Efficient Synthesis of Furochromone and Furocoumarin Natural Products (Khellin, Pimpinellin, Isophellopterin) by Thermal Rearrangement of 4-Furyl-4-hydroxycyclobutenones

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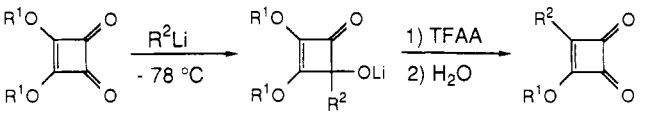
Diethyl squarate was converted in three steps to a highly functionalized benzofuran **6b**, which served as an intermediate in a high yield synthesis of khellinone (**9**), a versatile precursor to a variety of linear furochromones, including the natural product khellin. The use of dimethyl squarate gave a similar benzofuran intermediate **6a**, which was used in the first total syntheses of the furocoumarins pimpinellin (**14**) and isophellopterin (**15**). The key benzofuran intermediates were prepared by thermal rearrangement of (trimethylsilyl)ethynyl-substituted 4-furanyl-4-hydroxycyclobutenones **2a,b**. The alkynyl moiety of **6b** was readily converted to the acetyl group of khellinone by mercury-catalyzed hydrolysis. Alternatively, the TMS protecting group in **6a** was removed, and the lithium acetylide was treated with methyl chloroformate. The resulting trimethoxybenzofuran was treated with CAN to generate the quinone. Catalytic hydrogenation gave reduction of the quinone to the hydroquinone and alkyne to the *cis*-alkene. Simultaneous lactonization gave the desired coumarin **13**. Methylation of this at the phenolic site gave pimpinellin (**14**). The same phenol was prenylated to give isophellopterin (**15**). Finally, oxidation of the phenol with CAN gave a previously unknown orthoquinone, **16**, an angular isomer of psoralenquinone.

Due to its intriguing physiological activity, the naturally occurring furochromone khellin, obtained from the fruits and seeds of *Amni visnaga L.*, has a long history of attracting synthetic efforts. In regard to its biological activity, khellin has recently been shown to possess desirable lipid altering activity, thus making it a potential antiatherosclerotic agent.[1,2] Our interest in this compound was previously communicated as an efficient synthesis of khellinone (**9**), a versatile precursor to khellin and other furochromones.[3] Here, the experimental details of this work are presented along with further developments that provide access to a related class of compounds, the furocoumarins.[4]

Natural products in the furocoumarin series have been isolated from a variety of plant sources and classified as phytoalexins, i.e., part of the complex defensive response of the plant against fungal and insect challenges.[5] Thus, it is not surprising that many of these compounds have been shown to exhibit antibiotic, antifungal, molluscicidal, and piscocidal effects, while remaining relatively nontoxic toward mammals.[4] An example of particular note is 9-methoxypsoralen (methoxsalen), which has been increasingly used in photochemotherapy for management of such disorders as vitiligo, psoriasis, and mycosis fungoids.[6]

Although syntheses of many furocoumarins have been accomplished, no useful routes have been developed for the preparation of those natural products that contain a fully substituted aromatic B ring.[7] This problem has now been resolved by the methodology described here and is specifically illustrated in the syntheses of the angular furocoumarins pimpinellin (**14**) and isophellopterin (**15**) from a common intermediate employed in the khellinone synthesis.

Scheme I



Background

Most recent synthetic efforts toward khellin have been directed at its benzofuran precursor khellinone (**9**)[8] since it can be converted to khellin in 85% yield by a Claisen-like condensation with ethyl acetate, followed by acid-catalyzed cyclization and dehydration.[8c] Khellinone has the further advantage that it can be converted to khellin analogues when substituted acetates are used in the condensation.[2] Historically, construction of the fully substituted carbocyclic aromatic ring in khellinone in good yield has been the major synthetic challenge. Successful strategies must differentiate the four oxygen atoms on that ring, thus requiring the use of protecting groups. The most facile synthesis to date involves the cycloaddition of a furan chromium carbene complex with a substituted alkoxyalkyne, giving the fully substituted benzofuran directly.[8c] Although this approach solves many synthetic problems, the cycloaddition reaction proceeds in low yield (43%). The overall yield to khellinone was 17%, not including synthesis of the starting carbene complex or alkyne.

The key step in the khellinone synthesis given here rests on a recently reported new synthesis of highly substituted quinones and hydroquinones by thermal rearrangement of 4-alkynyl- and 4-aryl-4-hydroxycyclobutenones, respectively.[9] Synthesis of benzofurans by this method is straightforward and efficient. However, utilization of this rearrangement for the synthesis of furochromones or fu-

(1) Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672 and references therein.

(2) It is also of interest to note that the active ingredients of the khellah plant, of which khellin in a component, were used by the ancient Egyptians as an antispasmodic agent.

(3) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 3491.

(4) (a) For a review on the chemistry of furochromone and furocoumarin natural products, see: Mustafa, A. *Furopyrans and Furopyrones*; Wiley-Interscience: New York, 1967. (b) Ivie, G. W. *ACS Sym. Ser.* **1987**, *339*, 217.

(5) Berenbaum, M.; Feeny, P. *Science (Washington, D.C.)* **1981**, *212*, 927.

(6) Kornhauser, A.; Wamer, W. G.; Giles, A. L. *Science (Washington, D.C.)* **1982**, *217*, 733.

(7) For an attempted synthesis of isopimpinellin, see: Horton, W. J.; Paul, E. G. *J. Org. Chem.* **1982**, *24*, 2000.

(8) For recent khellin syntheses, see: (a) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863. (b) Gammill, R. B. *Tetrahedron Lett.* **1985**, *26*, 1385. (c) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *107*, 5823.

