27 H), 6.77–6.96 (m, Ar, 10 H). Anal. Calcd for $C_{34}H_{37}ClN_2S_3$: C, 67.46; H, 6.16; N, 4.63. Found: C, 67.41; H, 5.81; N, 4.58.

***N,N,N'*-Tris[(2,3,5,6-tetramethylphenyl)thio]-4-chlorobenzenecarboximidamide (2t)**: colorless needles (from hexane and then benzene-ethanol); mp 135–136 °C dec; yield 25%; NMR (CCl_4) δ 2.07, 2.19, and 2.49 (s, *syn*- and *anti*-, and *o*- and *m*-CH_3, 36 H) and 6.87–6.96 (m, Ar, 7 H). Anal. Calcd for $C_{37}H_{43}ClN_2S_3$: C, 68.65; H, 6.69; N, 4.33. Found: C, 68.36; H, 6.40; N, 4.39.

Although the reaction of unsubstituted or 4-chlorobenzenecarboximidamides with 2-methyl-2-propanesulfenyl chloride was carried out in the same manner as above, no precursors corresponding to **1** or **2** could isolated from the reaction mixtures. However, the benzene solutions of the concentrates of the reaction mixtures afforded a strong ESR signal due to **4** or **5**.

Isolation of Dimers 6. Precursor **1** (0.10 g) was completely dissolved in 10 mL of benzene with stirring. To this stirred solution was added 1 g of anhydrous K_2CO_3 and 1–1.5 g of PbO_2. After the mixture was stirred for 1 min, another 1–1.5 g of PbO_2 was added to the mixture and it was stirred for an additional 1–2 min. After filtration, the benzene was removed by freeze-drying to leave a dark green or purplish brown crystalline powder. To this powder was added 10 mL of hexane and the unressolved crystalline powder was collected and dried in vacuum [one spot on an alumina TLC (Merck art 1064), eluant benzene–hexane (1/4)]. These dimers thus obtained contained ~32 wt % of radical **3** as shown by ESR measurement.

Dimer 6f: dark green prisms; mp 104–106 °C dec; yield 45%; UV–vis (benzene) λ_{max} 371, 472 (sh) nm. Anal. Calcd for $(C_{19}H_{11}Cl_4N_2S_2)_2$: C, 48.23; H, 2.34; N, 5.92. Found: C, 47.89; H, 2.66; N, 5.80.

Dimer 6j: dark green powdery crystals; mp 112–114 °C dec; yield 54%; UV–vis (benzene) λ_{max} 357, 385 (sh), 474 (sh) nm. Anal. Calcd for $(C_{20}H_{13}Cl_4N_2S_2)_2$: C, 49.30; H, 2.69; N, 5.75. Found: C, 49.43; H, 2.92; N, 5.78.

Dimer 6l: dark purplish brown powdery crystals; mp 109.5–111 °C dec; yield 53%; UV–vis (benzene) λ_{max} 358, 385 (sh), 457 nm. Anal. Calcd for $(C_{20}H_{13}Cl_4N_4OS_2)_2$: C, 47.73; H, 2.60; N, 5.57. Found: C, 47.29; H, 2.67; N, 5.47.

Dimer 6q: dark green powdery crystals; mp 120.5–122 °C dec; yield 44%; UV–vis (benzene) λ_{max} 373, 475 (sh) nm. Anal. Calcd for $(C_{19}H_{10}Cl_5N_2S_2)_2$: C, 44.95; H, 1.99; N, 5.52. Found: C, 45.12; H, 2.26; N, 5.52.

ESR Measurements. Radicals **3** were generated in benzene or hexane by the following methods: (a) oxidation of **1** with inorganic oxidizing agents such as PbO_2 and Ag_2O in the presence of K_2CO_3 and (b) photolysis of **2** with a high-pressure mercury lamp.

ESR spectra were recorded with a JEOL JES-ME-3X spectrometer equipped with an X-band microwave unit and 100-kHz field modulation. Hyperfine splitting constants and *g* values were determined by comparison with those (a_N 13.09, *g* 2.0057) for Fremy's salt in K_2CO_3 aqueous solution.

Measurements of Equilibrium Constants. Dimer **6** (5–10 mg) was dissolved in 25 mL of benzene or toluene. Then, 0.40 mL of the solution was placed in an ESR cell and its integrated ESR signal was recorded with the ESR instrument equipped with a JEOL JES-ID-2 integrator. The area under the integrated ESR signal was determined by its weight. Calibration curves were obtained as follows: 0.40 mL of a benzene or toluene solution of 1,3,5-triphenylverdazyl[6] was placed in the same cell as used for the dimer solutions and its integrated ESR signal was recorded with the same instrument settings as above. The calibration curves were drawn with the verdazyl solutions of three different concentrations (0.20–1.00 mM). Equilibrium constants (*K*) were measured at four different temperatures between 6 and 35 °C when benzene was used as solvent and at five different temperatures between −5 and 35 °C when toluene was used as solvent. The temperatures of the ESR cavity were measured with a copper–constantan thermocouple.

