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Synthesis of Four Sesquiterpenoid Lactone Skeletons, Germacranolide, Elemanolide, Cadinanolide, and Guaianolide, from a Single Photoadduct

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The syntheses of four different sesquiterpenoid carbon skeletons, germacranolide, elemanolide, cadinanolide, and guaianolide, from the photoadduct **2** are described. Thermolysis of **3** and **9**, which both were derived from **2a**, gave germacranolides **4** and **10**, respectively, in which the lactone ring bridged C(4) and C(6) while thermolysis of **16** (also derived from **2a**) gave a mixture of isomeric germacranolides **17** and **18** in which the γ-lactone moiety bridged C(6) and C(7). A number of factors involved in the critical cycloreversion step to give the ten-membered ring of the germacranolides are discussed and MM1 calculations on the adduct precursors are used to support some of the suggestions. Thermolysis of **3** also gave the elemanolide **5** in addition to **4**. Thermolysis of **2b** gave the cadinanolide **26** after a remarkable sequence of thermal transformations. Finally, sensitized irradiation of **4** gave the guaianolide **30**. The conversion of a number of the products to more functionalized derivatives, some of which are related to known sesquiterpenoids, is also described.

Previous investigations by us[1] and by others[2] have shown that the photoaddition of substituted 2-cyclohexenones to cyclobutenes followed by thermolysis of the resultant adducts is an effective method for the synthesis of several sesquiterpenoid carbon skeletons. In this report we describe a highly convergent and versatile approach to the synthesis of four sesquiterpenoid lactone skeletons from a single, readily prepared photoadduct.

The critical photoadduct (**2a**) was prepared by [2 + 2] cycloaddition of 1-cyclobutenecarboxylic acid to the diastereomeric enone **1** in toluene using a 350-nm irradiation source (Scheme I).[3] The convergent and versatile nature of this approach is supported by the fact that this adduct not only contains all 15 carbons required for a sesquiterpenoid skeleton but it is richly and strategically functionalized with ketone, ester, and carboxylic acid groups. The first and major section below will describe the methodology employed in the conversion of adduct **2a** to a number of germacranolide isomers as well as to an elemanolide. Subsequent sections will describe the preparation of cadinanolide and guaianolide skeletons from the same precursor **2a**.

Synthesis of Germacranolide and Elemanolide Skeletons

Our goal was to develop methodology for the conversion of **2a** to germacranolides in which the lactone ring bridged C(4) and C(6) or C(6) and C(7) as either system is present in many of these natural terpenoids.[4] Reduction of the ketone function in **2a** from the less hindered β-face gave the α-alcohol which spontaneously lactonized to yield **3** as mentioned in a previous study.[3] Thermolysis of **3** in refluxing decane gave the melampolide (*cis,trans*-germacranolide) **4** (60%) and the elemanolide **5** (16%). The diastereomeric mixture in lactone **4** was separated by TLC to give upper and lower bands. The *Z* configuration of the 1(10) double bonds in both components was assigned on the basis of the ^{13}C NMR signals of the C-14 methyl groups at 22.9 and 21.6 ppm for the upper and lower bands, respectively.[5] The diastereomeric mixture of elemanolide **5** was not separable by TLC but the structure was assigned by detailed analysis of the 400-MHz ^1H NMR spectrum. The coupling constants of 7.9 Hz for $J_{H_{5,6}}$ and 10.9 Hz for $J_{H_{6,7}}$ are consistent with the cis and trans orientations of the respective protons. Also, the α-methylene γ-lactone

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(3) Lange, G. L.; Lee, M. *Synthesis* **1986**, 117.

(4) (a) Yoskioka, H.; Mabry, T. J.; Timmerman, B. N. *Sesquiterpene Lactones*; University of Tokyo Press: Tokyo, 1973. (b) Fischer, N. H.; Oliver, E. J.; Fischer, H. D.; Frank, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 50. (c) Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105.

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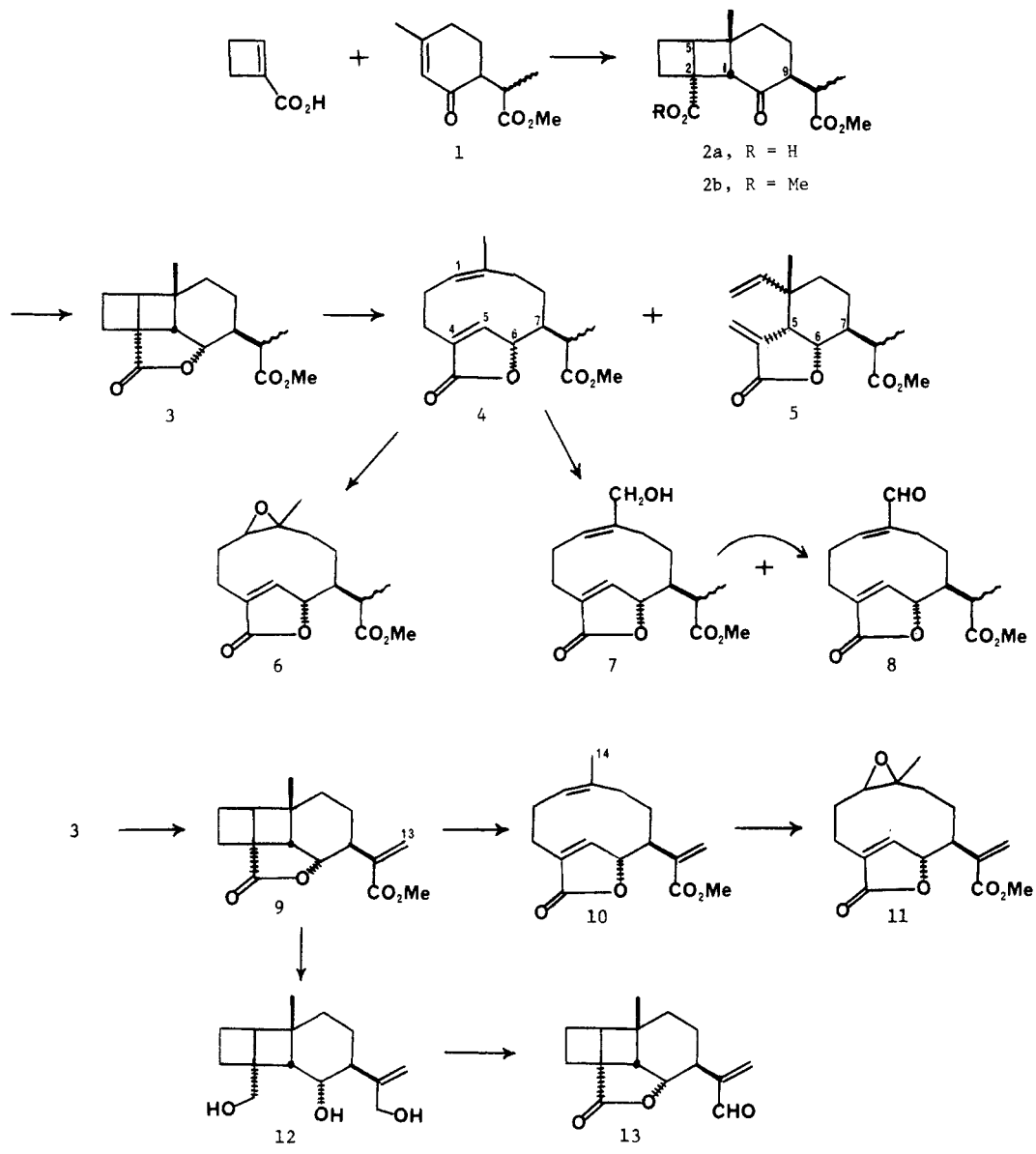
Scheme I



moiety in **5** was indicated by the presence of two doublets for the C(3) protons [e.g., δ 6.19 (J = 2 Hz) and 5.91 ppm (J = 2 Hz) for one of the diastereomers] and by the IR carbonyl absorption at 1775 cm^{-1}.[6] The *cis*-1,2-divinyl system in **5** is consistent with the breaking of the C(2)–C(5) and C(3)–C(4) bonds of **3** during the thermolysis.

