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Synthesis of benzofurans through coupling of dienylacetylenes with carbene complexes: total synthesis of egonol

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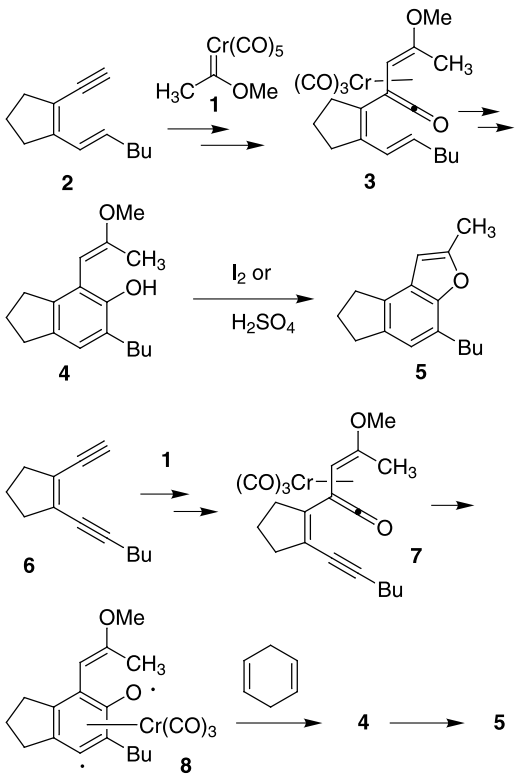
Abstract—The reaction of various carbene complexes with dienylacetylenes has been examined. The reaction has been used as the cornerstone for the preparation of the nor-neolignan natural product egonol in five steps from readily available components. In most examples of the carbene–alkyne coupling, the reaction proceeds to form benzofuran derivatives. In the case of one highly functionalized terminal alkyne, a competing rearrangement/cyclization process occurs in preference to the carbene coupling process. The use of silylated alkynes subverts this process. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In a series of papers the formation of benzo- and naphthofurans (e.g. **5**, Scheme 1) from the coupling of highly conjugated acetylene derivatives (e.g. **2**) with carbene complexes (e.g. **1**) has been demonstrated.[1] Reactions employing conjugated dienylacetylenes proceed via formation of a vinylketene (**3**), cyclization to the corresponding phenol derivative (**4**), and cyclization to the benzofuran derivative (**5**). Reactions employing conjugated enediynes (e.g. **6**) proceed through formation of a ketene (**7**) and generation of a chromium-complexed diradical (**8**),[2] followed by various intra- or intermolecular hydrogen abstraction reactions. In the example depicted in Scheme 1, the same benzofuran products are produced in comparable yield from the reaction of dienynes with carbene complexes or reaction of the corresponding enediyne with carbene complexes in the presence of 1,4-cyclohexadiene.[1b]

The benzofuran ring system is a common structural element that appears in a large number of medicinally important compounds.[3] Benzofuran neolignans and nor-neolignans, which are contained in most plants, have attracted much attention in medicinal chemistry for their various biological activities, including insecticidal, fungicidal, antimicrobial and antioxidant properties.[4] The most common synthetic strategy employed for benzofuran synthesis is the annulation of a furan ring onto a pre-existing benzene ring through Sonogashira coupling followed by palladium-catalyzed cyclization[5] or through benzannulation onto a preexisting furan ring.[6] Numerous benzofuran-containing natural products have been efficiently synthesized according to these methods. The synthesis of benzofurans using the reactions in Scheme 1 involves the simultaneous construction of both rings in a single reaction process.



Scheme 1.

Keywords: carbene complexes; benzofuran; Sonogashira coupling; conjugated alkynes.

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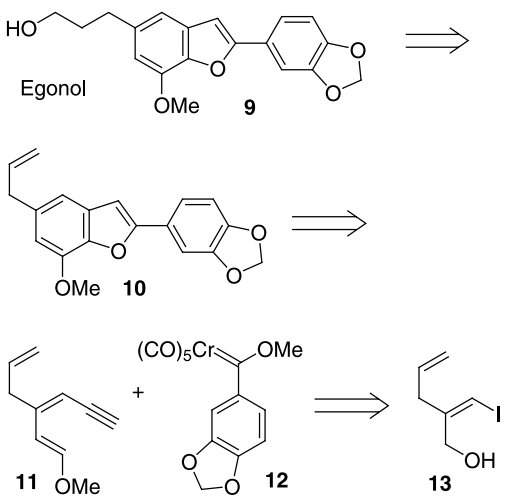
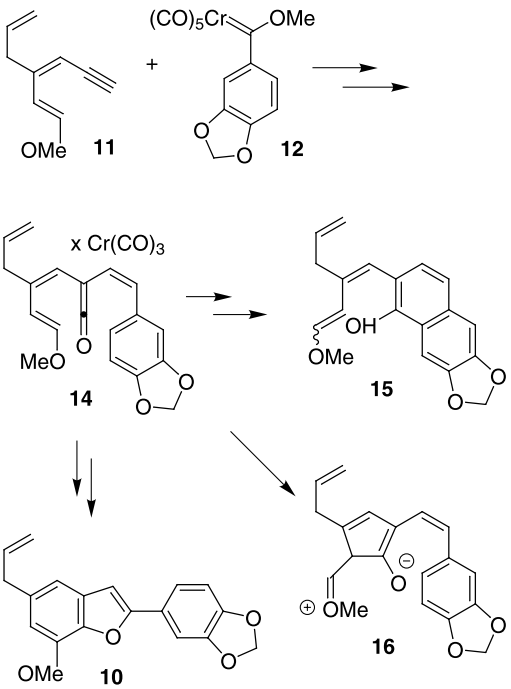


