JOC The Journal of Organic Chemistry

Article

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Total Syntheses of the Coumarin-Containing Natural Products Pimpinellin and Fraxetin Using Au(I)-Catalyzed Intramolecular Hydroarylation (IMHA) Chemistry

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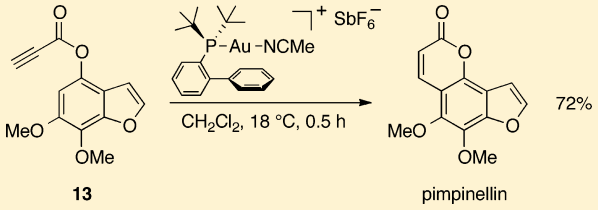
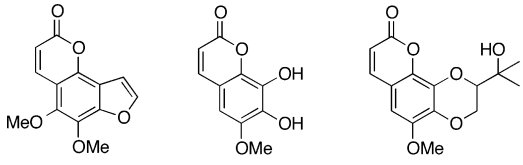
Supporting Information

ABSTRACT: The title natural products (**1** and **2**, respectively) have been synthesized by Au(I)-catalyzed intramolecular hydroarylation (IMHA) of the relevant aryl propiolate esters (e.g., **13**), which were themselves formed by reaction of the corresponding phenols with either 3-(trimethylsilyl)propiolic acid or propiolic acid and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide. (±)-Purpurasol (**3**) was readily derived from fraxetin (**2**) by established procedures.



INTRODUCTION

Coumarins (benzo-α-pyrones) have been isolated from a diverse range of plant sources as well as certain microorganisms and animals.[1] These natural products display an extraordinarily wide range of biological activities and, as a result, it has been suggested that their therapeutic potential is "immense".[2] The size of and structural diversity within the class has led to the identification of various subgroups, two important ones being the furocoumarins[3] and the 6,7-dihydroxycoumarins.[4] Certain members of these act as, inter alia, phytoalexins, antimitotic agents, vasodilators, and antibacterial agents and/or have been used in photochemotherapy for treating vitiligo, psoriasis, and atopic dermatitis.[5] Pimpinellin (**1**),[6] for example, is an angular furocoumarin, the structure of which has recently been confirmed by single-crystal X-ray analysis.[7] It has been isolated from a range of plant sources,[6] including *Pimpinella saxifraga* L. and members of the Umbelliferae family, and serves as a phytoalexin in parsley and celery as well as acting as an inhibitor of trichothecene toxin biosynthesis and nitric oxide synthase.[8] Fraxetin (**2**),[9] on the other hand, is a 6,7-dihydroxycoumarin derivative. It has been obtained by extraction of a diverse range of plants, including those belonging to the genus *Pulicaria* (Compositae) and the Mexican Tarragon (*Tagetes lucida*), or through acid-promoted hydrolysis of the glycosylated derivative fraxin, itself obtained from the bark of trees such as the common European ash (*Fraxinus excelsior* L.) or the horse chestnut tree (*Aesulus hippcastanum* L.).[9,10] Fraxetin not only acts against a range of bacteria, including *Vibrio cholerae*, but also exhibits hypouricemic and renal protective actions, inhibits inflammatory cytokine-mediated apoptosis in osteoblast cells (and may thus have potential in preventing osteoporosis), and acts as an antioxidant in certain cell lines.[11] It probably also serves as a biosynthetic precursor to a range of other coumarin-containing natural products, including the co-occurring purpurasol (**3**).[12] Certainly, it has been shown that naturally derived **2** is an effective starting material for the chemical synthesis of compound **3**[13] as well as certain other coumarin-containing natural products.[14]



1 **2** **3**

Despite the therapeutic potential of natural products **1** and **2**, only the former compound has been the subject of total synthesis studies, with the single such effort involving its assembly from diethyl squarate in 13 steps, including an elegant thermally induced electrocyclic ring-opening/ring-closure process.[15] In view of this, and given our ongoing interest[16] in the development of methods for the synthesis of coumarins using Au(I)-catalyzed intramolecular hydroarylation (IMHA) reactions of phenyl propiolates,[17] we now report total syntheses of the title natural products **1** and **2** along with that of **3**.

RESULTS AND DISCUSSION

Total Synthesis of Pimpinellin. The fully substituted nature of the benzenoid core associated with pimpinellin

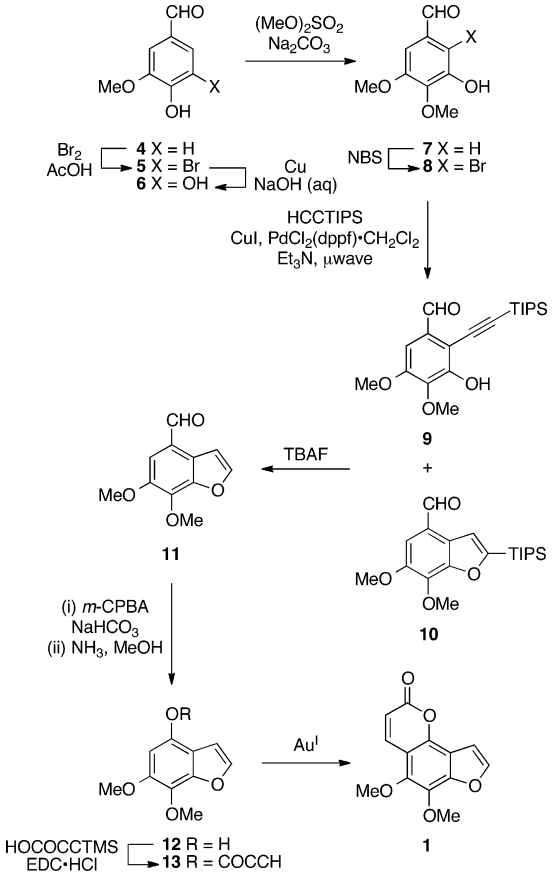
Received: July 21, 2013
Published: August 26, 2013

   dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876−9882

presents a significant synthetic challenge, not least because this bears annulated furan and α-pyrone rings. The demonstrated utility of the above-mentioned IMHA process in forming coumarins from phenolic scaffolds together with ability of *o*-hydroxyphenylacetylenes to participate in 5-endo-dig cyclization reactions, thus generating benzofurans,[18] prompted consideration of an approach wherein an appropriately substituted arene was used as the starting material. Sequential annulation of the five- and six-membered heterocyclic rings would then follow, with any regiochemical issues being addressed by exploiting the normally well-defined directing effects of substituents attached to the arene core. It was hoped that the protocols developed in the course of this work might ultimately find use in the assembly of other angular furocoumarins as well as their linear counterparts.

On the basis of the foregoing considerations, the route pursued in efforts to prepare pimpinellin (**1**) started with vanillin (**4**). Regioselective bromination of the latter compound using molecular bromine in acetic acid afforded the previously reported[19,20] bromoarene **5** (69%) (Scheme 1).

