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SYNTHESIS OF (±)-14-EPIUPIAL BY MANGANESE(III) γ-LACTONE ANNULATION

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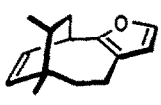
Abstract: The total synthesis of racemic 14-epiupial (3) is described. The preparation of 3 is achieved in 23 steps starting from 8. In the key step, manganese(III) acetate acts on the monocarboxylic acid derived from 17b to promote concurrent formation of the bicyclic[3.3.1]nonane and lactone rings required for the upial framework. The scope of this reaction was pursued with the epimeric MOM ethers 18b and 26. To a large extent, these processes led to decomposition, although 27 could be isolated in 9% yield. Alternative cyclization strategies were examined and found to be even less feasible.

Introduction and Background

The general expectation that the aquatic world would provide a plentiful source of new and unusual chemical structures has been met repeatedly during the explosive growth of marine natural products chemistry over the past two decades. One particular phase of this work has established that nudibranches, those conspicuously ornate, brightly colored, and soft bodied underwater animals and their sponge prey frequently enjoy a close association. So extensive is this parasitic relationship that the sponge's secondary metabolites often play an important role in the chemical defense systems of both types of organism.[2,3] The furanosesquiterpene nakafuran-8 (1) is a prototypical example. This fish antifeedant metabolite has been isolated from the nudibranch *Hypselodoris godeffroyana* and its sponge prey *Dysidea fragilis*.[2,3]



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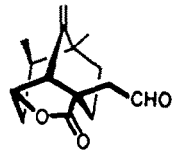


2

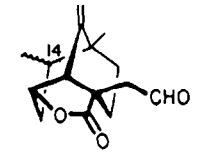
Interestingly, (+)-upial (2) has also been isolated from *Dysidea fragilis*,[4] but is not found in the associated nudibranch and displays no antifeedant properties.[5] The bicyclo-[3.3.1]nonane framework of this nonisoprenoid sesquiterpene aldehydo lactone is rarely found in nature. Scheuer and coworkers assigned the structure 2 on the basis of spectral and elemental analyses, as well as selected chemical transformations and accompanying lanthanide-induced shift studies. This formulation has recently been confirmed by Taschner and Shahripour by means of their stereocontrolled total synthesis of the (-)-enantiomer.[6] At least one additional report concerning construction of the basic carbobicyclic skeleton has made its appearance.[7]

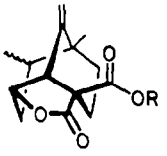
Our interest in upial stems principally from its unusual molecular topology. Whereas

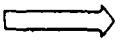
its bicyclo[3.3.1]nonane system is shared by the limonoid xylocarpin[8] and clovanediol,[9] the superimposed lactone bridge has no close precedent. Furthermore, the substance is reasonably oxygenated and is endowed with five stereochemical centers that punctuate the eight-membered ring periphery.

Results and Discussion

Retrosynthetic Strategy for Construction of the Upials. From the retrosynthetic perspective, intermediates 6, presumably available after suitable introduction of functional groups onto one or more substituted cyclohexanones, appeared ideal as precursors to upial (2) and its unnatural epimer 3. No extensive bioassay of 2 has yet been reported; the availability of both 2 and 3 for general screening purposes therefore appeared desirable. At the center of the scenario was a manganese(III) acetate oxidation of 6,[10]



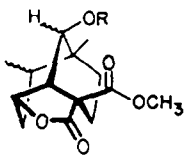


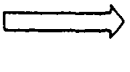


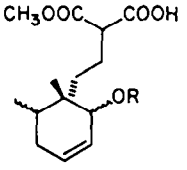
2, β-CH_3 at 14

3, α-CH_3 at 14

4







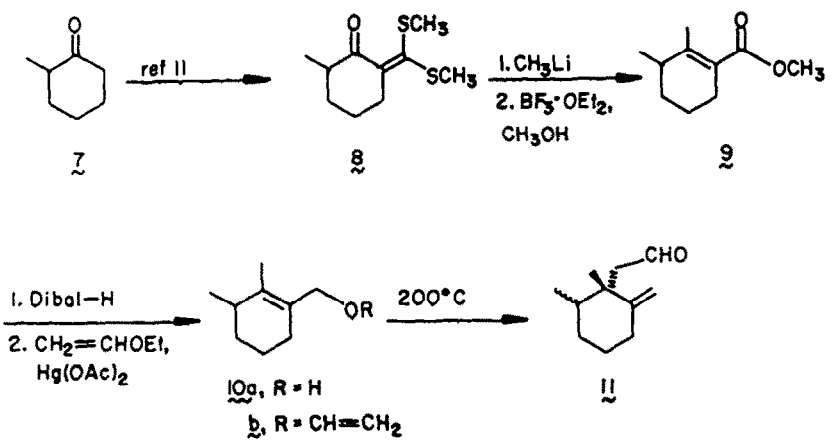
5 6

this sophisticated reaction expectedly providing the needed impetus for piecing together the bicyclo[3.3.1]nonane *and* lactone networks *simultaneously!* With arrival at 5, final introduction of functionality and crafting of the carbomethoxy groups into an acetaldehyde unit appeared straightforward, assuming, of course, that no regiochemical complications or steric problems would surface.

The protocols for arrival at 2 and 3 were to be the same. The distinguishing stereochemical feature, the configuration of the C-14 methyl group, was to offer a branching point in the scheme. Initially, the precise location of this bifurcation was not defined. Rather, we intended to take advantage of the chromatographic separability of the epimers at that point where it could be achieved with maximum ease and efficiency.

Construction of the Methylenecyclohexanes 11. Stereochemical Outcome of a Claisen Rearrangement. The acquisition of 11 began with the conversion of 2-methylcyclohexanone (7) to the conjugated ketene dithioacetal 8 (Scheme 1). Sequential in situ capture of the kinetic enolate derived from 7 with carbon disulfide and methyl iodide according to Dieter[11]

Scheme I



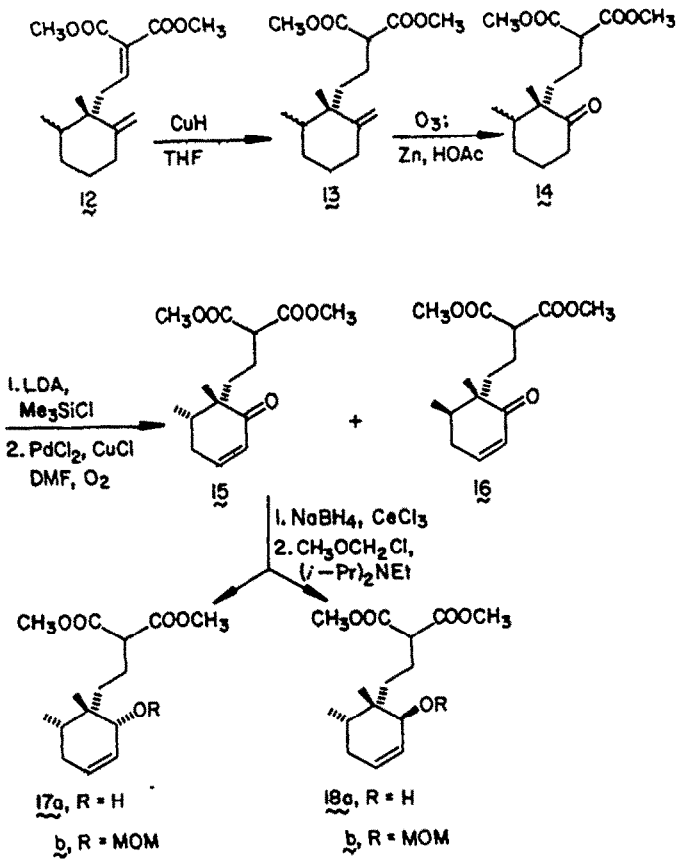
afforded the desired intermediate in 86% yield. Alkylative 1,3-carbonyl transposition within 8 was conveniently accomplished in a two-step sequence comprised of methyllithium addition and boron trifluoride-assisted methanolysis.[12,13] Reduction with diisobutylaluminum hydride and vinylation with ethyl vinyl ether in the presence of mercuric acetate led efficiently to 10b.

Despite the widely recognized synthetic utility of the Claisen rearrangement[14] and the intensity with which it has been scrutinized from the theoretical vantage point,[15] striking contrasts in stereoselectivities within carbocyclic systems continue to be observed and to invite mechanistic speculation. Whereas heating of the vinyl ether of 4-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene results predominantly (75%) in equatorial C-C bond formation,[16] analogous treatment of the vinyl ethyl derivative of the 5-*tert*-butyl isomer proceeds via exclusive axial attachment of the sidechain.[17] The response of structurally related pyranosides is to deliver products where axial attack is exercised predominantly if not exclusively.[18]

Since 10b is certain not to partake of any major conformational bias, little if any stereochemical discrimination was anticipated during its thermal activation. At the experimental level, a 1:1 mixture (^{1}H NMR analysis) of the two inseparable epimers of 11 was indeed realized.

Side Chain Attachment and Setting of the Proper Functional Groups. Advantage was next taken of the known propensity of aldehydes to participate efficiently in Knoevenagel reactions.[19] With dimethyl malonate as co-reagent, introduction of the three-carbon unit to give 12 was effected on a 20-25 g scale by employing ammonium acetate and acetic acid as catalysts in refluxing benzene solution (Scheme II). Chemospecific reduction of the conjugated double bond in 12 could be routinely realized in 95% yield by means of copper hydride.[20] The acquisition of 13 set the stage for ozonolytic cleavage of the remaining exocyclic double bond. The conversion to 14 proved initially to be vexacious. However, when recourse was made to a 3:1 mixture of methylene chloride and methanol as solvent in tandem with a zinc/acetic acid reduction,[21] yields in the range of 75% were consistently realized.

