Notes

Concise Synthesis of Espintanol and Selected Regioisomeric Analogs

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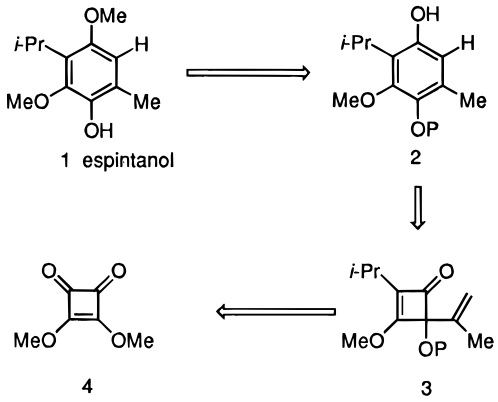
Reported here is the synthesis of the leishmanicidal and trypanocidal monoterpene espintanol (**1**) in 64% overall yield starting with dimethyl squarate. This antiparasitic monoterpene was isolated by Hocquemiller and co-workers in 1991 from *Oxandra espintana*. Its structure was established by spectroscopic methods and confirmed by a nine-step synthesis starting from carvacrol in an approximate 2% overall yield.[2] An improved seven-step synthesis (11% overall yield) starting from commercially available ethyl 3-ethoxy-2-butenoate was recently reported by Wadsworth and Losch.[3]

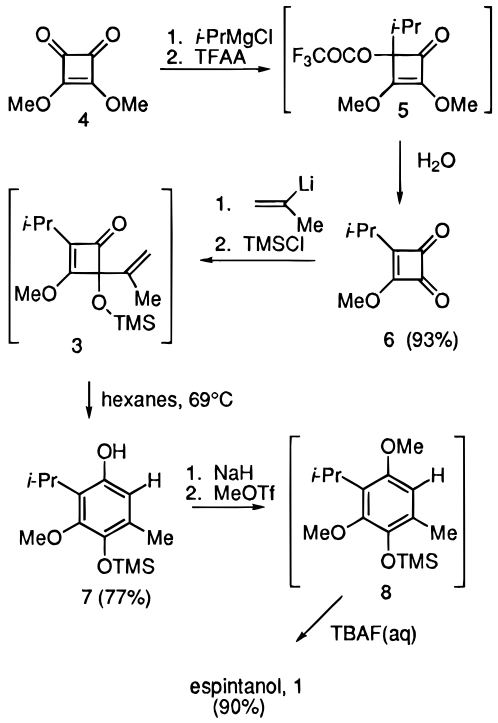
The successful retrosynthetic plan involves conversion of dimethyl squarate (**4**) to the 4-alkenylcyclobutenone **3** which leads to the phenol **2** upon thermal ring expansion (Scheme 1).[4−6] Methylation and deprotection then completes a regiospecific route to espintanol (**1**).

The new synthesis of espintanol (**1**) is shown in Scheme 2. Treatment of dimethyl squarate[7] (**4**) with isopropylmagnesium chloride at 0 °C followed by hydrolysis (TFAA/H_2O) gave **6** in 93% yield.[7] Treatment of **6** with 2-lithiopropene followed by a TMSCl quench resulted in 3-methoxy-4-(1-methylethenyl)-2-(1-methylethyl)-4-(trimethylsiloxy)-2-cyclobuten-1-one (**3**). This compound was not isolated but subjected to thermolysis (hexanes, 69 °C) directly to give the monoprotected phenol **7** in 77% yield. The ring expansion was found to be a facile process. For example, the phenol was realized when an ether/THF solution of crude **3** was heated at 45 °C (oil bath) for 4 h or simply left standing at room temperature for 2 days. Treatment of a THF solution of **7** with NaH followed by MeOTf and desilylation of the crude methylated product **8** during workup, gave espintanol (**1**) in 90% yield.

