Synthetic Studies on the Ginkgolides: Total Synthesis of (±)-Bilobalide

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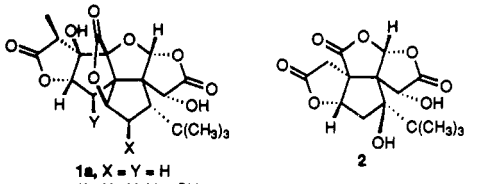
Abstract: Two syntheses of the C15 ginkgolide, bilobalide, are presented. One approach results in a formal synthesis by intersecting an intermediate in the Corey synthesis, while a second approach results in a completed total synthesis which is considerably shorter than the first. Both approaches rely on a stereoselective intramolecular [2 + 2] photocycloaddition to control much of the stereochemistry. A diastereoselective aldol condensation serves to establish the relative stereochemical relationship between the secondary and tertiary alcohols in the second approach. This circumvents problems of incorporation of the tertiary carbinol which were encountered in both previous approaches.

Ginkgo biloba, the "fossil tree", appeared on earth approximately 300 million years ago and flourished during the Jurassic period. It survives today because of its strong resistance to disease and insects and its remarkable regenerative abilities.[1] The extracts of this plant have been used as a therapeutic agent in Chinese folk medicine for 5000 years and are now marketed in Europe to treat cerebrovascular and peripheral circulatory problems in the elderly.[2] A number of structurally unusual compounds including the C20 hexacyclic trilactone ginkgolides **1a–c** and the C15



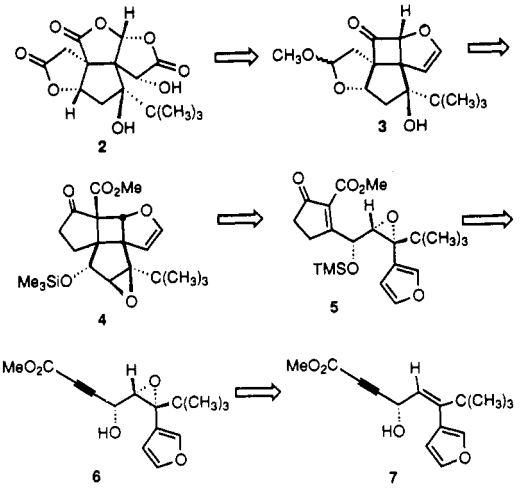
1a, X = Y = H
1b, X = H, Y = OH
1c, X = Y = OH

2

tetracyclic trilactone bilobalide **2** have been isolated from extracts of the ginkgo. The C20 ginkgolides A, B, and C were first isolated by Furakawa, and their structures were independently solved by two groups.[3] Bilobalide was isolated much later and its structure was determined spectroscopically by Nakanishi.[4]

Synthetic efforts on the ginkgolides to date have resulted in the total synthesis of (±)-bilobalide[5] and (–)-bilobalide[6] by the Corey group as well as the total synthesis of ginkgolides A[7] and B[8] and several analogs[9] including des-*tert*-butylginkgolide B.[10]

Scheme I



2 **3** **4** **5** **6** **7**

Herein is described two approaches[11] to the synthesis of bilobalide each relying on a stereoselective intramolecular [2 + 2] photocycloaddition as a key step.[12,13]

The initial strategy for the synthesis was to carry out a regioselective Baeyer–Villiger oxidation on cyclobutanone **3** followed by oxidation of the enol ether and methyl acetal moieties to produce bilobalide. The conversion of photoadduct **4** to cyclobutanone **3** would require cleavage of the cyclopentanone ring, oxidation of the cyclobutane carbon, and reductive opening of the epoxide. The photocycloaddition of enone **5** was predicted to proceed with the stereoselectivity shown based on model studies. The photosubstrate **5** would be prepared by a conjugate addition cyclization of the Kuwajima–Nakamura homoenolate on acetylenic ester **6**. The stereochemistry of ester **6** would be controlled by a directed Sharpless epoxidation on allylic alcohol **7** which could be derived from commercially available 3-furaldehyde.

Model Studies on the Stereoselectivity of the Photocycloaddition Reaction. Prior to beginning the synthesis, model studies were undertaken to determine what level of stereoselectivity might be

(1) Chamberlain, C. J. In *Gymnosperms: Structure and Evolution*; University of Chicago Press: Chicago, 1933. Benson, L. In *Plant Classification*; 2nd ed.; D.C. Heath and Co.: Toronto, 1979.
(2) Braquet, P. *Drugs Future* **1987**, *12*, 643.
(3) Furukawa, S. *Sci. Papers Inst. Phys. Chem. Res., Tokyo* **1932**, *19*, 27. Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89. Okabe, K.; Yamada, K.; Yamamura, S. Takada, S. *J. Chem. Soc. C* **1967**, 2201. Sakabe, N.; Takada, S.; Okabe, K. *J. Chem. Soc., Chem. Commun.* **1967**, 257.
(4) Nakanishi, K.; Habguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Bahr, W. *J. Am. Chem. Soc.* **1971**, *93*, 3544.
(5) Corey, E. J.; Su, W. *J. Am. Chem. Soc.* **1987**, *109*, 7534.
(6) Corey, E. J.; Su, W. *Tetrahedron Lett.* **1988**, *29*, 3423.
(7) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1989**, *29*, 3205.
(8) Corey, E. J.; Kang, M. C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649. Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201.
(9) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1989**, *30*, 6559.
(10) Corey, E. J.; Rao, S. *Tetrahedron Lett.* **1991**, *32*, 4623.
(11) A communication has appeared describing one of these approaches: Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 5445.
(12) For a review on intramolecular [2 + 2] photocycloadditions see: Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453. Crimmins, M. T.; Rheinhold, T. L. *Org. React.*, in press.
(13) For a previous example of an enone–furan photocycloaddition see: Crimmins, M. T.; Thomas, J. B. *Tetrahedron Lett.* **1989**, *30*, 5997.

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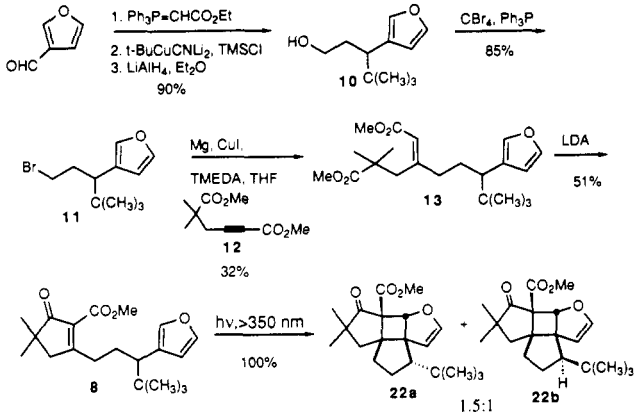
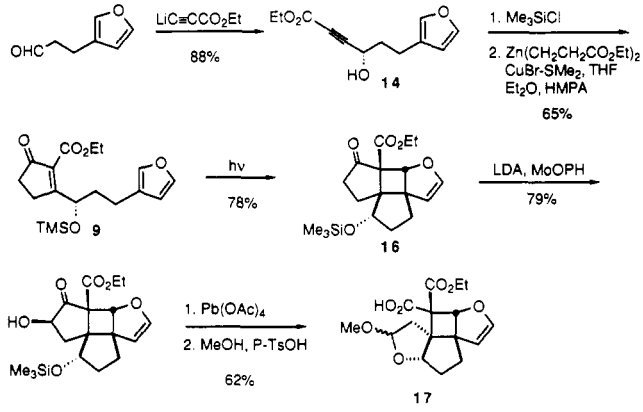
Scheme II



Scheme III



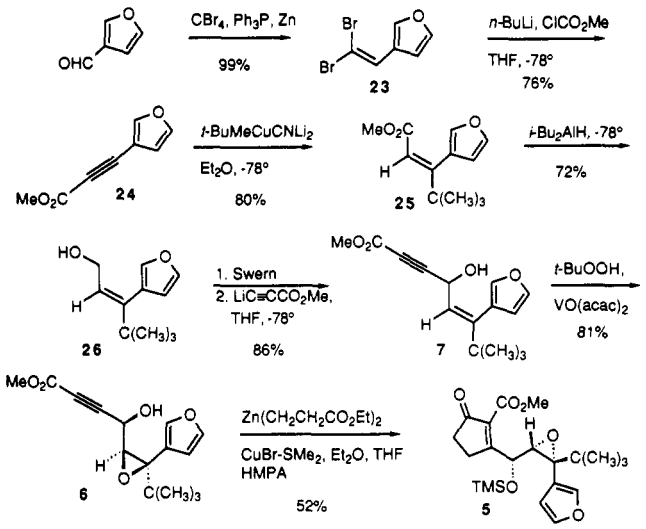
expected in the crucial photocycloaddition reaction. Two model substrates **8** (Scheme II) and **9** (Scheme III) were prepared to determine the directing effect of substituents in the two allylic positions on the tethering chain. Enone **8** was prepared from 3-furaldehyde as shown in Scheme II. Condensation of 3-furaldehyde with (carbethoxymethylene)triphenylphosphorane followed by reaction with t-$Bu_2CuCNLi_2$[14] and reduction of the ester with lithium aluminum hydride gave alcohol **10** in 90% overall yield. Treatment of the alcohol with CBr_4 and triphenylphosphine in acetonitrile produced 85% of bromide **11**. Addition of the Grignard reagent derived from bromide **11** to acetylenic diester **12** in the presence of copper iodide produced the unsaturated ester **13**.[15] Exposure of the ester **13** to LDA in THF at −78 °C gave the photosubstrate **8** in 51% yield.

Enone **9** was prepared from 3-furylpropanal[13] (Scheme III) by addition of the lithium acetylide of ethyl propiolate to the aldehyde to give acetylenic ester **14**. Treatment of the corresponding trimethylsilyl ether of **14** with zinc homoenolate **15** provided the photosubstrate **9** in good yield.[16]

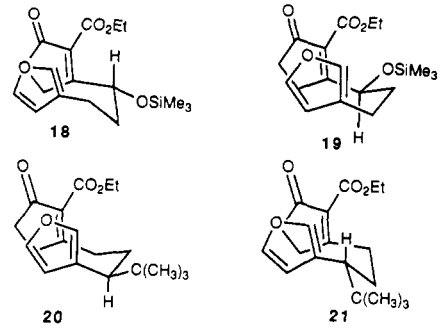
Irradiation of **9** produced a single diastereomeric photoadduct **16** as evidenced by its conversion to the acetal **17**. If the isomeric product had resulted, the cyclic acetal could not form since it would produce a trans [3.3.0] ring system. The major product is produced when the reaction proceeds through a transition-state conformation similar to **18** which is of lower energy ($\Delta\Delta G \approx 1.6$ kcal/mol based on MM2 calculations) than the diastereomeric transition state **19**. In contrast, the energies of conformations **20** and **21** for the photocycloaddition of **8** are very similar ($\Delta\Delta G \approx 0.2$ kcal/mol), and the result is very poor stereoselectivity in the photocycloaddition: 1.5:1 **22a**:**22b**. This would imply that if two stereogenic centers were incorporated into the tether as in

(14) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
(15) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 3033.
(16) Crimmins, M. T.; Nantermet, P. G. *J. Org. Chem.* **1990**, *55*, 4235.

Scheme IV



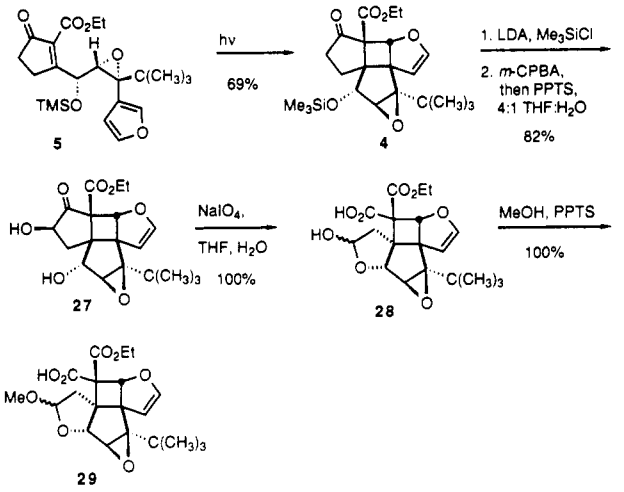
enone **5** which is required for the projected synthesis of bilobalide, the trimethylsilyloxy group should be the primary controlling factor for the stereochemistry of the photocycloaddition and the major product should be photoadduct **4**.



