First Concise Total Syntheses of Biologically Interesting Nicolaioidesin C, Crinatusin C_1, and Crinatusin C_2

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The efficient and concise total syntheses of naturally occurring dihydrochalcone nicolaioidesin C, crinatusin C_1, and crinatusin C_2 have been achieved from the readily available 2,6-dihydroxy-4-methoxyacetophenone and 2,4-dihydroxy-6-methoxyacetophenone. The key steps in the synthetic strategy were aldol reaction and Diels-Alder reaction.

Key Words : Dihydrochalcone, Nicolaioidesin C, Crinatusin C_1, Crinatusin C_2

Introduction

Dihydrochalcones are a subclass of the flavonoids that are widely distributed in nature (Figure 1).[1] Members have been associated with a wide variety of biological activities, and some plants have been used in traditional medicine.[2] Among these, panduratin A(**1**) was isolated from *Boesenbergia pandurata* as either a racemate or in the optically active form (Figure 1).[3] This plant is widely cultivated in some tropical countries,[4] and has been reported to have anti-HIV, antibacterial, antifungal, anti-inflammatory, analgesic, antipyretic, antispasmodic, antitumor, and insecticidal activities.[5] *Boesenbergia pandurata* is widely known as Seik-phoo in Myanmar, and it has been used extensively in the traditional medicine known as TMF-47 to treat asthma, diarrhea, indigestion, itching, and fever.[6] Extracts of this plant are also used in traditional Indonesian, Malaysian, and Thai medicine to treat diseases such as ulcers, dry mouth, stomach, discomfort, leucorrhea, and dysentery.[1c,7] It has been also used as a self-medication by AIDS patients in Thailand.[8]

Nicolaioidesins A (**2**), B(**3**), and C (**4**) are isomers of panduratin A (**1**) and have been isolated as optically inactive racemates from the roots of *Renealmia nicolaioides*.[9] This plant is known as "mishqui panga" in the Quechua dialect in Peru, which means tasty leaf.[9] As a part of ongoing systematic search for novel plant-derived cancer chemopreventive agents, the extracts of the roots of this plant was found to significantly induce quinine reductase (QR) activity with the cultured Hepa lclc7 mouse hepatoma cells.[10] The induction of phase II enzymes, such as QR, is considered to be an important mechanism for protection against tumor initiation.[11] Crinatusins C_1(**5**) and C_2 (**6**) were isolated as an inseparable 5:2 mixture of optically inactive form from the extracts of *Cyathocalyx crinatus*, which is used to obtain fresh water in the jungle.[12] The structures of these natural products **1**-**6** have been determined by spectroscopic analysis. However, no synthetic approaches have been reported. Interestingly, these natural products have similar structures to the dihydrochalcone moiety that has been isolated from other species. This wide range of biological activities and properties has stimulated interest in the synthesis of naturally occurring dihydrochalcones.

Recently, we developed a new and rapid route for the synthesis of biologically interesting natural products with benzopyrans and pyranochalcone skeletons.[13] As a part of ongoing study for this synthetic efficacy of biologically interesting natural products, we report herein the first concise total synthesis of nicolaioidesin C (**4**), crinatusin C_1(**5**), and crinatusin C_2 (**6**).

Results and Discussion

Scheme 1 shows the retrosynthetic strategy for the natural products **4**-**6**. The natural products **4**-**6** could be synthesized from chalcones **11** and **18** with myrcene (**13**) using (the) Diels-Alder reaction as a key-step. The crucial intermediates **11** and **18** could be prepared from the commercially available compounds **7** and **15** with benzaldehyde (**10**) through base-catalyzed aldol reactions.

