Total Syntheses of Fungal Metabolites and Functionalized Furanones†

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Simple, efficient syntheses of the fungal metabolites colletochlorin D and (±)-ascofuranone and one of its stereoisomers are described. Our investigations of functionalized furanones also enabled us to develop a nine-step (22% overall yield) synthesis of geiparvarin, a natural product isolated from the leaves of *Geigera parviflora* Lindl.

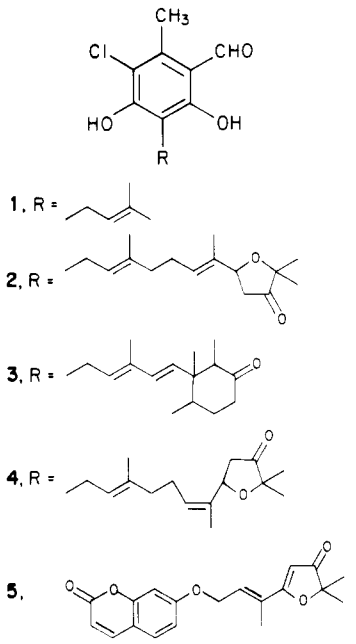
The syntheses of naturally occurring fungal metabolites containing a common hexasubstituted aromatic ring but different side chains such as colletochlorin D (**1**),[1a] ascofuranone (**2**),[1b] and ascochlorin (**3**)[1c] (Chart I) have attracted much attention because of their significant and varied biological activities.[1d-f]

The synthetic challenges presented by these molecules involve: the orientation of different functionality in the aromatic ring, the formation of the furanone or trimethylcyclohexanone moieties, and the olefin geometry of the sesquiterpenoidal chain.

We have previously reported model studies of ascofuranone[2] with an unsubstituted aromatic ring and other synthetic studies dealing with similar fungal metabolites.[3] Mori and co-workers have synthesized several of these prenylated phenols including colletochlorins A and B,[4] (±) ascochlorin,[5] (±) ascofuranone,[6] LL-Z1272, and other related compounds.[7]

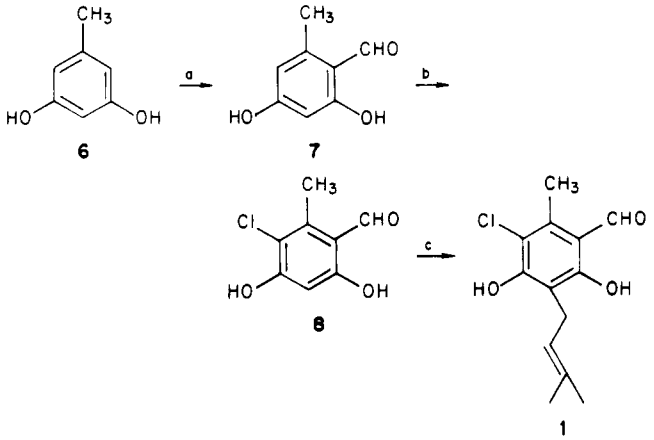
Our own interest in fungal metabolites and functionalized furanones led us to synthesize colletochlorin D (**1**),[8] (±)-ascofuranone (**2**),[9] and geiparvarin (**5**).[10] We now wish to report the details of these syntheses and the preparation of a stereoisomer (**4**) of ascofuranone (Chart I).

Chart I



Orcinol (**6**) (Scheme I) was formylated under Gatterman conditions[11] to afford aldehyde **7** in 76–85% yields. Chlorination of **7** with sulfuryl chloride, in ether, at 0 °C afforded an isomeric mixture, which was separated by column chromatography to give pure **8** in 75% yield. 5-Chloroorsellinaldehyde (**8**) was alkylated with 1-bromo-3-methyl-2-butene in 10% aqueous potassium hydroxide, at 0 °C, to afford **1**[12] in 25% yield.

Scheme I[a]



[a] (a) $Zn(CN)_2$, HCl (g); (b) SO_2Cl_2, Et_2O; (c) 10% KOH, H_2O, 1-bromo-3-methyl-2-butene.

The elimination of the protection and deprotection protocols provided a simple, inexpensive route to **1** in an overall yield of 16%. We planned to utilize the same strategy of a direct C-alkylation to synthesize **2** and, accordingly, divided the molecule into three portions: 5-chloroorsellinaldehyde, an *E*-trisubstituted unsaturated chain, and a previously prepared functionalized furanone (**9**) (Scheme II). We planned to construct the second double bond as was done in our model studies,[2] using the Wittig condensation.

The trisubstituted olefinic side chain, (*E*)-[4-methyl-6-(phenylmethoxy)-4-hexen-1-yl]triphenylphosphonium bromide (**17**) was prepared from geraniol (**10**) in seven steps (Scheme III). Selective epoxidation of geranyl benzyl ether (**11**) using van Tamelen's procedure[12] (*N*-bromosuccinimide in aqueous *tert*-butyl alcohol, followed by treatment with potassium hydroxide) afforded epoxide **12**, which was treated without purification with 3% perchloric acid, in aqueous tetrahydrofuran (THF) to give glycol **13**. Compound **13** was cleaved with 2 equiv of sodium periodate in THF to afford aldehyde **14** in 63–68% yield from **10**. Reduction of **14** with sodium borohydride in methanol gave alcohol **15**. Conversion of **15** to the

† Taken in part from the Ph.D. thesis of K.-M. Chen, submitted to the University of Pennsylvania, 1985; Also presented in part at the 188th National Meeting of the American Chemical Society, Philadelphia, August 26–31, 1984; ORGN 239.

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(2) Semple, J. E.; Guthrie, A. E.; Joullie, M. M. *Tetrahedron Lett.* **1980**, *21*, 4561.

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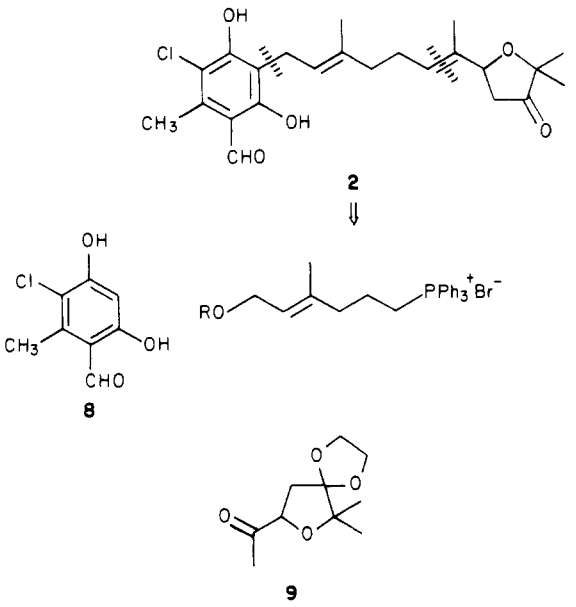
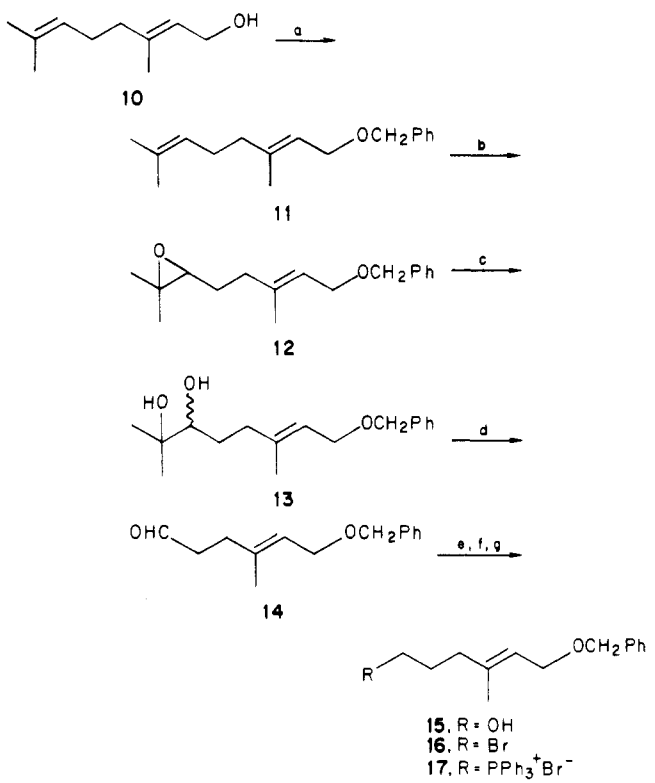
Scheme II



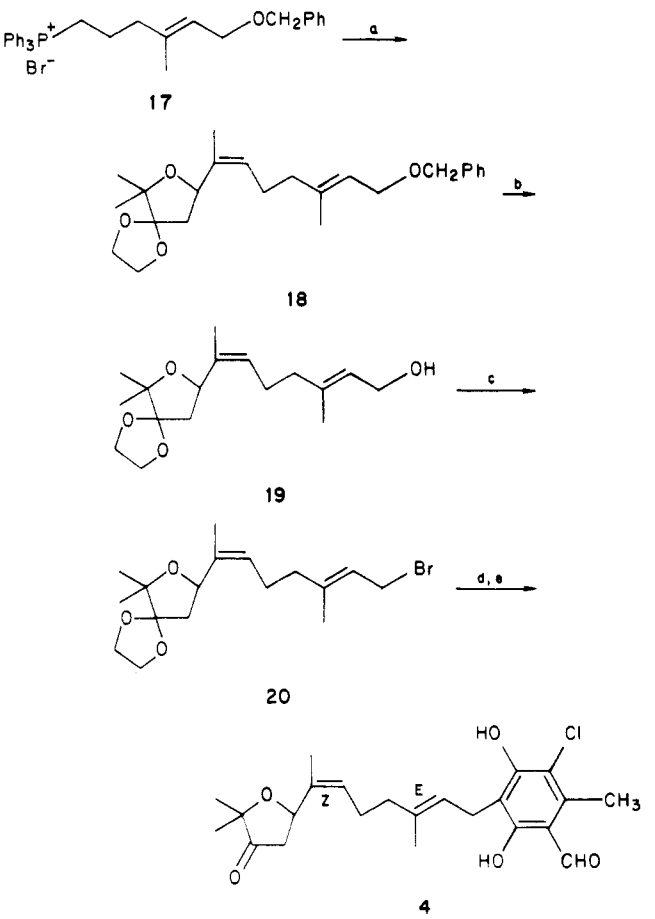
Scheme III[a]



[a] (a) NaH, $PhCH_2Br$; (b) (i) NBS, *t*-BuOH, H_2O, (ii) KOH, H_2O; (c) 3% $HClO_4$, THF, H_2O; (d) $NaIO_4$, THF; (e) $NaBH_4$, MeOH; (f) CBr_4, PPh_3; (g) PPh_3, MeCN, Δ.

corresponding bromide **16** was accomplished with carbon tetrabromide and triphenylphosphine, at 0 °C. Compound

Scheme IV[a]



[a] (a) *t*-AmOK, benzene, **9**; (b) (i) Li, NH_3, THF, −78 °C, (ii) NH_4Cl; (c) CBr_4, PPh_3, CH_2Cl_2, −78 °C; (d) **8**, KOH, H_2O, 0 °C; (e) 35% $HClO_4$, Et_2O.