Scheme II



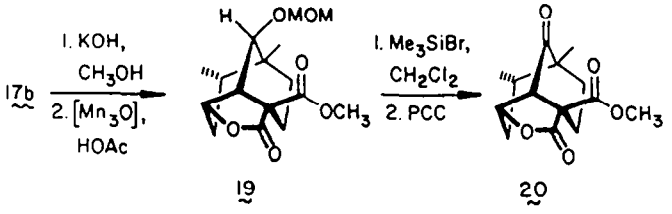
Introduction of an endocyclic double bond as in 15 and 16 was initially effected by conversion to the trimethylsilyl enol ether. When this transformation could not be achieved conventionally, recourse was made to premixing the lithium diisopropylamide and chlorotrimethylsilane in advance of addition of the keto diester. The actual methodology devised represents a modification of earlier described methods.[22] Under these conditions, good yields of the O-silylated products were obtained. Subsequent exposure to phenylselenenyl chloride was followed by elimination within the selenoxide oxidation product.[23] Given the modest yields realized along the later stages of this route, we were led to examine transition metal oxidation of the silyl enol ether as an alternative approach. Indeed, when recourse was made to the combination of palladium chloride and cupric chloride in dimethylformamide under an oxygen atmosphere,[24] conversion to the pair of enones was achieved in 60% yield.

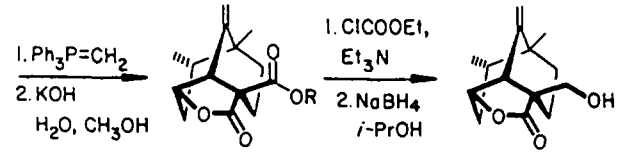
Workup of these reactions revealed that 15 and 16 were amenable to separation by a combination of selective crystallization and medium pressure chromatography. Stereochemical distinction between the crystalline 15 and oily 16 could not be made with certainty on the basis of their NMR spectra. The decision was, therefore, made to proceed with the crystalline isomer. The trans orientation of its vicinal methyl groups, qualifying it as the precursor for 14-epiupial (3), was ultimately established by X-ray analysis of a more highly crystalline substance acquired later in the scheme.

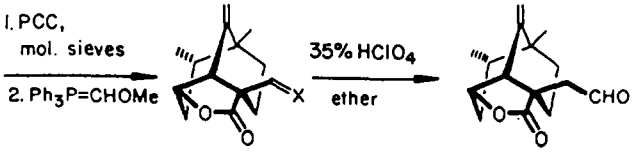
Controlled reduction of 15 with cerium trichloride-doped sodium borohydride[25] proceeded to give predominantly 17a. The major and minor allylic alcohols were independently transformed[26] into the methoxymethyl (MOM) ethers 17b and 18b for the purpose of examining their suitability as substrates for the impending cyclization.

Total Synthesis of 14-Epiupial. To set the stage for the intramolecular lactone annulation, it was necessary to hydrolyze one of the ester groups in 17b. In this way, eventual incorporation into the oxo-centered manganese(III) acetate species would be made possible.[10] Controlled treatment with methanolic potassium hydroxide afforded the desired monocarboxylate salt, which was treated directly with $[Mn_3O(OAc)_7](HOAc)\cdot 5H_2O$ – $[Mn_3O]$] in acetic acid at 70 °C. Subsequent chromatographic purification gave rise to 19 in 68% yield (Scheme III). Consequently, we had in hand what appeared to be a viable strategy for construction of the upial framework. At least in this example, the requisite one-electron oxidations and cyclization occurred faster than decarboxylation or other possible side reactions.

Scheme III







At this juncture, the MOM ether was cleaved chemospecifically under mild conditions with bromotrimethylsilane[27] and the resulting secondary alcohol was oxidized with pyridinium chlorochromate[28] to afford 20. The exceptional crystallinity of this keto lactone ester provided the occasion for an X-ray crystallographic analysis. The ORTEP diagram

presented in Figure 1 makes clear the fact that C-C and C-O bond formation had indeed materialized in the projected manner and reveals, in addition, the relative methyl group stereochemistry in the precursor intermediates 15-19. The configurational assignments to the hydroxy and MOM substituents follow from $Eu(fod)_3$ shift studies conducted on 17a and 18a.

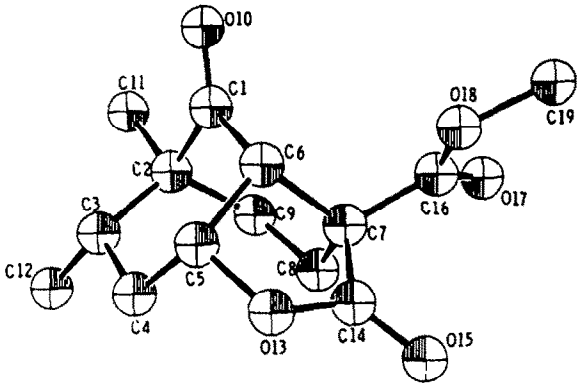


Figure 1. A computer-generated drawing of 20 derived from the X-ray coordinates with hydrogens omitted for clarity.

From among a number of alternate strategems now possible for arrival at 14-epiupial, we chose to introduce the exo-methylene group next by conventional Wittig chemistry. The ester and lactone functionalities in 21a now had to be distinguished. To this end, 21a was exhaustively saponified with potassium hydroxide in aqueous methanol and advantage was subsequently taken of the rapid relactonization that materializes on acidification. Decarboxylation proved not to be a serious competing process, as 21b was acquired in 98% yield.

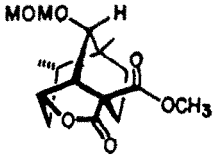
Activation of the free carboxyl group in 21b was then effected by conversion to the mixed anhydride with ethyl chloroformate. Ensuing sodium borohydride reduction in tetrahydrofuran containing isopropyl alcohol at 0 °C[29] furnished 22. The yield in both stages was very good and no evidence was seen for overreduction. Careful oxidation of 22 with PCC in the presence of powdered molecular sieves[30] delivered aldehydo lactone 23a most efficiently.

In our hands, chain extension was best achieved by application of the lithium-free modification of the Wittig reaction[31] involving (methoxymethyl)triphenylphosphonium chloride Deprotonation of this salt with potassium hexamethyldisilazide in a solvent system composed of tetrahydrofuran and hexamethylphosphoramide (4:1) and condensation of the resulting ylide with 23a afforded in 50% yield a 1:2.3 mixture of 23b and 23c. These vinyl ethers were separated and individually characterized. Following that, 23b and 23c were hydrolyzed independently with 35% perchloric acid in ether[32] to furnish 3. The spectral properties of 3, detailed in the Experimental Section, show this epimer to be easily distinguishable from natural upial.

Return to Oxidative Cyclization of Other Stereoisomeric Malonate Half-Esters. Having completed the 14-epiupial venture, we anticipated construction of upial itself by straight-

forward extension of the preceding methodology. First, we were led to examine the efficiency with which the minor MOM ether 18b might undergo cyclization in the presence of [Mn_3O]. The impact of this conversion on the overall throughput to 3 would be minimal. On the other hand, information relating to the possible influence of the MOM ether stereochemistry on the course of events was deemed important. To our dismay, all efforts to induce the oxidative cyclization of 18b met with total failure. Only tarry, ill-defined reaction mixtures were obtained in every circumstance, and no evidence could be garnered for the formation of 24, even in very small amounts. These observations provided their share of consternation, especially since the only structural difference was the relative orientation of the cyclohexenyl-oxygen bond, and prompted undelayed scrutiny of the behavior of 26.

As before with 15, the cyclohexenone 16 was transformed via 25 into the MOM ethers 26. Because separation of the two stereoisomers at either stage was judged not to be readily accomplishable, the intact mixture was subjected to the action of [Mn_3O]. Although a great deal of polymer formation was again in evidence, a finite amount of lactone ester 27 could



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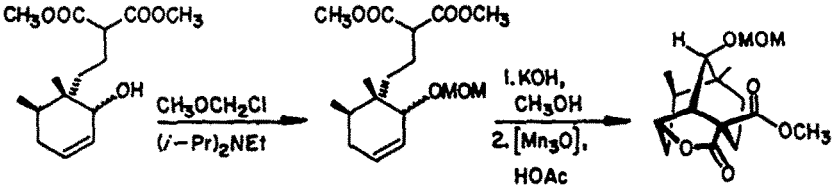


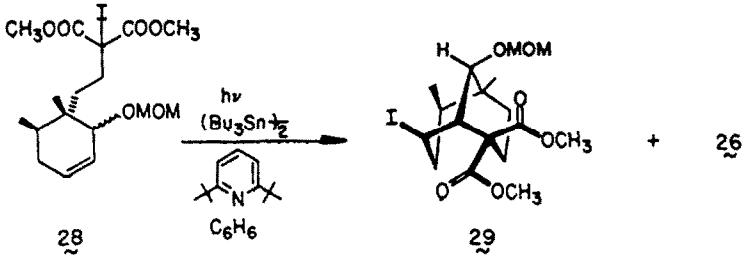
25 26 27

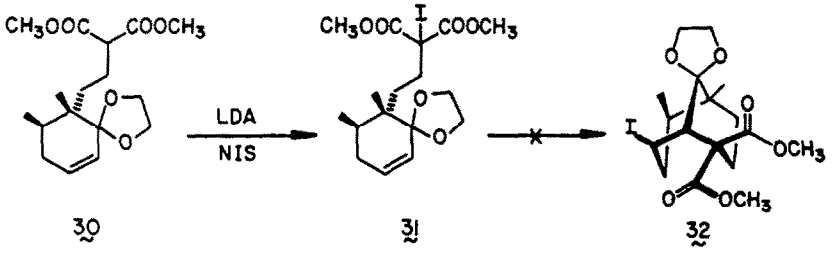
be isolated. However, its purified yield never exceeded 9%. Interestingly, this product was stereochemically homogeneous, suggesting that only one epimer of 26 was undergoing cyclization at a rate competitive with degradation. The kinetic retardation appears to have a steric origin, a state of affairs which is most serious when the 14-methyl group is oriented cis to the one-carbon bridge and the latter carries a syn-disposed MOM group. The syn stereochemistry of the MOM substituent may be the single major deterrent to lactonization, suggesting that an heteroatom effect may also be at play. The spectral data for 27 are similar to those for 19, but do not confirm unequivocally the relative configuration at the apical carbon. This assignment is made tentatively on the basis of this spectral comparison and the steric considerations just given.

