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 127 °C) δ 1.21 (dd, $J_1 = J_2$ = 7.0 Hz, 6 H), 1.45–1.49 (m, 2 H), 1.61 (d, J = 1.1 Hz, 3 H), 1.71 (ddd, J = 13.9, 7.4, 4.7 Hz, 1 H), 1.90–1.96 (m, 2 H), 2.04 (ddd, J = 13.8, 8.2, 3.6 Hz, 1 H), 2.62–2.88 (comp m, 7 H), 3.27 (s, 3 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 3.79–3.95 (m, 3 H), 3.87 (s, 3 H), 3.99–4.03 (comp m, 5 H), 4.26–4.34 (comp m, 3 H), 4.46 (d, J = 16.4 Hz, 1 H), 4.79 (ddd, J = 7.5, 3.6, 1.6 Hz, 1 H), 4.83 (d, J = 9.7 Hz, 1 H), 5.26–5.29 (m, 1 H), 5.39–5.44 (comp m, 2 H), 6.53–6.61 (comp m, 2 H), 6.74 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H), 7.21–7.31 (comp m, 5 H); mass spectrum (FAB, NBA matrix) m/z 888.4490 [M^+, calcd for $C_{50}H_{67}NO_{11}P$ 888.4450].

Phosphono Aldehyde (−)-58. A solution of dimethyl sulfoxide (67 μL, 0.945 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C, and oxalyl chloride (41 μL, 0.473 mmol) was added. After 15 min, a solution of phosphono alcohol (−)-**57** (280 mg, 0.315 mmol) in CH_2Cl_2 (4.0 mL) was introduced dropwise. Stirring was continued at −78 °C for 20 min, and then triethylamine (220 μL, 1.58 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 5 min and allowed to warm to ambient temperature. Following dilution with EtOAc, the mixture was washed with water and the aqueous phase extracted twice with EtOAc. The combined organic layers were washed twice with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (30% acetone/benzene eluant) afforded (−)-**58** (240 mg, 86% yield) as a colorless syrup: $[\alpha]^{20}_D$ −94.8° (c 0.215, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2940 (m), 1680 (m), 1660 (m), 1620 (s), 1520 (s), 1470 (m), 1450 (m), 1420 (m), 1395 (m), 1250 (s), 1220 (m), 1180 (m), 1040 (m), 970 (m) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 127 °C) δ 1.22 (apparent t, J = 6.4 Hz, 6 H), 1.42–1.53 (comp m, 2 H), 1.59 (s, 3 H), 1.86 (ddd, J = 12.3, 7.5, 4.8 Hz, 1 H), 1.90–1.99 (comp m, 2 H), 2.15 (ddd, J = 12.7, 7.9, 3.8 Hz, 1 H), 2.58–2.82 (comp m, 5 H), 2.90 (dd, J = 15.1, 6.6 Hz, 1 H), 3.30 (s, 3 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 3.82 (m, 1 H), 3.93 (s, 3 H), 3.96–4.02 (comp m, 3 H), 4.25–4.39 (comp m, 5 H), 4.46 (d, J = 16.4 Hz, 1 H), 4.52–4.58 (m, 1 H), 4.90 (dd, J = 7.4, 3.4 Hz, 1 H), 5.23–5.32 (m, 1 H), 5.37–5.47 (comp m, 2 H), 6.07 (d, J = 10.4 Hz, 1 H), 6.48–6.62 (comp m, 2 H), 6.74 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.5 Hz, 2 H), 6.96 (d, J = 8.5 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 2 H), 7.21–7.31 (comp m, 5 H), 10.21 (s, 1 H); mass spectrum (FAB, NBA matrix) m/z 886.4260 [M^+, calcd for $C_{50}H_{65}NO_{11}P$ 886.4290].