16 was heated with triphenylphosphine in acetonitrile for 16 h to give the phosphonium salt **17** in 85% yield from **14**. Condensation of **17** with the protected methyl ketone **9** (previously obtained from 3-hydroxy-3-methyl-2-butanone in 76% yield[2,3]) was carried out in the presence of potassium *tert*-amylate, in refluxing benzene, according to the procedure of McMorris and Schow,[13] reported to give high yields of *E*-trisubstituted olefin using unstabilized ylides (Scheme IV). Only one product (**18**) was obtained but ^1H NMR studies (NOE) showed that the double bond formed had the undesired stereochemistry *Z*. Nevertheless, we decided to complete the synthesis to further investigate strategy developed for the alkylation of 5-chloroorsellinaldehyde. Toward this end, benzyl ether **18** was deprotected to give the corresponding alcohol **19** (90% yield) with lithium in liquid ammonia. Compound **19** was converted to the bromide **20** in 93% yield using carbon tetrabromide and triphenylphosphine (−78 °C). Coupling of **20** with 5-chloroorsellinaldehyde in the presence of aqueous potassium hydroxide at 0 °C, under dilute conditions, was followed by deprotection of the ketofuranone to afford a stereoisomer of ascofuranone (**4**) (57% yield for two steps) (Scheme IV).

The infrared spectrum of **4** was almost identical with that of natural ascofuranone. The ^1H NMR spectra of the two compounds, however, showed different chemical shifts

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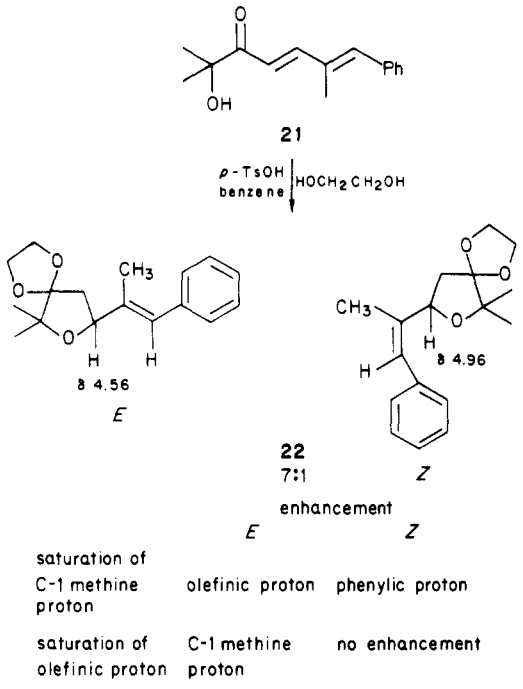
(11) Truce, W. E. "Organic Reactions"; Adams, R., Ed.; Wiley: New York, 1957; Vol. IX, p 37.
(12) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, *3*, 121.
(13) (a) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760. (b) McMorris, T. C.; Schow, S. R. *J. Org. Chem.* **1976**, *41*, 3759.

Scheme V



for the methine protons. To permit assignment of the double bond geometry, **21** was cyclized with ethylene glycol to give a mixture of (*E*)- and (*Z*)-6,6-dimethyl-8-(α-methylstyryl)-1,4,7-trioxaspiro[4.4]nonane (**22**) in a 7:1 ratio. The chemical shifts of the methine protons in these two isomers were observed at δ 4.56 for the *E* isomer and δ 4.96 for the *Z* isomer and were comparable to the chemical shifts of the methine protons in ascofuranone (**2**) and its stereoisomer **4**. In order to establish the configuration of the double bonds in these systems, we separated and isolated these geometrical isomers (Scheme V) and made stereochemical assignments using nuclear Overhauser effects. Saturation of the methine proton resulted in a 25% enhancement of the olefinic proton in the *E* isomer, and enhancement of phenylic protons in *Z* isomer. Additionally, saturation of the olefinic proton resulted in enhancement of the methine proton in the *E* isomer.

Using phosphonium salt **17**, we carried out several Wittig condensations of this compound with **9**, under a variety of conditions, in an effort to obtain an olefin, with *E* geometry. Three different procedures were tried: (1) generation of the ylide with LDA in THF, followed by reaction with **9** at −78 °C; (2) formation of the ylide with dimsyl sodium and reaction with **9** in dimethyl sulfoxide,[14] at 50 °C, for 20 h; (3) generation of the ylide with sodium methoxide and reaction with **9**, a catalytic amount of benzoic acid[15] in THF, at reflux (Scheme VI). The first two conditions afforded a (*Z*)-olefin as the major isomer. The yield of the product was 74%, for procedure 1 and 37% for procedure 2. Procedure 3 gave back the starting ketone. Alternative routes were investigated. The use of diphenylphosphine oxide, generated in situ from the corresponding phosphonium salt had been reported by Warren and co-workers[16] who prepared several di- and trisubstituted alkenes stereoselectively using Wittig–Horner reactions. We, therefore, prepared phosphine oxide **23** from the corresponding phosphonium salt in 92% yield, using aqueous sodium hydroxide at 90–95 °C for 2 h. Treatment of **23** with LDA or *n*-BuLi, in THF, at −78 °C, was followed by addition of **9** as shown in Scheme VI. Only undesired products were obtained. No further attempts were made to characterize these products. We surmised that the benzylic protons, in this case, were more acidic than those adjacent to the phosphine oxide group, therefore, leading to an undesired anion. However, a semistabilized ylide such as the one derived from benzylphosphonium salt **24** was employed in a Wittig reaction with **9** to afford a mixture of (*E*)- and (*Z*)-olefinic ketals **22** in a 2:1 ratio. These geometrical isomers were previously prepared by the cyclization of α-hydroxy dienone **21**. Other stabilized ylides were condensed with the same ketone (**9**). Treatment of ethyl(diethoxyphosphinyl)-acetate (**25**) with sodium hydride in DME, followed by addition of **9** afforded both *E*- and *Z*-conjugated esters **26** and **27** in a 6:1 ratio. These compounds could be separated by column chromatography to give 63–78% yields of *E*-conjugated ester **26**, which was then utilized in the synthesis of **2** (Scheme VII). The new strategy involved the use of a β-keto ester as a synthon. The β-keto ester was converted to an enol phosphate and subsequently coupled with a dialkyl cuprate to yield an olefin.[10] This method developed by Weiler and co-workers[17] has been used widely in the syntheses of natural products containing *E*-trisubstituted alkenes.[18] The utility of this transformation was demonstrated again in the synthesis of **2** (Scheme VII). *E*-Conjugated ester **26** was reduced to an allylic alcohol **28** in an almost quantitative yield by using DIBAL at −78 °C. Treatment of allylic alcohol **28** with carbon tetrabromide and triphenylphosphine gave the corresponding allylic bromide **29** in 95–100% yields. Compound **29** was alkylated with the dianion of methyl acetoacetate generated with sodium hydride and *n*-butyllithium at 0 °C to yield keto ester **30** (86%). Treatment of **30** with sodium hydride, in dry ether, followed by addition of diethyl chlorophosphate gave the (*Z*)-enol phosphate **31** stereoselectively in 90% yield. Subsequent reaction of **31** with lithium dimethylcuprate in ether afforded diene **32** with the desired *E* geometry in 85% yield and >95% stereoselectivity. The desired intermediate **32** was reduced by DIBAL at −78 °C to give the corresponding alcohol **33** in 96% yield. Bromination of **33** with carbon tetrabromide and triphenylphosphine at −78 °C, under nitrogen, afforded the prenylated bromide **34** in 94% yield. Coupling of **34** with **8**, using the same procedure employed in the synthesis of **4**, followed by hydrolysis of the 1,3-dioxolane ring, afforded (±)-ascofuranone in 17% yield (3.3–4.1% from orcinol and 3-hydroxybutanone). The physical and spectroscopic properties of the synthetic compound were identical in all respects with those of the natural product.

