perature. Catalase (0.2 mL of a 30% solution in glycerol, ca. 274 100 units/mL) was added, and after ca. 5 min the mixture was titrated directly with 0.02 N aqueous sodium thiosulfate; the titer showed a lower consumption of reductant than the parallel experiment carried out in the absence of catalase (runs 6a and 6b, Table I).

In view of the fact that the reaction of dioxirane **1** with an excess of iodide in acidic medium obeys the iodometric stoichiometry (runs 3 and 4, Table I), we can argue that the iodine titer derives from both dioxirane **1** and hydrogen peroxide. Furthermore, it was found that the formation of iodine depends on the amount and strength of the acid employed. In the presence of an excess of iodide and at a lower concentration of acid, less iodine is liberated (runs 4 and 7, Table I) than when higher concentrations and stronger acid are used (runs 7 and 8, Table I). These latter results reflect the effectiveness of superoxide trapping to afford hydrogen peroxide.[8]

Reaction of Methyl(trifluoromethyl)dioxirane (1) with Equimolar Iodide in the Presence of Benzoyl Chloride. To a mixture of 1 mL of a 0.27 M solution (0.27 mmol) of methyl(trifluoromethyl)dioxirane (**1**) in CH_2Cl_2 and 0.04 mL (0.35 mmol) of freshly distilled benzoyl chloride at 0 °C was added, with stirring, 0.8 mL of a 0.34 M solution (0.27 mmol) of tetrabutylammonium iodide in CH_2Cl_2. After 10 min at 0 °C the solvent was removed under vacuum and the residue dissolved in $DCCl_3$ and analyzed by NMR. The ^{13}C NMR spectrum (50 MHz) showed ca. 50% conversion of benzoyl chloride to benzoic anhydride. A control experiment revealed that under identical conditions dioxirane **1** is unreactive toward an excess of benzoyl chloride.

Reaction of Methyl(trifluoromethyl)dioxirane (1) with Lithium Iodide in the Presence of Chlorotrimethylsilane. To 0.1 mL of a 0.88 M solution (0.08 mmol) of dioxirane **1** in CH_2Cl_2 at 0 °C was added 0.01 mL (0.08 mmol) of freshly distilled chlorotrimethylsilane, quickly followed by the addition of 0.40 mL of a 0.2 M solution (0.08 mmol) of lithium iodide in acetone-d_6, with stirring. After 20 min, a ^1H NMR (80 MHz) spectrum was run; this showed total conversion of chlorotrimethylsilane into hexamethyldisiloxane. A control experiment revealed that dioxirane **1** oxidized chlorotrimethylsilane, but hexamethyldisiloxane was not found in the product mixture.

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Furans in Synthesis. 11.[1] Total Syntheses of (±)- and (-)-Fastigilin C

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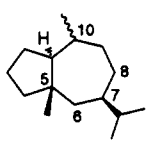
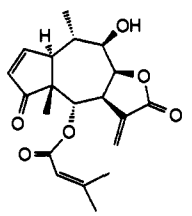
Contribution from The Upjohn Company, Medicinal Chemistry Research, 7246-209-6, Kalamazoo, Michigan 49001, Department of Chemistry, Ohio University, Athens, Ohio 45701, and The Upjohn Company, Physical and Analytical Chemistry, 7255-209-1, Kalamazoo, Michigan 49001. *Received May 18, 1992*

Abstract: Fastigilin C (**2**), a complex helenanolide, has been reported to exhibit cytotoxic and antineoplastic activity, thus making it an attractive target for total synthesis. We wish to report the first total syntheses of (±)- and (-)-fastigilin C ((±)- and (-)-**2**). As a result of our interest in the utilization of furan-terminated cyclizations as the key step in the construction of diverse ring systems, we envisioned (eq 1) furan **3** as the precursor to bicyclo[5.3.0]decane furan **4**, which should afford **2**. In the forward direction, a Mukaiyama Michael-aldol protocol affords **3** with complete control of relative stereochemistry. A mercury(II)-mediated-furan-terminated cyclization gives **4**, which is ultimately converted (17 steps, 24.6% overall yield) to (±)-fastigilin C ((±)-**2**). A porcine pancreatic lipase mediated resolution of 4-hydroxy-2-methyl-2-cyclopentenone leads to (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone, which is converted (17 steps) to (-)-fastigilin C ((-)-**2**) in 14% overall yield.

The pseudoguaianolides, a group of butyrolactone-containing bicyclo[5.3.0]decanoid sesquiterpenes, are divided into the ambrosanes (**1a**) (10β-CH_3, lactone fused via C-6-C-7 or C-7-C-8)



1a 10-β-CH_3 Ambrosanes
1b 10-α-CH_3 Helenanes



2 Fastigilin-C

and the helenanes (**1b**) (10α-CH_3, lactone fused via C-7-C-8). The helenanes are more highly oxygenated and stereochemically complex and have been associated with diverse biological activities which include cytotoxic,[2] antileukemic,[2] and antiinflammatory properties.[3] Fastigilin C (**2**),[4a,b] one of the most intriguing of the helenanolides, was isolated from *Gaillardia fastagiata* by Herz[4a] and from *Baileya multiradiata* by Pettit.[4b] Fastigilin C (**2**), which exhibits substitution at each position about the seven-membered B-ring, has been reported to exhibit cytotoxic and antineoplastic activity,[4] thus making it an attractive target for

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‡ Ohio University.
§ The Upjohn Company, Physical and Analytical Chemistry.

(1) For part 10 in this series see: Tanis, S. P.; McMills, M. C.; Scahill, T. A.; Kloosterman, D. A. *Tetrahedron Lett.* **1990**, *31*, 1977.

(2) (a) Williams, W. L., Jr.; Hall, I. H.; Grippo, A. A.; Oswald, C. B.; Lee, K. H.; Holbrook, D. J.; Chaney, S. G. *J. Pharm. Sci.* **1988**, *77*, 178. (b) Hall, I. H.; Grippo, A. A.; Lee, K. H.; Chaney, S. G.; Holbrook, D. J. *Pharm. Res.* **1987**, *4*, 509. (c) Hall, I. H.; Williams, W. L., Jr.; Chaney, S. G.; Gilbert, C. J.; Holbrook, D. J.; Muraoka, O.; Kiyokawa, H.; Lee, K. H. *J. Pharm. Sci.* **1985**, *74*, 250. (d) Chaney, S. G.; Williams, W. L., Jr.; Willingham, W., III; Considine, R. T.; Hall, I. H.; Lee, K. H. *Curr. Top. Cell. Regul.* **1984**, *24*, 251 and references cited therein.

(3) Hall, I. H.; Starnes, C. O., Jr.; Lee, K. H.; Waddell, T. G. *J. Pharm. Sci.* **1980**, *69*, 537. Hall, I. H. *Planta Med.* **1987**, *53*, 153.

(4) (a) Herz, W.; Rajappa, S.; Roy, S. K.; Schmid, J. J.; Mirrington, R. N. *Tetrahedron* **1966**, *22*, 1907. (b) Pettit, G. R.; Herald, C. H.; Gust, D.; Herald, D. L.; Vanell, L. D. *J. Org. Chem.* **1978**, *43*, 1092.

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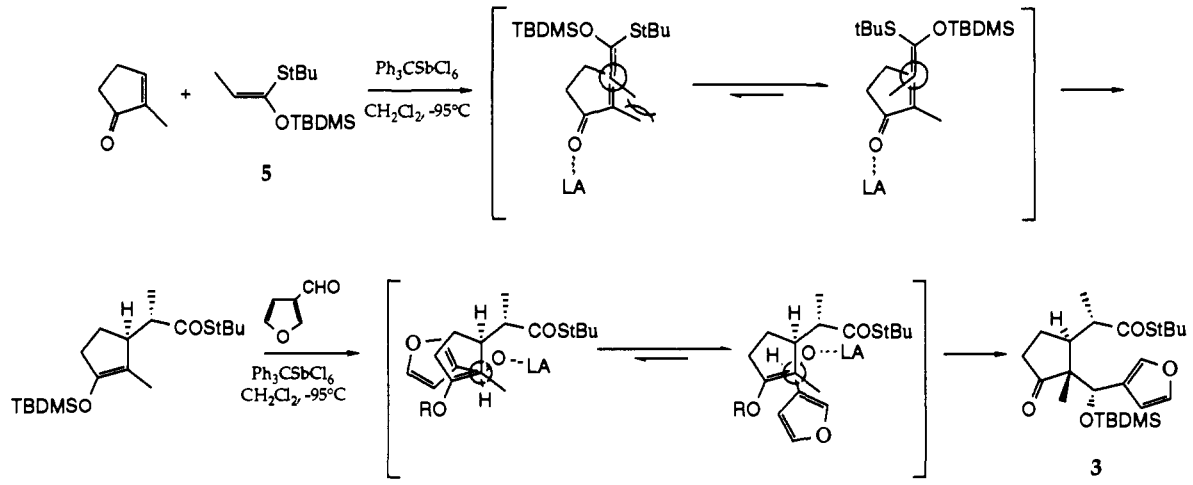
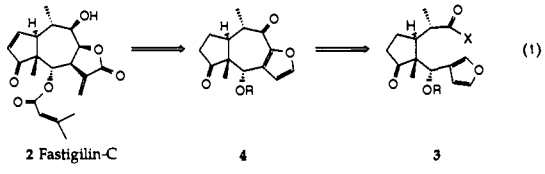


Figure 1. Mechanistic rationalization of the Michael–aldol addition leading to **3**.

total synthesis.[5,6,7] Lansbury[5] has recently reported an approach to **2** which provides 2,3-dihydrofastigilin C. Unfortunately the Lansbury group was unable to complete the synthesis of **2**, being foiled by the A-ring enone double bond during the final stages of the synthesis endeavor. We have recently completed efficient total syntheses of (±)- and (−)-fastigilin C ((±)- and (−)-**2**), and we report our efforts herein.

Results and Discussion

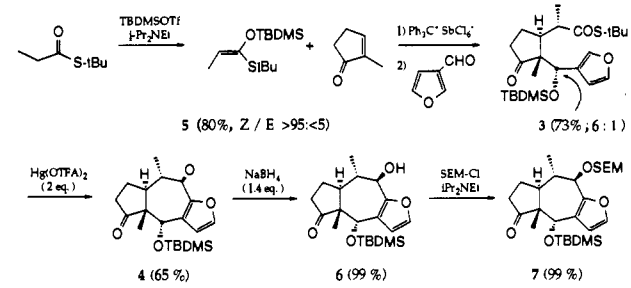
(a) First-Generation Approach to (±)-2. For the past several years we have been investigating furan-terminated cationic cyclizations as the key step in the construction of linearly fused-, bridged-, and spirocyclic-alkaloid and -terpenoid ring systems.[1,8] On the basis of our earlier work,[1,8] we envisioned constructing fastigilin C (**2**) as outlined in eq 1. We considered constructing



(1)

the furan-containing bicyclo[5.3.0]decane nucleus **4** from a cyclopentanone (**3**) which possessed a cyclization initiator (stabilized carbocation) and terminator (furan). Furan represents the stable equivalent of a variety of useful functionalities,[1,5,8,9] including a butyrolactone,[8,9] and its incorporation will allow excellent control of regiochemistry in the introduction of this subunit. An additional benefit of furan incorporation as shown in **4** is the possibility of routine control of stereochemistry about the periphery of the bicyclo[5.3.0]decane by inducing the normally flexible seven-membered B-ring to adopt a well-defined chair-like conformation (vide infra).[10] The 2,3-double bond would be introduced late in the eq 1 sequence and then masked while the butyrolactone was being produced. Thus cyclopentanone **3** became our initial target. Our first-generation approach, previously published,[1] is described in Scheme I.

Scheme I



The synthesis of cyclopentanones such as **3** requires control of two exocyclic stereocenters and concomitant trans addition of the elements of propionate and 3-furaldehyde to the 3- and 2-positions, respectively, of 2-methyl-2-cyclopentenone. Mukaiyama has recently described a trityl salt catalyzed, silicon transfer, tandem conjugate addition–aldol condensation sequence[11] to form a trans-substituted cyclopentanone with predictable exocyclic stereochemistry. Such a protocol appeared to be ideally suited for the synthesis of the target cyclopentanone **3**. Toward that end, the *tert*-butyldimethylsilyl enol ether **5**,[12] prepared from *tert*-butyl thiopropionate,[13] was combined with 2-methyl-2-cyclopentenone (CH_2Cl_2, −95 °C bath) and the resulting mixture was treated with 5 mol % of Ph_3CSbCl_6.[11] After the mixture was stirred for 20 min, 3-furaldehyde (in CH_2Cl_2) was added and the mixture was allowed to warm to room temperature over 12 h to furnish a mixture of **3** and *pro*-C-6-iso-**3** (73%, 6:1) that was difficult to separate. We were unable to detect the presence of any materials with alternative relative stereochemistries at *pro*-C-1, -5, and -10; the ratio of 6:1 at *pro*-C-6 is in agreement with the reports of Mukaiyama[11] and is temperature dependent. The ratio of **3** to 6β-**3**, which has been optimized at ca. 6:1 (−95 °C), falls to ca. 2.5:1 at −80 °C. Mukaiyama[11] has rationalized the stereochemical outcome of such a Michael–aldol addition as the result of consecutive conjugate addition and aldol reactions, which proceed

(5) Lansbury, P. T.; Nickson, T. E.; Vacca, J. P.; Sindelar, R. D.; Messinger, J. M., II. *Tetrahedron* **1987**, *43*, 5583.

(6) For an alternate approach to the synthesis of fastigilin C (**2**) see: Schultz, A. G.; Motyka, L. A.; Plummer, M. *J. Am. Chem. Soc.* **1986**, *108*, 1056.

(7) For reviews of recent synthetic activity directed toward guaianolides and pseudoguaianolides see: Vandewalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1982; Vol. 5. For some more recent efforts directed toward the synthesis of guaianolides and pseudoguaianolides see: (a) Cummins, W. J.; Drew, M. J. B.; Mann, J.; Markson, A. J. *Tetrahedron* **1988**, *44*, 5151. (b) Davis, H. M. L.; Oldenberg, C. E. M.; McAfee, M. J.; Nordahl, J. G.; Heiretta, J. P.; Romines, K. R. *Tetrahedron Lett.* **1988**, *29*, 975.

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(9) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451. Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, *22*, 5191 and references cited therein.

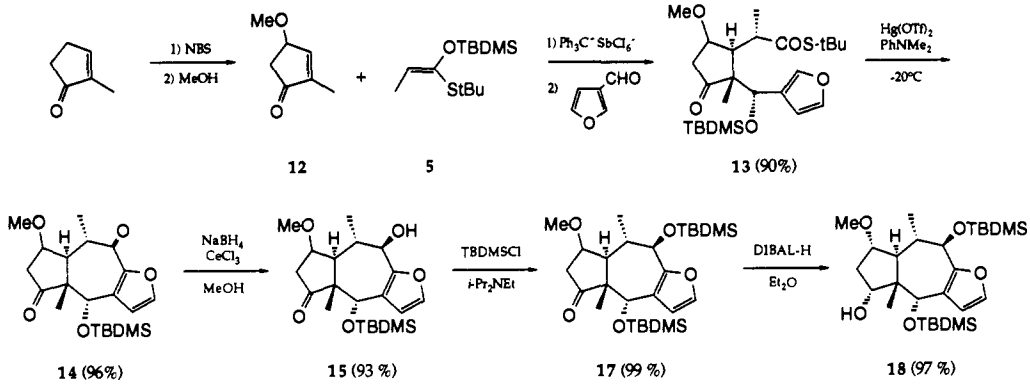
(10) For example: Glazer, E. S.; Knorr, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 6026 and references cited therein.

(11) (a) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1987**, 743. (b) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1817. (c) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1805. (d) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017.

(12) Gennari, C.; Beretta, M. G.; Berbardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

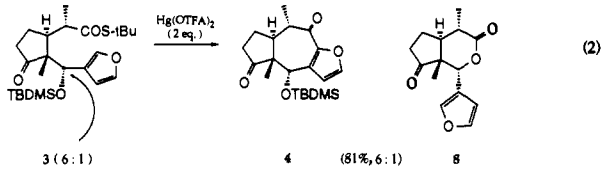
(13) Purchased from Columbia Organic Chemical Company, 1424 Mt. Zion Rd., Cassatt, SC 29032.

Scheme II



in a trans fashion across the cyclopentane 2- and 3-positions, through open transition states. Figure 1 provides a cartoon representation which rationalizes the stereochemical outcome of the conjugate addition–aldol reactions leading to **3** and 6β-**3**.

With our cyclization substrate in hand, we turned our attention to the ring-closing reaction. After several attempts (CuOTf,[14] $(Me)_3OBF_4$), we found that we could smoothly effect the desired cyclization by exposing **3** to $Hg(O(TFA))_2$[15] (2 equiv, anhydrous CH_3CN, room temperature) to furnish tricyclic furan **4** (65%) as a white crystalline solid. The facility of this closure when coupled with the difficult separation of **3** from *pro*-C-6-iso-**3** caused us to consider conducting the cyclization reaction on the **3**, *pro*-C-6-iso-**3** mixture. In the event (eq 2), the 6:1 mixture of **3** and



(2)

pro-C-6-iso-**3** was exposed to $Hg(O(TFA))_2$ to provide an 81% yield of a 6:1 mixture of **4** and lactone **8**. These two materials are readily separated, thus negating the need for the tedious purification of **3**. In a separate experiment, *pro*-C-6-iso-**3** was treated with $Hg(O(TFA))_2$ to give, exclusively, lactone **8**.

