resolution mass spectrum, calcd for $C_{18}H_{26}O_5$ m/e 322.178 02, found 322.178 99.

Acknowledgment. Financial support from the National Cancer Institute Grant No. 5-RO1-CA 18888 and 5-T32-CA 09112) is gratefully acknowledged.

Registry No. (±)-**1**, 73414-46-7; (±)-**3**, 73465-88-0; (±)-**4**, 73543-06-3; (±)-**7**, 81478-04-8; (±)-**8**, 73414-37-6; (*R**,*R**)-(±)-**9**, 81478-05-9; (*R**,*S**)-(±)-**9**, 81478-06-0; (*R**,*R**)-(±)-**10**, 73461-13-9; (*R**,*S**)-(±)-**10**, 73414-47-8; (*R**,*R**)-(±)-**11**, 81478-07-1; (*R**,*S**)-(±)-**11**, 81478-08-2; **12**, 81478-09-3; *cis*-(±)-**13**, 81478-10-6; *trans*-(±)-**14**, 73414-39-8; **15**, 73414-40-1; *trans*-(±)-**16**, 73414-41-2; *cis*-(±)-**17**, 81520-67-4; **18**, 81478-11-7; **18** C-3b allylic alcohol (isomer 1), 81478-12-8; **18** C-3b allylic alcohol (isomer 2), 81496-97-1; (±)-**19**, 81478-13-9; *trans*-(±)-**20**, 73414-42-3; *cis*-(±)-**20**, 81478-14-0; *trans*-(±)-**21**, 81478-15-1; *trans*-(±)-**22**, 73414-43-4; (±)-**23**, 73414-44-5; (±)-**24**, 73414-45-6; (±)-**25**, 81478-16-2; **26**, 70329-57-6; **27**, 81520-68-5; **28**, 81520-69-6; tetrahydropyran-4-carboxylic acid, 5337-03-1; (±)-2-(β-bromoethyl)butyrolactone, 81478-17-3.

Synthetic Studies of Fungal Metabolites: Ascofuranone and Colletochlorin D

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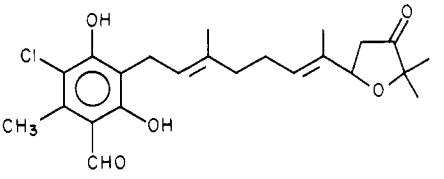
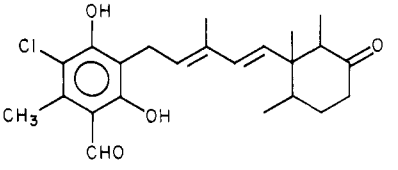
Procedures have been developed for the synthesis of hexasubstituted aromatic rings which are present in many fungal metabolites such as ascofuranone and colletochlorin D. (3-Bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde was synthesized from orcinol in eight steps. This aldehyde was converted to 2-bromo-6-chloro-3,5-dimethoxy-4-(3-methyl-2-butenyl)toluene which was subsequently formylated to afford 3-chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde. Although various demethylation procedures were tried, demethylation of both methoxy groups could not be accomplished. In our attempts to synthesize ascofuranone, (3-bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde was treated with isopropenylmagnesium bromide to afford an unstable allylic alcohol which was immediately subjected to the conditions of the "orthoacetate Claisen rearrangement" to give 2-bromo-6-chloro-4-[(*E*)-5-(ethoxycarbonyl)-3-methyl-2-pentenyl]-3,5-dimethoxytoluene. This compound was then converted to 2-bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-2-hexenyl-6-(triphenylphosphonio)-hex-2-enyl]toluene bromide in three steps. All attempts to carry out a Wittig reaction between this compound and 6,6-dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl methyl ketone failed. Other coupling methods were equally unsuccessful.

As part of our continuing interest in reduced furan natural products,[1-3] we have examined the synthesis of some fungal metabolites such as ascofuranone (**1**, Chart I). This compound has shown potent hypolipidemic and hypotensive activity,[4-14] and its biological properties have been studied extensively since it was isolated by Ando and co-workers in 1972.[4] An important feature of **1** is the hexasubstituted aromatic ring which is a common feature in several other fungal metabolites such as ascochlorin (**2**),[15-17] the LL-Z1272 series,[18,19] and the colletochlorins (**3**).[20-23] During the course of this investigation we also became interested in the synthesis of colletochlorin D, with

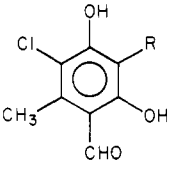
Chart I

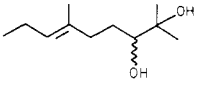


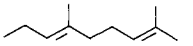
1

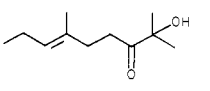


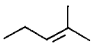
2



3a, R = 

b, R = 

c, R = 

d, R = 

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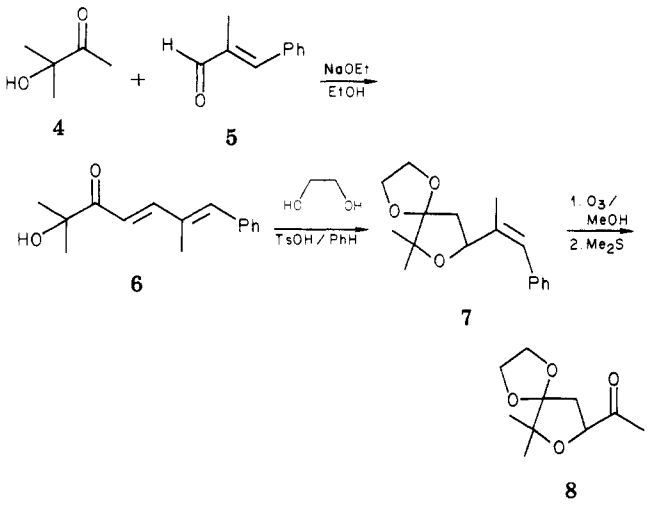
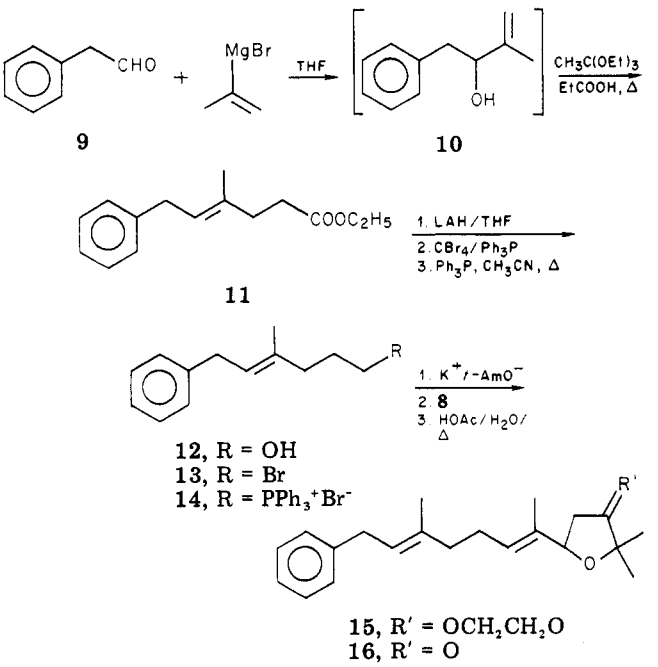
0022-3263/82/1947-2369$01.25/0