Preparation of the Photosubstrate. With the stereoselectivity of the photocycloaddition fairly well assured, the synthesis of bilobalide was initiated. The first phase of the synthesis required the efficient preparation of the photosubstrate and began again from 3-furaldehyde. Reaction of 3-furaldehyde with Corey–Fuchs reagent[17] produced a 99% yield of the dibromoolefin **23**. Treatment of unstable dibromide **23** with butyllithium effected elimination to the lithium acetylide which was trapped in situ with methyl chloroformate to provide acetylenic ester **24** in 76% yield. The *tert*-butyl group was next incorporated utilizing Henrick's mixed cuprate, t-BuMeCuLi,[18] to give the *Z*-alkene **25** upon quenching at low temperature. Only the *Z*-isomer could be detected by NMR. Conversion of the ester **25** to the alcohol **26** was executed by reduction with diisobutylaluminum hydride. Swern oxidation followed by addition of the lithium acetylide of ethyl propiolate to the aldehyde produced the allylic alcohol **7** in 90% yield. The Sharpless-directed epoxidation of **7** proceeded with extremely high regioselectivity and stereoselectivity. The furan activates the alkene while the ester deactivates the acetylene toward oxidation with the electrophilic reagent. The stereoselectivity can be attributed to the preference for the allylic hydrogen (rather than the acetylenic ester) to be in the plane of the alkene in the transition state of the oxidation. The result was that a single isomeric product **6** was detectable by ^1H NMR. The synthesis of the photosubstrate was completed by treatment of the hydroxy acetylenic ester with 4 equiv of the homoenolate prepared from zinc chloride and ethoxy[(trimethylsilyl)oxy]-

(17) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *3769*.
(18) Henrick, C. A.; Anderson, C. A.; Corbin, V. L.; Cotterrell, G. R.; Schaub, F.; Sidall, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 1197.

Scheme V



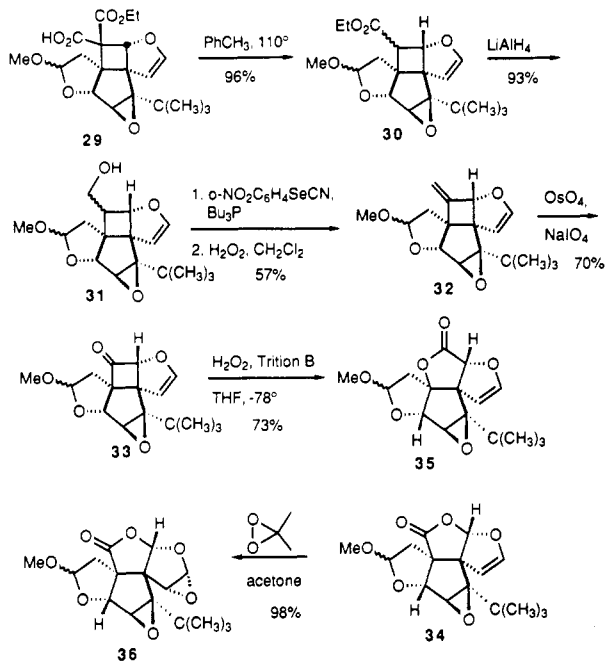
cyclopropane. This effects in situ protection of the hydroxyl as the TMS ether followed by conjugate addition–cyclization to produce 52% of enone **5**.[16]

Cycloaddition of the Photosubstrate and Modification of the Photoadduct. Enone **5** was irradiated as a solution in hexanes at >350 nm (uranium glass filter) to produce a 69% yield of a single diastereomeric photoadduct **4** after chromatography. While the stereochemical result of the Sharpless epoxidation[19] could be made with some confidence based on literature precedent, the ^{1}H NMR of the photoadduct **4** further solidified the assignment. The coupling constant between the protons on C2 and C3 (bilobalide numbering) were very similar to that observed in an intermediate in the Corey synthesis. The relative stereochemistry of the (trimethylsilyl)oxy group follows from the model studies and from further transformations.

The next task was to cleave the cyclopentanone ring of the photoadduct and to convert the cyclobutane carbon bearing the two carbonyl functionalities into a carbonyl group. Conversion of the ketone carbonyl of photoadduct **4** to its corresponding silylenol ether followed by Rubottom oxidation[20] gave a mixture of the epoxy enol ether and the α-siloxy ketone. This mixture was treated directly with PPTS in THF–H_2O to provide 82% of the diol **27** from the photoadduct. Oxidative cleavage of the α-hydroxy ketone with sodium periodate gave the hemiacetal **28** in quantitative yield. The hemiacetal was readily converted to acetal **29** by exposure to MeOH, *p*-toluenesulfonic acid, and trimethyl orthoformate. The failure of the enol ether to react under these conditions may be due to the steric interference of the *tert*-butyl group but is more likely a result of a thermodynamic preference for sp^2 hybridization at C6 to minimize nonbonded interactions with the *tert*-butyl group. The low reactivity of this enol ether in other acidic reactions was also noted.

Several approaches were investigated to convert the dicarboalkoxycyclobutane into a cyclobutanone. A carboxy inversion reaction[21] was attempted on the acid ester, but this failed to give any recognizable products. The ester was hydrolyzed to the diacid in an effort to effect an oxidative decarboxylation with $Pb(OAc)_4$[22] but the oxidation gave a mixture of several products. The acid ester could be readily decarboxylated in toluene at 110 °C to provide ester **30** (96% yield). Attempts to use the enolate of the ester in hydroxylation reactions or to trap the enolate as a silyl enol ether led to elimination of the β-oxygen. Ultimately, the ester was reduced to the primary alcohol **31** with lithium aluminum hydride. The epoxide moiety was unaffected by the reduction

Scheme VI



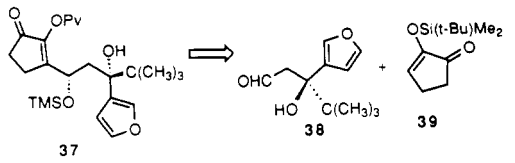
[a] Key: (a) $PhCH_3$, 110 °C; (b) $LiAlH_4$, Et_2O; (c) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF; (d) H_2O_2, CH_2Cl_2; (e) OsO_4, $NaIO_4$, THF, H_2O; (f) H_2O_2, Triton B, THF, –78 °C; (g) dimethyldioxirane, acetone.

indicating that it would not be possible to reductively open the epoxide at a late stage of the synthesis. This is consistent with the difficulties encountered in the Corey synthesis[5,6] with regard to manipulation of the epoxide. The primary alcohol was converted to the methylenecyclobutane **32** by elimination of the selenide prepared under Grieco's conditions.[23] Cleavage of the exocyclic double bond to produce the desired cyclobutanone **33** was accomplished in 70% yield with OsO_4 and $NaIO_4$. When the cyclobutanone **33** was treated with t-BuOOH, Triton B in dichloromethane at 0 °C a 1:1 mixture of lactones **34**:**35** was produced. The product ratio was changed to 1:4 **34**:**35** at –78 °C and to 1:5 when the more sterically demanding Ph_3COOH was utilized at 0 °C. Since a more sterically hindered peroxide caused an increase in the undesired isomer, the smaller H_2O_2 was tested in an effort to reverse the selectivity. When the cyclobutanone **33** was exposed to H_2O_2 and Triton B at –78 °C in THF a >97:3 mixture of **34**:**35** was obtained. Exposure of lactone **34** to dimethyldioxirane[24] in acetone provided bis-epoxide **36** which was spectroscopically identical to an intermediate in the Corey synthesis thus constituting a formal synthesis of bilobalide. The bis-epoxide **36** was converted to bilobalide **2** by Corey in 10 steps.[5] This completed formal synthesis had two major problems: the circuitous route required to convert the photoadduct into the desired cyclobutanone and the problem also common to the Corey synthesis: the failure of the epoxide to react under reductive conditions requiring a lengthy alternative route to introduce the tertiary carbinol.

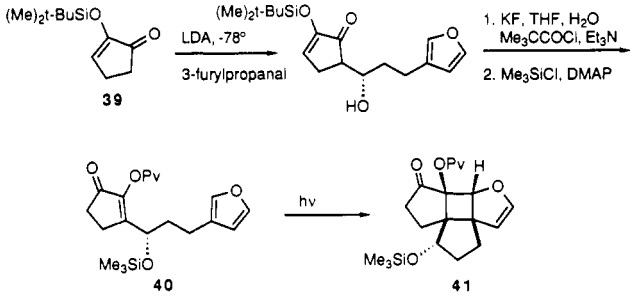
We thus set out to develop an alternate approach to bilobalide which would establish the tertiary carbinol center at an early stage of the synthesis and allow for a more direct conversion of the photoadduct to the cyclobutanone needed to execute the Baeyer–Villiger oxidation. The logical choice for a photosubstrate would be enone **37** which already incorporates the two necessary carbinol stereogenic centers on the tether and contains an α-alkoxy enone rather than the previous α-carbethoxy enone. This would avoid the problematic epoxide opening and should facilitate the

(19) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63.
(20) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.
(21) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.
(22) Tufariello, J. J.; Kissel, W. J. *Tetrahedron Lett.* **1966**, 6145.
(23) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *42*, 1485.
(24) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

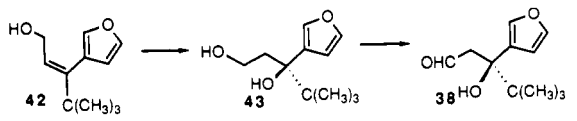
conversion of the photoadduct to the required cyclobutanone. This approach would require the preparation and irradiation of a 2-alkoxy-3-alkenylcyclopentenone. Enone **37** might be prepared by the aldol condensation of the enolate of ketone **39** with aldehyde **38**.



Intramolecular photocycloadditions of 2-(alkenyloxy)cyclopentenones have been studied by Pirrung[25] but no examples of 3-alkenyl-2-alkoxycyclopentenones have been reported. It seemed prudent to test a simple system in the photocycloaddition prior to construction of the required complex photosubstrate. Silylation of 1,2-cyclopentanedione[26] produced enol ether **39**. Addition of 3-furylpropanal to the enolate of ketone **39** gave the aldol product as a mixture of diastereomers. Various protecting groups were employed on the enol hydroxyl and the secondary hydroxyl in an attempt to identify the best combination for efficiency and stereoselectivity in the photocycloaddition reaction. The photocycloaddition reaction was found to be significantly enhanced by the use of acyl protecting groups on the enol hydroxyl. The best combination for both synthesis of the photosubstrate and the photocycloaddition was the enol pivalate and the secondary trimethylsilyl ether. Irradiation of enone **40** in hexanes gave a single diastereomeric photoadduct **41**.