Scheme 1



This was subjected to reaction with copper powder in the presence of aqueous sodium hydroxide using a modification of a protocol reported by Ellis and Lenger[20] to afford catechol **6** (93%), which could be selectively monomethylated using dimethyl sulfate in the presence of sodium carbonate to afford ether **7**[21] (87%).

As a prelude to establishing the furan ring of target **1**, bromination of compound **7** at C2 was accomplished using *N*-bromosuccinimide (NBS), and the ensuing pentasubstituted arene **8** (84%), the structure of which was confirmed by single-crystal X-ray analysis[22] (see the Supporting Information for details), was then subjected to a Sonogashira cross-coupling[23] reaction with triisopropylsilylacetylene. This produced a 1:8 mixture of acetylene **9** (5%) and the isomeric benzofuran **10** (39%) which were chromatographically separable, thereby allowing each to be subjected to comprehensive characterization. However, for synthetic purposes it was more convenient to treat the mixture with tetra-*n*-butylammonium fluoride (TBAF) thereby generating the desilylated benzofuran **11**, which was obtained as a colorless crystalline solid in 80% yield. The rather modest yields associated with the conversion **8** → **9** + **10** may be attributed to competitive oxidative coupling of the triisopropylsilylacetylene, although the (likely volatile) product of such a process was not detected in the crude product mixture.

The completion of the synthesis of pimpinellin from compound **11** required installation of the lactone ring, and this proved to be a straightforward matter. Aldehyde **11** was subjected to a Baeyer–Villiger oxidation using *m*-chloroperoxybenzoic acid (*m*-CPBA), and the ensuing formate ester was cleaved with ammoniacal methanol to give phenol **12** in 68% yield. Treatment of the latter compound with 3-(trimethylsilyl)-propiolic acid in the presence *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl)[24] afforded ester **13** (79% yield at 48% conversion) with accompanying loss of the TMS group associated with the alkyne (an event that probably took place during chromatographic purification). Upon treatment with a 5 mol % loading of Echavarren's gold(I) catalyst[25] in dichloromethane at 25 °C, compound **13** afforded pimpinellin (**1**) as a colorless, crystalline solid in 72% yield. All of the spectroscopic data derived from this material were consistent with the assigned structure and accorded well with those reported for the natural product.[15,26] Relevant comparisons of the ^{13}C and ^{1}H NMR data are presented in Table 1.

Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically-Derived Compound 1 with Those Reported for Pimpinellin

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
1[a]	pimpinellin[b]	**1**[c]	pimpinellin[d]
161.1	160.4	8.06 (d, *J* = 9.7 Hz, 1H)	8.08 (d, *J* = 9.7 Hz, 1H)
150.0	149.7	7.64 (d, *J* = 2.2 Hz, 1H)	7.65 (d, *J* = 2.2 Hz, 1H)
145.6	145.4	7.07 (d, *J* = 2.2 Hz, 1H)	7.08 (d, *J* = 2.2 Hz, 1H)
144.7	144.4	6.35 (d, *J* = 9.7 Hz, 1H)	6.37 (d, *J* = 9.7 Hz, 1H)
143.4	143.1	4.13 (s, 3H)	4.15 (s, 3H)
140.1	139.8	4.02 (s, 3H)	4.06 (s, 3H)
135.4	134.9		
114.4	115.5		
114.0	113.8		
109.7	109.3		
104.6	104.1		
62.6	62.2		
61.5	61.1		

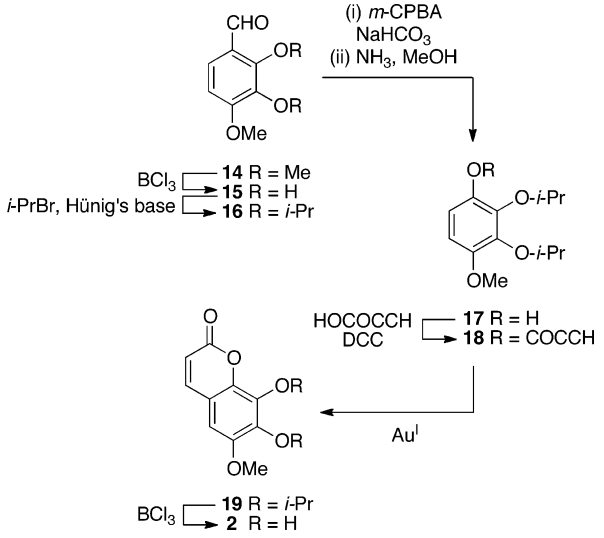
[a]Recorded in $CDCl_3$ at 100 MHz. [b]Obtained from ref 26; recorded in $CDCl_3$ at 22.6 MHz. [c]Recorded in $CDCl_3$ at 400 MHz. [d]Obtained from ref 15; recorded in $CDCl_3$ at 300 MHz.

Total Synthesis of Fraxetin. In principle at least, fraxetin (**2**) represents a less challenging synthetic target than congener **1** given the absence of an associated furan residue and the presence of five rather than six substituents on the benzenoid

dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876–9882

core. As such, the most notable task that needed to be addressed in establishing a route to compound **2** was the incorporation of the two free hydroxyl residues associated with the catechol substructure. In view of the utility of isopropyl ethers as protecting groups for phenolic OH groups,[27] the synthetic plan that was pursued (Scheme 2) started with the generation of an arene incorporating two such residues on adjacent benzenoid carbons.

Scheme 2



2,3,4-Trimethoxybenzaldehyde (**14**) was treated with an excess of boron trichloride according to a protocol defined by Hase et al.,[28] thereby producing catechol **15** in 76% yield. Treatment of the latter compound with ca. 2.5 molar equiv of isopropyl bromide in the presence of Hünig's base then gave the required bisether **16** in 73% yield. Subjection of the latter aldehyde to Baeyer–Villiger oxidation with *m*-CPBA in the presence of sodium bicarbonate gave the expected formate ester, which was immediately cleaved with ammoniacal methanol to afford phenol **17** (93% over two steps), the structure of which was confirmed by single-crystal X-ray analysis[22] (see the Supporting Information for details). Coupling of the latter compound with propiolic acid in the presence of dicyclohexylcarbodiimide (DCC) then gave ester **18** (98%), which readily engaged in the required IMHA reaction upon exposure to 3 mol % Echavarren's catalyst in dichloromethane at 25 °C for 5 h. By such means the bisether of fraxetin, **19**, was obtained in 96% yield. Finally, treatment of compound **19** with 3 equiv of boron trichloride at 18 °C in dichloromethane resulted in the selective cleavage of the two isopropyl ether residues, affording crystalline fraxetin (**2**) in 76% yield. The derived spectroscopic data were in complete accord with the assigned structure and proved to be a good match with those reported for the natural product.[29] A comparison of the two sets of ^{13}C and ^{1}H NMR spectroscopic data is presented in Table 2.