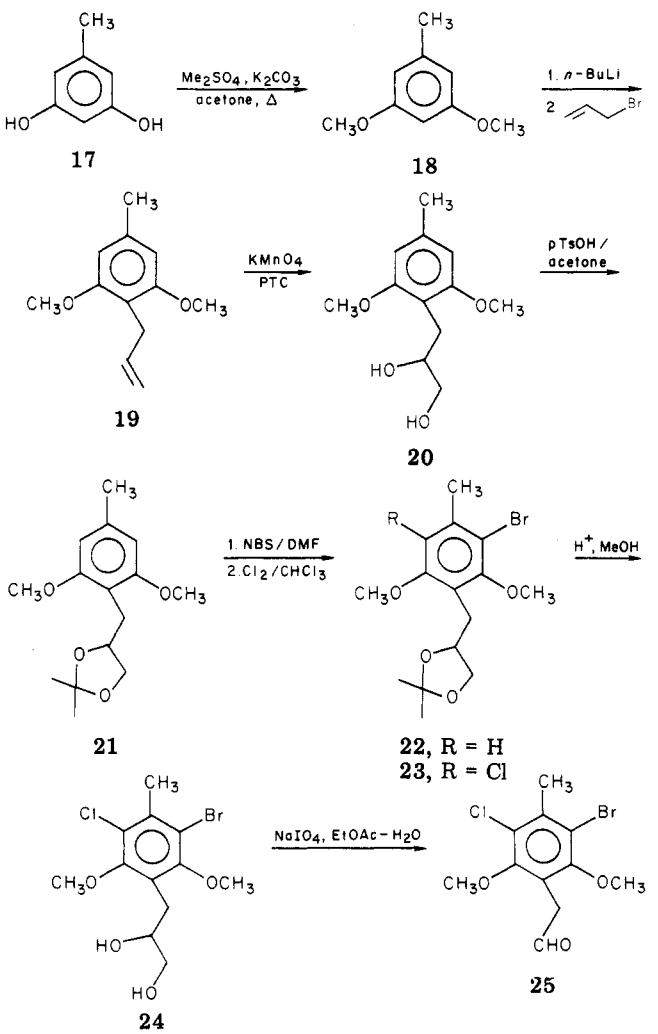
Scheme I



Scheme II



Scheme III



the synthesis of other fungal metabolites in mind.

In our first retrosynthetic analysis of 1, we divided the ascofuranone molecule into three portions, the aromatic ring, the chain, and the furanone moieties. Our first target was the methyl ketone, 6,6-dimethyl-1,4,7-trioxaspiro-[4.4]non-8-yl methyl ketone (8), which was synthesized from acyclic precursors (Scheme I). Many procedures were available for the synthesis of substituted furanones,[24] but we sought a procedure which utilized readily available starting materials and which would afford the protected furanone needed for the subsequent step. Therefore, we developed the procedure shown in Scheme I utilizing an acid-catalyzed cyclization in the presence of ethylene glycol and in refluxing benzene. The protected furanone was obtained in higher yields than had been previously reported.[25] Our procedure is amenable to the synthesis of several different furanones[25] and represents a novel synthesis of substituted furanones. Treatment of 7 with O_3/MeOH/−78 °C followed by quenching with Me_2S gave our target compound (8) in 76% overall yield from the starting material (4). With the furanone portion in hand, we turned our attention to the synthesis of the chain portion of ascofuranone.

Model studies were carried out by using phenylacetaldehyde (9) as the aromatic portion of the molecule (Scheme II). Phenylacetaldehyde was treated with isopropenylmagnesium bromide to afford an unstable allylic alcohol (10). This alcohol was used without purification and treated with triethyl orthoacetate and propanoic acid at 140 °C under the conditions of the "orthoacetate Claisen rearrangement"[26-30] to give the corresponding ester 11 in 51% overall yield. Compound 11 was converted to the phosphonium salt 14, which was then used in a Wittig

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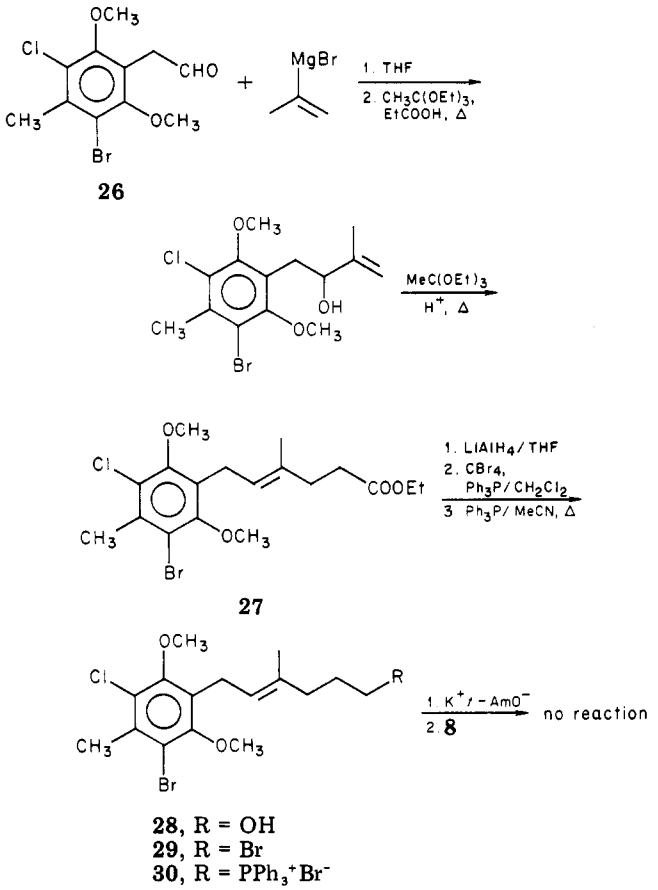
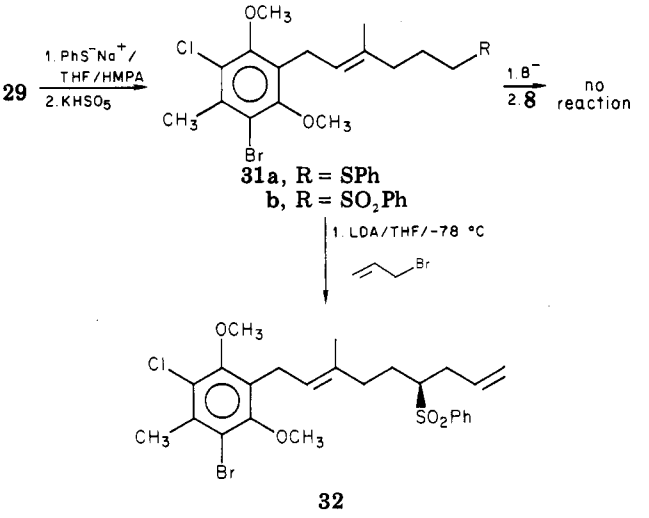
Scheme IV



reaction with the methyl ketone 8. The phosphonium salt was treated with potassium *tert*-amylate in refluxing benzene, followed by the addition of the methyl ketone according to the procedure of McMorris and Schow[31,32] which was reported to give high yields of *E* trisubstituted olefins. This procedure afforded the diene **15** in 54% yield. Hydrolysis of the ketal in acetic acid and water at reflux generated the ascofuranone model **16** in 77% yield, contaminated with approximately 20% of the *Z* isomer.