The allylic dimethyldihydrofuranone portion of **2** showed an interesting structural similarity to that of another natural product, geiparvarin (**5**), a compound isolated from the leaves of *Geigera parviflora* Lindl[19] and also found in the extracts of the fruit of the same plant.[20] Geiparvarin was reported to have antitumor activity.[21] Our continued interest in functionalized furanones[2,3,22,23]

(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
(15) (a) Ruchardt, C.; Eichler, S.; Panse, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 619. (b) Fliszar, S.; Hudson, R. F.; Salvadori, G. *Helv. Chim. Acta* **1964**, *47*, 159.
(16) (a) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **1979**, 3099. (b) Cornish, C.; Warren, S. *Tetrahedron Lett. 24* **1983**, 2603. (c) Buss, A. D.; Warren, S. *Tetrahedron Lett. 24*, **1983** 111.
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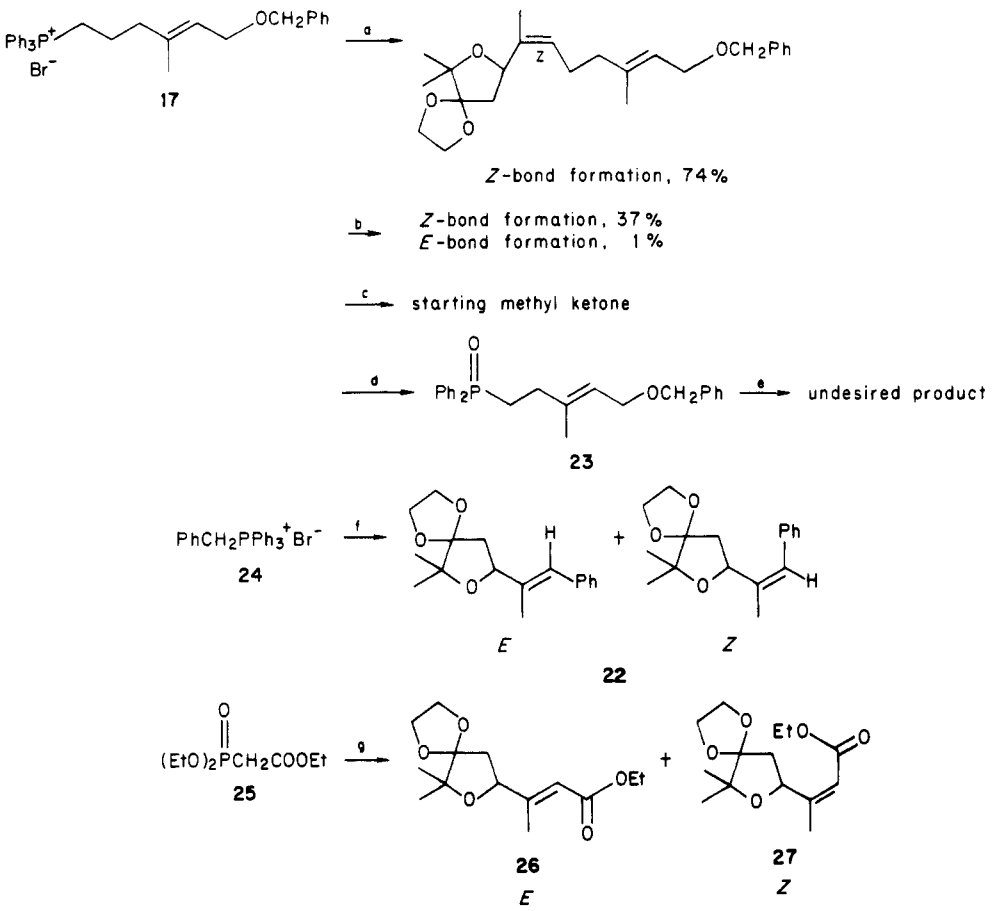
(18) (a) Sum, F. W.; Weiler, L. *J. Chem. Soc., Chem. Commun.* **1978**, 985. (b) Sum, F. W.; Weiler, L. *Tetrahedron Lett.* **1979**, *20*, 707. (c) Sum, F. W.; Weiler, L. *J. Am. Chem. Soc.* **1979**, *96*, 4401.
(19) Lakey, F. N.; MacLeod, J. K. *Aust. J. Chem.* **1967**, *24*, 1943.
(20) Dreyer, D. L.; Lee, A. *Phytochemistry*, **1972**, *11*, 763.
(21) Padmawinata, K. *Acta Pharm.* **1973**, *4*, 1; *Chem. Abstr.* **1973**, *79*, 75897*n*.

Scheme VI[a]



[a] (a) LDA, −78 °C, 9; (b) $Na^+C^-H_2SOCH_3$, Me_2SO, 9, 50 °C, 20 h; (c) NaOMe, CH_2Cl_2, 9, BzOH cat.; (d) NaOH, H_2O, Δ; (e) (i) LDA, THF, or *n*-BuLi, (ii) 9; (f) *t*-AmOK, 9; (g) NaH, DME, 9.

led us to synthesize compound **5** (Scheme VIII). Geiparvarin had already been synthesized by several research groups.[24a-g] Our approach utilized the previously prepared allylic alcohol **28**, which could be converted either to the chloride with *p*-toluenesulfonyl chloride and 4-(*N*,*N*-dimethylamino)pyridine[25] in methylene chloride (72% yield) or to the bromide with carbon tetrabromide and triphenylphosphine under nitrogen, at −60 °C (99% yield). Condensation of either halide with 7-hydroxycoumarin in the presence of potassium carbonate and a catalytic amount of potassium iodide in dimethylformamide–benzene solution at 85 °C afforded the product **37** in 92–93% yields. Hydrolysis of the protecting group followed by column chromatography afforded **38** in 92% yield. Dehydrogenation of the furanone ring was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in benzene, to give **5** in 75% yield. The overall yield of geiparvarin (**5**) from commercially available 3-hydroxy-3-methyl-2-butanone was 22–36%. Our synthesis provided high isolated yields for each step from starting material to product. We have also identified the two carbonyl absorption bands in the infrared spectrum of **5**, the band at 1728 cm^{-1} being assigned to the lactone carbonyl and that at 1685 cm^{-1} to the enone carbonyl group.

Experimental Section

General Methods. ^1H NMR spectra were obtained in designated solvents on a Varian EM-360A (60 MHz), a Bruker WM (250 MHz), or an IBM WP 200SY (200 MHz) Fourier transform spectrometer. High-resolution mass spectra were obtained on a Hitachi–Perkin-Elmer RMH-2 high-resolution, double focusing, electron-impact spectrometer or a vacuum Generator's V.G. 707H spectrometer interfaced with a Kratos DS-50-S data system. Infrared spectra (IR) were obtained on Perkin-Elmer infrared spectrophotometers, Models 137, 281, or 781, as a thin film (neat) on sodium chloride plates, in potassium bromide disks (KBr), or as solution in chloroform ($CHCl_3$) or carbon tetrachloride (CCl_4) in sodium chloride cells.

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at MicAnal Organic Microanalysis, Tucson, AZ. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates (250 μm) with a fluorescent indicator, supplied by E. Merck. Visualization was effected with ultraviolet light (UV) or 7% w/v ethanolic 12-phosphomolybdic acid (PMA). Preparative thin-layer chromatography (PTLC) was performed on precoated silica gel plates (1000 μm) with a fluorescent indicator, supplied by Analtech, Inc. Flash column chromatography was performed on Merck SG-60 (230–400 mesh) silica gel. All solvents used were reagent grade. Anhydrous benzene, 1,2-dimethoxyethane (DME), ether, and tetrahydrofuran (THF) were distilled from sodium and benzophenone; methanol was distilled from magnesium turnings and a small amount of iodine; methylene chloride, hexane, petroleum ether, and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride. Customary/standard workup means that solutions of products

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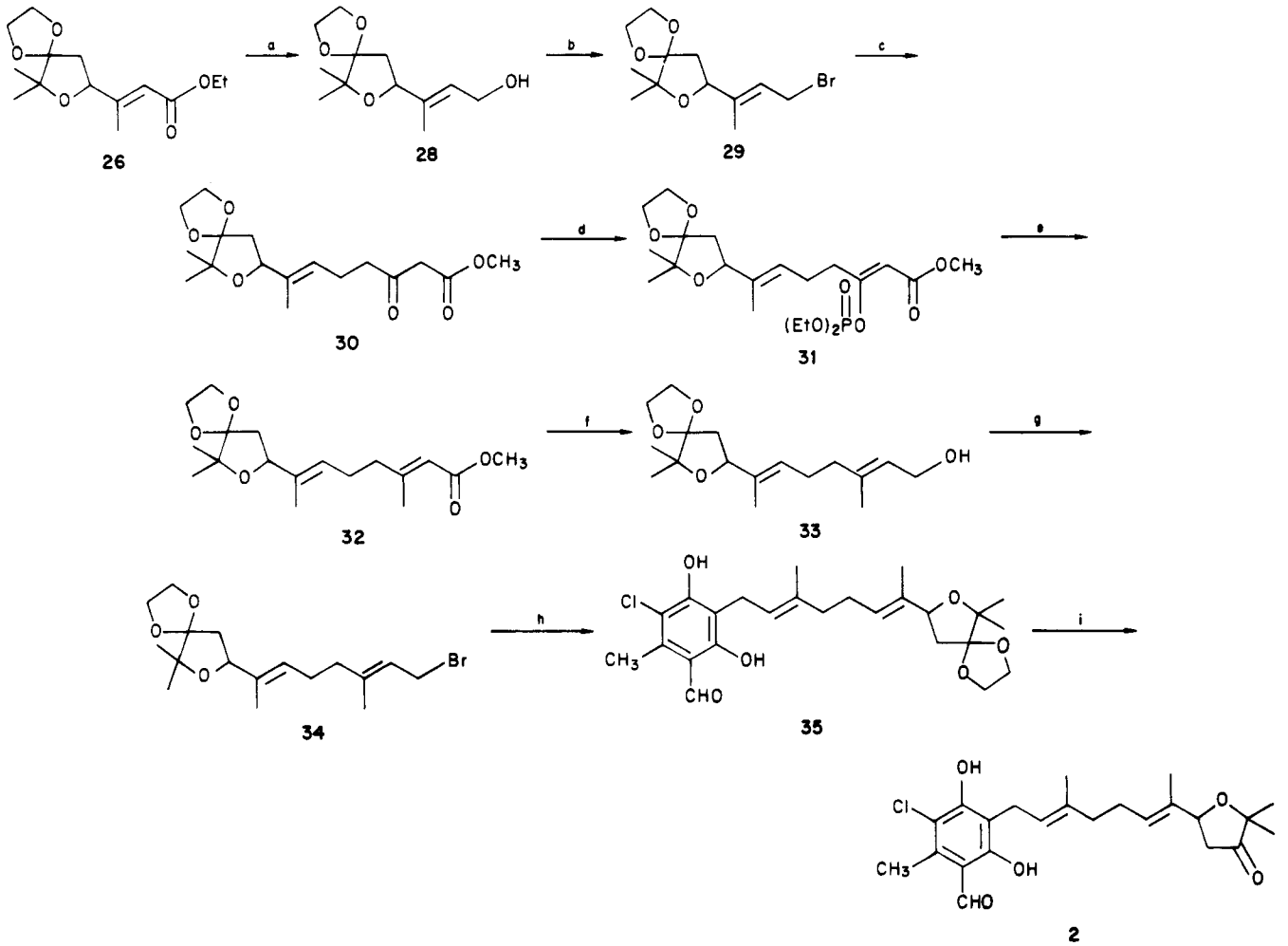
Scheme VII[a]



26 28 29 30 31 32 33 34 35 2

[a] (a) DIBAL, −78 °C; (b) CBr_4, PPh_3, −60 to −20 °C; (c) methyl acetoacetate, NaH, *n*-BuLi, 0 °C; (d) NaH, Et_2O, $ClP(O)(OEt)_2$; (e) Me_2CuLi, Et_2O, −78 °C; (f) DIBAL, −78 °C; (g) CBr_4, PPh_3, −78 °C; (h) **8**, KOH, H_2O, 0 °C; (i) HOAc, H_2O, Δ.

in organic solvents were washed with $NaHCO_3$ or NaOH and/or brine and dried over $MgSO_4$, followed by removal of solvent prior to crystallization or chromatography.

