Double Diastereoselection in Intramolecular Photocycloadditions: A Radical Rearrangement Approach to the Total Synthesis of the Spirovetivane Phytoalexin (±)-Lubiminol

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Abstract: The highly stereoselective total synthesis of the phytoalexin (±)-lubiminol (**1**) has been accomplished. The synthesis relies on three pivotal transformations: (1) a conjugate addition−cyclization reaction to prepare a highly functionalized 2-carbomethoxycyclopentenone as a photocycloaddition substrate, (2) a double diastereoselective intramolecular photocycloaddition for a stereoselective intramolecular photoaddition reaction which establishes the central quaternary spirocenter, and (3) the transformation of the photoadduct into the required spiro[5.4]decane through a radical fragmentation−rearrangement reaction.

Sensitive plant tissues are known to produce complex secondary metabolites as a result of external stress such as fungal infection, wounding, or chemical exposure.[1] Some of these stress metabolites have postinfection defensive abilities and are classified as phytoalexins. Several highly oxygenated spirovetivane phytoalexins[1] have been isolated from potato tubers infected with the fungi *Phytophthora infestans* or *Glomeralla cingulata*.[2] Lubiminol (**1**),[3] lubimin (**2**),[4] and oxylubimin (**3**)[4,5] are the more structurally complex members of this class and are intermediates in the biosynthesis of the potent antifungal agent rishitin (**4**)[6] from acetic acid[7] (Figure 1). Lubiminol, lubimin, and oxylubimin have been implicated in the toxicity of diseased food plants to humans and livestock.[2]

Establishing the five stereogenic centers on the spiro[4.5]-decane skeleton, particularly the relative stereochemistry of C5 and the remote stereogenic center at C7, is critical to a successful synthesis of any of the members of this class. Previous syntheses[4,5] of these important plant metabolites have utilized a benzenoid aromatic precursor to construct the stereochemically and functionally complex cyclohexane. We report here a unique approach to the synthesis of hydroxylated spirovetivanes and the full details of the synthesis of (±)-lubiminol (**1**).[8]

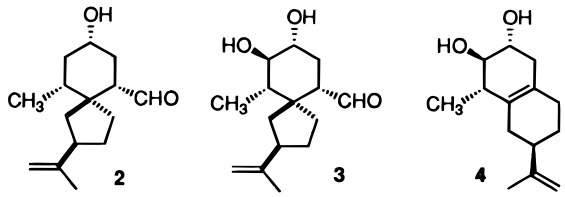

Figure 1.

The initial approach for the synthesis of lubiminol (**1**) was centered around the unique strategic combination of three recent observations from our laboratory: (1) functionalized zinc−copper reagents undergo efficient conjugate addition−cycloacylation reactions with acetylenic esters to prepare 2-carboalkoxycyclopentenones,[9] (2) high diastereoselectivity can be obtained in intramolecular photocycloadditions[10] as a result of double diastereodifferentiation by two substituents on the tether, and (3) cyclobutylcarbinyl radicals such as **5** can undergo regioselective fragmentation of the cyclobutane, allowing the resultant radical to undergo a Dowd−Beckwith type ring expansion[11] to

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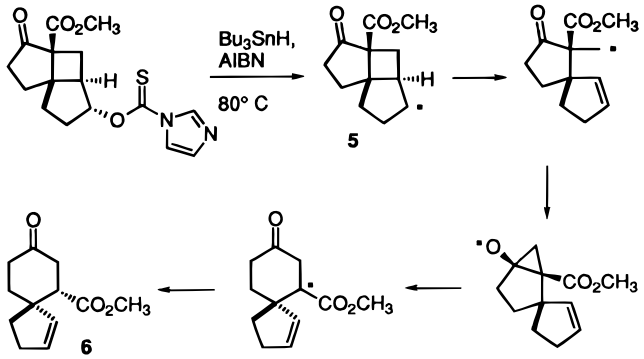
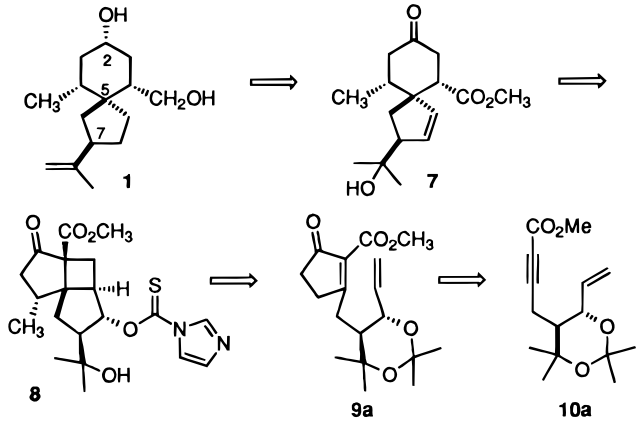
Scheme 1



Scheme 2



produce spirofused carbocycles such as **6**[12] (Scheme 1). The total synthesis of lubiminol reported herein is the first example of the application of the tandem radical fragmentation−rearrangement sequence in natural product synthesis.

Lubiminol (**1**) would be derived from the functionalized spirocycle **7** which would be the product of the radical fragmentation−rearrangement sequence described above starting with thiocarbamate **8** (Scheme 2). A novel double diastereoselective photocycloaddition[10] of enone−alkene **9** would provide access to the radical precursor **8**. In turn, enone **9** would be prepared through a conjugate addition cyclization protocol previously reported from our laboratory.[9]

The planned intramolecular photocycloaddition required that the two stereogenic centers on the tether have a cooperative or synergistic influence on the stereochemistry of the photoadduct to achieve high levels of stereocontrol. Thus, the relative stereochemistry of the two stereogenic centers of acetylene **10** is vital to obtaining high levels of asymmetric induction in the photocycloaddition. At the outset, virtually no information was available with regard to the interplay between two stereogenic centers with regard to asymmetric induction in the intramolecular [2+2] photocycloaddition and no examples of the specific substitution pattern required for the lubiminol synthesis had been reported. Our own initial predictions regarding the influence of the stereochemistry of the tether substituents on the outcome of the photocycloaddition were based on molecular mechanics calculations of conformations **11** through **14**. Calculations were made using the MM2 force field. The β-carbon of the enone and the internal carbon of the olefin were restricted at a distance of 2.5 Å, and the energy of the structure was minimized. The anti diastereomer **9a** was predicted to give

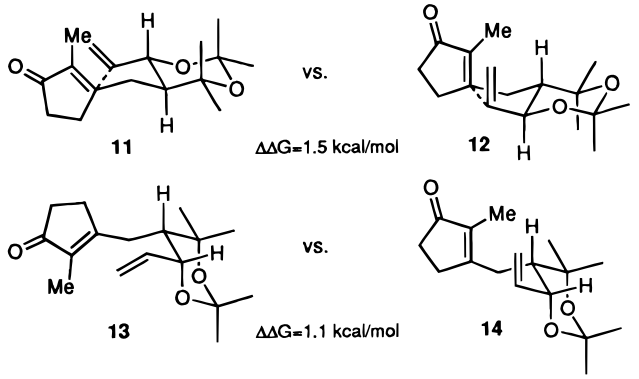
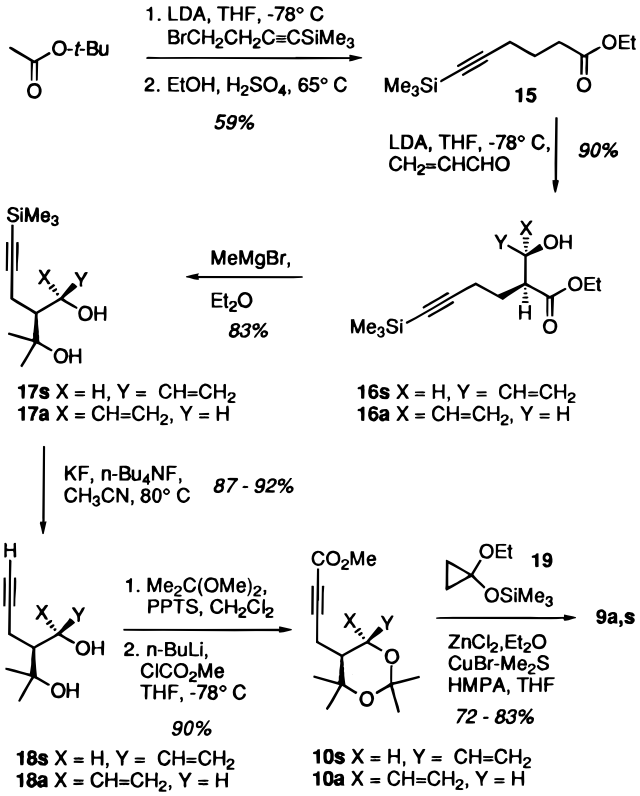


Figure 2.

Scheme 3



higher stereoselectivity on the basis of the larger difference in energy between **11** and **12** ($\Delta\Delta G$ = 1.5 kcal/mol) than was calculated for the two conformations of the syn diastereomer **13** and **14** ($\Delta\Delta G$ = 1.1 kcal/mol) (Figure 2). However, the relatively similar results prompted an investigation of both stereoisomers before a final decision was made with regard to the ultimate starting material.

Thus, the initial synthesis of acetylene **10**, illustrated in Scheme 3, was nonstereoselective with the intent of preparing both syn and anti diastereomers for evaluation in the photoaddition. Alkylation of the lithium enolate of *tert*-butyl acetate[13] with 4-bromo-1-(trimethylsilyl)butyne[14] followed by transesterification in acidic ethanol provided the ethyl ester **15** in 59% overall yield. Addition of the lithium enolate derived from ester **15** to acrolein at −78 °C produced a 90% yield of an inseparable 2:1 mixture of the syn/anti diastereomeric aldol products **16s**/**16a**. The mixture of aldol products was treated with excess

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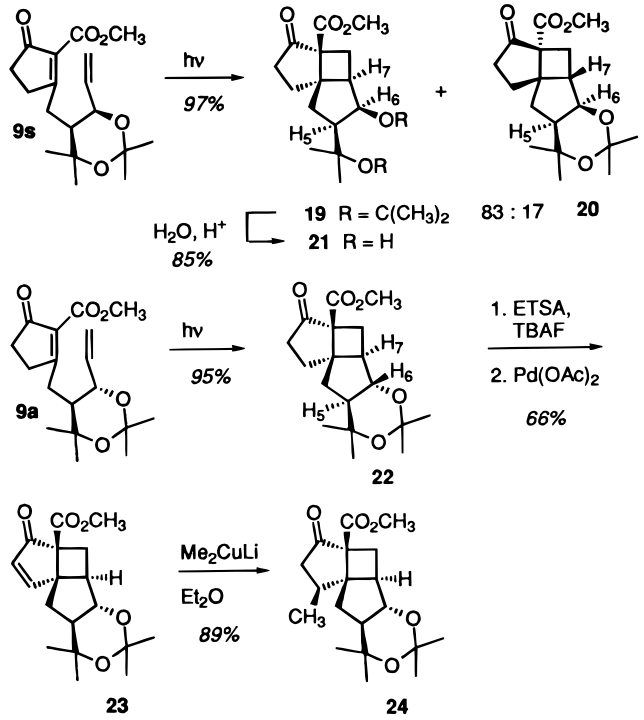
Scheme 4

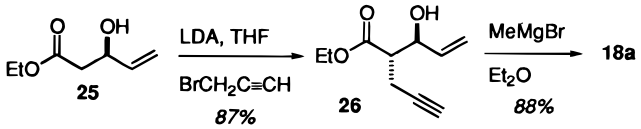


methylmagnesium bromide in ether at 0 °C to give a mixture of diols **17s** (54%) and **17a** (29%) which were readily separated by flash chromatography. The individual isomers were separately converted into the corresponding photosubstrates. Exposure of (trimethylsilyl)acetylenes **17s** and **17a** to potassium fluoride and catalytic tetrabutylammonium fluoride in acetonitrile produced the terminal acetylenes **18s** and **18a** in 87 and 92% yield, respectively. Protection of the 1,3-diol as its acetonide with dimethoxypropane and PPTS in dichloromethane followed by carbomethoxylation of the terminal acetylene gave the acetylenic esters **10s** and **10a** in high yield. Each of the diastereomers **10s** and **10a** was treated according to the standard protocol[9] previously described (zinc homoenolate **19**, CuBr−SMe_2, HMPA, 1:1 THF/Et_2O) for conversion to the 2-carbomethoxycyclopentenones **9s** and **9a** (72% yield and 83% yield, respectively).