Once the synthesis of the model was completed, we then attempted the synthesis of the fully substituted aromatic ring. Our first target was the phenylacetaldehyde derivative (3-bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde (**24**) which was synthesized from orcinol (**17**) in 33% overall yield (Scheme III). The use of the bromo substituent as a "masked" aldehyde was necessary since we had not been able to protect an aldehyde group in this particular position. The halogen proved to be an excellent precursor for the aldehyde group. Compound **18** was alkylated by treatment with *n*-butyllithium followed by reaction with allyl bromide to give **19** in 60% yield. The olefin was then converted to the diol **20** which was protected as its acetonide **21**. Bromination with NBS in DMF at room temperature[33] afforded the monobromo compound **22** in 92% yield. Chlorination was effected by treatment of **22** with chlorine in chloroform and pyridine. The acetonide was then hydrolyzed, and the diol was oxidized to the aldehyde **25**. Compound **25** was then subjected to the conditions used in the model study (Scheme IV). We had

Scheme V



been concerned about the effect of substituents on the aromatic ring in modifying the outcome of the reactions in the proposed scheme. These anticipated problems did not occur until we attempted the partial coupling via the Wittig reaction. This reaction was tried under many conditions with different bases and temperatures, but the desired product was never obtained. As we first suspected that the ketone might be hindered, we attempted to condense **28** with a more reactive aldehyde. Again, no reaction could be observed. It is possible that the presence of the electron-withdrawing substituents on the aromatic ring sufficiently activates the benzylic position so that the base instead of forming an ylide generates an anion in the benzylic position. The use of 2 equiv of base, however, still did not afford the desired product. We then sought a different approach to form the desired olefin.

The use of sulfone-stabilized anions has been found to be successful in the synthesis of many unsaturated products[34,35] and seemed most compatible with the aromatic substituents (Scheme V). Compound **29** was treated with sodium thiophenoxide in THF and HMPA to give the sulfide which was then oxidized to the sulfone by using potassium hydrogen persulfate.[36] The sulfone was treated with a base, and the methyl ketone **8** was added. Only starting material was recovered. Although this reaction is reported to be suitable for ketones,[34] it appears that with readily enolizable ketones the sulfone anion acts as a base instead of a nucleophile. Therefore, the enolate anion of the ketone is formed, and the reaction stops. To ascertain the formation of the sulfone anion, we attempted its alkylation. Alkylation of the anion of **28** with allyl bromide proceeded smoothly to afford **32** in 55% yield.

Although further work needs to be carried out on these coupling reactions, a more practical synthesis would involve building of the chain from the furanone portion of the molecule rather than the aromatic part. It has been shown that reactions with the phenylacetaldehyde derivative **25** occur readily; therefore, the final linking at that position should be successful.

During the course of our investigation of ascofuranone we also looked at the synthesis of colletochlorin D (Scheme VI). Compound **24** reacted readily with the ylide generated from isopropyltriphenylphosphonium bromide to give the corresponding alkene **33** in 72% yield. Treatment of

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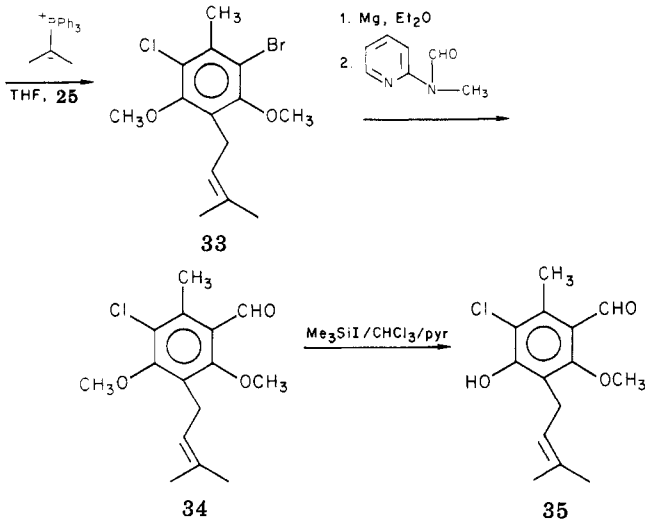
Scheme VI



33 with magnesium in refluxing ether to form the Grignard reagent followed by addition of the organomagnesium compound to a solution of 2-(formylmethylamino)pyridine according to Meyers' procedure[37] afforded the aldehyde **34** in 56% yield. Although many different reagents were tried, only one of the phenolic groups could be deprotected. Treatment of **34** with trimethylsilyl iodide in chloroform and pyridine for 4 days gave **35** in 31% yield.

We have developed new methods for the synthesis of functionalized furanones and for the synthesis of hexasubstituted aromatic rings. We are pursuing these investigations to complete the synthesis of both ascofuranone and colletochlorin D.

Experimental Section

General Methods. ^{1}H NMR spectra were obtained on Varian A-60 (60 MHz), Varian EM-360A (60 MHz), Varian HR-220 (220 MHz), Bruker WP-250 (250 MHz), and Bruker WH-360 (360 MHz) NMR spectrometers. High-resolution mass spectra were obtained on an 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 were recorded on a Perkin-Elmer 137 infrared spectrophotometer as a thin film (neat) on sodium chloride plates, in potassium bromide disks (KBr), or as solutions 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 Robertson Laboratory, Florham Park, NJ. 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 or 7% w/v ethanolic 12-molybdophosphoric acid. Column chromatography utilized Merck SG-60 (70–230 mesh) silica gel. Medium-pressure liquid chromatography (MPLC) and flash column chromatography employed columns filled with Merck SG-60 (230–400 mesh) silica gel. Tetrahydrofuran and ether were predried over sodium ribbon and distilled from sodium metal under a nitrogen atmosphere, with benzophenone ketyl as the indicator. *N,N*-Dimethylformamide was distilled from calcium hydride.

(*E,E*)-2-Hydroxy-2,6-dimethyl-7-phenyl-4,6-heptadien-3-one (6). Into a 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel, and calcium chloride drying tube were placed 3-hydroxy-3-methyl-2-butanone (0.03966 mol, 4.05 g, 4.17 mL), α-methylcinnamaldehyde (0.1190 mol, 17.40 g, 16.6 mL), and 75 mL of absolute ethanol. The mixture was stirred and cooled to 0 °C and a solution of sodium metal (0.0396 mol, 0.912 g) in 25 mL absolute ethanol was added to it at such a rate as to maintain the temperature below 5 °C. The mixture was stirred at 0 °C for 5 h, refrigerated at 0 °C for 17 h, and finally neutralized with concentrated hydrochloric acid (12 N, 3.31 mL). Removal of solvent in vacuo gave an oil which was purified by column chromatography (4 × 45 cm), initially eluting with methylene chloride and finally with ethyl acetate–petroleum ether (85:15). Evaporation of solvent in vacuo afforded 8.139 g (89.1% yield) of **6** as a viscous yellow oil: bp 140–142 °C (0.06 torr); IR (neat) 3390, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.41 (s, 6 H), 2.70 (d, 1 H), 3.97 (s, 1 H), 6.56 (d, 1 H), 6.95 (m, 1 H), 7.33 (br s, 5 H), 7.66 (d, 1 H). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.01; H, 7.89.

(*E*)- and (*Z*)-6,6-Dimethyl-8-(α-methylstyryl)-1,4,7-trioxaspiro[4.4]nonane (7). Into a 250-mL round-bottomed flask equipped with a Dean–Stark trap, a reflux condenser, and a magnetic stirring bar were placed (*E,E*)-2-hydroxy-2,6-dimethyl-7-phenyl-4,6-heptadien-3-one (**6**; 15.0 mmol, 3.45 g), ethylene glycol (75.0 mmol, 4.66 g), and 150 mL of benzene. *p*-Toluenesulfonic acid monohydrate (15.0 mmol, 2.85 g) was added to the mixture, and the reaction mixture was stirred and refluxed for 10 h. After being cooled to 23 °C, the mixture was washed with portions of saturated sodium bicarbonate solution (2 × 150 mL), portions of water (2 × 150 mL), and one portion of saturated sodium chloride solution (150 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave an oil which was purified by MPLC with ethyl acetate–petroleum ether (1:9) as the eluent. Evaporation of solvent gave **7**: 3.63 g (88.3% yield); bp 136–138 °C (0.10 torr); R_f 0.65, 0.60 (ratio ca. 1:9, ethyl acetate–hexane, 1:3); IR (neat) 1655, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.25 (s, 6 H), 1.84 (d, 3 H), (1.93, d, minor isomer), 2.13 (m, 2 H), 3.85 (s, 4 H), 4.47 (m, 1 H), 6.58 (m, 1 H), (6.45, m, minor isomer), 7.23 (m, 5 H). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.17; H, 8.24.

