Pergamon

Tetrahedron, Vol. 53, No. 26, pp. 8975-8996, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00581-4

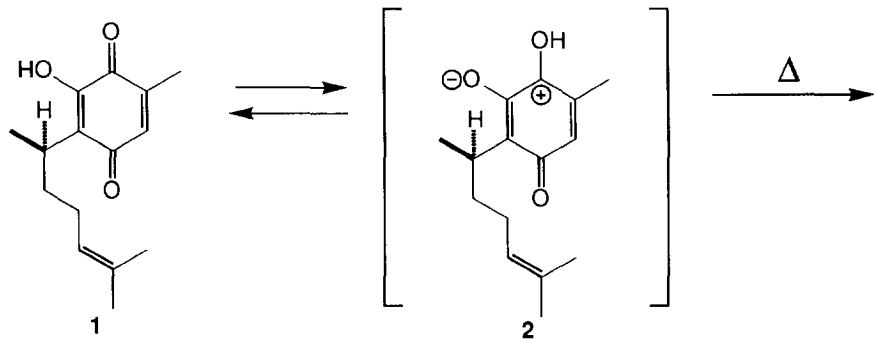
INTRAMOLECULAR CATIONIC [5 + 2] CYCLOADDITION REACTIONS PROMOTED BY TRIMETHYLSILYL TRIFLATE IN 3.0 M LITHIUM PERCHLORATE-ETHYL ACETATE: APPLICATION TO A FORMAL TOTAL SYNTHESIS OF (±)-ISOCOMENE

Paul A. Grieco* and John K. Walker
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

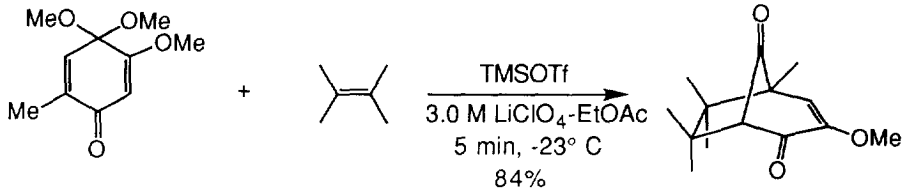
Dedicated to Samuel Danishefsky in recognition of his fundamental contributions to organic chemistry.

Abstract: Trimethylsilyl triflate is an effective reagent in 3.0 M lithium perchlorate-ethyl acetate for promoting intramolecular cationic [5 + 2] cycloaddition reactions. A formal total synthesis of the angular triquinane isocomene (**10**) is detailed. Cationic [5 + 2] cycloaddition of quinone monoketal **40** gives rise to tricyclic diketone **35** which is subsequently converted into the known tricyclic ketone **33**. Addition of methyl lithium followed by acid-catalyzed rearrangement employing the Pirrung protocol affords (±)-isocomene (**10**).

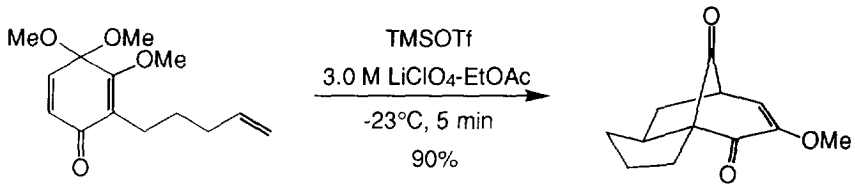
Since the initial discovery of the perezone to α- and ß-pipitzol transformation (cf **1** → **3** + **4**) by Joseph-Nathan over a quarter of a century ago,[1] no intramolecular all carbon cationic [5+2] cycloaddition reactions have been recorded in the literature.[2,3] The absence of intramolecular examples is surprising in view of the extensive studies that have been conducted on intermolecular variants featuring quinone monoketals and



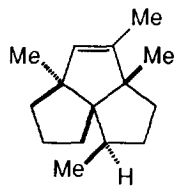
substituted styrenes.[4] The modest yields associated with these transformations have, in part, been responsible for the lack of continued activity in this area. We have recently reported that the yields for cationic [5+2] cycloaddition reactions can be dramatically increased by employing trimethylsilyl triflate in 3.0 M lithium perchlorate-ethyl acetate (cf **5** + **6** → **7**).[5] We now wish to report that trimethylsilyl triflate is a very effective reagent in 3.0 M $LiClO_4$-EtOAc for promoting intramolecular cationic [5+2] cycloaddition reactions (cf **8** → **9**). In addition, we detail a formal synthesis of the angular triquinane isocomene (**10**)[6].



5 **6** **7**



8 **9**



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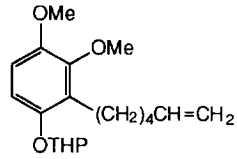
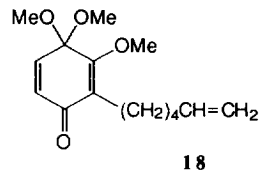
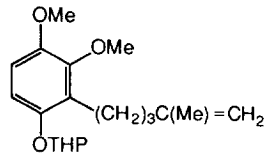
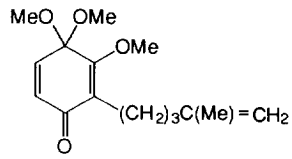
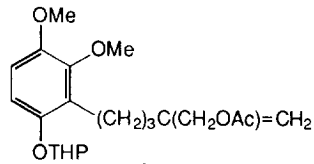
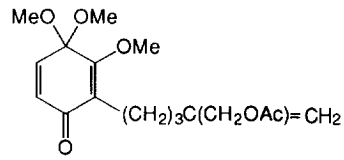
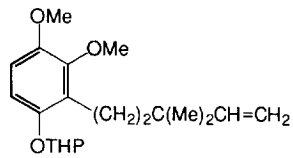
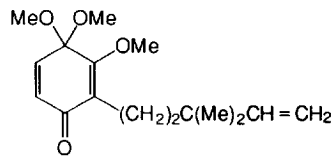
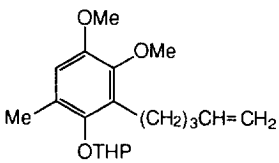
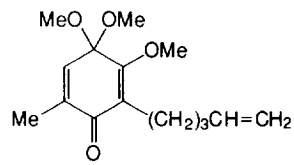
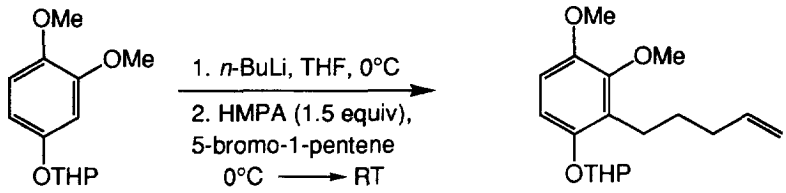
The quinone monoketals required for our study were prepared in straightforward fashion, with the exception of **20** and **22**, from the tetrahydropyranyl ether (**11**)[7] of 3,4-dimethoxyphenol. For example, selective ortho metalation[8] of **11** with *n*-butyllithium in tetrahydrofuran at 0°C followed by addition of 1.5 equiv of hexamethylphosphoramide and excess 5-bromo-1-pentene provided **12** in 61% yield. Substrates **13**, **14**, and **16** (Table 1) were prepared in similar fashion. Compound **15** (Table 1) was prepared by epoxidation (m-chloroperbenzoic acid) of **14** followed by sequential lithium 2,2,6,6-tetramethylpiperidide promoted isomerization of the intermediate epoxide and acetylation of the resultant allylic alcohol. Substrate **17** was prepared from **38** (*vide infra*).

Table I. Alkylation[a] of the Tetrahydropyranyl Ethers 11 and 38; Preparation[b] of *p*-Quinone Monoketals

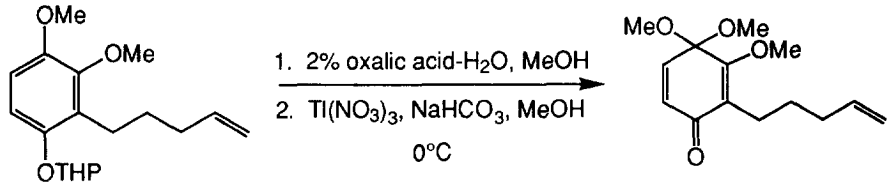
entry	alkylated product	yield[c] %	quinone monoketal	yield[c] %
1	 **13**	66	 **18**	84
2	 **14**	61	 **19**	72
3	 **15**[d]	47	 **20**	62
4	 **16**	36	 **21**	67
5	 **17**	50	 **22**[e]	53

a) Unless stated otherwise, alkylations were conducted on the appropriate tetrahydropyranyl ether, either **11** or **38**, employing selective ortho-metalation (see experimental). (b) Unless stated otherwise, quinone monoketals were prepared via a two-step process: acid-catalyzed cleavage of THP ethers and thallium(III) nitrate-mediated oxidation of the phenol (see experimental). (c) Isolated yields. (d) Prepared from **14** by epoxidation, base-induced epoxide opening and acetylation (see experimental). (e) The phenol obtained from **17** was oxidized with DDQ (see experimental).



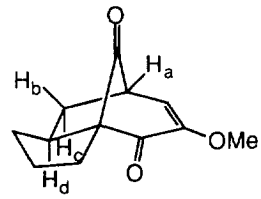
11 **12**

The quinone monoketals were synthesized via a two-step process: (1) acid catalyzed cleavage of the tetrahydropyranyl ether and (2) thallium(III) nitrate mediated oxidation[9] of the resultant phenol (cf **12** → **8**) with the exception of **22** (Table 1).



12 **8**

Initial studies focused on quinone monoketal **8** using the general reaction conditions developed in conjunction with our study of the intermolecular cationic [5+2] cycloaddition process. Thus, when a 0.2 M solution of **8** in 3.0 M lithium perchlorate-ethyl acetate cooled to -23°C was treated with a 1.05 equiv of trimethylsilyl triflate, reaction was complete in 5 min. Workup provided a 90% yield of **9**. The exclusive formation of the exo cycloadduct **9** follows from the 400 MHz(C_6D_6) ^{1}H NMR spectrum, which reveals the following coupling constants: J_{ab} = 5.6 Hz, J_{ac} = 0 Hz, J_{bc} = 12.4 Hz, J_{bd} = 6.4 Hz, and J_{cd} = 9.6 Hz.