The fifth of the seven B-ring stereocenters of fastigilin C (**2**) was then smoothly and selectively introduced (Scheme I) by reduction of the 9-one with $NaBH_4$ (EtOH) to provide the 9β-alcohol **6** (99%) as a single stereoisomer.[1] Alcohol **6** was protected (SEM-Cl)[16] as the related SEM ether, giving **7** (99%). At this juncture we were forced to consider *The End Game* (Figure 2); that is, how would we convert **7** to fastigilin C (**2**)? The Lansbury group had already demonstrated that the introduction of the A-ring double bond was problematic when the B–C-portion of the molecule was relatively fragile. We did not anticipate any such problems with the stability of **7**. However we were faced with a double-bond introduction which would be followed by a simultaneous double-bond–ketone protection. This was necessitated by the chemistry which would be employed in the elaboration of the furyl unit to a butyrolactone (vide infra). The final steps of the sequence would then follow the strategy which had been used by Lansbury. The advantages presented by the Scheme I route were (1) robust intermediates and (2) a well-defined conformation which would aid in the development of the final two B-ring stereocenters. Among the problems to be overcome in order to

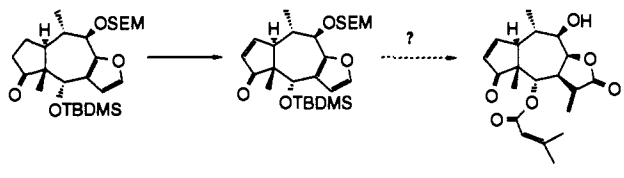
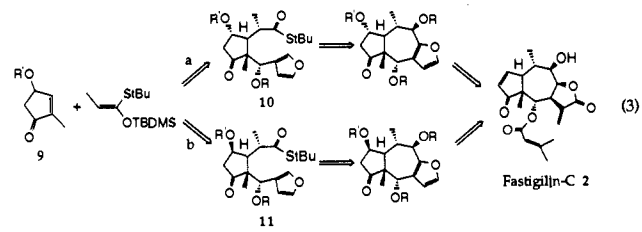


Figure 2. The End Game. How should **7** be converted to **2**?

efficiently carry bicyclo[5.3.0]decane **7** to fastigilin C (**2**) were (1) the development of a protocol to insure the survival of the developing A-ring functionality (2,3-double bond or surrogate) and (2) difficulties in transforming the route to (±)-**2** to access the natural optical antipode (−)-**2**.

(b) Synthesis of (±)-Fastigilin C ((±)-2). Having successfully constructed bicyclo[5.3.0]decane **7**, possessing five of the requisite seven B-ring stereocenters of (±)-**2**, we turned our attention to A-ring modifications which might facilitate the introduction of the 2,3-double bond. As an alternative to carrying the Scheme I route to fastigilin C (**2**), we considered modifying the sequence to introduce a 2,3-double-bond surrogate from the outset of the endeavor. This end might be achieved by substituting a 4-alkoxy-2-methyl-2-cyclopentenone into the Michael–aldol chemistry of Scheme I. The success of this racemic route would pave the way for an asymmetric synthesis in which the asymmetry might be introduced via a Michael–aldol sequence performed upon a chiral 4-alkoxy-2-methyl-2-cyclopentenone. After some deliberation, we decided to immediately examine this latter route as a means of completing the synthesis of (±)-**2**; our approach is outlined in eq 3.



(3)

The Figure 1 cartoon adequately rationalizes the stereochemical outcome of the Michael addition–aldol condensation in the absence of a stereogenic center on the cyclopentenone partner. However it is less useful in predicting which face of the 4-alkoxy-2-methyl-2-cyclopentenone will suffer initial attack in the conjugate addition process. The determination of the relative stereochemistry of the *pro*-C-2 center vs the *pro*-B-ring stereocenters would be required as a prerequisite for any synthesis of (−)-**2**. Our concerns, that is, path a (eq 3, leading to **10**) vs path b (eq 3, leading to **11**), result from recent reports by Danishefsky[17] of similar Michael–aldol additions in somewhat related systems. Danishefsky[17] has examined a wide variety of substrates and attributes the generally obtained path b syn-selectivity (entering nucleophile with respect to resident C–O-bond) to the two-electron stabilizing interactions suggested by Cieplak.[18] In the presence of over-

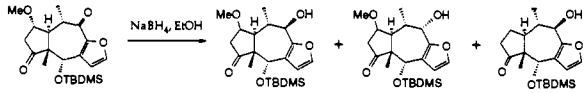
(14) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860.
(15) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W.-K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756. Masamune, S.; Kanata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515.
(16) Lipschutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(17) Chow, K.; Danishefsky, S. *J. Org. Chem.* **1989**, *54*, 6016. Jeroncic, L.; Cabal, M.; Danishefsky, S.; Schulte, G. M. *J. Org. Chem.* **1991**, *56*, 387.
(18) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

whelming steric constraints, the Danishefsky group[17] observes the path a approach.

The initiation of our synthesis of (±)-fastigilin C ((±)-**2**) is presented in Scheme II. A Mukaiyama Michael–aldol condensation[11] between 4-methoxy-2-methyl-2-cyclopentenone (**12**),[19] the TBDMS enol ether of *tert*-butyl thiopropionate (**5**), and 3-furaldehyde was mediated by trityl hexachloroantimonate and was performed in CH_2Cl_2 at −22 °C for the Michael phase (monitored by TLC) followed by cooling to −78 °C for the silicon transfer aldol condensation (addition of 3-furaldehyde). This protocol afforded (±)-**13** in 90% yield, uncontaminated by stereoisomers at any of the newly formed stereogenic centers.

We had anticipated obtaining the indicated relative stereochemistry at *pro*-C-1, -5, -6, and -10, respectively (vide supra). At this point, we were unable to discern the relative stereochemistry of the resident five-membered-ring methoxy-bearing center. We elected to proceed with the sequence and attempt to establish the *pro*-C-2-stereochemistry via either NMR or single-crystal X-ray analysis, performed upon a more rigid, and hopefully crystalline, bicyclo[5.3.0]decane. Furan-terminated cationic cyclization was initially examined with $Hg(O(TFA))_2$ as the thiophile to give a disappointing (ca. 12%) yield of the target bicyclo[5.3.0]decane **14**. The bulk of the material recovered was determined to be the carboxylic acid corresponding to **13**. We considered two possibilities for the failure of a previously useful technique for the formation of the seven-membered ring. The first attributed the poor closure to the nucleophilicity of the counteranion ($CF_3CO_2^-$) capturing the nascent acylium ion at a rate competitive with a slower cyclization. Alternatively, we considered this outcome to be the result of preferred, and unproductive, conformations of **13** relative to our first-generation substrate. The former of these two possibilities was much more readily examined via substitution of triflate for trifluoroacetate. In the event, **13** was exposed to a mercuric triflate–*N*,*N*-dimethylaniline complex, prepared as described by Nishizawa,[20] which provided the target bicyclo[5.3.0]decane (±)-**14** in an excellent 96% yield as a crystalline solid.

With ketone **14** in hand, we prepared to establish the remaining three stereocenters about the periphery of the seven-membered B-ring. Previously (Scheme I)[1] we had found that the 9-one could be selectively (regio- and stereo-) reduced with $NaBH_4$ in EtOH to furnish the desired C-9β-OH. Application of those conditions to **14** afforded a mixture of three alcohols (eq 4), a 2:1 mixture



(4)

of 9β:9α-alcohols **15** and **16** retaining the 2-methoxy group (46%) and a 12% yield of the 9β-alcohol *minus* the methoxy moiety **6** (see Scheme I). The isolation of **6** from the reaction of **14** with $NaBH_4$ secures the relative orientations of the C-1, C-5, C-6, and C-10 stereocenters of **14**. An extremely selective reduction of the 9-one of **14** in the presence of the 4-one, without β-elimination of the 2-OMe, was realized using a modification of the conditions of Luche[21] as is presented in Scheme II. In the event, $NaBH_4$ was added to MeOH and the resulting solution ($NaB(OMe)_mH_{4-m}$) was added to a solution of **14** and $CeCl_3 \cdot 7H_2O$ (MeOH, −78 °C), yielding only **15** (93%), thus establishing the fifth stereocenter about the periphery of the seven-membered ring with excellent (>95:<5) stereocontrol. The C-9-OH was then protected as the corresponding TBDMS ether (TBDMS-Cl, iPr_2NEt), giving **17** (99%).

At this juncture, we wished to block the 4-one as the related dioxolane; therefore **17** was treated with ethylene glycol–*p*-TsOH

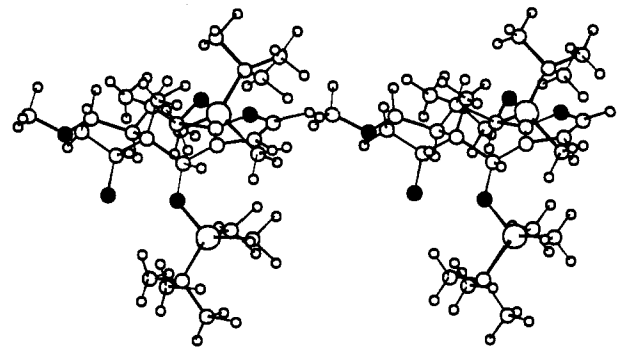


Figure 3. Relative stereochemistry of **18**.

(CH_3CN) and $(TMS)OCH_2CH_2O(TMS)$–$(TMS)OTf$[22] to no avail. A number of alternatives were examined for their ability to effect the desired protection with similar results. However we were able to smoothly reduce the 4-one to the corresponding 4α-alcohol **18** (DIBAL, 97%) as shown in Scheme II. The nicely crystalline, tris-protected tetrol **18** was then submitted to single-crystal X-ray analysis, which established the relative configuration of this series to be that depicted in Scheme II and Figure 3. The X-ray stereostructure of **18** (Figure 3)[23] indicates that

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(22) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946.

(23) Crystal data: $C_{27}H_{50}O_5Si_2$ (**18**) M_r = 510.87, orthorhombic, $P2_12_12_1$, a = 12.057 (1) Å, b = 15.533 (4) Å, c = 16.303 (3) Å, V = 3503.3 (8) (1) Å^3, Z = 4, D_c = 1.11 g/cm^3, graphite monochromatized Cu Kα radiation, λ = 1.5418 Å, μ(Cu Kα) = 12.14 cm^{-1}, T = 123 K, R = 0.083 for 3161 unique reflections. $C_{22}H_{26}O_6$ (Fastigilin C 9-*O*-acetate) M_r = 386.44, triclinic, $P1$, a = 10.302 (1) Å, b = 10.418 (3) Å, c = 10.756 (2) Å, α = 95.11 (2)°, β = 112.32 (1)°, γ = 97.44 (1)°, V = 1046.9 (3) (1) Å^3, Z = 4, D_c = 1.26 g/cm^3, graphite monochromatized Cu Kα radiation, λ = 1.5418 Å, μ(Cu Kα) = 6.50 cm^{-1}, T = 123 K, R = 0.065 for 3450 unique reflections. A clear, thin plate of **18** with dimensions 0.36 × 0.09 × 0.48 mm and a clear thin plate of fastigilin C 9-*O*-acetate of dimensions 0.30 × 0.80 × 0.60 mm were used for intensity measurements on a Siemens $P2_1$ (**18**) and a Siemens P1 (fastigilin C 9-*O*-acetate) diffractometer controlled by a Harris computer. Cu Kα radiation and a graphite monochromator were used for intensity measurements. The step-scan technique was used with scan rates of 2°/min (**18**) and 4°/min (fastigilin C 9-*O*-acetate), a scan width of 3.4°, and a $2\theta_{max}$ = 136°. Ten reflections periodically monitored showed no loss of intensity during the data collection. Of the 3161 unique reflections measured for **18**, 2667 had intensities > 3σ. Of the 3450 unique reflections measured for fastigilin C 9-*O*-acetate, 3214 had intensities > 3σ. Standard deviations in the intensities were approximated by the equation: $\sigma^2(I) = s^2(I)_{counting} + DI^2$, where the coefficient (D = 0.20 (**18**), 0.0313 (fastigilin C 9-*O*-acetate) of I was calculated from the variations in intensities of the monitored reflections. Unit cell parameters were determined accurately by least squares fit of Cu $K\alpha_1$ 2θ values ($\lambda(K\alpha_1)$ = 1.5402) for 25 high 2θ reflections.[24] Lorentz and polarization corrections appropriate for a monochromator with 50% perfect character were applied. No absorption correction for intensities was applied. A partial trial solution for **18**, 14 atoms, was obtained by direct methods, using MULTAN 80.[25] The trial solution was extended using successive Fourier syntheses. Hydrogen atoms were clearly found in difference maps very close to positions generated using planar or tetrahedral geometry; thus generated positions were used. The structure was refined by least squares with the coordinates and anisotropic thermal parameters for non-hydrogen atoms included in the refinement. Isotropic thermal parameters for hydrogen atoms were set $^1/_2$ unit higher than the isotropic equivalent of the thermal parameters of the attached heavier atom. Hydrogen parameters were included in the calculations but were not refined. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Atomic form factors were from Doyle,[26] except for hydrogen factors, which were from Stewart et al.[27] In the final refinement cycle, all shifts were <0.9σ. The final R values were 0.083 for **18** and 0.065 for fastigilin C 9-*O*-acetate, and the standard deviations of fit were 4.75 (**18**) and 4.14 (fastigilin C 9-*O*-acetate). A final difference map showed no peaks >0.45 e Å^{-3} for either structure. The CRYM system of computer programs was used.[28] Figures 3 and 4 are ball and stick drawings of **18** and fastigilin C 9-*O*-acetate with atom numbering of the respective structures. Further details of the diffraction analyses along with tables of atomic coordinates and structural parameters have been submitted as supplementary material and are deposited in the Cambridge Crystallographic Database.

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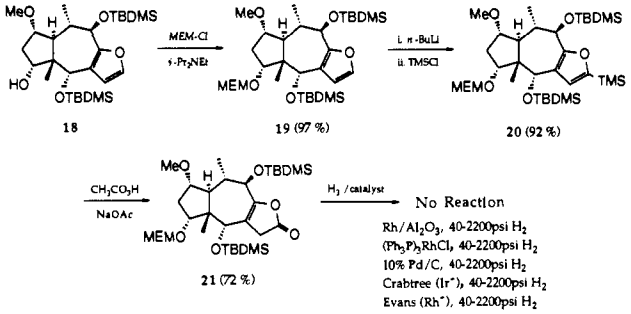
(25) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Universities of York, England, and Louvain, Belgium, 1980.

(26) Doyle, P. A.; Turner, P. S. *Acta Crystallogr.* **1968**, *A24*, 390.

Scheme III

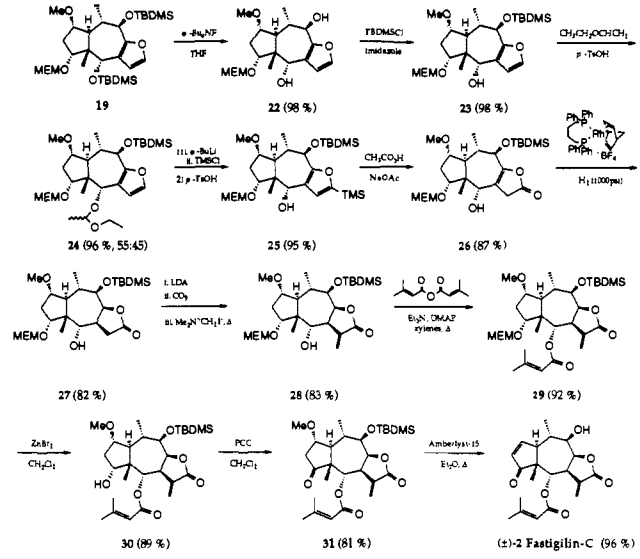


the relative C-2-OMe orientation is that expected from the eq 3 path, a steric approach of the Michael nucleophile in the Mukaiyama conjugate addition–aldol protocol, and establishes (*S*)-4-methoxy-2-methyl-2-cyclopentenone as the requisite starting material for the projected synthesis of (−)-fastigilin C ((−)-**2**). The axial C-6-O(TBDMS) group (Figure 3) appears to effectively shield the α-face of the molecule with the silicon projecting toward the furyl group; the C-9β-O(TBDMS) also projects the silicon under the mean ring plane and partially blocks the underside of the furan ring. The torsion angle between the 3β-H and the C-2α-OMe group is 125.6°, and the 3α-H-C-2-OCH_3 torsion angle is 4.93°; this array will be involved in the construction of the 2,3-double bond in the terminal stage of the synthesis endeavor. The obtention of a 4α-alcohol is noteworthy; this is doubtless the result of an effect of the resident C-2 and C-6 functionalities. Having established the relative stereochemistry present in **18**, we turned our attention to the furan–butyrolactone interconversion (Scheme III).