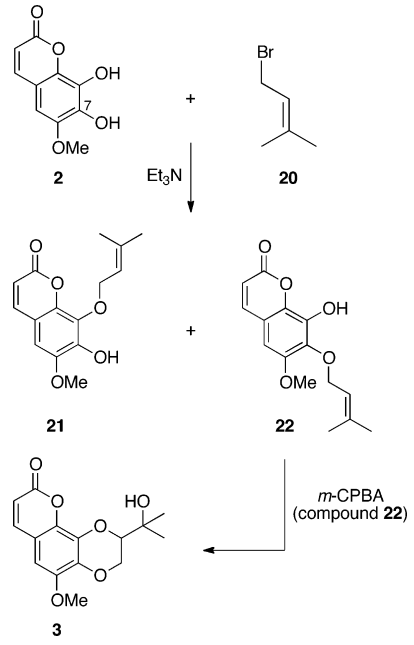
Total Synthesis of Purpurasol. The reaction sequence shown in Scheme 2 provided a ready means for generating significant quantities of fraxetin (**2**). Therefore, we sought to exploit this material for the purposes of generating fully synthetic samples of purpurasol (**3**) for biological testing. Accordingly, following the protocol reported by De Kimpe et al.,[13] an acetone solution of **2** containing triethylamine was treated with prenyl bromide to afford a chromatographically separable

Table 2. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically-Derived Compound 2 with Those Reported for Fraxetin

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
2[a]	fraxetin[b]	**2**[c]	fraxetin[d]
163.7	164.0	7.82 (d, *J* = 8.8 Hz, 1H)	7.84 (d, *J* = 9.6 Hz, 1H)
147.1	147.0	6.70 (s, 1H)	6.72 (s, 1H)
146.7	146.7	6.19 (d, *J* = 8.8 Hz, 1H)	6.23 (d, *J* = 9.6 Hz, 1H)
140.7	140.8	3.89 (s, 3H)	3.87 (s, 3H)
140.6	140.7		
134.0	134.0		
112.3	112.6		
112.2	112.2		
101.0	101.3		
56.8	56.8		

[a]Recorded in CD_3OD at 100 MHz. [b]Obtained from ref 29; recorded in CD_3OD at 100 MHz. [c]Recorded in CD_3OD at 400 MHz. [d]Obtained from ref 29; recorded in CD_3OD at 400 MHz.

Scheme 3



mixture of the regioisomeric prenyl ethers **21** (12%) and **22**[30] (40%) (Scheme 3), the structures of which were confirmed by comparison of the derived spectroscopic data with those reported previously.[13] The preferential formation of the latter ether in this reaction has been attributed to selective deprotonation of the more acidic and lactone-carbonyl-conjugated C7 phenolic group within fraxetin.[13] Epoxidation of compound **22** with *m*-CPBA in ethyl acetate at between 0 and 18 °C for 48 h afforded purpurasol (**3**) in 69% yield, presumably via 6-exo-tet cyclization of the intermediate epoxide. Compound **3** was obtained as a colorless, crystalline solid. The associated physical and spectroscopic properties were in accord with those reported by De Kimpe and co-workers.[13]

■ CONCLUSION

The synthetic sequences detailed in Schemes 1 and 2 serve to emphasize the utility of Echavarren's catalyst in effecting the IMHA of phenyl propiolates under mild conditions, thereby

dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876–9882

delivering highly substituted coumarins in good yield. Therefore, given the likely ready (and regiocontrolled) access to relevant precursor phenols, the protocols described here should be capable of straightforward extension to a range of other biologically interesting coumarins and furocoumarins.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. For ^{1}H NMR spectra, signals arising from the residual protio forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift δ (in ppm) [multiplicity, coupling constant(s) J, relative integral], where the symbols representing the multiplicity are defined as follows: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference the ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by IR spectroscopy (ν_{max}) as thin films on KBr plates. Samples for attenuated total reflectance (ATR) IR spectra were prepared by allowing a $CDCl_3$ solution of these to evaporate on the sampling plate before the spectrum was acquired. Low-resolution ESI mass spectra were recorded on a single-quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution electron impact (EI) mass spectra were recorded on a magnetic-sector machine. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[31] with silica gel 60 (40−63 μm) as the stationary phase and the indicated AR- or HPLC-grade solvents. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane (DCM) were dried using a solvent purification system based upon a technology originally described by Grubbs and co-workers.[32] Where necessary, reactions were performed under an argon atmosphere. All microwave irradiation experiments were carried out in a microwave apparatus operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. Each reaction was carried out in a 10 mL sealed vessel that had a working volume of 7 mL and was equipped with a magnetic stirrer. The temperature was measured with a fiber optic temperature sensor immersed in the reaction vessel. After the irradiation period, the reaction vessel was cooled rapidly (1−2 min) to ambient temperature by jet cooling using nitrogen gas.

Compound 5. A solution of molecular bromine (7.4 mL, 144.6 mmol) in acetic acid (40 mL) was added dropwise to a magnetically stirred suspension of vanillin (**4**) (20.0 g, 131.5 mmol) in acetic acid (120 mL). The ensuing mixture was stirred at 18 °C for 1 h before being treated with sodium hydrogen sulfate (20 mL of a saturated aqueous solution) and then filtered to afford 5-bromovanillin (**5**)[19] (21.8 g, 69%) as a colorless crystalline solid, mp 176−178 °C (lit.[19a] 179 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.62 (d, J = 1.7 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 6.47 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 149.1, 147.9, 130.3, 130.3, 108.4, 108.2, 56.8.

Compound 6. A magnetically stirred solution of vanillin **5** (4.6 g, 19.2 mmol) and sodium hydroxide (7.70 g, 192.4 mmol) in deoxygenated water (200 mL) was treated with copper powder (61 mg, 0.96 g-atom, 5 mol %), and the ensuing mixture was heated at reflux for 24 h. The cooled reaction mixture was treated with disodium hydrogen phosphate (273 mg, 1.924 mmol), and the resulting mixture was heated at reflux for 1 h and then cooled and filtered. The filtrate was treated with HCl (30 mL of a 1.0 M aqueous solution) and then extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with EDTA (1 × 100 mL of a saturated aqueous solution) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 2:1 v/v → 1:1 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.25 in 1:1 ethyl acetate/hexane), 3-methoxy-4,5-dihydroxybenzaldehyde (**6**)[20] (3.00 g, 93%) as a light-brown solid, mp 132 °C (lit.[20] 132−133 °C) [Found: (M + Na)$^+$, 191.0318; $C_8H_8NaO_4$ requires 191.0315]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.12 (d, J = 1.7 Hz, 1H), 7.06 (d, J = 1.7 Hz, 1H), 5.93 (s, 1H), 5.42 (broad s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 147.5, 144.2, 138.5, 129.3, 113.3, 103.0, 56.7; ν_{max} (KBr) 3345, 1673, 1595, 1514, 1463, 1335, 1205, 1142, 1093, 1003 cm^{-1}; MS (EI, 70 eV) m/z 168 (M$^{+\bullet}$, 100%), 167 (97).