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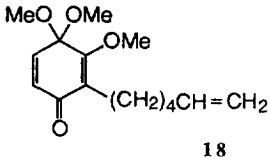
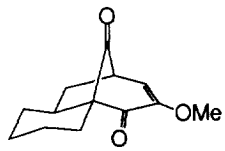
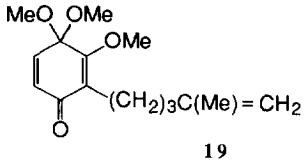
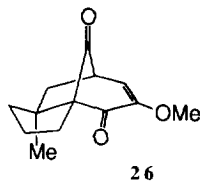
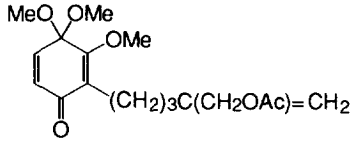
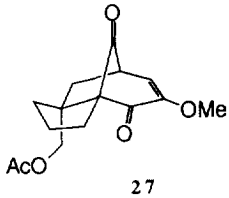
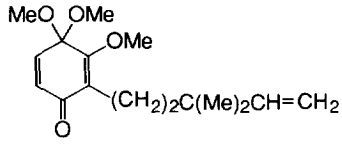
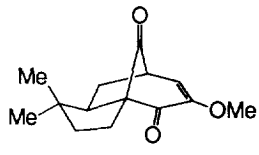
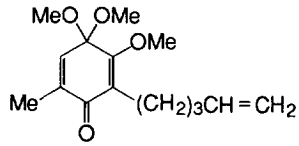
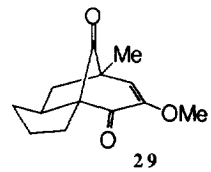
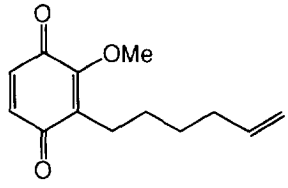
The general procedure outlined above with **8** has been extended to a number of substrates (Table 2). All reactions were complete in 5 min at -23°C. With only one exception (entry 1), yields were excellent. When quinone monoketal **18** (entry 1) was initially exposed to trimethylsilyl triflate in 3.0 M lithium perchlorate-ethyl

Table II. Cationic [5 + 2] Cycloaddition of *p*-Quinone Monoketals[a]

entry	substrate	product	yield[b] %
1[c]	 **18**	 **25**	48
2	 **19**	 **26**	86
3	 **20**	 **27**	85
4	 **21**	 **28**	78
5	 **22**	 **29**	82

(a) Unless stated otherwise, all reactions were performed 0.2 M in substrate in 3.0 M $LiClO_4$-EtOAc at -23°C followed by addition of 1.05 equiv of TMSOTf. Reactions were complete in 5 min. (b) Isolated yields. (c) Reaction was carried out 0.05 M in substrate. The structure of **25** was determined by extensive decoupling experiments.

acetate under the general reaction conditions outlined above, only a 26% yield of **25** was isolated. The major by-products were benzoquinone **30** (35%) and dibenzofuran **31** (13%). It was reasoned that the yield of **25** could be improved by lowering the concentration of **18** in the polar medium, thus suppressing bimolecular



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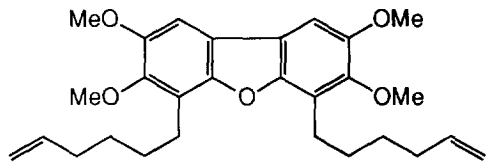
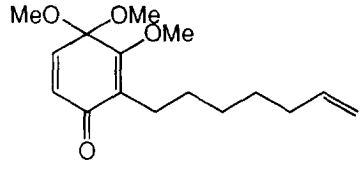


31

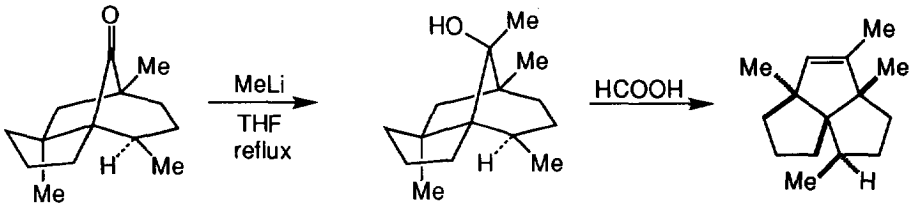
pathways. Toward this end, a 0.05 M solution of **18** in 3.0 M $LiClO_4$-EtOAc was treated (-23°C, 5 min) with 1.05 equiv of trimethylsilyl triflate. The yield of **25** improved to 48%. In addition, 31% of **30** and 8% of **31** were obtained. Going to higher dilution failed to give rise to any further improvement. When an additional methylene unit was installed in the tether (cf **32**) no [5+2] cycloadduct could be isolated.



32

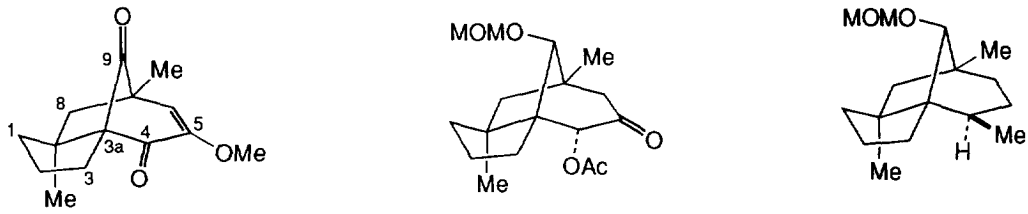
As we have noted previously with the intermolecular cationic [5+2] cycloaddition process, the use of lithium perchlorate is vital to the success of the intramolecular process. Performing these reactions in the absence of lithium perchlorate results in dramatically lower yields. For instance, when a 0.2 M solution of **22** in dry ethyl acetate cooled to -23°C was treated with 1.05 equiv of trimethylsilyl triflate, only a 34% yield of **29** was isolated.

In order to demonstrate the utility of this methodology for natural products synthesis, a formal total synthesis of the triquinane isocomene (**10**) was undertaken. The relationship between the bicyclo[3.2.1]octanes, generated via cationic [5+2] cycloadditions, and the polyquinane nucleus of isocomene is not immediately apparent. However, our strategy was based upon the known[10] conversion of tricyclic ketone **33** into isocomene (**10**) via an acid-catalyzed rearrangement of tertiary carbinol **34**. Thus, successful realization of the target molecule via a [5+2] cycloaddition process would necessitate synthesis of tricyclic ketone **35** and subsequent transformation into **33**. The conversion of **35** into **33** would require protection



33 **34** **10**

of the C(9) carbonyl prior to introduction of a methyl group at C(4) and deoxygenation of the masked carbonyl at C(5). It was anticipated that the methyl group could be incorporated selectively at C(4) via



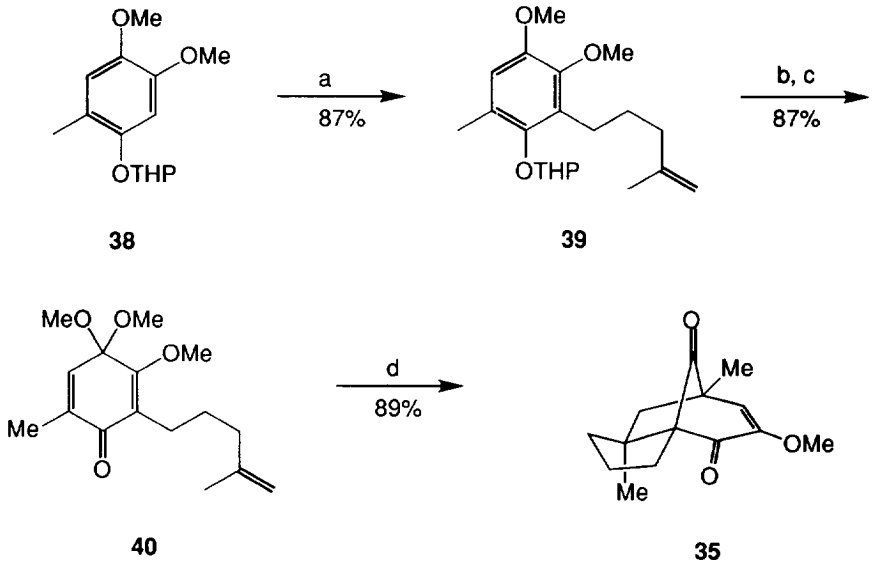
35 **36** **37**

alkylation of the regiospecifically generated enolate obtained from exposure of **36** to lithium in liquid ammonia. Subsequent deoxygenation at C(5) would provide **37** whose transformation into **33** should be a straightforward operation.

The key tricyclic intermediate **35** was prepared via a four-step sequence commencing with the tetrahydropyranyl ether **38** of 2-methyl-4,5-dimethoxyphenol (Scheme 1). The cationic [5+2] cycloaddition (cf **40** → **35**) proceeded smoothly (89%), employing the general conditions outlined above. Selective reduction ($NaBH_4$, MeOH, 0°C) of the C(9) carbonyl in **35** followed by protection (MOMCl, i-Pr_2NEt, $ClCH_2CH_2Cl$, reflux) of the resultant alcohol provided **41** in 82% overall yield. Subsequent reduction ($NaBH_4$, $CeCl_3$, EtOH) of the C(4) carbonyl followed by acetylation (Ac_2O, DMAP, pyr) and hydrolysis (2% oxalic acid, aq MeOH) afforded **36**, mp 84-85°C, in 71% yield.

With keto acetate **36** in hand, efforts were focused on incorporating a ß-oriented methyl group at C(4). Exposure of **36** to lithium in liquid ammonia-tetrahydrofuran (3:1) at -78°C followed by warming to -33°C and addition of methyl iodide gave rise (95%) to the desired product **42** along with unmethylated ketone **43** in a

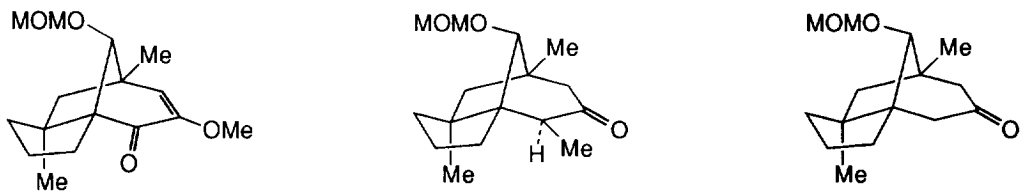
Scheme 1[a]



38 39 40 35

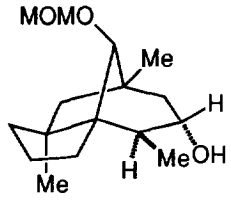
[a](a) n-BuLi, HMPA, THF, 0°C, alkyl halide; (b) 2% oxalic acid in MeOH; (c) DDQ, MeOH, 0°C; (d) TMSOTf, 3.0 M $LiClO_4$-EtOAc, -23°C.

ratio of 4.1:1. For convenience, **42** and **43** were not separated but immediately reduced with diisobutylaluminum hydride in toluene at 0°C, giving rise (98%) to alcohols **44**, **45**, and **46** in a ratio of 9:1:2.

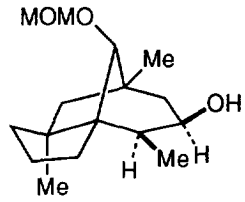


41 42 43

Deoxygenation of **44** at C(5) was realized in ca. 70% overall yield in a three-step sequence [(a) MsCl, Et_3N; (b) DBN, toluene, reflux, (c) 10% Pd/C, EtOAc, H_2] giving rise to **37**. Cleavage of the methoxymethyl ether and subsequent oxidation provided the known tricyclic ketone **33**.[10]



44



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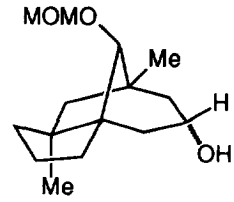

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Following the protocol of Pirrung,[10] ketone **33** was heated with excess methyl lithium at reflux for 3 h and the resultant tertiary carbinol **34** was exposed to 95% formic acid for 2 h at ambient temperatures giving rise to (±)-isocomene (**10**), 58-59°C (lit.[10] mp 57-59°C), in 50% overall yield.