Although the availability of 27 does in principle permit advancement to upial, the low yields associated with its acquisition by the above route discounted its immediate further utilization. To remedy this situation, a search for an alternative route to this key intermediate was set in motion.

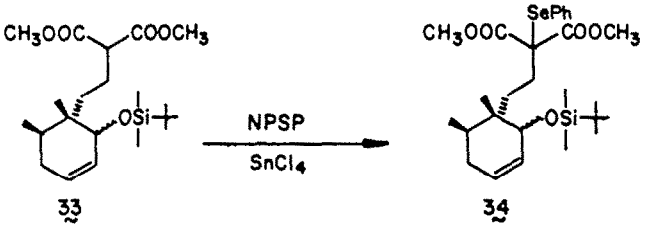
The recent discovery by Curran of the effectiveness of atom transfer cyclization[33]

led us to prepare 28 by iodination[34] of the enolate of 26. When benzene solutions of 28 were irradiated in the presence of small amounts of hexabutylditin and 2,6-di-*tert*-butylpyridine, the cyclized iodomalonate 29 could indeed be isolated, but only in 14% yield. The major product proved to be 26 (38%), the end result of simple deiodination, along with some 16. We did not find it possible to transform the related ethylene ketal 31 into 32 and this approach was therefore abandoned. Alcohol 25 and ketal 30 were equally unresponsive to [Mn_3O].





The possibility of elaborating the bicyclo[3.3.1]nonane framework by organoselenium-mediated cyclization[35] next occupied our attention. For this purpose, 25 was silylated[36] to give 33 and this malonate ester was treated with N-phenylselenophthalimide in the presence of stannic chloride and other Lewis acids. Cyclization did not ensue; instead, 34 was produced in low yield. Attempts to effect ring closure via this intermediate[37] was to no avail. Clearly, ring-forming reactions which proceed with reasonable facility in other contexts find difficulty in operating in the systems just described.



Summary. The first total synthesis of 14-epiupial has been achieved in 23 steps from 8. The original projection that the manganese(III) acetate cyclization could be extended as readily to 18b and 26 was not upheld. Evidently, intramolecular lactonization by this technique is quite sensitive to the relative stereochemistry of the multiple stereogenic centers.

Experimental Section

Methyl 2,3-Dimethylcyclohexenecarboxylate (9). A solution of 29.57 g (0.137 mol) of 8 in 400 mL of anhydrous tetrahydrofuran was cooled to -78 °C and 105 mL of a solution of methyllithium (1.35 *M* in ether, 0.142 mol) was added over a period of 1 h. The mixture was allowed to stir at -78 °C for 3 h before 250 mL of saturated ammonium chloride solution was added. After warming to room temperature, the layers were separated and the aqueous layer was extracted with ether (2 x 250 mL). The combined organic layers were washed with 5% hydrochloric acid (2 x 250 mL), water (200 mL), saturated sodium bicarbonate solution (2 x 250 mL), and brine (250 mL). Drying and evaporation of solvent afforded 31.18 g (98%) of crude alcohol which was used without further purification; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.9-3.1 (m, 1 H), 2.20 (s, 3 H), 2.15 (s, 3 H), 2.0-1.1 (m, 7 H), 1.15 (m, 3 H), 1.05 (d, J = 8 Hz, 3 H).

The above material (31.18 g, 0.134 mol) was placed in a 1 L flask and cooled in an ice bath as 87.5 g (0.617 mol) of boron trifluoride etherate was added over a period of 15 min. Heat was evolved and the mixture bubbled and turned brown as it was stirred for an additional 5 min. Methanol (300 mL) was added and the resulting mixture was heated at reflux for 29 h, cooled, and poured into 300 mL of water. Following extraction with chloroform (3 x 250 mL), the combined organic layers were washed with 5% sodium bicarbonate solution (2 x 200 mL), and brine (200 mL). Drying and solvent removal gave an oil which was distilled to give 15.58 g (69%) of 9 as a colorless oil, bp 75-78 °C at 1.5 torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3 H), 2.22-2.16 (m, 3 H), 1.95 (s, 3 H), 1.69-1.54 (m, 3 H), 1.43-1.37 (m, 1 H), 1.02 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 169.94, 148.83, 124.50, 51.20, 36.15, 30.36, 26.86, 20.19, 19.31, 18.98; MS m/z (M^+) calcd 168.1158, obsd 168.1154.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.67.

1-(Hydroxymethyl)-2,3-dimethylcyclohexene (10a). A solution of 8.81 g (0.052 mol) of 9 in 200 mL of petroleum ether was cooled to -78 °C and 131 mL (0.131 mol) of a 1 *M* solution of Dibal-H in hexane was added dropwise over a period of 1 h. After 3 h of stirring at -78 °C, 125 mL of a saturated Rochelle salt solution was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with ether (3 x 200 mL). The combined organic layers were washed with water (4 x 200 mL) and brine (200 mL), dried, and evaporated. Flash chromatography of the resulting oil (silica gel, 2.5% ethyl acetate in petroleum ether) gave 6.26 g (85%) of pure alcohol 10a: IR ($CHCl_3$, cm^{-1}) 3600-3100, 2970, 2940, 2870, 1450, 1355, 995; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 2 H), 2.07 (br s, 3 H), 1.9-1.3 (m, 5 H), 1.69 (s, 3 H), 1.01 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 135.11, 129.86, 63.43, 34.79, 31.18, 28.12, 19.75, 19.53, 16.80; MS m/z (M^+) calcd 140.1193, obsd 140.1197.

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.77; H, 11.39.

O-Vinylation of 10a. A solution of mercuric acetate (32.58 g, 0.102 mol) in 200 mL of ethyl vinyl ether was added at room temperature to a solution of 30.70 g (0.214 mol) of 10a in 1.5 L of ethyl vinyl ether. After 5 days of stirring, the solution was poured into a mixture of 1.5 L of ethyl ether and 2 L of water. The phases were separated and the aqueous portion was washed with 1 L of ethyl ether. The combined organic layers were extracted with water (4 x 1 L) and brine (1 L). Following drying and solvent evaporation, distillation afforded 29.03 g (82%) of 10b, bp 55-58 °C at 1 torr; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (m, 1 H), 4.23-4.11 (m, 3 H), 4.01-3.97 (m, 1 H), 2.21-2.04 (m, 3 H), 1.70-1.41 (m, 3 H), 1.70 (s, 3 H), 1.39-1.33 (m, 1 H), 1.03 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 152.10, 136.84, 126.35, 86.38, 68.84, 34.97, 31.16, 28.59, 28.27, 19.68, 19.57, 17.06; MS m/z (M^+) calcd 166.1351, obsd 166.1355.

Claisen Rearrangement of 10b. A Carius tube was charged with 3.75 g (0.023 mol) of 10b and sealed under vacuum. The tube was heated at 200 °C for 11 h and the resulting product was purified by flash chromatography (silica gel, 1% ether in petroleum ether) to give 3.04 g (82%) of 11 as a mixture of diastereomers in a 1:1 ratio. IR (film, cm^{-1}) 3100, 2980, 2940, 2870, 2740, 1730, 1645, 1450, 1380, 1035, 895; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, J = 3 Hz, 0.5 H), 9.59 (t, J = 3 Hz, 0.5 H), 4.85 (d, J = 12 Hz, 1 H), 4.71 (d, J = 16 Hz, 1 H), 2.74-2.60 (m, 1 H), 2.41-2.07 (m, 3 H), 1.81-1.36 (m, 5 H), 1.27 (s, 1.5 H), 1.11 (s, 1.5 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 203.97, 203.84, 153.44, 152.54, 109.11, 108.79, 50.87, 45.10, 43.06, 42.03, 41.78, 39.29, 33.28, 33.06, 30.73, 29.77, 27.40, 24.59, 23.70, 21.85, 16.23, 15.27; MS m/z (M^+-H_2O) calcd 148.1252, obsd 148.1242.

Knoevenagel Condensation of 11. A mixture of 22.60 g (0.1136 mol) of 11, 52.37 g, (0.680 mol) of ammonium acetate, 19.77 g (0.149 mol) of dimethyl malonate, 7.85 mL (0.136 mol) of acetic acid, and 500 mL of benzene was heated to reflux with azeotropic removal of water. After 2.5 h of reflux, ammonium acetate began to sublime and collect in the condenser. The mixture was refluxed for an additional 3 h, poured into 1 L of water, and extracted with ether (3 x 1 L). The combined organic layers were washed with water (3 x 1 L) and brine (1 L), dried, filtered, and freed of solvent. The crude product was purified on a Waters Prep 500 instrument (silica gel, 3% ethyl acetate in petroleum ether) to give 27.39 g (72%) of 11; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, J = 8, 7 Hz, 0.5 H), 6.91 (dd, J = 8, 7 Hz, 0.5 H), 4.83 (br d, J = 12 Hz, 1 H), 4.63 (br d, J = 16 Hz, 1 H), 3.83 (s, 3 H), 3.76 (s, 1.5 H), 3.75 (s, 1.5 H), 2.36-2.75 (m, 1 H), 2.24-2.06 (m, 2 H), 1.77-1.24 (m, 6 H), 1.07 (s, 1.5 H), 0.96 (s, 1.5 H), 0.88 (d, J = 6 Hz, 1.5 H), 0.82 (d, J = 7 Hz, 1.5 H); MS m/z (M^+) calcd 280.1675, obsd 280.1715.