Alcohol **18** was protected as the corresponding MEM ether[29] (MEM-Cl, iPr_2NEt, Scheme III) to furnish **19** (97%), which was then silylated ((i) nBuLi, (ii) TMS-Cl)[9] to afford **29** (92%). Our plan now called for silylfuran oxidation[9] and subsequent reduction[6] to provide the C-7 and C-8 stereochemistry as well as the requisite butyrolactone. The furan oxidation (CH_3CO_3H, NaOAc) proved to be uneventful, yielding **21** (72%). However, much to our dismay, butenolide **21** proved to be completely resistant to the reduction conditions of Schultz (Rh/Al_2O_3)[6] as well as toward reduction with a variety of other catalysts[30-32] under 40–2200 psi of hydrogen. Assuming that the conformation of **21** resembles that determined for **18** (Figure 3), we surmised that the bulk of the α-face-oriented silyl and MEM ethers was blocking approach to the catalyst, thus rendering **21** unreactive. A simple deblocking of the 6-OH should remove a portion of the steric blockade as well as enable the haptophilic effect to guide the butenolide to the catalyst from the α-face.[30-32]

Toward that end, we proceeded as is described in Scheme IV. Bis-TBDMS-protected MEM ether **19** was desilylated (nBu_4NF), giving **22** (98%). Attempted tris-silylation of **22** (C-6-OH, C-9-OH, furan) was unsuccessful, furnishing no products of furan silylation. Therefore, diol **22** was selectively monosilylated to furnish the 9-O(TBDMS) derivative **23** (98%). Alcohol **23** was then submitted to the conditions of furan silylation (nBuLi, TMS-Cl), producing no products of furan silylation. The failure of these (**22** and **23**) partially protected variants of **19** to suffer furan metalation and silylation suggested the necessity of masking both the C-6- and C-9-OH functions during that step. However the blocking function for the C-6-OH must be readily removed after silylation without concomitant deprotection at the C-9-position. This protocol will insure proper placement of the sen-

Scheme IV



ecioate ester in the final intermediates. Thus the 6-OH was protected as the readily removable ethoxyethyl ether analog **24** ($CH_3CH_2OCHCH_2$, *p*-TsOH; 96%), and the furan then was smoothly silylated (nBuLi, TMS-Cl), yielding **25** (95% overall) after careful ethoxyethyl ether cleavage (*p*-TsOH). As anticipated, silylfuran **25** was readily oxidized (CH_3CO_3H) to give butenolide **26** (87%), setting the stage for the crucial hydroxyl-directed hydrogenation.

We considered utilizing three catalyst systems which have been widely employed to accomplish directed homogeneous hydrogenation.[30] These were Wilkinson's catalyst ($(Ph_3P)_3RhCl$),[30] Crabtree's catalyst ($Ir(COD)py(P(Cy)_3)PF_6$),[30,31] and [Rh(NBD)(DIPHOS-4)]BF_4.[30,32] Wilkinson's catalyst and Crabtree's catalyst were examined for their ability to effect the desired hydrogenation at pressures ranging from 14 to 2200 psi. The former catalyst afforded none of the target butyrolactone (recovered **26**), while the slightly acidic Crabtree catalyst furnished the related conjugated lactone under similar conditions. The cationic rhodium catalyst also failed to reduce **26** at modest pressures (14–50 psi); however at 1000 psi, **26** was readily reduced, affording **27** in 82% yield. Having secured the nucleus of (±)-fastigilin C ((±)-**2**), we turned our attention to the completion of the synthesis of (±)-**2**.

Lactone **27** (Scheme IV) was smoothly converted to the corresponding α-methylene lactone **28** (83%) via the procedure of Lansbury,[5] carboxylation followed by treatment with Eschenmoser's salt (Δ). Lactone **28** was treated with the symmetrical anhydride derived from dimethylacrylic acid (DMAP, TEA), and the mixture was heated in refluxing xylenes to provide senecioate ester **29** (92%). Zinc bromide treatment of **29** smoothly and selectively deprotected the C-4α-oxygen function, leading to alcohol **30** (89%). Oxidation, to the 4-one, and β-elimination, to furnish the 2,3-double bond, remained before a total synthesis of (±)-**2** could be achieved.

After considerable experimentation, we found that PCC oxidation[33] of **30** afforded ketone **31** (72%), setting the stage for the heretofore troublesome[5] double-bond introduction. In the event, treatment of **31** with Amberlyst-15, in refluxing Et_2O, resulted in β-elimination *and* deprotection of the 9-OH to give (±)-fastigilin C ((±)-**2**) (96%). The structure of our synthetic (±)-**2** was secured after a comparison (^{1}H-NMR, TLC) of (±)-**2** with authentic samples if (−)-**2**.[34] The sequence from 4-methoxy-2-methyl-2-cyclopentenone to (±)-**2** was accomplished in 17 steps with an overall yield of 24.6%. The conformation and relative stereochemistry of (±)-**2** were further demonstrated by the conversion

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(28) Duchamp, D. J. CRYM, A System of Crystallographic Programs. The Upjohn Co., Kalamazoo, MI 49001, 1984.
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(30) For a recent review see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.
(31) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
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(33) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(34) We wish to thank Professors Werner Herz (Florida State University) and George Pettit (Arizona State University) for generous samples of (−)-**2**.

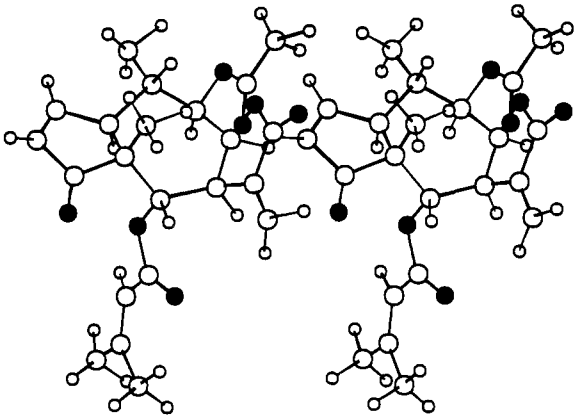
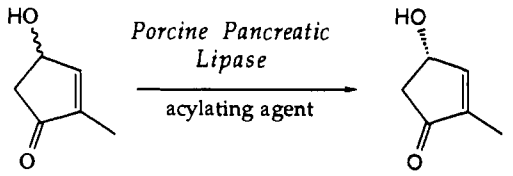


Figure 4. Relative stereochemistry of (±)-fastigilin C 9-*O*-acetate.



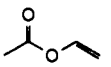
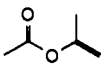
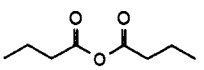
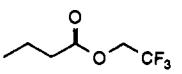
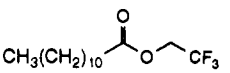
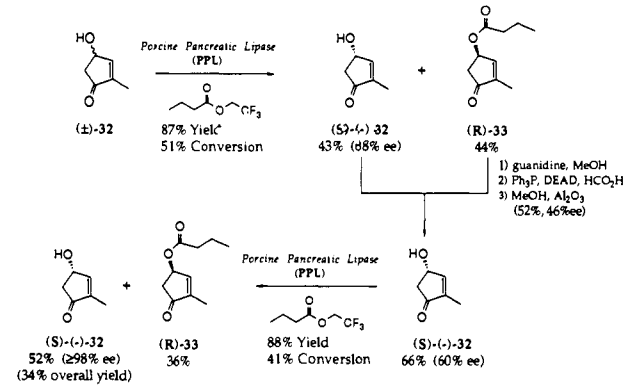
Entry	Acylating Agent	% ee
a		60% (60% conv.)
b		NR
c		0%
d		68% (51% conv.)
e		60% (55% conv.)

Figure 5. Effect of acylating agent on the resolution of (±)-32.

of (±)-**2** to the related 9-*O*-acetate and submission of this nicely crystalline derivative to single-crystal X-ray analysis. Figure 4 presents the result of this study, indicating that the cyclopentenone A-ring is quite flat, the B-ring is in a well-defined chair-like conformation, and the cis β-fused (C-7–C-8) butyrolactone moiety presents the C-8-oxygen in an axial-like arrangement.

(c) Synthesis of (−)-Fastigilin C ((−)-2). Given our successful synthesis of (±)-fastigilin C ((±)-**2**), the lone stumbling block to be overcome prior to realizing a synthesis of (−)-**2** was the preparation of (*S*)-(+)-**4**-methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-**12**) in reasonable quantities and with a high degree of optical purity. A perusal of the literature provided few prior syntheses of (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone, the likely precursor of (*S*)-(+)-**1**. One report[35] outlined an 11-step ca. 6% overall yield synthesis of the target alcohol from 2,4,6-trichlorophenol. We desired a shorter and perhaps higher yielding sequence which might afford greater quantities of (*S*)-(+)-**12**. After further consideration, we selected an enzymatic resolution protocol as perhaps the most likely route to yield quantities of material of sufficient optical purity.[36] This decision was facilitated

Scheme V



by a report from Wong describing efficient porcine pancreatic lipase (PPL)[37,38] catalyzed acetylations of a variety of 2-alkyl-4-hydroxy-2-cyclopentenones. The Wong group described excellent optical purities for the derived (*R*)-acetates (≥92% ee) as well as the recovered (*S*)-alcohols (≥92% ee). Thus our initial efforts were directed toward a lipase-catalyzed acylative resolution.

Toward that end, we exposed (±)-4-hydroxy-2-methyl-2-cyclopentenone (**32**)[19] to PPL in neat vinyl acetate (Figure 5). The reaction was monitored by analysis of aliquots for percentage conversion to the corresponding acetate and conversion of the isolated alcohol to the related MTPA ester[39] and analysis by NMR (^{1}H- and ^{19}F-). At ca. 60% conversion (Figure 5, entry a), the enantiomeric excess plateaued at ca. 60% ee. A closer inspection of the data of Wong[37] suggested that our difficulties might lie in the smaller size of the 2-methyl group of 4-hydroxy-2-methyl-2-cyclopentenone vs the 2-substituents (≥propargyl) employed in the literature study. The failure of this procedure[37] to afford 4-hydroxy-2-methyl-2-cyclopentenone of sufficient enantiomeric purity was cause for concern. Numerous variations on the enzyme resolution theme have been reported in the literature;[36] these include lipase-catalyzed butyrate hydrolyses,[36] coupling of lipase-catalyzed acylative and hydrolytic steps,[40] alternate lipases,[36] and alternate acylating agents.[36,41] We surveyed a variety of lipases, including Amano-PS30[36,42] and *Candida cylindracea*,[36,38,41] for their ability to furnish 4-hydroxy-2-methyl-2-cyclopentenone of higher optical purity to no avail. The lipase–vinyl acetate combinations were also studied in a variety of solvents ranging from hydrocarbons through ethers with similarly poor results. The PPL-catalyzed hydrolysis of the butyrate ester of (±)-4-hydroxy-2-methyl-2-cyclopentenone afforded (*R*)-(+)-4-hydroxy-2-methyl-2-cyclopentenone in 20% ee. This result suggested that the coupling of an acylative and a hydrolytic step[40] was not worth pursuing. Thus we shifted our effort to an evaluation of alternative acylating agents (Figure 5, entries b–e).

The treatment of (±)-4-hydroxy-2-methyl-2-cyclopentenone with PPL in neat isopropenyl acetate did not lead to acylation (Figure 5, entry b). The more reactive butyric anhydride furnished racemic butyrate and alcohol in the presence of PPL, suggesting a non-enzyme-catalyzed reaction (Figure 5, entry c). Alterations in the nature of the acylating group were suggested by the efforts of Oehschlager and Stokes.[41] These workers examined the effects of acylating agent leaving group and acyl chain length upon the optical purity of *C. cylindracea*-catalyzed resolutions of (±)-sulcatol, concluding that β,β,β-trifluoroethoxy constituted an improved leaving group when coupled to a butyrate or laureate skeleton. Application of these modifications to the resolution in question (Figure 5, entries d,e) provided (*S*)-(−)-4-hydroxy-2-

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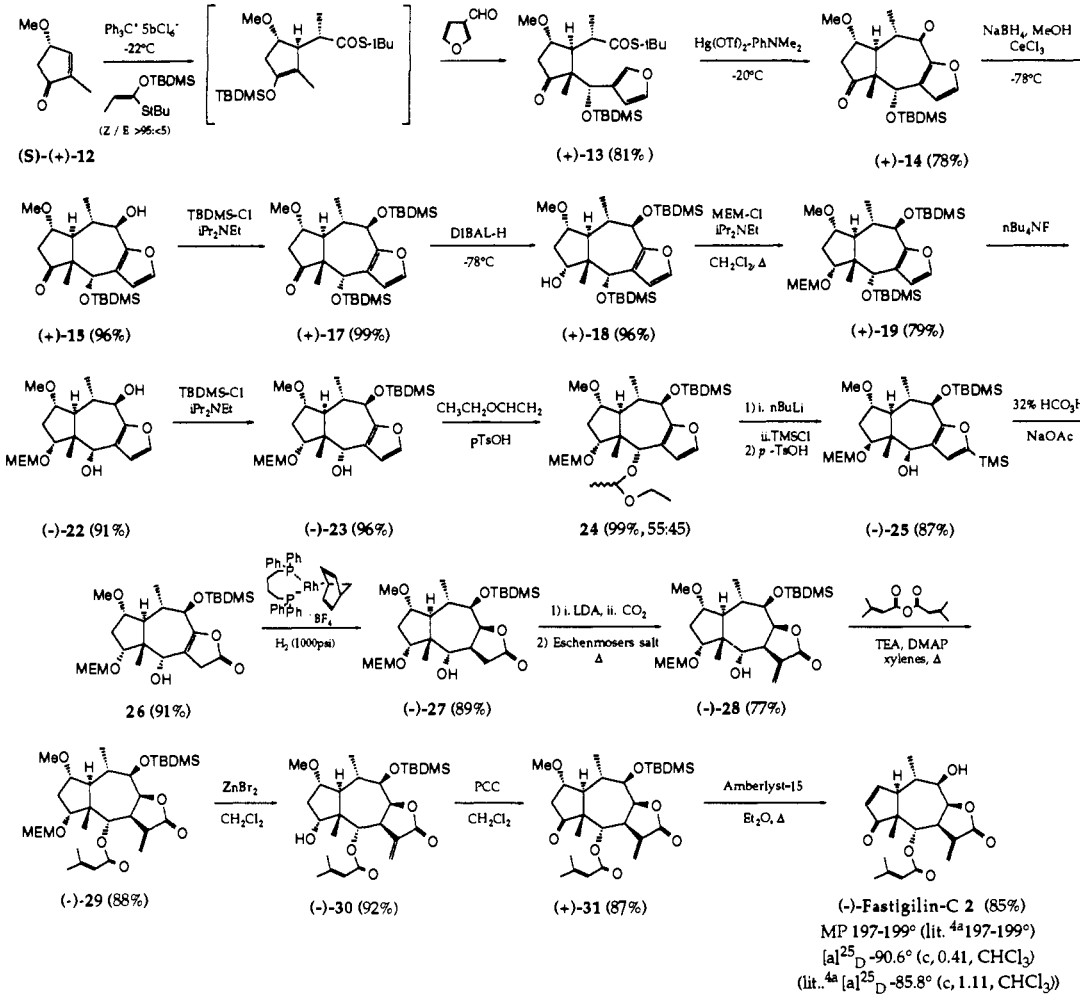
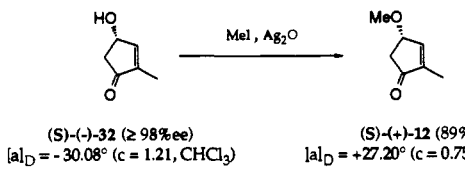
(36) Davies, H. G.; Green, R. H.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry*; Academic Press: San Diego, CA, 1989; pp 51–62.
(37) Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377.
(38) Purchased from Sigma Chemical Company, P.O. Box 14508, St. Louis, MO 63178.
(39) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(40) Chen, C.-S.; Liu, Y.-C. *J. Org. Chem.* **1991**, *56*, 1966.
(41) Stokes, T. M.; Oehschlager, A. C. *Tetrahedron Lett.* **1987**, *28*, 2091.
(42) Purchased from Amano International Enzyme Co. Inc., Aichi, Japan.

Scheme VI



methyl-2-cyclopentenone in 68% ee (51% conversion) and 60% ee (55% conversion), respectively. The improved optical purity for the β,β,β-trifluoroethylbutyrate–PPL resolution enabled us to carry out the large-scale preparation of (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone outlined in Scheme V.