Registry No. **1d**, 95674-83-2; **1e**, 95674-84-3; **1f**, 95674-85-4; **1g**, 95674-86-5; **1j**, 95674-87-6; **1l**, 95674-88-7; **1p**, 95674-89-8; **1q**, 95674-90-1; **1r**, 95674-91-2; **1u**, 95674-92-3; **2a**, 95674-93-4; **2b**, 95674-94-5; **2c**, 95674-95-6; **2d**, 95674-96-7; **2e**, 95674-97-8; **2f**, 95674-98-9; **2h**, 95674-99-0; **2i**, 95675-00-6; **2j**, 95675-01-7; **2k**, 95675-02-8; **2l**, 95675-03-9; **2m**, 95675-04-0; **2n**, 95675-05-1; **2o**, 95675-06-2; **2s**, 95675-07-3; **2t**, 95675-08-4; **3a**, 86602-13-3; **3b**, 86602-14-4; **3c**, 86602-15-5; **3d**, 86602-16-6; **3e**, 86602-17-7; **3f**, 86602-18-8; **3g**, 86602-19-9; **3h**, 95675-09-5; **3i**, 95675-10-8; **3j**, 95675-11-9; **3k**, 95675-12-0; **3l**, 95675-13-1; **3m**, 95675-14-2; **3n**, 95675-15-3; **3o**, 95675-16-4; **3p**, 95675-17-5; **3q**, 95675-18-6; **3r**, 95675-19-7; **3s**, 95675-20-0; **3t**, 95675-21-1; **3u**, 95675-22-2; **4**, 95675-23-3; **5**, 95675-24-4; **6f**, 95675-25-5; **6j**, 95675-26-6; **6l**, 95675-27-7; **6q**, 95675-28-8.

Total Synthesis of Pseudoguaianolides IV: A Stereoselective Approach to Balduilin

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9-Acetoxycamphor oxime undergoes Beckman fragmentation to provide an intermediate (**13**) from which bicyclo[5.3.0]decane synthons for balduilin are constructed. The vital C-6 β-hydroxy group is introduced in a highly stereoselective step (**14** → **15**) with remote asymmetric induction resulting from lithium ion chelation during 2-lithio-1,3-dithiane addition.

The pseudoguaianolides are among the most biogenetically advanced and structurally complex members of the sesquiterpene lactones.[1] The abundance of closely placed functional groups, along with up to seven chiral centers on the flexible seven-membered ring portion of the trans-fused bicyclo[5.3.0]decane framework have made these compounds attractive synthetic targets.[2] The challenge of total synthesis is additionally enhanced by the interesting biological activity displayed by many pseudo-

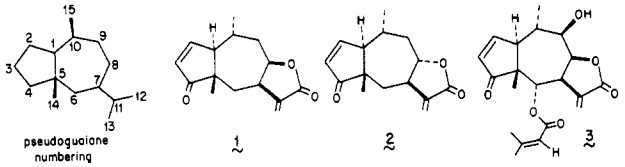
(1) (a) Fischer, N. H.; Olivier, E. J.; Fischer, H. D. "Fortschritte der Chemie Organischer Naturstoffe"; Zechmeister, L., Ed.; Springer-Verlag: Vienna, Austria, 1979; Vol. 38, pp 223–256. (b) Romo, J.; Romo de Vivar, A., ref 1a 1967; Vol. 25, pp 90–130.

(2) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F. "Total Synthesis of Natural Products", Ap Simon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 347–377.

0022-3263/85/1950-1632$01.50/0

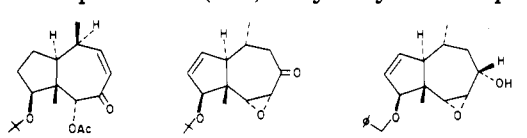
guaianolides.[3] The most cytotoxic compounds[3] have yet to be synthesized, in part because of their architectural complexity and also their sensitivity to nucleophilic destruction, via conjugate addition to electrophilic double bonds, and acid- or base-catalyzed epimerization at the ring fusion.

Our own research program on pseudoguaianolides has already provided first-time total syntheses of the helenanolides (αC-10 methyl) aromatin (**1**) and aromaticin (**2**).[4]



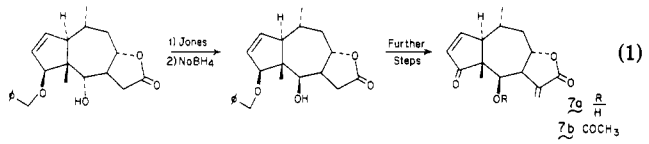
1 2 3

An ultimate goal is the total synthesis of fastigilin C (**3**), one of the most bioactive compounds, with three electrophilic double bonds for trapping sulfhydryl enzymes. The C-6 substituent in **3** and many other helenolides with 7,8-fused α-methylene γ-lactone rings is α-oriented.[1] Stereoselective introduction of such groups into appropriate intermediates has been achieved by our group, using lead tetraacetate oxidation[5] (→ **4**), and by Grieco's group,[6] via alkaline epoxidation (→ **5**) or hydroxyl-assisted peracid



4 5 6

oxidation (→ **6**). On the other hand, mexicanin I (**7a**) and linifolin A (**7b**) have C-6 substituents with the less common β-configuration. In their synthesis of **7a** and **7b**, Grieco et al.[7] generated a β-hydroxy group at that position from the α-epimer, by oxidation-reduction, as depicted in eq 1.

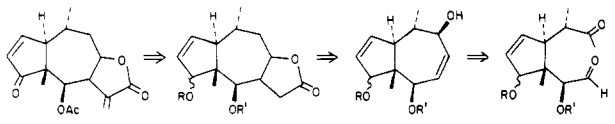


(1)

7a R = H
7b R = COCH3

Although that indirect sequence was successful,[7] there is the possibility that unwanted C-7 epimerization could occur at the C-6 ketone stage in similar cases.