(9) (a) Karlsson, J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392. (b) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (c) Leibeskind, L. S.; Jewell, C. F.; Iyer, S. *J. Org. Chem.* **1986**, *51*, 3065.

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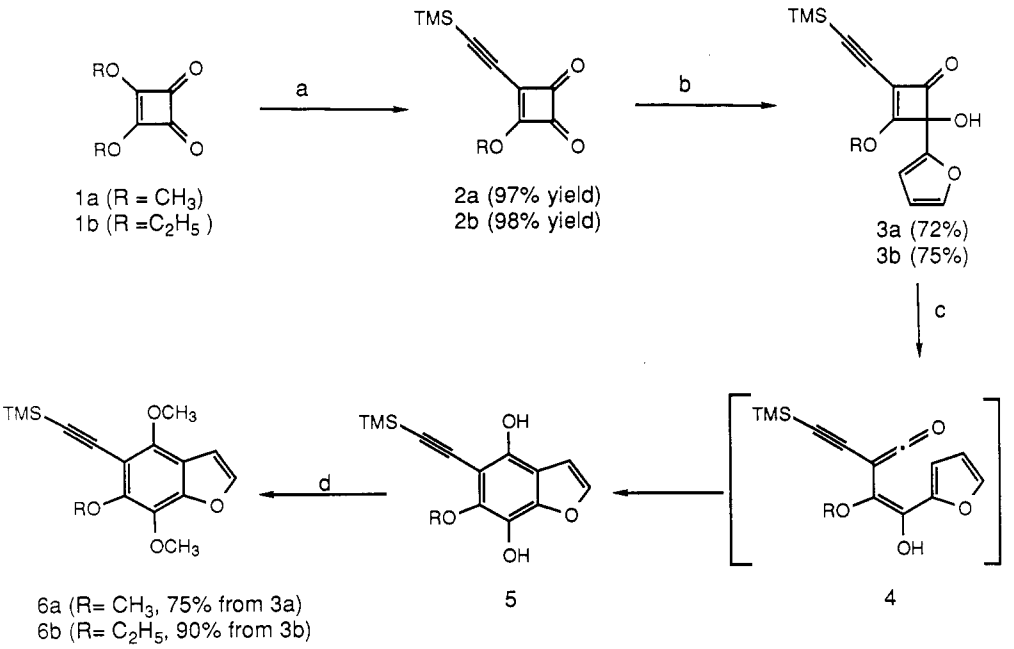
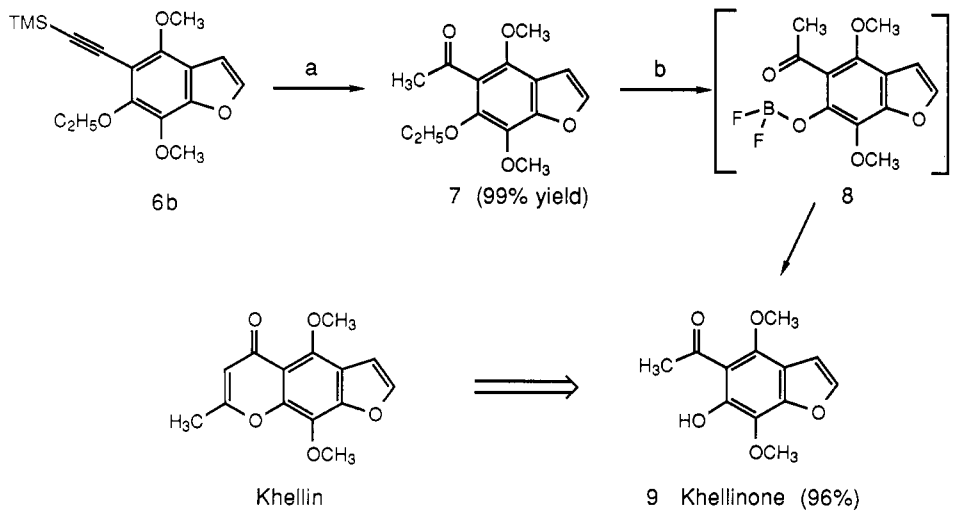
Scheme II[a]



[a] Reagents: (a) (i) TMS—≡—Li, THF; (ii) TFAA; (iii) H_2O; (b) 2-lithiofuran, THF/ether; (c) toluene reflux, 1 h; (d) MeI, K_2CO_3, 18-crown-6, toluene.

Scheme III[a]



[a] Reagents: (a) $HgSO_4$, H_2SO_4 (aqueous), THF; (b) (i) $BF_3 \cdot OEt_2$, CH_2Cl_2; (ii) NaOAc (aqueous).

rocoumarins hinges on construction of a suitably functionalized cyclobutenone bearing side chains that can ultimately be converted to the required γ-pyrone or δ-lactone ring. Fortunately, such compounds are now readily available from dialkyl squarates (dialkoxycyclobutenediones) and organolithium reagents in a one pot procedure as shown in Scheme I.[10]

A number of organolithium reagents that were considered to be useful synthons for the pyrone or lactone rings were investigated in this cyclobutenone synthesis. Lithio(trimethylsilyl)ethyne was ultimately found to provide an ideal synthetic equivalent for the acetyl group in khellinone and for the pimpinellin and isophellopterin syntheses since it was easily deprotected and functionalized to allow construction of the lactone ring needed in these furocoumarins.