Compound 7. A magnetically stirred suspension of aldehyde **6** (2.15 g, 12.8 mmol), dimethyl sulfate (1.2 mL, 14.1 mmol), and sodium carbonate (1.61 g, 2.8 mmol) in acetone (50 mL) was heated at reflux for 5 h. The cooled reaction mixture was concentrated under reduced pressure, and the ensuing residue was dissolved in ethyl acetate (60 mL). The resulting solution was extracted with NaOH (1 × 30 mL of a 1.0 M aqueous solution), and the separated aqueous phase was acidified with HCl (70 mL of a 2 M aqueous solution) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v mixture of hexane/ethyl acetate elution) then afforded, after concentration of the relevant fractions (R_f = 0.5), 3-hydroxy-4,5-dimethoxybenzaldehyde (**7**)[21] (2.02 g, 87%) as a light-yellow oil [Found: (M + Na)$^+$, 205.0478; $C_9H_{10}NaO_4$ requires 205.0472]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.09 (d, J = 1.8 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1H), 5.90 (broad s, 1H), 3.97 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 152.9, 149.8, 141.0, 132.3, 111.7, 104.0, 61.3, 56.3; ν_{max} (KBr) 3400, 2943, 2843, 1688, 1587, 1505, 1464, 1431, 1392, 1339, 1241, 1203, 1133, 1106 cm^{-1}; MS (EI, 70 eV) m/z 182 (M$^{+\bullet}$, 100%), 167 (53).

Compound 8. A magnetically stirred solution of compound **7** (1.83 g, 10.0 mmol) in dry THF (50 mL) maintained under nitrogen was cooled to 0 °C and then treated, in portions, with NBS (1.82 g, 10.2 mmol). The ensuing mixture was allowed to warm to 18 °C over 16 h and then concentrated under reduced pressure. The light-yellow solid thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the relevant fractions (R_f = 0.6), 2-bromo-3-hydroxy-4,5-dimethoxybenzaldehyde (**8**) (2.21 g, 84%) as a light-yellow solid, mp 55−56 °C [Found: (M + Na)$^+$, 282.9582; $C_9H_9{}^{79}BrNaO_4$ requires 282.9577]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.47 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H) (one signal obscured or overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 151.7, 147.1, 141.1, 128.8, 106.9, 104.7, 61.5, 56.4; ν_{max} (KBr) 3369, 1681, 1587, 1486, 1426, 1346, 1330, 1262, 1199, 1146, 1110, 1018, 993 cm^{-1}; MS (EI, 70 eV) m/z 262 and 260 (M$^{+\bullet}$, 99 and 100%, respectively).

Compounds 9 and 10. A tube suitable for placement in a microwave reactor was charged with aldehyde **8** (51 mg, 0.20 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (8 mg, 5 mol %), and copper(I) iodide (2 mg, 5 mol %). The tube and its contents were flushed with nitrogen for 0.17 h, after which dry acetonitrile (0.75 mL) was added, and nitrogen was bubbled through the resulting solution for 0.08 h. Triethylamine (0.50 mL) was then added to the reaction mixture, which was again flushed with nitrogen for 0.08 h. Finally, triisopropylsilylacetylene (130 μL, 0.59 mmol) was added dropwise, and nitrogen was bubbled through the resulting solution for 0.02 h. The dark-red solution thus obtained was immediately subjected to microwave irradiation (100 W, internal pressure of 200 psi) at 120 °C for 1.5 h before being cooled and then subjected to flash chromatography (silica, 4:1 v/v → 2:1 v/v hexane/ethyl acetate elution) to afford two fractions, A and B.

dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876−9882

Concentration of fraction A [R_f = 0.4(6) in 2:1 v/v hexane/ethyl acetate] gave compound **9** (4 mg, 5%) as colorless needles, mp 98−99 °C [Found: $(M + H)^+$, 363.1988; $C_{20}H_{31}O_4Si$ requires 363.1987]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 7.07 (s, 1H), 6.17 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 1.13 (broad s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 153.4, 151.5, 140.6, 132.0, 108.7, 103.8, 102.4, 96.9, 61.2, 56.4, 18.9, 11.5; ν_{max} (KBr) 3327, 2943, 2865, 2145, 1682, 1587, 1492, 1464, 1426, 1389, 1358, 1325, 1268, 1242, 1212, 1197, 1131, 1074, 1014, 882 cm^{-1}; MS (ESI) m/z 385 [$(M + Na)^+$, 100%], 363 [$(M + H)^+$, 15].

Concentration of fraction B [R_f = 0.4(7) in 2:1 v/v hexane/ethyl acetate] gave compound **10** (30 mg, 39%) as a clear yellow oil [Found: $(M + H)^+$, 363.1986; $C_{20}H_{31}O_4Si$ requires 363.1987]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.72 (s, 1H), 7.43 (s, 1H), 4.46 (s, 3H), 4.03 (s, 3H), 1.54−1.39 (complex m, 3H), 1.20 (d, J = 7.3 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 164.3, 148.6, 147.4, 140.1, 125.5, 120.9, 117.1, 113.7, 60.9, 57.7, 18.7, 11.2; ν_{max} (KBr) 2944, 2866, 1684, 1603, 1582, 1528, 1495, 1463, 1370, 1306, 1292, 1234, 1195, 1159, 1133, 1103, 1026, 987, 883 cm^{-1}; MS (EI, 70 eV) m/z 362 ($M^{+\bullet}$, 48%), 320 (43), 319 (100).

Compound 11. A magnetically stirred solution of the crude mixture of compounds **9** and **10** (460 mg, 1.27 mmol, obtained from the above-mentioned Sonogashira cross-coupling reaction) in THF (2 mL) maintained at 0 °C was treated with TBAF (7.6 mL of a 1.0 M solution in THF). The ensuing mixture was stirred for 1 h at 0 °C and then for a further 3 h at 18 °C before being concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 4:1 → 2:1 v/v hexane/ethyl acetate gradient elution) to give, after concentration of the relevant fractions (R_f = 0.2 in 2:1 v/v hexane/ethyl acetate), benzofuran **11** (210 mg, 80%) as a light-yellow powder, mp 77−78 °C [Found: $(M + H)^+$, 207.0652; $C_{11}H_{11}O_4$ requires 207.0652]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.38 (s, 1H), 4.35 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 147.7, 147.4, 145.9, 140.2, 124.5, 121.4, 113.8, 106.1, 61.0, 57.4; ν_{max} (KBr) 3143, 3109, 2958, 2849, 1680, 1588, 1536, 1509, 1461, 1394, 1376, 1347, 1298, 1247, 1212, 1187, 1131, 1078, 1047, 1015, 851, 781 cm^{-1}; MS (ESI) m/z 207 [$(M + H)^+$, 20%], 186 (100).