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H NMR) were recorded at 500 MHz on a Bruker AM-500 FT spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) were recorded at 125 MHz on a Bruker AM-500 FT spectrometer. Chemical shifts are reported in parts per million (δ) from an internal standard of residual chloroform (7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C NMR). NMR peak multiplicities are denoted as follows: s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet), b(broad). Coupling constants are given in Hertz(Hz). Infrared(IR) spectra were obtained on a Perkin-Elmer 298 spectrometer as a 5-10% solution in chloroform or as a KBr pellet. High resolution mass spectra were recorded on a Kratos mass spectrometer (MS 80/RFA). Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Kieselgel 60 F_{254} silica plates (0.25 mm, EM Science) were used for analytical thin layer chromatography.

Unless otherwise stated all experiments were run in oven-dried glassware under an argon atmosphere using reagent grade solvents. The solvents were dried and distilled as indicated prior to use and were transferred using only oven dried syringes or cannulas. Ether (diethyl ether), tetrahydrofuran (THF), and benzene were distilled from sodium-benzophenone ketyl. Dichloromethane, dichloroethane, and ethyl acetate were distilled from calcium hydride. Lithium perchlorate was dried at 150°C (0.1 mm Hg) in a vacuum oven for 12 h prior to use. Deionized water was used in all cases.

3,4-Dimethoxy-2-(pent-4-enyl)phenoxyltetrahydropyran (12). To a solution of 510 mg (2.14 mmol) of 3,4-dimethoxy-phenoxyl-tetrahydropyran in 10 mL of dry THF, at 0°C, was added 1.3 mL (3.21 mmol) of 2.54 M n-BuLi. The solution was allowed to warm to room temperature and stir for 2 h. The mixture was recooled to 0°C and was treated with 1.2 mL of HMPA (3.21 mmol) followed by the addition of 380 μL (6.42 mmol) of 5-bromopentene. The solution was allowed to warm to room temperature and stir for 2 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride. The layers were separated and the organic phase was washed with brine (1 x 10 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution with hexanes-ethyl acetate (5:1) afforded 255 mg (61%, based on recovered starting material) of **12** as a colorless oil: R_f 0.63 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3040, 2920, 1640, 1590,

1490, 1350, 1250, 1080, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 6.82 (d, J=8.2 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 5.87 (ddt, J = 17.0, 10.2, 5.7 Hz, 1H), 5.31 (s, 1H), 5.04 (d, J =17.0 Hz, 1H), 4.95 (d, J = 10.2 Hz, 1H), 3.90 (td, J = 10.5, 2.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.61 (m, 1H), 2.69 (m, 2H), 2.14 (q, J = 7.3 Hz, 2H), 2.0 (m, 1H), 1.66-1.64 (m, 8H); ^{13}C NMR (125 MHz) δ 149.6, 147.8, 147.6, 139.0, 126.3, 114.2 109.8, 109.4, 96.7, 61.8, 60.8, 56.0, 34.0, 29.3, 25.3, 23.8, 18.8; HRMS (EI) calcd for $C_{18}H_{26}O_4$ (M) *m/e* 306.1838, found 306.1842.

3,4,4-Trimethoxy-2-(pent-4-enyl)cyclohexa-2,5-dienone (8). To a solution of 200 mg (0.65 mmol) of tetrahydropyranyl ether **12** in 1.3 mL of methanol was added 200 μL of a 2% aqueous solution of oxalic acid. The solution was allowed to stir overnight. Saturated sodium bicarbonate (2 mL) was added and the mixture was diluted with ether (5 mL). The layers were separated and the ethereal layer was washed with brine (2 x 1 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude phenol was purified by flash chromatography. Elution with hexanes-ethyl acetate (3:1) afforded 136 mg (96%) of a colorless oil: R_f 0.41 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3550, 3400, 2920, 2890, 1640, 1600, 1460, 1420, 1250, 1150, 1080, 1020, 780 cm^{-1}; ^1H NMR (500 MHz) δ 6.64 (d, J = 8.7 Hz, 1H), 6.5 (d, J = 8.7 Hz, 1H), 5.87 (ddt, J = 17.0, 10.2, 6.5 Hz, 1H), 5.07 (dd, J = 17.0, 1.5 Hz, 1H), 5.04 (dd, J = 10.2, 1.0 Hz, 1H), 4.60 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.64 (t, J = 7.7 Hz, 2H), 2.14 (q, J = 7.2 Hz, 2 H), 1.65 (m, 2H); ^{13}C NMR (125 MHz) δ 148.1, 147.0, 138.9, 123.5, 114.6, 110.6, 109.8, 60.8, 56.3. 33.6, 28.8, 23.5; HRMS (EI) calcd for $C_{13}O_3H_{18}$ (M) *m/e* 222.1256, found 222.1253.

To a slurry of 100 mg (0.46 mmol) of the above phenol and 186 mg (2.21 mmol) of solid sodium bicarbonate in 5 mL of dry methanol, at 0°C, was added 220 mg (0.56 mmol) of $Tl(NO_3)_3$. The bright orange solution was stirred for 30 min at 0°C. The organic layer was diluted with ether (5 mL) and was washed with a saturated solution of sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude *p*-quinone ketal was purified by flash chromatography. Elution with hexanes-ethyl acetate (3:1) afforded 117 mg (99%) of **8** as a yellow oil: R_f 0.27 (hexanes-ethyl acetate, 3:1); IR ($CHCl_3$) 2980, 1660, 1630, 1605, 1450, 1390, 1300, 1210, 1105, 1080, 890, 700 cm^{-1}; ^1H NMR (500 MHz) δ 6.36 (d, J = 10.1 Hz, 1H), 6.31 (d, J =10.1 Hz, 1H), 5.82 (ddt, J = 16.9, 10.1, 6.2 Hz, 1H), 4.99 (dd, J = 16.9, 1.5 Hz, 1H), 4.92 (dd, J = 10.1, 1.0 Hz, 1H), 4.14 (s, 3H), 3.30 (s, 6H), 2.36 (t, J = 7.86 Hz, 2H), 2.04 (q, J = 7.52 Hz, 2H), 1.44 (tt, J = 7.8, 6.2 Hz, 2H); ^{13}C NMR (125 MHz) δ 186.2, 161.3, 139.4, 138.8, 131.8, 124.1, 114.3, 96.5, 58.8, 51.3, 33.8, 27.9, 22.1; HRMS (CI) calcd for $C_{14}H_{21}O_4$ (M + 1) *m/e* 253.1440, found 253.1427.

3,4-Dimethoxy-2-(hex-5-enyl)phenoxyltetrahydropyran (13). Prepared as described for **12** with 6-bromohexene giving 520 mg (66%) of **13** as a colorless oil: R_f 0.60 (hexanes-ethyl acetate, 2:1), IR ($CHCl_3$) 2920, 1640, 1595, 1470, 1250, 1120, 1080, 990 cm^{-1}; ^1H NMR (500 MHz) δ 6.82 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 5.82 (ddt, J = 17.2, 10.8, 6.4 Hz, 1H), 5.31 (t, J = 2.8 Hz, 1H), 5.04 (d, J = 17.2 Hz, 1H), 4.95 (d, J = 10.8 Hz, 1H), 3.90 (ddd, J = 12.0, 10.4, 2.6 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.61 (m, 1H), 2.68 (m, 2H), 2.10 (q, J = 6.5 Hz, 2H), 2.0 (m, 1H), 1.8 (m, 2H), 1.59-1.48 (m, 6H); ^{13}C NMR (125 MHz) δ 149.6, 147.7, 147.6, 139.1, 126.5, 114.1, 109.6, 109.3, 96.7, 61.8, 60.8, 56.0, 33.6, 30.7, 29.6, 29.2, 25.3, 24.1, 18.8; HRMS (CI) calcd for $C_{19}H_{29}O_4$ (M + 1) *m/e* 321.2067, found 321.2074.

3,4,4-Trimethoxy-2-(hex-5-enyl)cyclohexa-2,5-dienone(18). Cleavage of the tetrahydropyranyl in **13** was carried out as described for **8** giving 98 mg (96%) of phenol as a colorless oil: R_f 0.44 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3600, 3400, 2940, 1700, 1640, 1600, 1460, 1420, 1250, 1150, 1080, 1030, 800, 790 cm^{-1}; ^1H NMR (500 MHz) δ 6.63 (d, J = 8.7 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 5.82 (ddt, J = 16.2, 10.3, 6.5 Hz, 1H), 5.00 (dd, J = 16.2, 1.5 Hz, 1H), 4.93 (dd, J = 10.3, 1.0 Hz, 1H), 4.51 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.63 (q, J = 7.9 Hz, 2H), 2.10 (dt, J = 7.2, 6.5 Hz, 2H), 1.65-1.45 (m, 4H); ^{13}C NMR (125 MHz) δ 148.1, 147.0, 139.0, 123.6, 114.3, 110.5, 109.8, 60.8, 56.3, 33.6, 29.2, 28.9, 23.9; HRMS (EI) calcd for $C_{14}O_3H_{20}$ (M) *m/e* 236.1413, found 236.1414.

To a slurry of 95 mg (0.40 mmol) of the above phenol and 101 mg (1.2 mmol) of solid sodium bicarbonate in 3 mL of dry methanol at 0°C was added 203 mg (0.52 mmol) of $Tl(NO_3)_3$. The bright orange solution was stirred for 30 min at 0°C. Standard work up as described above for **8** provided crude *p*-quinone ketal which was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) afforded 94 mg (88%) of **18** as a yellow oil: R_f 0.59 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2970, 1660, 1630, 1600, 1450, 1390, 1300, 1210, 1105, 1060, cm^{-1}; ^1H NMR (500 MHz) δ 6.36 (d, J = 10.2 Hz, 1H), 6.31 (d, J = 10.1 Hz, 1H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.97 (dd, J = 16.9, 1.9 Hz, 1H), 4.91 (dt, J = 10.2, 1.0 Hz, 1H), 4.14 (s, 3H), 3.30 (s, 6H), 2.35 (t, J = 7.3 Hz, 2H), 2.04 (q, J = 6.7 Hz, 2H), 1.37-1.30 (m, 4H); ^{13}C NMR (125 MHz) δ 186.0, 161.0, 139.2, 138.9, 131.7, 124.2, 114.0, 96.4, 58.6, 51.1, 33.4, 28.7, 27.9, 22.0; HRMS (CI) calcd for $C_{15}H_{23}O_4$ (M + 1) *m/e* 267.1597, found 267.1602.

3,4-Dimethoxy-2-(4-methylpent-4-enyl)phenoxyltetrahydropyran(14). Prepared as described for **12** with 5-iodo-2-methyl-1-pentene[11] giving 1.15 g (61%) of **14** as a pale oil: R_f 0.61 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3080, 2960, 1650, 1600, 1490, 1350, 1290, 1060, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 6.81 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.31 (t, J = 2.9 Hz, 1H), 4.71 (s, 1H), 4.70 (s, 1H), 3.90 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.80 (m, 1H), 3.61 (m, 1H), 2.66 (m, 2H), 2.11 (t, J = 7.8 Hz, 2H), 2.0 (m, 1H), 1.86-1.68 (m, 10H); ^{13}C NMR (125 MHz) δ 149.6, 147.8, 147.6, 146.1, 126.5, 109.8, 109.5, 109.4, 96.7, 61.9, 60.8, 56.0, 38.2, 30.7, 28.1, 25.3, 24.0, 22.4, 18.9; HRMS (CI) calcd for $C_{19}H_{29}O_4$ (M + 1) *m/e* 321.2066, found 321.2075.