(±)-4-Hydroxy-2-methyl-2-cyclopentenone ((±)-**32**) and β,β,β-trifluoroethyl butyrate were dissolved in ether, and the resulting mixture was treated with PPL. The suspension was allowed to stir at room temperature, and the progress of the reaction (% conversion, enantiomeric excess of (*S*)-alcohol) was monitored by NMR (aliquot was filtered and concentrated in vacuo, and the ratio of butyrate/alcohol was determined by ^{1}H-NMR) every 24 h. After 6 days, the optical purity of the (*S*)-alcohol, as determined by ^{1}H- and ^{19}F-NMR analysis of the derived Mosher ester of (*S*)-(−)-**32**,[39] plateaued at 68% ee with 51% conversion to the butyrate (*R*)-**33**. The butyrate (*R*)-**33**, isolated by chromatography, was cleaved to the (*R*)-alcohol (78%, 46% ee) according to the procedure of Wong[37] (guanidine, MeOH), and the stereocenter was inverted via a Mitsunobu protocol ((i) Ph_3P, DEAD, HCO_2H, (ii) MeOH, Al_2O_3),[37] furnishing an additional quantity of the (*S*)-alcohol (−)-**32** (52%, 46% ee). The combined (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone ((−)-**32**) (60% ee) batches were again exposed to β,β,β-trifluoroethyl butyrate and PPL in ether to afford (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone ((*S*)(−)-**32**) in 52% isolated yield and ≥98% ee (determined by conversion to the Mosher ester and NMR analysis)[39] at 41% conversion. The absolute configuration of the alcohol was determined to be *S* as expected[37] and depicted via an application of the Trost *O*-methylmandelate method.[43] This alcohol was then smoothly converted to the target (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-**12**) as outlined in eq 5. With an ample



(5)

supply of (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-)12) in hand, we turned our attention to the synthesis of (−)-fastigilin C ((−)-**2**) as is illustrated in Scheme VI.

In the event, the large-scale Mukaiyama Michael–aldol condensation[11] between (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-**12**), the TBDMS enol ether of *tert*-butyl thiopropionate, and 3-furaldehyde afforded (+)-**13** in 81% yield, uncontaminated by stereoisomers at any of the newly formed stereogenic centers. Compound (+)-**13** was then exposed to a mercuric triflate–*N*,*N*-dimethylaniline complex, prepared as described by Nishizawa,[20] which provided the target bicyclo[5.3.0]decane (+)-**14** in 78% yield as a crystalline solid.

The initial B- and A-ring manipulations, establishing stereochemistry at C-9 and blocking the C-4-one, were accomplished as described above (vide supra). Toward that end, (+)-**14** (Scheme VI) was smoothly reduced via the modified Luche method[21] to provide alcohol (+)-**15** (96%), which was readily protected as the corresponding 9-O(TBDMS) ether ((+)-**17**) (99%). This initial phase of the B- and A-ring manipulation was closed with reduction of the 4-one (DIBAL-H) to the related 4α-ol (+)-**18** (96%) and protection of the 4-OH as the MEM ether (MEM-Cl, iPr_2NEt),[29] furnishing (+)-**19** in 79% yield. The optical purity of alcohol (+)-**18** of Scheme VI was determined by ^{1}H- and ^{19}F-NMR

(43) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

analysis of the derived Mosher ester[39] and found to be ≥98% ee. We therefore conclude that the formation of (+)-**13** occurred with complete transmission of chirality. The absolute configuration of (+)-**18** (Scheme VI) was determined to be as indicated via an application of the Trost *O*-methylmandelate method.[43] The stage was thus set for furan manipulation and completion of the synthesis of (−)-fastigilin C ((−)-**2**).

The bis(TBDMS) ether (+)-**19** was desilylated with nBu_4NF to furnish diol (−)-**22** (91%), which was selectively monosilylated (C-9-OH) to provide alcohol (−)-**23** in 96% yield. Furan silylation and oxidation was then accomplished as was reported for the case of (±)-**23** (vide supra). Alcohol (−)-**23** was protected with the disposable ethoxyethyl moiety (ethyl vinyl ether, *p*-TsOH), and the product 4-OEE ether (**24**, 99%, 55:45) was then metalated (nBuLi). The α-lithiofuran thus produced was silylated with freshly distilled TMS-Cl, and the reaction mixture was carefully worked up and exposed to a trace of *p*-TsOH in wet CH_2Cl_2 to remove the ethoxyethyl protecting group to give silylfuran (−)-**25** (87%). Silylfuran oxidation (CH_3CO_3H)[9] proceeded smoothly to give the unstable butenolide **26** (91%), setting the stage for the hydroxyl-directed hydrogenation. Butenolide **26** suffered smooth reduction upon hydrogenation (1000 psi of H_2) over (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) tetrafluoroborate,[30,32] furnishing the cis β-fused butyrolactone (−)-**27** in 89% yield. Lactone (−)-**27** (Scheme VI) was readily converted to the corresponding α-methylene lactone (−)-**28** (77%, vide supra) via the procedure of Lansbury,[5] and the senecioate ester was introduced (2,2-dimethylacrylic anhydride, TEA, DMAP, xylenes, Δ), providing ester (−)-**29** (88%). Lactone (−)-**29** was then treated with zinc bromide (MEM removal, 92%) to give alcohol (−)-**30**, which was oxidized (PCC)[33] to provide ketone (+)-**31** (87%). The preparation of (−)-fastigilin C ((−)-**2**) was realized after reaction of (−)-**31** with Amberlyst-15, in refluxing Et_2O as had been previously described, to give (−)-fastigilin C ((−)-**2**) (85%). The structure of our synthetic (−)-**2** was secured after a comparison (rotation, melting point, mixed melting point, ^{1}H-NMR, TLC) of (−)-**2** with authentic samples of (−)-**2**[34] kindly provided by Professors Werner Herz and George Pettit. The sequence from (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-**12**) to (−)-**2** was accomplished in 17 steps with an overall yield of 14%. Using this sequence, we have prepared gram quantities of (−)-**2**. The decrease in yield of the chiral approach vs the racemic synthesis can be attributed to the increase in scale without concomitant yield optimization.

Conclusion

We have accomplished the total syntheses of (±)-fastigilin C ((±)-**2**) and (−)-fastigilin C ((−)-**2**) in 17 steps and 24.6% and 14% overall yields, respectively. These efficient and relatively brief sequences establish seven stereocenters about the periphery of the normally flexible and difficult to control seven-membered B-rings of (±)-**2** and (−)-**2**. Central to the success of this venture is the construction of the bicyclo[5.3.0]decane nucleus via a Mukaiyama Michael–aldol sequence followed by an application of our furan-terminated cationic cyclization protocol. Worthy of note is the excellent transmission of relative and absolute stereochemistry from the starting 4-methoxy-2-methyl-2-cyclopentenones ((±)-**12** and (+)-**12**) to the bicyclo[5.3.0]decane moieties. Further applications of furan-terminated cationic cyclizations to the synthesis of natural products are currently under study. These results will be reported in due course.

Experimental Section

General Procedures. Tetrahydrofuran (THF) was dried by distillation, under argon, from sodium benzophenone ketyl; methylene chloride and acetonitrile were dried by distillation, under argon from calcium hydride. Diethyl ether was purchased from Mallinkrodt, Inc., St. Louis, MO, and was used as received. All other reagents were used as received unless otherwise stated. All reactions were performed in oven-dried (150 °C) glassware under nitrogen with rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Mass spectra, high-resolution mass spectra, infrared spectra, and combustion analyses were obtained by the Physical and Analytical Chemistry Department of The Upjohn Company. Optical rotations were measured on a Perkin-Elmer polarimeter, at 25 °C, in the solvents mentioned. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker AM-300 at 300 MHz in deuteriochloroform unless otherwise indicated. ^{13}C magnetic resonance spectra were recorded on a Bruker AM-300 at 75.4 MHz as solutions in deuteriochloroform unless otherwise indicated. ^{19}F-NMR were recorded on a Varian XL-300 spectrometer at 282.203 MHz as solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (δ scale) from the relevant internal standard (tetramethylsilane for ^{1}H and ^{13}C, and $FCCl_3$ for ^{19}F). Data are reported as follows: chemical shifts [multiplicity (s = singlet, br s = broad singlet, dd = doublet of doublets, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration]. Thin layer chromatography (TLC) was performed on Merck $SilG_{254}$ plates as indicated. Spots were made visible with UV light and/or by dipping into a solution of ammonium molybdate (75 g) and ceric sulfate (2.5 g) in water and concentrated sulfuric acid (500 mL; 9:1, v/v) followed by heating. Flash column chromatography was performed according to the procedure of Still[44] et al. by using the Merck silica gel mentioned and eluting with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters.

[1α(*S),2β(*S**),5α]-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-furanylmethyl]-α,2-dimethyl-5-methoxy-3-oxocyclopentaneethanethioic Acid *S*-(1,1-Dimethylethyl) Ester (13).** To a solution of trityl hexachloroantimonate (3.490 g, 6.048 mmol) in CH_2Cl_2 (0.4 L), cooled in a −20 °C bath, was added (±)-4-methoxy-2-methyl-2-cyclopentenone ((±)-**12**) (7.63 g, 60.48 mmol) in CH_2Cl_2 (50 mL) over 5 min. The TBDMS enol ether of *tert*-butyl thiopropionate (18.91 g, 72.58 mmol)[12] was then added over 5 min, and the solution was stirred an additional 20 min at −20 °C. The reaction vessel was cooled to −78 °C, and a solution of freshly distilled 3-furaldehyde (8.72 g, 90.72 mmol) in CH_2Cl_2 (0.1 L) was added over 20 min. The mixture was stirred for 0.5 h at −78 °C and transferred via cannula to a rapidly stirred solution (0.5 L) of a 1:1 mixture of saturated $NaHCO_3$ and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (0.5 L). The combined organic extracts were washed with brine (1.0 L), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by chromatography on a column of silica gel (230–400 mesh, 300 g, 70-mm o.d., Et_2O–hexanes (5:95), 200-mL fractions) using the flash technique to afford 26.38 g (54.64 mmol, 90%) of **13** as a viscous, clear, yellow liquid. ^{1}H-NMR: (C_6D_6) δ = 7.19 (t, *J* = 0.7 Hz, 1), 6.92 (t, *J* = 1.6 Hz, 1), 6.39 (d, *J* = 1.1 Hz, 1), 4.78 (s, 1), 3.65 (dd, *J* = 2.7, 8.7 Hz, 1), 3.31 (ddd, *J* = 1.8, 7.0, 8.8 Hz, 1), 2.81 (s, 3), 2.3 (m, 1), 2.29 (dd, *J* = 7.0, 17.3 Hz, 1), 2.05 (dd, *J* = 8.8, 17.3 Hz, 1), 1.32 (s, 9), 0.88 (d, *J* = 7.0 Hz, 3), 0.88 (s, 9), 0.63 (s, 3), 0.00 (s, 3), −0.23 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 215.2, 202.6, 142.7, 140.6, 125.5, 110.5, 76.5, 71.8, 57.8, 56.4, 47.7, 47.3, 45.3, 44.4, 29.8, 26.0, 18.3, 16.5, 13.5, −4.5, −5.4. IR: (Neat) 2960, 2929, 2896, 2885, 2859, 1744, 1682, 1472, 1463, 1456, 1364, 1258, 1253, 1162, 1116, 1088, 1063, 1024, 962, 946, 874, 867, 839, 778, 602 cm^{-1}. EI/MS: (70 eV) *m/z* 482 (M^+, 1), 426 (15), 425 (50), 369 (33), 337 (29), 212 (18), 211 (base). Anal. Calcd for $C_{25}H_{42}O_5SiS$: C, 62.20; H, 8.77. Found: C, 62.01; H, 8.79.

(4α,4aβ,7α,7aα,8α)-(±)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4a,6,7,7a,8-hexahydro-4a,8-dimethyl-7-methoxyazuleno[6,5-*b*]furan-5,9-dione ((±)-14). To a solution of yellow mercury oxide (6.56 g, 30.27 mmol) in dry CH_3CN (0.24 L), cooled in an ice–water bath, was added trifluoromethanesulfonic anhydride (5.1 mL, 30.27 mmol) over 10 min. A small amount of the orange-colored HgO remained after the addition of 1 equiv of the anhydride. This mixture was titrated to a clear solution by a further dropwise addition of trifluoromethanesulfonic anhydride and was allowed to stir at 0 °C for 1 h. *N,N*-Dimethylaniline (3.84 mL, 30.266 mmol) was then added, and the resulting yellow solution was stirred at 0 °C for 0.5 h. The reaction vessel was cooled to −20 °C, and a solution of **13** (4.80 g, 10.99 mmol) in CH_3CN (60 mL) was added over 20 min. The mixture was stirred for 1 h at −20 °C and diluted with water (100 mL) and Et_2O (200 mL). The organic layer was separated from the precipitated salts, which were washed with Et_2O (4 × 0.2 L). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. This material was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 45-mm o.d., Et_2O–hexanes (20:80), 50-mL fractions) using the flash technique to afford 3.81 g (9.70 mmol, 96%) of **14** as a white crystalline solid. Mp: 152–154 °C. ^{1}H-NMR: (C_6D_6) δ = 6.95 (d, *J* = 1.7 Hz, 1), 5.99 (d, *J* = 1.7 Hz, 1), 4.92 (s, 1), 3.28–3.18 (m, 2), 2.87 (s, 3), 2.55 (m, 1), 2.55 (dd, *J* = 6.8, 18.5 Hz, 1), 2.18 (dd, *J* = 8.3, 18.5 Hz, 1), 1.59 (d, *J* = 7.0 Hz, 3), 0.87 (s, 9), 0.62 (s, 3), 0.21 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 214.9, 190.0, 148.4, 146.1, 130.0, 114.1, 80.1, 70.0, 58.0, 56.5, 46.5, 44.5, 44.1, 25.8,

(44) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

18.1, 16.2, −4.1, −4.9. IR: (nujol) 2952, 2927, 1739, 1653, 1490, 1472, 1457, 1419, 1260, 1254, 1242, 1117, 1108, 1095, 1072, 1061, 969, 894, 876, 861, 845, 839, 789, 781 cm^{-1}. EI/MS: (70 eV) *m/z* 377 (1.8), 336 (24), 335 (base), 303 (19), 277 (16), 217 (13), 159 (11), 89 (18), 85 (8), 75 (27), 73 (12). Anal. Calcd for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.08; H, 8.25.

(4α,4aβ,7α,7aα,8α,9β)-(±)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4a,6,7,7a,8,9-hexahydro-4a,8-dimethyl-9-hydroxy-7-methoxyazuleno[6,5-*b*]furan-5(4*H*)-one ((±)-15). To a solution of **14** (0.197 g, 0.501 mmol) in $CeCl_3 \cdot 7H_2O$–CH_3OH (1.6 mL, 0.4 M), cooled in a dry ice–iPrOH bath, was added a solution of $NaBH_4$ (0.019 g, 0.501 mmol) dissolved in $CeCl_3 \cdot 7H_2O$–CH_3OH (1.6 mL, 0.4 M), and the reaction mixture was cooled in a dry ice–iPrOH bath. The mixture was stirred at −78 °C for 0.5 h, and the excess hydride was quenched by addition of acetone (2 mL). The solvents were evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (50 mL) and acidified with 5% aqueous HCl (pH 2). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (80 mL) and brine (80 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by chromatography on a column of silica gel (230–400 mesh, 10 g, 20-mm o.d., Et_2O–hexanes (20:80), 10-mL fractions) using the flash technique to afford 0.184 g (0.467 mmol, 93%) of **15** as a clear, viscous oil. ^{1}H-NMR: (C_6D_6) δ = 6.93 (d, *J* = 1.7 Hz, 1), 6.06 (d, *J* = 1.7 Hz, 1), 4.90 (s, 1), 4.42 (dd, *J* = 9.9, 3.3 Hz, 1), 3.33 (ddd, *J* = 9.6, 7.9, 7.5 Hz, 1), 3.00 (dd, *J* = 10.7, 9.6 Hz, 1), 2.94 (s, 3), 2.58 (dd, *J* = 18.7, 7.5 Hz, 1), 2.14 (dd, *J* = 18.7, 7.9 Hz, 1), 2.47 (d, *J* = 3.4 Hz, 1), 2.03 (m, 1), 1.51 (d, *J* = 6.7 Hz, 3), 0.94 (s, 9), 0.67 (s, 3), 0.26 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 215.6, 152.8, 139.7, 118.4, 114.0, 79.1, 74.4, 69.7, 58.1, 56.5, 46.0, 43.6, 38.9, 26.1, 18.4, 17.7, 16.2, −4.0, −4.8. IR: (neat) 3600–3200 br, 2978, 2955, 2930, 2894, 2887, 2857, 1745, 1716, 1472, 1463, 1388, 1373, 1361, 1249, 1233, 1126, 1113, 1074, 1046, 1005, 992, 891, 862, 837, 816, 795, 776, 744, 737 cm^{-1}. EI/MS: (70 eV) *m/z* 337 (66), 319 (79), 305 (39), 287 (31), 247 (37), 219 (40), 145 (33), 85 (24), 75 (base), 73 (58). Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.68. Found: C, 63.74; H, 8.96.