Irradiation (>350 nm) of a hexane solution of photosubstrate **9s** produced an 83:17 mixture of two diastereomeric photoadducts, **19**/**20.** The stereochemistry of the major isomer was determined by a combination of COSY and NOE difference spectra of the corresponding diol **21**.

The chemical shift assignments were unambiguously determined by a COSY experiment. In the NOE experiment, when H_6 (lubiminol numbering) was irradiated, a 6.4% and 7.7% enhancement of H_5 and H_7, respectively, was observed, indicating a cis relationship of H_5, H_6, and H_7. As additional proof, a single-crystal X-ray of the minor photoadduct **20** confirmed its stereochemistry as shown. The X-ray structure showed the molecule to be in a conformation similar to that predicted by molecular modeling of the photosubstrate. Irradiation of **9a** in hexanes provided a single, isolable photoadduct, **22** (Scheme 4). Attempted stereochemical assignment of **22** by NMR experiments was inconclusive. However, conversion of ketone **22** to enone **23** followed by treatment with lithium dimethyl cuprate gave a single β-methyl ketone, **24**, which provided crystals suitable for X-ray analysis. The crystal structure of **24** not only established the stereochemistry of the photoadduct **22** as that which had been predicted but also showed that the methyl

Scheme 5



group from the cuprate addition had been introduced from the exo face of the cyclopentenone. Two conclusions were obtained from this study. The first conclusion was that the diastereoselectivity predicted by the molecular mechanics calculations was supported experimentally, indicating that calculations of related systems will have substantial predictive value for planning other intramolecular photocycloadditions. The combination of these computational and experimental results are a first step toward better understanding and predicting the factors which influence diastereoselectivity in intramolecular [2+2] photocycloadditions. The second conclusion was that the anti diastereomer would provide excellent diastereocontrol in the photocycloaddition and significantly better selectivity than the syn diastereomer for the relative stereochemistry between C5 and C7 required for lubiminol. Consequently, a selective synthesis of the anti diastereomer **10a** was undertaken.

Since attempts to directly form the anti aldol product **16a** using known protocols[15] resulted in either enolate decomposition or poor selectivity, a two-step sequence based on Seebach's[16] precedent was investigated. Addition of the lithium enolate of ethyl acetate to acrolein at −78 °C produced the hydroxy ester **25** in 99% yield. Exposure of **25** to 3 equiv of LDA in THF followed by addition of propargyl bromide provided the desired anti aldol product **26** in 87% yield and >95% de (Scheme 5). The hydroxy ester **26** was then treated with 5 equiv of methylmagnesium bromide to give 88% of diol **18a** which was identical to that prepared by the previous method. The revised synthesis provided access to exclusively the anti diastereomer photoadduct **22** in seven steps in an overall yield of about 50%.

The C4 methyl group was introduced next since the photoadduct **22** contained all the required carbons for lubiminol except the C4 methyl group and since the rigid conformation and stereochemical bias of photoadduct **22** seemed to offer the potential for stereocontrol. As noted above, ketone **22** could be converted to enone **23** in a one-pot procedure by exposure to ethyl trimethylsilylacetate and catalytic tetrabutylammonium fluoride[17] in THF followed by oxidation with palladium acetate (66% overall).[18] Treatment of the enone with lithium dimethylcuprate gave a single diastereomer, **24**, with the incorrect C4 stereochemistry for lubiminol. Attempts to alter the stereochemical outcome of the reaction through the use of other organometallic reagents or additives[19] were unsuccessful. However, trapping the enolate from the cuprate addition as its trimethylsilyl enol ether followed by palladium acetate oxidation gave the β-methyl enone **27**. Hydrogenation of enone **27** in ethanol with palladium on carbon and a catalytic amount of HCl resulted in exclusive reduction from the β-face and also cleaved the acetonide to provide diol **28** in 99% yield.

Completion of the synthesis required that the planned radical rearrangement be executed and that the product be refunction-

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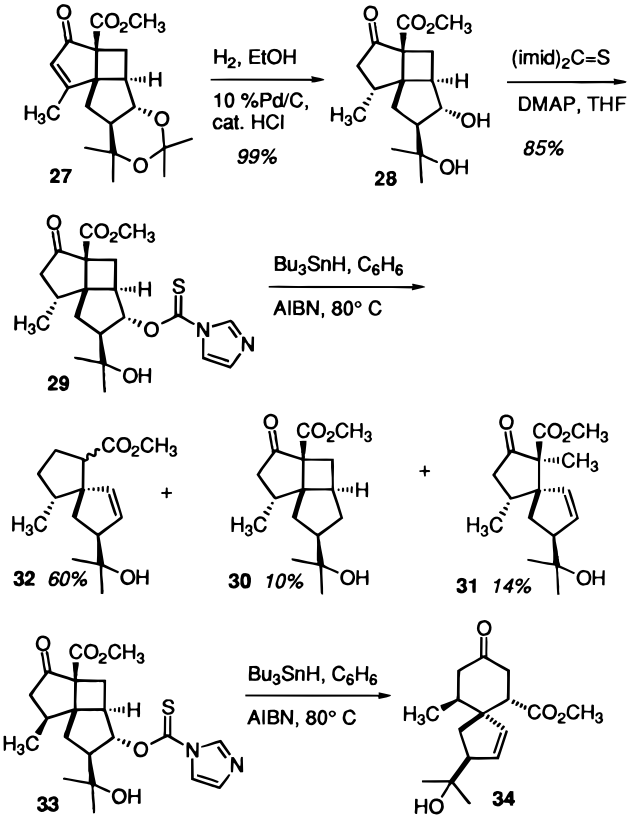
Scheme 6

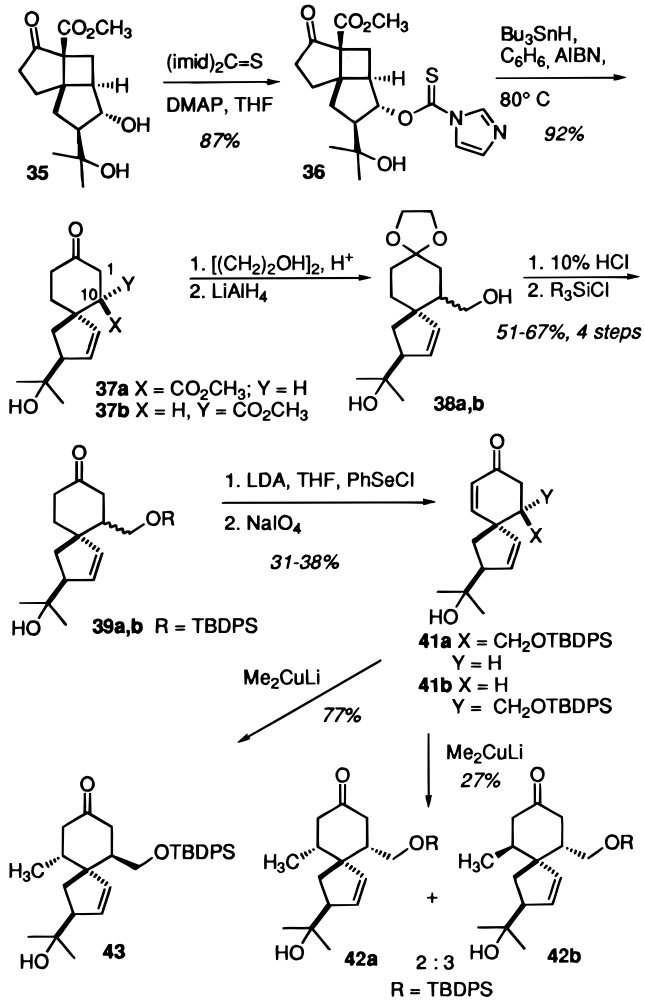


alized to lubiminol. To this end, diol **28** was converted to the thiocarbamate **29** with 1,1′-thiocarbonyldiimidazole in THF at 65 °C. Unfortunately, exposure of thiocarbamate **29** to tributyl tin hydride−AIBN in benzene at 80 °C resulted in the isolation of a mixture of three products, none of which were the desired rearrangement product (Scheme 6). The direct reduction product **30** (10%), the substituted spiro[4.4.0]nonane **31** which results from reduction of the primary methyl radical, and the ester **32** which has undergone a decarbonylation were the only products of the reaction. This disappointing result prompted a reevaluation of the radical rearrangement. The thiocarbamate **33** derived from the β-methyl isomer **24** was exposed to the same reduction conditions to provide the spiro[5.4.0] system **34**, albeit in low yield. Also, the photoadduct **22** was hydrolyzed to diol **35** and converted to the thiocarbamate **36** as before.

Slow addition of tributyltin hydride to thiocarbamate **36** over 5−6 h produced a 3:2 mixture of the expected rearrangement products **37a** and **37b** in 92% combined yield (Scheme 7). The failure of the α-methyl isomer **29** to undergo the desired rearrangement is probably related to the highly congested transition state for the addition of the primary radical to the adjacent carbonyl in the Dowd−Beckwith rearrangement. The 1,3 relationship of the primary radical with the α-C4-methyl group may either sterically prohibit addition to the carbonyl or result in hydrogen atom transfer from the α-methyl. Regardless, the incorporation of the methyl group, at least with the natural stereochemistry, had to be postponed until after the radical rearrangement.