3, 4-Dimethoxy-2-(4-methyl-pent-4-enyl)phenol (19). Cleavage of the tetrahydropyranyl ether in **14** was carried out as described for **8** giving 127 mg (98%) of a pale oil: R_f 0.45 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3800, 3420, 3060, 2940, 1650, 1600, 1460, 1430, 1260, 1150, 1070, 1030, 880 cm^{-1}; ^1H NMR (500 MHz) δ 6.43 (d, J = 8.7 Hz, 1H), 6.49 (d, J = 8.7 Hz, 1H), 4.7 (s, 2H), 4.5 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.62 (t, J = 7.8 Hz, 2H), 2.10 (t, J = 7.4 Hz, 2H), 1.73 (s, 3H), 1.69 (tt, J = 7.8, 7.4 Hz, 2H); ^{13}C NMR (125 MHz) δ 148.2, 147.1, 146.0, 123.5, 110.6, 109.9, 109.8, 60.8, 56.3, 37.7, 27.5, 23.6, 22.4; HRMS (CI) calcd for $C_{14}H_{21}O_3$ (M + 1) *m/e* 237.1491, found 236.1496.

Oxidation was carried out as described above for **8** giving rise to crude *p*-quinone ketal which was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) afforded **19** (73%) as a yellow oil: R_f 0.43 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2950, 1670, 1610, 1435, 1375 cm^{-1}; ^1H NMR (500 MHz) δ 6.39 (d, J = 10.2 Hz, 1H), 6.32 (d, J = 10.2 Hz, 1H), 4.69 (s 2H), 4.15 (s, 3H), 3.31 (s, 6H), 2.34 (t, J = 8.0 Hz, 2H), 2.03 (t, J = 7.8 Hz, 2H), 1.71 (s, 3H), 1.49 (tt, J = 8.0, 7.8 Hz, 2H); ^{13}C NMR (125 MHz) δ

186.2, 161.5, 146.0, 139.4, 131.8, 124.3, 109.7, 96.6, 58.8, 51.3, 37.9, 26.7, 22.3, 22.2; HRMS (CI) calcd for $C_{15}H_{23}O_4$ (M + 1) *m/e* 266.1597, found 267.1599.

3,4-Dimethoxy-2-(4-methyl-4-oxiranylpentane)phenoxyltetrahydropyran. To a slurry of 400 mg (1.25 mmol) of **14** and 500 mg (6.0 mmol) solid sodium bicarbonate in 35 mL of chloroform at 0°C was added 350 mg (2.0 mmol) of 98% *m*-chloroperbenzoic acid. After 2 h the reaction was poured into a cold saturated sodium bicarbonate solution and diluted with 20 mL of ether. The layers were separated and the ethereal layer was washed with sodium bisulfite (2 x 20 mL), sodium bicarbonate (2 x 10 mL), and brine (1 x 15 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude epoxide was purified by flash column chromatography. Elution with hexanes-ethyl acetate (3:1) yielded 373 mg (89%) of product as a pale yellow oil: R_f 0.41 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2970, 1600, 1490, 1360, 1250, 1210 cm^{-1}; ^1H NMR (500 MHz) δ 6.83 (d, J = 8.9 Hz, 1H), 6.68 (d, J = 8.9 Hz, 1H), 5.30 (s, 1H), 3.89 (s, 1H), 3.81 (s, 6H), 3.62 (m, 1H), 2.70 (m, 2H), 2.60 (d, J = 4.7 Hz, 1H), 2.55 (d, J = 4.8 Hz, 2H), 2.0 (m, 1H), 1.85 (m, 2H), 1.70-1.55 (m, 6H), 1.30 (s, 3H); ^{13}C NMR (125 MHz) δ 149.6, 147.7, 147.6, 125.8, 109.9, 109.4, 109.3, 96.8, 96.7, 61.8, 60.7, 56.9, 56.0, 53.7, 36.8, 30.6, 25.7, 25.2, 24.1, 20.8, 18.5; HRMS (EI) calcd for $C_{19}H_{28}O_5$ (M) *m/e* 336.1937, found 336.1929.

2-(4-Hydroxymethyl-pent-4-enyl)-3,4-dimethoxyphenoxyltetrahydropyran. To a solution of 1.25 mL (7.5 mmol) 2,2,4,4-tetramethylpiperidine in 15 mL of diethyl ether at 0°C was added 2.5 mL (6.25 mmol) of 2.54 M n-BuLi. The solution was allowed to warm to room temperature and stir for 30 min. To this solution was added all at once 420 mg (1.25 mmol) of the above epoxide dissolved in 5 mL of ether. The resulting red solution was stirred for 1 h. The reaction was quenched by addition of a saturated solution of ammonium chloride and diluting with ether. The layers were separated and the organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography. Elution with hexanes-ethyl acetate (3:1) yielded 250 mg (59%) of allylic alcohol as a pale yellow oil: R_f 0.21 (hexanes-ethyl acetate 2:1); IR ($CHCl_3$) 3610, 2960, 1610, 1490, 1250, 1120, 1080, 990, cm^{-1}; ^1H NMR (500 MHz) δ 6.81 (d, J = 9.0 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 5.30 (s, 1H), 5.02 (s, 1H), 5.01 (s, 1H), 4.91 (s, 1H), 4.08 (s, 2H), 3.91 (m, 1H), 3.81 (s, 6H), 3.60 (m, 1 H), 2.70 (m, 2H), 2.15 (t, J = 7.62 Hz, 2H), 2.0 (m, 1H), 1.90-1.6 (m, 6H); ^{13}C NMR (125 MHz) δ 149.5, 149.1, 147.7, 147.6, 126.1, 109.9, 109.5, 109.0, 96.9, 66.0, 62.0, 60.8, 56.0, 33.1, 30.6, 27.9, 25.3, 23.9, 19.0; HRMS (EI) calcd for $C_{19}H_{28}O_5$ (M) *m/e* 336.1937, found 336.1966.

2-(4-Acetoxymethyl-pent-4-enyl)-3,4-dimethoxyphenoxyltetrahydropyran(15). To a solution of 80 mg (0.23 mmol) of the above allylic alcohol in 500 μL of acetic anhydride was added 20 μL (.25 mmol) of pyridine. The solution was then stirred 30 min. The mixture was submitted directly to a flash chromatography. Elution with hexanes-ethyl acetate (5:1) yielded 78 mg (89%) of **15** as a yellow oil: R_f 0.41 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2950, 1730, 1480, 1250, 1110, 1080, 1030, cm^{-1}; ^1H NMR (500 MHz) δ 6.82 (d, J = 9.0 Hz, 1H), 6.68 (d, J = 9.0 Hz, 1H), 5.31 (s, 1H), 5.02 (s, 1H), 4.98 (s, 1H), 4.53 (s, 2H), 3.91 (m, 1H), 3.81 (s, 6H), 3.60 (m, 1H), 2.73-2.59 (m, 2H), 2.15 (t, J = 7.6 Hz, 2H), 2.0 (s, 3H), 1.85-1.67 (m, 8H); ^{13}C NMR (125 MHz) δ 170.7, 149.5, 147.7, 147.6, 143.9, 125.9, 111.8, 109.9, 109.4, 96.8, 66.9, 61.9, 60.8, 56.0, 33.3, 30.6, 29.9, 27.8, 25.3, 23.9, 20.9, 18.9; HRMS (EI) calcd for $C_{21}H_{30}O_6$ (M) *m/e* 378.2043, found 378.2056.

2-(4-Acetoxymethylpent-4-enyl)3,4,4-trimethoxycyclohexa-2,5-dienone(20). To a solution of 78 mg (0.02 mmol) of **15** in 3 mL of methanol was added 700 μL of a 2% solution of aqueous oxalic acid. The reaction was allowed to stir overnight. The reaction was diluted with ether (5 mL) and washed with a saturated sodium bicarbonate solution. The layers were separated and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure giving 57 mg (94%) of phenol as a yellow oil. The crude phenol was used directly in the next reaction without purification.

Oxidation was carried out as described above for **8** giving rise to crude *p*-quinone ketal which was purified by flash chromatography. Elution with hexanes-ethyl acetate (3:1) afforded **20** (66%) as a yellow oil: R_f 0.43 (hexanes-ethyl acetate, 2:1) IR ($CHCl_3$); 2950, 1670, 1610, 1435, 1375 cm^{-1}; ^1H NMR (500 MHz) δ 6.39 (d, J = 10.2 Hz, 1H), 6.32 (d, J = 10.2 Hz, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 4.52 (s, 2H), 4.15 (s, 3H), 3.31 (s, 6H), 2.34 (t, J = 8.0 Hz, 2H), 2.09 (s, 3H), 2.06 (m, 3H), 1.71 (s, 3H), 1.49 (tt, J = 8.0, 7.8 Hz, 2H); ^{13}C NMR (125 MHz) δ 186.2, 161.5, 146.0, 139.4, 131.8, 124.3, 112.1, 110.6, 109.7, 96.6, 58.8, 51.3, 37.9, 26.7, 22.3, 22.2; HRMS (CI) calcd for $C_{17}H_{25}O_6$ (M + 1) *m/e* 324.1573, found 324.1588.

3,4-Dimethoxy-2-(3,3-dimethylpent-4-enyl)phenoxyltetrahydropyran (16). To a solution of 681 mg (2.7 mmol) of 3,4-dimethoxy-phenoxyl-tetrahydropyran in 14 mL of dry THF, at 0°C, was added 1.4 mL (3.51 mmol) of 2.54 M n-BuLi. The solution was allowed to warm to room temperature and stir for 4 h. The mixture was recooled to 0°C and treated with 680 μL of HMPA (2.7 mmol) followed by the addition of 1.28 g (5.4 mmol) of 5-iodo-3,3-dimethylpentene. The solution was warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated solution of ammonium chloride. The layers were separated and the organic layer was washed with brine (1 x 10 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution with hexanes-ethyl acetate (9:1) afforded 280 mg (36%) of **16** as a colorless oil: R_f 0.68 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2970, 1600, 1470, 1250, 1080, 1020, 890, 870 cm^{-1}; ^1H NMR (500 MHz) δ 6.81 (d, J = 8.9 Hz, 1H), 6.66 (d, J = 8.9 Hz, 1H), 5.88 (dd, J = 17.5, 10.7 Hz, 1H), 5.31 (t, J = 3.1 Hz, 1H), 5.0 (m, 2H), 3.90 (ddd, J = 11.9, 10.4, 2.4 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.62 (m, 1H), 2.60 (t, J = 7.4 Hz, 2H), 2.16 (m, 1H), 1.86 (m, 2H), 1.75-1.45 (m, 6H), 1.08 (s, 6H); ^{13}C NMR (125 MHz) δ 149.5, 148.5, 147.7, 127.0, 110.3, 109.8, 109.5, 96.8, 61.8, 60.8, 56.1, 42.7, 36.9, 30.6, 26.7, 26.6, 25.3, 19.6, 18.8; HRMS (CI) calcd for $C_{20}H_{31}O_4$ (M + 1) *m/e* 335.2213, found 335.2208.