Compound 12. A magnetically stirred solution of benzofuran **11** (210 mg, 1.02 mmol) in dichloromethane (4 mL) maintained at 0 °C was treated with anhydrous $NaHCO_3$ (291 mg, 3.46 mmol) and then *m*-CPBA (211 mg of ca. 77% peracid, 1.22 mmol). The ensuing mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. The residue so formed was dissolved in ammonia-saturated methanol (12 mL), and the resulting mixture was maintained, with magnetic stirring, in a sealed vessel for 1 h at 18 °C before being opened to the atmosphere. After a further 0.18 h, the reaction mixture was concentrated under reduced pressure, and the resulting light-yellow residue was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to give, after concentration of the relevant fractions (R_f = 0.2), 6,7-dimethoxybenzofuran-4-ol (**12**) (135 mg, 68%) as a pale-cream solid, mp 142−143 °C [Found: $(M + Na)^+$, 217.0477; $C_{10}H_{10}NaO_4$ requires 217.0472]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.1 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 6.37 (s, 1H), 4.81 (broad s, 1H), 4.01 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.7, 143.9, 143.7, 129.5, 112.0, 103.5, 96.6, 61.5, 57.5; ν_{max} (KBr) 3290, 2976, 2850, 1640, 1618, 1545, 1520, 1471, 1448, 1429, 1364, 1290, 1227, 1210, 1149, 1135, 1080, 1046, 1012 cm^{-1}; MS (ESI) m/z 217 [$(M + Na)^+$, 15%], 186 (100).

Compound 13. A magnetically stirred solution of phenol **12** (50 mg, 0.257 mmol) and 3-(trimethylsilyl)propiolic acid (38 mg, 0.31 mmol) in dichloromethane (2 mL) was treated with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (59 mg, 0.309 mmol). The resulting mixture was stirred at 18 °C for 24 h and then concentrated under reduced pressure, and the residue so obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.2) gave the starting phenol **12** (26 mg, 52% recovery) as a pale-cream solid that was in all respects identical to an authentic sample.

Concentration of fraction B (R_f = 0.5) afforded propiolate ester **13** (24 mg, 79% at 48% conversion) as a light-brown solid, mp 72−73 °C (Found: $M^{+\bullet}$, 246.0526; $C_{13}H_{10}O_5$ requires 246.0523]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 2.3 Hz, 1H), 6.75 (s, 1H), 6.61 (m, 1H), 4.11 (s, 3H), 3.88 (s, 3H), 3.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 148.8, 147.8, 145.0, 136.4, 133.6, 116.5, 104.0, 103.1, 77.4, 74.2, 61.3, 57.5; ν_{max} (ATR) 2938, 2847, 2123, 1734, 1636, 1506, 1448, 1399, 1336, 1189, 1146, 1124, 1077, 1043 cm^{-1}; MS (EI, 70 eV) m/z 246 ($M^{+\bullet}$, 67%), 194 (45), 193 (100).

Pimpinellin (1). A magnetically stirred solution of ester **13** (20 mg, 0.081 mmol) in dichloromethane maintained at 18 °C was treated with Echavarren's catalyst (3 mg, 0.004 mmol, 5 mol %). The resulting mixture was stirred at 18 °C for 0.5 h and then filtered through a pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.5) gave pimpinellin (**1**)[6,7] (16 mg, 72%) as a colorless powder, mp 117−119 °C (lit.[6a] 117−119 °C) (Found: $M^{+\bullet}$, 246.0528; $C_{13}H_{10}O_5$ requires 246.0523). ^{1}H NMR (400 MHz, $CDCl_3$) δ, see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ, see Table 1; ν_{max} (ATR) 2986, 2948, 1737, 1626, 1579, 1482, 1451, 1419, 1388, 1340, 1323, 1156, 1125, 1114, 1092, 1063, 1035, 1013, 821, 748 cm^{-1}; MS (EI, 70 eV) m/z 246 ($M^{+\bullet}$, 100%), 231 (81).

Compound 15. A magnetically stirred solution of 2,3,4-trimethoxybenzaldehyde (**14**) (4.04 g, 20.6 mmol) in dry dichloromethane (50 mL) maintained under nitrogen at 18 °C was treated dropwise with boron trichloride (20 mL, 20 mmol), and the ensuing mixture was stirred at 18 °C for 2 h. Additional boron trichloride (40 mL, 40 mmol) was then added, and stirring was continued at 18 °C for a further 16 h. The ensuing mixture was then poured into $NaHCO_3$ (100 mL of a saturated aqueous solution), and the separated aqueous layer was acidified with HCl (50 mL of a 2.0 M aqueous solution) before being extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (1 × 100 mL) and brine (1 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 15:5:2 v/v/v ethyl acetate/hexane/methanol elution) to afford, after concentration of the appropriate fractions (R_f = 0.3 in 7:3 v/v hexane/ethyl acetate), 2,3-dihydroxy-4-methoxybenzaldehyde (**15**)[28] (2.65 g, 76%) as a light-yellow solid, mp 113−114 °C (lit.[28] 113−114 °C) (Found: $M^{+\bullet}$, 168.0423; $C_8H_8O_4$ requires 168.0418). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (s, 1H), 9.75 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 5.51 (s, 1H, OH), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 153.0, 149.0, 133.0, 126.1, 116.1, 103.6, 56.4; ν_{max} (KBr) 3370, 2914, 2848, 1647, 1506, 1454, 1276, 1104, 1028, 775, 699 cm^{-1}; MS (EI, 70 eV) m/z 168 ($M^{+\bullet}$, 100%), 167 (63), 122 (50).

Compound 16. A magnetically stirred solution of benzaldehyde **15** (2.61 g, 15.5 mmol) in DMF (30 mL) maintained under nitrogen was treated with anhydrous potassium carbonate (6.44 g, 45.6 mmol) and 2-bromopropane (5.73 mL, 46.6 mmol). The ensuing reaction mixture was heated at 90 °C for 16 h and then diluted with water (50 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic phases were then washed with water (1 × 100 mL) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) to give, after concentration of the relevant fractions (R_f = 0.4), 2,3-diisopropoxy-4-methoxybenzaldehyde (**16**) (3.05 g, 73%) as a light-yellow liquid [Found: $(M + Na)^+$, 275.1259; $C_{14}H_{20}NaO_4$ requires 275.1254]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 4.75 (m, 1H), 4.38 (m, 1H), 3.84 (s, 3H), 1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 159.8, 155.3, 139.7, 124.8, 123.5, 107.2, 75.9, 75.4, 56.1, 22.4, 22.2; ν_{max} (KBr) 2975, 2930, 2852, 1680, 1586, 1491, 1444, 1381, 1332, 1287, 1259, 1224, 1194, 1168, 1139, 1092, 1001, 965, 910, 810 cm^{-1}; MS (EI, 70 eV) m/z 252 ($M^{+\bullet}$, 33%), 168 (100), 167 (45), 122 (55).