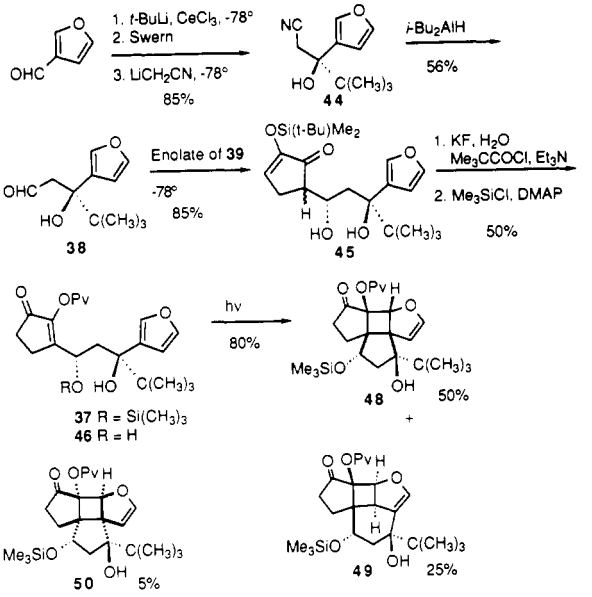


Preparation of the Photosubstrate. The aldehyde **38** could be readily prepared from the allylic alcohol **42** which had been used in the first approach. Sharpless epoxidation[19] of the allylic alcohol followed by reduction with lithium aluminum hydride provided the diol **43** which was oxidized under Swern conditions to give the desired aldehyde **38**. This approach required seven steps,

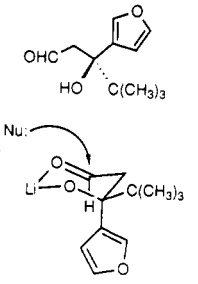


however, and a shorter route was investigated. Addition of t-BuCeCl$_2$[27] to 3-furaldehyde provided the secondary alcohol which was oxidized under Swern conditions. Addition of the ketone to a solution of lithioacetonitrile[28] gave an 85% overall yield of the β-hydroxynitrile **44**. Exposure of the nitrile to diisobutylaluminum hydride generated the desired aldehyde **38** after acidic workup. Addition of aldehyde **38** to 2 equiv of the lithium enolate of ketone **39** produced a 1:1 mixture of two

Scheme VII



diastereomers **45**. This mixture was of no consequence since the compounds were diastereomeric at the carbon adjacent to the ketone carbonyl and both isomers had the desired anti relationship between the hydroxyl on the tether. This was determined when the mixture of diastereomers was treated with aqueous KF to hydrolyze the silylenol ether followed by rearrangement of the enol to the more highly substituted double bond by exposure to triethylamine. In practice, the sequence was carried out without isolation of the enols; the more highly substituted enol was acylated in situ with pivaloyl chloride to give a single enol pivalate **46**. It is noteworthy that no β-elimination was detected when the intermediate enols were handled carefully and used immediately in the subsequent reaction. Silylation of the secondary hydroxyl completed the preparation of the photosubstrate **37** in 50% yield from the aldehyde **38**. The stereoselectivity in the aldol condensation can be rationalized through addition of the enolate to a six-membered ring chelate **47** in which the lithium alkoxide is coordinated to the aldehyde with the *tert*-butyl group occupying a pseudoequatorial position on the ring. Attack from the sterically more accessible face leads to the anti diol as observed for both diastereomers.



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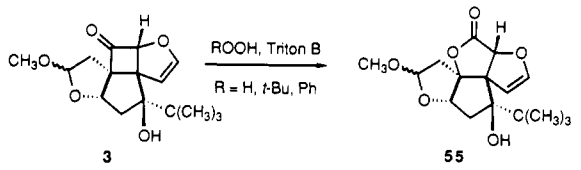
Conversion of the Photosubstrate to the Cyclobutanone. With an efficient, stereoselective synthesis of the photosubstrate in hand, the photoaddition was carried out to give a mixture of three products in 80% yield. The major product obtained in 50% isolated yield was the desired photoadduct **48** which results from cycloaddition through the transition state with both the (trimethylsilyl)oxy and the *tert*-butyl group occupying pseudoequatorial positions on the developing five-membered ring. About

(25) Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824.
(26) Tonari, K.; Machiya, K.; Ichimoto, I.; Ueda, H. *Agr. Biol. Chem.* **1980**, *44*, 2135.
(27) Immamoto, T.; Takiyama, N.; Nakmura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(28) Cuvigny, T.; Hullot, P.; Larcheveque, M. *J. Organomet. Chem.* **1973**, *57*, C36.

5% of the other diastereomer **50** was also obtained. The third product (about 25%) was the unexpected photoadduct **49** in which the [2 + 2] photoaddition had occurred between the enone and the less substituted furan double bond. This is the only enone–furan photoaddition, of the 10 to 15 which we have carried out, in which we have observed a photoadduct of this type. Attempts to improve this ratio by variation of the protecting groups on the enol or the secondary hydroxyl or employing different solvents or wavelengths have been unsuccessful.

The major product was readily separated and taken on in the synthesis. Hydroxylation of the photoadduct **48** by treatment with LDA and MoOPH[29] in THF provided the hydroxy ketone **51** in 80% yield. Cleavage of the cyclopentane ring with lead tetraacetate in methanol–benzene gave the aldehyde **52** which was directly converted to the acetal **53** (85% for two steps). The cyclobutanone carbonyl was then introduced in two steps by $LiAlH_4$ reduction of the two esters to give 1,2-diol **54** which was oxidatively cleaved with lead tetraacetate in benzene at 50 °C, 80% overall yield. This five-step conversion of the photoadduct to the desired cyclobutanone **3** was a significant improvement to the previous route in which 10 operations were required for a similar transformation.

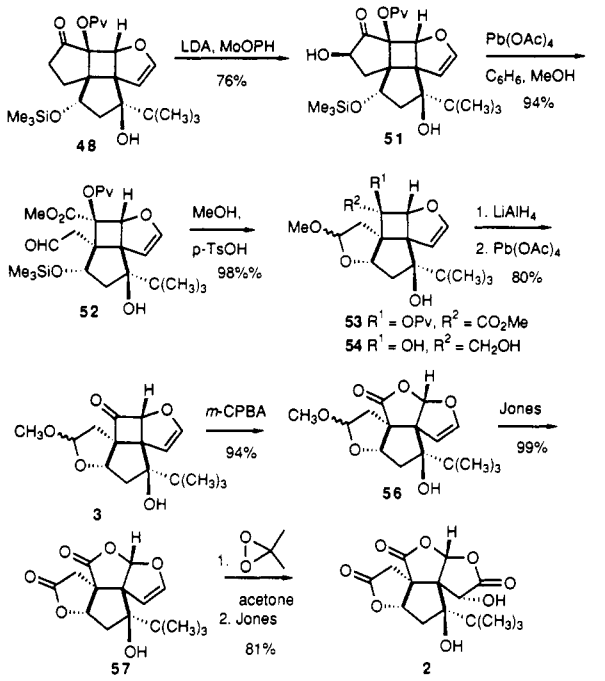
Completion of the Synthesis. With ready access to the cyclobutanone (13 steps) and our previous experience with the Baeyer–Villiger oxidation of cyclobutanone **33**, the completion of the synthesis seemed imminent. However, exposure of cyclobutanone **3** to the conditions which gave the best selectivity for cyclobutanone **33** (H_2O_2, Triton B, THF, −78 °C) resulted in the exclusive formation of the undesired lactone **55**. Different



solvents or bulkier peroxides had little or no effect on the selectivity. The original hope for the selectivity in this oxidation was that the oxygen-substituted carbon would migrate preferentially based on electronic grounds. We reasoned that perhaps stereoelectronic factors were overriding any electronic preference and that a more electrophilic reagent might favor migration based on electronic factors. When cyclobutanone **3** was exposed to *m*-CPBA in dichloromethane for 5 min the desired lactone **56** was the sole product. The enol ether was unreactive to these conditions even after extended reaction times. While the reasons for the dramatic change in selectivity are unclear, the result allowed the completion of the synthesis. The final stage of the synthesis required the oxidation of the acetal moiety to the lactone and conversion of the enol ether to an α-hydroxy lactone. While various scenarios can be envisioned, this sequence was best accomplished by selectively oxidizing the acetal and then operating on the enol ether. Exposure of lactone **56** to Jones reagent in refluxing acetone produced the dilactone **57** in 95% yield. The low reactivity of the enol ether was again apparent when the highly reactive dimethyldioxirane[24] required 24 h to effect oxidation. This stable epoxy enol ether was immediately oxidized with Jones reagent at room temperature for 20 min to produce synthetic (±)-bilobalide **2** which was spectrally identical to a sample of natural bilobalide.[30] This approach required 17 synthetic steps from 3-furaldehyde which is considerably shorter than our previous approach. The stereoselective aldol condensation to establish the stereogenic carbinol centers on the tether of the photosubstrate, the stereoselective photocycloaddition, the regioselective Baeyer–

(29) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 189.
(30) We thank Pierre Branquet and E. J. Corey for providing samples of natural bilobalide for comparison.

Scheme VIII



Villiger oxidation, and selective oxidation of the acetal and enol ether epoxides are noteworthy.

Experimental Section

Materials and Methods. All reagents were used as purchased from Aldrich Chemicals Co. unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium benzophenone ketyl immediately prior to use. Methylene chloride, triethylamine, diisopropylamine, and trimethylsilyl chloride were dried by distillation from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) and hexamethylphosphoramide (HMPA) were dried by refluxing over calcium hydride at reduced pressure followed by distillation and storage over 4-Å molecular sieves. Chromatography was performed according to the method of Still using silica gel with an average mesh of 40 μm. ^{1}H NMR spectra were recorded at 200 and 250 MHz on a Varian AC-200 spectrometer and a Bruker WM-250 spectrometer, respectively. All chemical shifts are reported as δ values in parts per million relative to the chloroform peak set at 7.24 ppm, if the solvent was $CDCl_3$, or the center peak set at 2.04 ppm, if the solvent was acetone-d^6. ^{13}C NMR spectra were recorded at 400 MHz on a Varian XL-400 spectrometer. Infrared spectra were recorded on a Beckman IR-4210. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Mass spectrometry was performed at the University of North Carolina School of Public Health. All reactions involving air-sensitive or moisture-sensitive processes were carried out under a nitrogen atmosphere and in glassware which had been flame dried with continuous nitrogen flushing.

Alcohol 10. A solution of 25 g (0.26 mol) of 3-furaldehyde and 90.48 g (0.26 mol) of (carbethoxymethylene)triphenylphosphorane in 200 mL of CH_2Cl_2 was stirred overnight, and the solvent was removed under reduced pressure. The crude residue was washed repeatedly with methylbutane, and the combined extracts were cooled and filtered. The filtrate was concentrated, and the residue was chromatographed to provide 40.56 g (94%) of unsaturated ester as white crystals, mp 38–38.5 °C; R_f (25% ethyl acetate/hexane) 0.63; ^{1}H NMR (200 MHz) δ 1.27 (t, J = 6.6 Hz, 3 H), 4.18 (q, J = 6.6 Hz, 2 H), 6.12 (d J = 15.5 Hz, 1 H), 6.53 (m, 1 H), 7.37 (m, 1 H), 7.53 (d, J = 15.5 Hz, 1 H), 7.60 (m, 1 H); IR ($CHCl_3$) 3115, 2985, 1710, 1665, 1320, 1225, 1160, 918 cm^{-1}; ^{13}C NMR (400 MHz) δ 14.33, 60.39, 107.45, 118.06, 122.65, 134.54, 144.39, 144.44, 166.99; HRMS calcd for $C_9H_{10}O_3$ 166.0629, found 166.0627.

To a mechanically stirred suspension of 15 g (0.618 mol) of copper(I) cyanide in 1000 mL of ethyl ether at −78 °C was added dropwise 197.6 mL (0.336 mol) of a 1.7-M solution of t-BuLi in pentane. After addition was complete, the suspension was stirred at −78 °C for 50 min and then warmed to −45 °C for 30 min and recooled to −78 °C. To this suspension was added 20 g of the unsaturated ester above in 200 mL of ether. The

resulting bright orange suspension was allowed to stir at −78 °C for 30 min and then at −45 °C for 1 h. Then 83.6 mL (0.6 mol) of triethylamine was added dropwise followed immediately by 76.1 mL (0.6 mol) of trimethylsilyl chloride. The mixture was stirred for 30 min and quenched with saturated NH_4Cl solution. The organic layer was washed sequentially with water, NH_4OH, and brine. The organic layer was dried and concentrated, and the residue was taken up in 500 mL of 95% ethanol and treated with 7 g of $KF-H_2O$ and 0.75 g of K_2CO_3. The suspension was stirred for 14 h at 25 °C whereupon the ethanol was removed. The crude product was taken up in ether and washed with water and brine. The organic layer was dried and concentrated. The residue was chromatographed through a short silica column to provide 26.8 g (100%) of the ester as a pale yellow liquid: R_f (25% ethyl acetate/hexanes) 0.57; ^{1}H NMR (200 MHz) δ 0.91 (s, 9 H), 1.11 (t, J = 6.6 Hz, 3 H), 2.67 (band, 3 H), 4.00 (q, J = 6.6 Hz, 2 H), 6.27 (m, 1 H), 7.20 (m, 1 H), 7.33 (t, J = 1.8 Hz, 1 H); IR 2965, 1740, 1160, 1032, 873 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1410.