2,4-Dihydroxy-6-methylbenzaldehyde (7). This compound was prepared in 76–85% yield: mp 181–182.5 °C (lit.[11] mp 178–180 °C); IR (KBr) 3100, 1650, 1490 cm^{-1}; ^1H NMR (C_3D_6O, 250 MHz) δ 2.54 (s, 3 H), 6.18 (d, 1 H, J = 2.1 Hz), 6.3 (d, 1 H, J = 2.1 Hz), 9.6 (br, 1 H), 10.1 (s, 1 H), 12.52 (br, 1 H).

5-Chloro-2,4-dihydroxy-6-methylbenzaldehyde (8). Orcinol aldehyde **7** (0.5 g, 3.3 mmol) was dissolved in 60 mL of anhydrous ether at 0 °C. To this solution was added dropwise sulfuryl chloride (freshly distilled, 0.36 mL, 1.25 equiv) dissolved in 15 mL of anhydrous ether. The reaction was stirred at 0 °C for 1.5 h and then at ambient temperature overnight. Customary workup followed by purification by flash column chromatography using 15% ethyl acetate in hexane as the eluant afforded pure product **8** (0.468 g, 75% yield) as a white solid: mp 168–170 °C; IR (KBr) 3000, 1650, 1600 cm^{-1}; ^1H NMR (C_3D_6O, 60 MHz) δ 2.65 (s, 3 H), 6.4 (s, 1 H), 9.7 (br, 1 H), 10.2 (s, 1 H), 12.52 (br, 1 H); high-resolution mass spectrum, M^+ calcd for $C_8H_7O_3Cl$ 186.0083, found 186.0079.

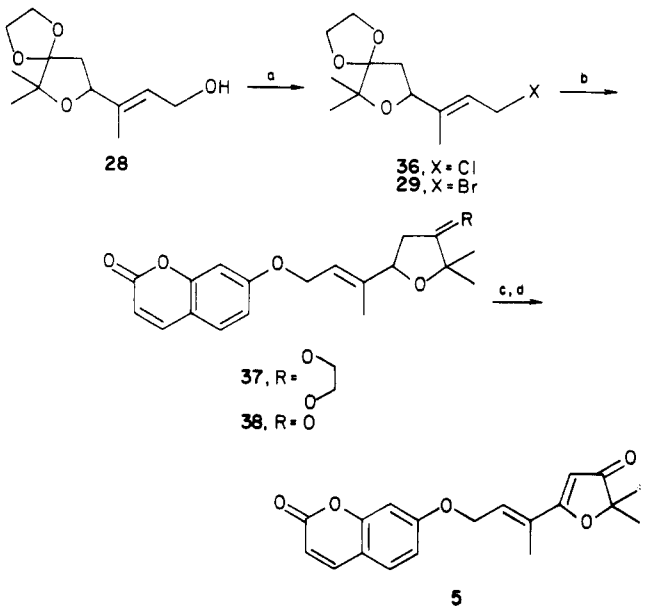
5-Chloro-2,4-dihydroxy-6-methyl-3-(3-methyl-2-butenyl)-benzaldehyde (1). 1-Bromo-3-methyl-2-butene (95.8 mg, 0.64 mmol) was added dropwise to a vigorously stirred, ice-cold solution of 5-chloroorsellinaldehyde (**8**) (100 mg, 5.36 mmol) in 10% aqueous potassium hydroxide (0.26 mL) containing crushed ice. The reaction was followed by TLC for 40 min. The reaction mixture was extracted with ether, washed with 1% HCl, water, and brine, and dried ($MgSO_4$). Concentration of the solvent and flash column chromatography (5% ether in petroleum ether) gave 40 mg of slightly impure **1**, which was purified by preparative TLC using silica gel plates (10% ether in petroleum ether) to give **1** (35 mg, 25% yield). Recrystallization from ether–hexane gave **1** as needles: mp 142–144 °C (lit.[1a] mp 140–142 °C); IR (KBr) 3200, 1650, 1280, 1170, 1100, 905, 795 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.79, 1.69 (2 s, 6 H), 2.6 (s, 3 H), 3.39 (d, 2 H, J = 7.1 Hz), 5.22 (t, 1 H, J = 7.1 Hz), 6.41 (br, 1 H), 10.14 (s, 1 H), 12.69 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.36, 17.79, 22.2, 25.7, 113.3, 113.74, 114.6, 121.05, 133.2, 137.6, 156.4, 162.3, 193.13; high-resolution mass spectrum, M^+ calcd for $C_{13}H_{15}O_3Cl$ 254.07097, found 254.0698.

(*E*)-3,7-Dimethyl-2,6-octadienyl Benzyl Ether (11). This compound was prepared in 92% yield as a colorless liquid: bp 88–93 °C (0.05 mm) [lit.[26] bp 113 °C (0.3 mm)]; IR (neat) 2940, 1660, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.60, 1.64, 1.67 (3 s, 9 H), 2.05 (m, 4 H), 4.03 (d, 2 H, J = 6.6 Hz), 4.5 (s, 2 H), 5.1 (m, 1 H), 5.40 (t, 1 H, J = 6.7 Hz), 7.3 (m, 5 H).

(*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octenyl Benzyl Ether (13). Geranyl benzyl ether **11** (5 g, 0.0205 mmol) was dissolved in 100 mL of *tert*-butyl alcohol and 13.73 mL of water. *N*-Bromosuccinimide (3.79 g, 0.0213 mmol) was introduced into the flask, and the reaction mixture was stirred for 1 h, at which time the bromohydrin (R_f 0.33, 15% ethyl acetate in hexane, UV, PMA) seemed to be the major product as shown by TLC analysis. A solution of potassium hydroxide (2.25 g in 6.6 mL of water) was added to convert the bromohydrin to the epoxide. The formation of epoxide was followed by TLC. Addition of solid NaCl and petroleum ether extraction gave 5.183 g of crude epoxide **12** (R_f

(26) Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915.

Scheme VIII[a]



[a] (a) (i) TsCl, DMAP, CH_2Cl_2, or (ii) CBr_4, PPh_3, CH_2Cl_2; (b) K_2CO_3, KI cat., 7-hydroxycoumarin, DMF, benzene; (c) HOAc, H_2O, Δ; (d) DDQ.

0.46, 15% ethyl acetate in hexane, UV, PMA), which was used immediately without further purification. Crude epoxide **12** was then dissolved in 103 mL of tetrahydrofuran and 68.65 mL of water, and 13.73 mL of 3% perchloric acid was introduced. The reaction was followed by TLC, and the formation of glycol was observed after 0.5–1 h. Addition of solid NaCl and ether extraction gave a crude mixture (6.55 g), which was purified by flash column chromatography using 40% ethyl acetate in hexane to give **13** (3.83 g, 68% yield) as a colorless liquid: IR (neat) 3350, 2890, 1650, 1372, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15, 1.19 (2 s, 6 H), 1.5 (m, 2 H), 1.66 (s, 3 H), 2.2 (m, 2 H); 2.25, 1.98 (m, 2 H, exchangeable with D_2O), 4.02 (d, 2 H, J = 6.7 Hz), 4.50 (s, 2 H), 4.45 (t, 1 H, J = 6.7 Hz), 7.3 (m, 5 H).

(*E*)-4-Methyl-6-(phenylmethoxy)-4-hexenal (14). To a solution of glycol **13** (3.83 g, 1.39×10^{-2} mmol) in 55 mL of tetrahydrofuran and 24.32 mL of water was added sodium periodate (6.082 g, 2.79×10^{-2} mmol). The mixture was stirred for 1 h and followed by TLC to ascertain cleavage of the glycol. Ether (61 mL) and water (30 mL) were added, and the customary workup afforded product **14** (3.04 g, 99% yield) as a light yellow oil: IR (neat) 2800, 1730, 1650, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.66 (s, 3 H), 2.5 (m, 4 H), 4.0 (d, 2 H, J = 6.6 Hz), 4.5 (s, 2 H), 5.42 (t, 1 H, J = 6.5 Hz), 7.34 (m, 5 H), 9.77 (m, 1 H).

(*E*)-4-Methyl-6-(phenylmethoxy)-4-hexen-1-ol (15). In a 250-mL, round-bottomed flask charged with aldehyde **14** (2.89 g, 0.01325 mol) in 60 mL anhydrous methanol was added sodium borohydride (0.38 g, 0.0103 mol), under a nitrogen atmosphere. During the time necessary to dissolve sodium borohydride completely, TLC analysis revealed that the starting material had reacted completely. The excess of sodium borohydride was decomposed with 2% HCl solution; evaporation, addition of water and ether extraction gave **15** (2.90 g, 99.6%), which appeared as one spot on the TLC plate and was used without further purification: IR (neat) 3330, 2850, 1650, 1450, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.42 (br, 1 H), 1.66 (s, 3 H), 1.72 (m, 2 H), 2.11 (m, 2 H), 3.64 (t, 2 H, J = 6.5 Hz), 4.02 (d, 2 H, J = 6.5 Hz), 4.5 (s, 2 H), 5.43 (t, 1 H, J = 6.6 Hz), 7.35 (m, 5 H).