Further reactions of germacranolide **4** led to more oxygenated derivatives. For example, regioselective reaction with *m*-chloroperbenzoic acid at the electron-rich 1(10) double bond gave epoxide **6** while allylic oxidation of **4** with selenium dioxide and *tert*-butyl hydroperoxide[7] gave a mixture of alcohol **7** (16%) and aldehyde **8** (17%). The alcohol could be oxidized quantitatively to the aldehyde with barium manganate to give an overall 33% conversion of **4** to **8**. Evidence for the cis configuration of the 1(10) double bond in **8** was obtained from the ^{1}H NMR chemical shift of the aldehyde proton at δ 9.3, a position diagnostic for a cis enal.[8] 1(10)-Epoxide and C(14) aldehyde functions are common in natural germacranolides[4] and above we have described procedures for elaborating both functions from precursor **4**.

The C(6)–C(7) trans-fused α-methylene γ-lactone moiety is present in many germacranolides[4] and is often essential to the biological (e.g., antitumor) activity of these substances.[9] We wished to explore more convergent approaches to this lactone system. Attempted trans-lactonization ($NaOCH_3$, $HOCH_3$) of **3**, to give a product in which C-6 and C-7 were bridged, was unsuccessful presumably because the desired *trans*-lactone would be more strained. Experience in the generation of α-methylene

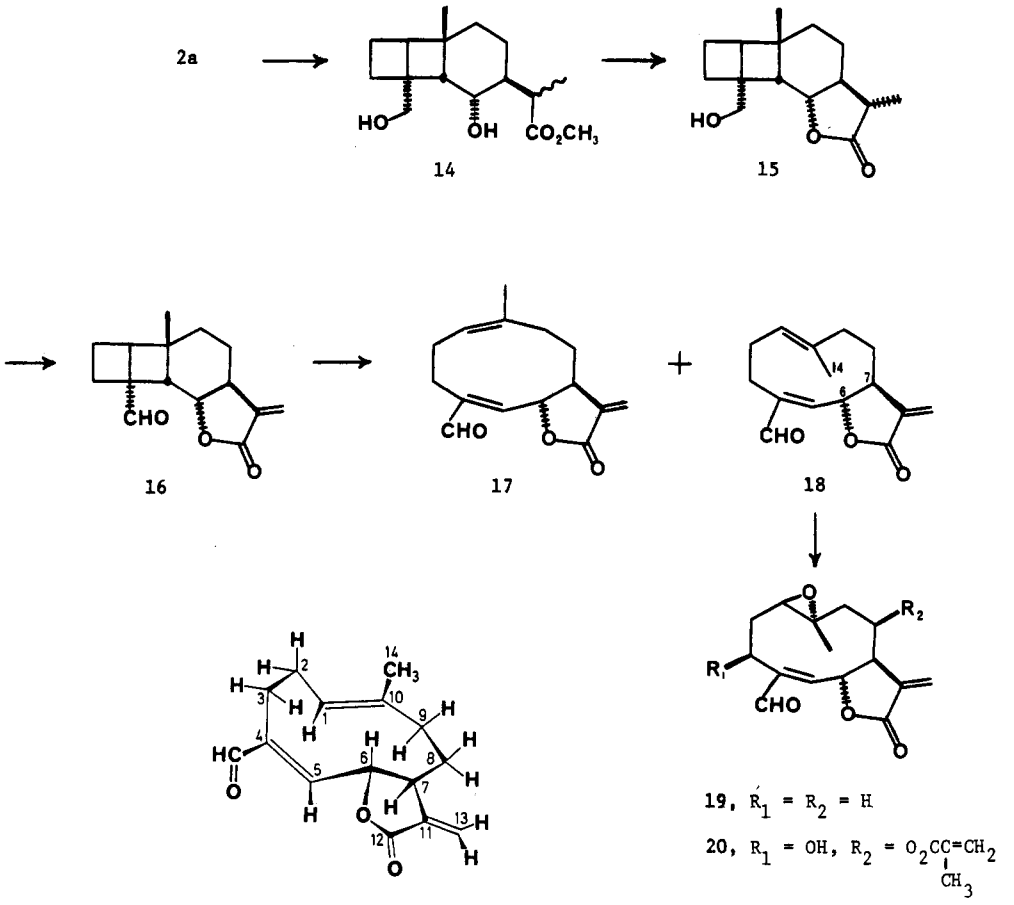
(6) (a) Ortega, A.; Maldonado, E. *Phytochemistry* **1985**, *24*, 2635. (b) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267.

(7) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Haruna, M.; Kazuo, I. *J. Chem. Soc., Chem. Commun.* **1981**, 483.

(8) The aldehyde proton of cis enals in germacranolides generally occurs at a chemical shift less than 10 ppm (upfield) while the same proton in trans enals is found downfield from 10 ppm: (a) Chan, K. C.; Jewell, R. A.; Nutting, W. H.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 3382. (b) Herz, W.; Sharma, R. P. *J. Org. Chem.* **1975**, *40*, 392. (c) Bohlmann, F.; Robinson, H.; King, R. M.; Jakupovic, J.; Schmeda-Hirshman, G. *Phytochemistry* **1984**, *23*, 1989.

(9) (a) Rodriquez, E.; Towers, G. H. M.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573. (b) Misra, R.; Pandey, R. C. In *Anti-tumor Compounds of Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed.; CRC Press: Boca Raton, FL, 1981; pp 145–146. (c) Cassady, J. M.; Suffness, M. In *Medicinal Chemistry*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; pp 201–203. (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94.