6,6-Dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl Methyl Ketone (8). Into a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a gas-inlet tube, and a gas-outlet tube were placed 75 mL of methanol and an *E/Z* mixture of 6,6-dimethyl-8-(α-methylstyryl)-1,4,7-trioxaspiro[4.4]nonane (**7**; 7.37 mmol, 2.021 g). The mixture was stirred and cooled to −78 °C by means of a dry ice–acetone bath. Ozone was then passed into the solution until TLC indicated the absence of starting material. A stream of oxygen was passed through the solution for 10 min, and then dimethyl sulfide (14.7 mmol, 915.3 mg, 1.08 mL) was added. The mixture was stirred at −78 °C for 20 min and then allowed to stir at 26 °C for 2 h. Removal of methanol in vacuo gave an oily residue which was purified by MPLC, initially eluting with methylene chloride to remove benzaldehyde followed by ether to afford, after evaporation of solvent in vacuo, 1.4 g (96.6% yield) of product: bp 58–63 °C (0.35 mm, Kugelrohr); R_f 0.31 (ethyl acetate–hexane, 1:3); IR (neat) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.18 (s, 6 H), 2.18 (s, 3 H), 2.37 (m, 2 H), 3.88 (s, 4 H), 4.19 (dd, 1 H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 59.73; H, 7.94.

Ethyl (*E*)-4-Methyl-6-phenyl-4-hexenoate (11). Into a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, condenser, addition funnel, and inert gas inlet and outlet tubes was placed magnesium turnings (0.234 mol, 5.70 g). The flask was flame dried under a nitrogen atmosphere and cooled to 25 °C, and then dry tetrahydrofuran (25 mL) was added to cover the magnesium metal. To this suspension was added isopropenyl bromide (0.239 mol, 29.0 g, 21.3 mL) dropwise and with stirring at such a rate as to maintain reflux. After the addition was complete, the mixture was refluxed for 1 h, diluted with 100 mL of dry tetrahydrofuran, and cooled to 0 °C. A solution of phenylacetaldehyde (0.283 mol, 34.0 g, 33.1 mL) in 200 mL dry tetrahydrofuran was added over a period of 30 min with ice-bath cooling. The mixture was then allowed to stir at 25 °C for 12 h. The mixture was poured into 300 mL of cold saturated ammonium chloride solution, and the aqueous solution was extracted with ether (4 × 150 mL). The combined organic layers were extracted with saturated sodium chloride solution (100 mL) and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo afforded 43.02 g of the crude alcohol as an

(37) A. I. Meyers and D. Comino, *Synthesis*, 403 (1978).
(38) G. Wittig and D. Wittenberg, *Justus Liebigs Ann. Chem.*, **606**, 1 (1957).

unstable, viscous oil which was stored in a freezer (−25 °C) or used directly as described below.

Into a 250 mL round-bottomed flask equipped with a magnetic stirring bar were placed the crude alcohol (0.146 mole, 23.72 g), triethyl orthoacetate (0.731 mol, 118.6 g, 134 mL), and propanoic acid (5.98 mmol, 442.8 mg, 0.45 mL). The flask was fitted with a Claisen distillation head, and a thermometer was suspended 2 cm from the top of the solution. The mixture was stirred and slowly heated to 145 °C in an oil bath during which time ethanol began to distill over. The flask was heated for 6 h, maintaining a vapor temperature of 140 °C above the reaction mixture, until no more ethanol distilled over. Excess triethyl orthoacetate was removed in vacuo, and the resulting liquid was distilled in vacuo to afford 15.03 g of crude ester, bp 93–96 °C (0.25 torr). This material was redistilled in vacuo to afford 12.09 g (35.6% overall yield) of product as a colorless liquid: bp 103–106 °C (0.25 mm); R_f 0.60 (petroleum ether–ether, 9:1); IR (neat) 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) 1.18 (t, 3 H), 1.72 (s, 3 H), 2.38 (s, 4 H), 3.32 (d, 2 H), 4.11 (q, 2 H), 5.42 (t, 1 H), 7.21 (br s, 5 H). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.70; H, 8.92.

(*E*)-4-Methyl-6-phenyl-4-hexen-1-ol (12). Into a 250-mL round-bottomed flask equipped with a magnetic stirring bar and a condenser fitted with a calcium chloride drying tube were placed ethyl (*E*)-4-methyl-6-phenylhex-4-enoate (11; 0.0250 mol, 5.810 g) and 100 mL of dry ether. Lithium aluminum hydride (0.025 mol, 0.949 g) was added portionwise over a period of 15 min, and the resultant mixture was stirred at 25 °C for 30 min. Water (5 mL) was added slowly to the solution, and after 30 min, the solution was dried with anhydrous magnesium sulfate. Removal of solvent in vacuo afforded 4.711 g (99.0% yield) of product as a colorless liquid: R_f 0.36 (ether–petroleum ether, 1:1); IR (neat) 3270 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.71 (s, 3 H), 1.85 (m, 4 H), 2.29 (s, 1 H), 3.36 (d, 2 H), 3.58 (t, 2 H), 5.43 (t, 1 H), 7.28 (br s, 5 H). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.83; H, 9.80.

(*E*)-6-Bromo-3-methyl-1-phenyl-2-hexene (13). Into a 50-mL round-bottomed flask equipped with a magnetic stirring bar was placed (*E*)-4-methyl-6-phenyl-4-hexen-1-ol (12; 10.0 mmol, 1.90 g), carbon tetrabromide (12.5 mmol, 4.15 g), and 15 mL of methylene chloride. The mixture was stirred and cooled to 0 °C, and then triphenylphosphine (15.0 mmol, 3.92 g) was added over a period of 15 min. The mixture was stirred at 0 °C for 10 min and allowed to warm to 25 °C. Removal of solvent in vacuo followed by filtration through a silica gel column (1 × 10 cm) with petroleum ether–ether (5:1) as the eluent gave the crude product. The material was chromatographed on silica gel (2 × 15 cm column) with petroleum ether as the eluent. Removal of solvent in vacuo gave 2.52 g (99.6% yield) of product as a colorless liquid: bp 85–90 °C (0.25 torr, Kugelrohr); IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.74 (s, 3 H), 2.05 (m, 4 H), 3.38 (d, 2 H), 3.39 (t, 2 H), 5.46 (t, 1 H), 7.27 (br s, 5 H); high-resolution mass spectrum, M^+ calcd for $C_{13}H_{17}Br$ *m/e* 252.0513, found *m/e* 252.0515.

(*E*)-(4-Methyl-6-phenyl-4-hexenyl)triphenylphosphonium Bromide (14). Into a 20-mL egg-shaped flask containing a magnetic stirring bar were placed (*E*)-6-bromo-3-methyl-1-phenyl-2-hexene (13; 1.4942 mmol, 378.3 mg), triphenyl phosphine (2.2413 mmol, 587.9 mg), and 3 mL of acetonitrile. The flask was equipped with a reflux condenser and a positive-pressure nitrogen-filled balloon. The mixture was stirred and refluxed for 16 h and cooled to 25 °C, and 15 mL of ether was added. The crude oily product was triturated several times with small portions of ether to remove unreacted starting material. Removal of volatile impurities under reduced pressure (0.5 mm) gave 707.9 mg (91.9% yield) of the crude phosphonium salt as a glass which was used without further purification: IR (neat) 1600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.56 (s, 3 H), 2.18 (m, 4 H), 3.30 (d, 1 H), 3.63 (m, 2 H), 5.45 (t, 1 H), 7.17 (br s, 1 H), 7.80 (m, 15 H).