Since the methyl group would have to be introduced into a spiro[5.4.0]decane system, an evaluation of the effect of the stereogenic center at C10 was undertaken. Regioselective incorporation of unsaturation at C3,4 was thus required to generate the intermediates for the cuprate addition. As might be anticipated, deprotonation of ketones **37a,b** was not selective,

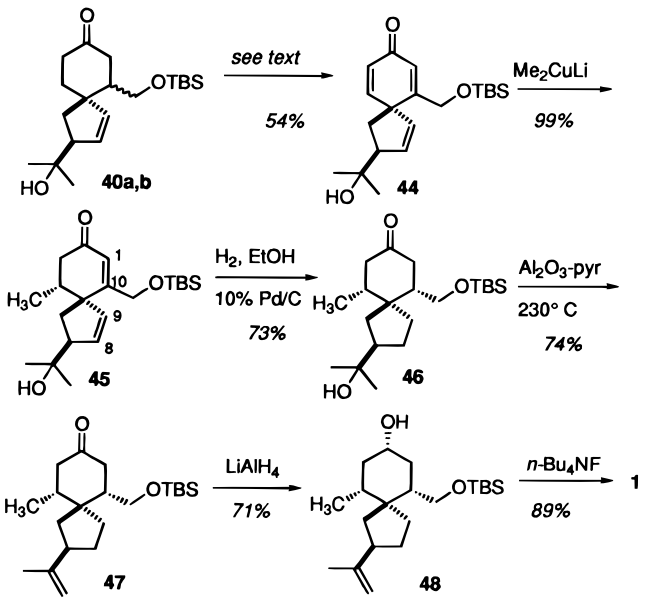
Scheme 7



and the methyl ester first needed to be converted to a protected hydroxymethyl group to sterically hinder deprotonation at C1. This was accomplished in four high-yield steps: protection of the ketone carbonyl as its dioxolane, reduction of the methyl ester, hydrolysis of the dioxolane, and protection of the primary hydroxyl as a *tert*-butyldiphenylsilyl ether (Scheme 7). The *tert*-butyldiphenylsilyl protecting group was required to ensure a highly regioselective formation of the ketone enolate. Deprotonation of ketone **39a** and trapping as the phenyl selenide followed by oxidation with sodium periodate provided the enone **41a** in modest yield. The isomeric **41b** was prepared from **37b** by the same sequence. Exposure of enone **41a**, which contains the stereochemistry at C10 required for lubiminol, to lithium dimethyl cuprate in ether at −40 °C produced a 2:3 mixture of the two diastereomers **42a,b**. In contrast, ketone **41b** gave a single diastereomeric product, **43**, with the desired stereochemistry of the methyl group at C4.

Since the α-C10 isomer **41a** gave a mixture of isomers **42a,b** in the cuprate addition and the β-isomer **41b** gave exclusively the α-product **43**, it seemed reasonable that the dienone **44** might give high levels of selectivity in the cuprate addition and allow the use of both the diastereomeric products from the radical rearrangement. To test this approach, dienone **44** was prepared as shown in Scheme 8. The keto esters **37a,b** were converted to the TBS ethers **40a,b** as described above for the preparation of the TBDPS ethers. Treatment of ketones **40a,b** with sodium hydride and methyl benzenesulfinate[20] followed by heating the crude product in benzene gave a mixture of regioisomeric

Scheme 8



enones. The crude mixture was treated with LDA and phenylselenenyl chloride with subsequent oxidation of the selenides to provide the dienone **44** in good yield. Exposure of the dienone **44** to lithium dimethyl cuprate in ether at −40 °C produced a single diastereomer, **45**, in 99% yield.

Having finally introduced the C4 methyl with the required stereochemistry, it remained to reduce the two alkenes and the C2 carbonyl as well as dehydrate the tertiary hydroxyl at C11. The critical hydrogenation of the C1,10 alkene was accomplished with high stereoselectivity and concomitant reduction of the C8,9 alkene by catalytic reduction with hydrogen and palladium on carbon in acid free ethanol to give ketone **46**. Heating the tertiary alcohol **46** in the presence of pyridine on alumina[4,21] at 230 °C resulted in regioselective dehydration of the tertiary alcohol to generate the isopropylidine **47**. Reduction of the C2 carbonyl was accomplished with lithium aluminum hydride to provide a 9:1 separable mixture of the equatorial/axial alcohols **48a,b**, respectively. Removal of the silyl protecting group with tetrabutylammonium fluoride completed the synthesis, providing lubiminol (**1**) which was spectroscopically identical (^{1}H and ^{13}C NMR, IR, TLC) to that previsously reported.[2,3]

A highly stereoselective synthesis of the hydroxylated spirovetivane lubiminol (**1**) has been accomplished. The synthesis is highlighted by exploitation of a unique strategic combination of three novel reactions: a conjugate addition−cyclization to prepare the photosubstrate **22**, a diastereoselective intramolecular photoaddition to establish the C5−C7 relative stereochemistry, and the first application of a radical fragmentation−rearrangement sequence in the synthesis of a natural product. The ability to closely predict the diastereoselective outcome of intramolecular [2+2] photocycloadditions by using a molecular mechanics model for the cycloaddition which have been demonstrated during the lubiminol synthesis should be of fundamental importance.

Experimental Section

Materials and Methods: Single-crystal X-ray analyses were performed by Peter White at the University of North Carolina. "Dry" solvents were distilled immediately prior to use from an appropriate drying agent. Diethyl ether, tetrahydrofuran (THF), and benzene were distilled from sodium metal and benzophenone. Alkylamines, dichloromethane, chlorotrimethylsilane, and acetonitrile were distilled from calcium hydride. Hexamethylphosphoramide (HMPA) was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Melting points are uncorrected.

Hydroxy Ester 25. To a solution of HMDS (38.0 mL, 180.0 mmol) in 270 mL of THF cooled to −78 °C under N_2 was added *n*-BuLi over 5 min (103.1 mL of a 1.6 M solution in hexanes, 165.0 mmol). After the solution was stirred for 25 min, ethyl acetate (14.7 mL, 150.0 mmol) in 30 mL of THF was added dropwise over 30 min. This mixture was stirred for 20 min, and acrolein (15.0 mL, 225.0 mmol) was added dropwise over 10 min via syringe. The solution was stirred for 20 min and then quenched with saturated NH_4Cl. This mixture was warmed to room temperature and diluted with ether. The organic layer was washed with 1% HCl (100 mL × 5), saturated $NaHCO_3$, and brine. It was then dried over magnesium sulfate and concentrated to give 21.35 g (148 mmol, 99%) of crude product **25** which was carried to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 2.49 (dd, J = 8.4, 16.0 Hz, 1H), 2.54 (dd, J = 4.0, 16.0 Hz, 1H), 2.97 (dd, J = 2.0, 4.4 Hz, 1H), 4.14 (quartet, J = 7.2 Hz, 2H), 4.50 (m, 1H), 5.13 (dm, J = 10.4 Hz, 1H), 5.28 (dm, J = 17.2 Hz, 1H), 5.85 (ddd, J = 5.2, 10.4, 17.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 172, 138.7, 115.4, 68.9, 60.77, 41.09, 14.13. IR (film): 3450 (br), 2980, 2930, 2900, 1730, 1430, 1365, 1270, 1170, 1120, 1020 cm^{-1}.

Anti β-Hydroxy Ester 26. To a solution of diisopropylamine (32.6 mL, 248.7 mmol) in 250 mL of THF under N_2 at −78 °C was added *n*-BuLi over 5 min (145.0 mL of a 1.6 M solution in hexanes, 232.5 mmol). After the solution was stirred for 30 min, the hydroxy ester **25** (11.160 g, 77.5 mmol) in 50 mL of THF was added dropwise. The solution was stirred at −78 °C for 1 h, warmed to −15 °C, and stirred for 30 min. It was then cooled again to −78 °C, and propargyl bromide (34.6 g, 80 wt % in toluene, 232.5 mmol) in 30 mL of THF was cannulated into the mixture dropwise over 30 min. The reaction mixture was stirred at −78 °C for 1 h and warmed slowly to 0 °C. It was quenched with saturated NH_4Cl. The aqueous layer was extracted with ether (100 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, concentrated, and flash chromatographed (10% EtOAc/hexanes) to afford 12.27 g (67.3 mmol, 87%) anti β-hydroxy ester **26**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 1.97 (t, J = 2.4 Hz, 1H), 2.49 (m, 2H), 2.63 (m, 1H), 2.94 (m, 1H), 4.31 (quartet, J = 7.2 Hz, 2H), 4.34 (m, 1H), 5.16 (dd, J = 1.6, 10.4 Hz, 1H), 5.28 (dd, J = 1.6, 17.2 Hz, 1H), 5.79 (ddd, J = 6.0, 10.4, 17.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 173, 137.5, 116.9, 80.54, 72.34, 70.39, 60.99, 49.51, 18.36, 14.13. IR (film): 3480 (br), 3300, 2990, 1730, 1430, 1375, 1180, 1030 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.82.

Acetylenic Diol 18a. To a solution of methylmagnesium bromide (101.0 mL of a 3.0 M solution in ether, 303.4 mmol) in 300 mL of ether in a three-neck round-bottom flask equipped with a reflux condenser, a nitrogen inlet, and a mechanical stirrer at room temperature was added the β-hydroxy ester **26** (12.270 g, 67.4 mmol) in 50 mL of ether dropwise slowly over 1 h under N_2. The reaction mixture was stirred at room temperature for 2 h. It was then cooled to 0 °C and quenched by dropwise addition of saturated NH_4Cl (100 mL). The mixture was diluted with 200 mL of ether, and 100 mL of 10% HCl was added to dissolve the solid residue. The aqueous layer was extracted with ether (100 mL × 3), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The product was purified by flash chromatography (15% EtOAc/hexanes) to give 10.00 g (59.5 mmol, 88%) of acetylenic diol **18a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.48 (s, 3H), 1.70 (m, 1H), 1.95 (s, 1H), 2.22 (m, 2H), 3.78 (br, 1H), 4.04 (br, 1H), 4.41 (t, J = 8.4 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 5.32 (d, J = 16.8 Hz, 1H), 5.85 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.6, 117.3, 82.31, 75.16, 74.21, 70.5, 50.56, 29.98, 25.63, 17.73. IR (film): 3300 (br), 2980, 2920, 1425, 1385, 1170, 1145, 1020 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.34; H, 9.63.

Syn Methyl Ester 10s. To a solution of syn acetylenic diol **18s** (454.9 mg, 2.710 mmol) in 50 mL of dichloromethane were added

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dimethoxypropane (1.66 mL, 13.5 mmol) and pyridinium *p*-toluenesulfonate (102.1 mg, 0.410 mmol), and the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with solid sodium bicarbonate. The solvent was removed and the residue diluted with ether, washed with water, saturated aqueous sodium bicarbonate, and brine, then dried over magnesium sulfate, filtered, and concentrated. Chromatography with 15% ethyl acetate/hexanes yielded syn acetonide (411.8 mg, 1.980 mmol, 77%, 85% based on recovered starting material). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.39 (s, 3H), 1.48 (s, 6H), 1.63 (dt, 1H), 1.94 (t, 1H), 2.35 (m, 2H), 4.76 (m, 1H), 5.26 (m, J = 11.2 Hz, 1H), 5.35 (m, J = 17.5 Hz, 1H), 5.87 (ddd, J = 3.7, 11.2, 17.5 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 137.17, 115.88, 99.05, 85.76, 74.30, 69.02, 68.66, 45.16, 31.51, 29.45, 28.60, 25.02, 14.01. IR (film): 3300, 2980, 2920, 2220 (w), 2100 (w), 1975 (w), 1270, 1245, 1190 cm^{-1}. To a solution of syn acetylenic acetonide from the reaction above (4.37 g, 0.0210 mol) in 200 mL of THF under a nitrogen atmosphere at −78 °C was added dropwise over 15 min *n*-butyllithium (10.1 mL of a 2.5 M solution in hexanes, 25.2 mmol). After 30 min of stirring, methyl chloroformate (1.95 mL, 25.2 mmol) was added rapidly. The reaction mixture was stirred for an additional 15 min at −78 °C and then warmed to room temperature and quenched with saturated aqueous ammonium chloride solution, diluted with ether, washed with water and brine, dried, over magnesium sulfate, filtered, dried and concentrated. Chromatography with 25% ethyl acetate/hexanes afforded syn methyl ester **10s** (3.69 g, 0.0139 mol, 66%, 80% based on recovered starting material) as a clear oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 1.63 (m, 1H), 2.51 (d (2.50), s (2.52), AB, 2H), 3.74 (s, 3H), 4.76 (m, 1H), 5.24−5.40 (m, 2H), 5.82 (ddd, J = 3.6, 10.5, 18.0 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 137.17, 115.88, 99.05, 85.76, 74.30, 69.02, 68.66, 45.16, 31.51, 29.45, 28.60, 25.02, 14.01. IR (film): 3300, 2980, 2920, 2220 (w), 2100 (w), 1975 (w), 1270, 1245, 1190 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.49; H, 8.31.