Scheme 2.

In order to demonstrate the synthetic utility of this reaction, efforts to synthesize the nor-neolignan natural product egonol (**9**, Scheme 2) have been undertaken.[7] The retrosynthetic analysis for this compound is depicted in Scheme 2. In theory, the readily-available iodo-alcohol derivative **13**[8] can be transformed to benzofuran derivative **10**, a known egonol precursor.[7a,e] Compound **10** is itself a naturally-occurring compound, isolated from the wood of *anaxagorea clavata*.[9] Egonol and related compounds have been evaluated as antibacterial[10] and anticancer agents.[11] The proposed synthetic route poses three major challenges (Scheme 3): (1) highly conjugated enol ether derivative **11** is likely unstable, (2) the Dötz reaction (formation of naphthol **15**, Scheme 3) can compete with the desired benzofuran-forming process,[12] and (3) the enol ether can undergo cyclization at the ketene carbon in intermediate **14** (resulting in **16**) as has been observed with related enamine intermediates.[13] In a related system the Dötz reaction was



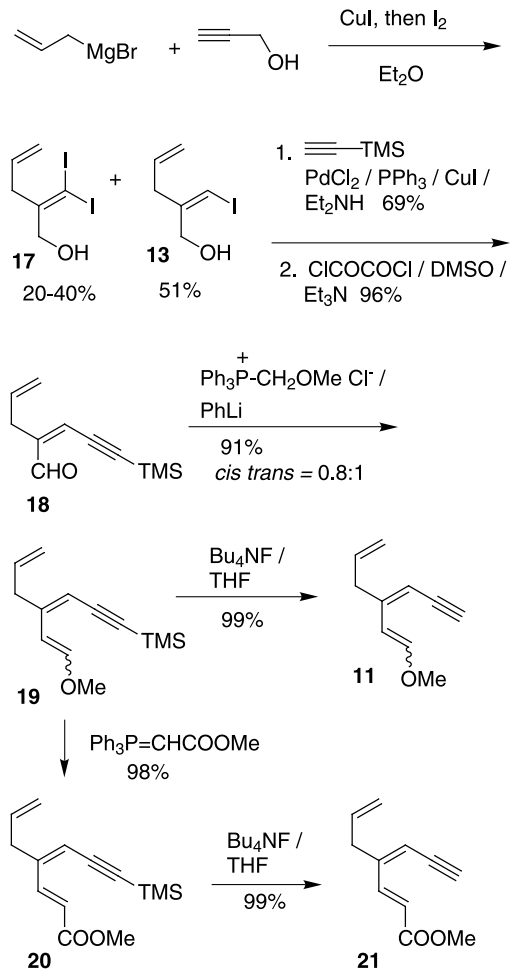
Scheme 3.

not a competing process; the cyclization selectivity was attributed to preferential complexation and cyclization at the non-oxygenated vinylketene ligand.[1c] At the inception of these studies, routes using dienyne **11** and an enediyne were both considered. Because of a report from the Liebeskind group that attempts to prepare methoxyacetylene were usually accompanied by fires,[14] the dienyne route was employed. In this manuscript the successful formal total synthesis of egonol is reported and several interesting observations concerning the properties of highly functionalized dienyne systems are reported.

2. Results and discussion

2.1. Synthesis of trienyne derivatives

The synthesis of trienyne **11** and related compounds is depicted in Scheme 4. In the synthesis of known iodo-alcohol **13**, a larger excess of allylic Grignard reagent was used relative to that previously reported[8] and the yield was slightly improved (51%). In addition to the desired compound, a substantial amount of product assigned as the diiodo compound **17** was also observed.[15] Sonogashira coupling of compound **13** and trimethylsilylacetylene followed by Swern oxidation afforded trienyne-aldehyde **18** in 66% yield. Wittig reaction and desilylation yielded



Scheme 4.

trienyne **11**. In addition to the dienyne required for the synthesis of egonol, the ester analogs **20** and **21** were also prepared. The successful synthetic route to the trienynes in Scheme 4 required considerable yield optimization and some interesting undesirable side reactions were noted during the optimization process. If the Swern oxidation was performed prior to the Sonogashira coupling, the opposite alkene isomer (*Z*) of aldehyde **18** was obtained, presumably due to isomerization of the intermediate β-iodo-α,β-unsaturated aldehyde. It was also noted that the Wittig reaction for the synthesis of the enol ether **19** was very sensitive with respect to double bond isomerization. If the temperature, reaction time, and amount of base (PhLi) are not carefully controlled, the major product of this Wittig reaction appears to be the product where the isolated alkene moves into conjugation.