Compound 17. A magnetically stirred solution of compound **16** (1.06 g, 4.41 mmol) in dichloromethane (100 mL) was cooled to 0 °C and then treated sequentially with potassium hydrogen carbonate

dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876−9882

(1.26 g, 12.6 mmol) and *m*-CPBA acid (4.12 g of ca. 77% peracid, 16.84 mmol). The ensuing mixture was allowed to warm to 18 °C and then was stirred at this temperature for 16 h before being concentrated under reduced pressure. The residue so obtained was dissolved in methanol (100 mL), and the resulting solution was treated with ammonium acetate (3.44 g, 44.7 mmol) and then stirred at 18 °C for 16 h. The ensuing mixture was diluted with water (100 mL) and then extracted with diethyl ether (2 × 100 mL). The combined organic phases were washed with water (1 × 100 mL) and brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 2,3-diisopropoxy-4-methoxyphenol (**17**) (980 mg, 93%) as a colorless crystalline solid, mp 28 °C (R_f = 0.5 in 7:3 v/v hexane/ethyl acetate) [Found: $(M + Na)^+$, 263.1256; $C_{13}H_{20}NaO_4$ requires 263.1254]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 5.39 (broad s, 1H), 4.74 (m, 1H), 4.41 (m, 1H), 3.76 (s, 3H), 1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 144.6, 140.4, 138.9, 108.1, 107.4, 75.4, 56.6, 22.7(3), 22.7(0) (one signal obscured or overlapping); ν_{max} (KBr) 3529, 3457, 2975, 2933, 2835, 1490, 1467, 1382, 1372, 1332, 1268, 1182, 1159, 1108, 1089, 1035, 967, 901, 793, 738 cm^{-1}; MS (ESI) m/z 263 [$(M + Na)^+$, 50%], 225 (100), 199 (95).

Compound 18. A magnetically stirred solution of DCC (2.83 g, 13.7 mmol) in THF (40 mL) was cooled to 0 °C and then treated with propiolic acid (962 mg, 13.7 mmol), and the resulting suspension allowed to stand for 2 h. In a separate flask, a magnetically stirred solution of phenol **17** (1.00 g, 5.43 mmol) in THF (50 mL) was cooled to 0 °C, treated with NaH (183 mg of a 60% dispersion in mineral oil, 7.63 mmol), and also allowed to stand for 2 h. The solution so formed was then added to the suspension in the first flask, and the resulting mixture was stirred at 18 °C for 16 h and then concentrated under reduced pressure. The resulting solid was treated with acetonitrile (50 mL), and the suspension thus obtained was filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 1:5 v/v mixture of diethyl ether/hexane elution) afforded, after concentration of the relevant fractions (R_f = 0.3), 2,3-diisopropoxy-4-methoxyphenyl propiolate (**18**) (1.20 g, 98%) as a clear, colorless oil [Found: $(M + H)^+$, 293.1389; $C_{16}H_{21}O_5$ requires 293.1384]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 4.53 (m, 1H), 4.45 (m, 1H), 3.82 (s, 3H), 3.03 (s, 1H), 1.27 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 151.1, 144.3, 141.7, 138.1, 116.3, 106.2, 76.7, 76.2, 75.9, 74.5, 56.2, 22.7 (one signal obscured or overlapping); ν_{max} (KBr) 2976, 2933, 2122, 1736, 1644, 1589, 1484, 1458, 1442, 1382, 1373, 1340, 1310, 1241, 1187, 1141, 1092, 1023, 969, 902, 791 cm^{-1}; MS (EI, 70 eV) m/z 292 ($M^{+\bullet}$, 40%), 208 (100), 193 (37), 165 (55), 156 (50), 155 (56).

Compound 19. A magnetically stirred solution of propiolate **18** (1.20 g, 4.11 mmol) in dichloromethane (50 mL) was treated with Echavarren's catalyst (95 mg, 0.12 mmol). The ensuing mixture was stirred at 18 °C for 5 h and then filtered through a pad of TLC silica gel, and the filtrate was concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.1), 7,8-diisopropoxy-6-methoxy-2H-chromen-2-one (**19**) (1.15 g, 96%) as a colorless crystalline solid, mp 97−98 °C [Found: $(M + H)^+$, 293.1391; $C_{16}H_{21}O_5$ requires 293.1384]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.8 Hz, 1H), 6.64 (s, 1H), 6.31 (d, J = 8.8 Hz, 1H), 4.62 (m, 2H), 3.86 (s, 3H), 1.33 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 151.2, 145.1, 144.1, 143.7, 140.2, 115.3, 114.5, 103.5, 76.6(0), 76.5(7), 56.4, 22.8 (one signal obscured or overlapping); ν_{max} (KBr) 2968, 2928, 1701, 1604, 1562, 1484, 1453, 1434, 1409, 1381, 1371, 1347, 1290, 1237, 1197, 1161, 1125, 1105, 1082, 1040, 954, 922, 909, 866, 817 cm^{-1}; MS (ESI) m/z 315 [$(M + Na)^+$, 27%], 293 [$(M + H)^+$, 58], 251 (100), 209 (98).

Fraxetin (2). A magnetically stirred solution of coumarin **19** (210 mg, 0.72 mmol) in dry dichloromethane (20 mL) maintained under nitrogen at 18 °C was treated dropwise with boron trichloride (2.16 mL, 2.16 mmol). The ensuing mixture was stirred at 18 °C for 3 h and then poured into $NaHCO_3$ (20 mL of a saturated aqueous solution), and the separated aqueous phase was acidified with HCl (30 mL of a 2 M aqueous solution) before being extracted using diethyl ether (3 × 50 mL). The combined organic phases were washed with water (1 × 20 mL) and brine (1 × 20 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1:2 v/v acetone/dichloromethane elution), and concentration of the relevant fractions (R_f = 0.3 in 4:1 v/v ethyl acetate/hexane) afforded fraxetin (**2**)[9] (53 mg, 76%) as a light-yellow solid, mp 224−226 °C (lit.[9] 228 °C) [Found: $(M + H)^+$, 209.0451; $C_{10}H_9O_5$ requires 209.0445]. ^{1}H NMR (400 MHz, CD_3OD) δ, see Table 2; ^{13}C NMR (100 MHz, CD_3OD) δ, see Table 2; ν_{max} (KBr) 3353, 1680, 1605, 1580, 1511, 1468, 1416, 1313, 1158, 1120, 1030 cm^{-1}; MS (ESI) m/z 209 [$(M + H)^+$, 100%].