(*E,E*)-8-(1,5-Dimethyl-7-phenyl-1,5-heptadienyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane (15). Into a 25-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and septum caps were placed (*E*)-(4-methyl-6-phenyl-4-hexenyl)triphenylphosphonium bromide (14; 1.00 mmol, 515.5 mg) and 2 mL of dry benzene. Under a positive-pressure nitrogen-filled balloon was added a solution of potassium *tert*-amylate (1.0 mmol, 0.57 mL of a 1.77 M solution of benzene) dropwise via a syringe. The resulting deep red solution was stirred and refluxed for 30 min, and then a solution of 6,6-dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl methyl ketone (1.00 mmol, 200.2 mg) dissolved in 2.5 mL of dry benzene was added 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 then diluted with 100 mL of ether. The organic phase was extracted with water (2 × 25 mL), 1 × 25 mL and saturated sodium chloride solution (25 mL) and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo afforded an oil which was purified by preparative TLC with petroleum ether–ether (15:1) as the eluent. The yield of viscous yellow oil was 194 mg (54.4%); R_f 0.42 (petroleum ether–ether, 6:1). The material was unstable and therefore was either stored in a freezer (−25 °C) under a nitrogen atmosphere or utilized immediately: IR (CCl_4) 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.23 (s, 6 H), 1.71 (br s, 6 H), 2.23 (m, 6 H), 3.33 (d, 2 H), 3.93 (s, 4 H), 4.93 (t, 1 H), 5.33 (t, 2 H), 7.24 (s, 5 H).

(*E,E*)-5-(1,5-Dimethyl-7-phenyl-1,5-heptadienyl)-2,2-dimethyl-3(2*H*)-furanone (16). Into a 20-mL egg-shaped flask containing a magnetic stirring bar and fitted with a reflux condenser were placed (*E,E*)-8-(1,5-dimethyl-7-phenyl-1,5-heptadienyl)-6,6-dimethyl-1,4,7-trioxaspiro[4.4]nonane[15] (0.262 mmol, 93.3 mg), 2 mL of acetic acid, and 1 mL of H_2O. The mixture was stirred and refluxed for 1.5 h, cooled to 25 °C, and diluted with 100 mL of ether. The ether solution was extracted with saturated sodium bicarbonate solution (1 × 15 mL), water (15 mL), and saturated sodium chloride solution (15 mL) and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo afforded an oil which was purified by preparative TLC with petroleum ether–ether (15:1) as the eluent. The yield of viscous yellow oil was 63.0 mg (77.0%): R_f 0.64 (petroleum ether–ether, 4:1); IR (CCl_4) 1758, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.18 (s, 3 H), 1.23 (s, 3 H), 1.72 (s, 6 H), 2.13 (m, 4 H), 2.30 (d, 2 H), 3.31 (d, 2 H), 4.98 (t, 1 H), 5.35 (t, 2 H), 7.13 (s, 5 H). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.97; H, 9.24.

3,5-Dimethoxy-4-(2-propenyl)toluene (19). Into a 100-mL, flame-dried, three-necked, round-bottomed flask equipped with rubber septum, a condenser, a 50-mL dropping funnel, and a magnetic stirring bar was placed freshly distilled 3,5-dimethoxytoluene (18; 3.16 g, 21 mmol) diluted with 10 mL of tetrahydrofuran. *n*-Butyllithium (1.2 equiv, 25 mmol) was then added to the stirred solution. The reaction mixture was allowed to stir overnight at ambient temperature under nitrogen. After approximately 1 h, a precipitate was observed (LiBr). Allyl bromide (1.2 equiv, 3.03 g, 24 mmol) dissolved in dry xylene (20 mL) was added dropwise to the reaction mixture. The precipitate dissolved during the addition, and the reaction mixture was heated to 80 °C and refluxed for 4 h. After 10 min a new precipitate was observed (LiBr). The reaction was cooled to 25 °C, poured into ice–water (20 mL), and diluted with ether (25 mL). The layers were separated, and the water layer was extracted with ether (2 × 25 mL). The ether extracts were combined, washed once with 5% sodium hydroxide (10 mL), once with water (20 mL), and once with a saturated sodium chloride solution (20 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a mixture of starting material and the desired alkylated product. These products could be separated by fractional distillation [Vigreux column; bp 108–111 °C (0.5 torr)] to afford the alkylated orcinol (2.5 g, 61% yield). The mixture was usually purified by simple distillation. The unreacted starting material was carried through the next two steps and then removed from the product by column chromatography: IR (neat) 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.45 (s, 3 H), 3.50 (m, 2 H), 3.90 (s, 6 H), 5.10 (m, 2 H), 5.8–6.2 (m, 1 H), 6.40 (s, 2 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.25; H, 8.61.

3,5-Dimethoxy-4-(2,3-dihydroxypropyl)toluene (20). 3,5-Dimethoxy-4-(2-propenyl)-toluene (19; 7.8 g, 41 mmol) was placed in a 3-L, two-necked, round-bottomed flask equipped with a mechanical stirrer and a 500-mL dropping funnel. Compound 19 was diluted with methylene chloride (200 mL), and the resulting solution was stirred and cooled to 0 °C. To the reaction mixture was added a freshly prepared solution of potassium permanganate (1.5 equiv, 9.6 g, 60 mmol) and tetra-*n*-butylammonium bromide (1.5 equiv, 20.3 g, 61 mmol) in methylene chloride (1000 mL) at such a rate as to not allow the temperature to rise above 5 °C.

The potassium permanganate was previously ground with a mortar and pestle to aid its dissolution. The reaction mixture was stirred at 0 °C until the solution turned from purple to brown (approximately 3 h). A 6% sodium hydroxide solution (200 mL) was then added, and the reaction mixture was allowed to stir at ambient temperature under nitrogen for 18 h. The brown reaction mixture was then filtered through Celite, and the two layers formed were separated. The water layer was extracted with methylene chloride (3 × 100 mL), and the organic layers were combined and evaporated in vacuo. A viscous yellow oil was obtained which was placed in a separatory funnel and diluted with water (100 mL). The aqueous solution was extracted six times with ether (50 mL). The procedure was designed to remove the quaternary ammonium salt which otherwise would contaminate the product. The ether layers were combined, washed once with water (100 mL) and once with a saturated sodium chloride solution (100 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the diol (6.8 g, 75% yield) as a white solid which was purified by recrystallization from ether: mp 93.5–94 °C; IR (KBr) 3300 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.35 (s, 3 H), 2.50 (t, 1 H), 2.74 (d, 1 H), 2.90 (m, 2 H), 3.48 (m, 1 H), 3.80 (s, 6 H), 3.90 (m, 2 H), 6.40 (s, 2 H). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.69; H, 8.04. Found: C, 63.91; H, 8.11.

4-[(2,6-Dimethoxy-4-methylphenyl)methyl]-2,2-dimethyl-1,3-dioxolane (21). Diol **20** (8.2 g, 36 mmol) was placed in a 250-mL round-bottomed flask equipped with a magnetic stirring bar and treated with acetone (120 mL) and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at ambient temperature, and the progress of the reaction was monitored by TLC (ethyl acetate/hexane, 1:3). Once the reaction was complete (approximately 5 h), the solution was made basic, to pH 8, by the addition of triethylamine. The acetone was then removed in vacuo, and the residue obtained was diluted with ether (150 mL), washed once with water (20 mL) and once with a saturated sodium chloride solution (20 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the desired product (9.38 g, 98% yield). Unreacted 3,5-dimethoxytoluene was separated from the product by using MPLC (silica gel; ethyl acetate/hexane, 1:10). This procedure afforded a pure product and the 3,5-dimethoxytoluene could be recycled back into the alkylation reaction: IR (neat) 2890, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.4 (s, 3 H), 1.5 (s, 3 H), 2.4 (s, 3 H), 3.0 (m, 2 H), 3.8 (s, 7 H), 4.3 (m, 1 H), 6.4 (s, 2 H); high-resolution mass spectrum, M^+ calcd for $C_{15}H_{22}O_4$ m/e 266.1518, found m/e 266.1523.