(*E*)-6-Bromo-3-methyl-1-(phenylmethoxy)-2-hexene (16). To a stirred solution of **15** (0.975 g, 4.43 mmol), in 7 mL of anhydrous methylene chloride, was added carbon tetrabromide (1.89 g, 5.69 mmol). The mixture was stirred and cooled to 0 °C, and triphenylphosphine (1.798 g, 6.86 mmol) was added over a period of 10 min. The reaction mixture was stirred at 0 °C for 10 min and allowed to warm to 25 °C. Filtration and evaporation gave a heterogeneous mixture; Ph_3PO was precipitated by addition of ether and petroleum ether in a 1:5 ratio. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (2.5 × 15 cm) using 5% ether in hexane as eluant to afford product **16** (0.983 g, 79% yield). The yields for this reaction varied between 79% and 93%: IR (neat) 2900, 2840, 1670, 1460, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.64 (s, 3 H), 2.1 (m, 4 H), 3.36 (t, 2 H, J = 6.6 Hz), 4.02 (d, 2 H, J = 6.6 Hz), 4.5 (s, 2 H), 5.44 (t, 1 H, J = 6.7 Hz), 7.35 (m, 5 H).

(*E*)-[6-(Benzyloxy)-4-methyl-4-hexen-1-yl]triphenylphosphonium Bromide (17). A mixture of bromo ether **16** (0.983 g, 3.48 mol) and triphenylphosphine (1.385 g, 5.28 mol) in acetonitrile (7 mL), under a nitrogen atmosphere, was refluxed for 14 h and cooled to 25 °C. The solvent was evaporated to afford an oily mixture. Excess Ph_3P was removed by continuously washing the mixture with anhydrous ether and triturating the mixture until a solid precipitated. Ether (10 mL) was added to the solid, and the mixture was kept refrigerated overnight. The phosphonium salt was collected and washed with ether to afford product **17** (1.737 g, 91.6%). Yields for this reaction varied between 91% and 95%: IR ($CHCl_3$) 2954, 1600, 1445, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.54 (s, 3 H), 1.77 (m, 2 H), 2.41 (m, 2 H), 3.86 (m, 2 H), 3.97 (d, 2 H, J = 6.7 Hz), 4.45 (s, 2 H), 5.32 (t, 1 H, J = 6.7 Hz), 7.35 (m, 5 H), 7.6–7.9 (m, 15 H).

(±)-(*Z*,*E*)-8-[1,5-Dimethyl-7-(phenylmethoxy)-1,5-heptadienyl]-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (18). In a 25-mL, one-necked, pear-shaped flask equipped with a stirring bar and reflux condenser were placed phosphonium salt **17** (0.8 g, 1.47 mol) and 2.97 mL of anhydrous benzene. A solution of potassium *tert*-amylate (1 M, 1.476 mL) was added dropwise to this solutin under a nitrogen atmosphere. The resulting deep red solution was stirred and refluxed for 30 min. A solution of methyl ketone **19** (0.295 g, 1.475 mol) dissolved in 3.69 mL of benzene was then introduced dropwise via a syringe, over a period of 10 min. The resulting mixture was refluxed under a nitrogen atmosphere for 14 h, cooled to 25 °C, and diluted with 125 mL of ether. Customary workup afforded 1.12 g of a crude mixture, which was purified by flash column chromatography (2.8 × 15 cm) using 15% ether in petroleum ether as eluant to give product **18** (0.31 g, 54.5%); R_f 0.29 (20% ether in petroleum ether, UV, PMA). The yield of this reaction can be increased to 74% by using 1.1 equiv of LDA in THF: IR (neat) 2900, 1660, 1458, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23, 1.21 (2 s, 6 H), 1.62 (s, 3 H), 1.71 (d, 3 H, J = 1.0 Hz), 2.0 (m, 2 H), 2.1 (m, 4 H), 3.91 (m, 4 H), 4.0 (d, 2 H, J = 6.7 Hz), 4.48 (s, 2 H), 4.9 (dd, 1 H, J = 7.0 Hz, J = 9.5 Hz), 5.27 (t, 1 H, J = 7.2 Hz), 5.38 (t, 1 H, J = 6.7 Hz), 7.35 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.45, 17.66, 22.37, 24.94, 25.62, 39.75, 39.71, 64.91, 65.59, 71.98, 81.41, 116.52, 121.32, 127.41, 127.73, 127.83, 128.27, 134.87, 138.72, 139.67; high-resolution mass spectrum, M^+ calcd for $C_{24}H_{34}O_4$ 386.2457, found 386.2476. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.56; H, 8.87. Found: C, 74.91; H, 8.83.

(±)-(*Z*,*E*)-7-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-3-methyl-2,6-octadien-1-ol (19). To a flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, gas inlet, Claisen adapter, a Dewar condenser cooled with dry ice–acetone, and a plastic stopper under a positive nitrogen atmosphere was introduced 40–50 mL of liquid ammonia which was previously distilled from sodium metal. Ketal ether **18** (489.4 mg, 1.26 mol) in 7.72 mL of anhydrous tetrahydrofuran was added to the ammonia solution via a syringe through the plastic stopper. Lithium metal (26 mg, 3.714 mol, washed with hexane, ethanol, ether) was added through the Claisen adapter to the stirring ammonia solution at −78 °C. Eventually the solution became deep blue in color. After 2.5–3 min, the blue solution was quenched with solid ammonium chloride (900–950 mg) until it became colorless. The solution was diluted with 15 mL of ether. Ammonia was removed under a slow stream of nitrogen, at 25 °C, and the residue was diluted with 70 mL of ether and 15 mL of water. The aqueous layer was extracted with 2 × 60 mL of ether, and the standard workup afforded a crude product, which was purified by flash column chromatography (2.5 × 10 cm) using 40% ether in hexane as the initial eluant and finally using 60% ether in hexane to give the product **19** (0.338 g, 90% yield) as a colorless liquid: IR (neat) 3300, 2900, 1660, 1440, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (br, 1 H), 1.22, 1.23 (2 s, 6 H), 1.67 (s, 3 H), 1.71 (d, 3 H, J = 1.5 Hz), 2.05 (m, 2 H), 2.18 (m, 4 H), 3.97 (m, 4 H), 4.08 (m, 2 H), 4.80 (dd, 1 H, J = 6.6 Hz, J = 9.9 Hz),

5.24 (m, 1 H), 5.35 (t, 1 H, J = 6.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) 16.27, 17.54, 22.36, 25.02, 25.53, 39.37, 39.47, 59.16, 65.04, 71.98, 81.62, 116.56, 124.89, 127.8, 134.95, 138.10; high-resolution mass spectrum, M^+ calcd for $C_{17}H_{28}O_4$ 296.1988, found 296.1999.

(±)-(*E*,*Z*)-8-(7-Bromo-1,5-dimethyl-1,5-heptadienyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (20). To a stirring solution of prenylated alcohol **19** (0.1762 g, 0.595 mol) in 3 mL of anhydrous methylene chloride, at −78 °C, was added carbon tetrabromide (0.253 g, 0.76 mol) in one portion under a nitrogen atmosphere. After the addition of carbon tetrabromide was completed, triphenylphosphine (0.19 g, 0.725 mol) was introduced in the reaction vessel, and the stirring solution was kept under a nitrogen atmosphere. The reaction was stirred between −78 and −60 °C for 3 h and monitored by TLC to completion. The reaction mixture was placed on a silica gel column (1 × 10 cm), and the crude product was obtained by eluting with 16% ether in hexane. Removal of the solvent under reduced pressure gave a colorless oil. The oil was dried at 40–50 °C (0.05 mm) for 5 min to afford pure product **20** (0.2 g, 93% yield): IR (neat) 2900, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.226 (s, 3 H), 1.245 (s, 3 H), 1.715 (s, 6 H), 2.17 (m, 6 H), 3.94 (m, 4 H), 4.02 (d, 2 H, J = 8.4 Hz), 4.89 (dd, 1 H, J = 6.9 Hz, J = 9.5 Hz), 5.25 (m, 1 H), 5.53 (t, 1 H, J = 8.4 Hz); high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{17}H_{27}O_3Br$ 359.1143, found 359.1163.

(±)-(*Z*,*E*)-3-Chloro-4,6-dihydroxy-2-methyl-5-[3-methyl-7-(tetrahydro-5,5-dimethyl-4-oxo-2-furanyl)-2,6-octadienyl]benzaldehyde (4). Prenylated bromide **20** (43 mg, 0.12 mol) was added to a vigorously stirred ice-cold solution of 5-chloro-orsellinaldehyde **8** (18.7 mg, 0.1 mol) dissolved in 3 mL of water, potassium hydroxide (11.3 mg), and crushed ice. The reaction was monitored by TLC over a period of 40 min. The mixture was then extracted with ether, washed with 1% HCl, water and brine, evaporated, and purified by preparative TLC on silica gel plates using 25% acetone in petroleum ether as the eluant to give protected **4** (9 mg, 19.2%). This product was placed in a 10-mL, round-bottomed flask, and 2.4 mL of ether and 1.4 mL of 35% hydrochloric acid solution were introduced into the flask. The reaction mixture was stirred at room temperature for 3–4 h and diluted with 60 mL of ether. Customary workup gave an oil, which was purified by preparative TLC on silica gel using 25% acetone in petroleum ether to afford racemic **4** (4.86 mg, 60% yield): IR ($CHCl_3$) 3505, 2980, 2920, 2850, 1750, 1630, 1460, 1420, 1375, 1325, 1285, 1250, 1200, 1165, 1105, 990, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.247, 1.307 (2 s, 6 H), 1.69 (s, 3 H), 1.77 (s, 3 H), 2.17 (m, 4 H), 2.42 (d, 2 H, J = 8.2 Hz), 2.60 (s, 6 H), 3.38 (d, 2 H, J = 7.1 Hz), 5.05 (t, 1 H, J = 8.6 Hz), 5.20, 5.35 (m, 2 H), 6.56 (s, 1 H), 10.14 (s, 1 H), 12.7 (s, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{23}H_{29}O_5Cl$ 420.1703, found 420.1709.