Compounds 21 and 22. A magnetically stirred solution of fraxetin **2** (247 mg, 1.1 mmol,) in acetone (30 mL) maintained under nitrogen at 18 °C was treated with triethylamine (330 μL, 2.37 mmol) and 4-bromo-2-methyl-2-butene (280 μL, 2.37 mmol). The resulting mixture was stirred at 18 °C for 24 h and then concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1:2 v/v hexane/diethyl ether elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 1:2 v/v hexane/diethyl ether) gave compound **21** (39 mg, 12%) as a light-yellow solid, mp 123−124 °C (lit.[13] 126.5 °C) (Found: $M^{+\bullet}$, 276.0997; $C_{15}H_{16}O_5$ requires 276.0993). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.5 Hz, 1H), 6.65 (s, 1H), 6.26 (d, J = 9.5 Hz, 1H), 6.13 (s, 1H), 5.54 (t, J = 7.4 Hz, 1H), 4.80 (d, J = 7.4 Hz, 2H), 3.93 (s, 3H), 1.75 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 144.6, 143.9, 143.3, 143.0, 140.7, 133.3, 119.4, 113.4, 111.2, 103.5, 70.4, 56.5, 25.9, 18.1; ν_{max} (KBr) 3262, 2968, 1689, 1567, 1498, 1455, 1411, 1320, 1245, 1190, 1155, 1121, 1087, 1019, 842 cm^{-1}; MS (ESI) m/z 299 [$(M + Na)^+$, 100%].

Concentration of fraction B (R_f = 0.3 in 1:2 v/v hexane/diethyl ether) gave capensin (**22**) (130 mg, 40%) as a light-yellow solid, mp 132−133 °C (lit.[13] 135 °C) [Found: $(M + H)^+$, 277.1077; $C_{15}H_{17}O_5$ requires 277.1071]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.5 Hz, 1H), 6.49 (s, 1H), 6.34 (d, J = 9.5 Hz, 1H), 5.51 (t, J = 8.9 Hz, 1H), 4.69 (d, J = 7.5 Hz, 2H), 3.89 (s, 3H), 1.76 (s, 3H), 1.68 (s, 3H) (one signal obscured or overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 149.8, 143.6, 140.6, 138.1, 138.0, 137.8, 119.5, 115.4, 114.4, 100.1, 70.0, 56.2, 25.9, 18.0; ν_{max} (KBr) 3324, 1702, 1571, 1494, 1414, 1302, 1152, 1117, 1076, 1032 cm^{-1}.

Purpurasol (3). A solution of compound **22** (20 mg, 0.07 mmol) in ethyl acetate (1 mL) was cooled to 0 °C and then treated with *m*-CPBA acid (30 mg of ca. 77% material, 0.07 mmol). The ensuing mixture was stirred at 18 °C for 48 h and then concentrated under reduced pressure. The residue thus obtained was dissolved in dichloromethane (10 mL), and the resulting solution was washed with sodium bicarbonate (1 × 10 mL of a saturated aqueous solution) and water (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give purpurasol (**3**) (12 mg, 69%) as a colorless crystalline solid, mp 145−147 °C (lit.[13] 148 °C) (Found: $M^{+\bullet}$, 292.0948; $C_{15}H_{16}O_6$ requires 292.0942). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 9.6 Hz, 1H), 6.50 (s, 1H), 6.29 (d, J = 9.6 Hz, 1H), 4.64 (dd, J = 1.9 and 11.3 Hz, 1H), 4.11 (dd, J = 9.1 and 11.3 Hz, 1H), 3.97 (dd, J = 1.9 and 9.1 Hz, 1H), 3.91 (s, 3H), 2.73 (br s, 1H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 145.8, 143.8, 139.0, 136.7. 132.4, 114.1, 111.6, 100.2, 79.1, 70.6, 65.6, 56.4, 26.0, 25.2; ν_{max} (KBr) 3442, 2971, 1703, 1573, 1414, 1302, 1133, 1040, 954, 833, 731 cm^{-1}; MS (EI, 70 eV) m/z 292 ($M^{+\bullet}$, 15%), 234 (15), 220 (40), 205 (100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIFs), anisotropic displacement ellipsoid plots, and unit cell packing diagrams derived from the single-crystal analysis of compounds **8**, **9**, and **17** and ^{1}H and ^{13}C NMR spectra for compounds **1**−**3**, **6**−**13**, **15**−**19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/jo401583q | J. Org. Chem. 2013, 78, 9876−9882

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Notes

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ACKNOWLEDGMENTS

We thank the Australian Research Council and the Institute of Advanced Studies for generous financial support. N.H. is grateful to the Government of Iran for the financial support provided during his sabbatical leave at the ANU. Ms. Amy Turnbull is thanked for carrying out some preliminary experiments. The authors are indebted to Dr. Brett Schwartz for much useful advice.

REFERENCES

(1) For useful points of entry into the substantial body of literature on coumarin-containing natural products, see: (a) Dugo, P.; Piperno, A.; Romeo, R.; Cambria, M.; Russo, M.; Carnovale, C.; Mondello, L. *J. Agric. Food Chem.* **2009**, *57*, 6543 and references cited therein. (b) Thuong, P. T.; Hung, T. M.; Ngoc, T. M.; Ha, D. T.; Min, B. S.; Kwack, S. J.; Kang, T. S.; Choi, J. S.; Bae, K. *Phytother. Res.* **2010**, *24*, 101 and references cited therein. (c) Leão, R. A. C.; de Moraes, P. de F.; Pedro, M. C. B. C.; Costa, P. R. R. *Synthesis* **2011**, 3692 and references cited therein. (d) Reddy, M. S.; Thirupathi, N.; Haribabu, M. *Beilstein J. Org. Chem.* **2013**, *9*, 180 and references cited therein.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) (a) *RÖMPP Encyclopedia: Natural Products*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, Germany, 2000; pp 248−249. (b) Traven, V. F. *Molecules* **2004**, *9*, 50. (c) Kitamura, T.; Otsubo, K. *J. Org. Chem.* **2012**, *77*, 2978 and references cited therein.

(4) (a) *RÖMPP Encyclopedia: Natural Products*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, Germany, 2000; pp 187−188. For commentaries on more highly oxygenated coumarins, see: (b) Maes, D.; Vervisch, S.; Debenedetti, S.; Davio, C.; Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 2505. (c) Maes, D.; Riveiro, M. E.; Shayo, C.; Davio, C.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4438. (d) Riveiro, M. E.; Maes, D.; Vázquez, R.; Vermeulen, M.; Mangelinckx, S.; Jacobs, J.; Debenedetti, S.; Shayo, C.; De Kimpe, N.; Davio, C. *Bioorg. Med. Chem.* **2009**, *17*, 6547.

(5) For example, see: (a) Sardari, S.; Mori, Y.; Horita, K.; Micetich, R. G.; Nishibe, S.; Daneshtalab, M. *Bioorg. Med. Chem.* **1999**, *7*, 1933. (b) Riveiro, M. E.; De Kimpe, N.; Moglioni, A.; Vázquez, R.; Monczor, F.; Shayo, C.; Davio, C. *Curr. Med. Chem.* **2010**, *17*, 1325. (c) Anand, P.; Singh, B.; Singh, N. *Bioorg. Med. Chem.* **2012**, *20*, 1175 and references cited therein. (d) Sinu, C. R.; Padmaja, D. V. M.; Ranjini, U. P.; Seetha Lakshmi, K. C.; Suresh, E.; Nair, V. *Org. Lett.* **2013**, *15*, 68.