Scheme 1



Scheme 2



The synthesis outlined here is efficient, high yielding, and ideally suited for the preparation of espintanol analogs. In this regard, selected syntheses of regioisomeric examples are given in Scheme 3. 3,4-Dimethoxy-5-methyl-2-(1-methylethyl)phenol (**10**) is particularly suited for the method and was prepared in 65% overall yield in three steps starting from **4**. Specifically, treatment of **6** with 2-lithiopropene (prepared from 2-bromopropene and *tert*-butyllithium) followed by methyl triflate gave **9.** This was subjected immediately to thermolysis in refluxing hexanes (69 °C) to give **10**.

In an analogous manner, 3,4-dimethoxy-6-methyl-2-(1-methylethyl)phenol (**14**) was prepared. In this case the lithium reagent was generated from a mixture of the *E*- and *Z*-isomers of 1-bromopropene upon treatment with *tert*-butyllithium. Under these conditions the corre-

(1) This work was accomplished primarily by Craig S. Tomooka, an undergraduate Honors student at UCI.

(2) Hocquemiller, R.; Cortes, D.; Arango, G. J.; Myint, S. H.; Cave, A.; Angelo, A.; Munoz, V.; Fournet, A. *J. Nat. Prod.* **1991**, *54*, 445.

(3) Wadsworth, D. J.; Losch, S. *Tetrahedron* **1994**, *50*, 8673.

(4) For recent reviews of this subject see: (a) Moore, H. W.; Yerxa, B. R. *ChemTracts* **1992**, *5*, 273. (b) Moore, H. W.; Yerxa, B. R. Synthetic Utility of Cyclobutenones. In *Strain in Organic Chemistry*; JAI Press: London, 1995; Vol. 4, pp 81−162.

(5) For selected examples of recent work describing the rearrangement of cyclobutenones to quinones or other compounds, see: (a) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.*, **1994**, *59*, 7572. (b) Sun, L. J.; Liebeskind, L. S. *J. Org. Chem.*, **1994**, *59*, 6856. (c) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783. (d) Liu, H.; Gayo, L. M.; Sullivan, R. W.; Choi, A. Y. H., Moore, H. W. *J. Org. Chem.* **1994**, *59*, 3284.

(6) For examples of the regioselective synthesis of cyclobutenones: (a) Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.*, **1992**, *57*, 6896. (b) Liebeskind, L. S.; Granburg, K. L.; Zhang, J. *J. Org. Chem.*, **1992**, *57*, 4345. (c) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.*, **1990**, *55*, 5350.

(7) Dimethyl squarate is commercially available. It can also be prepared from squaric acid: (a) Cohen, S.; Cohen, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 1533. (b) Liu, H.; Tomooka, C. S., Moore, H. W. Unpublished results.

(8) Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550.

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sponding *E*- and *Z*-isomers of 1-lithiopropene are generated along with 1-lithiopropyne. Treatment of **6** with this mixture followed by methyl triflate gave **13a**−**c**, thermolysis (69 °C, hexanes) of which resulted in the phenol **14** in 65% overall yield. It is noteworthy that all three cyclobutenone derivatives **13a**−**c** give **14**. This was established by the following control experiments. Generation of **13a** as described above except using pure (*E*)-1-bromopropene gave **14** in 77% upon thermolysis. Likewise **13c** was prepared using 1-lithiopropyne[8] and observed to give **14** in 44% yield.[9]

The synthesis of 2,4-dimethoxy-5-methyl-3-(1-methylethyl)phenol (**12**) was not as simple. However, the phenol was prepared in reasonable yield in analogy to the synthesis of **13**/**14**. Specifically, cyclobutenedione **6** was again converted to a mixture of **11a**−**c** upon treatment with the above mixture of lithium reagents followed by acetic anhydride. Thermolysis (hexanes, 69 °C), methylation (MeOTf), and ester hydrolysis (NaOH) then gave the phenol **12** in 41% overall yield.

In conclusion, we make the following significant points: (1) Espintanol (**1**) is now available in gram quantities from dimethyl squarate by the most efficient synthesis to yet appear in the literature. (2) This method can be employed to prepare numerous analogs of this biologically active molecule as illustrated by the regiospecific syntheses of 3,4-dimethoxy-5-methyl-2-(1-methylethyl)phenol (**10**), 2,4-dimethoxy-5-methyl-2-(1-methylethyl)phenol (**12**), and 3,4-dimethoxy-6-methyl-2-(1-methylethyl)phenol (**14**).