Macrolactam (−)-59. A solution of phosphono aldehyde (−)-**58** (239 mg, 0.270 mmol) in THF (40 mL) was cooled to −78 °C, and a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.27 mL, 0.27 mmol) was added dropwise. After 10 min the mixture was warmed to 0 °C and stirred for 2.5 h. The reaction mixture was then quenched with saturated NH_4Cl solution at 0 °C and extracted three times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (30% EtOAc/hexanes eluant) gave (−)-**59** (135 mg, 69% yield) as a colorless syrup: $[\alpha]^{20}_D$ −10° (c 0.89, $CHCl_3$); IR ($CHCl_3$) 3015 (m), 2940 (m), 2860 (w), 1680 (w), 1640 (s), 1585 (w), 1530 (s), 1460 (w), 1430 (w), 1330 (w), 1305 (w), 1250 (s), 1175 (m), 1080 (m), 1035 (w), 995 (w) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 127 °C) δ 1.40–1.45 (m, 2 H), 1.77 (br s, 3 H), 1.82–1.95 (m, 2 H), 1.99–2.08 (m, 2 H), 1.45 (ddd, J = 13.4, 8.2, 3.8 Hz, 1 H), 2.52–2.60 (m, 1 H), 2.62–2.73 (m, 2 H), 3.31 (s, 3 H), 3.68 (s, 3 H), 3.75 (s, 3 H), 3.81–3.85 (m, 1 H), 3.86 (s, 3 H), 4.03 (m, 1 H), 4.23 (d, J = 15.6 Hz, 1 H), 4.23 (d, J = 12.3 Hz, 1 H), 4.33 (d, J = 12.3 Hz, 1 H), 4.34 (d, J = 15.6 Hz, 1 H), 4.45 (m, 1 H), 4.82 (m, 1 H),

5.27–5.48 (m, 4 H), 6.29 (dd, J = 15.9, 10.1 Hz, 1 H), 6.67 (d, J = 8.5 Hz, 2 H), 6.83–6.88 (m, 3 H), 7.05–7.38 (m, 10 H); mass spectrum (CI, NH_3) m/z 732.3854 [$(M + H)^+$, calcd for $C_{46}H_{54}NO_7$ 732.3902].

***N*-(*p*-Methoxybenzyl)hitachimycin (+)-60.** A mixture of bis(*p*-methoxybenzyl) vinylogous ester (−)-**59** (135 mg, 0.184 mmol), CH_2Cl_2 (6.0 mL), and water (0.3 mL) was treated with DDQ (126 mg, 0.553 mmol) in one portion at ambient temperature. After 30 min, the reaction mixture was diluted with EtOAc and washed with 10% Na_2SO_3 solution. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine. An equal volume of 1 N HCl was then added, and the two-phase mixture was stirred gently at ambient temperature overnight. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic solutions were washed once with half-saturated brine and twice with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (2 → 5% MeOH/$CHCl_3$, gradient elution) afforded (+)-**60** (110 mg, 100% yield) as a colorless syrup or glassy solid: $[\alpha]^{20}_D$ +194° (c 0.4, $CHCl_3$); IR ($CHCl_3$) 3300–3600 (w), 3010 (m), 2940 (m), 2860 (w), 2840 (w), 1680 (s), 1640 (s), 1585 (m), 1540 (m), 1465 (m), 1415 (m), 1345 (m), 1320 (w), 1280 (w), 1255 (s), 1180 (m), 1160 (w), 1140 (m), 1040 (w), 1005 (m), 975 (w), 965 (w), 915 (w), 880 (w), 825 (w), 705 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15–1.40 (m, 2 H), 1.83 (s, 3 H), 1.94 (m, 1 H), 2.06–2.15 (m, 3 H), 2.32 (m, 1 H), 2.44 (d, J = 16.8 Hz, 1 H), 2.57 (br d, J = 13.5 Hz, 1 H), 2.68 (td, J = 13.0, 11.0 Hz, 1 H), 3.54 (s, 3 H), 3.72 (s, 3 H), 3.94 (br t, J = 9.4 Hz, 1 H), 4.01 (dt, J = 11.1, 5.6 Hz, 1 H), 4.30 (br s, 2 H), 4.47 (t, J = 7.8 Hz, 1 H), 5.21 (d, J = 11.0 Hz, 1 H), 5.48 (ddd, J = 4.5, 8.3, 15.0 Hz, 1 H), 5.58 (ddd, J = 3.8, 11.0, 15.0 Hz, 1 H), 6.09 (d, J = 14.8 Hz, 1 H), 6.28 (dd, J = 15.1, 11.2 Hz, 1 H), 6.39 (dd, J = 13.0, 3.0 Hz, 1 H), 6.66 (d, J = 8.7 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 7.03 (d, J = 15.1 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.26 (d, J = 7.5 Hz, 2 H), 7.36 (dd, J = 14.8, 11.2 Hz, 1 H), 7.41 (d, J = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 29.1, 34.6, 34.7, 35.3, 38.6, 45.3, 45.9, 55.1, 55.7, 58.0, 67.9, 80.7, 112.2, 113.7, 122.7, 127.2, 127.5, 127.7, 128.0, 128.4, 128.6, 130.0, 131.0, 132.8, 134.7, 136.3, 139.0, 143.5, 158.4, 168.9, 186.1, 196.4; mass spectrum (CI, NH_3) m/z 598.3114 [$(M + H)^+$, calcd for $C_{37}H_{44}NO_6$ 598.3170].