Scheme II



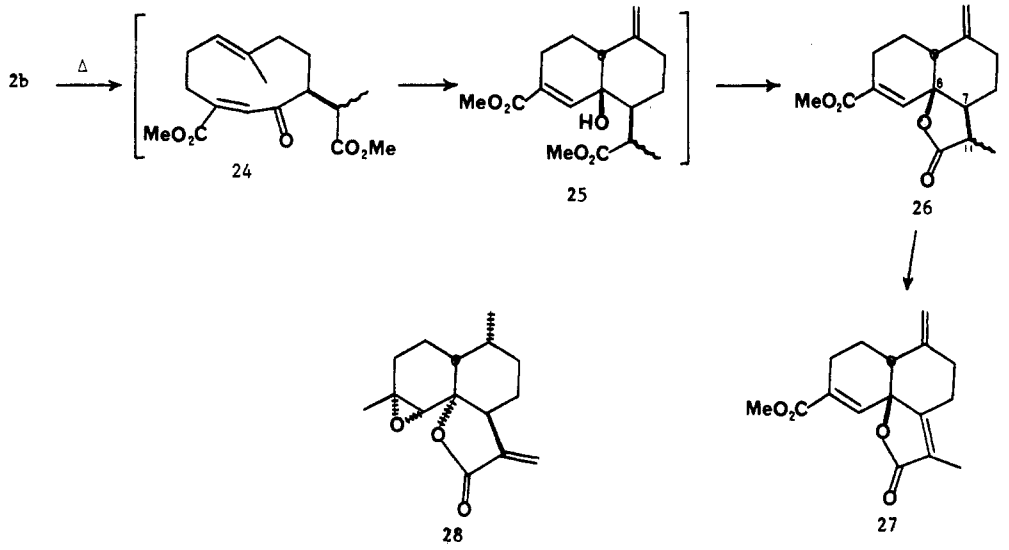
18a

systems was obtained by converting **3** to the α-phenylselenenyl derivative which upon oxidation and elimination gave the unsaturated ester **9**. The presence of H-13 singlets at δ 6.36 and 5.29 was confirmation that the elimination had proceeded in the desired direction. Thermolysis of **9** gave the germacranolide **10** in 72% yield and this upon epoxidation with *m*-chloroperbenzoic acid gave the multifunctional derivative **11**. The cis geometry of the 1(10) double bond in **10** was indicated clearly by the ^{13}C chemical shift of 22.9 ppm for the C-14 methyl group.[5] In another attempt to prepare the C(6)–C(7) γ-lactone, **9** was reduced with diisobutylaluminum hydride to give the triol **12**, which was then oxidized with barium manganate.[10] In light of previous reports with similar systems,[10] it was anticipated that the allylic alcohol would be oxidized preferentially to the aldehyde which would cyclize to the lactol which in turn would be oxidized to the desired lactone. In fact, the product formed in an overall yield of 37% from **9** was the lactone **13** (IR 1770, 1700 cm^{-1}). Similarly, treatment of **12** with Fetizon's reagent[11] gave **13** exclusively.

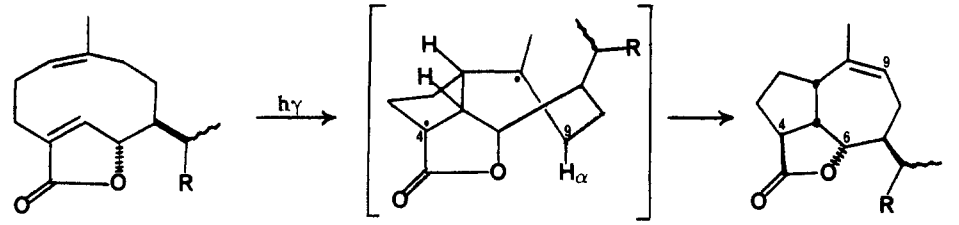
A successful approach to the formation of the desired *trans*-γ-lactone moiety bridging C(6) and C(7) is outlined in Scheme II. In the first step, the carboxylic acid and ketone functions of adduct **2a** were reduced selectively in the presence of the ester group by converting the carboxyl group to a mixed anhydride followed by reduction with excess sodium borohydride to give diol ester **14** (overall 44% yield from **1**).[3] Treatment of **14** with dilute acid gave the single epimer **15**, suggesting that C(11) must have undergone epimerization during the lactonization procedure.[3] Conversion of **15** to **16** was achieved in an overall yield of 64% by selenoxide elimination to yield the α-methylene γ-lactone and by PCC oxidation to generate the aldehyde function. The presence of these two groups was confirmed by the IR carbonyl absorptions at 1780 and 1705 cm^{-1}, respectively, and by the ^1H NMR resonances at δ 6.10 (d, J = 3.2 Hz), 5.41 (d, J = 3.0 Hz), and 9.73 (s). The trans geometry of the lactone bridge was confirmed by the coupling constant of 11.7 Hz between the H(6) and H(7) protons. As discussed previously,[3] electron-withdrawing substituents such as a formyl group at C(1) and C(4) in adducts such as **16** facilitate the next step, a cycloreversion, by stabilizing the diradical intermediate which is formed.[12] Thermolysis of **16** gave in 50% yield a 65:35 mixture of the *cis,cis*-germacranolide **17** and the *trans,cis*-heliangolide **18**, which was purified by preparative TLC. The ^1H and ^{13}C NMR spectra were most useful in establishing the structures of these two products. The cis-4-enal moiety (actually the *E* configuration) present in **17** and **18** was assigned on the basis of the ^1H NMR signal of the aldehyde protons at δ 9.37 and 9.43, respectively.[8] The configurations of the cis- and trans-1(10)-trisubstituted double bonds for **17** and **18** were established by the ^{13}C NMR chemical shifts of the C(14)-methyl groups at δ 22.0 and 16.1, respectively.[5] Further examination of the ^1H NMR spectrum of **18** suggested that the major conformer present in chloroform solution was that depicted in **18a**. In particular, the coupling constants of 10.0 Hz for $J_{H_{5,6}}$, 1.5 Hz for $J_{H_{6,7}}$, and 8.0 Hz for $J_{H_{1,2}}$ were in good agreement with those expected for a heliangolide skeleton and were very

(10) (a) Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.* **1978**, 839. (b) Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579.
(11) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.
(12) (a) Walters, W. D.; Zupan, M. *J. Am. Chem. Soc.* **1964**, *86*, 173. (b) Walters, W. D.; Roquitte, B. C. *J. Chem. Phys.* **1964**, *68*, 1606.

Scheme III



Scheme IV



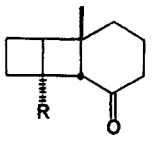
4, R = CO_2Me
31, R = Me

29

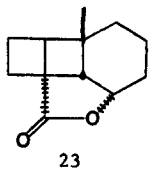
30, R = CO_2Me
32, R = Me

similar to those reported for eupaformonin,[13b] whose conformation was unambiguously determined by X-ray crystallography.[13c] The anti orientation of the C(14)-methyl and the C(15)-formyl groups suggested for **18** is also in good agreement with a number of other known heliangolides.[14] Regio- and stereoselective epoxidation of the 1(10) double bond of this conformer of **18** gave the highly functionalized product **19**. The IR and ^1H NMR spectra of **19** show the expected similarities to the closely related natural product eriophyllin C (**20**)[13b,d] and thus this sequence constitutes a total synthesis of 8-(deacyloxy)-3-dehydroxyeriophyllin C (**19**).