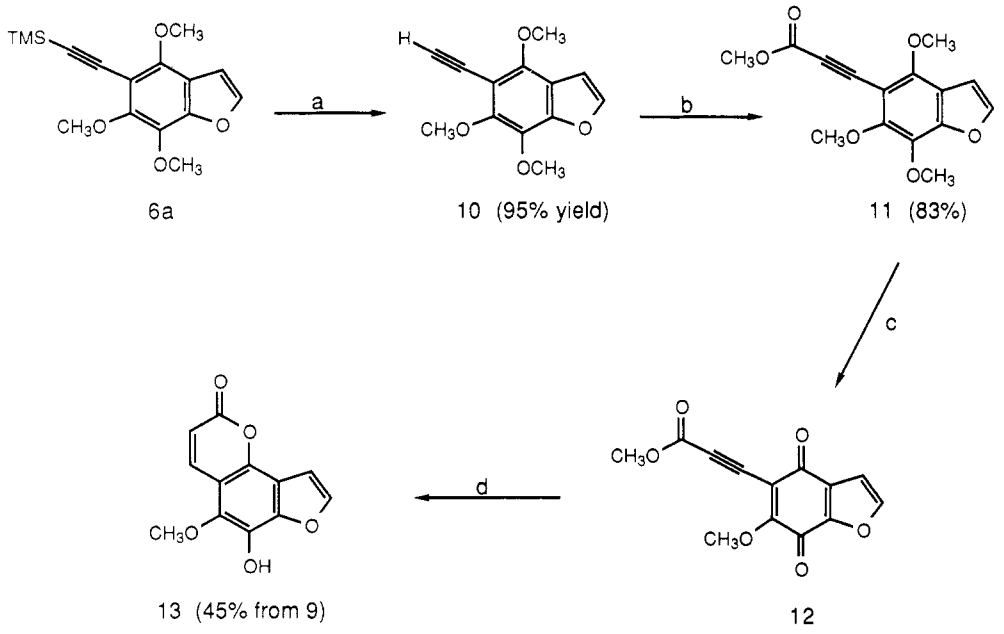
Results and Discussion

The key benzofuran intermediates **6a** and **6b** were prepared as outlined in Scheme II. The one-pot synthesis noted above was used to prepare 1-methoxy-2-(trimethylethynyl)cyclobutenedione **2a** in 97% chromatographed yield as a low-melting solid.[11] The regioselective addition of 2-lithiofuran to the more electron deficient carbonyl of **2a** was accomplished at −100 °C in dilute THF/diethyl ether (1:1). The resulting alcohol **3a** was obtained in 72% yield as a beige solid. Thermolysis of this solid in refluxing toluene (1 h) gave the desired hydroquinone **5** via electrocyclic ring closure of the conjugated ketene intermediate **4**. The hydroquinone was methylated in situ by treatment with methyl iodide, potassium carbonate, and 18-crown-6.[8a] The fully substituted benzofuran **6a** was isolated in 75% yield after chromatography.[12]

(10) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W., submitted for publication in *J. Org. Chem.*

(11) Dimethyl squarate was obtained in 80% yield from diethyl squarate by transesterification with methanol.

Scheme IV[a]



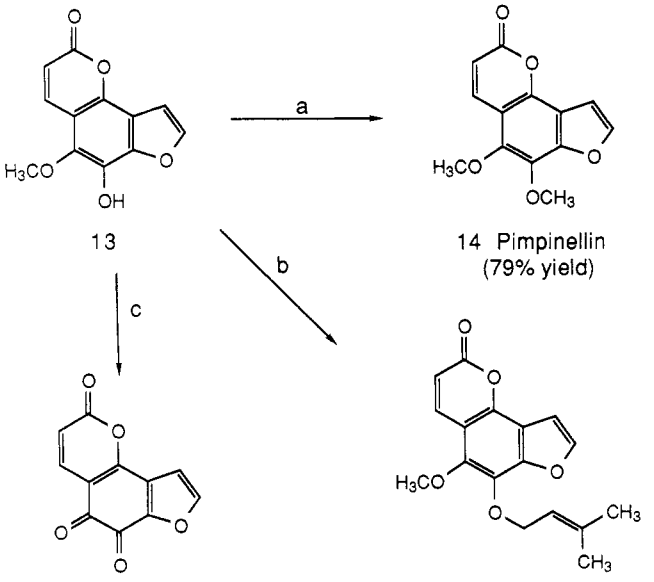
[a] Reagents: (a) (i) $AgNO_3$ (aqueous), EtOH; (ii) KCN (aqueous); (b) (i) *n*-BuLi, THF; (ii) CH_3OCOCl; (c) CAN, CH_3CN; (d) H_2, 5% Pd on $CaCO_3$ (Pb poisoned), THF.

The ethoxy-substituted benzofuran **6b** was prepared from commercially available diethylsquarate (**1b**) by the same procedure.

The benzofuran **6b** was taken on to khellinone (**9**) as outlined in Scheme III. Mercury(II)-catalyzed hydrolysis of **6b** generated the desired acetyl side chain, and **7** was obtained in close to quantitative yield after chromatography. The 6-ethoxy protecting group in **7** was selectively cleaved in the presence of the two methoxy groups by treatment with excess BF_3 etherate as was previously reported.[8c,13] An intermediate boron complex **8** could be isolated as an orange solid after simply quenching the reaction solution with water. The selectivity of this transformation is startling, and it remains unclear why this complex forms at the 6-position while the 4-methoxy group remains unreactive. It is of further interest to note that the 6-methoxy analogue of **7** was also selectively cleaved under these conditions.[14] Quenching of the boron complex with saturated sodium acetate gave clean conversion to khellinone **9**. The crude yellow solid (mp 97.5–99 °C) was essentially pure by ^1H NMR spectroscopy (96% yield). The overall yield of khellinone from commercially available diethyl squarate was 62% for the five-step sequence.