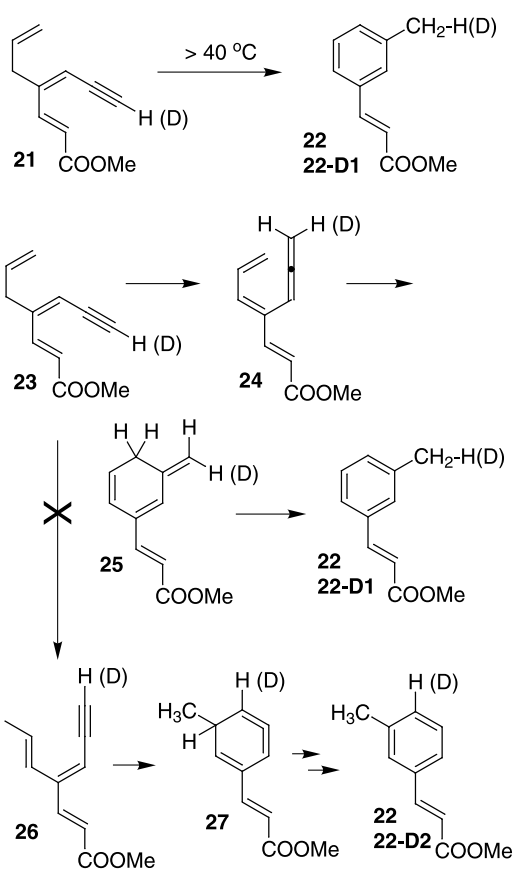
2.2. Coupling of carbene complexes and trienynes

The coupling of dienyne **11** with carbene complex **12** afforded a complex reaction mixture. The proton NMR of the crude reaction mixture showed no evidence of an intact allyl group as expected for benzofuran derivative **10**, and the integration for methoxy groups of the proton NMR spectrum was small compared with the aromatic signals. In order to test the efficacy of the cyclization reaction, ester **21** was tested in its reaction with carbene complex **12**; compounds similar to **21** have been successfully converted to benzofurans.[1b] Coupling of trienyne **21** and carbene complex **12** did not lead to a benzofuran either. The crude NMR spectrum showed that the α,β-unsaturated ester had survived the reaction, while the allyl group was consumed. The major product of this reaction was identified as cinnamate ester **22** (Scheme 5), indicating failure of the carbene-alkyne coupling. It was found that above 35–40°C, trienyne **21** cyclized to cinnamate ester **22**. Two mechanisms for the conversion of **21** to **22** are likely and differ with regard to the origin of the methyl group attached to the aromatic ring of **22**. The first mechanism involves 1,5-hydrogen shift to generate allene **24**, which could undergo electrocyclic ring closure to give intermediate **25** and **22** after a hydrogen shift. A similar mechanism was proposed for cyclization of propargylindole derivatives.[16] Alternatively, conjugation of the terminal alkene (affording **26**) followed by rearrangement could also afford **22**.[17] Intermediates similar to **27** have been suggested in the enyne-Diels–Alder reaction.[18] The compound where the alkyne hydrogen is replaced by deuterium afforded compound **22-D1**, featuring a deuterium in the methyl group, which is consistent with the first mechanism.

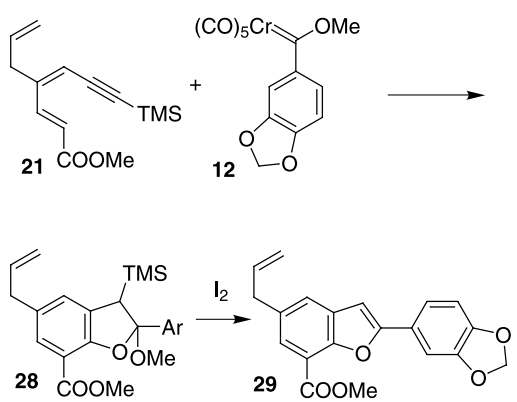
The ease of this apparently thermal cyclization was unexpected. The successful example of benzofuran formation involving a dienyne ester in Ref. 1b differs from **21** in that the substrate was an internal alkyne lacking the extra alkene functionality of compound **21**. Due to previous successes using an internal alkyne, the coupling reaction of silylated starting material **20** was examined (Scheme 6). This reaction afforded the desilylated benzofuran derivative **29** in 40% yield. The crude reaction mixture was treated with iodine prior to isolation of the final product to effect benzofuran formation and destroy arene complexes. Prior to iodine treatment, the likely product is ketal **28**,[1c] which then loses TMSOMe upon treatment with iodine.