To conclude this section, several points regarding the critical cycloreversion reaction of the tricyclo[4.4.0.$0^{2,5}$]-decane system (e.g., **3**) are worthy of note. As discussed previously[15] and noted above, a good radical stabilizing group at C(2) in these adducts accelerates the rate of the cycloreversion reaction (CHO > CO_2R > R). Another factor that has been found to influence this reaction rate is the inherent strain in the adduct. Using Allinger's MM1 force field program,[16] the strain energies of ester **21**, aldehyde **22**, and lactone **23** were determined to be 59.8, 60.0, and 66.3 kcal/mol, respectively. Thus, a lactone such as **9** (a derivative of **23**) undergoes cycloreversion more readily than esters related to **21**[15b] (reaction conditions: 183 °C for 3 h vs. 170 °C for 30 h, respectively). The MM1 calculations also indicated that the average length of the C(2)–C(5) bond in **21**, **22**, and **23** is 1.558 Å, which is considerably longer than the average length of all cyclobutane carbon–carbon bonds in these three compounds (1.539 Å). X-ray crystallographic data for adducts[2c,17] similar to the three mentioned above also showed that the C(2)–C(5) bond is unusually long.[18]



21, R = CO_2Me
22, R = CHO



23

Synthesis of Cadinanolide and Guaianolide Skeletons

Previous investigations showed that adducts obtained from photoaddition of substituted cyclobutenes and 2-cyclohexenones underwent thermal cycloreversion to yield 1,5-cyclodecadienes which then rearranged by a transannular ene reaction to yield bicyclo[4.4.0] systems.[1a,2b,19] In the first part of this section we describe the highly convergent synthesis of a cadinanolide skeleton using this protocol. Heating of diester **2b** resulted in a remarkable sequence of thermal reactions via diene **24** and hydroxy ester **25** to ultimately yield the desired lactone **26** (Scheme

(13) (a) Gnecco, S.; Poshey, J. P.; Silva, M.; Sammes, P. G.; Tyler, T. W. *Phytochemistry* **1973**, *12*, 2469. (b) Holub, M.; Samek, Z. *Collect. Czech. Chem. Commun.* **1977**, *42*, 1053. (c) McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 578. (d) Torrance, S. J.; Geissman, T. A.; Chedekel, M. R. *Phytochemistry* **1969**, *8*, 2381.

(14) (a) Begley, M. J.; Patteneden, G.; Mabry, T. J. *Tetrahedron Lett.* **1975**, 1105. (b) McPhail, A. T.; Onan, K. D.; Lee, K. H.; Ibuka, T. *Tetrahedron Lett.* **1974**, 3203.

(15) (a) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (b) Lange, G. L.; Otulakowski, J. A. *Ibid.* **1982**, *47*, 5093.

(16) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1.

(17) Williams, J. R.; Callahan, J. F.; Blount, J. F. *J. Cryst. Mol. Struct.* **1979**, *9*, 245.

(18) It should be noted that cyclobutane bond lengths calculated by the MM1 method are consistently shorter than those reported from X-ray data. Cotton, F. A.; Frenz, B. A. *Tetrahedron* **1974**, *30*, 1587.

(19) Wender, P. A.; Letendre, L. J. *J. Org. Chem.* **1980**, *45*, 367.

III). The stereochemistry of the product is consistent with that proposed previously in simpler systems.[2b,19] Dehydrogenation of **26** via its selenoxide gave **27** in which the new double bond was endocyclic and suggested that the phenylselenenyl group and the neighboring H(7) must have both been in the α-orientation for this syn elimination. Product **27** has a skeleton similar to than of the natural cadinanolide (-)-arteannuin B (**28**)[20] and a less concerted but related approach to this skeleton has been reported.[21]

In this last section will be discussed our approach to the synthesis of the guaianolide skeleton using precursors described above. It was reported previously that a *trans,trans*-1(10),4-germacradienolide underwent a photochemical cyclization to give a $\Delta^{10(14)}$-guaiane product[22] and unpublished results in our laboratory[23] showed that when the cis,trans-diene **31** was irradiated in the presence of a triplet sensitizer, the guaiane **32** was formed (Scheme IV). In the present study, sensitized irradiation of **4** gave in 45% yield the guaianolide **30** as a mixture of diastereomers. The relative stereochemistry of **30** could be rationalized by initial formation of a diradical **29** possessing a cis ring fusion followed by migration of the α proton (H_α) at C(9) to C(4) and concomitant formation of the 9(10) double bond. As mentioned above, the trans,trans-diene yielded the exocyclic $\Delta^{10(14)}$-system[22] while in the present study an endocyclic double bond is formed. The position of the double bond in **30** was established by the ^{1}H NMR signals at δ 5.54 for H(9) and singlets at δ 1.61 and 1.57 for the C(14) methyls of the two diastereomers.

In conclusion, we have shown that the readily prepared and versatile photoadduct **2** may be employed for the synthesis of four sesquiterpenoid carbon skeletons: germacranolide, elemanolide, cadinanolide, and guaianolide. In particular, it provides a highly convergent approach to germacranolides possessing a trans-fused α-methylene γ-lactone moiety bridging C(6) and C(7), a structural feature which is present in many biologically active members of this family of sesquiterpenoids.

Experimental Section

Melting points were correcred with phenacetin (mp 135 °C) as standard and were carried out on a Mel-Temp apparatus. IR spectra were recorded on a Perkin-Elmer Model 1330 or 180 spectrophotometer in either chloroform or carbon tetrachloride solution. ^{1}H NMR spectra were recorded on a Bruker WH-400 spectrometer with tetramethylsilane (δ = 0) as internal standard. The detailed analyses of the ^{1}H NMR spectra of **4a**, **4b**, **10**, **11**, **17**, and **19** were assisted by 2D-COSY experiments.[24] ^{13}C NMR spectra were recorded on either a Bruker WH-400 or an AM-250 spectrometer operating at 100 MHz or 62.5 MHz, respectively. The multiplicites for compounds **4a** and **4b** were determined by the proton-coupled technique (s = singlet, d = doublet, etc.) while the multiplicites for **10**, **17**, **18**, and **27** were established by the Attached Proton Test (APT)[25] with τ = 0.01 s. This value of τ produced positive (+) quaternary C and CH_2 signals and negative (-) CH and CH_3 signals. UV spectra were recorded on a Varian DMS 90 spectrophotometer and mass spectra on a Varian MAT CH7 or VG Micromass 7070F spectrometer. All nominal mass spectra and accurate mass measurements were determined at 70 eV ionizing energy unless otherwise stated. Chemical ionization mass spectra were conducted using isobutane. TLC analyses and preparative purifications were accomplished on silica gel GF with thicknesses of 0.25 and 1.0 mm, respectively, using the solvent system indicated with the procedure. Petrol is 30–60 °C petroleum ether. Flash chromatography purifications were performed on 230–400-mesh silica gel. Combustion analyses were performed by Guelph Chemical Laboratories of Guelph, Ontario.

Tetrahydrofuran (THF) was dried by distillation from sodium–benzophenone ketyl. Methylene chloride and methanol were dried over 4A molecular sieves and hexamethylphosphoramide (HMPA) and diisopropylamine were dried by distillation over barium oxide and calcium hydride, respectively, and then stored over 4A molecular sieves in a dessicator. Dry toluene was obtained by storing reagent grade toluene over sodium before distillation. Compounds **2** and **3** were prepared as 50:50 diastereomeric mixtures using previously described procedures.[3]

Thermolysis of 3. A solution of **3** (197 mg, 0.71 mmol) in decane (3.0 mL) was heated to reflux under N_2 for 3.5 h. Removal of the solvent with a Kugelrohr apparatus (21 mm, 71–74 °C) gave an oil which was purified by preparative TLC (25% ethyl acetate/petrol) to give 117 mg of lactone **4** (60%) and 30.7 mg of **5** (16%) as diastereomeric mixtures. **4** was further purified by TLC to give the upper (**4a**) and lower (**4b**) melampolides.