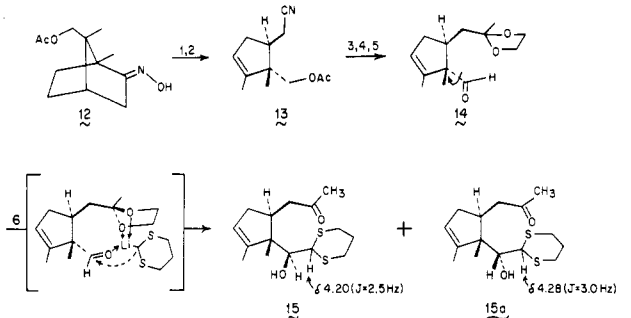
Several years ago, we became interested in balduilin[8] (**8**), whose retrosynthesis could be streamlined if a *direct* C-6 β-functionalization method were available (e.g., → **11**).



8 9 10 11

C-6 desoxy analogues of **10** (via aldol cyclization) and **9**

Scheme I[a]



12 13 14 15 15a

[a] Reagents: (1) *p*-TsCl, C_5H_5N; (2) *p*-TSA, C_6H_6; (3) 6 equiv of CH_3Li; (4) $(CH_2OH)_2$, *p*-TSA, C_6H_6, Δ ($-H_2O$); (5) PCC, NaOAc, CH_2Cl_2, (6) 2-lithio-1,3-dithiane, THF–hexane (or with 5 equiv of HMPA in addition, see Discussion section).

(using the Eschenmoser–Claisen rearrangement for 1,3-chirality transfer) had already been prepared by Ziegler in his aromatin synthesis.[9] Moreover, in planning a stereocontrolled entry to **11** (or a synthetic equivalent) we intend ultimately to use a readily available chiral building block, specifically (–)-camphor.[10] The preliminary studies reported herein were carried out with less expensive (±)-camphor and focus upon the C-6 functionalization problem.

Beckmann fragmentation[10a] of (±)-9-acetoxycamphor oxime (**12**) afforded the nitrile acetate **13**,[11] whose functionalities were suitably differentiated for selective elaboration into a trans-fused bicyclo[5.3.0]decane (Scheme I). Excess methyllithium cleaved the ester function in **13** and converted the nitrile into a methyl ketone.[11] The latter was blocked as an ethylene ketal,[11] which provided not only carbonyl protection but also basic sites for chelation control of remote asymmetric induction.[12] Subsequently, oxidation of the primary alcohol group provided aldehyde **14**,[11] the precursor for establishment of the C-6 stereocenter by addition of a formyl anion equivalent (→ **11**). Scheme I summarizes the above steps and also depicts the anticipated steric course for the addition of 2-lithio-1,3-dithiane to **14** (in brackets). The remote ketal function in **14** was expected to promote *cyclic* lithium chelation,[12a] thereby restricting rotation of the aldehyde group and presumably improving its diastereofacial bias. On this basis and from studying models, we expected that irreversible nucleophilic attack should occur predominantly from the α-side of the *rigid* lithium chelate (→ **15**). Indeed, after dithiane addition was carried out at –60 °C in THF–hexane and the product mixture was subjected to acidic deketalization, an 11:1 mixture of diastereomers **15** and **15a** was isolated. These were clearly discernible in the NMR spectra by dithiane proton doublets at δ 4.20 and 4.28, respectively (see structures), whose integration provided the above product ratio. Careful chromatography provided epimerically pure **15**[11] for use in elaborating the seven-membered ring by intramolecular aldol methodology. For the

(3) (a) Pettit, G. R.; Cragg, G. M. "Biosynthesis Products of Cancer Chemotherapy"; Plenum Press: New York, 1978; Vol. 2. (b) Cassady, J. M.; Douros, J. D. "Anticancer Agents Based on Natural Products Models"; Academic Press: New York, 1978; pp 204–221.

(4) (a) Lansbury, P. T.; Vacca, J. P. *Tetrahedron* **1982**, *38*, 2797. (b) Lansbury, P. T.; Hangauer, D. G. *Tetrahedron Suppl. 1* **1981**, *37*, 371. (c) Lansbury, P. T.; Serelis, A. K.; Hengeveld, J. E.; Hangauer, D. G. *Tetrahedron* **1980**, *36*, 2701.

(5) Lansbury, P. T.; Vacca, J. P. *Tetrahedron Lett.* **1982**, *23*, 2623.

(6) Grieco, P. A.; Ohfune, Y.; Majetich, G. F.; Wang, C. J. *J. Am. Chem. Soc.* **1982**, *104*, *4233 and references cited.*

(7) Grieco, P. A.; Ohfune, Y.; Majetich, G. F. *J. Org. Chem.* **1983**, *48*, 360 and references cited therein.

(8) Herz, W.; Mitra, R. B.; Jayaraman, P. *J. Am. Chem. Soc.* **1959**, *81*, 6061.

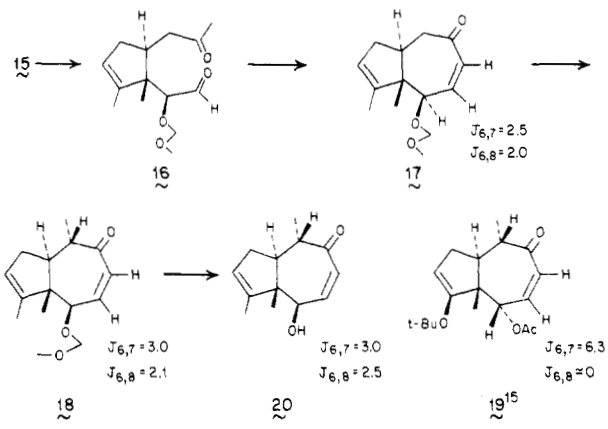
(9) Ziegler, F. E.; Fang, J. *J. Org. Chem.* **1981**, *46*, 825.