3,4,4-Trimethoxy-2-(3,3-dimethylpent-4-enyl)cyclohexa-2,5-dienone (21). Cleavage of the tetrahydropyranyl ether in **16** was carried out as described for **8** giving 150 mg (99%) of product as a pale oil: R_f 0.47 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$); 3600, 3400, 2980, 1600, 1470, 1420, 1250, 1140, 1100, 870 cm^{-1}; ^1H NMR (500 MHz) δ 6.63 (d, J = 8.7 Hz, 1H), 6.48 (d, J = 8.7 Hz, 1H), 5.88 (dd, J = 17.4, 10.8 Hz, 1H), 5.02 (m, 2H), 4.37 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.53 (m, 2H), 1.50 (m, 2H), 1.05 (m, 2H); ^{13}C NMR (125 MHz) δ 148.1, 148.0, 147.2, 124.1, 111.0, 110.5, 109.9, 100.8, 77.2, 60.8, 56.3, 42.3, 37.0, 26.6, 19.4; HRMS (EI) calcd for $C_{15}O_3H_{22}$ (M) *m/e* 250.1569, found 250.1570.

Oxidation was carried out as described above giving rise to crude *p*-quinone ketal was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) afforded **21** (68%) as a yellow oil: R_f 0.45 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2975, 1660, 1600, 1450, 1300, 1210, 1070, 960, 820 cm^{-1}; ^1H NMR (500 MHz) δ 6.34 (d, J = 10.2 Hz, 1H), 6.28 (d, J = 10.2 Hz, 1H), 5.80 (dd, J = 17.4, 10.8 Hz, 1H), 4.95 (m,

2H), 4.12 (s, 3H), 3.28 (s, 6H), 2.42 (dt, J = 17.3, 3.9 Hz, 2H), 1.27 (dt, 17.0, 3.5 Hz, 2H), 1.00 (s, 6H); ^{13}C NMR (125 MHz) δ 186.0, 160.9, 148.2, 139.3, 131.8, 125.0, 110.3, 96.5, 58.9, 51.2, 41.1, 36.8, 26.5, 18.0; HRMS (CI) calcd for $C_{19}H_{25}O_4$ (M + 1) *m/e* 281.1748, found 281.1753.

3,4-Dimethoxy-6-methyl-2-(pent-4-enyl)phenoxyltetrahydropyran (17). Prepared as described for **12** with 5-bromopentene and 3,4-dimethoxy-6-methylphenoxyltetrahydropyran giving 376 mg (50%) of **17** as a colorless oil: R_f 0.58 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2940, 2850, 1650, 1590, 1475, 1460, 1360, 1330, 1110, 1145, 1090, 1070, 1025, 995 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.55 (s, 1H), 5.86 (ddt, J = 16.8, 10.1, 6.5 Hz, 1H), 5.05 (dd, J = 16.8, 1.4 Hz, 1H), 4.94 (dd, J = 10.1, 1.1 Hz, 1H), 4.74 (dd, J = 6.3, 2.0 Hz, 1H), 4.08 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.48 (m, 1H), 2.76 (ddd, J = 16.1, 10.4, 5.6 Hz, 1H), 2.57 (ddd, J = 16.0, 10.4, 5.6 Hz, 1H), 2.27 (s, 3H), 2.12 (q, J = 7.4 Hz, 2H), 1.96 (m, 1H), 1.85 (m, 1H), 1.70-1.58 (m, 6H); ^{13}C NMR (125 MHz) δ 149.0, 148.5, 145.7, 139.1, 130.4, 126.44, 114.2, 112.0, 103.5, 64.6, 60.7, 55.8, 34.2, 31.4, 29.4, 25.2, 24.9, 20.7, 17.6; HRMS calcd for $C_{19}H_{29}O_4$ (M + 1) *m/e* 321.2061, found 321.2058.

3,4,4-Trimethoxy-6-methyl-2-(4-methylpent-4-enyl)cyclohexa-2,5-dienone (22). Cleavage of the tetrahydropyranyl ether in **17** was carried out as described for **8** giving 75.1 mg (92%) of product as a colorless oil: R_f 0.34 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3600, 3400, 2920, 1640, 1600, 1430, 1330, 1290, 1180, 1105, 1068, 975, 830 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.56 (s, 1H), 5.86 (ddt, J = 16.9, 10.2, 6.54 Hz, 1H), 5.08 (dd, J = 17.0, 1.6 Hz, 1H), 5.05 (dd, J = 10.2, 1.0 Hz, 1H), 4.41 (s, 1H), 3.80 (s, 6H), 2.64 (t, J = 7.8 Hz, 2H), 2.20 (s, 3H), 2.15 (q, J = 7.13 Hz, 2H), 1.60 (tt, J = 7.8, 7.5 Hz, 2H); ^{13}C NMR (125 MHz) δ 146.4, 146.0, 145.9, 138.8, 122.9, 118.0, 114.6, 112.6, 60.9, 56.3, 33.6, 30.5, 28.9, 23.6; HRMS (CI) calcd for $C_{14}H_{21}O_3$ (M + 1) *m/e* 237.1491, found 237.1496.

To a solution of the 71 mg (0.30 mmol) of the above phenol in 1.5 mL of methanol at 0°C was added 77 mg (0.36 mmol) of DDQ dissolved in 300 μL of methanol. The resulting orange solution was stirred for 30 min. The reaction was diluted with ether (5 mL) and was washed with a saturated sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude quinone was purified by flash column chromatography. Elution with hexanes-ethyl acetate (4:1) gave 35.6 mg (58%) of **22** as a yellow oil: R_f 0.33 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2940, 2860, 1610, 1450, 1310, 1210, 1150, 1050, 960 cm^{-1}; ^{1}H NMR (500 MHz) δ 6.14 (d, J = 1.5 Hz, 1H), 5.81 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 4.99 (dd, J = 17.0, 1.8 Hz, 1H), 4.92 (dd, J = 10.2, 1.0 Hz, 1H), 4.12 (s, 3H), 3.27 (s, 6H), 2.36 (t, J = 7.89 Hz, 2H), 2.04 (dt, J = 7.9, 7.9 Hz, 2H), 1.92 (s, 3H), 1.4 (m, 2H); ^{13}C NMR (125 MHz) δ 186.5, 161.0, 138.9, 138.6, 134.8, 123.9, 114.2, 96.8, 58.8, 51.1, 33.8, 28.0, 22.3, 15.5; HRMS (CI) calcd for $C_{15}H_{23}O_4$ (M + 1) *m/e* 267.1600, found 267.1594.

General Procedure for the [5+2] Cycloaddition Reaction. To a solution of ca. 1 mmol of the quinone monoketal in 500 μL of 3.0 M lithium perchlorate-ethyl acetate at -23°C was added 20 μL of TMSOTf (0.105 mmol). The resulting orange solution was allowed to stir for 5 min and quenched with a saturated solution of sodium bicarbonate and diluted with ethyl acetate (5 mL). The organic layer was washed with sodium bicarbonate (2 x 1 mL) and brine (2 x 1 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude dione was purified by flash chromatography.

(3α, 7β, 8aβ)-5-Methoxy-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4,9-dione (9). Isolation gave rise to 16.8 mg (90%) of **9** as a light yellow oil: R_f 0.29 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2970, 2940, 1760, 1680, 1610, 1450, 1350, 1230, 1200, 1070, 810 cm^{-1}; ^1H NMR (500 MHz) δ 6.19 (d, J = 8.1 Hz, 1H), 3.67 (s, 3H), 3.38 (dd, J = 8.1, 5.42 Hz, 1 H), 2.34 (m, 1H), 2.11 (dd, J = 12.5, 9.8 Hz, 1H), 2.0 (m, 2H), 1.75 (m, 3H), 1.34 (ddd, J = 12.5, 9.8, 7.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 203.6, 192.1, 152.6, 115.6, 75.5, 55.5, 49.2, 44.4, 33.7, 32.1, 27.9, 21.9; HRMS (CI) calcd for $C_{12}H_{15}O_3$ (M + 1) *m/e* 207.1022, found 207.1015.

(4α, 8β, 9aβ)-6-Methoxy-1,3,4,8,9,9a-hexahydro-2H-4a,8-methanobenzocycloheptene-5,10-dione (25). To a solution of 12.0 mg of **18** (0.045 mmol) in 1.0 mL of 3.0 M lithium perchlorate-ethyl acetate at -23°C was added 10 μL (0.051 mmol) of TMSOTf. After 5 min 1.0 mL of a saturated sodium bicarbonate solution was added. The layers were separated and the aqueous layer was extracted with ether (3 x 1 mL). The organic layers were combined, dried over magnesium sulfate, and concentrated *in vacuo*. The products were isolated by preparative thin layer chromatography (0.5 mm). Elution with hexanes-ethyl acetate (3:1) yielded 4.6 mg (48%) of **25** as a yellow oil [R_f 0.31 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2980, 1765, 1680, 1440, 1265 cm^{-1}; ^1H NMR (500 MHz) δ 6.44 (d, J = 8.48 Hz, 1H), 3.65 (s, 3H), 3.25 (dd, J = 8.8, 7.8 Hz, 1H), 2.3-1.2 (m, 11H); ^{13}C NMR (125 MHz) δ 201.4, 192.3, 153.4, 120.4, 55.7, 44.2, 37.5, 33.5, 33.0, 29.8, 23.4, 21.4, 20.7; HRMS (EI) calcd for $C_{13}H_{16}O_3$ (M) *m/e* 220.1100, found 220.1102] along with 2.0 mg (9%) of dimer **31** [IR ($CHCl_3$) 2930, 1640, 1460, 1420, 1280, 1260, 1120, 1020 cm^{-1}; ^1H NMR (500 MHz) δ 7.19 (s, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.98 (dd, J = 16.9, 10.2 Hz, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 2.98 (t, J = 8.4 Hz, 2H), 2.14 (q, J = 7.2 Hz, 2H), 1.79 (quin, J = 7.6 Hz, 2H), 1.53 (quin, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz) δ 150.2, 149.7, 139.1, 121.0, 119.2, 114.4, 100.0, 61.4, 56.4, 33.7, 29.3, 29.0, 24.3. HRMS (EI) calcd for $C_{28}H_{36}O_5$ (M) *m/e* 452.2563, found 452.2052] and 3.0 mg (34%) of benzoquinone **30**: IR (film) 3070, 2910, 2860, 1670, 1640, 1580, 1450, 1310, 1210, 990 cm^{-1}; ^1H NMR (400 MHz) δ 6.67 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.80 (ddt, J = 17.0, 10.2, 6.5 Hz, 1H), 5.01 (dd, J = 17.0, 2.0 Hz, 1H), 4.95 (dt, J = 10.0, 1.2 Hz, 1H), 4.03 (s, 3H), 2.45 (dt, J = 7.2, 2.4 Hz, 4H), 2.08 (q, J = 6.8 Hz, 2H), 1.45 (m, 4H); ^{13}C NMR δ 188.1, 183.6, 155.7, 138.7, 136.5, 134.7, 133.2, 114.5, 61.0, 33.5, 28.9, 28.3, 23.0; HRMS calcd for $C_{13}H_{16}O_3$ (M) *m/e* 220.1100, found 220.1098.

(3α,7b,8ab)-5-Methoxy-8a-methyl-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4,9-dione (26). Isolation gave rise to 12.1 mg (86%) of **26** as a light yellow oil: R_f 0.29 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2980, 2890, 1760, 1680, 1605, 1450, 1360, 1260, 1220, 1100, 1070, 1030, 820 cm^{-1}; ^1H NMR (500 MHz) δ 6.3 (d, J = 8.4 Hz, 1H), 3.68 (s, 3H), 3.48 (dd, J = 8.4, 7.8 Hz, 1H), 2.48 (ddd, J = 11.8, 9.8, 4.0 Hz, 1H), 2.14 (m, 2H), 1.8-1.75 (m, 3H), 1.65 (d, J = 12.8 Hz, 1H), 1.44 (dq, J = 11.8, 7.9 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (125 MHz) δ 203.7, 191.7, 153.2, 117.5, 79.4, 55.5, 48.4, 48.3, 43.0, 39.9, 24.7, 24.4, 20.4; HRMS (CI) calcd for $C_{13}H_{17}O_3$ (M + 1) *m/e* 221.1172, found 221.1185.