Anti Methyl Ester 10a. To a solution of the acetylenic diol **18a** (11.955 g, 71.7 mmol) in 150 mL of CH_2Cl_2 were added dimethoxypropane (35.0 mL, 284.6 mmol) and PPTS (1.8 g, 7.17 mmol), and the mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with solid sodium bicarbonate. The mixture was filtered, and the organic solvent was removed in vacuo. The residue was diluted with ether, washed with water, saturated aqueous sodium bicarbonate, and brine, then dried over magnesium sulfate, filtered, and concentrated. The product was purified by chromatography with 25% ethyl acetate/hexanes to give 12.418 g (59.6 mmol, 83%) of acetonide. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 1.71 (2 overlapping triplets, J = 11.2 Hz, 1H), 1.99 (t, J = 3.7 Hz, 1H), 2.24 (dd, J = 7.2, 10.4 Hz, 1H), 4.28 (dd, J = 7.5, 11.2 Hz, 1H), 5.28 (dd, J = 11.2, 1.2 Hz, 1H), 5.43 (d, J = 16.8 Hz, 1H), 5.88 (ddd, J = 7.5, 11.2, 16.8 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 137.11, 118.12, 98.11, 82.54, 74.21, 71.62, 70.15, 46.01, 31.70, 25.08, 24.54, 16.96. IR (film): 3300, 2980, 2925, 2230 (w), 2100 (w), 1980 (w), 1370, 1250, 1190 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.91; H, 9.72. To a solution of anti acetylenic acetonide (12.418 g, 59.6 mmol) from the reaction above in 120 mL of THF under nitrogen atmosphere at −78 °C was added dropwise over 30 min *n*-butyllithium (44.7 mL of a 1.6 M solution in hexanes, 71.6 mmol). After 20 min of stirring, methyl chloroformate (5.5 mL, 71.6 mmol) was added dropwise via syringe over 5 min. The reaction mixture was stirred at −78 °C for 15 min and then quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with ether (50 mL × 2). The combined organic layers were washed with brine, dried over magnesium sulfate, concentrated, and chromatographed with 8% ethyl acetate/hexanes to afford 14.368 g (54.0 mmol, 91%) of acetylenic methyl ester **10a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.73 (dt, J = 5.6, 10.4 Hz, 1H), 2.30 (d, J = 5.6 Hz, 2H), 3.72 (s, 3H), 4.20 (dd, J = 7.6, 10.0 Hz, 1H), 5.27 (dd, J = 1.6, 10.4 Hz, 1H), 5.39 (d, J = 17.2 Hz, 1H), 5.79 (ddd, J = 7.6, 10.4, 17.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 153.9, 136.6, 119.1, 98.37, 87.68, 74.47, 73.97, 71.88, 52.58, 45.8, 31.69, 25.05, 24.47, 17.34. IR (film): 2990, 2940, 2240, 1720, 1440, 1370, 1260, 1190, 1140, 1075, 1055 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.32. Found: C, 67.39; H, 8.24.

Syn Photosubstrate 9s. To a solution of ((1-ethoxycyclopropyl)oxy)trimethylsilane (4.52 mL, 3.92 g, 0.02256 mol) in 16 mL of diethyl ether at room temperature under nitrogen was added zinc(II) chloride (17.0 mL of a 1.0 M solution in diethyl ether, 17.0 mmol), and the mixture was subjected to ultrasonic irradiation for 30 min. The mixture was cooled to 0 °C, and copper(I) bromide−dimethyl sulfide complex (462 mg, 2.25 mmol) was added at once, whereupon the mixture was stirred for 10 min at 0 °C. Acetylenic ester **10s** (2.00 g, 0.0075 mol) in 35 mL of THF and hexamethylphosphoramide (4.0 mL, 23.0 mmol) were then added successively as rapidly as possible. The reaction was warmed to room temperature and stirred for 5 h before being quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted three times with ether, and the combined organic extracts were washed once with brine, dried over magnesium sulfate, filtered, and concentrated. Chromatography with 25−50% ethyl acetate/hexanes gave syn photosubstrate **9s** as a colorless oil (1.74 g, 0.005 39 mol, 72%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.43 (s), 1.47 (s, 3H), 1.49 (s, 3H), 1.79 (m, J = 5.6 Hz, 1H), 2.45 (t, J = 5.6 Hz, 2H), 2.58 (t, J = 5.6 Hz, 1H), 2.67 (t, J = 5.6 Hz, 1H), 2.82 (dd, J = 6.7, 16.8 Hz, 1H), 3.19 (dd, J = 6.7, 16.8 Hz, 1H), 3.84 (s, 3H), 4.77 (m, 1H), 5.18 (dt, J = 11.2 Hz, 1H), 5.34 (dt, J = 16.8 Hz, 1H), 5.76 (ddd, J = 3.7, 11.2, 16.8 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 203.43, 163.91, 137.13, 133.13, 115.90, 99.26, 74.39, 69.11, 51.83, 43.09, 34.73, 31.54, 30.79, 29.22, 28.57, 28.50, 24.99. IR (film): 2980, 2940, 1740, 1710, 1620, 1430, 1370, 1350, 1290, 1250, 1220, 1190, 1020 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.10; H, 8.17.

Anti Photosubstrate 9a. In a three-neck round-bottom flask equipped with a magnetic stir bar, solid zinc chloride (5.66 g, 41.5 mmol) was fused by flame under vacuum (<1 mmHg). Ether (45 mL) was then added under N_2 at room temperature, and the mixture was heated at reflux for 2.5 h until the zinc chloride solid dissolved (the cloudy mixture was allowed to settle, resulting in two layers of a clear colorless solution). To the above solution of zinc chloride in ether were added at once [(1-ethoxycyclopropyl)oxy]trimethylsilane (11.0 mL, 54.8 mmol) and 35 mL of ether, and the reaction mixture was irradiated in an ultrasonic bath for 40 min and then cooled to 0 °C. To the reaction mixture at 0 °C were then added copper(I) bromide−dimethyl sulfide complex (1.37 g, 6.64 mmol), 60 mL of THF (via syringe), HMPA (9.8 mL, 56.4 mmol) (via syringe), and the acetylenic methyl ester **10a** (4.416 g, 16.6 mmol) in 10 mL of THF (via cannula) as rapidly as possible. The ice bath was then removed, and the mixture was stirred at room temperature for 3 h until all of the starting material was consumed (TLC). The reaction was quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether (50 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, concentrated, and chromatographed (25−50% ethyl acetate/hexanes) to give 4.412 g (13.7 mmol, 83%) of photosubstrate **9a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.25 (s, 3H), 1.29 (s, 3H), 1.39 (s, 3H), 1.82 (m, 1H), 2.36 (t, J = 5.2 Hz, 1H), 2.49−2.65 (m, 3H), 2.77 (dd, J = 7.6, 15.2 Hz, 1H), 3.71 (s, 3H), 4.05 (dd, J = 8.4, 9.2 Hz, 1H), 5.06 (dd, J = 1.2, 10.4 Hz, 1H), 5.22 (dd, J = 0.4, 17.2 Hz, 1H), 5.59 (ddd, J = 7.6, 10.0, 17.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 203.1, 186.6, 163.6, 136.4, 133.1, 119, 98.06, 74.01, 72.65, 51.74, 45.91, 34.51, 31.58, 31.06, 30.79, 30.0, 24.75, 23.67. IR (film): 2980, 2940, 2240, 1780, 1720, 1710, 1620, 1430, 1370, 1345, 1250, 1195, 1045, 1020 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.92; H, 8.01.

Syn Photoadducts (Major, 19; Minor, 20). A solution of syn photosubstrate **9s** (1.74 g, 0.0539 mol) in hexanes and methylene chloride (135 mL, 10:1) was placed in a Pyrex torroidal (donut) reactor and irradiated with a 450-W medium-pressure mercury vapor lamp through a uranium glass filter for 12 h at room temperature. The solvent was removed, and chromatography (15% ethyl acetate/hexanes) afforded the major syn photoadduct **19** (1.45 g, 0.0450 mol, 83%, mp 132−134 °C) and the minor syn photoadduct **20** (244 mg, 0.756 mmol, 14%, mp 104−107 °C) as white crystalline solids. Spectral data for the major syn photoadduct **19** are as follows. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.46 (s, 3H), 1.51−1.65 (m,

2H,), 1.84 (dd, J = 9.3, 13.1 Hz, 1H), 2.02 (m, J = 3.7, 5.6, 13.1 Hz, 2H), 2.25 (t, J = 9.3 Hz, 1H), 2.46 (m, J = 4.8 Hz, 1H), 2.54 (m, 1H), 2.79 (m, J = 9.3, 11.2, 16.8 Hz, 1H), 3.14 (dd, J = 5.6, 13.1 Hz, 1H), 3.72 (s, 3H), 4.34 (dd, J = 3.7, 5.6 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 214.96, 169.82, 97.87, 71.12, 66.78, 58.78, 55.80, 51.87, 48.36, 43.25, 37.15, 33.93, 33.73, 31.76, 30.36, 30.18, 24.39, 21.51. IR (film): 2980, 2940, 1750, 1730, 1430, 1370, 1285, 1250, 1200, 1190 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.98; H, 8.10. Spectral data for the minor syn photoadduct **20** are as follows. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.13 (s, 3H), 1.23 (s, 3H), 1.44 (s, 6H), 1.59 (m, J = 12.1, 18.7 Hz, 1H), 1.92−2.10 (band, 5H), 2.25 (t, J = 9.3 Hz, 1H), 2.31 (dd, J = 7.5, 14.9 Hz, 1H), 2.47−2.63 (band, J = 3.7, 6.3 Hz, 2H), 2.78 (m, J = 9.3, 10.3, 18.7 Hz, 1H), 3.62 (s, 3H), 4.14 (d, J = 1.9 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 215.83, 170.03, 97.42, 73.54, 71.00, 58.46, 57.77, 52.01, 44.76, 44.03, 38.20, 32.62, 32.00, 31.63, 30.02, 29.93, 24.33, 23.71. IR (film): 2990, 2970, 2950, 2925, 1745, 1725, 1370, 1145 cm^{-1}.

Anti Photoadduct 22. A solution of photosubstrate **9a** (4.412 g, 13.7 mmol) in hexanes and CH_2Cl_2 (550 mL, 10:1) was placed in a Pyrex immersion well reactor and irradiated with a 450-W medium-pressure mercury vapor lamp, through a uranium glass filter for 15 h at room temperature. The solvent was removed, and flash chromatography (15% ethyl acetate/hexanes) afforded as the sole product anti photoadduct **22** (4.30 g, 13.4 mmol, 98%, mp 100−103 °C) as a white crystalline solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.27 (s, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.58−1.72 (band, 2H), 2.02 (m, J = 7.5, 13.1 Hz, 1H), 2.15−2.34 (band, 3H), 2.47−2.65 (band, 2H), 2.78 (ddd, J = 9.3, 13.1, 17.5 Hz, 1H), 3.71 (s, 3H), 3.77−3.87 (m, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 214.01, 170.13, 100.32, 79.58, 75.79, 57.81, 54.71, 52.16, 50.35, 42.49, 37.21, 34.06, 32.64, 31.76, 31.67, 30.24, 24.78, 22.35. IR (film): 2970, 2940, 2870, 1745, 1725, 1445, 1435, 1370, 1250, 1185 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.92; H, 8.07.