The total synthesis of nicolaioidesin C (**4**) was first

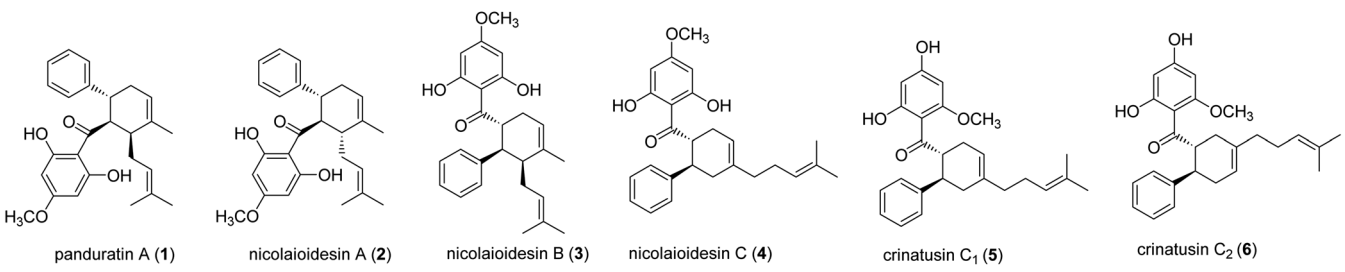
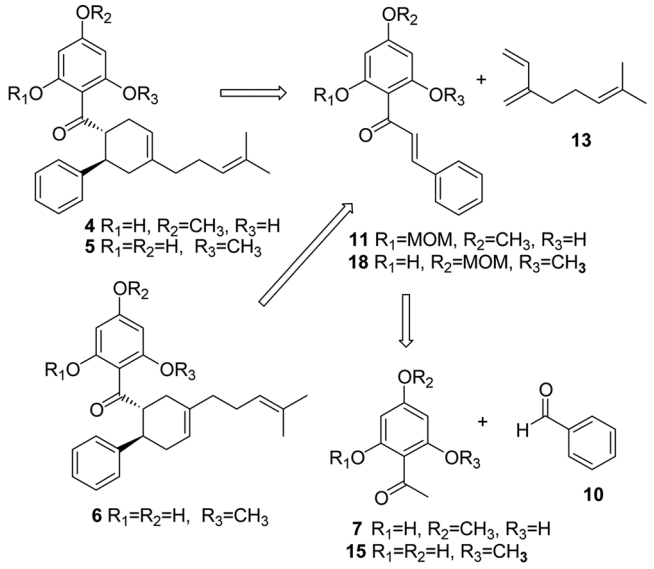


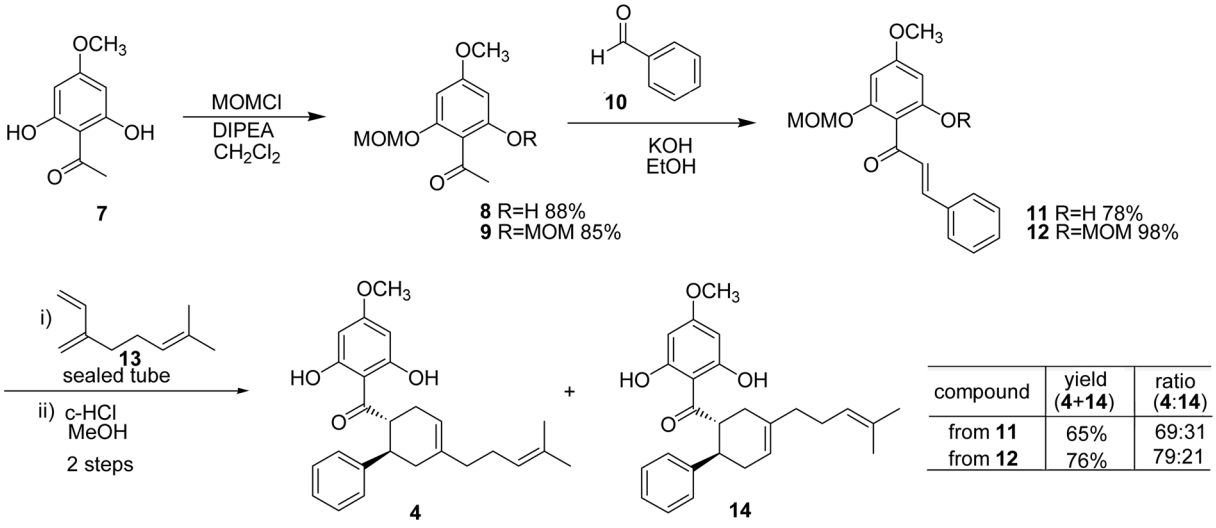
Figure 1. Selected naturally occurring dihydrochalcones.