The benzofuran **6a** was also found to be a valuable precursor to the natural furocoumarins **14** and **15** (Scheme IV). In this regard, the trimethylsilyl protecting group was removed by serial treatment with aqueous silver nitrate and aqueous potassium cyanide.[15] The terminal acetylene **10** was isolated in 95% yield after chromatography. Conversion of **10** to its lithium salt and treatment of this with excess methyl chloroformate gave the desired ester **11** in 83% yield after careful chromatography. Oxidative demethylation with ceric ammonium nitrate[16] generated the paraquinone as an orange solid after an aqueous workup. The crude product **12** was used directly for the following reduction. Hydrogenation of the quinone over a Lindlar type catalyst gave the corresponding hydroquinone. Simultaneous reduction to the cis alkene allowed lactonization to occur. The cyclization was difficult to follow by TLC since the hydroquinone intermediate(s) had a similar R_f value. Nevertheless, the phenol **13** was isolated in 45% yield after chromatography/recrystallization.[17]

Scheme V[a]



[a] Reagents: (a) CH_3I, K_2CO_3, acetone; (b) $(CH_3)_2CCHCH_2Br$, K_2CO_3, acetone; (c) CAN, CH_3CN.

(12) The corresponding quinone was isolated as a high R_f side product after the thermolysis/methylation of **3a**.

(13) For an related dealkylation, see: Horton, W. J.; Paul, E. G. *J. Org. Chem.* **1959**, *24*, 2000. We thank one of the referees for pointing us to this reference.

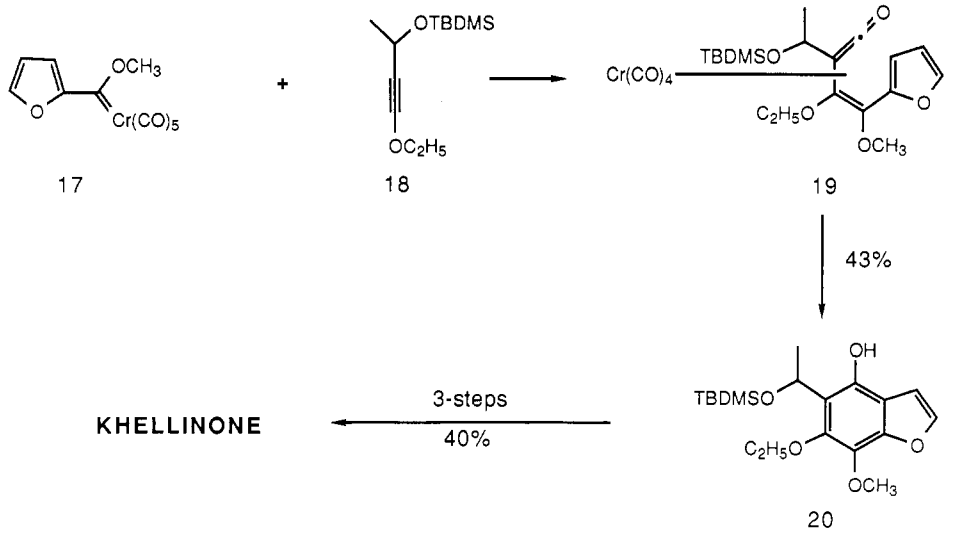
(14) The sequence from the methoxy compound **6a** gave somewhat lower yields than could be obtained with **6b**.

(15) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.

(16) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521.

(17) This phenol has previously been isolated as a degradation product during the structural determination of isophellopterin (**15**). See: Dreyer, D. L. *J. Org. Chem.* **1970**, *35*, 2294.

Scheme IV



The phenol **13** was converted to pinpinellin and isophellopterin as described in Scheme V. Although methylation of **13** with diazomethane is reported to give pimpinellin (**14**), we found the reaction with methyl iodide and potassium carbonate in acetone to be much cleaner. Recrystallization of the resulting crude product from methylene chloride/hexanes gave 79% yield of synthetic pimpinellin. Prenylation of phenol **13** with 4-bromo-2-methyl-2-butene and potassium carbonate in acetone gave synthetic isophellopterin in 89% recrystallized yield. These compounds showed physical and spectral properties identical with those reported for the natural products.

The novel *o*-quinone **16** (isopsoralenquinone), related to the previously reported *p*-quinone (psoralenquinone) was obtained in high yield by CAN oxidation of the phenol **13**. The regiochemistry of "isopsoralenquinone" was determined by reduction to the hydroquinone (SO_2) and methylation (CH_3I, K_2CO_3, acetone) to give pimpinellin.

Conclusions

The convergent syntheses of khellinone, pimpinellin, and isophellopterin presented here should facilitate the synthesis of analogues especially by modification of the furan ring.[2] Indeed, this is a particularly important area for subsequent investigations of khellin since modifications of the furan ring of this biologically significant compound has only recently gained serious attention.[18] A particularly interesting method would involve the benzofurans **6a,b** since they should undergo facile lithiation at the 2-position of the furan ring. Such lithiations and subsequent addition of electrophiles would provide a clear advantage over modification of khellin itself by an analogous route since the acidity of the C-7 methyl group in the pyrone nucleus of the natural product prevents selective metalation. It is further anticipated that the syntheses outlined here will allow not only modifications of the furan ring substitution pattern but also the incorporation of a variety of other heterocyclic and carbocyclic rings. In this light, it is instructive to compare the khellinone synthesis given here with the previously most efficient synthesis recently reported by Yamashita since both are convergent and could conceivably be used for analogue syntheses. (Schemes II and III vs Scheme VI).[8c] They are complimentary methods; however, the former requires fewer steps than the latter and results in a superior yield of khellinone—62% vs 17%. Also, the former starts with commercially available diethyl squarate and (trimethylsilyl)ethyne and the latter requires the synthesis of the chromium carbene complex and the ethoxyalkyne.