2.3. Synthesis of egonol precursor 10

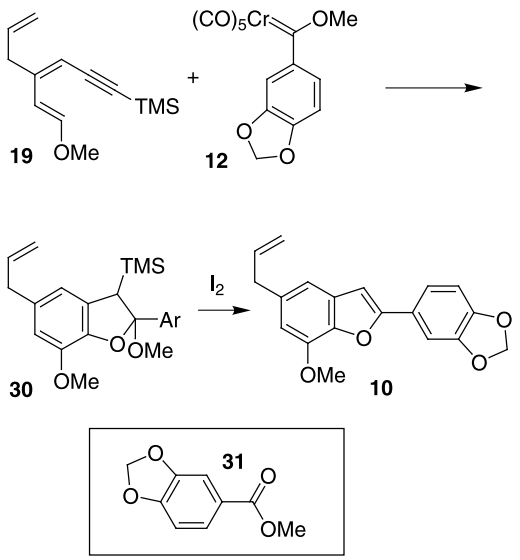
The success of benzofuran ring formation in the above reaction suggests that use of silylated methoxydienyne **19** is likely to provide egonol precursor **10** (Scheme 7). The coupling reaction in dioxane at 60–70°C in fact afforded the desired compound **10** in 47% yield accompanied by the carbene oxidation product **31** in 10–20% yield. Longer reaction times and/or higher temperatures led to the isomers where the alkene is conjugated. Hydroboration of **10** has been reported to provide egonol.[7a,e]



Scheme 5.



Scheme 6.



Scheme 7.

3. Conclusion

The nor-neolignan egonol has been formally synthesized in five steps from readily available components. Synthesis of benzofuran derivatives by this highly convergent route does not require the convenient availability of an appropriate aromatic ring for elaboration to the benzofuran, a strategy employed in all previous syntheses of egonol (**9**) and intermediate **10**,[7] and thus the method is amenable to the preparation of wide variety of structurally related benzofurans.

4. Experimental

4.1. General

Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Varian 200 or 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). The following symbols have been used to indicate multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). A Nicolet 5DXC FT-IR spectrometer was used to record the infrared spectra and band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band. C–H stretching frequencies in the region 2800–3100 cm^{-1} are not reported. Mass spectra (MS) were acquired at MS facilities at the University of California-Riverside or the University of Maryland; *m/e* values are reported, followed by the relative intensity in parentheses. Flash column chromatography was performed using thick walled glass columns and 'flash grade' silica. Thin layer chromatography was done using precoated 0.25 mm silica gel plates purchased from SAI Adsorbents. The relative proportion of solvents in mixed chromatography solvents refers to the volume/volume ratio. All commercially available reagents were in reagent grade and used without purification. Diethyl ether, THF and dioxane were distilled from sodium benzophenone ketyl. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of nitrogen.

4.1.1. Synthesis of carbene complex 12. To a solution of 4-bromo-1,2-(methylenedioxy)benzene (2.00 g, 9.948 mmol) in diethyl ether (30 mL) was added *n*-butyllithium (6.2 mL of 1.6 M hexane solution, 9.948 mmol) dropwise under nitrogen at −78°C. Then the mixture was stirred at 0°C for an additional 10 min, and was added directly to a suspension of chromium hexacarbonyl (2.189 g, 9.948 mmol) in diethyl ether (140 mL) at 0°C under nitrogen over a period of 15 min. The reaction mixture was allowed to warm to room temperature. Methyl trifluoromethanesulfonate (1.2 mL, 1.06 mmol) was added to the mixture at 0°C, and stirring was continued for an additional 2 h. The resulting deep red solution was poured into saturated aqueous sodium bicarbonate solution in a separatory funnel and then extracted with 2:1 hexane/ethyl acetate (3×35 mL). The organic layer was washed with water and saturated aqueous sodium chloride solution successively. After drying over magnesium sulfate, the solvent was removed on a rotary evaporator. Purification by flash chromatography on silica gel using 1:9 and then 1:4 ethyl acetate/hexane as the eluent afforded carbene complex **12** as a red solid (1.725 g, 4.846 mmol, 49%). ^{1}H NMR ($CDCl_3$): δ 7.36 (d, 1H, J=6.0 Hz), 7.03 (s, 1H), 6.96 (d, 1H, J=6.0 Hz), 6.03 (s, 2H), 4.81 (s, 3H); ^{13}C NMR (C_6D_6): δ 341.6, 224.1, 217.2, 151.4, 148.0, 125.4, 107.7, 105.1, 101.9, 69.6; IR (neat): 2058 (m), 1941 (vs) cm^{-1}; MS (FAB): *m/e* 356 (M, 16), 328 (28), 300 (42), 272 (20), 244 (66), 216 (36), 149 (100); HRMS calcd for $C_{14}H_8O_8Cr$ 355.96243, found 355.96350.