(6) (a) *RÖMPP Encyclopedia: Natural Products*; Steglich, W., Fugmann, B., Lang-Fugmann, S., Eds.; Thieme: Stuttgart, Germany, 2000; p 494. For various papers reporting the isolation of pimpinellin from natural sources, see: (b) Steck, W. *Phytochemistry* **1970**, *9*, 1145. (c) Vanhaelen, M.; Vanhaelen-Fastré, R. *Phytochemistry* **1974**, *13*, 306. (d) Reisch, J.; Wickramasinghe, A.; Kumar, V. *J. Nat. Prod.* **1989**, *52*, 1379. (e) Zobel, A. M.; Wang, J.; March, R. E.; Brown, S. A. *J. Chem. Ecol.* **1991**, *17*, 1859. (f) Müller, A. H.; Degáspari, L. R. O.; Vieira, P. C.; da Silva, M. F. das G. F.; Fernandes, J. B.; Pirani, J. R. *Phytochemistry* **1993**, *34*, 585. (g) Oliveira, F. M.; Sant'ana, A. E. G.; Conserva, L. M.; Maia, J. G. S.; Guilhon, G. M. P. *Phytochemistry* **1996**, *41*, 647.

(7) de Oliveira, P. E. S.; Conserva, L. M.; De Simone, C. A.; Pereira, M. A.; Malta, V. R. S.; Imbroisi, D. O. *Acta Crystallogr., Sect. C* **2004**, *60*, o900.

(8) (a) Shimomura, H.; Sashida, Y.; Nakata, H.; Kawasaki, J.; Ito, Y. *Phytochemistry* **1982**, *21*, 2213. (b) Desjardins, A. E.; Plattner, R. D.; Spencer, G. F. *Phytochemistry* **1988**, *27*, 767. (c) Desjardins, A. E.; Spencer, G. F.; Plattner, R. D. *Phytochemistry* **1989**, *28*, 2963. (d) Wang, C.-C.; Lai, J.-E.; Chen, L.-G.; Yen, K.-Y.; Yang, L.-L. *Bioorg. Med. Chem.* **2000**, *8*, 2701. (e) Singhuber, J.; Baburin, I.; Ecker, G. F.; Kopp, B.; Hering, S. *Eur. J. Pharmacol.* **2011**, *668*, 57.

(9) *The Merck Index*, 12th ed.; Merck: New York, 1996; p 722.

(10) (a) Yasuda, Y.; Fukui, M.; Nakazawa, T.; Hoshikawa, A.; Ohsawa, K. *J. Nat. Prod.* **2006**, *69*, 755. (b) Venkateswarlu, K.; Satyalakshmi, G.; Suneel, K.; Reddy, T. S.; Raju, T. V.; Das, B. *Helv. Chim. Acta* **2008**, *91*, 2081. (c) Céspedes, C. L.; Avila, J. G.; Martínez, A.; Serrato, B.; Calderón-Mugica, J. C.; Salgado-Garciglia, R. *J. Agric. Food Chem.* **2006**, *54*, 3521.

(11) (a) Paya, M.; Goodwin, P. A.; De Las Heras, B.; Hoult, J. R. S. *Biochem. Pharmacol.* **1994**, *48*, 445. (b) Molina-Jiménez, M. F.; Sánchez-Reus, M. I.; Benedi, J. *Eur. J. Pharmacol.* **2003**, *472*, 81. (c) Molina-Jiménez, M. F.; Sánchez-Reus, M. I.; Andres, D.; Cascales, M.; Benedi, J. *Brain Res.* **2004**, *1009*, 9. (d) Sánchez-Reus, M. I.; Peinado, I. I.; Molina-Jiménez, M. F.; Benedi, J. *Neurosci. Res.* **2005**, *53*, 48. (e) Kuo, P.-L.; Huang, Y.-T.; Chang, C.-H.; Chang, J.-K. *Int. Immunopharmacol.* **2006**, *6*, 1167. (f) Li, J.-M.; Zhang, X.; Wang, X.; Xie, Y.-C.; Kong, L. D. *Eur. J. Pharmacol.* **2011**, *666*, 196.

(12) Debenedetti, S. L.; Nadinic, E. L.; Gomez, M. A.; Coussio, J. D.; De Kimpe, N.; Boeykens, M. *Phytochemistry* **1996**, *42*, 563.

(13) Maes, D.; Van Syngel, K.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 4426.

(14) (a) Arnoldi, A.; Arnone, A.; Merlini, L. *Heterocycles* **1984**, *22*, 1537. (b) Tanaka, H.; Kato, I.; Ito, K. *Heterocycles* **1985**, *23*, 1991.

(15) Reed, M. W.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 4166.

(16) (a) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901. (b) Harris, E. B. J.; Banwell, M. G.; Willis, A. C. *Tetrahedron Lett.* **2011**, *52*, 6887.

(17) For analogous Pd- and Pt-catalyzed processes, see: (a) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518. (b) Oyamada, J.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6918. (c) Vadola, P. A.; Sames, D. *J. Org. Chem.* **2012**, *77*, 7804.

(18) For example, see: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

(19) (a) Rao, D. V.; Stuber, F. A. *Synthesis* **1983**, 308. (b) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(20) Ellis, J. E.; Lenger, S. R. *Synth. Commun.* **1998**, *28*, 1517.

(21) Radix, S.; Barret, R. *Tetrahedron* **2007**, *63*, 12379.

(22) CCDC 934659, 933272, and 941290 contain the crystallographic data for compounds **8**, **9**, and **17**, respectively. These data can be obtained free-of-charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(23) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

(24) Skotnicki, J. F.; Kearney, R. M.; Smith, A. L. *Tetrahedron Lett.* **1994**, *35*, 197.

(25) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(26) Sun, H.; Ding, J.; Lin, Z.; Yi, Y.; Fu, J. *Acta Pharm. Sin.* **1982**, *17*, 835.

(27) Flynn, B. L.; Banwell, M. G. *Heterocycles* **2012**, *84*, 1141.

(28) Kaisalo, L.; Latvala, A.; Hase, T. *Synth. Commun.* **1986**, *16*, 645.

(29) Liu, R.; Sun, Q.; Sun, A.; Cui, J. *J. Chromatogr., A* **2005**, *1072*, 195.

(30) Prenyl ether **22** is a naturally occurring compound known as capensin that has been isolated from, inter alia, the plant species *Bupleurum fruticosum* and *Phyllosma capensis*. See: (a) Campbell, W. E.; Cragg, G. M. L. *Phytochemistry* **1979**, *18*, 688. (b) Pistelli, L.; Bertoli, A.; Bilia, A. R.; Morelli, I. *Phytochemistry* **1996**, *41*, 1579.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(32) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.