Copper Hydride Reduction of 12. A 250 mL three-necked flask was charged with 15.35 g (0.107 mol) of cuprous bromide and 75 mL of dry tetrahydrofuran. The mixture was cooled under an argon atmosphere to -10 °C and 30.57 mL (0.107 mol) of a 3.5 *M* Red-Al solution in benzene was added dropwise while keeping the temperature below 1 °C. The mixture turned brown and then a black solid appeared. After being stirred for 0.5 h at 0 °C, the mixture

was cooled to -78 °C and 24.7 mL of anhydrous 2-butanol was added. After an additional 5 min at -78 °C, 5.00 g (0.018 mol) of 12 dissolved in 15 mL of tetrahydrofuran was added in one portion. The flask was transferred to a dry ice-CCl_4 bath and the mixture was stirred at -20 °C for 2 h. Water (100 mL) was added and the flask was allowed to warm to room temperature. The black mixture was poured into a flask containing 400 mL of ether and 400 mL of saturated ammonium chloride solution and stirred overnight. The next day the ether layer was colorless and clear, and the aqueous layer was blue. The layers were separated and the aqueous portion was extracted with ether (2 x 200 mL). The combined organic phases were washed with saturated ammonium chloride solution (4 x 200 mL) and brine (200 mL) prior to drying. Solvent evaporation afforded 13 (4.82 g, 96%): IR ($CHCl_3$, cm^{-1}) 3095, 3040, 2980, 2960, 2940, 2865, 1735, 1640, 1435, 1265, 1230, 1165; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (overlapping AB system, J = 12, 9 Hz, 2 H), 3.72 (s, 6 H), 3.28 (overlapping t, J = 7, 7 Hz, 1 H), 2.16-2.03 (m, 2 H), 1.87-1.13 (m, 9 H), 1.05 (s, 1.5 H), 0.93 (s, 1.5 H), 0.85-0.81 (2 d, J = 6, 7 Hz, 3 H); MS m/z (M^+) calcd 282.1831, obsd 282.1833.

Ozonolysis of 13. Argon was bubbled through a solution containing 1.03 g (3.63 mmol) of 13 dissolved in 75 mL of methylene chloride and 25 mL of methanol. The solution was cooled to -78 °C and, after 15 min, the argon flow was discontinued and a stream of ozone was introduced until the solution turned blue (10 min). Argon was again bubbled through until colorless (15 min). After 10 mL of acetic acid was added, zinc powder (3 g) was introduced in portions over a period of 45 min. The mixture was allowed to warm to room temperature with the occasional addition of more zinc powder. When the solution no longer gave a positive test with starch-potassium iodide solution, it was filtered through Celite and washed with water (2 x 100 mL), saturated sodium bicarbonate solution (2 x 100 mL), and brine (100 mL). Drying and solvent evaporation left an oil which was purified by MPLC (silica gel, 12% ethyl acetate in petroleum ether) to give 0.77 g (74%) of ketones 14: IR (film, cm^{-1}) 2980, 2890, 1770, 1765, 1750, 1715, 1470, 1460, 1445, 1285, 1245, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3 H), 3.67 (s, 1.5 H), 3.66 (s, 1.5 H), 3.31-3.21 (m, 1 H), 2.42-2.21 (m, 2 H), 1.98-1.83 (m, 1 H), 1.78-1.26 (m, 8 H), 1.08 (s, 1.5 H), 0.93 (s, 1.5 H), 0.86 (d, J = 5 Hz, 1.5 H), 0.85 (d, J = 5 Hz, 1.5 H); MS m/z (M^+) calcd 284.1624, obsd 284.1610.

O-Silylation of 14. A solution of 1.95 mL (1.4 g, 0.014 mol) of diisopropylamine in 40 mL of tetrahydrofuran was cooled to -10 °C under argon. Over a period of 10 min, 11.2 mL (0.014 mol) of a 1.24 *M* *n*-butyllithium solution in hexanes was added by syringe. The mixture was stirred at 0 °C for 0.5 h, then cooled to -78 °C. At this point, 3.52 mL (3.02 g, 0.028 mol) of trimethylsilyl chloride was added and the solution was allowed to stir for 1 h before a solution of 1.316 g (4.63 mmol) of 14 in 20 mL of tetrahydrofuran was introduced dropwise during 1 h. After being stirred at -78 °C for several hours, the mixture was allowed to warm to room temperature overnight. The solution was poured into a mixture of 150 mL of saturated sodium bicarbonate solution and 300 mL of ether. The aqueous layer was extracted with ether (100 mL) and the combined organic phases were washed with saturated sodium bicarbonate solution (2 x 100 mL) and brine (100 mL). The solution was dried, filtered, and evaporated to give an oil which was purified by MPLC (silica gel, 3% ethyl acetate in petroleum ether) to give 1.44 g (87%) of silyl enol ether; IR (film, cm^{-1}) 3040, 2960, 1760, 1740, 1660, 1455, 1440, 1255, 1195, 1175, 850; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (t, J = 4 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.29-3.23 (m, 1 H), 2.03-1.21 (m, 9 H), 1.03 (s, 1.5 H), 0.92 (d, J = 7 Hz, 1.5 H), 0.84 (s, 1.5 H), 0.83 (d, J = 7 Hz, 1.5 H), 0.17 (s, 9 H); MS m/z (M^+) calcd 356.2019, obsd 356.2019.

Selenylation of the Silyl Enol Ether. A solution of 0.440 g (1.24 mmol) of the preceding silyl enol ether in 5 mL of benzene was cooled to 5 °C in an ice bath as a solution of of 0.262 g (1.36 mmol) of phenylselenenyl chloride in 1.5 mL of benzene was introduced over a 0.5 h period. After being stirred at 5 °C for 0.5 h, the solution was warmed to room temperature for 0.5 h and poured into a mixture of 75 mL of ether and 25 mL of saturated sodium bicarbonate solution. The separated organic phase was washed with saturated sodium bicarbonate solution (2 x 25 mL) and brine (25 mL), dried, filtered, and evaporated to give the crude product which was purified by MPLC (silica gel, 20% ethyl acetate in petroleum ether) to give 0.920 g (75%) of the α-selenoketones; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.52 (m, 2 H), 7.29-7.26 (m, 3 H), 4.50-4.05 (m, 1 H), 3.75-3.70 (m, 6 H), 3.39-3.29 (m, 1 H), 2.50-1.30 (m, 9 H), 1.27-1.05 (m, 3 H), 0.98-0.86 (m, 3 H); MS m/z (M^+) calcd 440.1101, obsd 440.1095.

Selenoxide Elimination to 15 and 16. A solution of crude α-phenylselenoketones (formed from 1.855 g, 6.52 mmol of ketones 14) in 50 mL of anhydrous methylene chloride was cooled to -78 °C while purged with argon. After 15 min, a stream of ozone was introduced until the solution turned green (15 min). Argon was reintroduced until the solution was yellow, at which point 1.14 mL (8.11 mmol) of diisopropylamine was added. The cold solution was transferred by cannula into a refluxing mixture of 0.54 mL (4.07 mmol) of diisopropylamine in 100 mL of carbon tetrachloride. After 5 min of heating, the solution was allowed to cool to room temperature and washed sequentially with 5% hydrochloric acid solution (2 x 100 mL), saturated sodium bicarbonate solution (3 x 100 mL), and brine (100 mL). Drying, filtration, and evaporation of solvent left a crude oil which was purified by MPLC (silica gel, 15% ethyl acetate in petroleum ether) to give 0.823 g (45%) of a mixture of 15 and 16. From this mixture, 15 could be selectively crystallized while 16 was obtained as an oil following MPLC purification (silica gel, 12% ethyl acetate in petroleum ether) of the mother liquors.

For 15: mp 61-61.5 °C; IR ($CHCl_3$, cm^{-1}) 3040, 3020, 2960, 2890, 1750, 1730, 1660, 1450, 1435, 1390, 1280, 1220, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (dq, J = 10, 3 Hz, 1 H), 5.90 (dt, J = 10, 2 Hz, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.28 (t, J = 7 Hz, 1 H), 2.45-2.36 (m, 1 H), 2.22-2.04 (m, 1 H), 1.92-1.80 (m, 1 H), 1.71-1.36 (m, 4 H), 1.14 (s, 3 H), 0.97 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.66, 169.55, 169.52, 146.74, 127.96, 52.43 (2 C), 52.06, 47.88, 37.96, 31.73, 28.49, 23.25, 19.51, 15.24; MS m/z (M^+) calcd 282.1467, obsd 282.1462.

Anal. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.68; H, 7.79.

For 16: IR ($CHCl_3$, cm^{-1}) 3040, 2980, 2890, 1760, 1735, 1670, 1440, 1390, 1275, 1240, 1210, 1150, 1130; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dq, J = 10, 3 Hz, 1 H), 5.91 (dt, J = 10, 1 Hz, 1 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.31 (t, J = 8 Hz, 1 H), 2.40-2.09 (m, 3 H), 1.85-1.63 (m, 3 H), 1.33-1.22 (m, 1 H), 0.94 (d, J = 6 Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.61, 169.68, 169.63, 147.59, 128.62, 52.42, 52.35, 52.06, 48.48, 33.70, 32.15, 31.60, 23.56, 17.89, 14.73; MS m/z (M^+) calcd 282.1467, obsd 282.1465.