4.1.2. Improved synthesis of alcohol 13 (*Z*)-2-(iodomethylidene)-4-penten-1-ol.[8] (1) *Preparation of allylmagnesium bromide*. In a two neck flask fitted with a condenser and a dropping funnel was placed magnesium turnings (10.0 g, 412 mmol), dry ether (30 mL), and two crystals of iodine. A solution of allyl bromide (12.44 g, 102.9 mmol) in dry ether (110 mL) was added in small portions until the reaction began, and then kept adding at such a rate as to maintain gentle reflux of ether. The addition required about 1.5 h, after which the reaction mixture was refluxed on a heating metal for an additional hour. The freshly prepared allylmagnesium bromide ether solution was used immediately in the next step. (2) *Coupling of propargyl alcohol and allylmagnesium bromide*. A suspension of dry copper (I) iodide (0.476 g, 2.50 mmol) in a solution of propargyl alcohol (1.423 g, 25.00 mmol) in ethyl ether (30 mL) was vigorously stirred and cooled at −10°C as allylmagnesium bromide (140 mL of 0.64 M ether solution, 90 mmol) was added. After completion of the addition, the mixture was stirred for at least 2 h at room temperature. A saturated solution of iodine (8.765 g, 34.00 mmol) in ether (50 mL) was then added at −78°C (the first half portion was decolorized) and the mixture was allowed to warm to room temperature. After 1 h, ice was added to the mixture, which was then mixed with a saturated sodium thiosulfate solution (30 mL) and extracted two times with ether. The organic phases were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered through Celite and concentrated. The residue was purified by flash chromatography on a silica gel column with 4:1 hexane/ethyl acetate as eluent. Alcohol **13** (2.90 g, 51%)

was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 6.07 (s, 1H), 5.90–5.70 (m, 1H), 5.20–5.00 (m, 2H), 4.24 (s, 2H), 3.10–3.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 147.8, 134.4, 117.3, 77.1, 66.4, 39.2; IR (neat) 3600–3100 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[8] The major byproduct (never obtained free of alcohol **13**) was tentatively identified as diiodo alcohol **17** based on its ^{1}H NMR spectrum and its ability to undergo Sonogashira coupling.[19] ^{1}H NMR ($CDCl_3$): δ 5.90–5.70 (m, 1H), 5.20–5.05 (m, 2H), 4.30 (s, 2H), 3.06 (d, 2H, *J*=6.8 Hz), 1.62 (br s, 1H).

4.1.3. Synthesis of *Z* 2-(2-propen-1-yl)-5-trimethylsilyl-2-penten-4-yn-1-ol. A mixture of palladium (II) chloride (0.053 g, 0.30 mmol) and triphenylphosphine (0.158 g, 0.60 mmol) in diethylamine (30 mL) was stirred at room temperature for 10 min, then (*Z*)-2-(iodomethylidene)-4-penten-1-ol (**13**) (2.270 g, 10.05 mmol) in diethylamine (30 mL) was added. After this mixture was stirred for 10 min, copper iodide (0.115 g, 0.60 mmol) and then trimethylsilylacetylene (1.186 g, 12.06 mmol) were added. After 20 h of stirring at room temperature, the solvent was removed on a rotary evaporator. The residue was extracted with hexane and filtered through Celite. The hexane solution was washed with water, dried over sodium sulfate, and the solvent was removed on a rotary evaporator. The residue was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent. The enyne alcohol (1.344 g, 69%) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.77 (ddt, 1H, *J*=17.6, 9.5, 6.0 Hz), 5.43 (s, 1H), 5.10 (d, 1H, *J*=17.6 Hz), 5.08 (d, 1H, *J*=9.5 Hz), 4.35 (d, 2H, *J*=6.0 Hz), 2.92 (d, 2H, *J*=6.0 Hz), 1.88 (t, 1H, *J*=6.0 Hz), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 153.9, 134.9, 117.9, 107.5, 101.699.8, 63.1, 38.4, 0.1; IR (neat): 3300–3700 (s), 2127 (w) cm^{-1}; MS (EI): *m/e* 194 (M, 2), 179 (19), 161 (5), 153 (34), 125 (18), 99 (13), 75 (100); HRMS calcd for $C_{11}H_{18}OSi$ 194.11269, found 194.11348.