(+)-Hitachimycin (1). A solution of the *p*-methoxybenzyl derivative (+)-**60** (80 mg, 0.134 mmol) in trifluoroacetic acid (1.0 mL) was stirred at ambient temperature for 2.5 h. The reaction mixture was concentrated, and the residual trifluoroacetic acid was removed by coevaporation with several portions of $CHCl_3$. Flash chromatography (1 → 10% MeOH/$CHCl_3$, gradient elution) gave a solid which was dissolved in $CHCl_3$. The solution was washed with 1 N HCl and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crystalline residue was triturated with $CHCl_3$ to afford (+)-**1** (41 mg, 64% yield) as a colorless amorphous solid: mp 236–240 °C dec [natural (+)-**1**[41] mp 237–241 °C dec, mmp 236–240 °C dec]; $[\alpha]^{20}_D$ +101° (c 0.17, $CHCl_3$), +247° (c 0.17, DMSO) [natural **1**[41] $[\alpha]^{20}_D$ +105° (c 0.17, $CHCl_3$), +254° (c 0.17, DMSO)]; IR (KBr) 3460 (m), 3270 (m), 3030 (w), 2930 (m), 2870 (w), 2820 (w), 1640 (s), 1620 (s), 1540 (s), 1500 (w), 1450 (m), 1440 (m), 1390 (m), 1345 (s), 1330 (m), 1255 (s), 1215 (m), 1190 (m), 1155 (m), 1120 (s), 1080 (m), 1045 (s), 1000 (m), 970 (m), 925 (w), 885 (m), 830 (w), 750 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (m, 1 H), 1.21–1.30 (m, 1 H), 1.85–1.94 (m, 1 H), 1.88 (s, 3 H), 2.03–2.20 (m, 4 H), 2.31 (m, 1 H), 2.39 (d, J = 17.4 Hz, 1 H), 2.72 (br d, J = 13.3 Hz, 1 H), 3.53 (s, 3 H), 3.92 (br t, J = 10.0 Hz, 1 H), 3.99 (ddd, J = 10.8, 6.4, 3.7 Hz, 1 H), 4.46 (t, J = 7.6 Hz, 1 H), 5.21 (d, J = 10.8 Hz, 1 H), 5.29–5.37 (m, 2 H), 5.41 (ddd, J = 14.8, 9.0, 5.0 Hz, 1 H), 5.50 (ddd, J = 14.8, 10.5, 4.3 Hz, 1 H), 5.90 (d, J = 14.9 Hz, 1 H), 6.39 (dd, J = 15.2, 11.1 Hz, 1 H), 7.04 (d, J = 15.2 Hz, 1 H), 7.26–7.38 (m, 6 H); ^{13}C NMR (125 MHz, 20% $CD_3OD/CDCl_3$) δ 19.5, 28.8, 34.4, 34.9, 38.5, 41.1, 46.0, 51.8, 57.5, 67.4, 80.6, 112.0, 123.9, 126.0, 126.3, 126.8, 127.3, 128.2, 130.9, 133.9, 134.3, 136.4, 141.4, 141.6, 167.1, 184.7, 196.1. The ^1H and ^{13}C NMR spectra of synthetic **1** were identical in all respects with those of the natural product. Mass spectrum (CI, NH_3) m/z 478.2610 [$(M + H)^+$, calcd for $C_{29}H_{36}NO_5$ 478.2602] (natural **1** m/z 478.2616).

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Supplementary Material Available: Tables of X-ray crystallographic data for sulfoximine adduct **16** and epoxy olefin **37b** (10 pages). Ordering information is given on any current masthead page.

(41) These data of natural (+)-hitachimycin (**1**) were measured in the Smith laboratory on material kindly supplied by Professor Ōmura (Kitasato Institute, Tokyo, Japan).