Palladium(II)-Catalyzed Oxidation of the Silyl Enol Ethers. A mixture of 10.65 g (0.029 mol) of the silyl enol ethers, 5.30 g (0.299 mol) of palladium(II) chloride, and 3.55 g (0.359 mol) of copper(I) chloride in 150 mL of dimethylformamide was stirred under an oxygen atmosphere for 7 days. Ether (400 mL) was added and the mixture was filtered through Celite. Following solvent evaporation, the residue was taken up in 800 mL of ether and washed with saturated sodium bicarbonate solution (3 x 200 mL) and brine (200 mL). The solution was dried, filtered, and evaporated to give crude product which upon flash chromatography (silica gel, 20% ethyl acetate in petroleum ether) gave 5.04 g (60%) of a mixture of 15 and 16. These enones were separated as indicated above and gave identical spectral data.

Cerium Trichloride-Doped Sodium Borohydride Reduction of 15. A solution of 0.148 g (0.524 mmol) of 15 in 3 mL of methyl alcohol was stirred under argon while 0.217 g (0.583 mmol) of cerium trichloride heptahydrate was added. The mixture was stirred for 15 min at room temperature and 25.9 mg (0.685 mmol) of sodium borohydride was introduced. Vigorous bubbling occurred. After stirring for 15 min, an additional 5 mg of sodium borohydride was added and the solution was stirred for an additional 15 min. This solution was poured into a mixture of 75 mL of methylene chloride and 25 mL of saturated ammonium chloride solution. This mixture was stirred for 1.5 h and the aqueous phase was extracted with 25 mL of methylene chloride. The combined organic layers were washed with saturated ammonium chloride solution (2 x 25 mL) and brine (25 mL), dried, and evaporated. The product was purified by MPLC (silica gel, 35% ethyl acetate in petroleum ether) to yield 110 mg of 17a and 15 mg of 18a (84%).

For 17a: IR (film, cm^{-1}) 3700-3140, 3030, 2960, 2885, 1760-1715, 1650, 1460, 1450, 1435, 1350, 1280, 1245, 1195, 1090, 1020, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69-5.57 (m, 2 H), 3.80 (br s, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.30 (t, J = 6 Hz, 1 H), 2.20-2.10 (m, 2 H), 1.97-1.53 (m, 4 H), 1.37-1.26 (m, 2 H), 0.99 (s, 3 H), 0.89 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.22, 169.97, 129.46, 127.77, 76.01, 52.48, 52.41, 52.35, 38.67, 36.47, 31.22, 27.07, 24.45, 21.47, 15.55; MS m/z (M^+) calcd 284.1624, obsd 284.1645.

For 18a: IR ($CHCl_3$, cm^{-1}) 3680-3150, 3030, 2960, 2890, 1755-1730, 1690, 1455, 1440, 1380, 1345, 1280, 1250, 1200, 1160, 1110, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74-5.59 (m, 2 H), 3.84 (br s, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.29 (t, J = 7 Hz, 1 H), 2.18-2.04 (m, 1 H), 1.94-1.50 (m, 4 H), 1.48-1.20 (m, 3 H), 0.94 (s, 3 H), 0.86 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.74, 128.66, 128.24, 71.50, 52.37, 38.47, 32.77, 31.49, 30.95, 23.05, 19.03, 14.76 (3 C not observed); MS m/z (M^+-OH) calcd 267.1596, obsd 267.1575.

Preparation of MOM-Ether 17b. A solution of 0.101 g (0.355 mmol) of 17a in 3 mL of anhydrous methylene chloride was cooled to 0 °C under argon and 2 mL (11.5 mmol) of ethyl diisopropylamine was added. The solution was stirred for 5 min at which point 2 mL (26.5 mmol) of chloromethyl methyl ether was introduced. The mixture was kept at 0 °C for 0.5 h and allowed to warm to room temperture where it was stirred for an additional 0.5 h, and poured into a mixture of 75 mL of methylene chloride and 25 mL of saturated sodium bicarbonate solution. After 2 h more of stirring, the separated aqueous phase was extracted with 25 mL of methylene chloride. The combined organic layers were washed with water (2 x 25 mL) and brine (25 mL), dried, and evaporated to give crude product which was purified by MPLC (silica gel, 20% ethyl acetate in petroleum ether). There was isolated 0.090 g (77%) of 17b: IR ($CHCl_3$, cm^{-1}) 3040, 2960, 2890, 2845, 1750, 1735, 1450, 1435, 1270, 1240, 1210, 1150, 1100, 1030, 920; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (br s, 2 H), 4.61 (AB, J = 7 Hz, 2 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.63 (br s, 1 H), 3.34 (s, 3 H), 3.24 (t, J = 7 Hz, 1 H), 2.02-1.90 (m, 3 H), 1.79-1.65 (m, 1 H), 1.63-1.50 (m, 1 H), 1.35-1.30 (m, 2 H), 0.96 (s, 3 H), 0.87 (d, J = 8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.88, 127.52, 127.41, 96.55, 82.07, 55.39, 52.71, 52.20, 52.17, 38.46, 36.39, 31.27, 27.68, 24.45, 21.79, 15.59 (one carbon not observed); MS m/z (M^+-$C_2H_5O_2$) calcd 267.1596, obsd 267.1620.

Preparation of MOM-Ether 18b. This compound was prepared in the same manner as 17b; from 123 mg (0.434 mmol) of 18a, there was obtained 109 mg (77%) of 18b: IR ($CHCl_3$, cm^{-1}) 3040, 2960, 2900, 1760, 1740, 1440, 1245, 1150, 1100, 1040; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.65 (m, 2 H), 4.66 (AB, J = 7 Hz, 2 H), 3.74 (s, 3 H), 3.72 (s, 4 H), 3.37 (s, 3 H), 3.27 (t, J = 8 Hz, 1 H), 2.19-2.10 (m, 1 H), 1.97-1.63 (m, 4 H), 1.41-1.23 (m, 2 H), 0.95 (s, 3 H), 0.85 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.41, 128.46, 126.04, 96.02, 76.38, 55.14, 52.18, 52.05, 38.06, 32.59, 30.97, 30.79, 22.79, 19.32, 14.54 (2 carbons overlapping); MS m/z (M^+-$C_2H_5O_2$) calcd 267.1596, obsd 267.1609.

Cyclization of 17b. A solution of 0.700 g (2.123 mmol) of 17b in 10 mL of anhydrous methanol was cooled to 0 °C under argon and 1.12 mL (2.23 mmol) of a 1.99 *M* solution of potassium hydroxide in methanol was added dropwise over a period of 5 min. The solution was allowed to warm to room temperature and stirred for 7 days. The solvent was evaporated and 15 mL of glacial acetic acid together with 1.10 g (4.46 mmol) of manganese acetate were added. The brown solution was heated in an oil bath at 70 °C for 2 h, cooled, decolorized by the addition of solid sodium bisulfite (< 25 mg), and poured into 75 mL of water. The aqueous phase was extracted with ether (4 x 25 mL) and the combined organic layers were carefully added to 50 mL of saturated sodium bicarbonate solution. Solid sodium bicarbonate was added to this mixture in small portions until bubbling ceased and the solution was basic (pH = 9). The phases were separated and the aqueous portion was extracted with ether (2 x 25 mL). The combined organic layers were washed with saturated sodium bicarbonate

solution (2 x 25 mL) and brine (25 mL), dried, and evaporated to leave a residue which was purified by MPLC (silica gel, 35% ethyl acetate in petroleum ether). There was isolated 0.450 g (68%) of 19: mp 91.5-92 °C; IR ($CHCl_3$, cm^{-1}) 3040, 2960, 2940, 2880, 1770, 1740, 1480, 1460, 1435, 1285, 1220, 1145, 1110, 1050, 1040, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (br q, J = 7 Hz, 1 H), 4.55 (AB, J = 7 Hz, 2 H), 3.75 (s, 3 H), 3.56 (dd, J = 4, 7 Hz, 1 H), 3.34 (s and d, 4 H), 2.69 (br q, J = 9 Hz, 1 H), 2.28 (br t, J = 9 Hz, 1 H), 1.76-1.44 (m, 5 H), 0.96 (d, J = 6 Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.44, 170.38, 94.99, 75.54, 75.41, 55.92, 52.89, 50.27, 43.94, 37.17, 36.66, 35.09, 24.07, 23.81, 23.38, 15.70; MS m/z (M^+-$C_2H_5O_2$) calcd 251.1284, obsd 251.1268.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.50; H, 7.75. Found: C, 61.54; H, 7.72.

Ether Deblocking in 19. A solution of 55.5 mg (0.178 mmol) of 19 in 3 mL of anhydrous methylene chloride was stirred at -20 °C while 100 μL (0.748 mmol) of bromotrimethylsilane was added. Twice at 1 h intervals an additional 100 μL of the silyl bromide was introduced to the reaction mixture, which was subsequently poured into 50 mL of saturated sodium bicarbonate solution and extracted with methylene chloride (3 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL), dried, and evaporated to give crude product which was purified by MPLC (silica gel, 50% ethyl acetate in petroleum ether). There was obtained 32.8 mg (80%) of the hydroxy lactone ester: IR ($CHCl_3$, cm^{-1}) 3640-3260, 3020, 2970, 2950, 2880, 1775, 1740, 1290, 1220, 1145, 1115, 1055, 1015, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85-4.77 (m, 1 H), 3.79 (s, 3 H), 3.48-3.42 (m, 2 H), 2.68-2.58 (m, 1 H), 2.33-2.22 (m, 2 H), 1.80-1.65 (m, 2 H), 1.57-1.24 (m, 3 H), 0.98 (d, J = 6 Hz, 2 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.39, 171.46, 75.43, 71.39, 53.19, 49.94, 46.43, 37.29, 36.58, 35.23, 24.61, 23.59, 22.72, 15.70; MS m/z (M^+) calcd 268.1311, obsd 268.1301.