(3α,7β,8aβ)-5-Methoxy-3-acetoxymethyl-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4, 9-dione (27). Isolation gave rise to 13.0 mg (85%) of **27** as a yellow oil: R_f 0.24 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2990, 2940, 1780, 1750, 1690, 1620, 1460, 1380, 1250, 1100, 1050 cm^{-1}; ^1H NMR (500 MHz) δ 6.62 (d, J = 8.5 Hz, 1H), 3.89 and 3.85 (AB quartet, J = 12.9 Hz, 2H), 3.67 (s, 3H),

3.43 (dd, J = 8.5, 6.5 Hz, 1H), 2.49 (ddd, J = 14.5, 10.3, 5.8 Hz, 1H), 2.26 (ddd, J = 14.6, 8.8, 6.2 Hz, 1H), 2.1 (dd, J = 13.0, 6.2 Hz, 1H), 2.0 (s, 3H), 1.97 (m, 1H), 1.90-1.70 (m, 4H), 1.45 (dt, J = 13.3, 9.4 Hz, 1H); ^{13}C NMR (125 MHz) δ 202.1, 190.3, 170.6, 153.9, 116.2, 78.7, 66.7, 55.5, 51.4, 47.2, 38.4, 36.0, 23.1, 21.8, 20.4; HRMS (CI) calcd for $C_{15}H_{19}O_5$ (M + 1) *m/e* 279.1223, found 279.1223.

(3α,7β,8aβ)-5-Methoxy-1,1-dimethyl-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4,9-dione (28). Isolation gave rise to 13.8 mg (78%) of **28** as a yellow oil: R_f 0.28 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2990, 1760, 1690, 1610, 1250, 1080, 700 cm^{-1}; ^1H NMR (500 MHz) δ 6.19 (d, J = 8.2 Hz, 1H), 3.66 (s, 3H), 3.39 (dd, J = 8.1, 5.6 Hz, 1H), 2.42 (ddd, J = 13.5, 7.7, 4.1 Hz, 1H), 2.08-1.90 (m, 4H), 1.81 (dd, J = 12.8, 10.2 Hz, 1H), 2.08-1.90 (m, 4H), 1.66 (m, 1H), 1.63 (dd, J = 7.0, 4.1 Hz, 1H), 1.25 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz) δ 204.1, 192.1, 152.2, 116.0, 75.5, 55.5, 53.7, 49.4, 43.7, 41.4, 38.4, 28.6, 25.9, 22.9, 19.9; HRMS (CI) calcd for $C_{14}H_{19}O_3$ (M + 1) *m/e* 235.1334, found 235.1343.

(3α,7α,8aβ)-5-Methoxy-7-methyl-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4,9-dione (29). Isolation gave rise to 6.7 mg (85%) of **29**: R_f 0.28 (hexanes-ethyl acetate, 3:1); IR ($CHCl_3$) 2980, 2930, 1760, 1680, 1600, 1450, 1360, 1260, 1230, 1150, 1080, 1010, 840 cm^{-1}; ^1H NMR (500 MHz) δ 5.86 (s, 1H), 3.65 (s, 3H), 2.33 (m, 2H), 2.24 (dd, J = 12.3, 9.8 Hz, 1H), 2.04 (ddd, J = 14.3, 7.3, 7.3 Hz, 1H), 1.97 (tt, J = 13.05, 6.8 Hz, 1H), 1.72 (m, 2H), 1.48 (d, J = 12.3, 6.4 Hz, 1H), 1.37 (s, 3H), 1.32 (m, 1H); ^{13}C NMR (125 MHz) δ 205.1, 192.1, 152.0, 121.8, 75.7, 55.5, 52.6, 44.7, 40.1, 30.4, 27.7, 23.0, 18.2; HRMS (CI) calcd for $C_{13}H_{17}O_3$ (M + 1)*m/e* 221.1178, found 221.1167.

3,4-Dimethoxy-6-methyl-phenoxyl-tetrahydropyran (38). To a solution of 2.35 g (14 mmol) of 4,5-dimethoxy-2-methylphenol[4b] in 80 mL of methylene chloride was added 2 mL (21 mmol) of 2,3-dihydropyran and 551 mg (0.2 mmol) of PPTS. The reaction was stirred overnight and was quenched with water. The layers were separated and the organic layer was washed successively with 0.1 N HCl, a saturated sodium bicarbonate solution, and water. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude tetrahydropyran was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) afforded 3.12 g (92%) of **38** as a colorless oil: R_f 0.38 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2920, 1495, 1430, 1190 cm^{-1}; ^1H NMR (500 MHz) δ 6.76 (s, 1H), 6.67 (s, 1H), 5.26 (t, J = 3.36 Hz, 1H), 3.95 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58 (m, 1H), 2.20 (s, 3H), 2.02 (m, 1H), 1.87 (m, 2H), 1.64 (m, 3H); ^{13}C NMR (125 MHz) δ 149.0, 147.4, 143.7, 118.9, 114.3, 101.8, 97.8, 62.1, 56.4, 56.1, 30.7, 25.3, 19.0, 15.6; HRMS (CI) calcd for $C_{14}H_{21}O_4$ (M + 1) *m/e* 253.1440, found 253.1448.

3,4-Dimethoxy-6-methyl-2-(4-methylpent-4-enyl)phenoxyltetrahydropyran (39). To a solution of 2.0 g (8.0 mmol) of 3,4-dimethoxy-6-methylphenoxyltetrahydropyran (**38**) in 40 mL of dry THF at 0°C was added 3.5 mL (3.21 mmol) of 2.5 M n-BuLi. The resultant yellow solution was allowed to warm to ambient temperature and stir for 2 h. The reaction mixture was recooled to 0°C and 1.55 mL (8.8 mmol) of HMPA followed by 2.4 g (11.4 mmol) of 5-bromo-2-methyl-1-pentene as a solution in 5 mL of THF were added. The reaction was quenched by the slow addition of 5 mL of a saturated solution of ammonium chloride followed by dilution with ether. The layers were separated and the aqueous layer was extracted with ether (2 x 5 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by flash column chromatography. Elution with hexanes-ethyl acetate (5:1) afforded 2.32

g (87%) of **39** as a colorless oil: R_f 0.60 (hexanes-ethyl acetate, 2:1): IR ($CHCl_3$) 2940, 2850, 1650, 1590, 1475, 1460, 1360, 1330, 1145, 1110, 1090, 1070, 1025, 995 cm^{-1}; ^1H NMR (500 MHz) δ 6.56 (s, 1 H), 4.75 (dd, J = 6.10, 1.61 Hz, 1H), 4.71 (d, J = 3.74 Hz, 2H), 4.17 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.49 (m, 1H), 2.73 (ddd, J = 12.44, 10.76, 5.54 Hz, 1H), 2.55 (ddd, J = 12.40, 10.85, 5.58 Hz, 1H), 2.27 (s, 3H), 2.21 (t, J = 7.54 Hz, 1H), 1.96-1.86 (m, 3H), 1.74 (s, 3H), 1.65-1.58 (m, 6H); ^{13}C NMR (125 MHz) δ 149.0, 148.5, 146.1, 145.9, 130.5, 126.43, 111.9, 109.7, 103.5, 64.6, 60.7, 55.8, 38.4, 31.4, 28.2, 25.2, 25.1, 22.4, 20.7, 17.6; HRMS (CI) calcd for $C_{20}H_{31}O_4$ (M + 1) *m/e* 335.2223, found 335.2233.

3,4,4-Trimethoxy-6-methyl-2-(4-methylpent-4-enyl)cyclohexa-2,5-dienone (40). To a solution of 2.3 g (6.9 mmol) of **39** in 30 mL of methanol was added 3 mL of a 2% solution of oxalic acid. The initially cloudy solution was stirred for 5 h at room temperature. The methanol was removed under vacuum. The residue was dissolved in 10 mL ether and was washed with water (2 x 2 mL). The organic layer was dried with magnesium sulfate and concentrated *in vacuo*. The crude phenol was purified by flash chromatography. Elution with hexanes-ethyl acetate (2:1) gave 1.6 g (93%) of phenol as a colorless oil: R_f 0.36 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3600, 2920, 1430, 1330, 1290, 1180, 1105, 1068, 975, 830 cm^{-1}; ^1H NMR (500 MHz) δ 6.55 (s, 1H), 4.74 (s, 2H), 4.38 (s, 1H), 3.80 (s, 6H), 2.62 (t, J = 7.85 Hz, 2H), 2.20 (s, 3H), 2.11 (t, J = 7.49 Hz, 2H), 1.74 (s, 3H), 1.69 (tt, J = 7.85, 7.49 Hz, 2H); ^{13}C NMR (125 MHz) δ 146.4, 146.0, 145.9, 122.9, 118.0, 112.6, 109.9, 60.9, 56.3, 37.6, 27.5, 23.7, 22.4, 15.9; HRMS (CI) calcd for $C_{15}H_{23}O_3$ (M + 1) *m/e* 251.1569, found 251.1600.

To a solution of 1.6 g (6.3 mmol) of the above phenol in 32 mL of methanol at 0°C was added 1.9 g (8.3 mmol) of DDQ. The resulting bright orange solution was stirred for 30 min. The methanol was removed under vacuum and the residue was dissolved in 35 mL of ether and washed with a saturated sodium bicarbonate solution (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude quinone was purified by flash chromatography. Elution with hexanes-ethyl acetate (2:1) yielded 1.68 g (94%) of **40** as a yellow oil: R_f 0.34 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2950, 1690, 1620, 1450, 1375, 1315, 1295, 1210, 1160, 1140, 1070, 960, 890, 710 cm^{-1}; ^1H NMR (500 MHz) δ 6.19 (d, J = 1.39 Hz, 1H), 4.68 (s, 1H), 4.67 (s, 1H), 4.13 (s, 3H), 3.28 (s, 6H), 2.34 (t, J = 7.97 Hz, 2H), 2.03 (t, J = 7.70 Hz, 2H), 1.94 (d, J = 1.35 Hz, 3H), 1.71 (s, 3H), 1.58 (tt, J = 7.97, 7.76 Hz, 2H); ^{13}C NMR (125 MHz) δ 186.6, 161.1, 145.9, 138.6, 134.8, 124.1, 109.7, 96.9, 58.8, 51.1, 37.9, 26.8, 22.7, 22.3, 15.5; HRMS (EI) calcd for $C_{16}H_{24}O_4$ (M) *m/e* 281.1753, found 281.1744.