To a mechanically stirred suspension of $LiAlH_4$ in 450 mL of ethyl ether was added a solution of the above ester (10 g, 44.64 mmol) in 100 mL of ethyl ether. After the addition was complete, the suspension was stirred for 30 min and then quenched with 5% NaOH solution until a white free-flowing suspension formed. The reaction mixture was filtered, and the salts were washed with ether. The organic layer was dried and concentrated to provide 8.12 g (100%) of alcohol **10** as a clear oil: R_f (25% ethyl acetate/hexanes) 0.27; ^{1}H NMR (200 MHz) δ 0.88 (s, 9 H), 1.64 (band, 2 H), 1.95 (band, 1 H), 2.35 (dd, J = 1.5, 11.9 Hz, 1 H), 3.42 (band, 2 H), 6.23 (m, 1 H), 7.17 (m, 1 H), 7.32 (m, 1 H); ^{13}C NMR (400 MHz) δ 27.93, 32.64, 33.06, 43.06, 61.90, 110.93, 125.47, 140.19, 142.32; IR (neat) 3340, 2960, 1035, 870 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.15; H, 9.99.

Bromine 11. Triphenylphosphine, 2.37 g (9.05 mmol), which had been previously dried over P_2O_5 was dissolved in 30 mL of ether and cooled to 0 °C whereupon 3.00 g (9.05 mmol) of carbon tetrabromide was added in one portion. The heterogenous mixture was stirred for 30 min at 0 °C, and a solution of 823 mg (4.53 mmol) of alcohol **10** in 5 mL of ether was added rapidly. The solution was stirred at 25 °C for 4 h, and then 2 mL of ethanol was added and the mixture stirred for an additional 1 h. The reaction mixture was diluted with cold hexanes, filtered, and concentrated. Chromatography of the residue provided 945 mg (85%) of bromide **11** as a clear oil: R_f (25% ethyl acetate/hexanes) 0.79; ^{1}H NMR (200 MHz) δ 0.90 (s, 9 H), 1.97 (band, 1 H), 2.22 (band, 1 H), 2.47 (dd, J = 3.2, 12.4 Hz, 1 H), 3.08 (m, 1 H), 3.36 (m, 1 H), 6.24 (m, 1 H), 7.22 (m, 1 H), 7.36 (t, J = 1.5 Hz, 1 H). Anal. Calcd for C_7H_9BrO: C, 44.47; H, 4.80. Found: C, 44.12; H, 4.77.

Diester 13. A solution of 329 mg (1.34 mmol) of bromide **11** in 10 mL of THF was added to 44 mg (1.82 mmol) of magnesium turnings in 5 mL of THF at a rate to maintain gentle reflux. After addition, the mixture was heated at reflux for 1 h. The mixture was then cooled to 25 °C and cannulated into a mixture of 254 mg (1.36 mmol) of dry copper(I) iodide, 0.23 mL (1.52 mmol) of TMEDA, and 5 mL of THF at −78 °C. This was allowed to stir for 1 h, and 211 mg (1.07 mmol) of dimethyl 5,5-dimethylhex-2-ynedioate (**12**) in 3 mL of THF was added dropwise. The mixture was stirred for 75 min at −78 °C whereupon the reactive was quenched with saturated NH_4Cl. The mixture was diluted with ether, extracted with water (3 × 50 mL), dried, and concentrated. The residue was chromatographed to provide 153 mg (32%) of diester **13** as a yellow oil: R_f (25% ethyl acetate/hexanes) 0.63; ^{1}H NMR (200 MHz) δ 0.86 (s, 9 H), 1.14 (s, 6 H), 1.64 (band, 4 H), 2.12 (dd, J = 1.7, 11.9 Hz, 1 H), 3.03 (AB, J_{obs} = 12.7 Hz, 2 H), 3.52 (s, 3 H), 3.67 (s, 3 H), 5.67 (bs, 1 H), 6.19 (m, 1 H), 7.14 (m, 1 H), 7.34 (t, J = 1.7 Hz, 1 H); IR (neat) 2945, 2872, 1740, 1725, 1642, 1472, 1436, 1368, 1242, 1142, 869 cm^{-1}; HRMS calcd for $C_{17}H_{24}O_5$ 308.1624, found 308.1617.

Cyclopentenone 8. To a solution of 0.152 mL (1.12 mmol) of diisopropylamine in 12 mL of THF at −78 °C was added 0.448 mL (1.12 mmol) of a 2.5 M solution of n-BuLi in hexanes. The mixture was stirred for 30 min at −78 °C whereupon 153 mg (0.42 mmol) of diester **13** in 3 mL of THF was added dropwise. The mixture was stirred for 10 min and quenched with saturated NH_4Cl. The mixture was diluted with ether, washed with water, dried, and concentrated. The residue was chromatographed to give 71 mg (51%) of cyclopentenone **8** as a pale yellow oil: R_f (25% ethyl acetate/hexanes) 0.30; ^{1}H NMR (200 MHz) δ 0.87 (s, 9 H), 1.10 (s, 3 H), 1.30 (s, 3 H), 1.66 (band, 1 H), 1.96 (m, 1 H), 2.21 (dd, J = 2.9, 12.4 Hz, 1 H), 2.56 (band, 4 H), 3.78 (s, 3 H), 6.25 (m, 1 H); 7.18 (m, 1 H), 7.37 (t, J = 1.4 Hz, 1 H); IR (neat) 2960, 1744, 1720, 1625, 1380, 1360, 1212, 1142, 1020 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_4$ 276.1361, found 276.1366.

Photoadduct 22. A solution of cyclopentenone **8**, 71 mg (0.225 mmol), in 50 mL of 4:1 hexanes/dichloromethane was irradiated with a 450-W mercury vapor lamp through uranium glass for 5 h. The solvent was removed to provide 71 mg (100%) of photoadduct **22** as a 1.5:1 mixture of diastereomers: R_f (25% ethyl acetate/hexanes) 0.42; ^{1}H NMR (200 MHz), major diastereomers δ 0.93 (s, 9 H), 1.22 (s, 3 H), 1.28 (s, 3 H), 1.76 (band, 6 H), 2.33 (A of AB, J_{obs} = 13.3 Hz, 1 H), 3.73 (s, 3 H), 4.98 (s, 1 H), 5.23 (d, J = 3.5 Hz, 1 H), 6.27 (d, J = 3.5 Hz, 1 H); IR (neat) 2958, 2872, 1745, 1725, 1600, 1382, 1369, 1240, 1140, 1025, 732 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_4$ 276.1361, found 276.1359.

Photoadduct 16. A solution of cyclopentenone **9**, 2.65 g (7.8 mmol), in 150 mL of 50:1 hexanes/dichloromethane was irradiated with a 450-W mercury vapor lamp through uranium glass for 6 h. The solvent was removed, and the residue was chromatographed to provide 1.73 g (66%) of photoadduct **16** as a single diastereomer: ^{1}H NMR (200 MHz) δ 1.65–2.20 (band, 4 H), 2.52 (ddd, J = 3, 9, 15 Hz, 1 H), 2.91 (ddd, J = 10, 9, 19.5 Hz, 1 H), 3.72 (s, 3 H), 3.99 (t, J = 2 Hz, 1 H), 4.93 (s, 1 H), 5.04 (d, J = 3 Hz, 1 H), 6.38 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{17}H_{24}O_5Si$: C, 60.69; H 7.19. Found: C, 60.53; H, 7.06.

Furan Dibromide 23. A mechanically stirred slurry of 100 mL of methylene chloride and 13.076 g (0.2 mol) of zinc dust was cooled to 0 °C, and a solution of carbon tetrabromide (66.33 g, 0.2 mol) in 100 mL of methylene chloride was added dropwise. A solution of triphenylphosphine (52.46 g, 0.2 mol) in 100 mL of methylene chloride was then added dropwise, and the solution was stirred at room temperature for 6 h. The mixture was then cooled to 0 °C, and a solution of 3-furaldehyde (9.6 g, 0.1 mol) in 50 mL of methylene chloride was added dropwise. The reaction was then allowed to stir overnight. Addition of methyl butane (ca. 400 mL) to the reaction mixture caused the precipitation of a black residue. The solution was decanted, the residue was dissolved in a minimum of methylene chloride, and methylbutane was again added to cause precipitation. This process was repeated until the residue showed no traces of product by TLC analysis. The methylbutane solution was concentrated and chromatographed to afford 24.939 g (99%) of dibromide **23** as a brown oil, R_f = 0.56 (10% ethyl acetate/hexanes; UV active). This compound was not further characterized due to its marginal stability: ^{1}H NMR ($CDCl_3$) δ 6.79 (1 H, m), 7.27 (1 H, s), 7.42 (1 H, m), 7.83 (1 H, m).

Acetylenic Ester 24. To a mechanically stirred solution of 250 mL of THF and 24.939 g (0.099 mol) of dibromide **23** cooled to −78 °C was added dropwise 84.0 mL (0.210 mol) of 2.5 M *n*-butyllithium. After 25 min, 27.0 mL (0.350 mol) of methyl chloroformate was added in one portion. After 15 min, the dry ice/acetone bath was removed and the solution was stirred for an additional 10 min before being quenched with saturated NH_4Cl. The aqueous phase was extracted with ether, and the combined extracts were dried over $MgSO_4$. Chromatography afforded 11.296 g (76%) of ester **24** as yellow prisms: mp 44 °C; R_f = 0.32 (10% ethyl acetate/hexanes, UV active); ^{1}H NMR ($CDCl_3$) δ 3.83 (3 H, s), 6.55 (1 H, dd, J = 7.5, 1.7 Hz), 7.43 (1 H, dd, J = 1.7, 1.7 Hz), 7.82 (1 H, dd, J = 0.75, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 52.57, 78.69, 82.76, 104.63, 112.35, 143.33, 149.33, 152.13; IR (solution, CH_2Cl_2) 2214, 1729, 1710, 1516, 1352, 1162 cm^{-1}. Anal. Calcd for $C_8H_6O_3$: C, 63.70; H, 4.03. Found: C, 63.83; H, 4.07.

Methyl 4,4-Dimethyl-3-(3′-furyl)-2-pentenoate (25). To a mechanically stirred suspension of 11.046 g (58 mmol) of copper(I) iodide in 130 mL of ether (cooled to 0 °C) was added dropwise 38.7 mL (58 mmol) of 1.5 M methyllithium. After 30 min, the reaction was cooled to −78 °C, and 34.1 mL (58 mmol) of 1.7 M *tert*-butyllithium was added dropwise. The solution was warmed to −35 °C and then cooled back to −78 °C. A solution of ester **24** (8.18 g, 54 mmol) in 40 mL of THF was then added dropwise. After 45 min, the reaction was quenched at −78 °C with saturated NH_4Cl, filtered through a pad of Celite, and extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated to give 9.03 g (80%) of ester **25** as a yellow oil. The crude product was used for the next reaction without further purification: R_f = 0.33 (10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.12 (9 H, s), 3.57 (3 H, s), 6.00 (1-H, s), 6.26 (1 H, m), 7.19 (1 H, m), 7.43 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 28.68, 37.13, 51.00, 112.41, 117.04, 121.50, 138.64, 141.86, 158.66, 166.79; IR (film) 1746, 1645, 1506, 1027 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.09; H, 7.73.

4,4-Dimethyl-3-(3′-furyl)-2-penten-1-ol (26). A mechanically stirred solution of 200 mL of ether and 8.13 g (43 mmol) of unsaturated ester **25** was cooled to 0 °C. A solution of 1 M DIBAL (95 mL; 95 mmol) was added dropwise. The reaction was stirred at room temperature for 2 h, cooled to 0 °C, and then quenched by the careful addition of 10% HCl. The aqueous phase was extracted with ether. The combined extracts

were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Chromatography yielded 5.580 g (72%) of alcohol **26** as a viscous, yellow oil: R_f = 0.26 (25% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 1.07 (9 H, s), 3.95 (2 H, d, J = 6.6 Hz), 5.78 (1 H, t, J = 6.6 Hz), 6.21 (1 H, m), 7.16 (1 H, m), 7.42 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 29.21, 35.78, 60.91, 112.77, 121.63, 125.02, 139.54, 142.24, 144.59; IR 1506, 1270, 1173, 1032 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.37; H, 8.96.