Experimental Section

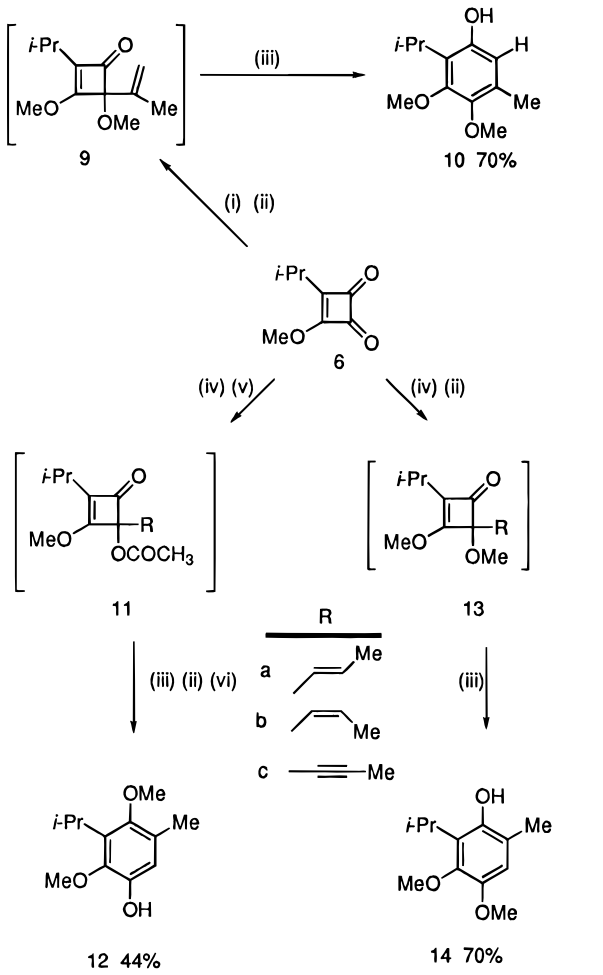
General Methods. All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran was distilled from sodium−benzophenone prior to use. All other reagents used were obtained from commercial sources and used without further purification. Flash chromatography was performed using silica gel 230−400 mesh. IR spectra were obtained from thin films prepared by evaporation of $CHCl_3$ solutions on NaCl plates. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$.

3-Methoxy-4-(1-methylethyl)-3-cyclobutene-1,2-dione (6). Under an atmosphere of nitrogen, isopropylmagnesium chloride (2.0 M in THF, 26 mL, 52 mmole) was added in a dropwise fashion to a solution of dimethyl squarate (7.11 g, 50.0 mmol) in anhydrous THF (300 mL) at −78 °C. After the reaction mixture was allowed to warm to 0 °C, trifluoroacetic anhydride (TFAA) (10.6 mL, 75 mmol) was added dropwise over a period of 2 min. After an additional 10 min at 0 °C, the solution was cooled to −78 °C and poured into H_2O (50 mL). After the reaction solution was then treated with 10% $NaHCO_3$ (50 mL), the resulting organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) afforded the desired cyclobutenedione **6** as a yellow oil (7.14 g, 93%): IR 1792, 1762, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 3H), 3.01 (hept, J = 7.1 Hz, 1H), 1.28 (d, J = 7.1 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 198.7, 195.6, 195.3, 189.3, 61.8, 27.7, 19.9 (2C); LRMS (CI) *m*/*e* 155 (M + 1, 100), 154 (M, 4), 127 (14), 126 (23), 111 (11); HRMS calcd for $C_8H_{11}O_3$ (M + 1) 155.0708, found 155.0710.