(10) (a) Stevens, R. V.; Gaeta, F. C. A.; Lawrence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713. (b) Hutchison, J. H.; Money, T.; Piper, S. E. *J. Chem. Soc., Chem. Commun.* **1984**, 455, and references cited.

(11) This compound was characterized by an appropriate combination of ^{1}H NMR, infrared, ultraviolet, and mass spectrometry.

(12) For chelation control of 1,2- and 1,3-asymmetric induction in organometallic addition to aldehydes and ketones, see: (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118 and references cited. (c) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.

Scheme II



moment, the correctness of our configurational assignments was postponed, while we sought to verify our hypothesis that cyclic chelation was largely responsible for promoting disastereoselective formation of **15**. According, we repeated the above reaction in the presence of 5 equiv of hexamethylphosphoramide (HMPA), in order to prevent cyclic lithium chelation. From this experiment **15** and **15a** were isolated in a 1:1 ratio, presumably a consequence of α-attack upon the *freely rotating* aldehyde group. Moreover, a control experiment in which the isolated, pure ketal precursor to **15** was resubjected to alkoxide formation (*n*-BuLi in THF–hexane *with* HMPA), followed by reisolation, hydrolysis, and recovery of pure **15** showed that equilibration to epimeric alkoxy–dithiane adducts was *not* occurring in the latter experiment.

Construction of the bicyclo[5.3.0]decane framework present in **8** began with protection of the C-6 hydroxyl group of **15** as a methoxymethyl ether,[11] after several other groups were found inappropriate. Methyl iodide was used to cleave the dithiane group, thus generating keto aldehyde **16**.[11] After much experimentation, we found that aldolization to **17** was best achievable by brief exposure to potassium *tert*-butoxide (→ ketol), followed by mesylation and DBU-induced elimination. Ketone **17**[11] (and **18**) showed NMR spectral data of great value for assigning stereochemistry at C-6 (see Scheme II and following discussion). Introduction of the required αC-10 methyl group was achieved by stereoselective alkylation of the kinetic dienolate from **17** with methyl iodide from the less-hindered side. The resulting **18**[11] was not epimerizable, as would have been expected with a C-10 β-methyl ketone.[13] We now address the stereochemical question raised when **14** was converted mainly to **15**, by examining the *dihedral angle-dependent* vicinal and allylic coupling constants in the proton NMR spectra of ketones **17** and **18**. Vicinal couplings tend to *decrease* in magnitude with dihedral angle going from 0° to 90°, while allylic couplings tend to *increase*.[14] The C_6–C_7 vicinal proton coupling constants and C_6–C_8 allylic proton coupling constants, listed with structures **17** and **18** in Scheme II, are "small" and "large", respectively. In contrast, a C-6 epimeric ketone (**19**) from a related study[15] shows "large" vicinal and "small" allylic proton coupling constants, consistent *only* with a chair conformation of the seven-membered ring in which hydrogens at carbon 6, 7, and 8 are approximately coplanar

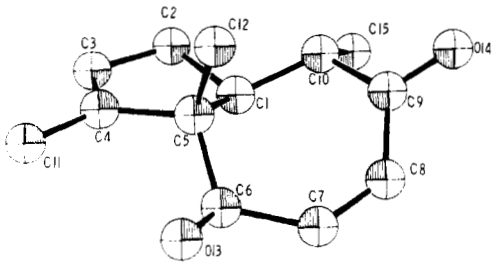
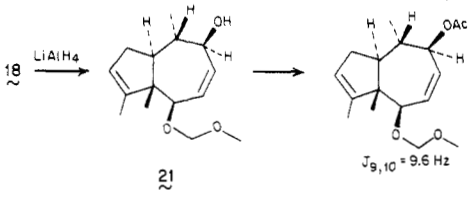


Figure 1. Perspective drawing of **20** derived from the X-ray coordinates with hydrogens omitted for clarity.

Scheme III



(cf. Dreiding models). Thus, it appeared that **17** and **18** have the relative configurations depicted, a hypothesis in accord with predictions for diastereoselective carbanion addition to **14** (see above). However, the finite possibility remained that **17** was α-oxygenated at C-6 and preferred a *boat* conformation for the seven-membered ring; were that the case, $J_{6,7}$ and $J_{6,8}$ might be expected to fall within the actual observed values. In order to obtain unambiguous confirmation of our configurational assignments in **17** and **18** (and subsequent synthetic intermediates!), a single-crystal X-ray analysis of the crystalline γ-hydroxy-α,β-unsaturated ketone **20** was performed (ketones **17** and **18** were oils).

Suitable crystals of **20** for X-ray diffraction studies formed as modest plates from an ether/hexane mixture, mp 102.5–103 °C. The space group symmetry was $P2_1/n$ with a = 6.762 (1) Å, b = 24.323 (4) Å, c = 7.115 (2) Å, and β = 91.21 (2)° for Z = 4. Of the 1642 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1328 were observed ($I \gtrsim 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[16] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.039. Table I–III (supplementary material) contain the full fractional coordinates, temperature parameters, bond distances, and bond angles. The only close intermolecular contact is a hydrogen bond defined by O13(H13)–O14 of total length 2.817 Å. The H6–C6–C7–H7 dihedral angle is −72° (Figure 1).