Acetylenic Ester 7. A solution of 30 mL of methylene chloride and 1.35 mL (31 mmol) of oxallyl chloride was cooled to −78 °C, and a solution of DMSO (2.2 mL, 31 mmol) in 10 mL of methylene chloride was cooled to −78 °C, and a solution of DMSO (2.2 mL, 31 mmol) in 10 mL of methylene chloride was added at a rate slow enough to keep the temperature below −65 °C. After 15 min, a solution of alcohol **26** (2.535 g, 14.1 mmol) in 15 mL of methylene chloride was added slowly. After 30 min, 7 mL (50 mmol) of triethylamine was added dropwise. The reaction was stirred for 5 min and then allowed to warm to room temperature. The reaction mixture was then poured into H_2O and extracted with methylene chloride. The combined extracts were washed with 10% HCl and saturated $NaHCO_3$ and then dried over $MgSO_4$. The crude aldehyde (2.39 g, 95%) was used immediately in the next reaction: R_f = 0.49 (25% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 1.27 (9 H, s), 6.22 (1 H, d J = 6.8 Hz), 6.41 (1 H, m), 7.34 (1 H, m), 7.49 (1 H, m), 9.43 (1 H, d J = 6.8 Hz).

To a solution of 40 mL of THF and 2.8 mL (20 mmol) of diisopropylamine cooled to −78 °C was added 8 mL (20 mmol) of 2.5 M *n*-butyllithium. After 10 min, a solution of ethyl propiolate (2.03 mL, 20 mmol) in 15 mL of THF was added over 30 min. After 20 min, a solution of the aldehyde above (2.38 g, 13 mmol) in 10 mL of THF was added dropwise. The reaction was stirred for 20 min and quenched at −78 °C with saturated NH_4Cl. The mixture was extracted with ether, and the combined extracts were dried with $MgSO_4$. Chromatography provided 3.335 g (90%) of ester **7** as a yellow oil: R_f = 0.31 (25% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 1.09 (9 H, s), 1.31 (3 H, t, J = 7.1 Hz), 4.79 (1 H, dd, J = 4.7, 8.7 Hz), 5.71 (1 H, d, J = 8.7 Hz), 6.26 (1 H, m), 7.25 (1 H, m), 7.43 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.00, 28.99, 31.32, 36.06, 60.26, 62.17, 86.94, 112.53, 120.74, 123.61, 140.10, 142.56, 147.38, 153.46; IR (film) 2213, 1701, 1238 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.46; H, 7.32.

Epoxy Alcohol 6. To a solution of 40 mL of methylene chloride, 3.335 g (12.07 mmol) of alcohol **7**, and 80 mg (0.3 mmol) of $VO(acac)_2$, cooled to 0 °C, was added dropwise 3.7 mL (15 mmol) of a 4.1 M *tert*-butyl hydroperoxide solution. The reaction was stirred overnight at room temperature, and then an aliquot was removed and concentrated. NMR analysis showed no remaining starting material, and the remainder of the reaction was concentrated and chromatographed to give 2.872 g (81%) of **6** as a yellow oil. The crude epoxide was used as soon as possible for the next reaction: R_f = 0.31 (25% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 0.97 (9 H, s), 1.33 (3 H, t, J = 7.1 Hz), 3.46 (1 H, d, J = 7.9 Hz), 3.83 (1 H, d, J = 7.9 Hz), 4.27 (2 H, q, J = 7.1 Hz), 6.41 (1 H, m), 7.37–7.41 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 1.99, 25.77, 34.09, 62.12, 62.37, 63.16, 66.07, 78.11, 83.06, 111.09, 120.61, 141.05, 142.47, 153.02, 189.19; IR (film) 2223, 1718, 1374, 1260 cm^{-1}.

Cyclopentenone 5. A mixture of 65 mL of ether, 13 mL (64.7 mmol) of [(1-ethoxycyclopropyl)oxy]trimethylsilane, and 32 mL of a 1.5 M $ZnCl_2$ solution was irradiated for 1 h with ultrasound in a Branson ultrasonic cleaner at which time a gelatinous precipitate was observed at the bottom of the flask. The mixture was stirred at room temperature for 10 min and then cooled to 0 °C. To this suspension was added 0.270 g (1.3 mmol, 10 mol % of ester) of $CuBr{\cdot}Me_2S$, a solution of ester **6** (3.78 g, 12.9 mmol) in 25 mL of THF, and 7.7 mL (65 mmol) of HMPA. After 5 h, the reaction was quenched with saturated NH_4Cl and extracted with ether. The combined extracts were dried over $MgSO_4$ and chromatographed to afford 2.853 g (52%) of enone **5** as a white solid: mp 108 °C; R_f = 0.28 (25% ethyl acetate/hexanes, UV active); ^1H NMR ($CDCl_3$) δ 0.11 (9 H, s), 0.94 (9 H, s), 1.27 (3 H, t, J = 7.1 Hz), 2.46–2.59 (2 H, band), 2.81–2.97 (2 H, m), 3.40 (1 H, d, J = 7.8 Hz), 4.04–4.27 (2 H, m), 4.51 (1 H, d, J = 7.8 Hz), 6.30 (1 H, m), 7.26 (1 H, m), 7.26 (1 H, m); ^{13}C NMR δ 0.061, 14.08, 26.01, 34.38, 34.70, 61.05, 62.22, 66.13, 69.13, 95.74, 111.07, 121.41, 127.57, 140.93, 142.53, 162.55, 178.18, 203.57; IR (solution, CH_2Cl_2) 1750, 1725, 1272 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_6Si$: C, 62.82; H, 7.67. Found: C, 62.81; H, 7.67.

Photoadduct 4. A solution of enone **5** (2.835 g, 6.8 mmol) in 125 mL of 10:1 hexanes/methylene chloride was irradiated in a toroidal-reactor with a 450-W Hanovia medium-pressure mercury vapor lamp fitted with a uranium glass sleeve (>350 nm) for 16 h. After the reaction was complete, the solution was concentrated and chromatographed to provide 1.984 (69%) of photoadduct **4** as a white solid: mp 112 °C; R_f = 0.49 (25% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 0.17 (9 H, s), 1.03 (9 H, s), 1.29 (3 H, t, J = 7 Hz), 1.93–2.02 (2 H, m), 2.34–2.70 (2 H, m), 3.44 (1 H, d, J = 0.5 Hz), 4.15–4.30 (2 H, m), 4.40 (1 H, d, J = 0.5 Hz), 5.15 (1 H, s), 5.31 (1 H, d, J = 2.9 Hz), 6.53 (1 H, d); ^{13}C NMR ($CDCl_3$) δ 0.07, 24.96, 26.42, 33.07, 39.67, 61.08, 61.33, 66.79, 67.20, 67.90, 73.18, 84.17, 102.80, 152.11, 167.12, 211.68; IR (solution, CH_2Cl_2) 1760, 1729, 1605, 1271 cm^{-1}. Anal. Calcd for $C_{22}H_{32}O_6Si$: C, 62.80; H, 7.67. Found: C, 62.76; H, 7.68.

Diol 27. To a solution of 10 mL of THF and 0.036 mL (0.26 mmol) of diisopropylamine at −78 °C was added dropwise 0.1 mL (0.26 mmol) of 2.5 M *n*-butyllithium. After 10 min, a solution of photoadduct **4** (100 mg, 0.24 mmol) in 8 mL of THF was added dropwise. After 30 min, a solution of TMSCl (0.04 mL, 0.30 mmol) in 4 mL of THF was added dropwise. The mixture was stirred for 15 min and then quenched by the addition of saturated $NaHCO_3$. The aqueous phase was extracted with ether, and the combined extracts were dried over Na_2SO_4. Chromatography afforded 115 mg (97%) of crude enol ether as a pale, yellow oil. The product was used immediately in the next reaction: R_f = 0.67 (25% ethyl acetate/hexanes, UV active); ^1H NMR ($CDCl_3$) δ 0.17 (9 H, s), 0.18 (9 H, s), 1.02 (9 H, s) 1.28 (3 H, t, J = 7.2 Hz), 2.16 (1 H, dd, J = 2.4, 17.1 Hz), 2.44 (1 H, dd, J = 2.4, 17.1 Hz), 3.39 (1 H, s), 4.06–4.35 (2 H, m), 4.38 (1 H, s), 4.82 (1 H, dd, J = 2.4, 2.4 Hz), 5.05 (1 H, d, J = 3 Hz), 5.24 (1 H, s), 6.48 (1 H, d, J = 3 Hz).

To a mixture of 15 mL of methylene chloride, 115 mg (0.23 mmol) of crude silyl enol ether, and 25 mg (0.3 mmol) of $NaHCO_3$ at 0 °C was added 86 mg (0.25 mmol) of *m*-CPBA. After 30 min, the reaction was allowed to warm to room temperature. The reaction was quenched after 2 h with 10% $NaHSO_3$. The aqueous layer was extracted with methylene chloride, and the combined extracts were concentrated in vacuo. The residue was dissolved in 20 mL of a 5:1 THF/H_2O solution, and 30 mg of PPTS was added. After 20 min, saturated $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and chromatographed to yield 74 mg (85%) of α-hydroxy ketone **27** as a white solid: mp 177–179 °C; R_f = 0.33 (75% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$) δ 1.05 (9 H, s), 1.31 (3 H, t, J = 7.3 Hz), 1.93 (1 H, A of ABX, J = 11.2, 14.3 Hz), 2.47 (1 H, B of ABX, J = 9.3, 14.3 Hz), 3.64 (1 H, d, J = 0.7 Hz), 4.22–4.33 (2 H, m), 4.52–4.56 (2 H), 5.13 (1 H, s), 5.40 (1 H, d, J = 3 Hz), 6.55 (1 H, d, J = 3 Hz); ^{13}C NMR (acetone-d_6) δ 14.54, 26.67, 33.71, 34.76, 61.50, 61.92, 64.78, 66.20, 68.51, 72.71, 74.36, 75.85, 84.53, 104.48, 153.00, 167.89, 211.27; IR (solution, CH_2Cl_2) 1767, 1720, 1604, 1270 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.26; H, 6.64. Found: C, 62.52; H, 6.63.

Hemiacetal 28. A mixture of α-hydroxy ketone **27** (23 mg, 0.063 mmol), 8 mL of a 2:1 methanol/water solution, and 69 mg (0.32 mmol) of $NaIO_4$ was stirred for 30 min at which time 5 mL of water and 2 mL of 2 N H_2SO_4 were added. The solution was extracted with $CHCl_3$, and the combined extracts were dried over Na_2SO_4. Hemiacetal **28** (24 mg, 100%) was isolated as a viscous, yellow oil. The crude product was used in the next reaction: ^1H NMR ($CDCl_3$) δ 0.98 (9 H, s), 1.30 (3 H, t, J = 7.2 Hz), 2.17 (1 H, A of ABX, J = 4.5, 14.2 Hz), 2.81 (1 H, B of ABX, J = 14.2 Hz), 3.63 (1 H, s), 4.29 (2 H, m), 4.51 (1 H, s), 5.30 (1 H, d, J = 2.8 Hz), 5.44 (1 H, s), 5.53 (1 H, d, J = 4.5 Hz), 6.42 (1 H, d, J = 2.8 Hz).

Methyl Acetal 29. A solution of hemiacetal **28** (27 mg, 0.071 mmol) and 10 mg of *p*-TsOH in 8 mL of 1:1 methanol/trimethyl orthoformate was stirred for 2 h. The mixture was diluted with water, and solid $NaHCO_3$ was added. The mixture was extracted with $CHCl_3$, and the combined extracts were dried over Na_2SO_4. Removal of the solvent yielded 28 mg (100%) of a mixture of anomers of methyl acetal **29** as a viscous, yellow oil. The crude product was used in the next reaction: ^1H NMR ($CDCl_3$) major anomer δ 0.96 (9 H, s), 1.24–1.32 (3 H, m), 2.14 (1 H, A of ABX, J = 4.6, 14.2 Hz), 2.73 (1 H, B of ABX, J = 14.2 Hz), 3.26 (3 H, s), 3.59 (1 H, s), 4.20–4.30 (2 H, m), 4.46 (1 H, s), 4.92 (1 H, d, J = 4.6 Hz), 5.21 (1 H, d, J = 2.8 Hz), 5.39 (1 H, s), 6.38 (1 H, d, J = 2.8 Hz); ^1H NMR minor anomer δ 0.97 (9 H, s), 1.24–1.32 (3 H, m), 2.57 (2 H, dd, J = 4.7, 14.2 Hz), 3.36 (3 H, s), 3.62 (1 H, s), 4.20–4.30 (2 H, m), 4.59 (1 H, s), 4.87 (1 H, dd, J = 4.7, 4.7 Hz), 5.06 (1 H, d, J = 2.9 Hz), 5.06 (1 H, d, J = 2.9 Hz), 6.48 (1 H, d, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) both anomers δ 14.05, 26.16, 26.19, 32.85, 32.88, 38.13, 38.73, 54.59, 55.58, 61.82, 61.87, 62.85, 63.06, 64.06, 66.25, 66.49, 66.92, 68.10, 74.55, 75.82, 82.07, 83.06, 83.69, 84.13, 101.28, 104.03, 105.33, 105.54, 149.60, 151.27, 149.60, 151.27, 166.35, 166.47, 170.32, 170.60; IR (film) 1738, 1607, 1363, 1262 cm^{-1}.