Syn Photoadduct Diol 21. The syn photoadduct **19** (438.0 mg, 1.360 mmol) was dissolved in 15 mL of 4:1 THF/H_2O at room temperature. To the solution was added pyridinium *p*-toluenesulfonate (85.4 mg, 0.340 mmol). After 2 days of stirring, the mixture was diluted with ether, washed with brine, dried over magnesium sulfate, filtered, concentrated, and chromatographed with 30% ethyl acetate/hexanes to afford syn diol **21** (341.5 mg, 1.211 mmol, 89%, mp 142−144 °C) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.44 (s, 3H), 1.65 (dd, J = 6.0, 13.5 Hz, 1H), 1.73 (m, J = 5.8, 13.5 Hz, 1H), 1.86 (dd, J = 9.0, 13.5 Hz, 1H), 2.02 (m, J = 5.4 Hz, 2H), 2.25 (t, J = 13.5 Hz, 1H), 2.44 (m, J = 7.5, 12.0 Hz, 1H), 2.53 (m, J = 3.6, 4.5, 6.0, 18.0 Hz, 1H), 2.74 (dt, J = 10.5, 12.0, 18.0 Hz, 1H), 3.01 (dd, J = 6.0, 13.5 Hz, 1H), 3.28 (br s, 1H), 3.68 (s, 3H), 4.46 (br t, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 215.31, 170.34, 73.40, 71.52, 57.63, 56.07, 54.74, 52.13, 43.58, 37.49, 33.03, 32.48, 29.97, 29.60, 21.50. IR (film): 3460 (br), 3200 (br), 2970, 2940, 2920, 2860, 1745, 1720, 1430, 1410, 1380, 1290, 1240, 1190, 1150, 1130 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.58; H, 7.79.

Anti Photoadduct Diol 35. To a solution of the photoadduct **22** (4.30 g, 13.4 mmol) in 100 mL of THF and 25 mL of H_2O at room temperature was added a catalytic amount of *p*-toluenesulfonic acid. After 3 h of stirring, the reaction mixture was diluted with 100 mL of ether, and the aqueous layer was extracted with ether (50 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, concentrated, and chromatographed with 30% ethyl acetate/hexanes to afford the tricyclic diol **35** (3.283 g, 11.6 mmol, 85% for two steps from the photosubstrate **22**) as a white crystalline solid (mp 108−110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.27 (s, 3H), 1.63 (m, J = 6.0, 10.5 Hz, 2H), 1.98 (dt, J = 9.0, 12.0 Hz, 1H), 2.08 (m, J = 1.5, 6.0, 7.5 Hz), 2.21 (m, J = 9.0, 12.0 Hz, 1H), 2.24−2.33 (m, 2H), 2.51 (m, 1H), 2.55 (m, J = 9.0, 16.5 Hz, 1H), 2.73 (ddd, J = 9.0, 12.0, 19.5 Hz, 1H), 3.67 (s, 3H), 4.13 (dd, J = 3.0, 9.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 215.06, 170.08, 82.69, 72.83, 57.68, 57.25, 56.08, 52.21, 45.42, 37.82, 33.90, 33.12, 31.24, 29.86, 24.18. IR (film): 3420 (br), 2960, 2940, 2870, 1740, 1725, 1440, 1430, 1370, 1280, 1255, 1205, 1135 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.57; H, 7.88.

Thiocarbonylimidazole Derivative 36. To a solution of the tricyclic diol **35** (0.945 g, 3.35 mmol) in 50 mL of freshly distilled $CHCl_3$ under nitrogen were added thiocarbonyldiimidazole (0.995 g, 90% technical grade, 5.03 mmol) and 4-(dimethylamino)pyridine all at once (0.082 g, 0.67 mmol). The reaction mixture was heated at reflux for 1 h and cooled to room temperature, and the solvent was removed in vacuo. Chromatography with 50% ethyl acetate/hexanes, then 75% ethyl acetate/hexanes, and then 100% ethyl acetate afforded the pure thiocarbonylimidazole derivative **36** (1.122 g, 2.86 mmol, 85%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.228 (s, 3H), 1.26 (s, 3H), 1.93 (dd, J = 8.0, 14.0 Hz, 1H), 2.09 (m, 4H), 2.37 (m, 2H), 2.60 (m, 3H), 2.74 (m, 1H), 3.67 (s, 3H), 5.41 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 7.56 (s, 1H), 8.25 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 214.5, 183.4, 169.7, 136.5, 130.8, 118.1, 91.23, 69.82, 57.42, 57.2, 56.23, 52.27, 45.06, 38.04, 32.36, 32.27, 29.69, 29.18, 29.04. IR (film): 3330 (br), 2970, 1745, 1730, 1465, 1385, 1335, 1285, 1240, 1210, 1145, 1090, 980 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{19}H_{24}O_5N_2S$: calcd 393.1484, found 393.1479.

Spiroketones 37a,b. In a three-neck 3-L round-bottom flask equipped with a reflux condenser, a mechanical stirrer, and an addition funnel, the thiocarbamate **36** (1.451 g, 3.702 mmol) was dissolved in 1000 mL of benzene (freshly distilled and subsequently degassed with N_2 for 1 h prior to use) under N_2 and heated to a gentle reflux. A solution of tributyltin hydride (1.19 mL, 4.442 mmol) and AIBN (0.121 g, 0.740 mmol) in 500 mL of degassed benzene was added to the reaction mixture very slowly over a 6-h period. The reflux was continued for 1 h after the addition was complete, and the solvent was then removed in vacuo. Purification by flash chromatography (25−50% ethyl acetate/hexanes) gave the spiroketones **37a** (0.552 g, 2.075 mmol, 56%, $R_{f\ 50\%}$ = 0.15) as the higher R_f diastereomer and **37b** (0.406 g, 1.526 mmol, 41%, $R_{f\ 50\%}$ = 0.13) as the lower R_f diastereomer. Spectral data for **37a** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 3H), 1.16 (s, 3H), 1.22 (m, 1H), 1.75 (m, 1H), 1.89 (m, 3H), 2.32 (m, 1H), 2.45 (m, 2H), 2.59 (m, 1H), 2.88 (m, 2H), 3.58 (s, 3H), 5.72 (dd, J = 1.2, 6.0 Hz, 1H), 5.75 (dd, J = 2.4, 6.0 Hz, 1H). ^{1}H NMR (300 MHz, benzene-d_6): δ 1.18 (s, 3H), 1.21 (s, 3H), 1.39 (m, 2H), 1.60 (m, 1H), 1.74 (dd, J = 7.8, 13.2 Hz, 1H), 1.88 (dd, J = 7.8, 13.2 Hz, 1H), 2.17 (m, 3H), 2.40 (dd, J = 3.6, 14.4 Hz, 1H), 2.57 (dd, J = 10.8, 14.1 Hz, 1H), 2.65 (dd, J = 3.9, 11.1 Hz, 1H), 2.79 (tt, J = 1.8, 8.1 Hz, 1H), 3.38 (s, 3H), 5.58 (dd, J = 2.7, 5.7 Hz, 1H), 5.73 (dd, J = 1.5, 5.7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 209.1, 172.9, 138.2, 131.1, 71.67, 55.76, 51.69, 50.89, 50.11, 40.66, 38.18, 35.66, 30.76, 28.06, 27.07. IR (film): 3480 (br), 2975, 2865, 1760, 1440, 1370, 1280, 1230, 1195, 1175, 1135 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{15}H_{22}O_4$: calcd 267.1596, found 267.1584. Spectral data for **37b** are as follows. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.19 (s, 3H), 1.28 (m, 1H), 1.50 (br, 1H), 1.65 (m, 1H), 1.78 (dd, J = 8.0, 12.8 Hz, 1H), 1.99 (m, 2H), 2.37 (m, 2H), 2.47 (dd, J = 5.2, 15.6 Hz, 1H), 2.60 (dd, J = 7.2, 15.6 Hz, 1H), 2.86 (m, 2H), 3.62 (s, 3H), 5.77 (dd, J = 2.0, 5.6 Hz, 1H), 5.88 (dd, J = 2.4, 5.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 208.7, 173.2, 136.7, 131.7, 71.4, 55.61, 51.75, 51.49, 50.32, 40.79, 38.02, 36.35, 35.16, 28.32, 27.11. IR (film): 3450 (br), 1970, 2870, 1730, 1440, 1365, 1280, 1195, 1170 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{15}H_{22}O_4$: calcd 267.1596, found 267.1593.

Anti Acetonide Enone 23. To a solution of the anti photoadduct **22** (480.3 mg, 1.492 mmol) and ethyl (trimethylsilyl)acetate (0.68 mL, 3.792 mmol) in 8 mL of dry THF at room temperature under nitrogen was added over 30 min a solution of tetrabutylammonium fluoride (7.5 μL of a 1.0 M solution in THF, 0.075 mmol) in 4 mL of dry THF. After 40 min of stirring, 20 mL of dry acetonitrile, palladium(II) acetate (335.0 mg, 1.492 mmol), and benzoquinone (323.0 mg, 2.984 mmol) were added at once. After being stirred at room temperature for 3 days, the reaction mixture was diluted with 50 mL of 1:1 ether/petroleum ether and filtered through Celite. Flash chromatography with 15% ethyl acetate/hexanes afforded anti acetonide enone **23** (267.5 mg, 0.8359 mmol, 56%, 66% based on recovered ketone **22**). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.27 (s, 3H), 1.33 (d, J = 13.1 Hz, 1H), 1.40 (s, 3H), 1.50 (s, 3H), 1.62 (m, J = 1.9, 7.5 Hz, 1H), 1.86 (dd, J = 7.5, 13.1 Hz, 1H), 2.08 (dd, J = 8.2, 14.2 Hz, 1H), 2.23 (m, J = 3.7, 8.2 Hz), 2.83 (dd, J = 3.7, 14.2 Hz, 1H), 3.73 (s, 3H), 3.99

(dd, $J = 7.5$, 11.2 Hz, 1H), 6.32 (d, $J = 5.6$ Hz, 1H), 7.64 (d, $J = 5.6$ Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 205.40, 166.68, 133.22, 100.38, 77.19, 76.73, 75.70, 58.56, 57.99, 52.38, 50.89, 45.82, 31.84, 31.64, 28.24, 26.93, 24.78, 22.45. IR (film): 2980, 2940, 2865, 1740, 1700, 1575, 1430, 1375, 1360, 1340, 135, 1280, 1265, 1255, 1240, 1190, 1150, 1115, 1095 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.22; H,7.58.