The fact that the seven-membered ring in hydroxy ketone **20** (and presumably **18** as well) has a boat conformation explains the desirable stereoselectivity that resulted when C-9 reduction was undertaken, enroute to appropriate balduilin intermediates[17] (cf. **9**, **10**). For example, lithium aluminum hydride reduction of **18** afforded mainly allylic alcohol **21**[11] (>10:1 isomer ratio) whose C-9 configuration (and the derived acetate[11]) was verified by ^{1}H NMR, showing $J_{9,10}$ = 8.7 Hz for trans hydrogens at C-9

(13) Lansbury, P. T.; Nickson, T. E. *Tetrahedron Lett.* **1982**, *23*, 2627.
(14) Jackman, L.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: New York, 1969; Part 4.
(15) Nickson, T. E. Ph.D. Dissertation, State University of New York at Buffalo, 1982.
(16) The following library of crystallographic programs was used: MULTAN80, University of York, York, England (1980; Structure Determination Package Plus V1.1, Enraf-Nonius Corporation, Delft, Holland (1983); ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN (1970).
(17) These exploratory results are discussed in the Ph.D. Dissertation of D. J. Mazur, SUNY at Buffalo, 1984.

and C-10 (Scheme III). "Peripheral" hydride attack at C-9 of the boat cycloheptenone (cf. Figure 1) is clearly preferable to perpendicular approach from the opposite side of the carbonyl group, where the C-5 methyl group provides severe steric hindrance. If **18** were in the chair conformation, the opposite result might have been expected (see Dreiding models). With allylic alcohol **21** in hand, stereocontrolled lactone construction (via 1,3-chirality transfer) commencing with Eschenmoser–Claisen rearrangement[9] is possible. Exploratory studies in our laboratories indicate that such a strategy is viable for future efforts directed toward baldiulin.[17]

Experimental Section

General Considerations. All reactions were conducted under nitrogen, using purified solvents and reagents. "Standard workup" refers to partitioning reaction mixtures between organic and aqueous phases, washing the former with dilute HCl and/or saturated $NaHCO_3$ as required and then saturated NaCl solution, and drying over $MgSO_4$ or Na_2SO_4; solvent removal was achieved by using rotary evaporation at a water aspirator followed by vacuum pumping. TLC analyses were performed on precoated plates of 250-μm GHLF silica gel (Analtech, Inc.), using 3:1 hexane–ethyl acetate solvent; column chromatography utilized 40–140-mexh silica gel (Baker) or Silicar CC-7 (Mallinckrodt).

Proton NMR spectra were obtained on a Varian EM-390 spectrometer, using $CDCl_3$ with internal Me_4Si. Infrared spectra were measured on a Perkin-Elmer 727B spectrometer, using neat liquids or $CHCl_3$ solutions of solids. Ultraviolet spectra in ethanol were recorded on a Perkin-Elmer 202 UV–vis spectrometer. Mass spectral analyses (EI, CI, and high resolution) were performed by the Cornell University mass spectral facility.

Preparation of Acetoxy Nitrile 13. A solution of 100 mL of dry pyridine, 100 mL of absolute ethanol, 27.5 g (0.131 mol) of (±)-9-acetoxycamphor,[18] and 27.5 g (0.395 mol, 3 equiv) of hydroxylamine hydrochloride was prepared in a 500-mL round-bottomed flask fitted with a reflux condenser. The solution was refluxed for 4 h on the steam bath. Standard workup with ether (600 mL) provided 28.3 g (0.125 mol, 96%) of oxime **12** as a clear oil which crystallized into white needles upon standing, mp 86.2–90.0 °C: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 9.06 (br, 1 H), 4.16 (d, J = 10.5, 1 H), 3.95 (d, J = 10.5, 1 H), (J = 10.5 Hz, 2 H), 2.08 (s, 3 H), 1.08 (s, 3 H); IR (neat) 3275, 2950, 1735, 1250, 1035, 930 cm^{-1}.

A solution of 36.0 g (0.159 mol) of (±)-9-acetoxycamphor oxime (**12**) in 60 mL of dry pyridine was added to a 500-mL round-bottom flask. A drying tube was attached, and the solution was cooled to 5 °C in an ice bath. Thirty-eight grams (0.199 mol, 1.25 equiv) of *p*-toluenesulfonyl chloride was then added to the vigorously stirred solution. The dark reaction mixture was kept at 5 °C for 26 h, quenched with water, and subjected to standard workup with ether (600 mL). A light yellow oil (23.98 g, 0.115 mol, 73%) was isolated, consisting of a 1.0 to 1.7 ratio of exocyclic and endocyclic double bond isomers, respectively. The ratio was obtained by comparison of the integrated vinylic proton resonances of each isomer in the NMR spectrum.

The crude reaction product was then dissolved in 250 mL of benzene in a 500-mL round-bottomed flask equipped with condenser and Dean–Stark trap. Crystalline *p*-toluenesulfonic acid monohydrate (1.61 g, 8.4 mmol, 0.07 equiv) was added, and the solution was refluxed for 45 h. Standard workup with ether (300 mL) provided a dark oil which was fractionally distilled (bp 93 °C, 0.2 mm) to yield 20.98 g (0.101 mol, 87.5%) of endocyclic isomer **13** as a clear oil: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.35 (m, 1 H), 4.02 (d, J = 12, 1 H), 3.85 (d, J = 12, 1 H), 2.42 (br d, 2 H), 2.6 (s, 3 H), 1.60 (m, 3 H), 0.92 (s, 3 H); IR (neat 3040, 2950, 2240, 1740, 1650, 1375, 1240, 1040 cm^{-1}.