Ester 30. A solution of 28 mg (0.071 mmol) of acid ester **29** in 10 mL of toluene was heated at reflux for 1.5 h and then cooled and concentrated in vacuo. Chromatography yielded 24 mg (96%) of ester **30** as a yellow oil: R_f = 0.67, 0.63 (50% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) major isomer δ 0.99 (9 H, s), 1.27 (3 H, t, J = 7.1 Hz), 1.99 (1 H, A of ABX, J = 4.5, 13 Hz), 2.45 (1 H, B of ABX, J = 13 Hz), 3.11 (1 H, d, J = 4.1 Hz), 3.29 (3 H, s), 3.63 (1 H, s), 4.06–4.27 (2 H, m), 4.49 (1 H, s), 4.90 (1 H, d, J = 4.5 Hz), 5.11 (1 H, d, J = 4.1 Hz), 5.21 (1 H, d, J = 2.9 Hz), 6.45 (1 H, d, J = 2.9 Hz); ^{1}H NMR minor anomer δ 1.01 (9 H, s), 1.27 (3 H, t, J = 7.1 Hz), 2.18 (1 H, A of ABX, J = 4.6, 14.2 Hz), 2.56 (1 H, B of ABX, J = 14.2 Hz), 3.27 (3 H, s), 3.47 (1 H, d, J = 7.1 Hz), 3.63 (1 H, s), 3.71 (1 H, s), 4.06–4.27 (2 H, m), 4.49 (1 H, s), 4.92 (1 H, d), 4.98 (1 H, d, J = 7.1 Hz), 5.17 (1 H, d, J = 2.7 Hz), 6.45 (1 H, d, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) both anomers δ 14.20, 14.32, 26.16, 26.36, 32.81, 32.96, 36.78, 41.65, 49.89, 50.65, 54.38, 54.45, 60.21, 60.60, 63.54, 64.71, 68.71, 68.25, 68.86, 75.97, 76.62, 80.98, 81.46, 81.98, 87.24, 103.46, 103.92, 104.70, 106.06, 148.78, 149.61, 169.69; IR (film) 1744, 1728, 1602, 1482, 1362 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.00; H, 7.43.

Alcohol 31. A solution of ester **30** (140 mg, 0.40 mmol) in 10 mL of THF was added dropwise to a suspension of 20 mg (0.66 mmol) of lithium aluminum hydride in 15 mL of THF at 0 °C. The reaction was stirred at room temperature for 2 h and then quenched with 10% NaOH. The precipitated salts were filtered and washed with ethyl acetate. The filtrate and the washings were dried over Na_2SO_4. Chromatography yielded 115 mg (93%) of alcohol **31** as a white solid: mp 84 °C; R_f = 0.33, 0.29 (50% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.95–0.99 (9 H, m), 1.73–1.85 (1 H, m), 2.22–2.52 (2 H, m), 3.24–3.33 (3 H, m), 3.65–3.83 (3 H, m), 4.51–4.59 (1 H, m), 4.84–4.96 (2 H, m), 5.11–5.19 (1 H, m), 6.42–6.52 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 26.13, 26.24, 26.40, 32.86, 34.83, 41.72, 45.94, 49.36, 54.41, 59.83, 63.33, 68.67, 68.82, 79.38, 81.02, 81.90, 81.99, 87.27, 104.06, 104.71, 105.72, 148.60, 149.25; IR (solution, CH_2Cl_2) 1604, 1482, 1362, 1100 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.19; 7.87.

Methylenecyclobutane 32. To a solution of 115 mg (0.37 mmol) of freshly chromatographed alcohol **31** and 100 mg (0.44 mmol) of *o*-NO_2-PhSeCN in 2 mL of THF was added 0.1 mL (0.44 mmol) of *n*-Bu_3P. The reaction immediately turned dark, and TLC showed the reaction was complete. The solution was concentrated and chromatographed to afford 144 mg (79%) of selenide as a yellow solid. The product was used immediately in the next reaction: R_f = 0.61, 0.58 (50% ethyl acetate/hexanes); ^{1}H ($CDCl_3$) major isomer δ 1.01 (9 H, s), 1.77–1.88 (1 H, m), 2.41–2.61 (2 H, m), 2.98–3.16 (2 H, m, $SeCH_2$), 3.28 (3 H, s), 3.75 (1 H, s), 4.54 (1 H, s), 4.59 (1 H, d, J = 3 Hz), 4.88–4.95 (1 H, m), 5.07 (1 H, d, J = 2.7 Hz), 6.47 (1 H, d, J = 2.7 Hz), 7.28–7.36 (1 H, m), 7.47–7.55 (2 H, m), 8.28 (1 H, d, J = 6.6 Hz); ^{1}H ($CDCl_3$) minor isomer δ 1.01 (9 H, s), 1.77–1.88 (1 H, m), 2.41–2.61 (2 H, m), 2.98–3.16 (2 H, m, $SeCH_2$), 3.37 (3 H, s), 3.70 (1 H, s), 4.54 (1 H, s), 4.57 (1 H, d, J = 3 Hz), 4.88–4.95 (1 H, m), 5.19 (1 H, d, J = 2.7 Hz), 6.43 (1 H, d, J = 2.7 Hz), 7.28–7.36 (1 H, m), 7.47–7.55 (2 H, m), 8.28 (1 H, d, J = 6.6 Hz).

To a solution of 144 mg (0.29 mmol) of selenide from the reaction above on 15 mL of THF at 0 °C was added 0.3 mL of 30% H_2O_2. The reaction was stirred for 2.5 h and quenched with 10% $Na_2S_2O_5$. The mixture was extracted with methylene chloride, and the combined extracts were dried over Na_2SO_4. Chromatography yielded 61 mg (72%) of alkene **32** as a waxy, yellow solid: mp 81 °C; R_f = 0.55 (25% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.01 (9 H, s), 1.92 (1 H, A of ABX, J = 4.5, 13.6 Hz), 2.42 (1 H, B of ABX, J = 13.6 Hz), 3.30 (3 H, s, CH_3OCH), 3.67 (1 H, s), 4.33 (1 H, s), 4.96 (1 H, d, J = 4.5 Hz), 5.09 (1 H, dd, J = 1.5, 1.5 Hz), 5.18 (1 H, d, J = 2.9 Hz), 5.19 (1 H, dd, J = 1.5, 1.5 Hz), 5.30 (1 H, dd, J = 1.5, 1.5 Hz), 6.46 (1 H, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 26.26, 32.98, 40.50, 54.44, 64.28, 69.11, 72.06, 76.21, 84.24, 86.74, 102.98, 105.74, 112.44, 149.35, 153.22; IR (solution, CH_2Cl_2) 1601, 1484, 1363, 1218, 1199, 1103 cm^{-1}. Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.32; H, 7.67.

Cyclobutanone 33. A solution of 1.2 mg (0.0041 mmol) of alkene **32**, 3 mL of THF, 1 mL of H_2O, 20 mg (0.09 mmol) of $NaIO_4$, and 0.2 mL (0.0008 mmol) of a 0.004 M solution of OsO_4 in dioxane was stirred for 48 h. The reaction mixture was diluted with H_2O and extracted with methylene chloride. The combined extracts were dried over Na_2SO_4 and chromatographed to afford 0.9 mg (70%) of cyclobutanone **67** as a white solid: mp 93 °C; R_f = 0.44 (25% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.05 (9 H, s), 2.14 (1 H, A of ABX, J = 4.3, 13.5 Hz), 2.42 (1 H, B of ABX, J = 13.5 Hz), 3.33 (3 H, s), 3.75 (1 H, s), 4.64 (1 H, s), 5.02 (1 H, d, J = 4.3 Hz), 5.31 (1 H, d, J = 2.8 Hz), 5.45 (1 H, s), 6.50 (1 H, d, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 26.13, 33.07, 36.72, 54.67, 60.24, 69.29, 84.99, 91.73, 94.83, 102.68, 105.96, 121.54, 149.77, 206.28; IR (solution, CH_2Cl_2) 1795, 1608, 1369 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1309.

Lactone 34. A mixture of 8.3 mg (0.028 mmol) of cyclobutanone **33**, 0.8 mL (0.24 mmol) of 30% H_2O_2, 0.1 mL (0.04 mmol) of a 40% solution of Triton B in methanol, and 3 mL of THF was stirred for 3 h at –78 °C. The reaction was quenched with saturated NH_4Cl and extracted with ether. The combined extracts were dried over Na_2SO_4 and chromatographed to afford 6.1 mg (73%) of lactone **34** as a white solid: mp 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (9 H, s), 2.28 (1 H, A of ABX, J = 13.6 Hz), 2.43 (1 H, B of ABX, J = 4.3, 13.6 Hz), 3.37 (3 H, s), 3.65 (1 H, s), 4.64 (1 H, s), 5.15 (1 H, d, J = 4.3 Hz), 5.42 (1 H, d, J = 2.9 Hz), 6.30 (1 H, s), 6.44 (1 H, d, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$) δ 26.39, 33.32, 42.52, 54.88, 65.66, 65.96, 66.96, 87.34, 106.63, 106.81, 108.99, 145.95, 150.41, 177.60; IR (solution, CH_2Cl_2) 1795, 1629, 1272, 1027 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_6$ 308.12599, found 308.12560.

Epoxide 36. A solution of 1.9 mg (0.006 mmol) of lactone **34** and 5 mL of 0.05 M solution of dimethyldioxirane in acetone was stirred for 18 h and concentrated. Chromatography of the residue provided 2 mg (100%) of diepoxide **36** which was spectroscopically identical to that reported by Corey: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 2.63 (dd, J = 4.4, 14.3 Hz), 2.85 (1 H, J = 14.3 Hz), 3.38 (s, 1 H), 3.64 (s, 1 H), 4.12 (d, J = 0.5 Hz, 1 H), 4.59 (s, 1 H), 5.18 (d, J = 4.4 Hz), 5.54 (d, J = 0.5 Hz, 1 H), 6.16 (s, 1 H).

Hydroxy Nitrile 44. A 500-mL three-necked flask, equipped with a closed stopcock-controlled nitrogen inlet, magnetic stirrer, and vacuum adapter, was charged with 11.6 g (31.2 mmol) of cerium trichloride heptahydrate and heated to 140 °C at 1 mmHg with stirring for 2 h. The vacuum was replaced with nitrogen, and the reaction flask was cooled to 0 °C. Tetrahydrofuran (150 mL precooled to 15 °C) was added in one portion and allowed to stir for 15 h at room temperature. The mixture was then cooled to –78 °C, and 18.35 mL of a 1.7 M solution of *tert*-butyl lithium (31.2 mmol) was added dropwise. The resulting orange mixture was stirred for 2 h, and 1.8 mL (20.8 mmol) of 3-furaldehyde in 5 mL of THF was added over a 5-min period. This mixture was stirred for 30 min at –78 °C and quenched with a saturated ammonium chloride solution. The mixture was warmed to 0 °C and diluted with 100 mL of diethyl ether. All solids were removed by filtration through a Celite pad, and the filter was washed with diethyl ether. The aqueous filtrate was extracted twice with diethyl ether. The combined organics were dried and concentrated to provide 3.04 g (98.5%) of alcohol, which was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (9 H, s), 1.98 (1 H, br s), 4.31 (1 H, s), 6.36 (1 H, m), 7.31 (1 H, m), 7.35 (1 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.42, 139.91, 126.62, 109.99, 75.60, 35.28, 25.70; IR (film) 3440 cm^{-1}.