Finally, there is an important mechanistic point to be emphasized in comparing the two routes. Specifically, this concerns the formation and chemistry of the conjugated ketenes **5** and **19**, which, upon electrocyclic ring closure, give the respective benzofurans **6** and **20**. The regiochemistry of **6a,b** is easily explained since it is controlled by the selectivity of the furanylation of **2a,b**, i.e., the selectivity of attack of 2-lithiofuran at the more electrophilic carbonyl group of the cyclobutenediones **2a,b**. Subsequent electrocyclic ring opening gives **4** and ultimately the benzofurans **6a,b**. The regioselectivity of the metelocarbene reaction is less obvious. The example given in Scheme VI is one of several such annelations to appear, and they have generally been rationalized to arise as follows.[19] The conjugated ketene evolves from an initial cycloaddition of the carbene complex to the alkyne, a transformation whose regioselectivity is still not adequately understood. This is followed by a regiospecific insertion of carbon monoxide into the metelocyclic species and subsequent rearrangement to a diene chromium ketene complex, e.g., **19**. It is suggested that such complexation is necessary in order to preserve the s-cis comformation and thus facilitate the electrocyclic ring closure.[20] This may be true, but, from the results presented here, the metal is not necessary in order to achieve high selectivity in the ring closure of aryl-substituted vinyl ketenes. This is evidenced by the fact that the "metal-free" thermal generation of **4** from **3** also results in complete selectivity in its electrocyclic ring closure to **5**.

Experimental Section

All air- or water-sensitive reactions were carried out in flame-dried glassware under a slight positive pressure of argon,

(18) (a) Gammill, R. B.; Nash, S. A. *J. Org. Chem.* **1986**, *51*, 3116. (b) Nash, S. A.; Gammill, R. B. *Tetrahedron Lett.* **1987**, *28*, 4003.

(19) Fischer, H.; Muhlemeier, J.; Markl, R.; Dotz, K. H. *Chem. Ber.* **1982**, *115*, 1355. For an overview of this chemistry, see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(20) See, for example: (a) Dotz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Weinheim, 1983. (b) Dotz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689. (c) For a recent synthetic application see Dotz, K. H.; Popall, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1158.

which was purified by passing through a column of Drierite. Ethereal solvents were distilled from sodium (benzophenone indicator). Unless specified as "dry", the solvents were of unpurified reagent grade. Removal of solvents at 15–30 Torr was accomplished on a rotary evaporator. Flash column chromatography was performed with E. Merck silica gel (230–400 mesh). Proton NMR spectra were recorded on a General Electric QE 300 NMR (FT, 300 MHz) spectrometer. Chemical shifts are reported in ppm, with TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer 283 double-beam spectrophotometer. Low-resolution mass spectra (MS) were determined on a Finnigan 4000 spectrometer; high-resolution mass spectra (HRMS) were measured with a VG Analytic 7070E spectrometer. Unless otherwise stated, yields refer to isolated yields of compounds of greater than 95% purity as determined by ^{1}H NMR spectroscopy. Melting points are uncorrected.

3-Methoxy-4-[2-(trimethylsilyl)-1-ethynyl]cyclobutene-1,2-dione (2a). TMS acetylene (1.22 g, 12.4 mmol) was taken up in 30 mL of dry THF and cooled to −78 °C under argon. *n*-Butyllithium (1.42 M, 7.4 mL, 10.5 mmol) was added dropwise via syringe. After 30 min at −78 °C, the solution was added via cannula to a −78 °C solution of dimethyl squarate **1a** (1.42 g, 10 mmol) in 60 mL of dry THF. After 15 min, trifluoroacetic anhydride (1.72 mL, 12 mmol) was added. The resulting pale yellow solution was stirred for 15 min and then quenched at −78 °C with 20 mL of water. After the ice melted, 160 mL of ether was added, and the layers were separated. The deep yellow organic layer was washed with 50 mL of 10% sodium bicarbonate and 50 mL of brine, dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography (4 × 4.5 cm silica, methylene chloride). The yellow band was collected and stripped of solvent to yield 1.97 g (97%) of a deep yellow syrup, which crystallized upon refrigeration: mp 37–37.5 °C; IR ($CHCl_3$) 1795, 1600, 1360 and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9 H), 4.47 (s, 3 H); MS (EI), *m/z* 209 (12), 208 (16), 180 (21), 165 (78), 152 (26), 137 (100), 122 (44), 109 (48), 75 (21); HRMS, *m/z* calcd for $C_{10}H_{12}O_3Si$ (M^+) 208.0555, found 208.0544.

3-Ethoxy-4-[2-(trimethylsilyl)-1-ethynyl]cyclobutene-1,2-dione (2b). The same general procedure was used to give 543 mg (98%) of the title compound as a deep yellow syrup after purification by flash chromatography: IR ($CHCl_3$) 2970, 2150, 1810-1760, 1590, 1405, 1375, 1340, 1255, 1090, 1030, 995, and 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9 H), 1.52 (t, 3 H, *J* = 7.1 Hz), 4.82 (q, 2 H, *J* = 7.1 Hz); MS (EI), *m/z* 222 (15), 194 (10), 179 (12), 166 (13), 165 (100), 123 (42), 109 (40); HRMS, *m/z* calcd for $C_{11}H_{14}O_3Si$ (M^+) 222.0712, found 222.0712.