(*E*)- and (*Z*)-6,6-Dimethyl-8-(α-methylstyryl)-1,4,7-trioxaspiro[4.4]nonane (22). These compounds were prepared in 86.2% yield: bp 115 °C (0.08 mm) [lit.[2,3] bp 136–138 °C (0.1 mm)]: R_f 0.7, 0.66 (ratio E/Z = 6.7/1, 1:3 ethyl acetate–hexane); IR (neat) 2940, 16558 1600 cm^{-1}. Pure (*E*)-**22** and (*Z*)-**22** could be obtained individually by separation from column chromatography with ether–hexane (1:20) as the eluant: ^1H NMR ($CDCl_3$, 250 MHz) δ [(*E*)-**22**] 1.267, 1.288 (2 s, 6 H), 1.86 (s, 3 H), 2.12 (dd, 1 H, J = 9.5 Hz, J = 12.8 Hz), 2.21 (dd, 1 H, J = 6.9 Hz, J = 12.8 Hz), 3.97 (m, 4 H), 4.56 (dd, 1 H, J = 6.9 Hz, J = 9.5 Hz), 6.59 (m, 1 H), 7.28 (m, 5 H), [(*Z*)-**22** 1.185, 1.26 (2 s, 6 H), 1.92 (d, 3 H, J = 1.4 Hz), 2.09 (dd, 1 H, J = 7.1 Hz, J = 12.9 Hz), 2.20 (dd, 1 H, J = 9.2 Hz, J = 12.9 Hz), 3.97 (m, 4 H), 4.96 (dd, 1 H, J = 7.1 Hz, J = 9.2 Hz), 6.47 (m, 1 H), 7.28 (m, 5 H).

Procedure A (LDA as Base). To a solution of phosphonium salt **17** (0.67 g, 0.0012 mol) in 2.6 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere was added LDA (0.00132 mol) at −78 °C. The resulting deep red solution was warmed to 0 °C for 10 min and then was stirred at −78 °C for 10 min, after which time the methyl ketone **9** (0.222 g, 0.0011 mol), dissolved in 3.0 mL of THF, was added dropwise. The reaction mixture was stirred at −78 °C for an additional hour, after which the color changed from red to yellow. The reaction was allowed to warm to room temperature and stirring was continued for 22 h. The resulting mixture was diluted with 100 mL of ether. Customary workup afforded the crude product, which was purified by flash column chromatography to give the diene benzyl ether **18** (0.317 g, 74% yield).

Procedure B (Sodium Dimsyl as Base). Dimsyl sodium (1.9 mL, 0.00158 mol) was added dropwise to a suspension of phosphonium salt **17** (0.7 g, 0.00129 mol) in 1.7 mL of Me_2SO under a nitrogen atmosphere. The reaction mixture turned red and was stirred at 30 °C for 20 min. The methyl ketone **9** (0.232 g, 0.00116 mol) dissolved in 1.6 mL of Me_2SO was introduced into the phosphorane solution. This mixture was stirred at 50 °C for 20 h. The reaction was then poured into 20 mL of ice water, and the mixture was extracted with 2 × 75 mL of ether. Customary workup gave the crude mixture, which was purified by flash column chromatography with ether–hexane (1:9) as the eluant to afford 37% yield of **18** and 1% yield of (*E*,*E*)-diene benzyl ether (based on NMR spectrum analysis).

Procedure C (Sodium Methoxide as Base and Assistance of Benzoic Acid). To a suspension of phosphonium salts **17** (0.7 g, 0.0129 mol), in 2.5 mL of anhydrous methylene chloride was added dropwise sodium methoxide (0.00144 mol, 1.5 mL), at 0 °C, over a period of 5 min. The mixture became yellow-orange color and was stirred for 30 min. The methyl ketone **9** (0.232 g, 0.00116 mol) and benzoic acid (16 mg), dissolved in 2.5 mL of methylene chloride, were introduced into the phosphorane solution. The reaction mixture was stirred at 55 °C for 50 h. However, no product could be found and only starting methyl ketone **9** remained.

(*E*)-6-(Diphenylphosphinyl)-3-methyl-1-(phenylmethoxy)-2-hexene (23). In a 25-mL, pear-shaped flask containing phosphonium salt **17** (3.25 g, 0.00598 mol) and 3.37 mL of water was added sodium hydroxide (1.2 g, 0.03 mol). The reaction mixture was heated at 90–95 °C for 2 h and was monitored by TLC until the reaction was completed. This mixture was cooled to room temperature and then extracted with 3 × 40 mL of $CHCl_3$. The organic layer was washed with a 5% HCl solution and brine and dried ($MgSO_4$). After evaporation, flash column chromatography (50% ethyl acetate in hexane) gave product **23** (2.22 g, 92% yield): IR ($CHCl_3$) 2950, 1600, 1445, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.55 (s, 3 H), 1.75 (m, 2 H), 2.18 (m, 4 H), 4.0 (d, 2 H, J = 6.6 Hz), 4.48 (s, 2 H), 5.37 (t, 1 H, J = 6.6 Hz), 7.38 (m, 5 H), 7.6 (m, 10 H); high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{26}H_{29}O_2P$ 405.1905, found 405.1995.

Wittig–Horner Reaction (Condensation of Diphenylphosphine Oxide 23 and Methyl Ketone 9). Diphenylphosphine oxide **23** (1.47 g, 0.0036 mol) was dissolved in 30 mL of anhydrous THF and was cooled to −78 °C. *n*-Butyllithium (0.875 N, 4.393 mL) was added dropwise to the flask. This mixture was stirred at −78 °C for 0.5 h, and the methyl ketone **9** (0.74 g, 0.0037 mol) in 5 mL of anhydrous THF was introduced dropwise into the solution. The reaction was allowed to warm to room temperature, and saturated ammonium chloride solution (20 mL) and ether (80 mL) were added. After usual workup followed by column chromatography, none of the diastereomeric alcohols were obtained.

Wittig Reaction (Semistabilized Ylide Condensed with Methyl Ketone 9). In the same way as in the preparation of **18**, reaction of benzylphosphonium bromide **24** (0.798 g, 0.0018 mol) in 3.7 mL of benzene, potassium *tert*-amylate (1 M, 1.843 mL), and methyl ketone **9** in 4.6 mL of benzene gave crude product **22**, which was purified by flash column chromatography to afford (*E*)-**22** and (*Z*)-**22** in 70% yield and in a ratio of 2:1. Spectral data for these will be found under the preparatin of **22**.

Ethyl (±)-(*E*) and -(*Z*)-3-(6,6-Dimethyl-1,4,7-trioxaspiro-[4.4]non-8-yl)-2-butenoate (26 and 27). To a stirred suspension of 0.38 g of NaH (1.58 × 10^{-2} mol) washed with 2 × 10 mL of petroleum ether) in 1,2-dimethoxyethane (50 mL) was added ethyl (diethoxyphosphinyl)acetate (2.6 g, 1.16 × 10^{-2} mol) dropwise, at 0 °C. After completion of the addition, the solution was stirred for 2 h until the evolution of gas (H_2) ceased. Ketone **9** (2 g, 1 × 10^{-2} mol) was added slowly to the resulting light yellow solution at a temperature below 10 °C. The reaction mixture was stirred for 3 h, during which time the ketone reacted completely. The reaction mixture was then extracted with ether and dried ($MgSO_4$). Removal of the drying agent followed by removal of the solvent under reduced pressure gave a crude mixture (2.4 g), which was purified by flash column chromatography (2.8 × 17 cm), initially eluting with 9% ethyl acetate in hexane and then with ethyl acetate–hexane (1:5) to afford pure *E* product **26** (1.67 g, 62% yield) and pure *Z* product **27**. **26**: R_f 0.53 (25% ethyl acetate in

hexane, UV, PMA). **27**: R_f 0.59 (25% ethyl acetate in hexane, UV, PMA). Yields for this reaction vary between 62% and 78% for the (*E*)-**26** product: IR (neat) 2950, 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ [**26**] 1.24 (2 s, 6 H), 1.26 (m, 3 H), 1.98 (dd, 1 H, J = 9.6 Hz, J = 12.6 Hz), 2.28 (dd, 1 H, J = 7.0 Hz, J = 12.6 Hz), 2.08 (d, 3 H, J = 1.2 Hz), 3.95 (m, 4 H), 4.16 (q, 2 H, J = 7.1 Hz), 4.4 (m, 1 H), 6.05 (m, 1 H), [**27**] 1.24 (s, 6 H), 1.24 (m, 3 H), 1.868 (m, 1 H), 1.96 (d, 3 H, J = 1.1 Hz), 2.537 (m, 1 H), 3.95 (m, 4 H), 4.12 (q, 2 H, J = 7.1 Hz), 5.67 (m, 2 H). Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.18; H, 8.20. Found: C, 61.93; H, 8.10.

(±)-(*E*)-3-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-2-buten-1-ol (28). Diisobutylaluminum hydride (8.14 mL, 1 M in solution) was added dropwise to an anhydrous methylene chloride solution (12.35 mL) of allylic ester **26** (1 g, 3.7×10^{-3} mol) at −78 °C under a nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred for 1–2 h and was monitored by TLC. A solution of 200 mL of ether and 25 mL of H_2O was introduced into the reaction mixture at −78 °C, and the mixture was allowed to warm up to room temperature. Anhydrous magnesium sulfate was added to remove all the water. The entire mixture was stirred overnight, the solid was collected and washed with 100 mL of ether, and the combined organic layers were evaporated to a crude product (0.87 g), which was purified by flash column chromatography (1.0 × 11 cm) initially eluting with 30% ethyl acetate in hexane and finally with 40% ethyl acetate in hexane to obtain the product **28** in pure form (0.84 g, 100%). The yields for this reaction varied between 95% and 100%: IR (neat) 3400, 2980, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (2 s, 6 H), 1.32 (m, 1 H), 1.67 (s, 3 H), 2.01 (dd, 1 H, J = 9.5 Hz, J = 12.8 Hz), 2.13 (dd, 1 H, J = 6.8 Hz, J = 12.8 Hz), 3.94 (m, 4 H), 4.2 (t, 2 H, J = 6.0 Hz), 4.4 (dd, 1 H, J = 6.9 Hz, J = 9.4 Hz), 5.74 (t, 1 H, J = 6.6 Hz); high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{12}H_{20}O_4$ 229.1362, found 229.1388. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.12; H, 8.83. Found: C, 63.24; H, 9.01.