4-[(3-Bromo-2,6-dimethoxy-4-methylphenyl)methyl]-2,2-dimethyl-1,3-dioxolane (22). Into a 100-mL round-bottomed flask equipped with a magnetic stirring bar were placed compound **21** (5.43 g, 20 mmol) and dry *N,N*-dimethylformamide (40 mL). The solution was stirred, and *N*-bromosuccinimide (1.0 equiv, 3.56 g) dissolved in *N,N*-dimethylformamide (20 mL) was added dropwise. For larger scale reactions, cooling was required during this addition. The reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was then poured into ice–water (100 mL) and the water layer extracted with a 1:1 mixture of ether/petroleum ether (6 × 75 mL). The organic extracts were combined, washed once with water (100 mL) and once with a saturated sodium chloride solution (100 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a yellow oil which was purified by MPLC (silica gel; ethyl acetate/hexane, 1:8). This treatment afforded the product (6.34 g, 92% yield) as a clear oil: IR 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.4 (s, 3 H), 1.6 (s, 3 H), 2.5 (s, 3 H), 2.9–3.2 (m, 2 H), 3.7–3.8 (br s, 7 H), 4.1–4.5 (m, 1 H), 6.6 (s, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{15}H_{21}O_4Br$ m/e 344.0623, found m/e 344.0634.

4-[(3-Bromo-5-chloro-2,6-dimethoxy-4-methylphenyl)methyl]-2,2-dimethyl-1,3-dioxolane (23). Into a 500-mL round-bottomed flask equipped with a magnetic stirring bar was placed the bromo compound **22** (14.3 g, 40 mmol), to which were added chloroform (150 mL) and pyridine (30 mL). The resulting solution was stirred and cooled to 0 °C. A solution of chlorine in chloroform was prepared, and its molarity was calculated. The chlorine solution (1.3 equiv, 54 mmol) was added dropwise to the reaction mixture. After the addition was complete, the reaction was stoppered, stirred for 1 h at 0 °C, and then placed in the refrigerator for 4 days. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 1:5). The chloro derivative had a slightly higher R_f than the starting material (R_f 0.6). The reaction mixture was then poured into water (50 mL), and the layers were separated. The organic layer was washed once with water (30 mL) and then with a saturated copper sulfate solution (50 mL) until all the pyridine was removed. The chloroform was washed with water (2 × 50 mL), and with saturated sodium chloride solution (75 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a green oil which was purified by filtration through silica gel (ether) to afford the desired product (14.6 g, 92% yield) as a yellow oil. This compound was used immediately in the next step: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.32 (s, 3 H), 1.45 (s, 3 H), 2.53 (s, 3 H), 2.97 (m, 2 H), 3.83 (m, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.95 (quintet, 1 H).

2-Bromo-6-chloro-2,5-dimethoxy-4-(2,3-dihydroxypropyl)toluene (24). In a 250-mL round-bottomed flask equipped with a magnetic stirring bar was placed compound **23** (2.46 g, 6.5 mmol) in 20 mL of methanol. To this solution was added a 2% solution of concentrated hydrochloric acid in methanol (100 mL). The reaction mixture was stoppered and stirred at ambient temperature. The reaction progress was monitored by TLC (ethyl acetate/hexane, 1:3) until all the starting material had disappeared (approximately 4 h). The reaction mixture was then neutralized with saturated sodium bicarbonate, and the methanol was removed in vacuo. The residue was placed in a separatory funnel, diluted with water (20 mL), and extracted with ether (7 × 75 mL). The organic layers were combined, washed once with water (50 mL) and once with a saturated sodium chloride solution (50 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded an oil which solidified on standing (2.19 g, 99.5% yield). Recrystallization from ether yielded a white solid: mp 99–100.5 °C; IR (KBr) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.41 (t, 1 H), 2.54 (s, 3 H), 2.92 (m, 2 H), 3.52 (m, 2 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 3.94 (m, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{12}H_{16}O_4BrCl$ m/e 337.9921, found m/e 337.9927.

(3-Bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde (25). Into a 500-mL round-bottomed flask equipped with a magnetic stirring bar was placed 2-bromo-6-chloro-3,5-dimethoxy-4-(2,3-dihydroxypropyl)toluene (**23**; 6.98 g, 21 mmol). Ethyl acetate (100 mL) and water (100 mL) were added to the flask. Sodium periodate (2.2 equiv, 9.7 g, 45 mmol) was added in one portion, and the reaction mixture was stoppered and stirred vigorously at ambient temperature overnight. The reaction was monitored by TLC [ethyl acetate/hexane, 1:3; R_f(product 0.5]. At the completion of the reaction, the layers formed were separated, and the water layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, washed once with a saturated sodium chloride solution (60 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo gave a yellow oil which was purified by MPLC (silica gel; ethyl acetate/hexane, 1:10) to afford the desired product: 6.40 g (99% yield); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.54 (s, 3 H), 3.72 (s, 3 H), 3.76 (s, 3 H), 3.78 (d, 2 H), 9.70 (t, 1 H). Anal. Calcd for $C_{11}H_{12}O_3ClBr$: C, 42.93; H, 3.90. Found: C, 42.89; H, 3.96.

2-Bromo-6-chloro-3,5-dimethoxy-4-(3-methyl-2-butenyl)toluene (33). Into a flame-dried, 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a rubber septum was placed isopropyltriphenylphosphonium iodide[37] (1.6 equiv, 7.9 g, 18 mmol). Dry tetrahydrofuran (40 mL) was added to this flask, and the reaction mixture was stirred. *n*-Butyllithium (1.3 equiv, 15 mmol) was added to the stirred suspension dropwise. The blood red solution was stirred at ambient temperature for 30 min, after which time it was cooled to 0 °C. (3-Bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde (3.52 g, 11 mmol) dissolved in tetrahydrofuran (25 mL) was added to the reaction mixture dropwise. The reaction was allowed to warm to room temperature, gently heated to 50 °C, and stirred at that temperature for 1 h. The reaction mixture was cooled to 25 °C, poured into water (30 mL), and extracted with ether (3 × 50 mL). The ether extracts were combined, washed twice with *cold* 10% hydrogen peroxide (75 mL), twice with 20% sodium bisulfite (100 mL), once with water (100 mL), and once with a saturated sodium chloride solution (100 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product which was purified by flash column chromatography (2.5 × 45 cm column, silica gel; ether/petroleum ether, 1:15) to give the pure product (2.85 g, 73% yield) as a yellow oil: IR (neat)

1570 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.68 (s, 3 H), 1.78 (s, 3 H), 2.52 (s, 3 H), 3.40 (d, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 5.68 (t, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{14}H_{18}BrClO_2$ m/e 332.0174, found m/e 332.0166.