(4α,4aβ,7α,7aα,8α,9β)-(±)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4a,6,7,7a,8,9-hexahydro-4a,8-dimethyl-7-methoxyazuleno[6,5-*b*]furan-5(4*H*)-one ((±)-17). To a solution of **15** (1.66 g, 4.21 mmol) in dry DMF (21 mL) was added in order imidazole (1.15 g, 16.83 mmol) and *tert*-butyldimethylsilyl chloride (1.27 g, 8.41 mmol). The mixture was stirred at room temperature for 18 h and was then diluted with Et_2O (0.25 L) and cast into 10% HCl (0.15 L). The organic phase was separated, the aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic extracts were washed with saturated $NaHCO_3$ (0.25 L) and brine (0.25 L) and dried with $MgSO_4$. Concentration in vacuo afforded the crude silyl ether as a pale yellow oil, which was purified by chromatography on a column of silica gel (230–400 mesh, 200 g, 60-mm o.d., Et_2O–hexanes (10:90), 100-mL fractions) using the flash technique to afford 2.13 g (99%) of **17** as a white solid. Recrystallization from Et_2O–hexanes gave **17** as fine white needles. Mp: 102–103 °C. ^{1}H-NMR: (C_6D_6) δ = 7.03 (d, *J* = 1.7 Hz, 1), 6.07 (d, *J* = 1.7 Hz, 1), 4.90 (s, 1), 4.66 (d, *J* = 9.7 Hz, 1), 3.33 (ddd, *J* = 9.5, 7.7, 7.6 Hz, 1), 3.00 (dd, *J* = 10.7, 9.6 Hz, 1), 2.95 (s, 3), 2.55 (dd, *J* = 18.8, 7.6 Hz, 1), 2.10 (m, 1), 2.09 (dd, *J* = 18.8, 7.4 Hz, 1), 1.41 (d, *J* = 6.9 Hz, 3), 1.20 (s, 9), 0.94 (s, 9), 0.57 (s, 3), 0.29 (s, 3), 0.24 (s, 3), 0.19 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 214.9, 153.5, 139.0, 118.3, 113.5, 78.8, 75.6, 69.2, 57.8, 56.3, 47.0, 43.0, 39.4, 26.2, 25.8, 18.7, 18.2, 17.2, 16.3, −4.3, −4.6, −4.7, −5.0. IR: (neat) 2980, 2955, 2930, 2894, 2889, 2858, 1749, 1473, 1463, 1361, 1258, 1250, 1137, 1118, 1099, 1085, 1065, 1006, 994, 895, 865, 837, 816, 795, 776 cm^{-1}. EI/MS: (70 eV) *m/z* 453 (13), 452 (33), 451 (92), 320 (24), 319 (base), 287 (17), 203 (14), 175 (23), 75 (29), 73 (65). Anal. Calcd for $C_{27}H_{48}O_5Si_2$: C, 63.73; H, 9.51. Found: C, 63.70; H, 9.66.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4a,6,7,7a,8-hexahydro-4a,8-dimethyl-5-hydroxy-7-methoxyazuleno[6,5-*b*]furan ((±)-18). To a solution of **17** (7.42 g, 14.57 mmol) in dry Et_2O (0.2 L), cooled in a dry ice–iPrOH bath, was added DIBAL-H (1 M in toluene, 22 mL, 21.86 mmol) over 60 min. The mixture was stirred at −78 °C for 0.5 h and then was carefully quenched by the addition of methanol (2 mL) followed by saturated aqueous sodium potassium tartrate (0.1 L). The mixture was allowed to warm to room temperature over 1.5 h and then was acidified (pH 3) with 10% aqueous HCl. The organic phase was separated, the aqueous layer was extracted with Et_2O (3 × 0.125 L), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (0.5 L) and dried ($MgSO_4$). Concentration in vacuo afforded the crude alcohol as a pale yellow oil, which was purified by chromatography on a column of silica gel (230–400 mesh, 500 g, 70-mm o.d., Et_2O–hexanes (50:50), 300-mL fractions) using the flash technique to afford 7.20 g (97%) of **18** as a white solid. Recrystallization from Et_2O–hexanes gave **18** as fine white needles. Mp: 110–112 °C. ^{1}H-NMR: (C_6D_6) δ = 6.89 (d, *J* = 1.4 Hz, 1), 5.86 (d, *J* = 1.4 Hz, 1), 4.70 (t, *J* = 2.30 Hz, 1), 4.60 (t, *J* = 9.60 Hz, 1), 4.50 (s, 1), 3.95 (br s, 1), 3.25 (dt, *J* = 7.8, 3.3 Hz, 1), 2.99 (s, 3), 2.83 (dd, *J* = 10.8, 7.6 Hz, 1), 1.80–1.95 (3), 1.31 (d, *J* = 6.7 Hz, 3), 1.09 (s, 9), 0.83 (s, 9), 0.27 (s, 3), 0.16 (s, 3), 0.11 (s, 3), 0.00 (s, 3), −0.30 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 154.0, 138.8, 119.2, 112.7, 85.4, 82.1, 74.9, 73.6, 55.6, 49.7, 48.2, 40.2, 37.9, 26.2, 25.8, 20.0, 18.6, 18.1, 17.0, −3.85, −4.38, −4.75, −5.13. IR: (nujol) 3447, 2954, 1390, 1377, 1258, 1250, 1114, 1102, 1084, 1069, 1058, 1025, 1005, 895, 865, 838, 815, 810, 795, 777 cm^{-1}. EI/MS: (70 eV) *m/z* 510 (M^+, 12), 453 (31), 421 (13), 321 (42), 289 (63), 229 (21), 215 (27), 197 (39), 75 (55), 73 (base). Anal. Calcd for $C_{27}H_{50}O_5Si_2$: C, 63.48; H, 9.86. Found: C, 63.46; H, 9.90.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((±)-19). To a solution of **18** (1.42 g, 2.78 mmol) in dry CH_2Cl_2 (8 mL) was added iPr_2NEt (2.15 g, 16.6 mmol) followed by MEM-Cl (1.73 g, 13.88 mmol). The mixture was warmed under reflux for 1 h and then was cooled to room temperature, diluted with CH_2Cl_2 (0.1 L), and cast into 10% aqueous HCl (0.1 L). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (0.25 L), dried ($MgSO_4$), and concentrated in vacuo to give the crude MEM ether **19** as a clear, pale yellow, viscous oil. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 50-mm o.d., Et_2O–hexanes (30:70), 50-mL fractions) using the flash technique to afford 1.61 g (97%) of **19** as a clear, colorless, viscous oil. ^{1}H-NMR: (C_6D_6) δ = 7.04 (d, *J* = 1.7 Hz, 1), 6.15 (d, *J* = 1.7 Hz, 1), 4.69 (s, 1), 4.60–4.77 (m, 2), 4.64 (d, *J* = 9.1 Hz, 1), 3.56–3.73 (m, 4), 3.40 (dd, *J* = 5.1. 5.0 Hz, 1), 3.27 (m, 1), 3.16 (s, 3), 3.09 (s, 3), 2.81 (br m, 1), 2.75 (m, 1), 2.25 (m, 1), 1.77 (m, 1), 1.38 (d, *J* = 6.9 Hz, 3), 1.09 (s, 9), 0.98 (s, 9), 0.66 (s, 3), 0.21 (s, 3), 0.18 (s, 3), 0.15 (s, 3), 0.00 (s, 3). IR: (neat) 2953, 2929, 2886, 2858, 2819, 1473, 1463, 1389, 1361, 1254, 1200, 1188, 1156, 1115, 1099, 1083, 1072, 1060, 1048, 1006, 896, 866, 837, 817, 775 cm^{-1}. EI/MS: (70 eV) *m/z* 598 (M^+, 17), 541 (29), 231 (21), 199 (19), 197 (26), 163 (29), 133 (93), 89 (base). Anal. Calcd for $C_{31}H_{58}O_7Si_2$: C, 62.16; H, 9.76. Found: C, 62.37; H, 9.83.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-4,9-Bis(hydroxy)-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((±)-22). To a solution of **19** (2.40 g, 4.01 mmol) in anhydrous THF (5 mL), cooled in an ice–water bath, was added tetrabutylammonium fluoride (1.0 M in THF, 20 mL, 20.0 mmol) over 15 min. The mixture was allowed to warm to room temperature over 1 h and then was warmed under reflux for 12 h. The resulting pale yellow solution was cooled to room temperature, cast into CH_2Cl_2 (0.125 L), and washed with brine (0.125 L). The aqueous phase was extracted with CH_2Cl_2 (5 × 50 mL), and the combined organic phases were dried ($MgSO_4$). Concentration in vacuo afforded the crude diol as a sticky, pale yellow solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 50-mm o.d., Et_2O, 0.5 L, EtOAc, 0.5 L, 50-mL fractions) using the flash technique to afford 1.45 g (98%) of the target diol **22** as a white crystalline solid. Recrystallization from Et_2O–hexanes gave the diol **22** as white needles. Mp: 110–112 °C. ^{1}H-NMR: (C_6D_6) δ = 7.05 (d, *J* = 1.8 Hz, 1), 6.25 (d, *J* = 1.8 Hz, 1), 4.66 (s, 2), 4.50 (m, 1), 4.49 (d, *J* = 7.1 Hz, 1), 4.33 (d, *J* = 7.1 Hz, 1), 3.81 (dd, *J* = 5.5, 2.2 Hz, 1), 3.55 (m, 1), 3.40 (m, 1), 3.25 (m, 2), 3.20 (dt, *J* = 7.8, 3.4 Hz, 1), 3.10 (s, 3), 3.00 (s, 3), 2.93 (dd, *J* = 11.0, 7.8 Hz, 1), 2.73 (br s, 1), 1.95 (m, 1), 1.75 (m, 1), 1.60 (m, 1), 1.46 (d, *J* = 6.5 Hz, 3), 0.45 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 153.3, 139.2, 119.5, 113.4, 93.4, 89.6, 85.0, 73.2, 71.8, 71.5, 67.5, 58.4, 55.8, 49.9, 47.7, 39.2, 34.1, 20.5, 16.5. IR: (nujol) 3465, 3417, 2995, 2976, 1299, 1137, 1105, 1067, 1055, 1034, 1009, 966, 851 cm^{-1}. EI/MS: (70 eV) *m/z* 370 (M^+, 3), 294 (10), 281 (11), 264 (7), 248 (7), 235 (16), 214 (20), 203 (12), 185 (18), 159 (17), 145 (15), 126 (25), 125 (24), 124 (24), 108 (27), 107 (68), 89 (31), 59 (base). Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16. Found: C, 61.25; H, 8.19.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((±)-23). To a solution of diol **22** (1.45 g, 3.90 mmol) in dry DMF (8 mL) was added imidazole (0.34 g, 5.0 mmol) followed by the addition of a solution of TBDMS-Cl (0.69 g, 4.58 mmol) in DMF (2 mL) over 5 min. The mixture was allowed to stir for 18 h at room temperature and then was diluted with EtOAc (0.1 L) and cast into 10% aqueous HCl (75 mL). The organic phase was separated, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (0.25 L) and dried ($MgSO_4$). Concentration in vacuo afforded the crude mono-TBDMS ether **23** as a clear, pale yellow, viscous oil, which was purified by chromatography on a column

of silica gel (230–400 mesh, 200 g, 50-mm o.d., Et_2O–hexanes (70:30), 1.0 L, EtOAc, 1.0 L, 100-mL fractions) using the flash technique to afford 1.85 g (98%) of **23** as a white crystalline solid. Recrystallization from Et_2O–hexanes gave **23** as white needles. Mp: 85–86 °C. ^{1}H-NMR: (C_6D_6) δ = 7.00 (d, J = 1.6 Hz, 1), 6.17 (d, J = 1.6 Hz, 1), 4.79 (d, J = 9.6 Hz, 1), 4.56 (s, 1), 4.49 (s, 1), 4.42 (d, J = 7.1 Hz, 1), 4.28 (d, J = 7.1 Hz, 1), 3.70 (br d, J = 3.9 Hz, 1), 3.45 (m, 1), 3.35 (m, 1), 3.20 (m, 2), 3.15 (dt, J = 3.2, 7.9 Hz, 1), 3.02 (s, 3), 2.94 (s, 3), 2.90 (dd, J = 7.9, 10.7 Hz, 1), 1.80 (m, 1), 1.70 (m, 1), 1.55 (m, 1), 1.28 (d, J = 6.7 Hz, 3), 1.05 (s, 9), 0.31 (s, 3), 0.88 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 153.8, 139.0, 119.9, 113.5, 93.7, 87.8, 85.2, 74.7, 72.1, 71.9, 67.8, 58.7, 56.1, 50.3, 48.6, 40.4, 34.4, 26.5, 20.4, 18.9, –4.3, –4.7. IR: (nujol) 3469, 2811, 1388, 1134, 1123, 1108, 1072, 1048, 1031, 1018, 990, 895, 865, 842, 782 cm^{-1}. EI/MS: (70 eV) m/z 484 (M^+, 1.3), 469 (2.5), 427 (base), 395 (37), 351 (16), 321 (20), 289 (14), 277 (10), 247 (16), 231 (24), 211 (3), 199 (50). Anal. Calcd for $C_{25}H_{44}O_7Si$: C, 61.95; H, 9.15. Found: C, 61.91; H, 8.99.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-4-(1-ethoxyethoxy)-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((±)-24). To a solution of **23** (1.43 g, 2.95 mmol) in anhydrous Et_2O (3 mL) was added ethyl vinyl ether (2.13 g, 29.51 mmol) followed by the addition of a few crystals of *p*-TsOH. The mixture was allowed to stir for 18 h at room temperature and then was diluted with Et_2O (0.1 L) and cast into saturated aqueous $NaHCO_3$ (0.1 L). The organic phase was separated, the aqueous layer was extracted with Et_2O (5 × 50 mL), and the combined organic phases were washed with brine (0.25 L) and dried ($MgSO_4$). Concentration in vacuo afforded the crude ethoxyethyl ethers **24** as a clear, pale yellow, viscous oil, which was purified by chromatography on a column of silica gel (230–400 mesh, 200 g, 50-mm o.d., Et_2O–hexanes (25:75), 50-mL fractions) using the flash technique to afford 1.49 g (96%) of a 55:45 mixture of ethoxyethyl ether diastereomers **24** as a waxy, white semisolid. The mixture was employed in the next reaction without further purification. ^{1}H-NMR: (C_6D_6) δ = 7.02 (br s, 1), 6.92 (m, 1), 6.27 (d, J = 1.7 Hz, 0.55), 6.07 (d, J = 1.7 Hz, 0.45), 4.91 (q, J = 5.3 Hz, 0.55), 4.56 (d, J = 6.9 Hz, 0.45), 4.35–4.55 (3.45), 4.24 (s, 0.55), 3.10–3.70 (8), 3.02 (s, 1.65), 3.04 (s, 1.35), 2.99 (s, 1.65), 2.96 (s, 1.35), 2.69 (br t, J = 9.9 Hz, 0.55), 2.54 (br t, J = 9.9 Hz, 0.45), 1.85–2.15 (2), 1.60 (m, 1), 1.15–1.40 (4.65), 1.07 (d, J = 5.3 Hz, 1.35), 0.85–1.05 (12), 0.63 (s, 1.35), 0.57 (s, 1.65), 0.06 (s, 1.65), 0.03 (s, 1.35), 0.01 (s, 1.35), 0.00 (s, 1.65). ^{13}C-NMR: (C_6D_6) δ = 151.8, 151.5, 139.6, 138.8, 120.5, 120.1, 113.9, 112.1, 102.7, 101.0, 98.1, 95.5, 95.3, 84.3, 82.9, 81.8, 81.6, 77.6, 76.4, 76.2, 74.4, 72.3, 72.2, 67.3, 67.2, 60.0, 58.6, 58.2, 56.2, 50.3, 49.6, 48.1, 47.3, 38.6, 37.5, 26.3, 26.2, 23.0, 21.0, 20.3, 20.0, 18.7, 18.6, 16.9, 16.5, 15.6, 15.5, –4.2, –4.5, –4.6. IR: (nujol) 2811, 1389, 1252, 1165, 1126, 1113, 1099, 1081, 1049, 1017, 896, 855, 838, 777 cm^{-1}. Anal. Calcd for $C_{29}H_{52}O_8Si$: C, 62.50; H, 9.41. Found: C, 62.65; H, 9.52.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-2-(trimethylsilyl)azuleno[6,5-*b*]furan ((±)-25). To a solution of ethoxyethyl ether **24** (0.40 g, 0.73 mmol) in anhydrous THF (14 mL), cooled in an ice–water bath, was added n-BuLi (1.6 mol in hexanes, 2.27 mL, 3.62 mmol) over 5 min. The mixture was stirred for 30 min at 0 °C, during which time the mixture became red-orange; then freshly distilled TMS-Cl (0.44 mL, 0.376 g, 3.47 mmol) was added until the red-orange color was discharged. The reaction mixture was stirred for 0.5 h at 0 °C and then warmed to room temperature over 0.5 h. The colorless solution was diluted with Et_2O (25 mL) and cast into water (10 mL) and 3.7% aqueous HCl (5 mL). The organic phase was separated, the aqueous layer was extracted with Et_2O (3 × 15 mL), and the combined organic phases were stirred with a few crystals of *p*-TsOH until TLC analysis suggested that the ethoxyethyl ether had been completely cleaved. The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration in vacuo afforded the crude silylfuran **25** as a white solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 50 g, 40-mm o.d., Et_2O–hexanes (90:10), 25-mL fractions) using the flash technique to afford 0.39 g (95%) of **25** as a white crystalline solid. Recrystallization from Et_2O–hexanes gave **25** as white needles. Mp: 86–87 °C. ^{1}H-NMR: (C_6D_6) δ = 6.58 (s, 1), 4.86 (d, J = 9.7 Hz, 1), 4.65 (s, 1), 4.60 (br s, 1), 4.43 (d, J = 7.1 Hz, 1), 4.27 (d, J = 7.1 Hz, 1), 3.73 (d, J = 4.2 Hz, 1), 3.55 (m, 1), 3.35 (m, 1), 3.25 (m, 2), 3.15 (dt, J = 7.9, 3.1 Hz, 1), 3.00 (m, 1), 3.02 (s, 3), 2.92 (s, 3), 1.95 (m, 1), 1.65 (m, 1), 1.55 (m, 1), 1.30 (d, J = 6.7 Hz, 3), 1.09 (s, 9), 0.33 (s, 3), 0.22 (s, 9), 0.11 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 158.5, 155.8, 124.2, 119.9, 93.5, 87.8, 85.2, 74.9, 72.0, 67.6, 58.6, 55.9, 50.2, 48.6, 40.2, 34.1, 26.3, 20.3, 18.7, 17.1, 1.35, –1.21, –4.37, –4.84. IR: (nujol) 3471, 2811, 1388, 1134, 1123, 1108, 1072, 1048, 1031, 1018, 990, 895, 865, 842, 782 cm^{-1}. EI/MS: (70 eV) m/z 556 (M^+, 2.8), 499 (32), 467 (19), 423 (15), 393 (14), 361 (5), 349 (7), 319 (12), 303 (10), 283 (36), 271 (20), 259 (6), 231 (11), 89 (24), 73 (base). Anal. Calcd for $C_{28}H_{52}O_7Si_2$: C, 60.39; H, 9.41. Found: C, 59.98; H, 9.41.