4-(2-Furanyl)-4-hydroxy-3-methoxy-2-[2-(trimethylsilyl)-1-ethynyl]-2-cyclobuten-1-one (3a). To a −15 °C solution of 1.2 mL of furan in 35 mL of dry THF was added 3.25 mL (4.6 mmol, 1.42 M in hexane) of *n*-butyllithium. After 30 min at −15 °C and 2 h at 0 °C, the solution was cooled to −78 °C and added via canula to a −100 °C solution of 914 mg (4.39 mmol) of dione **2a** in 120 mL of dry THF and 120 mL of ether. After 15 min at −100 °C and 10 min at −78 °C, the reaction was quenched with 100 mL of pH 7 buffer. When the ice melted, the layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography (4 × 6.5 cm silica gel, 20% ethyl acetate/hexane) to give 876 mg (72%) of the title compound as a tan solid. Off-white crystals could be obtained after recrystallization from methylene chloride/hexane: mp 113.5–114 °C; IR ($CHCl_3$) 3300 (br), 1745, 1615, 1355, and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9 H), 4.35 (s, 3 H), 6.38 (dd, 1 H, *J* = 3.2 Hz, 1.7 Hz), 6.48 (d, 1 H, *J* = 3.2 Hz), 7.41 (d, 1 H, *J* = 1.7 Hz); MS (EI), *m/z* 277 (4), 276 (22), 248 (22), 233 (22), 95 (25), 75 (26), 73 (100); HRMS, *m/z* calcd for $C_{14}H_{16}O_4Si$ (M^+) 276.0817, found 276.0818.

3-Ethoxy-4-(2-furanyl)-4-hydroxy-2-[2-(trimethylsilyl)-1-ethynyl]-2-cyclobuten-1-one (3b). The same general procedure was used to give 345 mg (75%) of the title compound as a beige solid after purification by flash chromatography. Off-white crystals could be obtained after recrystallization from methylene chloride/hexane: mp 103.5–104.5 °C; IR (KBr) 3500–3100, 2955, 2150, 1755, 1595, 1380, 1335, 995, 850, and 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9 H), 1.49 (t, 3 H, *J* = 7.1 Hz), 3.35 (s, 1 H), 4.71 (m, 2 H), 6.39 (m, 1 H), 6.47 (m, 1 H), 7.41 (m, 1 H); MS (EI), *m/z* 290 (35), 262 (25), 261 (11), 247 (12), 245 (26), 233 (11), 219 (23), 201 (10), 123 (15), 95 (27), 75 (25), 73 (100); HRMS, *m/z* calcd for $C_{15}H_{18}O_4Si$ (M^+) 290.0974, found 290.0937.

4,6,7-Trimethoxy-5-[2-(trimethylsilyl)-1-ethynyl]benzofuran (6a). A solution of 876 mg (3.17 mmol) of cyclobutenone **3a** in 75 mL of dry toluene was heated at 120 °C for 1 h, under argon. After the solution cooled off (3 h), 1.75 g (7.0 mmol) of 18-crown-6, 0.97 g (7.0 mmol) of potassium carbonate, and 2.1 mL (70 mmol) of methyl iodide were added under a flow of argon. The mixture was stirred for 12 h at 60 °C, diluted with 30 mL of ether, and washed with four 20-mL portions of water and 20 mL of brine. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (4 × 4 cm silica gel, 5% ethyl acetate/hexane); 723 mg (75%) of the title compound was isolated as a pale yellow oil: IR ($CHCl_3$) 3300 (br), 1745, 1615, 1355, and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 3.96 (s, 3 H), 4.04 (s, 3 H), 4.08 (s, 3 H), 6.82 (d, 1 H, *J* = 2.2 Hz), 7.52 (d, 1 H, *J* = 2.2 Hz); MS (EI), *m/z* 305 (18), 304 (100), 289 (48), 274 (21), 259 (26), 145 (21), 137 (28), 73 (64); HRMS, *m/z* calcd for $C_{16}H_{20}O_4Si$ (M^+) 304.1130, found 304.1111. Anal. Calcd for $C_{16}H_{20}O_4Si$: C, 63.13; H, 6.62. Found: C, 62.93; H, 6.66.

4,7-Dimethoxy-6-ethoxy-5-[2-(trimethylsilyl)-1-ethynyl]-benzofuran (6b). The same general procedure was used to give 350 mg (90%) of the title compound as a pale yellow oil after purification by flash chromatography: IR ($CHCl_3$) 2970, 2155, 1610, 1480, 1435, 1390, 1350, 1255, 1130, 1095, 1065, 1030, and 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 1.43 (t, 3 H, *J* = 7.1 Hz), 4.03 (s, 3 H), 4.08 (s, 3 H), 4.18 (q, 2 H, *J* = 7.1 Hz), 6.83 (d, 1 H, *J* = 2.3 Hz), 7.52 (d, 1 H, *J* = 2.3 Hz); MS (EI), *m/z* 318 (100), 289 (32), 275 (23), 261 (11), 260 (51), 245 (18), 231 (10), 73 (48); HRMS, *m/z* calcd for $C_{17}H_{22}O_4Si$ (M^+) 318.1287, found 318.1302.

5-Acetyl-4,7-dimethoxy-6-ethoxybenzofuran (7). To a solution of 339 mg (1.07 mmol) of the TMS alkyne **6b** in 28 mL of THF and 3 mL of water was added 6.1 mL of a saturated solution of mercuric sulfate in 1% aqueous sulfuric acid. After stirring for 15 h, the mixture was partitioned between 30 mL of brine and 80 mL of ether. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (3.5 × 3.5 cm silica, methylene chloride) to give 278 mg (99%) of the known title compound as a pale yellow oil:[8c] IR ($CHCl_3$) 2995, 1715, 1610, 1485, 1435, 1385, 1350, 1265, 1135, 1070, and 880 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz), 2.53 (s, 3 H), 3.98 (s, 3 H), 4.07 (s, 3 H), 4.12 (q, 2 H, *J* = 7.1 Hz), 6.86 (d, 1 H, *J* = 2.4 Hz), 7.56 (d, 1 H, *J* = 2.4 Hz).