3-Chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)-benzaldehyde (34). Into a 100-mL three-necked, round-bottomed flask fitted with a magnetic stirring bar, a condenser, a nitrogen-inlet tube, and a rubber septum was placed magnesium turnings (1.1 equiv, 0.17 g, 6.9 mmol). The flask was then flame dried under nitrogen. Dry ether (60 mL) and 2-bromo-6-chloro-3,5-dimethoxy-4-(3-methyl-2-butenyl)toluene (**33**; 2.16 g, 6.3 mmol) were added to the flask, and the reaction mixture was heated to reflux. In all cases it was necessary to initiate the formation of the reagent by adding small amounts of 1,2-dibromoethane (approximately 10–20 μL). The reaction mixture was refluxed for 4 h after which time it was cooled to ambient temperature. Into another flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a rubber septum was placed 2-(formylmethylamino)pyridine (1.0 equiv, 0.85 g) dissolved in dry tetrahydrofuran (20 mL). This solution was stirred and cooled to 0 °C. The Grignard reagent was added dropwise via a syringe to this stirred solution. Stirring was continued at 0 °C for 20 min. The reaction mixture was then poured into *cold* 5% hydrochloric acid (25 mL), and the two layers formed were separated. The water layer was extracted with ether (3 × 40 mL). The organic layers were combined, washed once with water (25 mL) and once with a saturated sodium chloride solution (30 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product which was purified by flash column chromatography (1.5 × 30 cm, silica gel; ether/petroleum ether, 1:25) to give the aldehyde (0.99 g, 56% yield) as a pale yellow oil: IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.69 (s, 3 H), 1.79 (s, 3 H), 2.63 (s, 3 H), 3.89 (d, 2 H), 3.82 (s, 3 H), 3.88 (s, 3 H), 5.13 (t, 1 H), 10.42 (s, 1 H); high-resolution mass spectrum, M^+ calcd for $C_{15}H_{19}O_3Cl$ m/e 282.0980, found m/e 282.0991.

3-Chloro-4-hydroxy-6-methoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (35). Into a 25-mL round-bottomed flask fitted with a rubber septum and purged with nitrogen were placed 3-chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (34; 52 mg, 0.18 mmol), chloroform (2 mL), dry pyridine (6.0 equiv, 85 mg, 1.2 mmol), and trimethylsilyl iodide (8.0 equiv 300 mg, 1.5 mmol). The reaction mixture was heated in an oil bath, without stirring, to 60 °C for 4 days. Additional chloroform had to be added during this heating period to keep the solvent level constant. The reaction mixture was cooled to room temperature, and methanol (2 mL) was added to the reaction mixture. The solvents were removed in vacuo, leaving a yellow solid. This residue was diluted with water and extracted with chloroform (3 × 15 mL). The organic extracts were combined, washed twice with 10 mL of water and once with a saturated sodium chloride solution (15 mL), and dried ($MgSO_4$). Removal of the solvents in vacuo afforded a red-brown oil which was purified by preparative TLC (ether/petroleum ether, 1:6; R_f 0.4). This operation afforded the product (15 mg, 31% yield) as an off white solid: IR ($CHCl_3$) 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.71 (s, 3 H), 1.80 (s, 3 H), 2.66 (s, 3 H), 3.41 (d, 2 H), 3.84 (s, 3 H), 5.18 (t, 1 H), 6.35 (s, 1 H), 10.37 (s, 1 H); high-resolution mass spectrum, calcd for $C_{14}H_{17}O_3Cl$ m/e 268.0866, found m/e 268.0883.

2-Bromo-6-chloro-4-[(*E*)-5-(ethoxycarbonyl)-3-methyl-2-pentenyl]-3,5-dimethoxytoluene (27). (3-Bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)acetaldehyde (**26**; 6.72 g, 0.022 mol) was treated under the same conditions used to synthesize 11. The product was purified by flash column chromatography (silica gel; ethyl acetate/hexane, 1:10) and was obtained as a yellow oil: 4.68 g (51% yield); IR (neat) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.20 (t, 3 H), 1.80 (s, 3 H), 2.36 (m, 4 H), 2.52 (s, 3 H), 3.42 (d, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.08 (q, 2 H), 5.22 (t, 1 H); high-resolution mass spectrum, calcd for $C_{18}H_{24}O_4ClBr$ m/e 418.0547, found m/e 418.0492.

2-Bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-6-hydroxyl-3-methyl-2-hexenyl]toluene (28). Compound **28** was synthesized according to the procedure used to synthesize **12**. This procedure afforded **28** in 96% yield as a pale yellow oil: IR (neat) 3250 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.64 (m, 3 H), 1.79 (s, 3 H), 2.05 (t, 2 H), 2.52 (s, 3 H), 2.41 (d, 2 H), 3.59 (t, 2 H), 3.79 (s) and 3.80 (s, 6 H), 5.23 (t, 1 H); high-resolution mass spectrum, calcd for $C_{16}H_{22}O_3BrCl$ m/e 376.0441, found m/e 376.0430.

2-Bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-6-bromo-3-methyl-2-hexenyl]toluene (29). Compound **29** (1.44 g, 3.8 mmol) was synthesized according to the same procedure used to synthesize compound **13**. The purification varied as follows. It was difficult to separate the product from the triphenylphosphine oxide by filtration since some of the product adhered to the solid. Therefore, the product and triphenylphosphine oxide were redissolved in methylene chloride. Silica gel (5 g) was added to the solution and the solvent was removed in vacuo, depositing the compound on the silica gel. This residue was then placed on the top of a flash chromatography column and eluted with ether to separate the bromide from the triphenylphosphine oxide. The solvent was removed in vacuo to afford a yellow oil which was purified by flash column chromatography (silica gel; ether/petroleum ether, 1:25). This procedure yielded the pure bromide (1.28 g, 77% yield) as a yellow oil: IR (neat) 1580 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.78 (s, 3 H), 1.92 (m, 2 H), 2.10 (m, 2 H), 2.51 (s, 3 H), 3.34 (t, 2 H), 3.41 (d, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.24 (t, 1 H); high-resolution mass spectrum, calcd for $C_{16}H_{21}O_2Br_2Cl$ m/e 437.9597, found m/e 437.9666.

2-Bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-6-(triphenylphosphonio)hex-2-enyl]toluene Bromide (30). Compound **30** was prepared by the same procedure used to make **14**. The product was purified by flash column chromatography (2.5 × 40 cm, silica gel; chloroform/methanol, 2:1) to afford the phosphonium salt (85% yield) as a glass. This product was not characterized by either high-resolution mass spectroscopy or analytical data but was used immediately in the next step: ^1H NMR ($CDCl_3$, 250 MHz) 1.62 (br s, 2 H), 1.70 (s, 3 H), 2.34 (m, 2 H), 2.48 (s, 3 H), 2.28 (d, 2 H), 2.68 (m, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.21 (t, 1 H), 7.6–7.9 (m, 15 H). Attempts to couple this compound with **8** led only to the decomposition of **30**.

2-Bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-6-(phenylthio)-2-hexenyl]toluene (31a). Into a 25-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a rubber septum was placed sodium hydride (1.3 equiv, 11 mg, 0.46 mmol) and dry tetrahydrofuran (10 mL). The suspension was stirred, and to it was added distilled thiophenol (1.4 equiv, 55 mg, 0.50 mmol) dropwise. A precipitate formed in the reaction mixture, and hexamethylphosphoric triamide (2 drops) was added to solubilize the sodium thiophenoxide. The reaction mixture was stirred at ambient temperature for 15 min, and to it was added 2-bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-6-bromo-3-methyl-2-hexenyl]toluene (**29**; 156 mg, 0.35 mmol) dissolved in tetrahydrofuran (3 mL) dropwise. Almost immediately a white precipitate formed, and the reaction mixture was stirred at ambient temperature for 30 min. The reaction mixture was then poured into water (15 mL) and extracted with ether (3 × 25 mL). The organic extracts were combined, washed twice with 10% sodium hydroxide (30 mL), once with water (25 mL), and once with a saturated sodium chloride solution (25 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded a yellow oil which was purified by preparative TLC, (ether/petroleum ether, 1:15) to afford the pure sulfide: 151 mg (92% yield); IR (neat) 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.74 (br s, 5 H), 2.10 (t, 2 H), 2.49 (s, 3 H), 2.84 (t, 2 H), 3.41 (d, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.20 (t, 1 H), 7.1–7.3 (m, 5 H); high-resolution mass spectrum, M^+ calcd for $C_{22}H_{26}O_2BrClS$ m/e 468.0525, found m/e 468.0522.