(3α,7α,8aβ)-5-Methoxy-7,8a-dimethyl-1,2,3,7,8,8a-hexahydro-3a,7-methanoazulene-4,9-dione (35). To a solution of 1.65 g (6.3 mmol) of **40** in 35 mL of 3.0 M $LiClO_4$-EtOAc at -23°C was added 1.35 mL (6.4 mmol) of TMSOTf. After 5 min, the orange solution was quenched by the addition of 10 mL of a saturated sodium bicarbonate solution. The layers were separated and the organic layer was washed with saturated sodium bicarbonate (5 mL) and brine (2 x 5 mL), and dried over magnesium sulfate. The crude dione was purified by flash column chromatography. Elution with hexanes-ethyl acetate (3:1) yielded 1.34 g (90%) of **35** as an oil: R_f 0.28 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2980, 2950, 2880, 1760, 1690, 1610, 1460, 1385, 1360, 1280, 1260, 1235, 1205, 1195, 1150, 1110, 1070, 990, 840, 710 cm^{-1}; ^1H NMR (500 MHz) δ 5.94 (s, 1H), 3.65 (s, 3H), 2.47 (ddd, J = 13.6, 9.7, 3.7 Hz, 1H), 2.20 (m, 1H), 1.84 (s, 2H), 1.71 (m, 3H), 1.41 (m, 1H), 1.37 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz) δ 205.1, 191.6,

152.5, 123.4, 79.4, 55.4, 51.6, 48.3, 47.8, 43.2, 24.3, 24.1, 20.8, 18.8; HRMS (EI) calcd for $C_{14}H_{18}O_3$ (M) m/e 235.1335, found 235.1338.

(3α,7α,8aβ,9R*)-5-Methoxy-9-methoxymethoxy-7,8a-dimethyl-2,3,4,7,8,8a-hexahydro-1H-3a,7-methanoazulene-4-one (41). To a solution of 571 mg of **35** (2.4 mmol) in 12 mL methanol at 0°C was added 31 mg (0.80 mmol) of sodium borohydride. The solution was maintained at this temperature for 1 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous phase was extracted with ether (3 x 10 mL). The ethereal layers were combined and dried over magnesium sulfate. The crude alcohol was purified by flash chromatography. Elution with hexanes-ethyl acetate (3:1) yielded 535 mg (93%) of alcohol as a white crystalline solid, mp 146-147°C: R_f 0.22 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3650, 3490, 2980, 2920, 2860, 1680, 1620, 1450, 1370, 1360, 1280, 1250, 1235, 1200, 1150, 1125, 1070, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 5.73 (s, 1H), 3.60 (s, 3H), 3.39 (s, 1H), 2.61 (ddd, J = 11.2 Hz, 1H), 2.06 (d, J = 12.2 Hz, 1H), 1.97 (m, 1H), 1.90-1.69 (m, 4H), 1.59 (dd, J = 11.2, 6.3 Hz, 1H), 1.54 (d, J = 12.2 Hz, 1H), 1.29 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz) δ 196.5, 151.6, 121.4, 84.2, 74.9, 55.2, 53.7, 50.3, 48.5, 44.6, 29.7, 27.1, 25.7, 22.3, 20.8; HRMS (EI) calcd for $C_{14}H_{20}O_3$ (M) *m/e* 237.1418, found 237.1413.

A two-neck round bottom flask, equipped with a reflux condenser and under argon atmosphere was charged with 535 mg (2.21 mmol) of the above alcohol in 11.9 mL of dichloroethane. To this solution was added 11.3 mL (64.7 mmol) of N, N-diisopropylethylamine followed by the addition of 3.5 mL (44.1 mmol) of chloromethyl methyl ether. The resulting red solution was refluxed for 10 h. The mixture was cooled to 0°C and a saturated solution of sodium bicarbonate was slowly added dropwise. The mixture was diluted with ether and the layers were separated. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude enone was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) yielded 450.7 mg (76%) of pure **41** as an oil: R_f 0.22 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2970, 1685, 1628, 1450, 1370, 1230, 1200, 1150, 1080, 1065, 1035 cm^{-1}; ^1H NMR (500 MHz) δ 5.74 (s, 1H), 4.68 and 4.65 (AB quartet, J = 6.65 Hz, 2H), 3.59 (s, 3H), 3.41 (s, 3H), 3.29 (s, 1H), 2.59 (dt, J = 11.2, 3.18, 1H), 2.00 (m, 2H), 1.87-1.65 (m, 3H), 1.54 and 1.52 (AB of ABX, J_{ab} = 11.2 Hz, J_{ax} = 6.1 Hz, J_{bx} = 0 Hz, 2H), 1.26 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz) δ 196.5, 151.5, 124.7, 98.2, 91.6, 75.0, 55.2, 53.5, 50.4, 49.0, 44.2, 25.8, 25.5, 22.8, 21.4; HRMS calcd for $C_{16}H_{24}O_4$ (M) *m/e* 280.1675, found 280.1687.

(3α,4β,7α,8aβ,9R*)-4-Acetoxy-9-methoxymethoxy-7,8a-dimethyl-2,3,4,5,6,7,8,8a-octahydro-1H-3a,7-methanoazulene-5-one (36). To a solution of 1.17 g (4.36 mmol) of **41** in 22 mL of absolute ethanol was added 1.78 g (4.8 mmol) of cerium trichloride heptahydrate. The mixture was stirred for 15 min at room temperature. The mixture was cooled to 0°C and 162.6 mg (4.36 mmol) of sodium borohydride were added. The mixture was stirred for 1 h at 0°C. The mixture was diluted with 50 mL of ether followed by slow addition of a saturated ammonium chloride solution. The layers were separated and the ethereal layer was washed with brine (2 x 10 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) yielded 1.09 g (93%) of alcohol as a white foam: R_f 0.31 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 3610, 2950, 2890, 1660, 1460, 1370, 1300, 1240, 1145, 1030, 970, 800 cm^{-1}; ^1H NMR (500 MHz) δ 4.71 and

4.64 (AB quartet, J = 6.69 Hz, 2H), 4.54 (s, 1H), 4.49 (s, 1H), 3.54 (s, 3H), 3.42 (s, 3H), 3.26 (s, 1H), 1.93-1.77 (m, 5H), 1.54 (dd, J = 11.2, 1.15 Hz, 1H), 1.42 (m, 2H), 1.15 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz) δ 152.8, 104.8, 98.2, 92.7, 75.9, 56.2, 55.2, 54.7, 51.6, 47.4, 45.2, 30.3, 27.7, 27.3, 26.8, 21.4; HRMS (EI) calcd for $C_{16}H_{26}O_4$ (M) *m/e* 282.1831, found 282.1857.

To a solution of 1.1 g (4.3 mmol) of the above alcohol and 120 mg (0.43 mmol) of DMAP in 22 mL of acetic anhydride was added 1.5 mL (62 mmol) of pyridine. The solution was stirred at room temperature for 12 h. The mixture was diluted with diethyl ether (50 mL) and washed with a saturated sodium bicarbonate solution (5 x 20 mL). The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude acetate was purified by flash chromatography. Elution with hexanes-ethyl acetate (5:1) yielded 1.3 g (93%) of product as a white solid; mp 64-65°C: R_f 0.551 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2920, 2880, 1720, 1645, 1440, 1360, 1270, 1240, 1160, 1130, 1090, 1030, 960, 900, 800 cm^{-1}; ^{1}H NMR (500 MHz) δ 5.88 (s, 1H), 4.70 and 4.67 (AB quartet, J = 6.62 Hz, 2H), 4.54 (s, 1H), 3.46 (s, 3H), 3.41 (s, 3H), 3.37 (s, 1H), 2.10 (s, 3H), 1.92 (m, 2H), 1.83 (m, 1H), 1.76 (dt, J = 9.9, 9.2 Hz, 1H), 1.68-1.56 (m, 2H), 1.41 (m, 2H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz) δ 171.2, 151.2, 106.3, 98.3, 92.6, 75.5, 62.1, 56.2, 55.2, 54.9, 51.9, 47.2, 44.8, 27.8, 27.6, 26.8, 21.4, 21.2; HRMS (EI) calcd for $C_{18}H_{28}O_5$ (M) *m/e* 324.193, found 324.197.

To 1.3 g (4.0 mmol) of the above acetate dissolved in 20 mL of methanol was added 5 ml of a 2% aqueous solution of oxalic acid. The resulting cloudy solution was stirred overnight. The mixture was diluted with ether (30 mL) and was washed with a saturated solution of sodium bicarbonate (3 x 15 mL). The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude ketone was purified by flash chromatography. Elution with hexanes-ethyl acetate (4:1) yielded 1.05 g (85%) of **36** as a white solid; mp 84-85°C: R_f 0.47 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2940, 2860, 1730, 1720, 1445, 1360, 1235, 1205, 1140, 1080, 1030, 790 cm^{-1}; ^{1}H NMR (500 MHz) δ 5.33 (s, 1H), 4.78 and 4.74 (AB quartet, J = 6.80 Hz, 2H), 3.66 (s, 1H), 3.46 (s, 3H), 2.39 and 2.36 (AB quartet, J = 13.0 Hz, 2H), 2.18 (s, 3H), 2.04 (m, 1H), 1.96 (m, 2H), 1.76-1.62 (m, 3H), 1.45 (m, 2H), 1.08 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz) δ 203.1, 170.2, 98.4, 93.7, 79.5, 62.8, 56.4, 52.8, 51.7, 47.8, 45.1, 29.8, 26.5, 25.0, 24.7, 22.3, 20.8; HRMS (CI) calcd for $C_{17}H_{27}O_5$ (M + 1) *m/e* 311. 1859, found 311.1871.

(3α,4α,7α,8aβ,9R*)-9-Methoxymethoxy-4,7,8a-trimethyl-2,3,4,5,6,7,8,8a-octahydro-1H-3a,7-methanoazulene-5-one (42). Liquid ammonia (15 mL) was distilled from lithium into a three-neck round bottom flask at -78°C fitted with a dry ice condenser. Lithium, 75 mg, (12.9 mmol) was added and the solution was stirred at -78°C until the blue color persisted for 30 min. To the liquid ammonia was added 395 mg (1.29 mmol) of acetate **36** dissolved in 5 mL of anhydrous THF. The reaction was stirred for 1 h at -78°C. The reaction was quenched by the addition of isoprene. To the resulting white mixture was added 1.5 mL (25.8 mmol) of methyl iodide and the mixture was warmed to -33°C and refluxed for 1 h. Solid ammonium chloride was added and the ammonia was allowed to evaporate off. The mixture was diluted with 20 mL of ether and washed with water (2 x 5 mL) and brine (1 x 8 mL). The layers were separated and the organic layer was dried over magnesium sulfate and concentrated *in vacuo* giving 322 mg of a 4.1 to 1 mixture of **42** and **43** which for convenience was carried on without separation: ^{1}H NMR (500 MHz) δ 4.76 and 4.72 (AB quartet, J = 6.98 Hz, 2H), 3.85 (s, 1H), 3.46 (s, 3H), 2.49 (q, J = 7.72 Hz), 2.42 and 2.43 (AB quartet,

J = 16.3 Hz, 2H), 2.08-1.9 (m, 2H), 1.89-1.55 (m, 4H), 1.4-1.3 (m, 2H), 1.14 (q, J = 7.72 Hz, 3H), 1.04 (s, 3H), 0.92 (s, 3H).