5-Acetyl-4,7-dimethoxy-6-hydroxybenzofuran (Khellinone) (9). To a 0 °C solution of 182 mg (0.690 mmol) of the ethyl ether **7** in 20 mL of methylene chloride was added 0.87 mL (6.9 mmol) of boron trifluoride etherate. After being stirred under argon for 15 h at room temperature, the orange solution of the boron complex was quenched with a saturated solution of sodium acetate in water. The yellow organic layer was washed with water, dried over magnesium sulfate and concentrated to give 155 mg (96%) of the title compound as a yellow solid (mp 97.5–99 °C). Recrystallization from methanol/water gave yellow crystals (mp 98–99 °C); mp was undepressed upon admixture with an authentic sample of khellinone: IR ($CHCl_3$) 1635, 1475, 1420, 1370, 1300, 1280, 1150, and 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3 H), 4.03 (s, 3 H), 4.14 (s, 3 H), 6.89 (d, 1 H, *J* = 2.3 Hz), 7.50 (d, 1 H, *J* = 2.3 Hz); MS (EI), *m/z* 236 (100), 221 (64) 206 (27), 203 (22); HRMS, *m/z* calcd for $C_{12}H_{12}O_5$ (M^+) 236.06845, found 236.0691.

If the intermediate boron complex was quenched with water and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated, the boron complex could be isolated as an orange solid: ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3 H), 4.01 (s, 3 H), 4.34 (s, 3 H), 7.00 (d, 1 H, *J* = 2.5 Hz), 7.53 (d, 1 H, *J* = 2.5 Hz); MS (CI), *m/z* for $C_{12}H_{11}BF_2O_5$ (M^+) 285 (14); isotope cluster abundance calcd (M^+ − HF) 264 (24), 265 (100), 266 (13); found 264 (24), 265 (100), 266 (12).

5-Ethynyl-4,6,7-trimethoxybenzofuran (10). To a solution of 887 mg (2.92 mmol) of TMS acetylene **6a** in 33 mL of ethanol was added a solution of 817 mg (4.80 mmol) of silver(I) nitrate in 16 mL of water. After the gelatinous yellow mixture was stirred for 45 min, a solution of 2.0 g of potassium cyanide in 8 mL of

water was added. After 1.5 h, the colorless solution was partitioned between 120 mL of ether and 30 mL of water. The aqueous layer was extracted with two 35-mL portions of ether. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was purified by flash chromatography (4 × 4 cm silica gel, 5% ethyl acetate/hexane) to give 648 mg (96%) of the title compound as a colorless oil: IR ($CHCl_3$) 3315, 1605, 1485, 1345, 1085, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.47 (s, 1 H), 3.99 (s, 3 H), 4.07 (s, 3 H), 4.11 (s, 3 H), 6.88 (d, 1 H, J = 2.2 Hz), 7.56 (d, 1 H, J = 2.2 Hz); MS (EI), m/z 232 (100), 217 (73), 174 (32); HRMS, m/z calcd for $C_{13}H_{12}O_4$ (M^+) 232.0735, found 232.0738.

5-[2-(Methoxycarbonyl)-1-ethynyl]-4,6,7-trimethoxybenzofuran (11). To a −78 °C solution of 648 mg (2.79 mmol) of the alkyne **10** in 50 mL of dry THF was added 2.1 mL (2.9 mmol, 1.4 M in hexane) of *n*-butyllithium. After 5 min, 1.5 mL of methylchloroformate was added and the mixture was stirred for 15 min at −78 °C; 15 mL of 10% ammonium chloride solution and 60 mL of ether were added. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The solid residue was purified by flash chromatography (5 × 6 cm silica, 10% ethyl acetate/hexane) to give 670 mg (83%) of the title compound as a white solid. An analytical sample was prepared by recrystallization from methylene chloride/hexane: mp 115.5–116 °C; IR ($CHCl_3$) 2945, 2220, 1710, 1605, 1485, 1240, 1105, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 4.01 (s, 3 H), 4.06 (s, 3 H), 4.15 (s, 3 H), 6.90 (d, 1 H, J = 2.1 Hz), 7.58 (d, 1 H, J = 2.1 Hz); MS (EI), m/z 290 (100), 275 (69), 201 (21); HRMS, m/z calcd for $C_{15}H_{14}O_6$ (M^+) 290.0790, found 290.0781.

6-Methoxy-5-[2-(methoxycarbonyl)-1-ethynyl]-4,7-benzofuranquinone (12). To a 0 °C solution of 670 mg (2.31 mmol) of the trimethyl ether **11** in 32 mL of acetonitrile and 3 mL of water was added a solution of 2.77 g (5.05 mmol) of ceric ammonium nitrate in 10 mL of water. After 15 min at 0 °C, the mixture was partitioned between 25 mL of water and 50 mL of methylene chloride. The aqueous layer was extracted with 50 mL of methylene chloride, and the combined organic layers were washed with 25 mL of water, dried over magnesium sulfate, and concentrated to give the title compound in greater than quantitative yield as an orange solid. This material was converted directly to the phenol **13**. The compound could be purified (with decomposition) by flash chromatography: mp 90–95 °C; IR ($CHCl_3$) 2220, 1720, 1700, 1685, 1330, 1280, and 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 4.49 (s, 3 H), 6.90 (d, 1 H, J = 1.6 Hz), 7.77 (d, 1 H, J = 1.6 Hz); MS (EI), m/z 260 (61), 229 (49), 202 (52), 201 (73), 174 (92), 145 (35), 101 (60), 94 (47), 92 (61), 66 (100); HRMS calcd for $C_{13}H_8O_6$ (M^+) 260.0321, found 260.0327.