(4α,4aβ,5α,7α,7aα,8α,9β)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan-2(3*H*)-one ((±)-26). To a solution of **25** (0.66 g, 1.18 mmol) in CH_2Cl_2 (6 mL), cooled in an ice–water bath, was added NaOAc (0.68 g, 8.29 mmol) followed by the addition of CH_3CO_3H (32%, 1.49 mL, 7.10 mmol) over 5 min. The mixture was allowed to stir for 2 h at 0 °C and then was cast into CH_2Cl_2 (50 mL), saturated aqueous $NaHCO_3$ (40 mL), and 10% aqueous $Na_2S_2O_3$ (10 mL). The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), and the combined organic phases were washed with brine (75 mL) and dried ($MgSO_4$). Concentration in vacuo afforded the furanone **26** as a pale yellow, viscous oil, which was purified by chromatography on a column of silica gel which had been deactivated by the addition of 10% (w/w) of H_2O to the silica gel prior to use. Purification (230–400 mesh, 50 g, 40-mm o.d., Et_2O–hexanes (90:10), 25-mL fractions) using the flash technique afforded 0.52 g (87%) of **26** as a clear, colorless, viscous oil. ^{1}H-NMR: (C_6D_6) δ = 4.29 (d, J = 6.9 Hz, 1), 4.18 (d, J = 6.9 Hz, 1), 4.06 (d, J = 8.1 Hz, 1), 3.79 (s, 1), 3.70 (d, J = 1.5 Hz, 1), 3.40 (t, J = 6.2 Hz, 1), 3.35 (m, 1), 3.25 (m, 1), 3.20 (m, 1), 3.15 (m, 2), 2.95 (s, 3), 2.93 (m, 1), 2.90 (s, 3), 2.50 (m, 2), 1.90 (m, 2), 1.40 (m, 1), 1.15 (d, J = 6.8 Hz, 3), 0.95 (s, 9), 0.51 (s, 3), 0.21 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 173.9, 151.9, 112.6, 94.5, 86.2, 82.7, 74.5, 72.1, 71.8, 67.8, 58.6, 56.2, 48.8, 46.7, 39.3, 37.3, 36.1, 26.3, 21.3, 18.7, 18.1, –3.8, –4.7. IR: (neat) 2951, 2931, 2887, 2858, 2822, 1803, 1775, 1473, 1463, 1388, 1253, 1208, 1181, 1166, 1132, 1109, 1071, 1059, 1033, 1010, 972, 960, 936, 839, 779 cm^{-1}.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan-2(3*H*)-one ((±)-27). A 25-mL test tube was charged with **26** (0.13 g, 0.25 mmol) and dry CH_2Cl_2 (2 mL). The solution was placed under argon, and [Rh(NBD)(DIPHOS-4)]BF_4 (18 mg) in CH_2Cl_2 (0.5 mL) was added. The mixture was hydrogenated in a Parr high-pressure bomb, under 1000 psi of H_2 for 2 h. Concentration in vacuo afforded the crude furanone **27**, which was purified by chromatography on a column of silica gel (230–400 mesh, 20 g, 20-mm o.d., Et_2O–hexanes–EtOAc (40:40:20), 10-mL fractions) using the flash technique to give 0.104 g (82%) of **27** as a white solid. Recrystallization from hexanes–EtOAc provided **27** as white needles. Mp: 93.0–93.5 °C. ^{1}H-NMR: (C_6D_6) δ = 4.47 (d, J = 6.4 Hz, 1), 4.39 (d, J = 6.4 Hz, 1), 4.41 (m, 1), 4.14 (dd, J = 9.5, 2.0 Hz, 1), 3.80 (m, 2), 3.35 (m, 2), 3.12 (m, 2), 3.00 (m, 1), 2.99 (s, 3), 2.88 (s, 3), 2.80 (m, 1), 2.60 (m, 2), 1.91 (dd, J = 12.1, 8.0 Hz, 1), 1.70 (m, 2), 1.44 (dd, J = 12.1, 2.7 Hz, 1), 1.05 (br m, 1), 0.94 (d, J = 7.3 Hz, 3), 0.88 (s, 3), 0.86 (s, 9), 0.11 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 175.1, 128.6, 94.4, 84.7, 80.2, 79.5, 79.2, 72.1, 68.3, 58.5, 56.0, 52.0, 50.0, 42.7, 38.1, 35.3, 34.9, 25.9, 20.5, 19.7, 18.0, 4.96. IR: (nujol) 3530, 2857, 1764, 1466, 1365, 1259, 1223, 1203, 1138, 1099, 1076, 1063, 1055, 1032, 1025, 975, 920, 833, 774 cm^{-1}. EI/MS: (70 eV) m/z 445 (M^+ – 57, 0.5), 427 (3), 339 (65), 307 (39), 247 (10), 221 (10), 195 (9), 159 (7), 145 (27), 133 (13), 107 (10), 89 (84), 75 (30), 59 (base). Anal. Calcd for $C_{25}H_{46}O_8Si$: C, 59.73; H, 9.22. Found: C, 59.47; H, 9.33.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]furan ((±)-28). To a solution of LDA (1.5 M in cyclohexane, 1.8 mL, 2.7 mmol) in anhydrous THF (6 mL), cooled in a dry ice–iPrOH bath, was added a solution of **27** (0.308 g, 0.613 mmol) in anhydrous THF (4 mL) over 5 min. The mixture was allowed to stir for 45 min at –78 °C; then bone dry CO_2 was bubbled into the solution for a period of 50 min. After the addition of CO_2 was complete, the solution was allowed to slowly warm to –20 °C; then the reaction was quenched with water (10 mL) and diluted with Et_2O (50 mL), and the pH of the aqueous phase was carefully adjusted to pH 3 with 2% aqueous HCl. The organic phase was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic phases were washed with brine (0.1 L) and dried ($MgSO_4$). Concentration in vacuo afforded the crude α-carboxyfuranone, which was immediately submitted to the α-methylenation protocol. To a solution of the crude acid in CH_3CN (12 mL) was added Eschenmoser's salt ((*N*,*N*-dimethylmethyleneammonium iodide) 0.227 g, 1.226 mmol). The dark mixture was warmed under reflux for 3 h and then was cooled to room temperature, diluted with CH_2Cl_2 (0.1 L), and cast into 4% aqueous HCl (50 mL). The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (0.1 L) and brine (0.1 L) and dried ($MgSO_4$). Concentration in vacuo afforded the crude α-methylene lactone as a sticky,

yellow solid. The crude material was purified by chromatography on a column of silica gel (230–400 mesh, 50 g, 40-mm o.d., Et_2O–hexanes (70:30), 25-mL fractions) using the flash technique to give 0.263 g (83%) of the target α-methylene lactone **28** as a white solid. Recrystallization from hexanes–CH_2Cl_2 provided **28** as white, feathery, needles. Mp: 102–104 °C. ^{1}H-NMR: (C_6D_6) δ = 6.44 (br s, 1), 6.33 (br s, 1), 4.50 (d, J = 6.4 Hz, 1), 4.41 (m, 1), 4.39 (d, J = 6.4 Hz, 1), 4.15 (d, J = 8.9 Hz, 1), 3.86 (br d, J = 4.7 Hz, 1), 3.79 (s, 1), 3.25–3.40 (3), 3.05–3.20 (3), 3.00 (m, 1), 2.99 (s, 3), 2.87 (s, 3), 1.92 (dd, J = 20.1, 7.8 Hz, 1), 1.65–1.75 (2), 1.43 (dd, J = 15.2, 2.7 Hz, 1), 0.92 (d, J = 7.3 Hz, 3), 0.88 (s, 3), 0.85 (s, 9), 0.12 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ 169.9, 137.7, 124.4, 94.1, 84.7, 79.3, 77.7, 77.6, 76.8, 71.5, 68.1, 58.9, 56.4, 51.4, 50.0, 45.7, 37.4, 34.4, 25.6, 20.4, 19.3, 17.7, −4.9, −5.5. IR: (nujol) 3575, 2817, 1754, 1389, 1267, 1148, 1138, 1106, 1062, 1050, 1033, 1021, 1008, 838, 781 cm^{-1}. EI/MS: (70 eV) *m/z* 457 (M^+ − 57, 5), 438 (4), 351 (66), 319 (38), 291 (3), 259 (5), 233 (2), 183 (6), 143 (21), 133 (7), 89 (72), 73 (23), 59 (base). Anal. Calcd for $C_{26}H_{46}O_8Si$: C, 60.67; H, 9.01. Found: C, 60.39; H, 9.08.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((±)-29). To a solution of α-methylene lactone **28** (0.175 g, 0.34 mmol) in xylenes (2 mL) was added in order Et_3N (0.172 g, 1.70 mmol), DMAP (0.041 g, 0.34 mmol), and 3-methyl-2-butenoic anhydride (0.31 g, 1.7 mmol). The mixture was warmed under reflux for 48 h and then was cooled to room temperature, diluted with CH_2Cl_2 (50 mL), and cast into 4% aqueous HCl (25 mL). The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (75 mL) and dried (Na_2SO_4). Concentration in vacuo afforded crude **29** as a pale yellow, viscous oil. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30-mm o.d., EtOAc–hexanes (40:60), 10-mL fractions) using the flash technique to give 0.148 g (92%) of **29** as a clear, colorless, very viscous oil. ^{1}H-NMR: (C_6D_6) δ = 6.35 (d, J = 11.5 Hz, 1), 6.25 (br s, 1), 5.69 (br s, 1), 5.45 (br s, 1), 4.81 (d, J = 6.8 Hz, 1), 4.73 (d, J = 6.8 Hz, 1), 3.99 (dd, J = 8.8, 2.2 Hz, 1), 3.90 (d, J = 2.2 Hz, 1), 3.80 (m, 2), 3.60 (d, J = 4.8 Hz, 1), 3.37 (t, J = 4.8 Hz, 2), 3.08 (s, 3), 2.95–3.05 (2), 2.95 (s, 3), 2.02 (s, 3), 1.50–1.80 (3), 1.42 (s, 3), 1.40 (m, 1), 1.00 (s, 9), 0.95 (d, J = 7.3 Hz, 3), 0.84 (s, 3), 0.26 (s, 3), 0.10 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 168.7, 165.5, 157.9, 137.6, 123.4, 115.8, 95.8, 85.9, 79.4, 76.6, 74.8, 72.3, 67.7, 58.7, 56.1, 51.2, 50.4, 42.7, 38.1, 35.7, 26.9, 26.0, 20.5, 20.1, 19.6, 18.3, −4.9. IR: (neat) 2949, 2928, 2885, 2858, 1769, 1722, 1649, 1472, 1451, 1391, 1260, 1222, 1151, 1139, 1047, 1006, 874, 778 cm^{-1}. EI/MS: (70 eV) *m/z* 597 (M^+, 1), 521 (1), 497 (1), 391 (1), 351 (2), 319 (2), 289 (1), 259 (3), 227 (2), 199 (2), 83 (base). Anal. Calcd for $C_{31}H_{51}O_9Si$: C, 62.49; H, 8.63. Found: C, 62.45; H, 8.60.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-hydroxy-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((±)-30). To a solution of **29** (0.423 g, 0.71 mmol) in dry CH_2Cl_2 (1.5 mL) was added finely ground anhydrous $ZnBr_2$ (0.80 g, 3.54 mmol). The mixture was allowed to stir for 1 h at room temperature and then was cast into CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$). Concentration in vacuo afforded the crude alcohol **30** as a pale yellow, viscous oil. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 50 g, 40-mm o.d., EtOAc–hexanes (50:50), 20-mL fractions) using the flash technique to give 0.32 g (89%) of the target alcohol **30** as a white solid. Recrystallization from hexanes–CH_2Cl_2 afforded **30** as fine white needles. Mp: 92–93 °C. ^{1}H-NMR: δ = 6.07 (d, J = 2.8 Hz, 1), 5.94 (d, J = 11.6 Hz, 1), 5.61 (m, 1), 5.48 (d, J = 2.8 Hz, 1), 4.61 (dd, J = 9.0, 2.0 Hz, 1), 3.93 (d, J = 2.0 Hz, 1), 3.85 (br d, J = 3.2 Hz, 1), 3.65 (m, 1), 3.35 (m, 1), 3.17 (s, 3), 2.75 (br s, 1), 2.20 (m, 1), 2.05 (d, J = 1.0 Hz, 3), 1.80–2.05 (2), 1.81 (d, J = 1.1 Hz, 3), 1.57 (dd, J = 15.4, 2.2 Hz, 1), 1.02 (d, J = 7.0 Hz, 3), 0.89 (s, 3), 0.79 (s, 9), 0.00 (s, 6). ^{13}C-NMR: δ = 169.2, 164.3, 159.7, 136.1, 124.9, 114.4, 85.4, 80.3, 78.3, 65.7, 56.7, 51.2, 49.8, 42.8, 37.5, 36.4, 27.3, 25.7, 20.5, 20.3, 19.1, 17.9, 15.1, −4.85, −5.33. IR: (nujol) 3580, 3533, 2808, 1742, 1717, 1651, 1146, 1071, 1004, 977, 957, 778 cm^{-1}. EI/MS: (70 eV) *m/z* 508 (M^+, 0.2), 451 (1), 351 (14), 319 (10), 83 (base). Exact mass for $C_{27}H_{44}O_7Si + H^+$: calcd, 509.2934; found, 509.2934.

(3aα,4α,4aβ,7α,7aα,8α,9β,9aα)-(±)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-7-methoxy-3-methylene-2,5-dioxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((±)-31). To a solution of 5α-alcohol **30** (0.310 g, 0.61 mmol) in dry CH_2Cl_2 (6.1 mL) was added NaOAc (0.5 g, 6.10 mmol) followed by the addition of PCC (0.305 g, 1.83 mmol) in four portions over 1 h. The mixture was allowed to stir at room temperature for 18 h and then was diluted with CH_2Cl_2 (15 mL) and filtered through Celite. The filter cake was rinsed with CH_2Cl_2 (25 mL), and the combined filtrates were concentrated in vacuo to give crude **31** as a sticky reddish solid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 20 g, 20-mm o.d., Et_2O–hexanes (30:70), 10-mL fractions) using the flash technique to give 0.25 g (81%) of **31** as a white solid. Recrystallization from hexanes–CH_2Cl_2 afforded the desired alcohol **31** as fine white prisms. Mp: 182–183 °C. ^{1}H-NMR: δ = 6.33 (d, J = 2.5 Hz, 1), 6.05 (br d, J = 2.5 Hz, 1), 5.56 (m, 1), 5.26 (d, J = 1.8 Hz, 1), 4.66 (dd, J = 8.1, 1.8 Hz, 1), 3.55–3.80 (2), 3.47 (dd, J = 8.3, 2.3 Hz, 1), 3.29 (s, 3), 2.95 (dd, J = 19.4, 7.8 Hz, 1), 2.35 (m, 1), 2.25 (dd, J = 9.0, 8.1 Hz, 1), 2.14 (d, J = 1.1 Hz, 3), 2.06 (dd, J = 19.4, 6.5 Hz, 1), 1.86 (d, J = 1.2 Hz, 3), 1.12 (d, J = 6.8 Hz, 3), 0.85 (s, 9), 0.81 (s, 3), 0.04 (s, 3), 0.00 (s, 3). ^{13}C-NMR: δ = 212.4, 169.7, 164.9, 159.4, 137.1, 124.9, 83.5, 77.8, 57.1, 56.5, 49.5, 44.5, 42.1, 33.8, 27.5, 25.8, 25.7, 20.4, 18.1, 16.8, 15.6, −4.5, −4.8. IR: (nujol) 3523, 3020, 3002, 2856, 1768, 1751, 1713, 1651, 1474, 1363, 1345, 1275, 1253, 1227, 1150, 1073, 1008, 993, 947, 866, 827, 820, 781 cm^{-1}. FAB/MS: *m/z* 507 (M + H^+, 1.0), 483 (2.4), 449 (1.1), 407 (19), 83 (base). Exact mass for $C_{27}H_{42}O_7Si$: calcd, 507.2778; found, 507.2745.