Keto Ester Lactone 20. A suspension of 81 mg (0.377 mmol) of pyridinium chlorochromate, 23 mg (0.283 mmol) of anhydrous sodium acetate, and 100 mg of Celite in 2 mL of anhydrous methylene chloride was stirred at 0 °C. A solution of 50 mg (0.189 mmol) of the above alcohol dissolved in 2 mL of methylene chloride was added to the suspension and the mixture was stirred at 0 °C for 1 h and at room temperature for 7 h. Anhydrous ether (20 mL) was introduced and the resulting precipitate was washed three times with ether (10 mL). After filtration and evaporation of the solvent, the crude product was purified by flash chromatography (silica gel, 35% ethyl acetate in petroleum ether) to give 20 in quantitative yield: mp 82.5-83.5 °C; IR ($CHCl_3$, cm^{-1}) 2980, 2940, 2880, 1780, 1740, 1720, 1450, 1275, 1235, 1180, 1140, 1130, 1050, 1010, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09-5.00 (m, 1 H), 3.78 (s, 3 H), 3.67 (d, J = 9 Hz, 1 H), 2.49-2.32 (m, 2 H), 2.24-2.13 (m, 2 H), 1.85-1.69 (m, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.27, 172.93, 168.42, 76.15, 59.05, 52.95, 52.19, 46.22, 37.97, 35.77, 30.71, 24.60, 20.19, 15.36; MS m/z (M^+) calcd 266.1155, obsd 266.1149.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.25; H, 6.81.

X-ray Crystal Structure Analysis of 20. Suitable crystals of 20 ($C_{14}H_{18}O_5$) for X-ray diffraction studies formed with space group symmetry of $P2_12_12_1$ and cell constants of a = 7.076(1)Å, b = 8.348(1)Å, and c = 22.907(2)Å with Z = 4 and a calculated density of 1.307 g/cm^3. Of the 1089 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 799 were observed ($I > 3\sigma I$). The structure was solved with a multi-solution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques.[38] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\Sigma w(|Fo|-|Fc|)^2$ with $w = 1/(\sigma Fo)^2$ was minimized to give an unweighted residual of 0.045. No abnormally short intermolecular contacts were noted. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer generated perspective drawing of 20 from the final X-ray coordinates showing the relative stereochemistry.

Methylenation of 20. Into a flame-dried flask was placed 18 mg (0.37 mmol) of sodium hydride (50% in mineral oil). After the solid had been rinsed with anhydrous hexanes (3 x 5 mL), 3 mL of anhydrous dimethyl sulfoxide was added. The mixture was stirred as it was heated to 80 °C for 1 h. The solution was cooled to room temperature and 0.133 g (0.371 mmol) of methyltriphenylphosphonium bromide was introduced. The solution turned yellow as it was stirred at room temperature for 45 min. A solution of 0.076 g (0.286 mmol) of 20 dissolved in 2 mL of dimethyl sulfoxide was added and the reaction mixture was kept at room temperature for 1 h prior to heating at 80 °C for 3 h. After being cooled, the solution was poured into a mixture of 40 mL of saturated brine and 60 mL of ether. The layers were separated and the aqueous portion was extracted with ether (20 mL). The combined organic layers were washed with saturated brine (2 x 30 mL), dried, and evaporated. MPLC purification (silica gel, 20% ethyl acetate in petroleum ether) of the residue gave 0.058 g (77%) of 21a: IR ($CHCl_3$, cm^{-1}) 3030, 2970, 2940, 2880, 1770, 1740, 1650, 1480, 1460, 1440, 1280, 1220, 1050, 1000, 980; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 1 H), 4.83 (s, 1 H), 4.83-4.75 (m, 1 H), 3.78 (s, 3 H), 3.71 (d, J = 8 Hz, 1 H), 2.53-2.44 (m, 1 H), 2.38-2.32 (m, 1 H), 1.99-1.86 (m, 2 H), 1.66-1.36 (m, 3 H), 1.05 (s, 3 H), 0.98 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.03, 170.06, 148.75, 108.92, 77.66, 55.37, 52.98, 49.99, 39.11, 37.42, 37.23, 30.90, 25.25, 24.58, 16.51; MS m/z (M^+) calcd 264.1361, obsd 264.1377.

Saponification of 21a. Into a 50 mL flask was placed 0.860 g (0.325 mmol) of 21a, 15 mL of 1.99 *M* potassium hydroxide in methanol solution, and 15 mL of water. This mixture was heated at the reflux temperature for 10 days. The reaction mixture was cooled, washed with ether (2 x 50 mL), and acidified with concentrated hydrochloric acid (pH = 1). The acidic solution was stirred with 100 mL of ether for 5 h as the diacid was converted to the acid lactone. The layers were separated and the aqueous phase was extracted with ether (50 mL). The combined organic layers were washed with 50 mL of saturated brine, dried, and freed of solvent to give 0.792 g (98%) of 21b: IR ($CHCl_3$, cm^{-1}) 3400-2400, 3040, 2970, 2930, 2880, 1770, 1710, 1645, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1 H), 4.88 (s, 1 H),

4.82 (br q, J = 8 Hz, 1 H), 3.75 (d, J = 8 Hz, 1 H), 2.50-2.31 (m, 2 H), 2.02-1.86 (m, 2 H), 1.66-1.37 (m, 3 H), 1.07 (s, 3 H), 0.99 (d, J = 6 Hz, 3 H); MS m/z (M^+) calcd 250.1205, obsd 250.1194.

Reduction of 21b. A solution of 20 mg (0.08 mmol) of 21b in 2 mL of tetrahydrofuran was stirred at 0 °C under argon while 13.4 μL (0.096 mmol) of triethylamine was added. The solution was stirred for 0.5 h and 11.5 μL (0.12 mmol) of ethyl chloroformate was introduced. The reaction mixture became cloudy as it was stirred at 0 °C for 1.5 h. At this point, 0.5 mL (6.53 mmol) of isopropyl alcohol was added, followed 5 min later by 9.1 mg (0.24 mmol) of sodium borohydride. The mixture was stirred at 0 °C for 6 h, diluted with ether (10 mL), treated dropwise with 1 mL of 5% hydrochloric acid, and poured into a mixture of 15 mL of ether and 10 mL of 1% hydrochloric acid. The aqueous phase was extracted with ether (2 x 10 mL) and the combined organic phases were washed with saturated sodium bicarbonate solution (2 x 10 mL) and brine (1 x 10 mL), dried, and evaporated. Flash chromatography (silica gel, 22% ethyl acetate in petroleum ether) gave 15.0 mg (79%) of 22, mp 88.5-89 °C; IR ($CHCl_3$, cm^{-1}) 3700-3000, 3040, 2980, 2940, 2880, 1755, 1650, 1460, 1380, 1275, 1050, 980; ^1H NMR (300 MHz, $CDCl_3$ with D_2O added) δ 4.92 (d, J = 1 Hz, 1 H), 4.84 (d, J = 1 Hz, 1 H), 4.80-4.70 (m, 1 H), 3.63 (AB, J = 11 Hz, 2 H), 3.26 (d, J = 8 Hz, 1 H), 2.45-2.29 (m, 1 H), 1.91-1.49 (m, 4 H), 1.34-1.20 (m, 2 H), 1.06 (s, 3 H), 0.96 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 180.72, 150.34, 108.37, 77.60, 64.06, 49.33, 47.13, 39.42, 37.99, 37.94, 30.54, 24.90, 24.74, 16.58; MS m/z (M^+) calcd 236.1413, obsd 236.1445.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.16; H, 8.56.

Oxidation of 22. A suspension of 12 mg (0.058 mmol) of pyridinium chlorochromate and 3.4 mg (0.042 mmol) of anhydrous sodium acetate in 2 mL of methylene chloride was cooled to 0 °C. Powdered 3Å sieves were added to make a slurry and to this mixture was added 6.2 mg (0.026 mmol) of 22 dissolved in 2 mL of methylene chloride. The mixture was stirred at 0 °C for 4 h, diluted with 30 mL of ether, filtered, and evaporated. The residue was chromatographed (silica gel, 22% ethyl acetate in petroleum ether) to give 4.4 mg (72%) of 23a: IR ($CHCl_3$, cm^{-1}) 2980, 2940, 2880, 1765, 1725, 1650, 1600, 1480, 1455, 1180, 1130, 980; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1 H), 4.97 (s, 1 H), 4.85 (s, 1 H), 4.87-4.79 (m, 1 H), 3.64 (d, J = 8 Hz, 1 H), 2.44-2.22 (m, 2 H), 2.05-1.89 (m, 2 H), 1.63-1.50 (m, 1 H), 1.36-1.19 (m, 2 H), 1.06 (s, 3 H), 0.98 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 195.61, 174.87, 148.19, 109.30, 78.05, 58.51, 46.51, 39.17, 37.79, 37.49, 30.47, 24.67, 23.62, 16.59; MS m/z (M^+) calcd 234.1256, obsd 234.1239.