(±)-(*E*)-8-(3-Bromo-1-methyl-1-propenyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (29). To a solution of the allylic alcohol **28** (0.53 g, 2.33×10^{-3} mol) in 9.5 mL of dry methylene chloride was added freshly sublimed carbon tetrabromide (1.0076 g, 3.035×10^{-3} mol) in one portion under a nitrogen atmosphere at −60 °C. After the addition of carbon tetrabromide, recrystallized triphenylphosphine (0.765 g, 2.92×10^{-3} mol) was introduced into the reaction mixture in five portions, and the stirring temperature was slowly permitted to reach −20 °C over a period of 2–3 h. When the reaction was completed, the reaction mixture was diluted with 2 mL of methylene chloride and placed on a silica gel column (1 × 10 cm). The crude product was eluted with 60 mL of an ether and hexane mixture in a 1:2 ratio. The solvent was evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (2.8 × 8 cm) eluting with ether–hexane (1:6) to obtain product **29** (0.677 g, 99% yield). The yields for this reaction varied between 95% and 99%: IR (neat) 2950, 1650, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22, 1.24 (2 s, 6 H), 1.71 (d, 3 H, J = 1.2 Hz), 1.983 (dd, 1 H, J = 9.5 Hz, J = 12.8 Hz), 2.165 (dd, 1 H, J = 6.9 Hz, J = 12.8 Hz), 3.96 (m, 4 H), 4.02 (d, 2 H, J = 8.6 Hz), 4.4 (dd, 1 H, J = 7.0 Hz, J = 9.2 Hz), 5.88 (t, 1 H, J = 8.5 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 22.32, 24.87, 28.1, 40.3, 65.1, 78.3, 82.04, 116.23, 121.23, 142.5; high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{12}H_{19}BrO_3$ 291.0512, found 291.0491.

(±)-Methyl (*E*)-7-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-3-oxo-6-octenoate (30). To a stirred suspension of sodium hydride (0.12 g of 60% dispersion in mineral oil, 3 mmol), in 7.0 mL of THF (anhydrous, distilled from sodium metal) under a nitrogen atmosphere at 0 °C, was introduced methyl acetoacetate (0.3 g, 2.58 mmol) dropwise. The colorless solution was stirred at 0 °C for 10 min. *n*-Butyllithium (2.71 mL, 1.0 M in hexane) was added dropwise to the monoanion solution. The color of the mixture changed from yellow to orange due to the formation of the dianion. The reaction mixture was stirred at 0 °C for an additional 10 min. The allylic bromide **29** (0.62 g, 2.14 mmol) dissolved in 1.0 mL of tetrahydrofuran was added dropwise to the dianion solution at 0 °C. After completion of the addition, the reaction mixture was allowed to warm slowly to room temperature over a period of 30 min. The reaction mixture was diluted with 60 mL of ether at 0 °C and then with a 10% hydrochloric acid solution to quench the anion. Standard workup gave the crude product (0.855 g), which was purified by flash column chromatography using 20% ethyl acetate in hexane as the eluant to give product **30** (0.596 g, 85.5%): IR (neat) 2975, 1760, 1730, 1665, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21, 1.23 (2 s, 6 H), 1.62 (s, 3 H), 2.03 (m, 2 H), 2.31 (m, 2 H), 2.58 (m, 2 H), 3.44 (s, 2 H), 3.73 (s, 3 H), 3.94 (m, 4 H), 4.36 (m, 1 H), 5.45 (t, 1 H, J = 7.1 Hz); high-resolution mass spectrum, M^+ calcd for $C_{17}H_{26}O_6$ 326.1780, found 326.1722.

(±)-Methyl (*Z*,*E*)-3-[(Diethoxyphosphinyl)oxy]-7-(6,6-dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-2,6-octadienoate (31). A solution of keto ester **30** (0.59 g, 1.81 mmol) in 4 mL of dry ether was added to a suspension of sodium hydride (0.08 g of 60% dispersion in mineral oil, 2 mmol) in 4 mL of anhydrous ether under a nitrogen atmosphere at 0 °C. The mixture was stirred for 20 min at 0 °C, then diethyl phosphorochloridate (0.345 g, 2 mmol) was introduced, and the reaction mixtue was stirred for 1.5 h at room temperature. The reaction was diluted with 50 mL of ether and then quenched with saturated NH_4Cl solution. The organic layer was washed with saturated NH_4Cl solution, $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford a crude mixture, which was purified by flash column chromatography (2 × 10 cm) using 25% ethyl acetate in hexane as the initial eluant followed by 40% ethyl acetate in hexane to give the product **31** (0.708 g, 85% yield). A second reaction using a larger amount of sodium hydride (1.2 equiv) resulted in a better yield (91%): IR (neat) 2980, 1730, 1670, 1440, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21, 1.23 (2 s, 6 H), 1.36 (t, 6 H, J = 7.1 Hz), 1.62 (s, 3 H), 2.04 (m, 4 H), 2.32 (m, 2 H), 2.42 (m, 2 H), 3.69 (s, 3 H), 3.94 (m, 4 H), 4.26 (q, 4 H, J = 7.1 Hz), 4.36 (dd, 1 H, J = 7 Hz, J = 9.2 Hz), 5.35 (s, 1 H), 5.45 (t, 1 H, J = 7 Hz); high-resolution mass spectrum, M^+ calcd for $C_{21}H_{36}O_9P$ 463.2039, found 463.2040.

(±)-Methyl (*E*,*E*)-7-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-3-methyl-2,6-octadienoate (32). A 100-mL, three-necked, round-bottomed flask was charged with anhydrous cuprous iodide (0.248 g, 1.3 mmol) under a nitrogen atmosphere and was flamed both before and after the addition of cuprous iodide and allowed to cool under a stream of nitrogen. Dry ether (4 mL) was added to the flask, and the resulting slurry was stirred at 0 °C in an ice bath. A solution of methyllithium (1.758 mL of a 1.48 M in ether solution) was added dropwise to generate a brown solution of lithium dimethyl cuprate (Me_2CuLi). The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. The cold solution of enol phosphate **31** (0.3 g, 0.65 mmol) in 4 mL ether was introduced dropwise into the solution of Me_2CuLi with a double-ended needle. The reaction mixture was then stirred at −78 °C for 3 h and then slowly warmed to −47 °C over a period of 1 h. The reaction mixture was diluted with 50 mL of ether, and solid ammonium chloride was added to quench the mixture. The solution was filtered through Celite. Standard workup followed by purification by flash column chromatography (1 × 10 cm) using 11% ethyl acetate in hexane gave pure **32** (0.175 g, 83% yield): IR (neat) 2972, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21, 1.23 (2 s, 6 H), 1.62 (s, 3 H), 2.04 (m, 2 H), 2.16 (d, 3 H, J = 1.1 Hz), 2.18 (m, 4 H), 3.68 (s, 3 H), 3.95 (m, 4 H), 4.37 (m, 1 H), 5.45 (m, 1 H), 5.66 (s, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1931.

(±)-7-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-3-methyl-2(*E*),6(*E*)-octadien-1-ol (33). Diisobutylaluminum hydride (0.975 mL, 1 M solution) was added dropwise to ester **32** (143.7 mg, 0.43 mmol) in 2 mL of methylene chloride solution, at −78 °C, under a nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred for 1 h and monitored by TLC. The reaction mixture was diluted with 30 mL of ether, and 3 mL of water was added to it at −78 °C. It was then allowed to reach room temperature. The water was removed ($MgSO_4$). The mixture was stirred for 3 h, the drying agent was removed by filtration, and the filter cake was washed with 30 mL of ether. The combined organic solvents were evaporated under reduced pressure to give a crude mixture, which was purified by flash column chromatography (1 × 13 cm) using 40% ether in hexane as the initial eluant and finally using 40% ethyl acetate in hexane. The prenylated alcohol **33** (126.2 mg) was obtained in 96% yield: IR (neat) 3460, 2990, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21, 1.23 (2 s, 6 H), 1.35 (br, 1 H), 1.61 (s, 3 H), 1.67 (s, 3 H), 2.02 (m, 2 H), 2.1 (m, 4 H), 3.92 (m, 4 H), 4.13 (d, 2 H, J = 6.9

Hz), 4.37 (t, 1 H, J = 8.2 Hz), 5.39–5.48 (m, 2 H); high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{17}H_{28}O_4$ 297.1988, found 297.2052.

(±)-8-(7-Bromo-1,5-dimethyl-1(*E*),5(*E*)-heptadienyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (34). To a stirring solution of allylic alcohol **33** (125 mg, 0.42 mmol) in 2 mL of anhydrous methylene chloride, at −78 °C, was added carbon tetrabromide (182 mg, 0.55 mmol) in one portion, under a nitrogen atmosphere. After the addition of carbon tetrabromide, triphenylphosphine (139 mg, 0.53 mmol) was introduced in the reaction vessel. The reaction was stirred between −78 and −60 °C for 3 h and monitored by TLC until the reaction was completed. The reaction mixture was placed on a silica gel column (1 × 8 cm), and the crude product was obtained by eluting with 16% ether in hexane. Removal of the solvent under reduced pressure gave the concentrated mixture, which was purified by flash column chromatography using 10% ether in hexane as eluant to afford the prenylated bromide **34** (144.2 mg, 94% yield): IR (neat) 2990, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22, 1.24 (2 s, 6 H), 1.616 (s, 3 H), 1.72 (d, 3 H, J = 1.2 Hz), 2.03 (m, 2 H), 2.11 (m, 4 H), 3.95 (m, 4 H), 4.01 (d, 2 H, J = 8.5 Hz), 4.37 (m, 1 H), 5.45–5.46 (m, 2 H); high-resolution mass spectrum (CI), $M^+ + 1$ calcd for $C_{17}H_{27}O_3Br$ 359.1143, found 359.1120.