4.1.4. Synthesis of enyne aldehyde 18. To a solution of dry oxalyl chloride (1.339 g, 10.59 mmol) in dichloromethane (50 mL) at −78°C was added dimethyl sulfoxide (1.674 g, 21.46 mmol). After stirring for 10 min, a solution of the enyne-alcohol from the previous experiment (1.344 g, 6.92 mmol) was added. After stirring for 1 h at −78°C, triethylamine (3.499 g, 34.60 mmol) was added. The reaction mixture was stirred for 15 min at −78°C and then allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was poured into water and extracted three times with diethyl ether. The combined ether extracts were washed successively with 1% aqueous hydrochloric acid, water, and 1% aqueous sodium bicarbonate and then dried over sodium sulfate. The solvent was removed on a rotary evaporator. The residue was used in the next reaction without additional purification. Enyne aldehyde **18** (1.283 g, 6.676 mmol, 96% yield) was obtained as an orange oil. ^{1}H NMR ($CDCl_3$): δ 10.23 (s, 1H), 6.49 (s, 1H), 5.73 (ddt, 1H, *J*=16.6, 10.4, 6.6 Hz), 5.09 (d, 1H, *J*=10.3 Hz), 5.08 (d, 1H, *J*=16.6 Hz), 2.97 (d, 1H, *J*=6.6 Hz), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 191.4, 148.9, 133.7, 125.8, 117.9, 107.3, 98.7, 32.5, −0.6; IR (neat): 2138 (w), 1676 (s), 1595 (m) cm^{-1}. This compound should be used immediately in the next reaction.

4.1.5. Synthesis of trienyne 19. To a suspension of (methoxymethyl)triphenylphosphonium chloride (0.486 g, 1.417 mmol) in ether (12 mL) was added phenyllithium (0.75 mL of 1.8 M cyclohexane/ether solution, 1.350 mmol) at −78°C dropwise over a 10 min period. The resulting yellow mixture was then warmed to room temperature and stirred for an additional 20 min. A solution of enyne aldehyde **18** (0.147 g, 0.766 mmol) in ether (8 mL) was added slowly at 0°C, and then the mixture was stirred overnight. After the reaction was complete, saturated ammonium chloride solution (10 mL) was added and the precipitate dissolved. The reaction mixture was extracted three times with diethyl ether, washed with sodium bicarbonate solution, and dried over sodium sulfate. Evaporation of the solvent and purification by flash column chromatography (silica gel, 50:1 hexane/ethyl acetate) gave trienyne **19** (0.153 g, 0.694 mmol, 91% yield) as a yellow oil. This compound contains a *cis* and a *trans* isomer and a single impurity identified as biphenyl (3–5 mol%), which could not be efficiently separated; the ratio appears to be 0.8:1 *cis*/*trans*. These chromatographic conditions were optimal; slower eluting solvent systems separated out biphenyl but afforded significant amounts of aldehydic impurities. ^{1}H NMR ($CDCl_3$): δ 6.89 (d, 1H, *J*=13.2 Hz, *trans* isomer), 6.17 (d, 1H, *J*=13.2 Hz, *trans* isomer), 5.99 (d, 1H, *J*=6.0 Hz, *cis* isomer), 5.90–5.77 (m, 1H, common to both isomers), 5.55 (d, 1H, *J*=6.0 Hz, *cis* isomer), 5.22–4.95 (m, 3H, common to both isomers); 3.68 (s, 3H, one isomer) 3.65 (s, 3H, one isomer), 3.18 (d, 2H, *J*=6.0 Hz, one isomer) 2.94 (d, 1H, *J*=6.0 Hz, one isomer), 0.18 (s, 9H, common to both isomers); ^{13}C NMR: ($CDCl_3$): δ 152.2, 149.5, 149.3, 148.0, 136.6, 135.6, 117.1, 115.1, 105.2, 104.5, 104.3, 104.1, 103.8, 103.6, 100.0, 99.6, 56.5, 56.4, 40.1, 36.7, 0.3, −0.2; IR (neat): 2123 (m), 1639 (s), 1629 (s) cm^{-1}. This compound was used immediately for subsequent reactions.

4.1.6. Synthesis of trienyne 11. To a solution of silylated trienyne **19** (0.195 g, 0.89 mmol) in THF (10 mL) at room temperature was added tetrabutylammonium fluoride (1.77 mL of a 1 M THF solution, 1.77 mmol). The mixture was stirred for 30 min at room temperature and poured into 1 M aqueous hydrochloric acid. The aqueous layer was extracted three times with pentane. The combined pentane extracts were washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 50:1 hexane/ethyl acetate as eluent. Trienyne **11** (0.124 g, 99%) was obtained as a yellow oil. This mixture contains the *cis* and *trans* isomers in a 57:43 ratio, and they could not be separated via column chromatography. Numerous alkene-containing baseline impurities are visible in this spectrum.

Compound **11**. ^{1}H NMR ($CDCl_3$): δ 6.77 (d, 1H, *J*=12.8 Hz, *trans* isomer), 6.02 (d, 1H, *J*=6.0 Hz, *cis* isomer), 5.90–5.70 (m, 1H, common to both isomers), 5.81 (s, 1H, *cis* isomer), 5.51 (d, 1H, *J*=12.8 Hz, *trans* isomer), 5.17–5.03 (m, 2H, common to both isomers), 4.75 (d, 1H, *J*=6.0 Hz, *cis* isomer), 3.64 (s, 3H, *trans* isomer), 3.59 (s, 3H, *cis* isomer), 3.30–3.10 (m, 3H, common to both isomers).