Preparation of Ketal Aldehyde 14. A dry 2-L, three-necked, round-bottomed flask was fitted with a septum, flushed with nitrogen, and cooled to 0 °C in an ice bath. A double-ended needle apparatus was used to force 370 mL of a 1.3 M methyllithium–ether solution (0.481 mol, 5.8 equiv) via nitrogen pressure into the flask. Seventeen grams (0.082 mol) of nitrile acetate **13** was dissolved in 30 mL of anhydrous ether and 200 mL of hexane was added dropwise, with stirring, over a 30-min period. After being stirred for 1 h at 0 °C, the reaction mixture was slowly quenched with 150 mL of saturated ammonium chloride solution. Water (50 mL) was then added and the mixture was allowed to stir for 30 min, during which the white precipitate dissolved. Standard workup with ether (300 mL) provided 15.1 g (0.082 mol, 97%) of hydroxy ketone as a clear oil, shown free of starting material by the absence of the nitrile stretch at 2240 cm^{-1} in the infrared spectrum: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.35 (m, 1 H), 3.52 (d, J = 11.5, 1 H), 3.32 (d, J = 11.5, 1 H), 2.53 (br d, 2 H), 2.13 (s, 3 H), 1.61 (m, 3 H), 0.75 (s, 3 H); IR (neat) 3400, 3040, 2950, 1710, 1655, 1440, 1375, 1050, 805 cm^{-1}.

To a 1-L, round-bottomed flask, fitted with condenser and Dean–Stark trap, was added 15.1 g (0.082 mol) of the above ketone dissolved in 40 mL of dry benzene, 120 mL (133.2 g, 2.15 mol, 25 equiv) of ethylene glycol, and 0.78 g (4.1 mmol, 0.05 equiv) of *p*-toluenesulfonic acid monohydrate, under nitrogen. The solution was heated to benzene reflux and vigorously stirred for 23 h. The reaction mixture was quenched into 100 mL of saturated sodium bicarbonate solution, and after standard workup with ether (500 mL), yielded 18.26 g (0.081 mol, 98%) of ketal as a light yellow oil, shown free of starting material by the absence of any carbonyl absorption in the infrared spectrum.

A solution of 12.34 g (0.054 mol) of the above ketal in 150 mL of dry methylene chloride was added to a 500-mL round-bottomed flask, under nitrogen. Vigorous stirring was initiated after the addition of 1.56 g (0.019 mol, 0.35 equiv) of anhydrous sodium acetate as a buffer. Pyridinium chlorochromate (26.5 g, 0.123 mol, 2.25 equiv) was then slowly added, and stirring was continued for 3.25 h. The dark viscous liquid was rapidly eluted through a Florisil column (50 g) with 400 mL of methylene chloride (CH_2Cl_2) and 500 mL of ether. The solution was then concentrated on the rotary evaporator and subjected to standard workup with ether (100 mL). This provided 10.25 g (0.046 mol, 84%) of aldehyde **14** as a clear oil, shown free of starting material by the absence of any hydroxyl stretch in the infrared spectrum: ^{1}H NMR ($CDCl_3$, 90 MHz) δ ..35 (s, 1 H), 5.51 (m, 1 H), 3.87 (br s, 4 H), 1.56 (m, 3 H), 1.19 (s, 3 H), 1.00 (s, 3 H); IR (neat) 3040, 2950, 2745, 1730, 1655, 1450, 1380, 1050, 950, 805 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3$: C, 63.96; H, 8.19. Found: C, 63.47; H, 8.53.

Preparation of Hydroxy Dithiane 15. A solution of 2-lithio-1,3-dithiane was prepared via the procedure of Corey and Seebach.[19] A 1-L three-necked, round-bottomed flask was flame-dried and fitted with septum under an inert atmosphere. To a solution of 12.0 g (0.10 mol, 2.2 equiv) of 1,3-dithiane in 250 mL dry THF, cooled to −40 °C, was slowly added 62.2 mL of a 1.47 M *n*-butyllithium–hexane solution (0.091 mol, 2.0 equiv). Anion formation was maximized by stirring for 2 h at −25 to −15 °C. The light yellow solution was then cooled to −65 °C, and 10.25 g (0.046 mmol) of aldehyde **14** dissolved in 25 mL of dry THF was rapidly added, via syringe. The reaction mixture was allowed to stir for warming to −55 °C, and then was quenced with water (50 mL). Standard workup with methylene chloride (500 mL), and drying of the organic layer with potassium carbonate in place of sodium sulfate, led to the isolation of 22.7 g of crude product, which was carried on without further purification.

Deketalization was achieved by dissolving the crude product from above in 100 mL of THF in a 500-mL round-bottomed flask. Stirring was initiated, and 25 mL of a 7% hydrochloric acid solution was added. After 2 at room temperature the acid was carefully neutralized with sodium bicarbonate. Standard workup with ether (500 mL) provided 23.6 g of a bright yellow oil. The material was then chromatographed (EtOAc/hexane) to yield 5.2 g (0.017 mol, 38% over two steps) of a light yellow oil consisting of an 11 to 1 ratio of keto dithiane adduct **15** to C-6 α-diastereomer **15a**, largely separated by chromatography, R_f (20% ethyl acetate/hexane) 0.17 for **15a**; mp 122–124 °C, 0.22 for **15** (oil). **15**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.33 (m, 1 H), *4.20* (d, J = 2.5 Hz, 1 H), 3.74 (d of d, J = 2.5 Hz, 6.0 Hz), 2.87 (br, 4 H), 2.18 (s, 3 H), 1.67 (m, 3 H), 1.03 (s, 3 H); MS (CI, CH_4), m/e 301 (M^+ +

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(19) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1975**, *40*, 231.