3-Methoxy-5-methyl-2-(1-methylethyl)-4-(trimethylsiloxy)phenol (7). Under an atmosphere of nitrogen, *tert*-butyllithium (1.7 M in pentane, 12.4 mL, 21.0 mmole) was added in a dropwise fashion to anhydrous THF (20 mL) at −78 °C. After 5 min, 2-bromopropene (0.93 mL, 10.5 mmole) was added dropwise to this solution over a 2 min period. After an additional 5 min, the resulting lithium reagent was added via cannula to a −78 °C anhydrous THF (50 mL) solution of **6** (1.54 g, 10.0 mmol). Chlorotrimethylsilane (1.5 mL, 12.0 mmol) was then added via syringe. The solution was allowed to warm to 0 °C, recooled to −78 °C, and poured into a solution of 5% $NaHCO_3$ (50 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give crude 3-methoxy-4-(1-methylethenyl)-2-(1-methylethyl)-4-(trimethylsiloxy)-2-cyclobuten-1-one (**3**) [^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.01 (s, 1H), 3.96 (s, 3H), 2.49 (hept, J = 7.1 Hz, 1H), 1.71 (s, 3H), 1.15 (d, J = 7.0 Hz, 6H), 0.14 (s, 9H)]. Hexanes (1000 mL) were added, and the resulting solution was heated at 69 °C for 1 h. The concentrated product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to yield the phenol **7** (2.06 g, 77%) (hexanes) as a white solid: mp 82.0−83.0 °C; IR 3410 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 4.47 (s, 1H), 3.68 (s, 3H), 3.41 (hept, J = 7.2 Hz, 1H), 2.11 (s, 3H), 1.34 (d, J = 7.2 Hz, 6H), 0.22 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 149.7, 148.3, 141.2, 127.3, 125.5, 113.1, 60.4, 25.3, 21.3 (2C), 16.5, 0.4 (3C); LRMS (CI) *m*/*e* 268 (M, 100), 253 (33), 238 (25); HRMS calcd for $C_{14}H_{24}O_3Si$ 268.1495, found 268.1489.

2,4-Dimethoxy-6-methyl-3-(1-methylethyl)phenol (Espintanol, 1). Under an atmosphere of nitrogen, anhydrous THF (10 mL) was added to a mixture of **7** (0.27 g, 1.0 mmol) and sodium hydride (50% in mineral oil, 0.19 g, 4.0 mmol) at −78 °C. The reaction mixture was allowed to warm to 0 °C, was maintained at this temperature for 30 min, and then recooled

Scheme 3



(i) 2-lithiopropene/THF/-78 °C; (ii) MeOft; (iii) hexanes, 69°C; (iv) E- and Z-1-bromopropene/THF/-78 °C/*tert*-butyllithium 2 min; (v) acetic anhydride; (vi) NaOH

(9) The mechanism of this reaction involves ring expansion of the cyclobutenone to a diradical intermediate and subsequent H-atom abstraction from the hexanes solvent. For details on the diradical formation, see: Foland, L. D.; Karlsson J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

to −78 °C. Methyl trifluoromethanesulfonate (0.17 mL, 1.5 mmol) was added dropwise to the green solution over a 2 min period to give 3,5-dimethoxy-1-methyl-4-(1-methylethyl)-2-(trimethylsiloxy)benzene. In a separate experiment this compound was isolated and purified by flash chromatography on silica gel and shown to have the following properties: mp 29.0−29.5 °C (hexanes); IR 2955, 1484, 1413, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.44 (hept, J = 7.1 Hz, 1H), 2.17 (s, 3H), 1.31 (d, J = 7.0 Hz, 6H), 0.22 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 152.7, 149.6, 141.3, 127.6, 126.7, 108.8, 60.4, 55.7, 25.4, 21.4 (2C), 16.9, 0.5 (3C); LRMS (CI) m/e 282 (M, 100), 267 (30), 252 (19); HRMS calcd for $C_{15}H_{26}O_3Si$ 282.1651; found 282.1666.

A THF solution of the above compound was cooled to 0 °C and stirred for 10 min, and then H_2O (1 mL) was added to the beige solution, followed by TBAF (1.1 M in THF, 1.1 mL, 1.2 mmol). The green solution was poured into 10% NH_4Cl (40 mL). After the organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give espintanol (**1**) (0.19 g, 90%) as a white solid: mp 45.0−45.5 °C (cold hexanes) (lit.[2] mp 42.3−43.0 °C); IR 3444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 1H), 5.40 (s, 1H), 3.76 (s, 6H), 3.35 (hept, J = 7.1 Hz, 1H), 2.23 (s, 3H), 1.34 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 144.8, 141.1, 126.8, 121.4, 110.0, 61.8, 55.8, 25.9, 21.2 (2C), 15.7; LRMS (EI) m/e 210 (M, 92), 195 (100), 180 (27); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found; 210.1263.