(3aα,4α,4aβ,7aα,8α,9β,9aα)-(±)-2,3,3a,4,4a,5,7a,8,9,9a-Decahydro-9-hydroxy-4a,8-dimethyl-3-methylene-2,5-dioxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((±)-2) (fastigilin C). To a solution of **31** (30.7 mg, 0.0605 mmol) in anhydrous Et_2O (2 mL) was added Amberlyst-15 (20 mg). The mixture was warmed under reflux for 3 h and then cooled to room temperature. The Amberlyst-15 was removed by filtration, the resin was washed with Et_2O (8 × 15 mL), and the combined filtrates were concentrated in vacuo to give crude (±)-**2** (fastigilin C) as a white solid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 20 g, 20-mm o.d., Et_2O–hexanes (50:50), 10-mL fractions) using the flash technique to give 0.0196 g (96%) of (±)-**2** (fastigilin C) as a white solid. Recrystallization from hexanes–EtOAc afforded (±)-**2** (fastigilin C) as fine, white, feathery, needles. Mp: 167–168 °C. ^{1}H-NMR: δ = 7.65 (dd, J = 6.4, 1.7 Hz, 1), 6.42 (d, J = 2.6 Hz, 1), 6.23 (d, J = 2.6 Hz, 1), 6.01 (dd, J = 6.4, 3.2 Hz, 1), 5.45 (m, 1), 5.20 (br s, 1), 4.92 (dd, J = 8.1, 2.6 Hz, 1), 3.60 (dm, J = 8.45 Hz, 1), 3.50 (tm, J = 7.72 Hz, 1), 2.17 (m, 1), 2.10 (d, J = 4.8 Hz, 1), 2.08 (d, J = 1.2 Hz, 3), 1.80 (d, J = 1.3 Hz, 3), 1.31 (d, J = 6.7 Hz, 3), 0.89 (s, 3). The identity of (±)-**2** (fastigilin C) was secured upon comparison of spectral data measured for (±)-**2** with data acquired from authentic samples of (−)-**2** supplied by Professors Werner Herz and George Pettit.

(*S*)-(−)-4-Hydroxy-2-methyl-2-cyclopentenone ((*S*)-(−)-32). A. To (±)-4-hydroxy-2-methyl-2-cyclopentenone ((±)-**32**) (64.0 g, 0.57 mol)[19] in ether (0.3 L) was added β,β,β-trifluoroethylbutyrate (97.1 g, 0.57 mol)[41] followed by porcine pancreatic lipase (PPL) (64 g). The mixture was allowed to stir at room temperature, and the progress of the reaction was monitored by ^{1}H-NMR analysis of aliquots. After the mixture was stirred for 2 days, analysis of the mixture indicated that it consisted of ca. 49% alcohol and 51% butyrate. The enzyme was then removed by filtration through a pad of Celite, the filter cake was rinsed with ether (0.25 L), and the combined filtrates were concentrated in vacuo to give the crude mixture as a pale yellow liquid. The crude material was purified by chromatography on a column of silica gel (230–400 mesh, 500 g, 70-mm o.d., Et_2O–hexanes (50:50), 250-mL fractions) using the flash technique to afford 45.84 g (44%) of the butyrate (*R*)-**33** and 27.49 g (43%) of partially resolved (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone (*S*)-(−)-**32**. The enantiomeric excess of the alcohol was determined to be 68% ee by conversion of an aliquot to the corresponding MTPA ester, prepared from (*S*)-methoxy(trifluoromethyl)phenylacetic acid,[39] and integration of one of the 5-H resonances. ^{1}H-NMR: δ = 2.36 (dd, J = 18.81, 1.94 Hz, 0.84), 2.25 (dd, J = 18.79, 1.94 Hz, 0.16).

B. The butyrate (*R*)-**33** prepared above (45.84 g, 0.248 mol) was dissolved in MeOH (85 mL), and the mixture was cooled in an ice–water bath. The resulting clear solution was treated, over 1 h, with a ca. 0.5 M solution of guanidine in MeOH (0.2 L, prepared from guanidine carbonate and NaOMe in MeOH as described by Wong).[37] The mixture was allowed to stir (ice–water) until TLC analysis indicated disappearance of the starting butyrate (ca. 1.5 h); then the mixture was treated with glacial acetic acid until neutral (pH 7). The mixture was concentrated in vacuo, and the residue was purified by chromatography on a column of silica gel (230–400 mesh, 350 g, 70-mm o.d., Et_2O–hexanes (50:50), 250-mL fractions) using the flash technique to afford 21.95 g (78%) of partially resolved (*R*)-4-hydroxy-2-methyl-2-cyclopentenone. The enantiomeric excess of the alcohol was determined to be 46% ee by conversion of an aliquot to the corresponding MTPA ester, prepared from (*S*)-methoxy(trifluoromethyl)phenylacetic acid,[39] and integration of one of the 5-H resonances. ^{1}H-NMR: δ = 2.35 (dd, J = 18.80, 1.94 Hz,

0.27), 2.26 (dd, J = 18.81, 1.93 Hz, 0.73).

C. The partially resolved (*R*)-alcohol (21.95 g, 0.196 mol, prepared from the butyrate (*R*)-**33** as outlined above) was dissolved in dry THF (0.4 L) and cooled in an ice–water bath. To this solution was added triphenylphosphine (56.5 g, 0.215 mol) and anhydrous formic acid (9.91 g, 0.215 mol, 8.2 mL) followed by the addition of DEAD (37.5 g, 0.215 mol, 34 mL) in THF (0.1 L) over 1 h.[37] The mixture was allowed to warm to room temperature over 18 h and then was concentrated in vacuo to give a clear oil. The oil was dissolved with *tert*-butyl methyl ether (0.1 L), and the resulting solution was added to hexanes (0.4 L) and cooled in an ice–water bath, over ca. 0.5 h. The solution and precipitate were allowed to stir for 0.5 h; then the precipitate was removed by filtration through a pad of Celite. The filter cake was rinsed with *tert*-butyl methyl ether (0.1 L), and the combined filtrates were concentrated in vacuo to furnish a clear, slightly viscous liquid. The crude (*S*)-formate was dissolved in MeOH (0.3 L), and the solution was treated with neutral alumina (200 g). The suspension was allowed to stir for 5 h at room temperature, at which time TLC indicated complete formate cleavage.[37] The alumina was then removed by filtration, and the solvent was removed in vacuo, yielding the crude (*S*)-4-hydroxy-2-methyl-2-cyclopentenone ((*S*)-(−)-**32**) as a clear liquid. The crude alcohol was purified by chromatography on a column of silica gel (230–400 mesh, 350 g, 70-mm o.d., Et_2O–hexanes (40:60), 100-mL fractions) using the flash technique to afford 14.93 g (68%) of partially resolved (*S*)-4-hydroxy-2-methyl-2-cyclopentenone ((*S*)-(−)-**32**). The enantiomeric excess of the alcohol was determined to be 46% ee by conversion of an aliquot to the corresponding MTPA ester, prepared from (*S*)-methoxy(trifluoromethyl)phenylacetic acid,[39] and integration of one of the 5-H resonances. ^{1}H-NMR: δ = 2.35 (dd, J = 18.80, 1.94 Hz, 0.73), 2.26 (dd, J = 18.81, 1.93 Hz, 0.27).

D. The batches of alcohols (*S*)-(−)-**32**, prepared in steps A and C above, were combined to afford material of ca. 60% ee. A portion of this partially resolved (*S*)-4-hydroxy-2-methyl-2-cyclopentenone (42.00 g, 0.378 mol) was dissolved in Et_2O (0.25 L) and treated with β,β,β-trifluoroethyl butyrate (43.1 g, 0.25 mol)[41] followed by porcine pancreatic lipase (PPL) (42 g). The mixture was allowed to stir at room temperature, and the progress of the reaction was monitored by ^{1}H-NMR analysis of aliquots. After the mixture was stirred for 4 days, analysis of it indicated that the reaction consisted of ca. 59% alcohol and 41% butyrate. The enzyme was then removed by filtration through a pad of Celite, the filter cake was rinsed with ether (0.25 L), and the combined filtrates were concentrated in vacuo to give the crude mixture as a pale yellow liquid. The crude material was purified by chromatography on a column of silica gel (230–400 mesh, 400 g, 70-mm o.d., Et_2O–hexanes (50:50), 200-mL fractions) using the flash technique to afford 24.79 g (36%) of the butyrate (*R*)-**33** and 21.84 g (52%) of the known[35] resolved (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone ((*S*)-(−)-**32**). ^{1}H-NMR: δ = 7.15 (m, 1), 4.87 (br s, 1), 2.85 (br s, 1), 2.73 (dd, J = 18.54, 5.97 Hz, 1), 2.23 (dd, J = 18.54, 1.90 Hz, 1), 1.72 (t, J = 1.5 Hz, 3). ^{13}C-NMR: δ 207.0, 157.2, 143.5, 68.3, 44.45, 9.90. IR: (neat) 3400 (br), 1709, 1640, 1445, 1404, 1327, 1253, 1081, 1049, 606 cm^{-1}. EI/MS: (70 eV) m/z 112 (M^+, 99.9), 97 (21.1), 84 (base), 69 (87.9). $[\alpha]^{25}_D$ −30.08° (c = 1.21, $CHCl_3$). The optical purity of the isolated (*S*)-(−)-4-hydroxy-2-methyl-2-cyclopentenone was determined to be ≥98% ee by conversion of an aliquot to the corresponding MTPA ester, prepared from (*S*)-methoxy(trifluoromethyl)phenylacetic acid,[39] and integration of one of the 5-H resonances. ^{1}H-NMR: δ = 7.43 (m, 2), 7.35 (m, 3), 7.15 (m, 1), 5.91 (m, 1), 3.48 (q, J = 1.10 Hz, 3), 2.83 (dd, J = 18.82, 6.32 Hz, 1), 2.24 (dd, J = 18.82, 2.03 Hz, 1), 1.78 (t, J = 1.60 Hz, 3). ^{19}F-NMR: δ = −75.8143 (s).

(*S*)-(+)-4-Methoxy-2-methyl-2-cyclopentenone ((*S*)-(+)-12). (*S*)-(−)-4-Hydroxy-2-methyl-2-cyclopentenone (11.86 g, 0.106 mol) was dissolved in dry CH_2Cl_2 (25 mL), and the solution was cooled in an ice–water bath. To this cooled solution was added CH_3I (75.12 g, 0.53 mol, 33 mL) over 15 min followed by the addition of Ag_2O (27 g, 0.116 mol). The mixture was allowed to stir for 2 h in the ice–water bath and then was warmed to room temperature, and stirring was continued to 18 h. Silver oxide and silver salts were removed by filtration through a pad of Celite, the filter cake was rinsed with ether (0.25 L) and CH_2Cl_2, and the combined filtrates were concentrated in vacuo to furnish the crude product (*S*)-(+)-**12** as a clear, pale yellow liquid. The crude methyl ether was purified by chromatography on a column of silica gel (230–400 mesh, 350 g, 70-mm o.d., Et_2O–hexanes (20:80), 100-mL fractions) using the flash technique to afford 11.88 g (89%) of (*S*)-(+)-**12** as a clear colorless liquid. ^{1}H-NMR: δ = 7.07 (m, 1), 4.29 (m, 1), 3.85 (br s, 1), 3.24 (s, 3), 2.52 (dd, J = 18.33, 5.81 Hz, 1), 2.14 (dd, J = 18.33, 2.02 Hz, 1), 1.64 (t, J = 1.53 Hz, 3). ^{13}C-NMR: δ = 205.75, 154.17, 144.03, 56.70, 41.07, 9.79. IR: (neat) 2927, 2825, 1717, 1447, 1327, 1195, 1100, 1074, 991 cm^{-1}. EI/MS: (70 eV) m/z 126 (M^+, 24.7), 111 (18.5), 98 (base), 83 (47.2), 67 (72.9). $[\alpha]^{25}_D$ +27.20° (c = 0.75, $CHCl_3$). Exact mass for $C_7H_{10}O_2$: calcd, 126.0681; found, 126.0677.

[1α(*S*),2β(*S*),5α]-(+)-2-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-furanylmethyl]-α,2-dimethyl-5-methoxy-3-oxocyclopentaneethanethioic Acid *S*-(1,1-Dimethylethyl) Ester ((+)-13). According to the procedure described for the preparation of (±)-**13**, trityl hexachloroantimonate (2.47 g, 4.28 mmol) in CH_2Cl_2 (0.3 L), (*S*)-(+)-4-methoxy-2-methyl-2-cyclopentenone **12** (5.40 g, 42.80 mmol), and the TBDMS enol ether of *tert*-butyl thiopropionate (14.84 g, 56.93 mmol) were reacted at −20 °C; then the mixture was cooled to −78 °C, and a solution of freshly distilled 3-furaldehyde (8.23 g, 85.61 mmol) in CH_2Cl_2 (0.1 L) was added over 30 min to give 16.65 g (34.67 mmol, 81%) of (+)-**13** as a viscous, clear, pale yellow oil. $[\alpha]^{25}_D$ +164.86° (c = 1.11, $CHCl_3$). Anal. Calcd for $C_{25}H_{42}O_5SiS$: C, 62.20; H, 8.77. Found: C, 62.11; H, 8.80.

(4α,4aβ,7α,7aα,8α)-(+)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4a,6,7,7a,8-hexahydro-4a,8-dimethyl-7-methoxyazuleno[6,5-*b*]furan-5,9-dione ((+)-14). According to the procedure described for the preparation of (±)-**14**, a solution of yellow mercury oxide (22.41 g, 103.5 mmol) in distilled (CaH_2) CH_3CN (0.6 L), cooled in an ice–water bath, was treated with trifluoromethanesulfonic anhydride (17.4 mL, 103.5 mmol) over 30 min. This mixture was titrated to a clear solution by a further dropwise addition of trifluoromethanesulfonic anhydride and was allowed to stir at 0 °C for 1 h. *N*,*N*-dimethylaniline (13.11 mL, 103.5 mmol) was then added over 5 min, and the resulting yellow solution was stirred at 0 °C for 0.5 h. The reaction vessel was cooled to −20 °C (dry ice–CCl_4), and a solution of (+)-**13** (16.65 g, 34.48 mmol) in CH_3CN (90 mL) was added over 30 min to afford 10.55 g (26.89 mmol, 78%) of (+)-**14** as a white crystalline solid. Mp: 113–114 °C. FAB/MS: m/z 393 (M^+ + 1, 29.9), 377 (3.5), 335 (12.9), 303 (3.3), 277 (2.8), 261 (5.6), 229 (3.7), 217 (4.2), 201 (5.5), 159 (14.1), 73 (base). $[\alpha]^{25}_D$ +248.82° (c = 1.82, $CHCl_3$). Exact mass for $C_{21}H_{32}O_5Si + H^+$: calcd, 393.2097; found, 393.2105.

(4α,4aβ,7α,7aα,8α,9β)-(+)-4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-4a,6,7,7a,8,9-hexahydro-4a,8-dimethyl-9-hydroxy-7-methoxy-azuleno[6,5-*b*]furan-5(4*H*)-one ((+)-15). According to the procedure described for the preparation of (±)-**15**, a solution of (+)-**14** (10.55 g, 26.87 mmol) in $CeCl_3 \cdot 7H_2O$–CH_3OH (335 mL, 0.4 M), cooled in a −78 °C bath, was treated with a solution of $NaBH_4$ (1.00 g, 26.87 mmol) dissolved in $CeCl_3 \cdot 7H_2O$–CH_3OH (10 mL, 0.4 M) at −78 °C to give 10.18 g (25.80 mmol, 96%) of (+)-**15** as a clear, viscous oil. FAB/MS: m/z 393 (M^+ − H, 3.6), 361 (2.1), 337 (3.5), 319 (6.0), 287 (2.5), 263 (5.0), 245 (15.7), 213 (9.1), 203 (10.1), 185 (8.8), 159 (8.2), 145 (8.0), 85 (8.7), 73 (base). $[\alpha]^{25}_D$ +162.00° (c = 0.50, $CHCl_3$). Exact mass for $C_{21}H_{34}O_5Si$ − H: calcd, 393.2097; found, 393.2085. The enantiomeric excess of the alcohol (+)-**15** was determined to be ≥98% ee by conversion of an aliquot of (+)-**15** to the corresponding MTPA ester, prepared from (*S*)-methoxy(trifluoromethyl)phenylacetic acid,[39] and integration of the 9-H resonance. ^{1}H-NMR: (C_6D_6) δ = 6.09 (d, J = 10.44 Hz, 1).