4.1.7. Synthesis of trienyne 20. To a solution of methyl (triphenylphosphoranylidene)acetate (0.640 g, 1.91 mmol) in dichloromethane (20 mL) at 0°C was added a solution of enyne aldehyde **18** (0.283 g, 1.47 mmol) in dichloromethane (18 mL). After an additional 20 h stirring at room temperature, the solvent was evaporated and the residue was extracted three times with hexane. The combined hexane solution was filtered through Celite. Evaporation of the solvent and column chromatography (silica gel, hexane/ethyl acetate=9:1) gave dienyne **20** (0.360 g, 98% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 1H, J=16.0 Hz), 6.04 (d, 1H, J=16.0 Hz), 5.86 (ddt, 1H, J=16.0, 9.8, 6.5 Hz), 5.73 (s, 1H), 5.10 (d, 1H, J=9.8 Hz), 5.08 (d, 1H, J=16.0 Hz), 3.76 (s, 3H), 3.00 (d, 2H, J=6.5 Hz); ^{13}C NMR ($CDCl_3$): δ 167.3, 146.4, 141.4, 134.3, 120.3, 117.7, 116.4, 80.1, 77.8, 51.6, 36.5, 0.29; MS (EI): *m/e* 248 (M, 47), 233 (36), 208 (20), 207 (100), 203 (22), 201 (22), 176 (19), 116 (21), 115 (25), 89 (87), 76 (27), 74 (83), 59 (69), 41 (21); HRMS calcd for $C_{14}H_{20}O_2Si$ 248.1233, found 248.1249.

4.1.8. Synthesis of trienyne 21. To a solution of silylated trienyne **20** (0.258 g, 1.04 mmol) in THF (10 mL) at room temperature was added tetrabutylammonium fluoride (2.07 mL of a 1 M THF solution, 2.07 mmol). The mixture was stirred for 30 min at room temperature and poured into 1 M aqueous hydrochloric acid. The aqueous layer was extracted three times with pentane. The combined pentane extracts were washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent. Trienyne **21** (0.178 g, 99%) was obtained as a pale yellow oil. The proton NMR reveals that this sample is contaminated by aromatic compound **22** (see Section 4 for **22** below). The ratio of **21**:**22** is 92:8 as determined by integration of the peaks for the CH_2 peak at δ 3.01 in **21** relative to the ArCH_3 peak at δ 2.33 in **22**. ^{1}H NMR ($CDCl_3$) (only peaks for **21** listed): δ 7.90 (d, 1H, J=16.0 Hz), 6.06 (d, 1H, J=16.0 Hz), 5.89–5.66 (m, 1H), 5.70 (s, 1H), 5.15–5.02 (m, 2H), 3.76 (s, 3H), 3.40 (s, 1H), 3.01 (d, 2H, J=6.0 Hz). This compound was used immediately for subsequent reactions.

4.1.9. Formation of cinnamate ester 22; cyclization of trienyne 21. The procedure for synthesizing dienyne **21** was followed except for increasing the temperature in the product concentration step to 40°C. After column chromatography (silica gel/9:1 hexane/ethyl acetate), a colorless oil (0.060 g, 40%) identified as compound **22** was obtained. ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1H, J=16.0 Hz), 7.34–7.12 (m, 4H), 6.38 (d, 1H, J=16.0 Hz), 3.76 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.3, 144.9, 138.4, 134.3, 130.9, 128.6, 125.1, 117.4, 111.6, 51.4, 21.1. The spectral data are in agreement with those reported previously for this compound.[20]

4.1.10. Formation of benzene derivative 22-D1; cyclization of dienyne 21-D. To a solution of silylated trienyne **20** (0.150 g, 0.604 mmol) in THF (3 drops of D_2O was added) was added tetrabutylammonium fluoride (1.21 mL of a 1 M THF solution, 1.21 mmol). After the addition was complete, the mixture was heated at 45°C for 12 h. The mixture was stirred for 30 min at room temperature and poured into 1 M aqueous hydrochloric acid. The aqueous layer was extracted three times with pentane. The combined pentane extracts were washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulfate, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 50:1 hexane/ethyl acetate as eluent. Cinnamate esters **22** and dienyne **22-D1** were obtained as a pale oil (0.214 g, 50%) in a 2:1 ratio; deuterium incorporation is about 33%. ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1H, J=16.0 Hz), 7.34–7.12 (m, 4H), 6.38 (d, 1H, J=16.0 Hz), 3.76 (s, 3H), 2.33 (s, 2.6H); ^{13}C NMR ($CDCl_3$): δ 167.3, 144.9, 138.4, 134.3, 130.9, 128.6, 125.1, 117.4, 111.6, 51.4, 29.6, 21.1, 21.0 (2 lines of 3-line signal); MS (EI): 177 (M with ^{2}H, 32), 176 (M with all ^{1}H, 67), 175 (21), 161 (21), 146 (51), 145 (100), 118 (18), 117 (36), 116 (32), 115 (51), 92 (10), 91 (26); HRMS calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0838; HRMS calcd for $C_{11}H_{11}DO_2$ 177.0900, found 177.0896. Incorporation of deuterium at the methyl group is indicated by the following facts: (1) in the mass spectrum, the fragment ion at 161 ($M-CH_3$)[21] is not accompanied by a significant fragment ion at 162, (2) the methyl group protons at δ 2.33 integrate for less than 3H's, and (3) there appears to be additional lines in the base of the peak at δ 21.1 of the ^{13}C NMR which might be attributed to the deuterium-labeled material.