3,4-Dimethoxy-5-methyl-2-(1-methylethyl)phenol (10). Under an atmosphere of nitrogen, *tert*-butyllithium (1.7 M in pentane, 2.5 mL, 4.2 mmol) was added in a dropwise fashion to anhydrous THF (10 mL) at −78 °C. After 5 min, 2-bromopropene (0.19 mL, 2.1 mmol) was added dropwise to this solution over a 2 min period. After an additional 5 min, the resulting lithium reagent was added via cannula to at −78 °C to an anhydrous THF (20 mL) solution of **6** (0.31 g, 2.0 mmol). Upon addition of methyl trifluoromethanesulfonate (0.36 mL, 3.2 mmol), the yellow solution gradually turned clear as it was allowed to warm to 0 °C and maintained at this temperature for 10 min. After the solution was recooled to −78 °C, it was poured into a solution of 5% $NaHCO_3$ (20 mL). The organic layer was separated; the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give crude 3,4-dimethoxy-4-(1-methylethenyl)-2-(1-methylethyl)-2-cyclobuten-1-one (**9**) [^1H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.04 (s, 1H), 3.96 (s, 3H), 3.36 (s, 3H), 2.54 (hept, J = 7.0 Hz, 1H), 1.75 (s, 3H), 1.14 (d, J = 7.0 Hz, 6H)]. Hexanes (200 mL) were added, and the clear solution was warmed to 69 °C for 2 h. The product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give the title compound **10** (0.38 g, 70%) as a white solid: mp 52.5−53.5 °C (hexanes); IR 3387 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.04 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.44 (hept, J = 7.1 Hz, 1H), 2.18 (s, 3H), 1.35 (d, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 150.5, 145.2, 129.3, 126.1, 113.0, 61.0, 60.3, 25.2, 21.3 (2C), 15.6; LRMS (EI) m/e 210 (M, 81), 195 (100), 180 (39); HRMS calcd for $C_{12}H_{18}O_3$ 210.125;, found 210.1249.

2,4-Dimethoxy-5-methyl-3-(1-methylethyl)phenol (12). Under an atmosphere of nitrogen, *tert*-butyllithium (1.7 M in pentane, 2.47 mL, 4.2 mmole) was added in a dropwise fashion to anhydrous THF (10 mL) at −78 °C. After 5 min, 1-bromo-1-propene (as a mixture of *E*- and *Z*-isomers) (0.18 mL, 2.1 mmol) was added dropwise to this solution over a 2 min period. After an additional 5 min, the resulting lithium reagent was added via cannula to a −78 °C anhydrous THF (20 mL) solution of **6** (0.31 g, 2.0 mmol). Once acetic anhydride (0.23 mL, 2.4 mmol) was added, the solution was allowed to warm to 0 °C, maintained at this temperature for 10 min, recooled to −78 °C, and poured into a cold solution of 5% $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a mixture of the *E*- and *Z*-isomers of **11** along with a small amount of the 4-propynyl analog. *E*-Isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.9−5.7 (m, 1H), 5.57 (d, J = 12.0 Hz, 1H), 4.07 (s, 3H), 3.38 (s, 3H), 2.54 (hept, J = 7.0 Hz, 1H), 2.09 (s, 3H), 1.75 (s, 3H), 1.16 (d, J = 7.0 Hz, 6H). *Z*-Isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 6.0−5.8 (m, 1H), 5.56 (d, J = 12.0 Hz, 1H), 4.02 (s, 3H), 2.56 (hept, J = 7.0 Hz, 1H), 2.09 (s, 3H), 1.77 (s, 3H), 1.17 (d, J = 7.0 Hz, 6H). 4-Acetoxy-3-methoxy-2-(1-methylethyl)-4-(1-propynyl)-2-cyclobutene-1-one: ^1H NMR (500 MHz, $CDCl_3$) δ 4.17 (s, 3H), 3.50 (s, 3H), 2.56 (hept, J = 7.1 Hz, 1H), 2.09 (s, 3H), 1.93 (s, 3H), 1.17 (d, J = 7.0 Hz, 6H). After hexanes (200 mL) were added, the clear solution was warmed to 69 °C for 2 h. The concentrated yellow product was then added to sodium hydride (50% in mineral oil, 0.19 g, 4.0 mmol) and cooled to −78 °C. After the addition of THF (30 mL), the reaction mixture was allowed to warm to 0 °C, maintained at this temperature for 30 min, and then recooled to −78 °C. Methyl trifluoromethanesulfonate (0.17 mL, 1.5 mmol) was added dropwise to the dark brown solution over a 2 min period. Once the orangish-red mixture was rewarmed to 0 °C and maintained at this temperature for 30 min, a solution of sodium hydroxide (5 N, 2 mL, 10 mmol) was added, along with tetrabutylammonium iodide (0.04 g, 0.20 mmol). After 6 h hydrchloric acid (5 N, 2 mL) was added. The organic phase of the mixture was separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The concentrated product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give the title compound **12** (0.18 g, 44%) as a white solid: mp 103.0−104.0 °C; IR 3487 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H), 5.23 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 3.39 (s, J = 7.0 Hz, hept), 2.22 (s, 3H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 145.0, 143.7, 134.2, 127.5, 115.2, 61.6, 61.1, 26.1, 22.3 (2C), 16.4; LRMS (CI) m/e 210 (M, 100), 195 (21), 180 (5); HRMS calcd for $C_{14}H_{24}O_3Si$ 210.1256; found 210.1262.