(4α,4aβ,7α,7aα,8α,9β)-(+)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4a,6,7,7a,8,9-hexahydro-4a,8-dimethyl-7-methoxyazuleno[6,5-*b*]furan-5(4*H*)-one ((+)-17). According to the procedure described for the preparation of (±)-**17**, a solution of (+)-**15** (10.60 g, 26.87 mmol) in dry DMF (90 mL) was treated in order with imidazole (2.75 g, 40.31 mmol) and *tert*-butyldimethylsilyl chloride (5.06 g, 33.59 mmol) to afford 13.53 g (26.6 mmol, 99%) of (+)-**17** as a white solid. Recrystallization from Et_2O–hexanes gave (+)-**17** as fine white needles. Mp: 129–130 °C. EI/MS: (70 eV) m/z 453 (12), 452 (33), 451 (93), 320 (24), 319 (base), 287 (18), 203 (13), 175 (23), 75 (29), 73 (65). $[\alpha]^{25}_D$ +154.51° (c = 0.965, $CHCl_3$). Anal. Calcd for $C_{27}H_{48}O_5Si_2$: C, 63.73; H, 9.51. Found: C, 63.63; H, 9.72.

(4α,4aβ,5α,7α,7aα,8α,9β)-(+)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4a,6,7,7a,8-hexahydro-4a,8-dimethyl-5-hydroxy-7-methoxy-azuleno[6,5-*b*]furan ((+)-18). According to the procedure described for the preparation of (±)-**18**, to a solution of (+)-**17** (15.15 g, 29.78 mmol) in dry Et_2O (0.3 L), cooled in a dry ice–iPrOH bath, was added DIBAL-H (1 M in toluene, 45 mL, 44.67 mmol) over 60 min to give 14.67 g (28.59 mmol, 96%) of (+)-**18** as a white solid. Recrystallization from Et_2O–hexanes gave (+)-**18** as fine white needles. Mp: 146–147 °C. FAB/MS: m/z 510 (M^+, 0.73), 379 (7.8), 347 (5.5), 289 (9.5), 247 (11.0), 231 (4.1), 215 (10.1), 197 (8.6), 115 (13.0), 75 (27.0), 73 (base). $[\alpha]^{25}_D$ +154.51° (c = 0.965, $CHCl_3$). Exact mass for $C_{27}H_{50}O_5Si_2$: calcd, 510.3197; found, 510.3192.

(4α,4aβ,5α,7α,7aα,8α,9β)-(+)-4,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((+)-19). According to the procedure described for the preparation of (±)-**19**, a solution of (+)-**18** (14.67 g, 28.71 mmol) in dry CH_2Cl_2 (60 mL) was treated with iPr_2NEt (25 mL, 18.56 g, 0.143 mol) followed by MEM-Cl (9.8 mL, 10.73 g, 86.14 mmol) to afford 13.67 g (27.85 mmol, 79%) of (+)-**19** as a clear, colorless, viscous oil. EI/MS: (70 eV) m/z 598 (M^+, 17), 541 (29), 231 (21), 199 (19), 197 (26), 163 (29), 133 (93), 89 (base). $[\alpha]^{25}_D$ +76.07°

(c = 5.73, $CHCl_3$). Anal. Calcd for $C_{31}H_{58}O_7Si_2$: C, 62.16; H, 9.76. Found: C, 61.94; H, 9.88.

(4α,4aβ,5α,7α,7aα,8α,9β)-(−)-4,9-Bis(hydroxy)-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((−)-22). According to the procedure described for the preparation of (±)-**22**, to a solution of (+)-**19** (13.67 g, 22.82 mmol) in anhydrous THF (50 mL), cooled in an ice–water bath, was added tetrabutylammonium fluoride (1.0 M in THF, 114 mL, 114 mmol) over 45 min to furnish 7.65 g (91%) of the target diol (−)-**22** as a viscous, clear, colorless oil. EI/MS: (70 eV) m/z 370 (M^+, 3), 294 (10), 281 (11), 264 (7), 248 (7), 235 (16), 214 (20), 203 (12), 185 (18), 159 (17), 145 (15), 126 (25), 125 (24), 124 (24), 108 (27), 107 (68), 89 (31), 59 (base). $[\alpha]^{25}_D$ −48.27° (c = 0.895, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16. Found: C, 61.38; H, 7.94.

(4α,4aβ,5α,7α,7aα,8α,9β)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((−)-23). According to the procedure described for the preparation of (±)-**23**, a solution of diol (−)-**22** (7.65 g, 20.65 mmol) in dry DMF (70 mL) was treated with imidazole (2.40 g, 35.27 mmol) followed by the addition of a solution of TBDMS-Cl (3.91 g, 25.94 mmol) in DMF (15 mL) over 15 min to afford 9.65 g (19.82 mmol, 96%) of (−)-**23** as a clear, colorless, viscous oil. FAB/MS: m/z 483 (M^+ − 1, 4.6), 427 (4.6), 395 (2.5), 231 (57.2), 199 (25.4), 89 (37.4), 73 (base). $[\alpha]^{25}_D$ −26.32° (c = 1.045, $CHCl_3$). Exact mass for $C_{25}H_{44}O_7Si$ − H: calcd, 483.2778; found, 483.2783.

(4α,4aβ,5α,7α,7aα,8α,9β)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-4-(1-ethoxyethoxy)-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan ((−)-24). According to the procedure described for the preparation of (±)-**24**, to a solution of (−)-**23** (1.62 g, 3.33 mmol) in anhydrous Et_2O (3.3 mL) was added ethyl vinyl ether (6.4 mL, 4.81 g, 66.68 mmol) followed by the addition of a few crystals of p-TsOH to provide 1.84 g (3.30 mmol, 99%) of a 55:45 mixture of ethoxyethyl ether diastereomers **24** as a waxy, white semisolid. The mixture was immediately employed in the next reaction. Anal. Calcd for $C_{29}H_{52}O_8Si$: C, 62.56; H, 9.41. Found: C, 62.40; H, 9.37.

(4α,4aβ,5α,7α,7aα,8α,9β)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-2-(trimethylsilyl)azuleno[6,5-*b*]furan ((−)-25). According to the procedure described for the preparation of (±)-**25**, a solution of ethoxyethyl ether **24** (1.40 g, 2.51 mmol) in anhydrous THF (45 mL), cooled in a dry ice–CCl_4 bath, was treated with nBuLi (1.6 mol in hexanes, 7.85 mL, 12.55 mmol) over 5 min. The mixture was stirred for 30 min at −20 °C, during which time the mixture became red-orange; then freshly distilled TMS-Cl (1.60 mL, 1.36 g, 12.55 mmol) was added until the red-orange color was discharged. The mixture was stirred for 0.5 h at −20 °C, then warmed to 0 °C, stirred for 0.5 h, and finally warmed to room temperature over 0.5 h. The colorless solution was diluted with Et_2O (75 mL), and the reaction was quenched with pH 7 buffer (50 mL). The mixture was allowed to stir for 0.5 h, the organic phase was separated, the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic phases were stirred with a few crystals of p-TsOH and 3 drops of water until TLC analysis suggested that the ethoxyethyl ether had been completely cleaved (24 h) to provide 1.23 g (2.21 mmol, 87%) of (−)-**25** as a clear colorless oil. FAB/MS: m/z 555 (M^+ − H, 1.64), 499 (1.83), 303 (22.9), 89 (13.4), 73 (base). $[\alpha]^{25}_D$ −13.86° (c = 2.49, $CHCl_3$). Exact mass for $C_{28}H_{52}O_7Si_2$ − H: calcd, 555.3173; found, 555.3145.

(4α,4aβ,5α,7α,7aα,8α,9β)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-4,4a,5,6,7,7a,8,9-octahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan-2(3*H*)-one ((−)-26). According to the procedure described for the preparation of (±)-**26**, a solution of (−)-**25** (0.76 g, 1.35 mmol) in CH_2Cl_2 (7 mL), cooled in an ice–water bath, was treated with NaOAc (0.89 g, 10.85 mmol) followed by the addition of CH_3CO_3H (32%, 1.7 mL, 8.14 mmol) over 5 min to give 0.62 g (1.235 mmol, 91%) of **26** as a clear, colorless, viscous oil. The unstable butenolide resisted elemental analysis and was immediately utilized in the next reaction. ^{1}H-NMR: (C_6D_6) δ = 4.29 (d, J = 6.9 Hz, 1), 4.18 (d, J = 6.9 Hz, 1), 4.06 (d, J = 8.1 Hz, 1), 3.79 (s, 1), 3.70 (d, J = 1.5 Hz, 1), 3.40 (t, J = 6.2 Hz, 1), 3.35 (m, 1), 3.25 (m, 1), 3.20 (m, 1), 3.15 (m, 2), 2.95 (s, 3), 2.93 (m, 1), 2.90 (s, 3), 2.50 (m, 2), 1.90 (m, 2), 1.40 (m, 1), 1.15 (d, J = 6.8 Hz, 3), 0.95 (s, 9), 0.51 (s, 3), 0.21 (s, 3), 0.00 (s, 3). ^{13}C-NMR: (C_6D_6) δ = 173.9, 151.9, 112.6, 94.5, 86.2, 82.7, 74.5, 72.1, 71.8, 67.8, 58.6, 56.2, 48.8, 46.7, 39.3, 37.3, 36.1, 26.3, 21.3, 18.7, 18.1, −3.8, −4.7. IR: (neat) 2951, 2931, 2887, 2858, 2822, 1803, 1775, 1473, 1463, 1388, 1253, 1208, 1181, 1166, 1132, 1109, 1071, 1059, 1033, 1010, 972, 960, 936, 893, 779 cm^{-1}.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxyazuleno[6,5-*b*]furan-2-(3*H*)-one ((−)-27). According to the procedure described for the preparation of (±)-**27**, a 25-mL test tube was charged with **26** (1.002 g, 2.00 mmol) and dry CH_2Cl_2 (6 mL). The solution was placed under argon, and [Rh(NBD)(DIPHOS-4)]BF_4 (0.142 g) in CH_2Cl_2 (2 mL) was added. The mixture was hydrogenated in a Parr high-pressure bomb, under 1000 psi of H_2 for 2 h to give 0.893 g (89%) of (−)-**27** as a clear, colorless, viscous oil. FAB/MS: m/z 503 (M^+ + 1, 0.84), 427 (7.6), 89 (53.4), 73 (95), 59 (base). $[\alpha]^{25}_D$ −30.73° (c = 0.96, $CHCl_3$). Anal. Calcd for $C_{25}H_{46}O_8Si$: C, 59.73; H, 9.22. Found: C, 59.48; H, 9.06.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-hydroxy-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]furan ((−)-28). According to the procedure described for the preparation of (±)-**28**, a solution of LDA (1.5 M in cyclohexane, 7.0 mL, 10.48 mmol) in anhydrous THF (30 mL), cooled in a dry ice–iPrOH bath, was added to a solution of (−)-**27** (1.20 g, 2.38 mmol) in anhydrous THF (10 mL) over 10 min. The mixture was allowed to stir for 45 min at −78 °C; then bone dry CO_2 was bubbled into the solution for a period of 50 min to give the crude α-carboxyfuranone, which was immediately submitted to the α-methylenation protocol. To a solution of the crude acid in CH_3CN (24 mL) was added Eschenmoser's salt (*N,N*-dimethylmethyleneammonium iodide) 0.882 g, 4.76 mmol). The dark mixture was warmed under reflux for 3 h to yield 0.889 g (77%) of (−)-**28** as a viscous, clear, colorless oil. EI/MS: (70 eV) m/z 457 (M^+ − 57, 5), 438 (4), 351 (66), 319 (38), 291 (3), 259 (5), 233 (2), 183 (6), 143 (21), 133 (7), 89 (72), 73 (23), 59 (base). $[\alpha]^{25}_D$ −22.55° (c = 0.745, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_8Si$: C, 60.67; H, 9.01. Found: C, 60.33; H, 9.07.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-[(2-methoxyethoxy)methoxy]-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]-furan-4-yl 3-Methyl-2-butenoate ((−)-29). According to the procedure described for the preparation of (±)-**29**, a solution of α-methylene lactone (−)-**28** (0.633 g, 1.23 mmol) in xylenes (10 mL) was treated in order with Et_3N (0.86 mL, 0.623 g, 6.15 mmol), DMAP (0.15 g, 1.234 mmol), and 3-methyl-2-butenoic anhydride (1.12 g, 6.15 mmol). The mixture was warmed under reflux for 48 h to give 0.643 g (88%) of (−)-**29** as a clear, colorless, very viscous oil. EI/MS: (70 eV) m/z 539 (M^+ − 57, 0.6), 351 (15.1), 319 (7.3), 165 (10.7), 83 (base). $[\alpha]^{25}_D$ −14.89° (c = 0.855, $CHCl_3$). Anal. Calcd for $C_{31}H_{51}O_9Si$: C, 62.49; H, 8.63. Found: C, 62.72; H, 8.44.

(3aα,4α,4aβ,5α,7α,7aα,8α,9β,9aα)-(−)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-5-hydroxy-7-methoxy-3-methylene-2-oxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((−)-30). According to the procedure described for the preparation of (±)-**30**, to a solution of (−)-**29** (0.643 g, 1.07 mmol) in dry CH_2Cl_2 (2.0 mL) was added finely ground anhydrous $ZnBr_2$ (1.21 g, 5.38 mmol). The mixture was allowed to stir for 3 h at room temperature to provide 0.501 g (92%) of the target alcohol (−)-**30** as a viscous, clear, colorless oil. FAB/MS: m/z 509 (M^+, 0.16), 409 (12.3), 83 (base). $[\alpha]^{25}_D$ −11.02° (c = 1.235, $CHCl_3$). Anal. Calcd for $C_{27}H_{44}O_7Si$: C, 63.75; H, 8.71. Found: C, 63.50; H, 8.84.

(3aα,4α,4aβ,7α,7aα,8α,9β,9aα)-(+)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3a,4,4a,5,6,7,7a,8,9,9a-decahydro-4a,8-dimethyl-7-methoxy-3-methylene-2,5-dioxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((+)-31). According to the procedure described for the preparation of (±)-**31**, a solution of (−)-**30** (0.60 g, 1.18 mmol) in dry CH_2Cl_2 (12 mL) was treated with NaOAc (0.97 g, 11.79 mmol) and Celite (1.25 g) followed by the addition of PCC (1.27 g, 5.90 mmol) in four portions over 1 h to give 0.52 g (87%) of (+)-**31** as a white solid. Recrystallization from hexanes–CH_2Cl_2 afforded the desired alcohol (+)-**31** as fine white needles. Mp: 168–170 °C. FAB/MS: m/z 507 (M^+ + H, 0.83), 483 (1.5), 407 (17.2), 83 (base). $[\alpha]^{25}_D$ +61.86° (c = 1.235, $CHCl_3$). Anal. Calcd for $C_{27}H_{42}O_7Si$: C, 64.00; H, 8.35. Found: C, 63.82; H, 8.63.

(3aα,4α,4aβ,7aα,8α,9β,9aα)-(−)-2,3,3a,4,4a,5,7a,8,9,9a-Decahydro-9-hydroxy-4a,8-dimethyl-3-methylene-2,5-dioxoazuleno[6,5-*b*]furan-4-yl 3-Methyl-2-butenoate ((−)-fastigilin C). According to the procedure described for the preparation of (±)-fastigilin C ((±)-**2**), a solution of (+)-**31** (0.27 g, 0.531 mmol) in anhydrous Et_2O (5 mL) containing 1 drop of MeOH–H_2O (50:50) was treated with Amberlyst-15 (0.3 g). The mixture was warmed in a 50 °C oil bath for 3 h and then cooled to room temperature to give 0.162 g (85%) of (−)-**2** (fastigilin C) as a white solid). Recrystallization from hexanes–EtOAc afforded (−)-**2** (fastigilin C) as fine, white, feathery, needles. Mp: 197–199 °C (lit.[4a] 197–199 °C). ^{1}H-NMR: δ = 7.65 (dd, J = 6.4, 1.7 Hz, 1), 6 42 (d, J = 2.6 Hz, 1), 6.23 (d, J = 2.6 Hz, 1), 6.01 (dd, J = 6.4, 3.2 Hz, 1), 5.45 (m, 1), 5.20 (br s, 1), 4.92 (dd, J = 8.1, 2.6 Hz, 1), 3.60 (dm, J = 8.45 Hz, 1), 3.50 (tm, J = 7.72 Hz, 1), 2.17 (m, 1), 2.10 (d, J = 4.8 Hz, 1), 2.08 (d, J = 1.2 Hz, 3), 1.80 (d, J = 1.3 Hz, 3), 1.31 (d, J = 6.7 Hz, 3), 0.89

(s, 3). $[\alpha]^{25}_D$ −90.6° (c = 0.41, $CHCl_3$) (lit.[4a] $[\alpha]^{25}_D$ −85.8° (c = 1.11, $CHCl_3$)).

The identity of (−)-**2** (fastigilin C) was secured upon comparison of the optical rotation, melting point, mixed melting point, TLC, and ^{1}H-NMR of synthetic (−)-**2** with authentic samples of (−)-**2** supplied by Professors Werner Herz and George Pettit.

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Supplementary Material Available: Tables of atomic numbering schemes, crystallographic data, atomic positional parameters and thermal parameters, bond lengths and angles, and selected torsion angles for **18** and the acetate of (±)-**2** (9 pages); a listing of structure factors for **18** and the acetate of (±)-**2** (36 pages). Ordering information is given on any current masthead page.