A solution of 12.15 mL (24.3 mmol) of 2 M oxalyl chloride in 200 mL of methylene chloride was cooled to –78 °C, and 3.45 mL (48.6 mmol) of dimethyl sulfoxide in 10 mL of methylene chloride was added at such a rate as to keep the internal temperature of the reaction below –65 °C. After the solution was stirred for 15 min, 2.5 g (16.2 mmol) of the alcohol above, in 10 mL of methylene chloride, was added at such a rate as to keep the reaction temperature below –65 °C. The resulting mixture was stirred for 2 h at –78 °C before 17.5 mL (128 mmol) of triethylamine was added, dropwise, over a 15-min period. This mixture was stirred for 30 min at –78 °C, warmed to 0 °C, and diluted with 50 mL of water and 50 mL of 5% HCl. The aqueous layer was extracted with methylene chloride, and the extracts were washed with $NaHCO_3$, dried, and concentrated. The residue was flash chromatographed to yield 2.17 g (88%) of the ketone: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (9 H, s), 6.74 (1 H, m), 7.36 (1 H, m), 7.98 (1 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.92, 146.37, 142.78, 124.50, 110.41, 43.94, 27.50; IR (film) 1655 cm^{-1}.

A solution of 150 mL of THF and 3.195 mL (22.8 mmol) of diisopropylamine was cooled to –78 °C, and 9.12 mL (22.8 mmol) of a 2.5 M solution of *n*-butyllithium was added dropwise. After the solution was stirred for 5 min, 1.08 mL (20.7 mmol) of acetonitrile in 5 mL of THF was added dropwise, followed by the rapid addition of 3.97 mL (22.8 mmol) of HMPA. This mixture was stirred at –78 °C for 40 min, and 2.1 g (13.8 mmol) of *tert*-butylfuryl ketone in 20 mL of THF was added dropwise. After being stirred for 30 min, the reaction mixture was warmed to –20 °C and quenched with saturated NH_4Cl, and 50 mL of water was added. The mixture was extracted with ether, and the organic extracts were dried, filtered, and concentrated. Flash chromatography of the concentrate provided 2.55 g (95.6%) of the white solid β-hydroxy nitrile **44**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (9 H, s), 2.66 (1 H, br

s), 2.83 (1 H, d, J = 16.8 Hz, [B of AB]), 2.89 (1 H, d, J = 16.8 Hz, [A of AB]), 6.29 (1 H, m), 7.36 (2 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.81, 140.22, 127.66, 118.15, 109.89, 76.25, 37.89, 27.74, 25.10; IR (in $CDCl_3$) 3480, 2260, 1165 cm^{-1}. Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.36; H, 7.82. Found: C, 68.28; H, 7.81.

β-Hydroxy Aldehyde 38. A mechanically stirred mixture of 150 mL of ethyl ether and 2.55 g (13.2 mmol) of nitrile **44** was cooled to −78 °C. Diisobutylaluminum hydride, 29 mL of a 1 M solution of in hexanes (29 mmol), was added dropwise. The reaction was stirred for 15 min at −78 °C, warmed to room temperature for 1 h, cooled to 0 °C, and quenched with a 5% sulfuric acid solution. The aqueous phase was extracted with ether, and the combined extracts were washed with saturated $NaHCO_3$, dried, and concentrated. Chromatography yielded 1.47 g (56%) of aldehyde **38**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (9 H, s), 2.79 (1 H, dd, J = 16.7, 1.4 Hz, [B of ABX]), 3.06 (1 H, dd, J = 16.7, 2.1 Hz, [A of ABX]), 6.32 (1 H, m), 7.32 (1 H, m), 7.37 (1 H, m), 9.7 (1 H, dd, J = 2.1, 1.4 Hz, [X of ABX]); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.00, 142.56, 140.02, 128.78, 110.31, 76.67, 48.67, 37.94, 24.97; IR (film) 3520, 2740, 1720, 1165 cm^{-1}. HRMS calcd for $C_{11}H_{16}O_3$ 196.1099 found 196.1100.

Cyclopentenones 45. A solution of 20 mL of THF and 0.42 mL (3.0 mmol) of diisopropylamine was cooled to −78 °C, and 1.2 mL (3.0 mmol) of 2.5 M n-butyllithium in hexanes was added. After 10 min, a solution of ketone **39** (0.616 g, 2.9 mmol) in 10 mL of THF was added dropwise. After 30 min, a solution of aldehyde **38** (0.275 g, 1.4 mmol) in 15 mL of THF was added dropwise. The reaction was stirred for 20 min and quenched at −78 °C with a saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 and then with ethyl acetate. The combined extracts were dried and concentrated. Chromatography provided 0.53 g (93%) of addition products **45**: ^{1}H NMR (200 MHz, $CDCl_3$) both diastereomers δ 0.15–0.2 (12 H, m), 0.9–1.0 (36 H, m), 1.8–2.1 (4 H, m), 2.35–2.45 (2 H, m), 2.5–2.7 (2 H, m), 3.2–3.6 (4 H, broad), 3.72 (1 H, m), 4.07 (1 H, m), 6.15–6.21 (2 H, m) (1 H, m), 6.62 (1 H, t, J = 3 Hz), 6.68 (1 H, t, J = 3 Hz), 7.35 (4 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) one diastereomer δ 206.85, 152.94, 142.09, 141.06, 136.76, 129.46, 110.46, 78.36, 71.50, 48.05, 38.22, 38.08, 25.46, 25.31, 24.34, 18.23, 4.59.

Pivalate Ester 46. A mixture of 0.24 g (0.587 mmol) of silyl enol ethers **45** and excess KF in 10 mL of water and 20 mL of THF was stirred vigorously for 1 h and then quenched with saturated NH_4Cl. The water layer was extracted with ethyl acetate, and the combined organics were dried and concentrated. The crude product was taken up in 50 mL of dry CH_2Cl_2, and 0.245 mL (1.76 mmol) of triethylamine was added. The reaction was stirred for 30 min before 0.072 mL (0.59 mmol) of pivaloyl chloride was added in one portion. The resulting solution was stirred for 1 h, the reaction was quenched with a saturated NH_4Cl, and the water layer was extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated. Chromatography yielded 0.107 g (48%) of pivalate **46**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (9 H, s), 1.25 (9 H, s), 1.89 (1 H, dd, J = 14.6, 1.9 Hz, [B of ABX]), 2.18 (1 H, dd, J = 14.6, 11 Hz, [A of ABX]), 2.44 (2 H, t, J = 4.3 Hz, [X_2 of ABX2]), 2.62 (1 H, dt, J = 18.3, 4.3 Hz, [B of ABX_2]), 2.75 (1 H, dt, J = 18.3, 4.3 Hz, [A of ABX_2]), 3.64 (1 H, s), 3.15 (1 H, d, J = 2.6 Hz), 4.64 (1 H, ddd, J = 11, 2.6, 1.9 Hz), 6.18 (1 H, m), 6.33 (1 H, m), 6.36 (1 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.39, 175.86, 162.39, 144.15, 142.39, 140.84, 128.50, 110.41, 79.38, 66.31, 39.04, 38.41, 37.71, 32.18, 27.05, 25.19, 21.83; HRMS calcd for $C_{21}H_{30}O_6$ 378.2042, found 378.2045.

Photosubstrate 37. A solution of 0.013 g (0.034 mmol) of diol **46** and 0.01 mL (0.075 mmol) of triethylamine in 10 mL of CH_2Cl_2 was stirred for 5 min before 0.0095 mL (0.075 mmol) of chlorotrimethylsilane and 4-(dimethylamino)pyridine (catalytic) were added. The mixture was stirred for 15 min and quenched with a saturated NH_4Cl solution. The water layer was extracted with CH_2Cl_2, and the combined extracts were dried, filtered, and concentrated. Chromatography yielded 0.014 g (91%) of photosubstrate **37**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.09 (9 H, s), 0.89 (9 H, s), 1.29 (9 H, s), 1.86 (1 H, dd, J = 14.6, 2.3 Hz, [B of ABX]), 2.13 (1 H, dd, J = 14.6, 11.6 Hz, [A of ABX]), 2.45 (2 H, m), 2.64 (2 H, m), 4.53 (1 H, s), 4.71 (1 H, dd, J = 11.6, 2.3 Hz), 6.16 (1 H, m), 7.32 (2 H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.09, 175.25, 161.48, 144.07, 141.98, 141.08, 128.95, 110.84, 78.31, 66.97, 38.99, 38.21, 37.47, 32.23, 27.09, 25.13, 21.29, 0.65; IR (film) 3490, 1760, 1720, 1110, 1090 cm^{-1}; HRMS calcd for $C_{24}H_{38}O_6Si$ 450.2438, found 450.2431.

Cyclobutane 48. A solution of enone **37** (1.02 g, 2.26 mmol) in 350 mL of hexanes was irradiated in a toroidal reactor with a 450-W Hanovia medium-pressure mercury lamp fitted with a uranium glass sleeve (>350 nm) for 18 h. After irradiation, the solution was concentrated and chromatographed to provide 0.51 g (50%) of photoadduct **48**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (9 H, s), 1.08 (9 H, s), 1.22 (9 H, s), 1.7 (1 H, br s), 1.9–2.2 (2 H, m), 2.23–2.38 (2 H, m), 2.48–2.84 (2 H, m), 3.75 (1 H, dd, J = 6.4, 2.1 Hz), 5.18 (1 H, d, J = 3 Hz), 5.2 (1 H, s), 6.36 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.21, 177.43, 150.30, 103.38, 86.05, 83.26, 82.53, 70.64, 66.32, 65.42, 46.60, 38.42, 38.16, 37.04, 26.97, 26.78, 23.63, 0.05; IR (film) 3530, 1750, 1725 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_6Si$: C, 63.96; H, 8.50. Found: C, 63.80; H, 8.44.

α-Hydroxy Ketone 51. A mixture of 200 mL of THF and 0.364 mL (2.6 mmol) of diisopropylamine was cooled to −78 °C, and 1.04 mL (2.6 mmol) of a 2.5 M solution of n-butyllithium in hexanes was added. After 5 min 0.532 g (1.18 mmol) of keto ester **48** in 10 mL of THF was added dropwise. The reaction was warmed to 0 °C and stirred for 15 min. Solid oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) (2.17 g, 5 mmol) was added in one portion, and the resulting mixture was stirred for 30 min at 0 °C before being quenched with a saturated NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the extracts were dried, filtered, and concentrated. Chromatography yielded 0.416 g (76%) of hydroxy ketone **51**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (9 H, s), 1.06 (9 H, s), 1.22 (9 H, s), 2.0–2.18 (2 H, m), 2.23–2.35 (1 H, dd, J = 15.0, 2.8 Hz, [A′ of A′B′X′]), 2.51 (1 H, dd, J = 14.7, 9 Hz, [A of ABX]), 3.78 (1 H, dd, J = 6.3, 2.8 Hz), 4.76 (1 H, t, J = 9 Hz), 5.21 (1 H, s), 5.22 (1 H, d, J = 3 Hz), 6.32 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.75, 177.54, 150.38, 104.04, 85.85, 82.42, 82.31, 74.42, 70.40, 66.52, 63.32, 46.48, 38.31, 37.05, 34.53, 27.00, 26.78, 0.03; IR (film) 3490, 1760, 1725, 1140 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_7Si$: C, 61.77; H, 8.21. Found: C, 61.86, H, 8.18.