Lactone 4a: TLC (25% ethyl acetate/petrol) R_f 0.43; IR (CCl_4) 3020, 1760, 1730, 1670, 910 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (s, H-5), 5.15 (t, J = 8.0 Hz, H-1), 5.00 (d, J = 5.5 Hz, H-6), 3.77 (s, OCH_3), 2.60 (m, H-11), 2.37 (m, H-3 and H-7), 2.10 (m, H-2 and H-8), 1.61 (m, H-9a), 1.60 (s, CH_3-14), 1.27 (d, J = 8.0 Hz, H-13), 1.06 (m, H-9b); ^{13}C NMR ($CDCl_3$) δ 175.2 (s), 170.0 (s), 146.7 (d), 138.6 (s), 134.2 (s), 120.1 (d), 80.3 (d), 51.9 (q), 43.6 (d), 39.8 (d), 28.3 (t) 26.8 (t), 24.1 (t), 23.3 (t), 22.9 (q, C-14), 15.3 (q); UV (EtOH) λ_{max} 218 nm (ϵ 6200); MS, m/e (relative intensity) 278 (M$^+$, 9), 260 (26), 232 (14), 218 (18), 191 (61), 190 (43), 174 (16), 173 (100). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.58; H 8.36.

Lactone 4b: TLC (25% ethyl acetate/petrol) R_f 0.36; IR (CCl_4) 3020, 1760, 1735, 1650, 950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19 (s, H-5), 5.27 (d, J = 5.5 Hz, H-6), 5.14 (t, J = 8.0 Hz, H-1), 3.75 (s, H-16), 2.70 (m, H-11), 2.46 (m, H-7), 2.38 (m, H-3), 2.16 (m, H-2), 1.90 (m, H-2), 1.58 (s, CH_3-14), 1.34 (d, J = 8.0, H-13), 1.28 (m, H-9a), 1.12 (m, H-9b); ^{13}C NMR ($CDCl_3$) δ 175.7 (s), 174.6 (s), 147.9 (d), 138.2 (s), 133.9 (s) 120.3 (d), 80.9 (d), 51.9 (q), 43.9 (d), 39.3 (d), 28.3 (t), 26.2 (t), 23.9 (t), 23.0 (t), 21.6 (q, C-14), 16.3 (q); UV (EtOH) λ_{max} 218 nm (ϵ 6600); MS, m/e (relative intensity) 278 (M$^+$, 3), 260 (25), 232 (18), 218 (19), 191 (62), 190 (41), 174 (16), 173 (100). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.94. Found: C, 68.91; H, 8.37.

Elemanolide 5: TLC (25% ethyl acetate/petrol) R_f 0.76; IR (CCl_4) 3020, 1775, 1735, 1639, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.19 (d, J = 2.0 Hz, 1 H), 5.95 (dd, J = 10.5, 17.5 Hz, 1 H), 5.91 (d, J = 2.0 Hz, 1 H) 5.11 (d, J = 10.5, 1 H), 5.07 (d, J = 17.5 Hz, 1 H), 4.79 (dd, J = 7.9, 10.9 Hz, 1 H), 3.72 (s, 3 H), 2.98 (br dd, J = 2.0, 8.3 Hz, 1 H), 1.21 (d, J = 6.8 Hz, 1 H), 1.10 (s, 3 H); other diastereomer δ 6.28 (d, J = 2.0 Hz, 1 H), 5.74 (d, J = 2.0 Hz, 1 H), 5.66 (dd, J = 10.5, 17.5 Hz, 1 H), 5.1 (m, 2 H), 4.54 (dd, J = 7.9, 10.9 Hz, 1 H), 3.69 (s, 3 H), 2.83 (br dd, J = 2.0, 8.0 Hz, 1 H), 1.22 (d, J = 6.8, Hz, 3 H), 1.10 (s, 3 H); MS, m/e (relative intensity) 278 (M$^+$, 3), 247 (15), 246 (11), 219 (5), 192 (16), 191 (100). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.94. Found: C, 68.68; H, 8.23.

Preparation of Epoxide 6. To a stirred solution of lactone **4** (43.5 mg, 0.16 mmol, mixture of diastereomers) in chloroform (3 mL) at 0 °C was added *m*-chloroperbenzoic acid (41.4 mg, 0.24 mmol). The solution was stirred at 0 °C for 2 h, diluted with chloroform (10 mL), and washed with an aqueous saturated solution of sodium bicarbonate (one time), water (one time), and brine (one time). After drying (anhydrous magnesium sulfate) and concentration in vacuo, the resultant oil was purified by preparative TLC (40% ethyl acetate/petrol, R_f 0.28) to give epoxide **6** (29.0 mg, 63%) as a diastereomeric mixture which solidified: mp 78–81 °C; IR (CCl_4) 3020, 1755, 1650, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 1 H), 5.24 (br s, 1 H), 3.72 (s, 3 H), 2.75 (m, 1 H), 2.38–2.65 (m, 4 H), 1.53–1.84 (m, 3 H), 1.38–0.80 (m, 3 H), 1.35 (d, J = 7.0 Hz, 3 H), 1.18 (s, 3 H); other diastereomer δ 7.33 (s, 1 H), 4.94 (br s, 1 H), 3.74 (s, 3 H), 2.75 (m, 1 H), 1.27 (d, J = 7.0 Hz, 3 H), 1.22 (s, 3 H), plus overlapping signals; MS, m/e (relative intensity) 294 (M$^+$, 1), 207 (10), 189 (9). Anal. Calcd

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for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.24; H, 7.49.

Allylic Oxidation of 4. After stirring a suspension of selenium dioxide (33.7 mg, 0.30 mmol) in dry methylene chloride (5.0 mL) and 70% *tert*-butyl hydroperoxide (0.12 mL, 1.1 mmol) at room temperature for 1.5 h, a solution of lactone **4** (135 mg, 0.49 mmol) in methylene chloride (1.0 mL) was added dropwise. The flask was covered with foil and stirring was continued for an additional 14 h. After removal of the solvent, the products were dissolved in ether (150 mL), and this organic phase was washed with 10% aqueous potassium hydroxide (three times) and with brine (one time and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by preparative TLC (25% ethyl acetate/chloroform) to give alcohol **7** (23.0 mg, 16%, R_f 0.22) and aldehyde **8** (24.1 mg, 17%, R_f 0.47) both as mixtures of diastereomers. A solution of **7** (3.9 mg) in dry methylene chloride (1.0 mL) was heated to reflux with barium manganate (40 mg) for 3.5 h under N_2. After filtering the reaction mixture through a pad of Celite, the solvent was removed to give **8** (3.8 mg) which was one spot by TLC analysis.

Alcohol 7: IR ($CHCl_3$) 3680, 3620–3300, 3020, 1740 (br), 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 1 H), 5.47 (m, 1 H), 5.01 (d, J = 4.0 Hz, 1 H), 3.96 (m, 2 H), 3.75 (s, 3 H), 1.34 (d, J = 7.0 Hz, 3 H); other diastereomer δ 7.22 (s, 1 H), 5.47 (m, 1 H), 5.21 (d, J = 4.0 Hz, 1 H), 3.96 (m, 2 H), 3.73 (s, 3 H), 1.28 (d, J = 7.0, 3 H); MS, m/e (relative intensity) 294 (M^+, 1), 276 (13), 217 (31), 207 (23), 189 (68), 188 (35), 171 (27), 159 (29), 145 (26), 143 (49); MS (CI mode, isobutane), m/e (relative intensity) 295 (M + 1, 10), 277 (100).