1), 151 (base peak). **15a**: ^{1}H NMR ($CDCl_3$, 90 mHz) δ 5.35 (m, 1 H), 4.28 (d, J = 3.0 Hz, 1 H), 3.72 (br t, J = o.0 Hz, 1 H), 2.90 (br, 4 H), 2.15 (s, 3 H), 1.67 (m, 3 H), 1.02 (s, 3 H); IR (neat) 3450, 3035, 2950, 1715, 1425, 1385, 1050, 790 cm^{-1}; MS (CI, CH_4) 301 (M^+ + 1), 151 (base peak). Anal. Calcd for $C_{15}H_{24}O_2S_2$: C, 60.00; H, 7.99. Found: for **15**, C, 59.74; H, 8.08; for **15a**, C, 59.89; H, 8.08.

Preparation of Keto Aldehyde 16. A solution of the alcohol **15** (1.95 g, 6.49 mmol) dissolved in 25 mL of dry CH_2Cl_2 was added to a 100-mL round-bottomed flask under inert atmosphere. After cooling to 5 °C in an ice bath, 2.50 mL (2.36 g, 19.5 mmol, 3.0 equiv) of *N,N*-dimethylaniline and 1.48 mL (2.27 g, 18.1 mmol, 2.8 equiv) of bromomethyl methyl ether was added to the stirred solution. The ice bath was removed and the dark green solution was allowed to stir for 16 h at room temperature. Upon standard workup with ether (100 mL), the reaction mixture provided 2.12 g (6.15 mmol, 95%) of the methoxymethyl ether as a light yellow oil: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.37 (m, 1 H), 5.10, 4.65 (two nonequivalent d, J = 7.0 Hz, 2 H), 4.31 (d, J = 1.0 Hz, 1 H), 3.65 (d, J = 1.0 Hz, 1 H), 3.45 (s, 3 H), 2.83 (br, 4 H), 2.17 (s, 3 H), 1.70 (m, 3 H), 0.99 (s, 3 H); IR (neat) 3045, 1710, 1040, 1160 cm^{-1}.

A solution of the above thioacetal (1.26 g, 3.66 mmol) in 60 mL of acetonitrile and 8 mL of water was added to a 250-mL round-bottomed flask equipped with condenser and kept under inert atmosphere. Calcium carbonate (1.1 g, 11.0 mmol, 3 equiv), followed by 5.7 mL (13.0 g, 0.091 mol, 20 equiv) of methyl iodide, was added to the vigorously stirred solution. The reaction mixture was heated at 40 °C for 31 h. After 20 h, an additional 1.2 mL (2.7 g, 0.019 mol, 5 equiv) of methyl iodide was added. When the reaction was complete, it was quenched with 5 mL of saturated sodium bicarbonate solution. Standard workup provided 0.84 g (3.30 mmol, 90%) of keto aldehyde **16** as a clear oil: R_f 0.35; ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.67 (d, J = 2.0 Hz, 1 H), 5.35 (m, 1 H), 4.64 (s, 2 H), 3.83 (d, J = 2.0 Hz, 1 H), 3.40 (s, 3 H), 2.14 (s, 3 H), 1.71 (m, 3 H), 1.02 (s, 3 H); IR (neat) 3050, 2950, 2750, 1735, 1715, 1155, 1105, 1040, 920 cm^{-1}.

Preparation of α,β-Unsaturated Ketone 17. A 250-mL round-bottomed flask containing 1.20 g (4.72 mmol) of keto aldehyde **16** was flushed with nitrogen and 38 mL of deoxygenated *tert*-butyl alcohol was added, with stirring, to dissolve the material. A solution of 0.210 g (1.88 mmol, 0.4 equiv) potassium *tert*-butoxide in 38 mL of deoxygenated *tert*-butyl alcohol was then added in one portion to the rapidly stirred solution. After 30 s, the deep orange reaction was quenched with 10 mL of saturated ammonium chloride solution. Standard workup with ether (150 mL) led to the isolation of 1.13 g (4.44 mmol, 94%) of ketol as a light yellow oil, R_f 0.25, which was carried on without further purification.

A solution of 1.13 g (4.44 mmol) of the above ketol in 30 mL of methylene chloride was prepared in a 100-mL round-bottomed flask under inert atmosphere. The flask was cooled in an ice bath and 0.98 mL (0.71 g, 7.05 mmol, 1.6 equiv) of triethylamine was added, followed by the addition of 0.43 mL (0.64 g, 5.6 mmol, 1.2 equiv) of methanesulfonyl chloride, with stirring. After 50 min at 0 °C, the orange solution was quenched into 10 mL of saturated sodium bicarbonate solution. Standard workup with a 2:1 pentane–methylene chloride mixture (90 mL) provided 1.26 g (3.8 mmol, 86%) of crude mesylate as a light yellow oil. This material was carried on without further purification.

The crude mesylate (1.31 g, 3.94 mmol) was dissolved in 30 mL of CH_2Cl_2 and 1.18 mL (1.20 g, 7.88 mmol, 2 equiv) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. After 1.25 h at room temperature, the dark solution was added to 150 mL of ether and subjected to standard workup. An orange oil was obtained which was purified by Kugelrohr distillation (105–120 °C, 0.050 mm) to yield 0.827 g (3.50 mmol, 89%) of enone **17** as a clear oil, R_f 0.50. **17**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.33 (d, of d, $J_{7,8}$ = 13.5 Hz, $J_{6,7}$ = 2.5 Hz, 1 H), 5.84 (d of d, $J_{7,8}$ = 13.5 Hz, $J_{6,7}$ = 2.5 Hz, 1 H), 5.84 (d of d, $J_{7,8}$ = 13.5 Hz, $J_{6,8}$ = 2.0 Hz, 1 H), 5.30 (m, 1 H), 4.80 (s, 2 H), 4.00 (br t, $J_{6,7}$ = 2.5 Hz, $J_{6,8}$ = 2.0 Hz, 1 H), 3.42 (s, 3 H), 2.62 (m, 2 H), 1.72 (m, 3 H), 0.99 (s, 3 H); IR (neat) 3040, 2950, 1660, 1245, 1100, 1040 cm^{-1}; UV $\lambda_{max}^{95\%EtOH}$ 233 nm, ϵ 7020.