4.1.11. Coupling of carbene complex 12 with trienyne 20. A solution of trienyne **20** (194 mg, 0.78 mmol) and carbene complex **12** (334 mg, 0.93 mmol) in dioxane (20 mL) was heated at reflux for 24 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed on a rotary evaporator. Hexane was added and the resulting green suspension was filtered through Celite. Iodine (381 mg, 1.50 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction mixture was poured into aqueous sodium thiosulfate solution in a separatory funnel and the aqueous layer was extracted two times with hexane. The combined hexane layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was removed on a rotary evaporator and final purification was achieved by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent. Benzofuran **29** (0.104 g, 40% yield) was obtained as a yellow oil. This compound appears to be homogenous by NMR and TLC analysis. ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1H), 7.52 (s, 1H), 7.43 (d, 2H, J=8.0 Hz), 7.34 (s, 1H), 6.88 (d, 1H, J=8.0 Hz), 6.81 (s, 1H), 6.01 (ddt, 1H, J=16.0, 10.0, 6.2 Hz), 6.00 (s, 2H), 5.11 (m, 2H), 4.03 (s, 3H), 3.48 (d, 2H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$): δ 165.4, 156.8, 151.8, 148.0, 137.2, 134.4, 131.2, 126.7, 125.1, 124.1, 119.3, 115.9, 114.2, 108.5, 105.4, 101.2, 99.3, 52.0, 44.7, 39.6; MS (EI): 336 (M, 0), 248 (21), 233 (19), 207 (55), 203 (13), 201 (16), 175 (12), 173 (11), 145 (12), 116 (14), 115 (21), 91 (19), 89 (65), 83 (14), 76 (23), 74 (100), 59 (64), 41 (24). HRMS calcd for $C_{20}H_{16}O_5$ 336.0998, found 336.0994.

4.1.12. Coupling of carbene complex 12 with trienyne 19. A solution of trienyne **19** (180 mg, 0.82 mmol) and carbene complex **12** (310 mg, 0.87 mmol) in dioxane (34 mL) was heated to 60°C for 32 h. The reaction mixture was allowed to cool to room temperature. Iodine (207 mg, 0.82 mmol) was added and the solution was stirred at room temperature

for 16 h. The reaction mixture was poured into aqueous sodium thiosulfate solution in a separatory funnel and the aqueous layer was extracted three times with 4:1 hexane/ethyl acetate. The combined hexane layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The solvent was removed on a rotary evaporator and final purification was achieved by flash column chromatography on silica gel (30 g) using 20:1 hexane/ethyl acetate as the eluent. Separation of benzofuran **10** from carbene oxidation product **31** proved to be extremely difficult; but was achieved by use of excessive amount of silica gel indicated. A colorless oil identified as benzofuran **10** (0.119 g, 47% yield) was obtained. ^{1}HNMR ($CDCl_3$): δ 7.40 (dd, 1H, J=8.1, 1.8 Hz), 7.31 (d, 1H, J=1.5 Hz), 6.96 (br d, 1H, J=1.8 Hz), 6.86 (d, 1H, J=8.1 Hz), 6.79 (s, 1H), 6.61 (d, 1H, J=1.5 Hz), 6.03 (s, 2H), 5.99 (ddt, 1H, J=16.9, 11.3, 6.6 Hz), 5.10 (d, 1H, J=16.9, 5.09 Hz (d, 1H, J=11.3 Hz), 4.02 (s, 3H), 3.44 (d, 2H, J=6.6 Hz); ^{13}CNMR ($CDCl_3$): δ 156.3, 148.3, 148.2, 145.0, 142.9, 138.1, 135.9, 131.3, 124.9, 119.4, 115.8, 112.8, 108.8, 107.9, 105.8, 101.5, 100.6, 56.4, 40.7. The spectral data are in agreement with those previously reported for this compound.[9] The major byproduct of this reaction was tentatively identified as the carbene oxidation product **31**: ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, 1H, J=8.1, 1.8 Hz); 7.47 (d, 1H, J=1.8 Hz), 6.82 (d, 1H, J=8.1 Hz), 6.02 (s, 2H), 3.86 (s, 3H). The chemical shifts are consistent with those previously reported for this compound.[22]

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