***β*-Methyl Enone Anti Acetonide 27.** To a suspension of copper(I) bromide−dimethyl sulfide complex (448.9 mg, 2.183 mmol) in 15 mL of ether cooled to 0 °C was added methyllithium (2.57 mL of a 1.5 M solution in ether, 4.00 mmol) rapidly by syringe. The cuprate was stirred for 15 min, and chlorotrimethylsilane (0.28 mL, 2.183 mmol) was added all at once. The solution remained clear and colorless. A solution of anti acetonide enone **23** (232.9 mg, 0.7278 mmol) in 20 mL of ether was added dropwise over 10 min to the cuprate, turning it cloudy yellow. The ice bath was removed, and the reaction mixture was stirred at room temperature for 1 h before being quenched with saturated aqueous ammonium chloride. The mixture was diluted with ether, washed with water and brine, dried over sodium sulfate, filtered, and concentrated to afford β-methyl trimethylsilyl enol ether (anti) (241.8 mg, 0.5926 mmol, 81%) as a crude product. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.21 (s, 9H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.24 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.82 (dd, $J = 6.7$, 13.1 Hz, 1H), 2.18 (m, 1H), 2.44 (d, $J = 3.0$ Hz, 1H), 2.47 (d, $J = 3.7$ Hz, 1H), 2.58 (m, $J = 3.0$ Hz, 1H), 3.68 (s, 3H), 3.80 (dd, $J = 4.5$, 11.2 Hz, 1H), 4.81 (d, $J = 1.9$ Hz).

To a solution of trimethylsilyl enol ether (408.3 mg, 1.00 mmol) in 25 mL of dry acetonitrile at room temperature was added palladium(II) acetate (225 mg, 1.00 mmol), and the reaction was stirred for 2 days. Solvent was removed and the residue chromatographed using 25% ethyl acetate/petroleum ether to yield recovered ketone **24** (186.6 mg, 0.559 mmol, 56%) and enone **27** (86.7 mg, 0.260 mmol, 26%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.29 (s, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 1.63 (ddd, $J = 7.5$, 11.2 Hz, 1H), 1.88 (dd, $J = 7.5$, 13.1 Hz, 1H), 2.04−2.16 (band, $J = 7.5$ Hz, 2H), 2.28 (m, $J = 3.7$, 13.1 Hz, 1H), 2.34 (d, $J = 0.75$ Hz, 3H), 2.84 (dd, $J = 3.7$, 13.1 Hz, 1H), 3.74 (s, 3H), 4.00 (dd, $J = 7.5$, 11.2 Hz, 1H), 6.12 (d, $J = 0.75$ Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 204.06, 178.83, 170.19, 131.40, 100.44, 76.88, 75.79, 60.38, 59.54, 52.32, 52.07, 45.52, 31.91, 31.64, 28.33, 27.12, 24.78, 22.34, 13.89. IR (film): 2985, 2950, 1740, 1705, 1610, 1435, 1380, 1365, 1300, 1245, 1190, 1150, 1100 cm^{-1}. HRMS (FAB) (*m*/*e*) for $C_{19}H_{26}O_5$ (M^+): calcd 335.1858, found 335.1862. Ketone **24** was recovered as a pale yellow crystalline solid (mp 110−113 °C) as a byproduct from the palladium acetate oxidation of the trimethylsilyl enol ether above. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.06 (d, $J = 7.5$ Hz, 3H), 1.24 (s, 3H), 1.29 (s, 3H), 1.20−1.25 (m, 1H), 1.40 (s, 3H), 1.47 (s, 3H), 1.58 (ddd, $J = 5.6$, 15.0 Hz, 1H), 1.95 (dd, $J = 5.6$, 13.1 Hz, 1H), 2.21−2.42 (band, 3H), 2.65 (m, 1H), 3.07 (dd, $J = 7.5$, 16.8 Hz, 1H), 3.72 (d, $J = 3.7$ Hz, 1H), 3.74 (s, 3H), 3.83 (dd, $J = 5.6$, 11.2 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 214, 171, 100.44, 79.57, 77.24, 75.88, 58.37, 57.32, 52.42, 49.88, 45.19, 42.95, 36.80, 31.76, 30.75, 26.81, 24.88, 22.41, 17.31. IR (film): 2980, 2975, 2940, 2900, 2880, 1750, 1725, 1455, 1435, 1415, 1375, 1360, 1325, 1300, 1280, 1265, 1255, 1225, 1195, 1175, 1145, 1125, 1105, 1085 cm^{-1}.

***β*-Methyl Ketone Anti Diol 28.** To a flask containing enone **27** (35.5 mg, 0.106 mmol) and 10% Pd on activated carbon (Pd/C) (35 mg, 10 wt %) were added 2 mL of ethanol and 1 drop of 10% aqueous hydrochloric acid. The reaction mixture was stirred under a hydrogen atmosphere of 1 atm at 25 °C for 1 h. A spatula tip of solid sodium bicarbonate was added and the solvent removed. Chromatography with 50% ethyl acetate/hexanes gave ketone **28** (31.2 mg, 0.105 mmol, 99%, mp 84−87 °C) as a white crystalline solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.14 (d, $J = 6.3$ Hz, 3H), 1.25 (s, 3H), 1.28 (s, 3H), 1.63 (q, $J = 13.1$ Hz, 1H), 1.72 (dd, $J = 7.5$ Hz, 1H), 1.96−2.14 (band, 2H), 2.25 (dd, $J = 8.2$, 13.1 Hz, 1H), 2.33−2.62 (band, 5H), 3.71 (s, 3H), 4.16 (m, $J = 2.6$, 3.7, 9.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 213.48, 170.07, 82.91, 72.75, 59.41, 59.07, 57.06, 52.07, 45.10, 40.80, 38.67, 33.02, 31.06, 29.95, 24.14, 13.79. IR (film): 3410 (br), 2960, 2925, 2865, 1740, 1725, 1455, 1430, 1405, 1375, 1275, 1255, 1235, 1200, 1135 cm^{-1}.

***β*-Methyl Thiocarbonylimidazole Derivative 29.** To a solution of diol **28** (31.2 mg, 0.105 mmol) in 3 mL of THF under nitrogen were added 90% technical grade thiocarbonyldiimidazole (41.6 mg, 0.210 mmol) and 4-(dimethylamino)pyridine (2.6 mg, 0.021 mmol). The solution was stirred at reflux for 1 h and then cooled, and the THF was removed. Chromatography with 50% ethyl acetate/hexanes, then 75% ethyl acetate/hexanes, and then 100% ethyl acetate afforded pure thiocarbonylimidazole derivative **29** (32.8 mg, 0.0808 mmol, 77%) as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.09 (d, $J = 7.5$ Hz, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.93−2.67 (band, 9H), 2.76 (dd, $J = 7.5$, 14.2 Hz, 1H), 3.70 (s, 3H), 5.50 (dd, $J = 1.9$, 7.5 Hz, 1H), 7.03 (s, 1H), 7.59 (s, 1H), 8.29 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 213.37, 169.72, 131.01, 91.54, 70.02, 61.46, 60.41, 59.52, 57.89, 57.10, 52.35, 45.56, 40.76, 37.87, 31.37, 29.18, 29.08, 21.07, 14.21, 13.66. IR (film): 3400 (br), 2960, 2890, 2870, 1745, 1725, 1520, 1465, 1385, 1330, 1285, 1240, 1225, 1135, 1100 cm^{-1}.

Rearrangement of 29. Thiocarbonylimidazole derivative **29** (43.7 mg, 0.108 mmol) was dissolved in 22 mL of benzene (to make a 0.005 M solution), deoxygenated with argon for 15 min, and heated to 80 °C in an oil bath. A deoxygenated mixture of tributyltin hydride (0.035 mL, 0.130 mmol) and catalytic AIBN initiator (3.5 mg, 0.022 mmol) in 10 mL of degassed benzene was added via a syringe pump over a 6 h period while the temperature was maintained at 80 °C. The mixture was concentrated and chromatographed with 20% ethyl acetate/petroleum ether to yield a 5:1 mixture of diastereomers of rearrangement product **32** (18.0 mg, 0.064 mmol, 60%) as a clear oil, spiro[4.4]nonane product **31** (4.2 mg, 0.015 mmol, 14%) as a clear oil, and direct reduction product **30** (3.0 mg, 0.011 mmol, 10%) as a white solid. Spectral data for **32** are as follows. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (d, $J = 7.5$ Hz, 3H), 1.17 (s, 3H), 1.24 (s, 3H), 1.52 (dd, $J = 8.2$, 13.1 Hz, 1H), 1.58 (dd, $J = 8.2$, 13.1 Hz, 1H), 1.80−1.96 (band, $J = 7.5$ Hz, 2H), 1.96−2.07 (band, 1H), 2.07−2.19 (band, 1H), 2.26 (m, 1H), 2.36 (dd, $J = 5.6$, 17.9 Hz, 1H), 2.90 (tt, $J = 1.1$, 8.2 Hz, 1H), 3.74 (s, 3H), 5.64 (dd, $J = 3.0$, 6.7 Hz, 1H), 5.73 (dd, $J = 1.1$, 3.7 Hz, 1H). ^{13}C NMR (major diastereomer) (250 MHz, $CDCl_3$): δ 173.01, 171.58, 140.87, 136.04, 130.19, 96.25, 72.18, 55.65, 51.37, 35.00, 34.33, 33.67, 30.14, 28.57, 26.99, 16.25. IR (film): 3432 (br), 2961, 2930, 2872, 1742 (w), 1715 (w), 1659, 1620, 1443, 1362, 1271, 1202 cm^{-1}. Spectral data for spiro[4.4]nonane **31** are as follows. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.96 (d, $J = 6.7$ Hz, 3H), 1.19 (s, 3H), 1.24 (s, 3H), 1.75 (dd, $J = 8.2$, 14.9 Hz, 1H), 1.87 (dd, $J = 11.2$, 18.7 Hz, 1H), 1.25 (dd, $J = 8.2$, 13.1 Hz, 1H), 2.58 (m, $J = 6.7$ Hz, 1H), 2.72 (dd, $J = 8.2$, 18.7 Hz, 1H), 2.86 (tt, $J = 1.9$, 8.2 Hz, 1H), 3.70 (s, 3H), 5.29 (dd, $J = 3.0$, 5.6 Hz, 1H), 5.95 (dd, $J = 2.2$, 5.6 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$): δ 214.73, 134.65, 131.72, 72.21, 64.66, 63.72, 57.29, 52.20, 44.71, 38.40, 32.18, 29.68, 28.24, 26.90, 15.07, 14.30. IR (film): 3439 (br), 2965, 2916, 2872, 2849, 1748 (s), 1728 (s), 1653, 1460, 1377, 1260, 1217, 1111 cm^{-1}.