3,4-Dimethoxy-6-methyl-2-(1-methylethyl)phenol (14). Under an atmosphere of nitrogen, *tert*-butyllithium (1.7 M in pentane, 2.5 mL, 4.2 mmol) was added in a dropwise fashion to anhydrous THF (10 mL) at −78 °C. After 5 min, 1-bromo-1-propene (as a mixture of *E*- and *Z*-isomers) (0.18 mL, 2.1 mmol) was added dropwise to this solution over a 2 min period. After an additional 5 min, the resulting lithium reagent was added via cannula to a −78 °C anhydrous THF (20 mL) solution of 3-methoxy-4-(1-methylethyl)-3-cyclobutene-1,2-dione **6** (0.31 g, 2.0 mmol). Upon addition of methyl trifluoromethanesulfonate (0.4 mL, 3.2 mmol), the yellow solution gradually turned clear as it was allowed to warm to 0 °C and maintained at this temperature for 10 min. After the solution was recooled to −78 °C, it was poured into a cold solution of 5% $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a mixture of the *E*- and *Z*-isomers of 3,4-dimethoxy-2-(1-methylethyl)-4-(1-propenyl)-2-cyclobuten-1-one (**13a**,**b**) along with the 4-propynyl analog **13c** in a ratio of 1:5:4, respectively. These were not isolated in a pure state but shown to have the following properties from analysis of spectral data obtained on the partially purified products. *E*-Isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 6.0−5.8 (m, 1H), 5.58 (d, J = 15.6 Hz, 1H), 4.00 (s, 3H), 3.38 (s, 3H), 2.54 (hept, J = 7.0, 1H), 1.75 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.9 Hz, 6H). *Z*-Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 5.9 (m, 1H), 5.59 (d, J = 10.1 Hz, 1H), 4.00 (s, 3H), 3.40 (s, 3H), 2.52, (hept, J = 7.0 Hz, 1H), 1.77 (d, 3H), 1.18 (d, J = 7.0 Hz, 6H). 3,4-Dimethoxy-2-(1-methylethyl)-4-(1-propynyl)-2-cyclobuten-1-one: ^1H NMR (500 MHz, $CDCl_3$) δ 4.14 (s, 3H), 3.50 (s, 3H), 2.50 (hept, J = 7.0 Hz, 1H), 1.94 (s, 3H), 1.16 (d, J = 6.9 Hz, 6H). After hexanes (200 mL) was added, the clear solution was warmed to 69 °C for 2 h. The concentrated product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give the title compound **14** (0.26 g, 70%) as a white solid: mp 53.0−54.0 °C; IR 3452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.11 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.45 (hept, J = 7.1 Hz, 1H), 2.18 (s, 3H), 1.35 (d, J = 7.1, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 150.3, 145.3, 129.9, 126.0, 112.9, 61.0, 60.3, 25.2, 21.3 (2C), 15.6; LRMS (CI) m/e 210 (M, 100) 195 (20), 169 (10); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256; found 210.1252.