6-Hydroxy-5-methoxyangelicin (13). To a solution of the crude quinone **12** in 100 mL of dry THF was added 300 mg of 5% palladium on calcium carbonate (lead poisoned). The mixture was stirred under a balloon of hydrogen for 2 h and then filtered through Celite (washed with THF). Removal of solvent gave a brown solid residue, which was triturated with methylene chloride. The resulting beige solid was saved, and the supernatant was purified by flash chromatography (4 × 7 cm silica, 40% ethyl acetate/hexane). The fractions containing the desired product were combined with the beige solid. Recrystallization from chloroform gave 239 mg (45%) of the title compound as a beige solid (mp 228.5–230 °C). Another recrystallization gave a yellow solid: mp 231–231.5 °C; IR (KBr) 3200 (br), 1695, 1620, 1580, 1405, 1385, 1360, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (s, 3 H), 5.70 (s, 1 H), 6.42 (d, 1 H, J = 9.8 Hz), 7.09 (d, 1 H, J = 2.2 Hz), 7.68 (d, 1 H, J = 2.2 Hz), 8.02 (d, 1 H, J = 9.8 Hz); MS (EI), m/z 232 (88), 217 (89), 189 (35), 77 (34), 71 (34), 69 (41), 67 (41), 57 (100), 55 (63); HRMS calcd for $C_{12}H_8O_5$ (M^+) 232.03715, found 232.0363.

5,6-Dimethoxyangelicin (Pimpinellin) (14). To a solution of 55.0 mg (0.237 mmol) of the phenol **13** in 20 mL of acetone was added 138 mg (1.0 mmol) of potassium carbonate and 0.50 mL of methyl iodide. After 3 h, the mixture was partitioned between 40 mL of methylene chloride and 20 mL of water. The aqueous layer was extracted with 20 mL of methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The residue was recrystallized from methylene chloride/hexane to give 46.1 mg (79%) of the title compound as an off-white solid: mp 117–118 °C (lit. mp 119 °C) (The ^1H NMR spectrum was identical with the published values.[16]): IR ($CHCl_3$) 1735, 1635, 1585, 1485, 1350, 1125, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.06 (s, 3 H), 4.15 (s, 3 H), 6.37 (d, J = 9.7 Hz, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 7.65 (d, J = 2.2 Hz, 1 H), 8.08 (d, J = 9.7 Hz, 1 H); MS (EI), m/z 246 (100), 231 (82), 175 (30), 160 (25), 147 (47), 104 (26), 91 (22), 76 (25), 66 (42); HRMS, m/z calcd for $C_{13}H_{10}O_5$ (M^+) 246.0528, found 246.0546.

6-Isopentenyl-5-methoxyangelicin (Isophellopterin) (15). To a solution of 50 mg (0.215 mmol) of the phenol (**13**) in 17 mL of acetone was added 161 mg (1.07 mmol) of prenyl bromide and 148 mg (1.07 mmol) of anhydrous potassium carbonate. After being stirred for 4 h, the mixture was partitioned between 50 mL of methylene chloride and 20 mL of water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The solid residue was recrystallized from methylene chloride/hexane to give 57.3 mg (89%) of the title compound as an off-white solid, mp 87.5–89 °C (lit.[16] mp 95–96 °C) (The ^1H NMR spectrum was identical to the published values.): IR ($CHCl_3$) 1730, 1345, 1120, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (s, 3 H), 1.77 (s, 3 H), 4.05 (s, 3 H), 4.82 (d, 2 H, J = 7.2 Hz), 5.58 (t, 1 H, J = 7.2 Hz), 6.37 (d, 1 H, J = 9.8 Hz), 7.08 (d, 1 H, J = 2.2 Hz), 7.66 (d, 1 H, J = 2.2 Hz), 8.10 (d, 1 H, J = 9.8 Hz); MS (EI), m/z 300 (0.4), 232 (100), 217 (65), 69 (83); HRMS, m/z calcd for $C_{17}H_{16}O_5$ (M^+) 300.09975, found 300.09975.

Isopsoralenquinone (16). To a 0 °C solution of 94.2 mg (0.406 mmol) of the phenol **13** in 50 mL of acetonitrile was added a solution of 493 mg (0.900 mmol) of ceric ammonium nitrate in 10 mL of water. After 30 min at 0 °C, the mixture was taken up in 110 mL of methylene chloride and washed with 20 mL of water and 20 mL of brine. The organic layer was dried over magnesium sulfate and concentrated. The residue was recrystallized from absolute ethanol (30 mL) to give 73.4 mg (84%) of dark red needles: mp 214 °C dec; IR (KBr) 3125, 1730, 1680, 1550, 1435, 1410, 1330, 1010, and 795 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.41 (d, 1 H, J = 9.7 Hz), 7.13 (d, 1 H, J = 1.8 Hz), 7.88 (d, 1 H, J = 9.7 Hz), 8.28 (d, 1 H, J = 1.8 Hz); MS (EI), m/z 216 (76), 188 (67), 160 (100), 132 (29), 104 (55), 103 (23), 76 (42), 66 (48); HRMS, m/z calcd for $C_{11}H_4O_5$ (M^+) 216.00585, found 216.0059. The regiochemistry of **16** was proven by reduction to the hydroquinone (sulfur dioxide, water) followed by methylation (methyl iodide, potassium carbonate, acetone). The crude solid product had the same ^1H NMR spectrum as pimpinellin (**14**).

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