Aldehyde 8: IR (CCl_4) 1765, 1740, 1696, 908 cm^{-1}; UV (EtOH) λ_{max} 210 nm; ^1H NMR ($CDCl_3$) δ 9.33 (s, 1 H), 7.41 (s, 1 H), 6.50 (t, J = 9.0 Hz, 1 H), 5.27 (d, J = 3.8 Hz, 1 H)8 3.75 (s, 3 H), 1.23 (d, J = 6.4 Hz, 3 H); other diastereomer δ 9.31 (s, 1 H), 7.28 (s, 1 H), 6.48 (t, J = 9.0 Hz, 1 H), 5.03 (d, J =3.8 Hz, 1 H), 3.74 (s, 3 H), 1.21 (d, J = 6.4 Hz, 3 H); MS, m/e (relative intensity) 292 (M^+, 5), 260 (20), 232 (31), 196 (56), 164 (38), 147 (22), 145 (26), 136 (100); exact mass calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1304.

Preparation of Lactone 9. To a stirred solution of lithium diisopropylamide (2.20 mmol) in dry THF (4.0 mL) at −78 °C was added dropwise over 15 min a solution of **3** (306 mg, 1.10 mmol) in THF (4.0 mL). After stirring the mixture at −78 °C for an additional hour, a solution of benzeneselenenyl bromide (406 mg, 1.72 mmol) in THF (2.0 mL) was added. The clear solution was stirred for 5 min at −78 °C and then allowed to warm to room temperature over 15 min. The solution was recooled to 0 °C and water (1.1 mL) was added, followed by glacial acetic acid (0.22 mL) and 30% hydrogen peroxide (1.0 mL). The resultant solution was stirred at room temperature for 1 h, an aqueous saturated solution of sodium bicarbonate (30 mL) was added, and the products were extracted with ether (3 times). The combined ether extracts were washed with water (1 time), with 0.1 M HCl solution (1 time), with water (1 time), and with brine (1 time) and were dried ($MgSO_4$). Removal of the solvent followed by TLC purification (25% ethyl acetate/petrol, R_f 0.43) gave lactone **9** (101 mg, 33%) as fine needles: mp (ether/petrol) 91–92 °C; IR (CCl_4) 3020, 1765, 1725, 1620, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.36 (s, 1 H), 5.29 (s, 1 H), 4.73 (d, J = 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.27 (br t, J = 4.0 Hz, 1 H), 2.81 (dd, J = 9.0, 3.0 Hz, 1 H), 2.75 (dd, J = 12.0, 6.0 Hz, 1 H), 2.45 (d, J = 9.0 Hz, 1 H), 2.38 (m, 1 H), 2.19 (m, 2 H), 1.87 (tt, J = 14.0, 4.0 Hz, 1 H), 1.66 (dq, J = 4.0, 14.0 Hz, 1 H), 1.43 (dt, J = 4.0, 14.0 Hz, 1 H), 1.29 (m, 1 H), 1.28 (s, 3 H); UV (EtOH) λ_{max} 206 nm; MS, m/e (relative intensity) 276 (M^+, 1), 244 (9), 216 (12), 81 (100). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.60; H, 7.34.

Thermolysis of Lactone 9. A degassed solution of **9** (10.8 mg, 0.039 mmol) in toluene (1.0 mL) was heated at 183 °C for 3 h in a sealed tube using a Wood's metal bath. Removal of the solvent gave a crude product which was crystallized from ether/petrol to give **10** (7.8 mg, 72%) as needles: mp 97–98 °C; IR (CCl_4) 3020, 1765, 1721, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (s, H-5), 6.33 (s, H-13a), 5.75 (s, H-13b), 5.33 (br s, H-6), 5.15 (t, J = 6.6 Hz, H-1), 3.81 (s, OCH_3), 3.28 (br s, H-7), 2.44 (m, H-3a), 2.24 (m, H-3b), 2.16 (m, H-2a), 2.11 (m, H-2b), 1.91 (m, H-8a), 1.69 (m, H-8b), 1.63 (m, H-9a), 1.62 (s, CH_3-14), 1.40 (m, H-9b); ^{13}C NMR ($CDCl_3$) δ 175.0 (+), 166.8 (+), 147.2 (−), 138.7 (+), 138.5 (+), 133.6 (+), 126.0 (+), 120.5 (−), 80.7 (−), 52.2 (−), 43.2 (−), 28.6 (+), 27.9 (+), 27.6 (+), 24.6 (+), 22.9 (−, C-14); UV (EtOH) λ_{max} 215 nm; MS, m/e (relative intensity) 276 (M^+, 22), 258 (100), 244 (47), 173 (21), 216 (40). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.33. Found: C, 69.44; H, 7.33.

Epoxide 11. To a stirred solution of **10** (8.8 mg, 0.032 mmol) in chloroform (1.0 mL) at 0 °C was added *m*-chloroperbenzoic acid (8.9 mg, 0.051 mmol). The solution was stirred at 0 °C for 1.5 h, ether (50 mL) was added, and the organic phase was washed with an aqueous saturated solution of sodium carbonate (2 times) and with brine (1 time) and dried ($MgSO_4$). Removal of the solvent gave an oily residue which was purified by TLC (40% ethyl acetate/petrol, R_f 0.14) to give epoxide **11** (3.5 mg, 38%) as an oil: IR (CCl_4) 3020, 1765, 1725, 1630, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (s, H-5), 6.38 (s, H-13a), 5.65 (s, H-13b), 5.39 (br s, H-6), 3.81 (s, OCH_3), 3.56 (br s, H-7), 2.61 (dd, J = 3.7, 11.1 Hz, H-1), 2.50 (m, H-3), 1.99 (m, H-8a), 1.77 (s, CH_3-14), 1.67 (m, H-8b), 1.40 (m, H-2a), 1.35 (m, H-2b), 1.12 (m, H-9a), 0.76 (m, H-9b); MS, m/e (relative intensity) 260 (M − CH_3OH,5), 231 (6), 217 (9), 189 (17), 171 (16), 124 (39), 97 (100); MS (CI mode, isobutane), m/e (relative intensity 293 (M + 1, 46), 261 (10). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.60; H, 6.64.

Aldehyde 13. To a solution of **9** (30.6 mg, 0.11 mmol) in dry toluene (5.0 mL) under N_2 at room temperature was added a 1.0 M solution of diisobutylaluminum hydride in methylene chloride (0.41 mL, 0.41 mmol). After stirring the reaction for 3 h, water (0.5 mL) was added and the gelatinous mixture was filtered through a pad of Celite. The pad was washed thoroughly with methylene chloride, the filtrate was dried ($MgSO_4$), and the solvent was removed to give crude triol **12**: TLC (35% ethyl acetate/petrol) R_f 0.08; IR ($CHCl_3$) 3620, 3600–3300, 1620, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.27 (s, 1 H), 5.19 (s, 1 H), 5.04 (s, 1 H), 4.76 (s, 1 H), 4.10 (m, 2 H), 3.77 (dd, J = 7.0, 10.5 Hz, 1 H), 3.64 (d, J = 10.5 Hz, 1 H), 1.07 (s, 3 H). The crude triol **12** (20 mg, 0.08 mmol) was dissolved in dry methylene chloride (2.0 mL) and barium manganate (262 mg, 1.02 mmol) was added. The stirred reaction mixture was heated to reflux under N_2 for 4 h and then cooled and filtered through a pad of Celite. The pad was thoroughly washed with methylene chloride and the solvent removed to give aldehyde **13** (7.2 mg, 37%) which by TLC analysis (35% ethyl acetate/petrol) showed only one spot at R_f 0.67: IR (CCl_4) 3020, 2820, 2700, 1770, 1700, 1670, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52 (s, 1 H), 6.19 (s, 1 H), 6.09 (s, 1 H), 4.69 (d, J = 8.3 Hz, 1 H), 2.79 (m, 2 H), 2.73 (d, J = 8.3 Hz, 1 H), 2.48–2.13 (m, 5 H), 1.88 (m, 1 H), 1.63 (m, 2 H), 1.30 (s, 3 H); MS, m/e (relative intensity) 264 (M^+, 9) 228 (64), 217 (26), 173 (33), 147 (51), 191 (28), 189 (33), 161 (53); exact mass calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256 and for (M − CHO) 217.1216, found 246.1344 (M^+) and 217.1240 (M − CHO).