3,4-Dimethoxy-6-methyl-2-(1-methylethyl)phenol (14) Using (*E*)-1-Bromopropene. Under an atmosphere of nitrogen,

tert-butyllithium (1.7 M in pentane, 2.5 mL, 4.2 mmol) was added in a dropwise fashion to anhydrous THF (10 mL) at −78 °C. After 5 min, *trans*-1-bromo-1-propene (0.18 mL, 2.1 mmol) was added dropwise to this solution over a 2 min period. After stirring 2 h, the resulting lithium reagent was added via cannula to a −78 °C anhydrous THF (20 mL) solution of 3-methoxy-4-(1-methylethyl)-3-cyclobutene-1,2-dione **6** (0.308 g, 2.00 mmol). Upon the addition of methyl trifluoromethanesulfonate (0.34 mL, 3.0 mmol), the yellow solution gradually turned clear as it was allowed to warm to 0 °C. After this temperature was maintained for 10 min, the solution was recooled to −78 °C and poured into a cold solution of 5% $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. After hexanes (200 mL) was added, the clear solution was warmed to 69 °C for 2 h. The concentrated product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give the title compound **14** (0.286 g, 77%) as a white solid.

3,4-Dimethoxy-6-methyl-2-(1-methylethyl)phenol (14) from 3,4-Dimethoxy-2-(1-methylethyl)-4-propynylcyclobutenone (13c). Under an atmosphere of nitrogen, *tert*-butyllithium (1.2 M in hexanes, 2.0 mL, 2.4 mmol) was added in a dropwise fashion to anhydrous THF (10 mL) at −78 °C. After 5 min, 1-bromo-1-propene (a mixture of *E*- and *Z*-isomers) (0.24 mL, 2.80 mmol) was added dropwise to this solution over a 2 min period. After 2 h of stirring,, the resulting 1-lithiopropyne[8] was added via cannula to a −78 °C anhydrous THF (20 mL) solution of 3-methoxy-4-(1-methylethyl)-3-cyclobutene-1,2-dione **6** (0.308 g, 2.00 mmol). Upon the addition of methyl trifluoromethanesulfonate (0.34 mL, 3.0 mmol), the yellow solution gradually turned clear as it was allowed to warm to 0 °C and was maintained at this temperature for 10 min. After the solution was recooled to −78 °C, it was poured into a cold solution of 5% $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phase was then washed with brine (40 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The concentrated product was then purified by column chromatography (silica gel, 4:1 hexanes/ethyl acetate). After hexanes (200 mL) was added, the clear solution was warmed to 69 °C for 2 h. The concentrated product was then purified by column chromatography (silica gel, 9:1 hexanes/ethyl acetate) to give the title compound **14** (0.102 g, 44%) as a white solid.

4-Acetoxy-3-methoxy-6-methyl-2-(1-methylethyl)phenol. A sample of the title compound was isolated from the above experiment and observed to have the following spectral properties: mp 95.5−96.5 °C; IR 3387 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 4.84 (s, 1H), 3.73 (s, 3H), 3.47 (hept, J = 7.1 Hz, 1H), 2.31 (s, 3H), 2.10 (s, 3H), 1.36 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 151.0, 148.2, 136.9, 128.2, 121.6, 119.2, 61.6, 25.4, 21.0 (2C), 20.8, 15.6; LRMS (CI) *m*/*e* 239 (M + 1, 49), 238 (M, 42), 196 (100), 181 (30); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205; found 238.1210.

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Supporting Information Available: Copies of NMR spectra for compounds **1**, **6**−**8**, **10**, **12**, **14**, and intermediates (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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