(3α,4α,5β,7α,8aβ,9R*)-9-Methoxymethoxy-4,7,8a-trimethyl-2,3,4,5,6,7,8,8a-octahydro-1H-3a,7-methanoazulene-5-ol (44). To 322 mg (1.3 mmol) of the above mixture of ketones **42** and **43** dissolved in 6 mL of dry toluene at 0°C was added 1.8 mL (1.8 mmol) of 1.0 M solution of Dibal-H in toluene. After 1.5 h a saturated solution of sodium potassium tartrate was added and the mixture was diluted with 10 mL of ether. The layers were separated and the ethereal layer was washed with brine (2 x 10 mL), dried over magnesium sulfate and concentrated under reduced pressure. The crude alcohols were purified by flash chromatography. Elution with hexanes-ethyl acetate (95:5) yielded 245 (74%) of **44** as a colorless oil [R_f 0.37 (hexanes-ethyl acetate, 70:30); IR ($CHCl_3$) 3620, 3480, 2915, 1450, 1370, 1260, 1210, 1150, 1090, 1030, 990 cm^{-1}; ^1H NMR (500 MHz) δ 4.68 and 4.64 (AB quartet, J_{ab} = 6.75 Hz, 2H), 3.64 (dt, J = 6.67, 2.16 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 1H), 2.12 (AB quartet, J = 11.4 Hz, 2H), 2.08 (dq, J = 7.42, 2.16 Hz, 1H), 1.97 (ddd, J = 14.75, 6.89, 1.33 Hz, 1H), 1.85 (ddd, J = 13.41, 9.1, 4.39 Hz), 1.74 (ABX, J_{ab} = 12.65 Hz, J_{ax} = 1.34 Hz, J_{bx} = 0 Hz, 2H), 1.63 (m, 2H), 1.45 (ddd, J = 11.89, 8.77, 3.23 Hz, 1H), 1.20 (s, 3H), 1.03 (d, J = 7.4 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz) δ 97.8, 90.7, 72.9, 61.8, 56.0, 51.4, 49.5, 48.6, 46.1, 45.6, 45.5, 31.7, 24.5, 23.8, 23.7, 18.6; HRMS (CI) calcd for $C_{16}H_{30}O_3$ (M-MOM) *m/e* 223.1699, found 223.1697] plus 27 mg (8%) of the epi-alcohol **45** and 50 mg (18%) of **46**.

(3α,4α,7α,8aβ,9R*)-5-(Methanesulfonyl)oxy-9-methoxymethoxy-4,7,8a-trimethyl-2,3,4,5,7,8,8a-octahydro-1H-3a,7-methanoazulene (37). A mixture of 478 mg (1.88 mmol) of alcohol **44** and 789 μL (5.64 mmol) of triethylamine was dissolved in 9.4 mL of methylene chloride. The mixture was cooled to 0°C and 290 mg (3.76 mmol) of methanesulfonyl chloride was added. The reaction was stirred for 1 h. The reaction was quenched by the addition of water and the layers were separated. The organic layer was washed with brine (2 x 5 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude mesylate was purified by flash chromatography. Elution with hexanes-ethyl acetate (95:5) yielded 484 (82%) of mesylate as a colorless oil [R_f 0.44 (hexanes-ethyl acetate, 2:1); IR ($CHCl_3$) 2950, 1455, 1330, 1180, 1150, 1100, 1040, 1030, 970, 860, 810 cm^{-1}; ^1H NMR (500 MHz) δ 4.69 and 4.60 (AB quartet, J = 6.70 Hz, 2H), 4.53 (d, J = 6.81 Hz, 1H), 3.67 (s, 1H), 3.40 (s, 3H), 2.98 (s, 3H), 2.38 (q, J = 7.47 Hz, 1H), 2.17 (ddd, J = 11.00, 10.68, 10.65 Hz, 1H), 2.07 (ddd, J = 15.7, 6.94, 1.00 Hz, 1H), 1.92 (d, J = 15.66 Hz, 1H), 1.86 (ddd, J = 13.60, 8.55, 5.07, 1H), 1.76 and 1.72 (AB of ABX, J_{ab} = 13.41 Hz, J_{ax} = 1.10 Hz, J_{bx} = 0.2 Hz, 2H), 1.65(m, 2H), 1.48 (ddd, J = 11.79, 8.30, 3.45 Hz, 1H), 1.40 (m, 1H), 1.14 (s, 3H), 1.11 (d, J = 7.47 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz) δ 97.8, 90.2, 82.5, 61.7, 56.1, 51.5, 48.1, 46.1, 45.9, 45.6, 44.2, 38.5, 31.3, 23.7, 23.5, 23.2, 18.0; HRMS (EI) calcd for $C_{16}H_{27}O_2$ (M-OMs) *m/e* 251.2012, found 251.2007] plus 15 mg (6%) of recovered **44**.

To a solution of 590 mg (1.88 mmol) of the above mesylate dissolved in 9.4 mL of toluene was added 1.4 mL (9.4 mmol) of DBU. The resulting yellow solution was refluxed for 15 h. The solution was cooled to ambient temperature and diluted with methylene chloride (15 mL). The mixture was washed with 1N HCl (2 x 5 mL), saturated sodium bicarbonate solution (2 x 5 mL), and brine (1 x 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Elution with pentane afforded 353.3 mg (75%) of the desired olefin [R_f 0.61 (hexanes-ethyl acetate, 4:1); IR ($CHCl_3$) 2940, 2880, 1610,

1460, 1370, 1260, 1150, 1100, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 5.41 (dd, J = 9.3, 0.98 Hz, 1H), 5.28 (dd, J = 9.3, 4.0 Hz, 1H), 4.68 and 4.25 (AB quartet, J = 6.7 Hz, 2H), 3.64 (s, 1H), 3.43 (s, 3H), 2.32 (dq, J = 6.9, 4.0 Hz, 1H), 1.94 (m, 2H), 1.77-1.41 (m, 5H), 1.03-1.00 (m, 9H); ^{13}C NMR (125 MHz) δ 137.1, 130.4, 98.0, 89.4, 61.7, 56.1, 53.7, 51.9, 48.8, 45.6, 41.2, 30.6, 25.9, 25.3, 20.8, 18.7; HRMS (CI) calcd for $C_{16}H_{27}O_2$ (M + 1) *m/e* 251.2012, found 251.2010] along with 86.5 mg (17%) of **44**.

To 350 mg (1.41 mmol) of the above olefin in 7.1 mL of ethyl acetate was added 35 mg of 10% Pd/C (0.14 mmol). The resulting suspension was stirred vigorously for 12 h under an atmosphere of hydrogen. The reaction contents were filtered through a pad of celite. The pad was rinsed with 1:1 hexane/ethyl acetate. The solvent was concentrated under reduced pressure giving crude **37** which was purified by flash chromatography. Elution with pentane afforded 331 mg (95%) of **37** as a colorless oil: R_f 0.73 (hexanes-ethyl acetate, 5:1); IR ($CHCl_3$) 2940, 2880, 1460, 1370, 1260, 1150, 1100, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 4.69 and 4.60 (AB quartet, J = 6.70 Hz, 2H), 3.64 (s, 1H), 3.43 (s, 3H), 2.14 (dt, J = 10.68, 10.65 Hz, 1H), 1.87 (m, 2H), 1.83 (q, J = 7.1 Hz, 1H), 1.70-1.58 (m, 3H), 1.52 (m, 1H), 1.44 (m, 1H), 1.35-1.25 (m, 2H), 1.11 (dd, J = 13.1, 6.0 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 3H), 0.96 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz) δ 98.0, 92.0, 62.2, 56.0, 51.7, 49.1, 47.6, 45.4, 38.11, 37.45, 31.3, 26.6, 24.0, 23.3, 21.7, 18.0; HRMS (EI) calcd for $C_{14}H_{24}O$ [(M-MOM) + 1] *m/e* 208.1828, found 208.1827.

(3a,4a,7a,8ab)-4,7,8a-Trimethyl-2,3,4,5,7,8,8a-octahydro-1H-3a,7-methanoazulene-9-one (33). To 330 mg (1.33 mmol) of **37** in 6.6 mL of 9:1 H_2O:THF was added 6N HCl (200 μL). The mixture was heated to 50°C for 9 h. The mixture was cooled to 0°C, diluted with ether (10 mL), and neutralized by slow addition of a saturated solution of sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude alcohol was purified by flash chromatography. Elution with hexanes-ethyl acetate (95:5) afforded 150 mg (54%) of product as a colorless oil: R_f 0.58 (hexanes-ethyl acetate, 5:1); IR ($CHCl_3$) 3620, 2940, 1460, 1380, 1260, 1060, cm^{-1}; ^1H NMR (500 MHz) δ 3.50 (s, 1H), 2.10 (dt, J = 10.30, 10.24 Hz, 1H), 1.88 (m, 2H), 1.83 (q, J = 7.1 Hz, 1H), 1.72 (d, J = 13.3 Hz, 1H), 1.65 (m, 2H), 1.51 (m, 2H), 1.38 (m, 3H), 1.30 (dd, J = 13.1, 6.5 Hz, 1H), 1.12 (dd, J = 14.2, 6.5 Hz, 1H), 1.04 (s, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz) δ 84.9, 62.1, 51.9, 49.1, 47.4, 45.9, 37.8, 37.2, 30.7, 26.7, 24.2, 22.3, 22.1, 18.9; HRMS (EI) calcd for $C_{14}H_{24}O$ (M) *m/e* 208.1828, found 208.1833.

A slurry of 150 mg (1.33 mmol) of the above alcohol, 273 mg (3.32 mmol) of sodium acetate, and 3.60 g celite in 7 mL of methylene chloride at 0°C was treated with 860 mg (3.99 mmol) of PCC. The mixture was maintained at 0°C for 15 min then allowed to warm to room temperature and stirred for 3 h. The reaction mixture was diluted with ether and the insoluble salts were filtered and washed with ether. The crude ketone was purified by flash chromatography. Elution with hexanes-ethyl acetate (95:5) afforded 125 mg (84%) of known ketone **33**: IR (film) 1740, 1450, 1380, 1320, 1300, 1270, 1260, 1190, 1140, 1015, 985, 920, 800 cm^{-1}; ^1H NMR δ 0.80 (d, J = 7 Hz, 3H), 1.00 (s, 3H), 1.13 (s, 3H).

(±)-Isocomene. To 364 μL (0.509 mmol) of 1.4 M MeLi in 850 μL of THF was added 38 mg (0.18 mmol) of ketone **33** as a solution in 365 μL of THF. The reaction heated to 60°C for 2 h. The mixture was allowed to cool to ambient temperature and 1 mL of a saturated ammonium chloride solution was added, followed by dilution with ether. The layers were separated and the aqueous layer was extracted with ether (3 x

2 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

The crude alcohol was dissolved in 750 μl of 95% formic acid and stirred for 5 h. The mixture was diluted with ether and was washed with water and a saturated solution of sodium bicarbonate. The layers were separated and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (elution with pentane) gave 27 mg (75%) of (±) isocomene: R_f 0.75; mp 58-59°C (lit.[10] mp 57-60). IR ($CHCl_3$) 3020, 2950, 2875, 1670, 1455, 1375, 1330, 1190, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 4.86 (s, 1H), 2.0 (tt, J = 6.29 Hz, 1H), 1.73 (dd, J = 12.2, 2.5 Hz, 1H), 1.56 (s, 3H), 1.45-1.11 (mm, 7H), 1.56-1.45 (m, 1H), 1.04 (s 3H), 1.03 (s, 3H) 0.86 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz) δ 142.8, 132.7, 63.8, 59.9, 56.6, 42.6, 39.9, 37.3, 33.6, 32.0, 24.0, 23.7, 23.2, 17.3, 13.0.

Acknowledgments: This investigation was supported in the U.S. by a Public Health Service Research Grant from the National Institutes of General Medical Sciences (GM 33605) and Zeneca Pharmaceuticals.

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(*Received* 21 *March* 1997; *revised* 15 *April* 1997; *accepted* 1 *May* 1997)