Preparation of 16. To a stirred solution of lithium diisopropylamide (0.37 mmol) in dry THF (1.0 mL) under N_2 at −78 °C was added dropwise a solution of lactone **15** (62.5 mg, 0.25 mmol) in THF (1.0 mL). After stirring the mixture for 20 min, a solution of benzeneselenenyl bromide (87 mg, 0.37 mmol) in THF (1.0 mL) and HMPA (0.07 mL) was added rapidly. The resultant clear solution was stirred at −78 °C for an additional 20 min and then gradually warmed to 0 °C over 10 min. An aqueous saturated solution of ammonium chloride (5.0 mL) was added to the mixture and the product was extracted with ether (3 times). The combined ether extracts were washed with water (1 time) and brine (1 time) and then dried ($MgSO_4$). Removal of the solvent gave the crude selenide product (140 mg) as an oil: TLC (40% ethyl acetate/petrol) R_f 0.50; IR (CCl_4) 3640, 3050, 1770, 1540, 1455, 1260, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (dd, J = 1.1, 7.8 Hz, 2 H), 7.42 (t, J = 7.7 Hz, 1 H), 7.33 (t, J = 7.5 Hz, 2 H), 4.58 (dd, J = 6.8, 12.0 Hz, 1 H), 3.89 (d, J = 11.8 Hz, 1 H), 3.73 (d, J = 11.8 Hz, 1 H), 2.33 (m, 1 H), 2.25 (m, 1 H), 2.17 (m, 1 H), 2.01 (m, 2 H), 1.56 (s, 3 H), 1.44 (m, 2 H), 1.22 (m, 1 H), 1.21 (s, 3 H); MS, m/e (relative intensity) 406 (M + 1, 3), 404 (M − 1, 2), 249 (4), 219 (32), 177 (58), 176 (38), 159 (65), 148 (25), 147 (100). The crude selenide was redissolved in THF (10 mL) containing glacial acetic acid (0.1 mL), the solution was cooled to 0 °C, and 30% hydrogen peroxide (0.40 mL) was added. The mixture was stirred at this temperature for 1 h and at room temperature for 30 min. A saturated solution of sodium bicarbonate (5.0 mL) was added and the products were extracted with ether (3 times). The combined ether extracts were washed with brine (1 time) and dried ($MgSO_4$), and the solvent was

removed to give an oil which was purified by TLC to give the alcohol product (40.0 mg): TLC (45% ethyl acetate/petrol) R_f 0.46; IR (CCl_4) 3640, 3600–3100, 3020, 1780, 1680, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.12 (d, J = 3.0 Hz, 1 H), 5.44 (d, J = 3.0 Hz, 1 H), 4.02 (dd, J = 6.4, 12.2 Hz, 1 H), 3.94 (dd, J = 1.8, 11.7 Hz, 1 H), 3.73 (br q, J = 11.7 Hz, 1 H), 2.93 (d, J = 5.9 Hz, 1 H), 1.21 (s, 3 H); MS, m/e (relative intensity) 217 (M – OCH_3, 6), 173 (7), 145 (27), 119 (28), 81 (100). To a suspension of pyridinium chlorochromate (45 mg, 0.21 mmol) in dry methylene chloride (2.0 mL) at 0 °C under N_2 was added a solution of the above alcohol (40.0 mg, 0.16 mmol) in methylene chloride (2.0 mL). The mixture was stirred at 0 °C for 5 min and at room temperature for 1 h. The dark brown solution was filtered through silica gel using suction and the product was eluted with ethyl acetate. Removal of the solvent gave aldehyde **16** (39.5 mg, 64% overall from **15**) which was essentially homogeneous by TLC analysis: TLC (25% ethyl acetate/petrol) R_f 0.38; IR (CCl_4) 3020, 2825, 2715, 1780, 1705, 1670, 990, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 6.10 (d, J = 3.2 Hz, 1 H), 5.41 (d, J = 3.0 Hz, 1 H), 4.00 (dd, J =5.8, 11.7 Hz, 1 H), 3.20 (d, J = 5.9 Hz, 1 H), 2.20 (m, 1 H), 2.10 (m, 4 H), 1.85 (m, 1 H), 1.80 (m, 2 H), 1.40 (m, 2 H), 1.19 (s, 3 H); MS, m/e (relative intensity) 246 (M^+, 13), 217 (4), 191 (40), 162 (22), 173 (14); exact mass calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1253.

Thermolysis of 16. Two samples of **16** (39.5 mg, 0.16 mmol; 21.9 mg, 0.089 mmol) were each dissolved in toluene (2.0 mL) and heated in degassed sealed tubes at 175 °C for 3.5 h using a Wood's metal bath. The solvent was removed from the combined reactions and the residue was purified by flash chromatography (25% ethyl acetate/petrol) to give **17** (20.0 mg) and **18** (10.6 mg) in a combined yield of 50%.

Lactone 17: TLC (25% ethyl acetate/petrol) R_f 0.33; IR (CCl_4) 3020, 2820, 2720, 1775, 1695, 1655, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.37 (s, H-15), 6.36 (d, J = 2.7 Hz, H-13a), 6.32 (d, J = 9.0 Hz, H-5), 5.66 (d, J = 2.2 Hz, H-13b), 5.16 (dd, J = 6.1, 9.0 Hz, H-6), 5.10 (br t, J = 7.8 Hz, H-1), 2.76 (m, H-7), 2.52 (m, H-2a), 2.47 (m, H-8a), 2.20 (m, H-2b), 2.08 (m, H-8b), 2.06 (m, H-3a), 1.80 (m, 4-9), 1.70 (m, H-3a), 1.67 (s, CH_3-14); ^{13}C NMR ($CDCl_3$) δ 194.2 (–), 149.9 (–), 141.5 (+), 138.5 (+), 135.4 (+), 124.7 (–), 123.4 (+), 78.3 (–), 42.0 (–), 32.1 (+), 27.7 (+), 23.9 (+), 23.2 (+), 22.0 (–, C-14); MS, m/e (relative intensity) 246 (M^+, 5), 217 (5), 192 (36), 191 (40), 175 (29), 83 (100), 81 (35); exact mass calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1245.