Preparation of 23b and 23c. Into a flame-dried flask was placed 0.108 g (0.315 mmol) of (methoxymethyl)triphenylphosphonium chloride, 2 mL of tetrahydrofuran, and 0.5 mL of hexamethylphosphoramide. The solution was cooled to 0 °C and 0.29 mL (0.263 mmol) of a 0.9 M solution of potassium bis(trimethylsilyl)amide was added by syringe. The ice bath was removed and the red-orange solution was stirred at room temperature for 15 min, cooled to -78 °C, and treated with a solution of 10 mg (0.042 mmol) of 23a in 1 mL of tetrahydrofuran. The mixture was stirred at -78 °C for 0.5 h, allowed to warm to room temperature over the course of 1 h, and stirred at this temperature for 0.5 h. Sodium sulfate decahydrate (250 mg) was added to the solution and the mixture was stirred for 10 min while the red-orange color disappeared. Ether (5 mL) was introduced and the resulting precipitate was triturated with ether (3 x 5 mL). The combined ether extracts were filtered and evaporated. The resulting oil was chromatographed (silica gel, 15% ethyl acetate in petroleum ether) to give 1.7 mg of 23b and 3.9 mg of 23c (50%).

For 23b: mp 79-80 °C; IR ($CHCl_3$, cm^{-1}) 3100, 3040, 3010, 2980, 2940, 2880, 2860, 1760, 1660, 1485, 1460, 1120, 1000, 975, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 6 Hz, 1 H), 4.82 (d, J = 1 Hz, 1 H), 4.78 (d, J = 1 Hz, 1 H), 4.75-4.67 (m, 1 H), 4.29 (d, J = 6 Hz, 1 H), 3.60 (s, 3 H), 3.41 (d, J = 8 Hz, 1 H), 2.35-2.30 (m, 1 H), 2.06-1.70 (m, 3 H), 1.65-1.51 (m, 1 H), 1.40-1.25 (m, 2 H), 1.05 (s, 3 H), 0.97 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.86, 150.93, 147.95, 107.53, 107.35, 77.17, 59.87, 51.26, 47.52, 39.51, 37.72, 37.51, 30.90, 30.35, 25.01, 16.78; MS m/z (M^+) calcd 262.1569, obsd 262.1572.

For 23c: IR ($CHCl_3$, cm^{-1}) 3100, 3020, 3010, 2970, 2940, 1760, 1660, 1485, 1460, 1190, 1010, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, J = 13 Hz, 1 H), 4.93 (d, J = 13 Hz, 1 H), 4.91 (s, 1 H), 4.86 (s, 1 H), 4.72-4.64 (m, 1 H), 3.53 (s, 3 H), 3.14 (d, J = 8 Hz, 1 H), 2.40-2.33 (m, 1 H), 2.17-2.01 (m, 1 H), 1.86-1.79 (m, 1 H), 1.74-1.56 (m, 2 H), 1.43-1.23 (m, 2 H), 1.07 (s, 3 H), 0.98 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.84, 150.53, 148.67, 108.29, 104.26, 77.17, 55.80, 51.65, 45.99, 39.86, 37.76, 37.65, 30.70, 30.11, 24.88, 16.64; MS m/z (M^+) calcd 262.1569, obsd 262.1555.

14-Epiupial (3). A solution of 5.0 mg (0.019 mmol) of 23c in 3 mL of ether was cooled to 0 °C and 0.5 mL of 35% perchloric acid was added. The reaction mixture stirred at 0 °C for 0.5 h, and poured into 10 mL of ether and 10 mL of water. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (2 x 10 mL) and brine (10 mL), dried, and evaporated. The crude product was purified by flash chromatography (silica gel, 15% ethyl acetate in petroleum ether) to give 3.2 mg (68%) of 3: IR ($CHCl_3$, cm^{-1}) 2980, 2930, 2870, 2850, 1765, 1725, 1650, 1455, 1385, 1115, 1075, 1005, 985, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1 H), 4.85 (s, 2 H), 4.83-4.76 (m, 1 H), 3.21 (d, J = 8 Hz, 1 H), 2.75 (d, J = 1.5 Hz, 2 H), 2.38-2.32 (m, 1 H), 2.04-1.84 (m, 2 H), 1.67-1.53 (m, 2 H), 1.33-1.15 (m, 2 H), 1.07 (s, 3 H), 0.97 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.42, 179.79, 150.00, 108.90, 77.53, 49.40, 48.22, 45.25, 39.39, 37.55, 37.31, 30.09, 29.52, 24.91, 16.78; MS m/z (M^+) calcd 248.1413, obsd 248.1427.

A sample of 23b (2.0 mg, 0.008 mmol), when treated in the same manner, gave 1.6 mg (84%) of 3.

Reduction of 16. The procedure described above for 15 was employed. From 0.153 g (0.543 mmol) of 15, there was obtained 0.106 g (81%) of a 2.3:1 mixture of the allylic

alcohols 25. Separation of the epimers was extremely difficult and could only be achieved by peak shaving on a Waters Prep 500 chromatograph (silica gel, 25% ethyl acetate in petroleum ether).

For 25a (minor): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 2 H), 3.79 (br s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.35 (t, J = 7 HZ, 1 H), 2.14-1.25 (m, 8 H), 0.84 (d, J = 6 Hz, 3 H), 0.74 (s, 3 H).

For 25b (major): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66-5.62 (m, 1 H), 5.56-5.51 (m, 1 H), 4.23 (br s, 1 H), 3.75 (s, 6 H), 3.34 (t, J = 7 Hz, 1 H), 2.10-1.22 (m, 8 H), 0.86 (d, J = 6 Hz, 3 H), 0.71 (s, 3 H).

For the mixture: IR ($CHCl_3$, cm^{-1}) 3680-3140, 3040, 2960, 2900, 2840, 1760, 1730, 1430, 1240, 1160, 1020; ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.07, 169.86, 169.76, 130.57, 130.04, 127.32, 127.29, 70.58, 70.22, 52.37, 52.29, 51.99, 51.91, 39.36, 38.52, 33.13, 32.73, 32.05, 31.93, 31.89, 30.92, 22.88, 22.22, 15.10, 14.78, 14.50, 12.79 (3 carbons overlapping); MS m/z (M^+) calcd 284.1624, obsd 284.1628.

Conversion of 25 to MOM-Ethers 26. By means of the procedure described above, 0.312 g (1.10 mmol) of 25 gave 0.304 g (85%) of 26: IR ($CHCl_3$, cm^{-1}) 3040, 2960, 2900, 1755, 1740, 1440, 1350, 1275, 1245, 1155, 1100, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74-5.60 (m, 2 H), 4.85-4.61 (m, 2 H), 4.09 (br s, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.39, 3.36 (2 s, 3 H), 3.34-3.24 (m, 1 H), 2.15-1.22 (m, 7 H), 0.85, 0.84 (2 d, J = 7, 7 Hz, 3 H), 0.83, 0.74 (2 s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.86, 169.70, 129.75, 128.26, 127.57, 126.05, 96.47, 995.97, 77.15, 55.57, 55.53, 52.53, 52.36, 52.32, 52.27, 39.07, 38.31, 32.89, 32.84, 32.22, 31.87, 31.70, 23.24, 22.41, 17.28, 15.08, 14.41, 13.82 (6 carbons overlapping); MS m/z M^+-$C_2H_5O_2$) calcd 267.1595, obsd 267.1595.

Oxidative Cyclization of 26. A solution of 0.144 g (0.437 mmol) of 26 in 5 mL of methanol was cooled to 0 °C and 0.242 mL (0.480 mmol) of a 1.99 *M* solution of potassium hydroxide in methanol was introduced. The mixture was allowed to warm to room temperature, stirred for 5 days, and freed of solvent. Manganese acetate was then introduced (0.258 g, 0.961 mmol) along with 5 mL of acetic acid. The cinnamon brown mixture was placed in an oil bath at 70 °C (where it became colorless in 10 min), cooled to room temperature, and added to a mixture of 50 mL of water and 100 mL of ether. The aqueous phase was extracted with ether (2 x 50 mL), the combined organic layers were carefully added to 100 mL of saturated sodium bicarbonate solution, and solid sodium bicarbonate was added until the aqueous phase was basic (pH = 9). The organic layer was washed with saturated sodium bicarbonate solution (2 x 50 mL) and brine (50 mL), dried, and freed of solvent. Chromatography (silica gel, 35% ethyl acetate in petroleum ether) gave 12 mg (9%) of 27: mp 78-79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (q, J = 8 Hz, 1 H), 4.50 (AB, J = 7 Hz, 2 H), 3.77 (s, 3 H), 3.70 (d, J = 4 Hz, 1 H), 3.57 (dd, J = 4, 8 Hz, 1 H), 3.34 (s, 3 H), 2.85-2.78 (m, 1 H), 2.04-1.82 (m, 5 H), 1.42-1.35 (m, 1 H), 0.97 (d, J = 7 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 175.72, 170.62, 94.99, 76.22, 71.28, 55.84, 52.98, 50.78, 43.73, 37.60, 35.22, 34.09, 31.37, 24.58, 24.42, 18.35; MS m/z (M^+-$C_2H_5O_2$) calcd 251.1284, obsd 251.1288.

Iodination of 26. A solution of 0.085 mL (0.607 mmol) of diisopropylamine in 5 mL of tetrahydrofuran was cooled to 0 °C and 0.386 mL (0.607 mmol) of a 1.57 *M* solution of *n*-butyllithium in hexanes was added. The reaction mixture was stirred for 0.5 h at 0 °C, cooled to -78 °C, and treated with a solution containing 0.166 g (0.506 mmol) of 26 in 2 mL of tetrahydrofuran. The solution was kept at -78 °C for 1 h and 0.180 g (0.708 mmol) of iodine in the same solvent (2 mL) was introduced. After being stirred at -78 °C for 1 h, the solution was allowed to warm to room temperature and poured into a mixture of 50 mL of ether and 50 mL of saturated sodium bicarbonate solution. The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic layers were washed with 10% of sodium bisulfite solution (25 mL), saturated sodium bicarbonate solution (2 x 25 mL), and brine (25 mL). Drying and solvent removal followed by flash chromatography (silica gel, 16% ethyl acetate in petroleum ether) yielded 0.111 g (48%) of 28 along with 0.041 g (25%) of recovered 26.