(±)-(*E*,*E*)-3-Chloro-5-[7-(6,6-dimethyl-1,4,7-trioxaspiro-[4.4]non-8-yl)-3-methyl-2,6-octadienyl]-4,6-dihydroxy-2-methylbenzaldehyde (35). Prenylated bromide **34** (35.8 mg, 0.1 mmol) was added to a vigorously stirred ice-cold solution of 5-chloroorsellinaldehyde **8** (17.71 mg, 0.095 mmol) dissolved in 3 mL of water and KOH (10.5 mg) and crushed ice. The reaction was monitored by TLC over 40 min. The mixture was extracted with 60 mL of ether and the ether layer was washed with 10 mL of 1% HCl solution, 2 × 10 mL of water, and 1 × 10 mL of saturated sodium chloride solution. The solvent was removed under reduced pressure, and the crude mixture was purified by preparative TLC on silica gel plates using 25% acetone in petroleum ether as eluant to afford product **35** (11.5 mg, 26%): IR ($CHCl_3$) 3503, 2995, 2925, 2880, 1630, 1460, 1420, 1370, 1280, 1250, 1140, 1105, 1020, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21, 1.20 (2 s, 6 H), 1.58 (s, 3 H), 1.77 (s, 3 H), 2.00 (m, 2 H), 2.15 (m, 4 H), 2.6 (s, 3 H), 3.38 (d, 2 H, J = 7 Hz), 3.94 (m, 4 H), 4.34 (t, 1 H, J = 8.1 Hz), 5.2 (t, 1 H), 5.4 (t, 1 H), 6.53 (s, 1 H), 10.13 (s, 1 H), 12.68 (s, 1 H).

(±)-(*E*,*E*)-5-Chloro-2,4-dihydroxy-6-methyl-3-[7-(3,3-dimethyl-4-oxo-2-oxacyclopentyl)-3,7-dimethyl-2,6-heptadienyl]benzaldehyde (2). Into a 15-mL, pear-shaped flask equipped with a magnetic stir bar and a refluxing condenser was placed ketal **35** (11.5 mg, 0.0247 mmol), 0.8 mL of acetic acid, and 0.4 mL of water. The mixture was stirred and heated at 120 °C for 10 min. It was then cooled to room temperature and diluted with ether. Standard workup gave a viscous oil, which was purified by preparative TLC on silica gel using 25% acetone in petroleum ether to afford racemic product **2** (7.3 mg, 70% yield) as a white solid: mp 89–92 °C; IR ($CHCl_3$) 3505, 2998, 2960, 2916, 2850, 1750, 1630, 1450, 1410, 1365, 1280, 1240, 1165, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22, 1.28 (2 s, 6 H), 1.628 (s, 3 H), 1.786 (s, 3 H), 2.01–2.09 (m, 2 H), 2.1–2.2 (m, 2 H), 2.34 (dd, 1 H, J = 9.5 Hz, J = 18.15 Hz), 2.43 (dd, 1 H, J = 6.8 Hz, J = 18.15 Hz), 2.6 (s, 3 H), 3.38 (d, 2 H, J = 7.1 Hz), 4.54 (dd, 1 H, J = 6.8 Hz, J = 9.5 Hz), 5.2 (t, 1 H, J = 7.2 Hz), 5.5 (t, 1 H, J = 6.9 Hz), 6.44 (s, 1 H), 10.14 (s, 1 H), 12.7 (s, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{23}H_{29}O_5Cl$ 420.1703, found 420.1707 [M^+: $M^+ + 2$ = 2.85:1].

(±)-(*E*)-8-(3-Chloro-1-methyl-1-propenyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (36). To a solution of allylic alcohol **28** (105 mg, 4.63 × 10^{-3} mmol) and DMAP (108 mg, 9.2 × 10^{-4} mmol) in anhydrous methylene chloride (2 mL) was added, at 0 °C, *p*-toluenesulfonyl chloride (110 mg, 5.78 × 10^{-4} mmol). The reaction mixture was stirred at room temperature and followed by TLC. The reaction took 2–3 h, after which time the solution was diluted with 60 mL of ether and was washed with 2 × 7 mL of saturated copper sulfate solution and 2 × 10 mL of brine. The organic layer was dried ($MgSO_4$) and the solution filtered after removal of the drying agent. The solvent was evaporated to give product **36** (82 mg, 72%), which was used in the next step without purification. The ^1H NMR showed the presence of a small amount of *p*-toluenesulfonyl chloride: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.23 (s, 6 H), 1.71 (d, 3 H, J = 1.1 Hz), 2.0 (dd, 1 H, J = 9.5 Hz, J = 12.7 Hz), 2.16 (dd, 1 H, J = 6.9 Hz, J = 12.7 Hz), 3.95 (m, 4 H), 4.10 (d, 2 H, J = 8.1 Hz), 4.41 (dd, 1 H, J = 7.0 Hz, J = 9.5 Hz), 5.79 (t, 1 H, J = 8 Hz).

(±)-(*E*)-7-[[3-(6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl)-2-butenyl]oxy]-2*H*-1-benzopyran-2-one (37). To the allylic chloride **36** (82 mg, 3.34 × 10^{-4} mmol), 7-hydroxycoumarin (44.1 mg, 2.72 × 10^{-4} mmol), potassium carbonate (92 mg, 6.7 × 10^{-4} mmol) and potassium iodide (5 mg) were added 1.2 mL of anhydrous DMF and 1.2 mL of anhydrous benzene. The mixture was stirred and heated at 85 °C for 3 h and cooled and the solution then diluted with 50 mL of chloroform. Customary workup gave a crude mixture, which was purified by flash column chromatography (1 × 10 cm) initially eluting with chloroform following with elution with 20% and 30% ethyl acetate in hexane and finally with 40% ethyl acetate in hexane to afford **37** (94.4 mg, 93.2% yield).

Preparation of 37 from 29. To the allylic bromide **29** (0.263 g, 9.07 × 10^{-4} mmol), 7-hydroxycoumarin (0.121 g, 7.49 × 10^{-4} mmol), potassium carbonate (0.255 g, 1.84 × 10^{-3} mmol), and potassium iodide (14 mg) were added 3.4 mL of benzene and 3.4 mL of DMF. The mixture was stirred and heated at 85 °C for 3 h. The reaction mixture was worked up and purified as described in the previous section to give **37** (253.8 mg, 91.5%): IR (neat) 2980, 1730, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.24 (2 s, 6 H), 1.75 (s, 3 H), 2.02 (dd, 1 H, J = 9.4 Hz, J = 12.7 Hz), 2.188 (dd, 1 H, J = 6.9 Hz, J = 12.7 Hz), 3.95 (m, 4 H), 4.45 (dd, 1 H), 4.64 (d, 2 H, J = 6.3 Hz), 5.84 (t, 1 H, J = 6.3 Hz), 6.24 (d, 1 H, J = 9.4 Hz), 6.81 (dd, 1 H), 6.85 (d, 1 H, J = 2.4 Hz), 7.35 (d, 1 H, J = 8.4 Hz), 7.63 (d, 1 H, J = 9.5 Hz); high-resolution mass spectrum, M^+ calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1585.

(±)-(*E*)-7-[[3-(Tetrahydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butenyl]oxy]-2*H*-1-benzopyran-2-one (38). Into a 25-mL, pear-shaped flask containing a magnetic stir bar and fitted with a reflux condenser were introduced ketal **37** (94 mg, 2.52 × 10^{-4} mmol), 3 mL of acetic acid, and 1.5 mL of water. The mixture was stirred, refluxed for 0.5 h, cooled to 25 °C, and then diluted with chloroform. Standard workup afforded an oil, which was purified by flash column chromatography (1 × 11 cm) using chloroform as the initial eluant and followed by elution with 25% ethyl acetate in hexane to give **38** (76 mg, 91.7% yield) as a viscous yellow oil: IR ($CHCl_3$) 3010, 1750, 1728, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) 1.25, 1.33 (2 s, 6 H), 1.81 (s, 3 H), 2.44 (dd, 1 H, J = 10.2 Hz, J = 18.2 Hz), 2.65 (dd, 1 H, J = 6.3 Hz, J = 18.2 Hz), 4.63 (m, 1 H), 4.68 (d, 2 H, J = 6.3 Hz), 5.91 (t, 1 H, J = 6.2 Hz), 6.26 (d, 1 H, J = 9.5 Hz), 6.82 (m, 1 H), 6.86 (d, 1 H, J = 2.3 Hz), 7.38 (d, 1 H, J = 8.3 Hz), 7.64 (d, 1 H, J = 9.5 Hz); high-resolution mass spectrum, M^+ calcd for $C_{19}H_{20}O_5$ 328.1311, found 328.1298.

7-[[3-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl-2(*E*)-butenyl]oxy]-2*H*-1-benzopyran-2-one (5). Into a 25-mL, pear-shaped flask containing a magnetic stirring bar and fitted with a reflux condenser were placed **38** (72 mg, 2.2 × 10^{-4} mmol), DDQ (100 mg, 4.4 × 10^{-4} mmol), and 2.5 mL of benzene. The reaction mixture was refluxed for 6 h and then heated at 80 °C for another 3 h. The solvent was evaporated, and the crude mixture was purified by flash column chromatography using 25% ethyl acetate in hexane as eluant and finally using 40% ethyl acetate in hexane to afford pure **5** as a white solid (53.5 mg): mp 159–160 °C (lit.[19] mp 160–161 °C); 75% yield; IR ($CHCl_3$) 3009, 1728, 1699, 1653, 1616, 1562, 1508, 1475, 1406, 1381, 1365, 1279, 1232, 1201, 1174, 1159, 1124, 1016, 837, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.41 (s, 6 H), 2.03 (d, 3 H, J = 1.0 Hz), 4.84 (d, 2 H, J = 5.9 Hz), 5.63 (s, 1 H), 6.28 (d, 1 H, J = 9.4 Hz), 6.75 (t, 1 H, J = 5.85 Hz), 6.88 (dd, 1 H, J = 2.5 Hz, J = 8.5 Hz), 6.83 (d, 1 H, J = 2.5 Hz), 7.41 (d, 1 H, J = 8.6 Hz), 7.66 (d, 1 H, J = 9.5 Hz); high-resolution mass spectrum, M^+ calcd for $C_{19}H_{18}O_5$ 326.1154, found 326.1157.

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