Lactone 18: TLC (25% ethyl acetate/petrol) R_f 0.26; IR (CCl_4) 3020, 2820, 2720, 1775, 1695, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.43 (s, H-15), 6.41 (d, J = 2.6 Hz, H-13a), 6.22 (d, J = 10.0 Hz, H-5), 5.76 (d, J = 2.1 Hz, H-13b), 5.06 (br t, J = 8.0 Hz, H-1), 4.82 (br dd, J = 1.5, 10.0 Hz, H-6), 2.75 (m, H-7), 1.60 (s, CH_3-14), 2.70–1.40 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 194.2 (–), 150.5 (–), 141.8 (+), 138.6 (+), 135.1 (+), 123.8 (–), 123.4 (+), 79.7 (–), 42.6 (–), 31.0 (+), 27.9 (+), 23.6 (+), 23.4 (+), 16.1 (–, C-14); MS, m/e (relative intensity) 246 (M^+, 28), 217 (20), 191 (18), 175 (67), 147 (23), 145 (31), 83 (15), 81 (100); exact mass calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256 and (M – CHO) 217.1216, found 246.1238 and 217.1209, respectively.

Epoxide 19. A solution of **18** (6.0 mg, 0.025 mmol) and *m*-chloroperbenzoic acid (8.7 mg, 0.050 mmol) in chloroform (2.0 mL) was stirred at 0 °C under N_2 for 1 h and then diluted with ether (50 mL). The ether solution was washed with a saturated solution of sodium carbonate (2 times) and with brine (1 time) and dried ($MgSO_4$). Removal of the solvent and purification by TLC (35% ethyl acetate/petrol, R_f 0.15) gave epoxide **19** (4.5 mg, 69%) as an oil: IR (CCl_4) 3020, 1765, 1690, 1650, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52 (s, H-15), 6.45 (d, J = 2.5 Hz, H-13a), 6.33 (d, J =10.5 Hz, H-5), 5.80 (d, J =2.1 Hz, H-13b) 5.28 (dd, J = 2.3, 10.5 Hz, H-6), 2.80 (m, H-1 and H-7), 2.30 (m, H-2a), 2.25 (m, H-3), 2.30 (m, H-2b), 1.85 (m, H-9a), 1.55 (m, H-8), 1.46 (s, H-14), 1.20 (m, H-9b); UV (EtOH) λ_{max} 226 nm; MS (20 eV), m/e (relative intensity) 262 (M^+, 6), 244 (9), 243 (17), 233 (16), 217 (11), 215 (13), 191 (100), 175 (34); MS (CI mode, isobutane), m/e (relative intensity) 263 (M^+ + 1, 15), 262 (M^+, 1), 245 (7), 233 (1); exact mass (20 eV) calcd for $C_{15}H_{18}O_4$ 262.1205, found 262.1166.

Thermolysis of 2b. A solution of diester **2b** (100 mg, 0.33 mmol) in decane (2.0 mL, bp 174 °C) was heated to reflux under N_2 for 10 h. After removal of the solvent by using a Kugelrohr apparatus (75–77 °C, 20 torr), the residue was purified by TLC (25% ethyl acetate/petrol, R_f 0.37) to afford lactone **26** (55.7 mg, 62%) as a diastereomeric mixture which solidified: mp (ether/petrol) 99–101 °C; IR (CCl_4) 3020, 1780, 1725, 1655, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (s, 1 H), 4.90 (s, 1 H), 5.00 (s, 1 H), 3.77 (s, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), plus other poorly resolved signals; other diastereomer δ 6.75 (s, 1 H), 4.96 (s, 1 H), 4.84 (s, 1 H), 3.77 (s, 3 H), 1.45 (d, J = 7.0 Hz, 3 H), plus other signals, UV (EtOH) λ_{max} 215 nm (ϵ 9700); MS, m/e (relative intensity) 278 (M^+, 100), 245 (23), 244 (26), 217 (47), 216 (53). Anal. Calcd for $C_{16}H_{20}O_3$: C, 69.55; H, 7.30. Found: C, 69.74; H, 7.32.

Cadinanolide 27. A solution of **26** (106 mg, 0.38 mmol) in dry THF (2.0 mL) was added slowly to a solution of lithium diisopropylamide (0.50 mmol) in THF (2.0 mL) at –78 °C, and the mixture was stirred for 1 h. Benzeneselenenyl bromide (136 mg, 0.58 mmol) in THF (1.5 mL) was added rapidly and after 5 min at –78 °C the mixture was allowed to warm to room temperature over 15 min. After cooling to 0 °C, the solution was treated with water (1.0 mL), glacial acetic acid (0.1 mL), and 30% hydrogen perioxide (0.33 mL) and after 5 min at 0 °C the ice bath was removed and the reaction was allowed to proceed at room temperature for 1 h. A saturated solution of sodium bicarbonate (5.0 mL) was added and the product was extracted with ether (3 times). The combined either extracts were washed with water (1 time) and with brine (1 time) and dried ($MgSO_4$). Removal of the solvent gave an oil which was purified by TLC (35% ethyl acetate/petrol, R_f 0.37) to afford **27** (43.7 mg, 42%) as a crystalline solid: mp (ether/petrol) 130–131 °C; IR (CCl_4) 3020, 1770, 1730, 1640, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.82 (s, 1 H), 4.82 (br s, 1 H), 4.72 (br s, 1 H), 3.75 (s, 3 H), 2.75 (m, 4 H), 2.52 (m, 1 H), 2.44 (dt, J = 8.9, 12.8 Hz, 1 H), 2.32 (dt, J = 8.9, 14.8 Hz, 1 H), 2.15 (m, 1 H), 1.96 (m, 1 H), 1.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.2 (+), 165.3 (+), 140.9 (+), 136.0 (+), 135.6 (–), 124.1 (+), 110.9 (+), 52.0 (–), 45.9 (–), 34.5 (+), 25.5 (+), 22.3 (+), 18.0 (+), 8.7 (–); UV (EtOH) λ_{max} 218 nm; MS, m/e (relative intensity) 274 (M^+, 8), 243 (28), 242 (100), 215 (55), 214 (45). Anal. Calcd for $C_{16}H_{18}O_3$: C, 70.06; H, 6.61. Found: C, 70.16; H, 6.48.

Guaianolide 30. A solution of **4** (117 mg, 0.42 mmol) and acetophenone (3.0 μL, sensitizer) in benzene (9.0 mL) in a Pyrex tube was degassed with N_2, sealed, and then irradiated for 43 h in a Rayonet RPR 208 preparative reactor equipped with 350-nm lamps. Removal of the solvent and purification of the residue by TLC (25% ethyl acetate/petrol, R_f 0.29) gave **30** (53 mg, 45%) of a diastereomeric mixture as an oil: IR (CCl_4) 3020, 1780, 1740, 1670, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.54 (br s, 1 H), 4.50 (t, J = 4.0 Hz, 1 H), 3.71 (s, 3 H), 2.83 (m, 1 H), 1.61 (s, 3 H), 1.29 (d, J = 7.0 Hz, 3 H), plus other overlapping signals; other diastereomer δ 5.54 (br s, 1 H), 4.70 (t, J = 4.0 Hz, 1 H), 3.74 (s, 3 H), 2.83 (m, 1 H), 1.57 (s, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), plus other overlapping signals; MS, m/e (relative intensity) 278 (M^+, 10), 247 (3), 232 (27), 173 (64), 172 (19), 145 (100); exact mass calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1518.

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