Acetal 53. A mixture of 0.301 g (0.763 mmol) of α-hydroxy ketone **51**, 8 mL of methanol, and 16 mL of benzene was cooled to 10 °C. Solid lead tetraacetate (0.474 g, 1.068 mmol) was added in one portion, and the solution was stirred for 10 min before being quenched with saturated $NaHCO_3$. The mixture was filtered through a Celite pad which was subsequently washed with ethyl acetate. The resulting filtrate was dried, filtered, and concentrated to give 0.304 g (94%) of aldehyde **52** which was used without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (9 H, s), 0.98 (9 H, s), 1.28 (9 H, s), 1.7 (1 H, br s), 1.9–2.1 (2 H, m), 2.48 (1 H, dd, J = 17, 3 Hz, [B of ABX]), 3.14 (1 H, dd, J = 17, 0.5 Hz, [A of ABX]), 3.61 (3 H, s), 4.87 (1 H, dd, J = 7.6, 6.7 Hz), 5.06 (1 H, d, J = 3 Hz), 5.18 (1 H, s), 6.39 (1 H, d, J = 3 Hz), 9.6 (1 H, dd, J = 3, 0.5 Hz, [X of ABX]); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.64, 176.64, 167.47, 149.78, 101.95, 85.46, 84.17, 81.28, 72.02, 65.92, 62.66, 52.07, 44.83, 40.52, 38.86, 37.24, 26.96, 26.93, 0.33.

A solution of 0.085 g (0.172 mmol) of aldehyde **52**, p-toluenesulfonic acid (catalytic), and trimethyl orthoformate (1 mL, 6.1 mmol) in 10 mL of MeOH was stirred for 15 min before being quenched with a saturated $NaHCO_3$. Methanol was removed on a rotary evaporator, and the residue was taken up in water and extracted with ethyl ether. The combined extracts were dried, filtered, and concentrated. Chromatography yielded 0.074 g (98%) of a mixture of acetals **53**: ^{1}H NMR (250 MHz, $CDCl_3$) less polar diastereomer δ 0.98 (9 H, s), 1.21 (9 H, s), 1.68 (1 H, br s), 1.98 (1 H, dd, J = 14.2, 7.1 Hz, [B′ of A′B′X′]), 2.12 (1 H, dd, J = 15.3, 3.7 Hz, [B of ABX]), 2.40 (1 H, dd, J = 14.2, 7.1 Hz, [A′ of A′B′X′]), 3.02 (1 H, dd, J = 15.3, 6.2 Hz, [A of ABX]), 3.29 (3 H, s), 3.63 (3 H, s), 4.45 (1 H, t, J = 7.1 Hz), 4.92 (1 H, dd, J = 6.2, 3.7 Hz, [X of ABX]), 5.20 (1 H, d, J = 3 Hz), 5.25 (1 H, s), 6.27 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) less polar diastereomer δ 177.56, 167.73, 148.80, 108.14, 103.79, 86.74, 84.04, 83.54, 83.11, 68.02, 67.49, 55.47, 51.93, 43.93, 38.46, 37.48, 36.90, 26.87, 26.33; IR (film) 3570, 1755, 1735 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) more polar diastereomer δ 1.02 (9 H, s), 1.24 (9 H, s), 2.05 (1 H, dd, J = 16.0, 6.11 Hz), 2.40–2.70 (3 H, m), 3.23 (3 H, s), 3.65 (3 H, s), 4.25 (1 H, d, J = 6.1 Hz), 4.90 (1 H, dd, J = 5.6, 1.7 Hz), 5.06 (1 H, d, J = 3 Hz), 5.20 (1 H, s), 6.35 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) more polar diastereomer δ 176.40, 167.69, 150.14, 105.73, 101.19, 87.96, 84.05, 82.65, 82.17, 69.18, 67.49, 54.34, 51.98, 42.09, 38.49, 37.72, 26.92, 26.69.

Diol 54. A mixture of 20 mL of ethyl ether and 0.049 g (1.23 mmol) of lithium aluminum hydride was cooled to 0 °C, and 0.108 g (0.246 mmol) of diester **53** in 15 mL of ethyl ether was added dropwise. The reaction was warmed to room temperature and stirred for 30 min before being quenched with 6 M NaOH and water. The mixture was filtered through a Celite pad which was subsequently washed with ethyl acetate. The filtrate was dried and concentrated to provide 0.07 g (87%) of a mixture of marginally stable diols **54** which were used immediately in the next reaction: ^{1}H NMR (250 MHz, $CDCl_3$) both diastereomers δ 0.99 (9 H, s), 1.02 (9 H, s), 1.9–2.1 (5 H, m), 2.2 (3 H, m), 2.4–3.0 (6 H,

broad), 3.26 (3 H, s), 3.3 (3 H, s), 3.59 (1 H, d, J = 11 Hz), 3.78 (3 H, m), 4.68 (1 H, s), 4.95 (5 H, m), 5.09 (1 H, d, J = 3 Hz), 5.12 (1 H, d, J = 3 Hz), 6.38 (1 H, d, J = 3 Hz), 6.42 (1 H, d, J = 3 Hz). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.48; H, 8.40.

Cyclobutanone 3. A mixture of 30 mL of benzene and 0.07 g (0.214 mmol) of diol **54** was warmed to 60 °C to effect dissolution. The mixture was cooled to 30 °C, and 0.153 g (0.344 mmol) of solid lead tetraacetate was added. The mixture was stirred for 15 min before being quenched with a saturated $NaHCO_3$ and filtered through a Celite pad. The Celite filter was washed with ether, and the filtrate was dried and concentrated. Chromatography provided 0.058 g (92%) of cyclobutanones **3**: ^{1}H NMR (250 MHz, $CDCl_3$) more polar diastereomer δ 1.05 (9 H, s), 1.96 (1 H, s), 2.1–2.4 (3 H, m), 2.61 (1 H, dd, J = 16.2, 1.7 Hz), 3.28 (3 H, s), 4.58 (1 H, dd, J = 7.4, 1.6 Hz), 5.01 (1 H, dd, J = 5.0, 1.2 Hz), 5.07 (1 H, d, J = 2.9 Hz), 5.78 (1 H, s), 6.44 (1 H, d, J = 2.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) more polar diastereomer δ 204.65, 150.31, 127.52, 105.97, 100.26, 95.64, 88.72, 82.14, 67.26, 54.56, 43.57, 37.85, 35.99, 26.41; ^{1}H NMR (250 MHz, $CDCl_3$) less polar diastereomer δ 1.03 (9 H, s), 1.5 (1 H, s), 2.10–2.42 (4 H, m), 3.29 (3 H, s), 4.90 (1 H, t, J = 7.3 Hz), 5.04 (1 H, dd, J = 5.1, 0.8 Hz), 5.25 (1 H, d, J = 3 Hz), 5.52 (1 H, s), 6.45 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) less polar diastereomer δ 205.50, 148.28, 127.29, 107.60, 103.49, 95.29, 87.99, 87.24, 65.24, 54.52, 47.07, 37.42, 37.19, 25.00; IR (film) 3540, 1785 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1477.

Lactone 56. To a solution of 30 mL of CH_2Cl_2 and 0.044 g (0.15 mmol) of cyclobutanone 3 was added solid 50% *m*-chloroperoxybenzoic acid (0.103 g, 0.3 mmol) and solid (0.025 g, 0.3 mmol) in one portion. The mixture was stirred for 10 min before being quenched with a 10% sodium thiosulfate solution. This mixture was stirred vigorously for 15 min before 10 mL of a saturated $NaHCO_3$ was added and the water layer was extracted with CH_2Cl_2. The combined extracts were dried, filtered, and concentrated. Chromatography provided 0.0435 g (94%) of lactones **56**: ^{1}H NMR (250 MHz, $CDCl_3$) more polar diastereomer δ 1.02 (9 H, s), 2.0–2.1 (2 H, m), 2.27 (1 H, dd, J = 14.1, 5 Hz), 2.37 (1 H, dd, J = 13.8, 6.8 Hz), 3.37 (3 H, s), 4.86 (1 H, t, J = 7.0 Hz), 5.02 (1 H, d, J = 3 Hz), 5.10 (1 H, dd, J = 4.9, 2.3 Hz), 6.36 (1 H, s), 6.45 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) more polar diastereomer δ 178.79, 146.38, 107.58, 107.37, 103.22, 89.00, 83.97, 69.59, 62.60, 55.21, 43.60, 40.99, 37.83, 26.28; ^{1}H NMR (250 MHz, $CDCl_3$) less polar diastereomer δ 1.00 (9 H, s), 2.22–2.37 (4 H, m), 3.31 (3 H, s), 4.89 (1 H, t, J = 7.5 Hz), 5.14 (1 H, dd, J = 4.5, 0.5 Hz), 5.28 (1 H, d, J = 3 Hz), 6.40 (1 H, d, J = 3 Hz), 6.41 (1 H, s); ^{13}C NMR (400 MHz, $CDCl_3$) less polar diastereomer δ 180.53, 145.33, 107.95, 107.82, 105.90, 88.27, 87.15, 70.02, 63.58, 54.45, 44.82, 42.59, 37.53, 26.15; IR (film) 3500, 1760 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_6$ 310.1416, found 310.1417.

Dilactone 57. A mixture of 25 mL of acetone, 23 mg (0.074 mmol) of lactone **56**, and 1.5 mL of Jones reagent was heated to reflux for 10 min. The reaction was cooled to room temperature and quenched with 2-propanol before being filtered through a Celite pad. The filter was washed with ethyl acetate, and the filtrate was dried and concentrated to yield 21.5 mg (99%) of dilactone **57**: ^{1}H NMR (250 MHz, acetone-d_6) δ 1.05 (9 H, s), 2.28 (1 H, dd, J = 13.1, 9.1 Hz), 2.66 (1 H, dd, J = 13.1, 6.5 Hz), 2.66 (1 H, d, J = 18.8 Hz), 3.00 (1 H, d, J = 18.8 Hz), 4.48 (1 H, s), 5.01 (1 H, dd, J = 9.0, 6.5 Hz), 5.67 (1 H, d, J = 3 Hz), 6.47 (1 H, s), 6.65 (1 H, d, J = 3 Hz); ^{13}C NMR (400 MHz, acetone-d_6) δ 179.53, 174.42, 147.39, 108.87, 104.85, 86.95, 86.82, 84.59, 59.77, 43.38, 38.36, 36.76, 26.47; HRMS calcd for $C_{15}H_{18}O_6$ 294.1104, found 294.1099.

Bilobalide. A solution of 5 mg (0.017 mmol) of dilactone **27** and 10 mL of a 0.1 M solution of dimethyldioxirane in acetone was stirred for 15 h before solid sodium sulfate was added to the reaction mixture. After being stirred for 20 min, the mixture was filtered and the filtrate was concentrated to provide 5 mg (88%) of the desired epoxide: ^{1}H NMR (250 MHz, acetone-d_6) δ 1.10 (9 H, s), 2.51 (1 H, dd, J = 12.8, 10.0 Hz), 2.72 (1 H, ddd, J = 12.8, 5.8, 0.7 Hz), 2.91 (1 H, d, J = 18.7), 3.49 (1 H, d, J = 18.7 Hz), 4.45 (1 H, dd, J = 1.5, 0.8 Hz), 4.62 (1 H, s), 5.07 (1 H, dd, J = 10.0, 5.8 Hz), 5.78 (1 H, d, J = 1.4 Hz), 6.54 (1 H, s); ^{13}C NMR (400 MHz, acetone-d_6) δ 178.15, 174.68, 111.24, 88.44, 86.45, 86.36, 84.14, 70.56, 59.60, 43.84, 38.02, 37.68, 26.93.

A solution of 5 mg (0.015 mmol) of epoxide, 10 mL of acetone, and 1 mL of Jones reagent was stirred for 5 min before being quenched with 2-propanol and filtered through a Celite pad. The Celite pad was washed with ethyl acetate, and the filtrate was dried over sodium sulfate. Filtration and removal of solvent provided 4.5 mg (92%) of synthetic bilobalide **1** which was spectroscopically identical (^{1}H, ^{13}C NMR, IR) to an authentic sample: ^{1}H (acetone-d^6) δ 1.20 (s, 9 H), 2.32 (dd, J = 13.6, 7.0 Hz, 1 H), 2.74 (dd, J = 13.6, 7.0 Hz, 1 H), 2.80 (d, J = 18.0 Hz, 1 H), 3.02 (d, J = 18.0 Hz, 1 H), 4.63 (s, 1 H), 4.99 (t, J = 7.0 Hz, 1 H), 5.40 (d, J = 4.3 Hz, 1 H), 6.36 (s, 1 H), 6.38 (d, J = 4.3 Hz, 1 H); ^{13}C (acetone-d^6) δ 27.04, 36.87, 38.23, 43.19, 59.04, 66.43, 69.74, 83.79, 87.43, 100.45, 173.44, 173.63, 178.28.

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