Alkylation of Ketone 17. A 50-mL, two-necked, round-bottomed flask was flame-dried and fitted with a septum under an inert atmosphere. A solution of 0.68 mL (0.516 g, 3.2 mmol, 2.0 equiv) of hexamethyldisilazane in 8 mL of dry THF was prepared in the flask. After cooling to −65 °C, stirring was initiated and 1.7 mL of a 1.60 M *n*-butyllithium–hexane solution (2.7 mmol, 1.7 equiv) was added via syringe. After 45 min at −65 to −55 °C, the enone **17** (0.389 g, 1.64 mmol), dissolved in 2 mL of dry THF, was added dropwise to the solution at −65 °C. The bright yellow mixture was stirred for an additional 30 min and then quenched with 1.0 mL (16.0 mmol, 10 equiv of methyl iodide. The solution was allowed to warm to 0 °C over 2 h, becoming cloudy at the end. The reaction mixture was then poured into standard ammonium chloride solution (5 mL) and standard workup with ether (75 mL) was performed. In addition, the organic layer was washed several times with sodium bisulfite solution to remove iodine generated during workup. The yield of C-10-methylated enone **18** was 0.389 g (1.55 mmol, 95%), isolated as a light yellow oil, R_f 0.59. Coupling constants and proton assignments at C-6, -7, and -8 in the NMR spectrum were confirmed by decoupling experiments: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 6.32 (d of d, $J_{6,7}$ = 3.0 Hz, $J_{7,8}$ = 13.5 Hz, 1 H), 5.82 (d of d, $J_{7,8}$ = 13.5 Hz, $J_{6,8}$ = 2.1 Hz, 1 H), 5.30 (m, 1 H), 4.77 (t, J = 7.0 Hz, 2 H), 3.91 (br t, $J_{6,7}$ = 3.0 Hz, $J_{6,8}$ = 2.1 Hz, 1 H), 3.39 (nonequivalent (s, 3 H), 1.70 (m, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 0.93 (s, 3 H); IR (neat) 3040, 1660, 1445, 1270, 1145, 1095, 1040, 820, 805 cm^{-1}; UV $\lambda_{max}^{95\%EtOH}$ 229 nm; MS (high resolution) exact mass, m/e 250.1570, calcd for $C_{15}H_{22}O_3$ 250.1569.

Preparation of Allylic Alcohol 21. A solution of 0.414 g (1.65 mmol) of enone **18** in 15 mL of dry THF was added to a 50-mL round-bottomed flask under an inert atmosphere. The solution was cooled to −65 °C and 0.90 mL of a 2.0 M lithium aluminum hydride–ether solution (1.8 mmol, 1.1 equiv) was added to the rapidly stirred mixture. The reaction was quenched with 1 mL of dilute hydrochloric acid after 35 min at −65 °C. Standard workup with ether (100 mL) provided 0.394 g (1.56 mmol, 95%) of alcohol **21** as a light yellow oil, R_f 0.33. The ratio of C-9 β-alcohol **21** to the C-9 α-isomer is estimated to be between ten and twenty to one. This was calculated by comparison of the NMR peak height of the singlet for the C-7,8 protons in the chromatographically pure C-9 β-isomer to that of the reaction mixture in which the C-7,8 protons for the C-9 α-isomer are visible as a collapsed d of d, having a lower maximum peak height: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.66 (m, 2 H), 5.29 (m, 1 H), 4.68 (s, 2 H), 3.95 (br s, 1 H), 3.70 (br d, $J_{9,10}$ = 8.7 Hz, 1 H), 3.42 (s, 3 H), 1.77 (m, 3 H), 1.03 (d, J = 6.0 Hz), 0.93 (s, 3 H); IR (neat) 3400, 3040, 2950, 1655, 1450, 1380, 1140, 1110, 1045, 920, 805, 740, 670 cm^{-1}.

In the acetate prepared from **21** (excess acetic anhydride in pyridine with 4-(*N,N*-dimethylamino)pyridine) the C-9 proton had δ 4.93 (ddd) with $J_{9,10}$ = 9.6 Hz (with decoupling of vinyl protons).

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Registry No. (±)-**8**, 95840-01-0; (±)-**12**, 95764-58-2; (±)-**13**, 95764-59-3; (±)-**14**, 95764-60-6; (±)-**15**, 95764-61-7; (±)-**15** (ethylene ketal), 95764-68-4; (±)-**15** (methoxymethyl ether), 95764-69-5; (±)-**15a**, 95840-02-1; (±)-**15a** (ethylene ketal), 95840-04-3; (±)-**16**, 95764-62-8; (±)-**17**, 95764-63-9; **17** (ketol), 95764-70-8; **17** (ketol mesylate), 95764-71-9; (±)-**18**, 95764-64-0; (±)-**21**, 95764-65-1; H_2NOH·HCl, 5470-11-1; (±)-7-acetoxycamphor, 95840-03-2; (±)-*trans*-2,3-dimethyl-2-(hydroxymethyl)-3-cyclopenten-1-yl-acetone, 95764-66-2; (±)-*trans*-2-[2,3-dimethyl-2-(hydroxymethyl)-3-cyclopenten-1-yl]-2-methyl-1,3-dioxolane, 95764-67-3.

Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for **20** (3 pages). Ordering information is given on any current masthead page.