Dioxolane Alcohol 38a. A solution of the spiroketone **37a** (220 mg, 0.827 mmol), ethylene glycol (0.18 mL, 3.31 mmol), and PPTS (0.2 mmol) in 20 mL of benzene was heated at reflux for 1 h with the removal of H_2O using a Dean−Stark trap. After being cooled to room temperature, the reaction mixture was concentrated and chromatographed (25% ethyl acetate/hexanes) to afford the dioxolane ester (216 mg, 0.697 mmol, 84%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.06 (s, 3H), 1.33 (dt, $J = 3.6$, 14.0 Hz, 1H), 1.55 (m, 3H), 1.70 (m, 4H), 1.88 (br, 1H), 2.62 (m, 2H), 3.11 (s, 3H), 3.82 (m, 4H), 5.51 (dd, $J = 1.2$, 6.0 Hz, 1H), 5.54 (dd, $J = 2.0$, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174, 140.2, 129, 107.9, 71.55, 64.17, 64.12, 55.55, 51.1, 51.06, 47.85, 34.25, 34.04, 31.81, 28.65, 27.92, 26.78. IR (film): 3500 (br), 2970, 2890, 1735, 1440, 1360, 1305, 1260, 1195, 1165, 1135, 1100, 1030 cm^{-1}. To a suspension of lithium aluminum hydride (111 mg, 2.79 mmol) in 10 mL of ether under nitrogen was added dropwise over 15 min the dioxolane ester (216 mg, 0.697 mmol) in 10 mL of ether. After 1 h of stirring at room temperature, the reaction was quenched with 2 drops of H_2O, 2 drops of 15% NaOH aqueous solution, and 6 drops of H_2O consecutively. The mixture was filtered, and the filter pad was washed with hot ethyl acetate six times until no product could be detected in the filtrate. The combined organic solutions were concentrated in vacuo to afford the crude product, the dioxolane alcohol **38a**, which was

brought directly to the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 3H), 1.14 (s, 3H), 1.24 (dt, J = 3.6, 13.2 Hz, 1H), 1.36 (t, J = 13.2 Hz, 1H), 1.48 (td, J = 4.4, 13.2 Hz, 1H), 1.62 (m, 5H), 1.76 (m, 1H), 2.71 (m, 2H), 3.30 (t, J = 5.6 Hz, 1H), 3.39 (quintet, J = 5.6 Hz, 1H), 3.46 (quintet, J = 5.6 Hz, 1H), 3.84 (m, 4H), 5.48 (dd, J = 2.0, 6.0 Hz, 1H), 5.55 (dd, J = 1.2, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 141.9, 128.9, 109, 71.73, 64.37, 64.04, 55.62, 51.21, 43.48, 35.36, 35.02, 31.69, 28.55, 27.91, 27.67. IR (film): 3400 (br), 2940, 2880, 1440, 1360, 1185, 1090 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{16}H_{26}O_4$: calcd 283.1909, found 283.1912.

Dioxolane Alcohol 38b. A solution of the spiroketone **37b** (308 mg, 1.158 mmol), ethylene glycol (0.26 mL, 4.63 mmol), and a catalytic amount of PPTS in 20 mL of benzene was heated at reflux for 1 h with the removal of H_2O using a Dean−Stark trap. After the solution was cooled to room temperature, the solvent was removed in vacuo and the residue purified by column chromatography (25% ethyl acetate/hexanes) to provide the dioxolane ester (256 mg, 0.831 mL, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.049 (s, 3H), 1.134 (s, 3H), 1.45 (s, 1H), 1.63 (m, 5H), 1.80 (m, 2H), 2.02 (t, J = 13.2 Hz, 1H), 2.72 (dd, J = 4.0, 12.8 Hz, 1H), 2.78 (tt, J = 2.0, 8.0 Hz, 1H), 3.56 (s, 3H), 3.91 (m, 4H), 5.67 (dd, J = 1.6, 6.0 Hz, 1H), 6.16 (dd, J = 2.4, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 173.9, 136.3, 130.6, 108, 71.53, 64.34, 64.29, 54.98, 51.37, 50.69, 48.87, 37.12, 36.81, 35.43, 32.12, 28.29, 26.89. IR (film): 3470 (br), 2960, 2880, 1730, 1435, 1365, 1305, 1260, 1160, 1110, 1090, 1040 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{17}H_{26}O_5$: calcd 311.1858, found 311.1850. To a suspension of $LiAlH_4$ (271 mg, 7.13 mmol) in 40 mL of ether under nitrogen was added dropwise the dioxolane ester (554 mg, 1.787 mmol) in 20 mL of ether. After 1 h of stirring at room temperature, the reaction was quenched with 0.3 mL of H_2O, 0.3 mL of 15% NaOH aqueous solution, and 1 mL of H_2O. The mixture was filtered, and the filter pad was washed with hot ethyl acetate until no product could be detected from the filtrate. The organic solutions were combined and concentrated in vacuo. The crude dioxolane alcohol product **38b** was brought directly to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.113 (s, 3H), 1.219 (s, 3H), 1.57 (m, 6H), 1.76 (m, 2H), 2.05 (dd, J = 8.0, 13.6 Hz, 1H), 2.15 (br, 1H), 2.77 (tt, J = 2.4, 8.4 Hz, 1H), 2.92 (br, 1H), 3.43 (dd, J = 5.6, 11.6 Hz, 1H), 3.58 (dd, J = 5.6, 11.6 Hz, 1H), 3.91 (m, 4H), 5.72 (dd, J = 2.0, 6.0 Hz, 1H), 5.96 (dd, J = 2.8, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 136.3, 131.3, 109, 71.83, 65.07, 64.22, 64.21, 55.07, 51.06, 44.07, 37.74, 36.4, 36.13, 32.17, 28.78, 27.64. IR (film): 3400 (br), 2940, 2880, 1365, 1170, 1110, 1075 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{16}H_{26}O_4$: calcd 283.1909, found 283.1920.

Ketone 40b. To a solution of the crude dioxolane alcohol **38b** obtained from the previous step in 50 mL of acetone was added 1 mL of 10% HCl. After 15 h of stirring at room temperature, the reaction was quenched with 1.5 mL of saturated $NaHCO_3$, and the solvent was subsequently removed in vacuo. The residue was diluted with ether and saturated $NaHCO_3$. The aqueous layer was separated and reextracted with ether three times. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. Purification by chromatography (25% ethyl acetate/hexanes) afforded the ketone alcohol (337 mg, 1.416 mmol, 57% for three steps from the ketone **37b**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.167 (s, 3H), 1.277 (s, 3H), 1.73 (ddd, J = 6.0, 9.6, 13.2 Hz, 1H), 1.79 (dd, J = 8.8, 13.2 Hz, 1H), 1.88 (m, 1H), 2.98 (m, 1H), 2.09 (dd, J = 7.6, 13.2 Hz, 1H), 2.33 (m, 2H), 2.39 (m, 2H), 2.85 (m, 1H), 2.90 (br, 1H), 3.60 (m, 2H), 5.85 (dd, J = 2.0, 6.0 Hz, 1H), 6.06 (dd, J = 2.8, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.8, 135.8, 132.3, 71.85, 64.26, 55.12, 51.03, 47.3, 42.28, 38.73, 38.45, 36.26, 28.89, 27.74. IR (film): 3400 (br), 2970, 2870, 1705, 1430, 1375, 1130, 1030 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{14}H_{22}O_3$: calcd 239.1647, found 239.1649. To a solution of the ketone alcohol (110 mg, 0.462 mmol), *tert*-butyldimethylsilyl chloride (139 mg, 0.924 mmol), and a catalytic amount of DMAP (0.15 mmol) in 2.5 mL of CH_2Cl_2 under nitrogen was added Et_3N (0.13 mL, 0.924 mmol). The reaction mixture was stirred for 12 h at room temperature, diluted with ether, and quenched with saturated $NaHCO_3$. The aqueous layer was reextracted with ether three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. Column chromatography (10% ethyl acetate/hexanes) afforded the tributylsilyl ether **40b** (143 mg, 0.406 mmol, 88%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.85 (s, 9H), 1.167 (s, 3H), 1.24 (s, 3H), 1.39 (m, 1H), 1.65 (m, 1H), 1.86 (d, J = 8.0 Hz, 2H), 1.95 (m, 2H), 2.33 (m, 3H), 2.51 (dd, J = 5.6, 15.2 Hz, 1H), 2.88 (tt, J = 2.4, 8.0 Hz, 1H), 3.54 (dd, J = 5.6, 10.4 Hz, 1H), 3.69 (dd, J = 4.4, 10.4 Hz, 1H), 5.78 (dd, J = 1.6, 6.0 Hz, 1H), 6.01 (dd, J = 2.4, 6.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.2, 137.1, 131.3, 71.84, 64.5, 55.51, 50.77, 47.59, 42.42, 38.61, 36.82, 36.72, 28.56, 27.23, 25.85, 18.2, −5.565, −5.61. IR (film): δ 3450 (br), 2930, 2860, 1715, 1470, 1265, 1090 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{20}H_{36}O_3Si$: calcd 353.2512, found 353.2508.

Ketone 40a. To a solution of the crude dioxolane alcohol **38a** obtained from the previous reaction in 45 mL of acetone was added 0.5 mL of 10% HCl. The reaction was stirred at room temperature for 2 h and subsequently quenched with 0.5 mL of saturated $NaHCO_3$. The solvent was removed in vacuo and the residue diluted with 15 mL of ether and 10 mL of saturated $NaHCO_3$. The aqueous layer was separated and reextracted with hot ethyl acetate six times. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (25% ethyl acetate/hexanes) afforded the ketone alcohol (151 mg, 0.634 mmol, 76% for three steps from the ketone **37a**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.152 (s, 3H), 1.248 (s, 3H), 1.65 (m, 2H), 1.87 (m, 2H), 1.99 (dd, J = 7.6, 13.6 Hz, 1H), 2.33 (m, 3H), 2.42 (m, 1H), 2.75 (br, 1H), 2.84 (m, 1H), 3.51 (dd, J = 5.2, 11.6 Hz, 1H), 3.57 (dd, J = 4.8, 11.6 Hz, 1H), 3.67 (br, 1H), 5.58 (dd, J = 2.8, 5.6 Hz, 1H), 5.73 (dd, J = 2.0, 5.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 212, 140.1, 130.3, 71.85, 63.82, 55.73, 51.43, 46.55, 41.73, 38.49, 37.72, 29.09, 28.75, 27.96. IR (film): 3400 (br), 2970, 2870, 1710, 1375, 1140, 1040, 1015 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{14}H_{22}O_3$: calcd 239.1647, found 239.1653. To a solution of the ketone alcohol (253 mg, 1.063 mmol), *tert*-butyldimethylsilyl chloride (224 mg, 1.488 mmol), and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (26 mg, 0.213 mmol) in 5 mL of CH_2Cl_2 under nitrogen was added triethylamine (0.22 mL, 1.595 mmol). The reaction mixture was stirred at room temperature for 15 h and quenched with saturated $NaHCO_3$. The aqueous layer was reextracted with ether four times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by chromatography (10% ethyl acetate/hexanes) to give the tributylsilyl ether **40a** (327 mg, 0.926 mmol, 87%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.043 (s, 6H), 0.81 (s, 9H), 1.13 (s, 3H), 1.19 (s, 3H), 1.63 (m, 1H), 1.74 (m, 2H), 1.85 (dd, J = 8.0, 13.2 Hz, 1H), 1.93 (m, 1H), 2.23 (dd, J = 10.8, 14.4 Hz, 1H), 2.30 (m, 1H), 2.39 (m, 1H), 2.46 (m, 1H), 2.86 (m, 1H), 3.51 (dd, J = 6.0, 10.4 Hz, 1H), 3.58 (dd, J = 4.4, 10.4 Hz, 1H), 5.66 (dd, J = 2.4, 5.6 Hz, 1H), 5.70 (dd, J = 1.6, 5.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.2, 140.2, 130.4, 71.87, 64.34, 55.88, 51.05, 46.81, 41.9, 38.66, 36.19, 30.56, 28.24, 27.2, 25.83, 18.15, −5.536, −5.581. IR (film): 3450 (br), 2960, 2930, 2860, 1715, 1465 (w), 1360 (w), 1255, 1110, 1085 cm^{-1}. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.27; H, 10.33.