For 28: IR ($CHCl_3$, cm^{-1}) 3035, 2980, 2890, 2840, 1735, 1650, 1435, 1260, 1245, 1150, 1140, 1095, 1040, 960; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76-5.62 (m, 2 H), 4.88, 4.73 (AB, J = 7 Hz; overlapping m, 2 H), 3.95, 3.61 (2 br s, 1 H), 3.78, 3.79 (2 s, 6 H), 3.40, 3.37 (2 s, 3 H), 2.19-1.02 (m, 7 H), 0.87-0.78 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.78, 168.71, 168.63, 129.81, 128.76, 127.43, 126.09, 97.36, 96.01, 78.54, 77.20, 55.74, 55.67, 53.84, 53.80, 53.76, 45.04, 44.34, 39.22, 38.23, 34.56, 33.81, 33.05, 32.80, 32.57, 31.93, 31.78, 17.39, 15.11, 14.50, 13.91 (3 carbons overlapping); MS m/z (M^+-$C_2H_5O_2$) calcd 393.0563, obsd 393.0598; (M^+-I) calcd 327.1807, obsd 327.1827.

Cyclization of 28. A solution of 5.9 mg (0.013 mmol) of 28, 2.0 μL (0.004 mmol) of hexabutylditin, and 10 μL (0.045 mmol) of 2,6-di-*tert*-butylpyridine in 1 mL of benzene was irradiated with a 275 W sunlamp for 10 min. The solvent was evaporated and the resulting oil was submitted directly to chromatography (silica gel, 12% ethyl acetate in petroleum ether) to give 0.8 mg (14%) of 29 along with 1.6 mg (38%) of 26.

For 29: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87-4.80 (m, 1 H), 4.49 (AB, J = 7 Hz, 2 H), 4.31 (d, J = 4 Hz, 1 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.49 (br s, 1 H), 3.40 (s, 3 H), 2.55-2.45 (m, 2 H), 2.17-1.87 (m, 3 H), 1.29-1.22 (m, 2 H), 1.23 (d, J = 8 Hz, 3 H), 0.96 (s, 3 H); MS m/z (M^++1) (CI) calcd 254.9, obsd 254.9; (M^+-I) calcd 327.1807, obsd 327.1762.

Ketalization of 16. A mixture of 0.084 g (0.298 mmol) of 16, 0.50 mL (8.30 mmol) of ethylene glycol, and 10 mg (0.05 mmol) of *p*-toluenesulfonic acid monohydrate in 20 mL of benzene was heated to reflux with azeotropic removal of water for 24 h. An additional 0.25 mL of ethylene glycol and 10 mg of the sulfonic acid were introduced and the mixture was again heated for 24 h. The contents were poured into saturated sodium bicarbonate solution

(25 mL) and the aqueous phase was extracted with benzene (2 x 20 mL). The resulting organic layers were washed with saturated sodium bicarbonate solution (3 x 20 mL) and brine (25 mL), dried, and evaporated. The crude product was purified by flash chromatography (silica gel, 16% ethyl acetate in petroleum ether) to give 41 mg (42%) of 30 along with 12 mg (14%) of recovered 16.

For 30: IR ($CHCl_3$, cm^{-1}) 3025, 2980, 2960, 2885, 1750, 1730, 1440, 1250, 1155, 1130, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60-5.45 (m, 2 H), 3.98-3.93 (m, 4 H), 3.73 (s, 6 H), 3.24 (t, J = 7 Hz, 1 H), 2.55-2.40 (m, 1 H), 2.25-1.98 (m, 4 H), 1.54-1.29 (m, 2 H), 0.96 (d, J = 7 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.93, 132.79, 122.24, 112.68, 64.70, 64.34, 52.85, 52.30, 42.27, 37.60, 33.41, 32.12, 25.16, 16.59, 14.78 (2 carbons overlapping); MS m/z (M^+) calcd 326.1729, obsd 326.1724.

Iodination of 30. A solution of 30.8 μL (0.22 mmol) of diisopropylamine in 10 mL of tetrahydrofuran was cooled to 0 °C and 0.143 mL (0.220 mmol) of a 1.54 M solution of n-butyllithium in hexanes was added. This solution was allowed to stir at 0 °C for 1 h, cooled to -78 °C, and treated dropwise with a solution of 0.060 g (0.183 mmol) of 30 in 2 mL of tetrahydrofuran during 10 min. The reaction mixture was allowed to stir for 1 h at -78 °C before 0.050 g (0.22 mmol) of N-iodosuccinimide in 2 mL of tetrahydrofuran was introduced. After being stirred at -78 °C for 2 h, the mixture was allowed to warm to room temperature and added to a mixture of ether (50 mL) and saturated ammonium chloride solution (50 mL). The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic layers were washed with saturated ammonium chloride solution (25 mL), 5% sodium thiosulfate solution (25 mL), saturated sodium bicarbonate solution (2 x 25 mL), and brine (25 mL) prior to drying and solvent evaporation. The crude product was purified by chromatography (silica gel, 16% ethyl acetate in petroleum ether) and gave 0.059 g (72%) of pure 31; IR ($CHCl_3$, cm^{-1}) 3030, 2980, 2960, 2890, 1735, 1440, 1255, 1155, 1130, 1050, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54-5.40 (m, 2 H), 4.03-3.92 (m, 4 H), 3.74 (s, 6 H), 2.52-2.41 (m, 1 H), 2.31-2.04 (m, 4 H), 1.59-1.35 (m, 2 H), 0.97 (d, J = 8 Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.79, 168.74, 132.66, 122.26, 112.53, 64.56, 64.25, 53.73, 45.58, 42.20, 37.67, 36.29, 33.26, 31.76, 16.87, 14.60 (one carbon overlapping); MS m/z (M^+) calcd 452.0722, obsd 452.0709.

Silylation of 25. A solution of 1 mL (7.17 mmol) of triethylamine in 3 mL of anhydrous methylene chloride was cooled to 0 °C and 1 mL (4.35 mmol) of *tert*-butyldimethylsilyl triflate was introduced. This mixture was stirred for 15 min before a solution of 0.134 g (0.470 mmol) of 25 in 2 mL of methylene chloride was added. After 1 h, the reaction mixture was poured into 30 mL of methylene chloride and 50 mL of saturated sodium bicarbonate solution. The aqueous phase was extracted with methylene chloride (2 x 20 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (3 x 20 mL) and brine (20 mL), dried, and concentrated. The residual oil was purified by flash chromatography (silica gel, 5% ethyl acetate in petroleum ether) to give 0.154 g (82%) of 33; IR ($CHCl_3$, cm^{-1}) 3030, 2960, 2930, 2890, 2860, 1750, 1730, 1470, 1460, 1435, 1260, 1100, 1070, 1035, 860, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67-5.41 (m, 2 H), 4.14, 3.83 (2 br s, 1 H), 3.74-3.71 (4 s, 6 H), 3.29-3.20 (m, 1 H), 2.14-1.61 (m, 5 H), 1.55-1.36 (m, 1 H), 1.26-1.07 (m, 1 H), 0.89, 0.87 (2 s, 9 H), 0.87, 0.86 (2 d, J = 8, 9 Hz, 3 H), 0.78, 0.70 (2 s, 3 H), 0.08-0.04 (3 s, 6 H); MS m/z (M^+-1) (FAB) calcd 399.2, obsd 399.2; (M^+-C_4H_9) calcd 341.1784, obsd 341.1789.

Selenenylation of 33. A solution of 0.0198 mL (0.135 mmol) of diisopropylamine in 2 mL of tetrahydrofuran was cooled to 0 °C and 0.0911 mL (0.135 mmol) of a 1.48 M solution of n-butyllithium in hexanes was added. This mixture was stirred for 0.5 h, cooled to -78 °C, and treated with a solution of 44.8 mg (0.112 mmol) of 33 dissolved in 1 mL of tetrahydrofuran. After being stirred at -78 °C for 45 min, a solution of 47.5 mg (0.1574 mmol) of N-phenylselenophthalimide in 2 mL of tetrahydrofuran was introduced. The solution was kept at -78 °C for 0.5 h, warmed to 0 °C, and kept at that temperature for 0.5 h before being added to a mixture of 50 mL of saturated sodium bicarbonate solution and 50 mL of ether. The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic layers were washed with saturated sodium bicarbonate solution (2 x 25 mL) and brine (25 mL). After being dried and the solvent removed, the resulting oil was purified by flash chromatography (silica gel, 5% ethyl acetate in petroleum ether) to give 44.8 mg (72%) of 34: IR ($CHCl_3$, cm^{-1}) 3030, 2960, 2930, 2890, 2860, 1735, 1440, 1260, 1200, 1100, 1070, 845, 770-700; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.58 (m, 2 H), 7.39-7.27 (m, 3 H), 5.62-5.48 (m, 2 H), 4.04, 3.88 (2 br s, 1 H), 3.67, 3.67, 3.63 (3 s, 6 H), 2.13-1.34 (m, 7 H), 0.90-0.85 (m, 12 H), 0.78, 0.74 (2 s, 3 H), 0.08, 0.06 (2 s, 6 H); MS m/z (M^+-C_4H_9) calcd 497.1282, obsd 497.1272.

Supplementary Material. Tables of the atomic positional and thermal parameters, bond distances, and bond angles for 20 (3 pages). These crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

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