2-Bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-methyl-6-(phenylsulfonyl)-2-hexenyl]toluene (31b). Into a 50-mL round-bottomed flask equipped with a magnetic stirring bar were placed 2-bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-6-(phenylthio)-2-hexenyl]toluene (**31a**; 151 mg, 0.32 mmol), methanol (10 mL), and tetrahydrofuran (2 mL). The reaction mixture was cooled to 0 °C, and to it was added potassium hydrogen persulfate[36] (4.0 equiv, 390 mg, 1.3 mmol) dissolved in water (8 mL). A precipitate formed immediately, and the reaction mixture was stirred at ambient temperature for 6 h. The reaction mixture was diluted with water (20 mL) and extracted four times with chloroform (100 mL). The organic extracts were combined, washed once with water (10 mL) and once with a saturated sodium chloride solution (20 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude sulfone which was purified

by preparative TLC (petroleum ether/ether, 1:3). This operation afforded the product (122 mg, 76% yield) as a clear viscous oil: IR (neat) 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.70 (s, 3 H), 1.86 (m, 2 H), 2.06 (t, 2 H), 2.52 (s, 3 H), 5.11 (t, 1 H), 7.4–7.6 (m, 3 H), 7.80 (m, 2 H); high-resolution mass spectrum, M^+ calcd for $C_{22}H_{26}O_4ClBrS$ m/e 500.0496, found m/e 500.0514.

2-Bromo-6-chloro-3,5-dimethoxy-4-[3-methyl-6-(phenylsulfonyl)-2,8-nonadienyl]toluene (32). Into a flame-dried, 25 mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen-inlet tube, and a rubber septum were placed dry tetrahydrofuran (3 mL) and diisopropylamine (1.5 equiv, 33 mg, 0.33 mmol). The solution was stirred and cooled to −78 °C (dry ice–acetone), and to it was added *n*-butyllithium (1.1 equiv, 0.24 mmol) dropwise. This mixture was stirred at −78 °C for 30 min after which time 2-bromo-6-chloro-3,5-dimethoxy-4-[(*E*)-3-methyl-6-(phenylsulfonyl)-2-hexenyl]toluene (**31b**; 110 mg, 0.22 mmol) dissolved in tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred at −78 °C for an additional 30 min, and allyl bromide (1.5 equiv, 40 mg, 0.33 mmol) was added to the bright yellow solution. The color slowly disappeared, and the reaction mixture was allowed to reach ambient temperature. Stirring was continued overnight. The reaction mixture was then poured into water (10 mL), and the water layer was extracted with ether (4 × 25 mL). The organic extracts were combined, washed once with water (10 mL) and once with a saturated sodium chloride solution (10 mL), and dried ($MgSO_4$). Removal of the solvent in vacuo afforded the crude product which was purified by preparative TLC (ether/petroleum ether, 2:3). This operation afforded the product (66 mg, 55% yield) as a clear oil: IR ($CHCl_3$) 1575, 1555 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.71 (br s, 5 H), 2.00–2.46 (m, 4 H), 2.50 (s, 3 H), 3.01 (m, 1 H), 3.42 (d, 2 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 5.04 (m, 2 H), 5.16 (t, 1 H), 5.70 (m, 1 H), 7.5–7.7 (m, 3 H), 7.82 (m, 2 H); high-resolution mass spectrum, M^+ calcd for $C_{25}H_{30}O_4ClBrS$ m/e 540.0737, found m/e 540.0717.

Registry No. **1**, 38462-04-3; **3d**, 53939-17-6; **4**, 115-22-0; **5**, 101-39-3; **6**, 77363-83-8; (*E*)-**7**, 81520-51-6; (*Z*)-**7**, 81520-52-7; **8**, 81476-90-6; **9**, 122-78-1; **10**, 77311-61-6; **11**, 43043-88-5; **12**, 77364-02-4; **13**, 77363-86-1; **14**, 77363-87-2; **15**, 81476-91-7; (*E,E*)-**16**, 81476-92-8; (*E,Z*)-**16**, 81476-93-9; **17**, 504-15-4; **18**, 4179-19-5; **19**, 81476-94-0; **20**, 81476-95-1; **21**, 81476-96-2; **22**, 81476-97-3; **23**, 81476-98-4; **24**, 81476-99-5; **25**, 81477-00-1; **27**, 81477-01-2; **28**, 81477-02-3; **29**, 81477-03-4; **30**, 81477-04-5; **31a**, 81477-05-6; **31b**, 81477-06-7; **32**, 81477-07-8; **33**, 81477-08-9; **34**, 81477-09-0; **35**, 81477-10-3; isopropenyl bromide, 557-93-7; allyl bromide, 106-95-6; 2-(formylmethylamino)pyridine, 67242-59-5; 1-(3-bromo-5-chloro-2,6-dimethoxy-*p*-tolyl)-3-methyl-3-buten-2-ol, 81477-11-4.

Synthesis of Phosphorins by Reaction of 1,2,5-Triphenylphosphole with Alkynes

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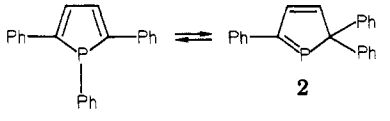
When heated several days at 230 °C, 1,2,5-triphenylphosphole yields 2,2′,3,3′,5,5′-hexaphenyl-1,1′-biphospholyl through a transient 2*H*-phosphole. The reactions of this biphospholyl with lithium, manganese carbonyl, and molybdenum carbonyl are described. If selected alkynes are added to the reaction medium, the transient 2*H*-phosphole is trapped to give 1-phosphanorbornadiene which spontaneously loses diphenylcarbene under the reaction conditions to give phosphorin. With unsymmetrical alkynes, only one phosphorin is obtained with the less bulky substituent at the α-position.

Three basic routes to the phosphorin ring have been described in the literature. The first, introduced by Märkl, relies upon an oxygen → phosphorus exchange in pyrylium salts. The second, introduced by Ashe, relies upon a tin → phosphorus exchange in 1,4-dihydrostannabenzenes. The third, again described by Märkl starts from a 3-oxo-1,2,3,6-tetrahydrophosphorin which is converted into the phosphorin through a multistep procedure. These syntheses have been presented and discussed in several reviews.[1-4] We have recently described two methods for converting phospholes into phosphorins.[5,6] These methods are interesting because they provide phosphorins with substitution patterns not easily obtained by the other routes and because the starting phospholes are very readily available.[7,8] Hereafter we describe in some depth the various possibilities offered by the method which relies upon the reaction of 1,2,5-triphenylphosphole (1) with alkynes. Only the synthesis of 2,3,6-triphenylphosphorin was described in a preliminary communication.[6]

Results and Discussion

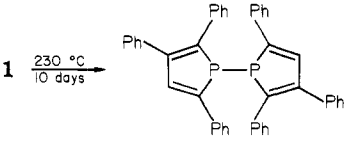
According to the postulated mechanism,[6] the first step of this phosphorin synthesis is a 1,5-shift of the P-phenyl substituent of **1**, giving the 2*H*-phosphole **2** (eq 1).



(1)

1 **2**

We immediately wondered what would happen if **1** was thermolyzed alone, or, in other words, what would be the behavior of **2** if no trapping reagent was added to the reaction medium. When pyrolyzing **1** at 230 °C for 10 days, we recovered the 1,1′-biphospholyl **3** (eq 2) as the



(2)

3 (64%)

major product of the reaction and a little quantity of starting material. The formula of this compound was unambiguously established by elemental analysis and mass

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