Dienone 44. To oil-free KH (5 mmol) suspended in 10 mL of THF under N_2 at room temperature was cannulated a mixture of the tributylsilyl ethers **40a** and **40b** (188 mg, 0.534 mmol) in 8 mL of THF followed by methyl benzenesulfinate (175 mg, 1.122 mmol) in 2 mL of THF over 5 min. After 5 min of stirring, the reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The residue was dissolved in 20 mL of benzene, solid Na_2CO_3 (2.5 mmol) was added, and the reaction mixture was heated at reflux for 1.5 h. After being cooled to room temperature, the mixture was filtered, the solvent removed in vacuo, and the residue purified by column chromatography (25−50% ethyl acetate/hexanes) to give a mixture of regioisomers of enones (166 mg, 0.474 mmol, 89%) which was brought directly to the next step.

To a solution of diisopropylamine (0.20 mL, 1.53 mmol) in 10 mL of THF at −78 °C under N_2 was added *n*-BuLi over 10 min (0.89 mL of a 1.6 M solution in hexanes, 1.42 mmol). After 20 min of stirring at −78 °C, the mixture of the enones (166 mg, 0.474 mmol) in 10 mL of THF was cannulated to the LDA solution followed by phenylsele-

nenyl chloride (273 mg, 1.42 mmol) in 5 mL of THF. The reaction was stirred at −78 °C for 30 min and quenched with saturated NH_4Cl. After the mixture was warmed to room temperature and separated, the aqueous layer was reextracted with ether. The combined organic layers were washed with brine, dried over sodium sulfate, concentrated, and chromatographed to give a mixture of phenyl selenides. The phenyl selenides were taken up in 15 mL of THF, 12 mL of H_2O, 68 mg (0.806 mmol) of solid $NaHCO_3$, and 304 mg (1.42 mmol) of solid $NaIO_4$. The mixture was stirred at room temperature for 3 h, when TLC indicated the reaction was complete. The mixture was diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried over sodium sulfate. Removal of the solvent in vacuo followed by column chromatography (50% ethyl acetate/hexanes) yielded the dienone **44** (100 mg, 0.287 mmol, 61% for the second step, 54% from the TBS ethers **40**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.0243 (s, 3H), 0.0292 (s, 3H), 0.85 (s, 9H), 1.16 (s, 3H), 1.26 (s, 3H), 1.95 (dd, J = 8.4, 13.6 Hz, 1H), 2.08 (dd, J = 9.2, 13.6 Hz, 1H), 3.04 (tt, J = 2.0, 8.4 Hz, 1H), 4.17 (dd, J = 2.0, 16.8 Hz, 1H), 4.48 (dd, J = 2.0, 16.8 Hz, 1H), 5.33 (dd, J = 2.8, 5.6 Hz, 1H), 6.06 (dd, J = 2.0, 5.6 Hz, 1H), 6.12 (dd, J = 2.0, 9.6 Hz, 1H), 6.48 (m, 1H), 6.65 (d, J = 10.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 186.6, 163.7, 152.9, 135.9, 134.3, 126.5, 124.4, 71.59, 62.1, 56.79, 55.27, 36.32, 28.74, 27.26, 25.82, 18.31, −5.479. IR (film): 3440 (br), 2960, 2930, 2860, 1660, 1620, 1470 (w), 1380 (w), 1255, 1150, 1035 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.84; H, 9.20.

Methyl Enone 45. To copper(I) bromide−dimethyl sulfide complex (295 mg, 1.44 mmol) suspended in 10 mL of ether under N_2 at −50 °C was added CH_3Li (2.05 mL of a 1.4 M solution in ether, 2.87 mmol) over 5 min. After 10 min of stirring, the dienone **44** (100 mg, 0.287 mmol) in 10 mL of ether was cannulated over 5 min to the colorless solution of lithium dimethyl cuprate, and the mixture was warmed to 0 °C. The reaction was stirred at 0 °C for 15 min and then quenched with saturated NH_4Cl. The mixture was separated, the aqueous layer was reextracted with ether, and the combined organic layers were washed with brine and dried over $NaSO_4$. Removal of the solvent in vacuo followed by flash chromatography (35% ethyl acetate/hexanes) afforded the methyl enone **45** (104 mg, 0.286 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.0122 (s, 3H), 0.0162 (s, 3H), 0.86 (s, 9H), 0.93 (d, J = 7.12 Hz, 3H), 1.15 (s, 3H), 1.24 (s, 3H), 1.73 (dd, J = 8.8, 13.2 Hz, 1H), 2.08 (m, 1H), 2.19 (m, 2H), 2.70 (dd, J = 4.8, 16.8 Hz, 1H), 2.86 (tt, J = 2.0, 8.8 Hz, 1H), 4.11 (dd, J = 2.0, 18 Hz, 1H), 4.19 (dd, J = 2.0, 18 Hz, 1H), 5.69 (dd, J = 2.4, 6.0 Hz, 1H), 5.91 (dd, J = 1.6, 6.0 Hz, 1H), 6.15 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 198.8, 166.2, 135.3, 134.4, 121.8, 71.76, 62.48, 56.12, 55.47, 43.26, 38.93, 35.55, 28.69, 27.19, 25.85, 18.32, 16.21, −5.475. IR (film): 3450 (br), 2960, 2860, 1655, 1465 (w), 1380 (w), 1255, 1145, 1090, 1040 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 69.22; H, 9.90.

Ketone 46. To a solution of the methyl enone **45** (35 mg, 0.096 mmol) in 3 mL of acid-free ethanol was added 15 mg of 10% Pd/C. The reaction mixture was stirred at room temperature under H_2 at atmospheric pressure for 18 h. After TLC indicated the reaction was complete, the mixture was filtered through Celite and the solvent removed in vacuo. Purification by flash chromatography (20% ethyl acetate/hexanes) provided the ketone **46** (26 mg, 0.071 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.0177 (s, 3H), −0.0105 (s, 3H), 0.82 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H), 1.17 (s, 3H), 1.18 (s, 3H), 1.45 (m, 3H), 1.78 (m, 6H), 2.07 (m, 2H), 2.25 (dd, J = 12.8, 14.8 Hz, 1H), 2.47 (dd, J = 4.0, 14.8 Hz, 1H), 3.54 (dd, J = 6.8, 10.4 Hz, 1H), 3.80 (dd, J = 4.0, 10.4 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 211.5, 71.45, 64.07, 51.27, 50.02, 46.67, 46.64, 42.92, 42.61, 36.32, 28.55, 28.33, 28.20, 25.82, 24.65, 18.16, 16.51, −5.528, −5.604. IR (film): 3470 (br), 2960, 2880, 1715, 1465, 1255, 1105, 1070 cm^{-1}. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.42; H, 10.94. Found: C, 68.33; H, 10.87.

Alkene 47. The ketone **46** (10 mg, 0.027 mmol) was mixed with 21 mg of pyridine-modified alumina in the presence of 0.5 mL of CH_2Cl_2. The solvent was evaporated under a stream of nitrogen, and the mixture was heated in an oil bath at 230 °C for 8 min. After being cooled to room temperature, the mixture was washed with hot ethyl acetate three times. The combined organic washes were concentrated to give 7 mg (0.020 mmol, 74%) of alkene **47**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.0075 (s, 3H), 0.015 (s, 3H), 0.86 (s, 9H), 0.96 (d, J = 6.4 Hz, 3H), 1.45 (m, 3H), 1.65 (m, 3H), 1.73 (s, 3H), 1.82 (m, 3H), 2.10 (d, J = 9.6 Hz, 1H), 2.30 (dd, J = 12.8, 15.2 Hz, 1H), 2.40 (m, 1H), 2.50 (m, J = 5.2, 15.2 Hz, 1H), 3.57 (dd, J = 6.4, 10.0 Hz, 1H), 3.75 (dd, J = 3.6, 10.0 Hz, 1H), 4.70 (broad, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 191.0, 147.8, 108.5, 64.19, 49.69, 47.21, 46.93, 46.77, 43.03, 42.67, 40.28, 32.52, 25.9, 24.86, 21.34, 18.25, 16.66, −5.478, −5.533. IR (film): 2950, 2860, 1720, 1640, 1460, 1255, 1080 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{21}H_{38}O_2Si$: calcd 351.2719, found 351.2703.

Alcohol 48. To 20 mg (0.53 mmol) of $LiAlH_4$ suspended in 2 mL of ether at −78 °C under N_2 was cannulated the alkene **47** (7 mg, 0.020 mmol) in a 5-mL ether solution. After the reaction mixture was stirred at −78 °C for 30 min, TLC indicated the reaction was complete. The reaction was quenched with saturated NH_4Cl and warmed to room temperature. The aqueous layer was reextracted with hot ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. Purification by column chromatography (25% ethyl acetate/hexanes) afforded the alcohol **48** (5 mg, 0.014 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.018 (s, 6H), 0.87 (s, 9H), 0.89 (d, J = 7.1 Hz, 3H). 1.01 (quartet, J = 12.0 Hz, 1H), 1.10 (quartet, J = 12.0 Hz, 1H), 1.27 (m, 2H), 1.33−1.60 (band, 4H), 1.64 (m, 3H), 1.71 (s, 3H), 2.18 (m, 1H), 2.33 (m, 1H), 3.34 (dd, J = 8.4, 10.0 Hz, 1H), 3.61 (m, 1H), 3.82 (dd, J = 3.6, 10.0 Hz, 1H), 4.66 (br, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 148.2, 108.2, 70.23, 64.53, 48.29, 47.39, 46.68, 41.12, 41.03, 40.55, 36.86, 32.78, 26.0, 25.34, 21.3, 16.67, −5.355. IR (film): 3400 (br), 2960, 2860, 1645, 1470, 1265, 1080 cm^{-1}. HRMS (MH^+) (*m/e*) for $C_{21}H_{40}O_2Si$: calcd 353.2876, found 353.2878.

Lubiminol (1). The alcohol **48** (5 mg, 0.014 mmol) was dissolved in 1 mL of THF, and 2 drops of Bu_4NF (1.0 M solution in THF) was added. The reaction mixture was stirred at room temperature for 12 h. Removal of the solvent in vacuo followed by flash chromatography (50% ethyl acetate/hexanes) afforded lubiminol (**1**) (3 mg, 0.013 mmol, 89%) spectroscopically identical to that previously reported.[2,3] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 3H), 1.03 (quartet, J = 12.0 Hz, 1H), 1.13 (quartet, J = 12.0 Hz, 1H), 1.24 (m, 1H), 1.28 (dd, J = 6.0, 10.8 Hz, 1H), 1.35 (dd, J = 6.0, 12.4 Hz, 1H), 1.43 (m, 4H), 1.56 (br, 2H), 1.65 (m, J = 12.4 Hz, 2H), 1.71 (s, 3H), 1.75 (m, 1H), 2.22 (m, 1H), 2.36 (m, 1H), 3.34 (dd, J = 9.2, 10.0 Hz, 1H), 3.63 (m, 1H), 3.94 (dd, J = 2.8, 10.0 Hz, 1H), 4.66 (br, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 148.1, 108.2, 69.96, 64.42, 48.45, 47.3, 46.6, 41.06, 40.91, 40.54, 36.74, 32.68, 25.34, 21.51, 16.69. IR (film): 3320 (br), 2930, 2860, 1645, 1465, 1375, 1020 cm^{-1}.

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Supporting Information Available: Experimental procedures and spectral data (^{1}H and ^{13}C NMR, IR) for compounds **15**−**18**, **33**, **34**, **39a,b**, **41a,b**, **42a**, and **43** (9 pages). See any current masthead page for ordering information and Web access instructions.

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