Scheme 1. Retrosynthetic analysis of natural products **4**-**6**.

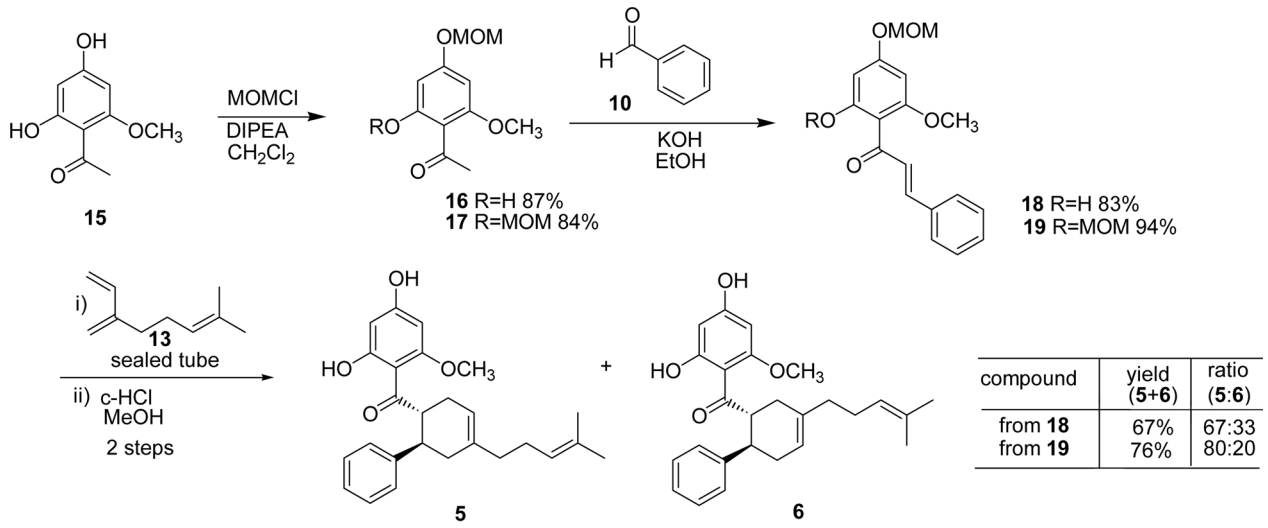
attempted starting from the commercially available 2,6-dihydroxy-4-methoxyacetophenone (**7**), as shown in Scheme 2. Attempts to directly condense compound **7** with bezaldehyde (**10**) with several bases such as KOH, LDA, and LiHMDS were unsuccessful due to the two acidic phenolic groups. Therefore, we attempted to introduce the chalcone moiety by protecting the acidic phenolic group. The methoxymethyl (MOM) group appeared to be an ideal protecting group of the OH groups of compound **7**. Treatment of compound **7** with 1 equivalent of methoxymethyl chloride and *N*,*N*-diisopropylethylamine in methylene chloride at room temperature for 8 h gave only the product **8** in 88% yield, whereas treatment with 2.2 equivalents of methoxymethyl chloride in refluxing methylene chloride for 24 h afforded the diprotected product **9** as two MOM ethers in 85% yield. Condensation of compounds **8** and **9** with benzaldehyde (**10**) in ethanolic KOH at room temperature for 48 h afforded chalcones **11** and **12** in 78 and 98% yields, respectively. Thermal reaction of the chalcone **11** with myrcene in benzene in a sealed tube at 220 °C for 24 h followed by the cleavage of MOM ether with conc-HCl in methanol at room temperature for 2 h gave the expected nicolaioidesin C (**4**) together with its unnatural regioisomer **14** in 65% yield (2 steps) as a 69:31 ratio. Interestingly, further reaction of the chalcone **12** with myrcene improved the yield (76%, 2 steps) and the selectivity of compounds **4** to **14** to 79:21 probably due to bulky two MOM ethers. These two inseparable compounds were readily assigned by comparison with reported data. The 600 MHz ^{1}H NMR spectrum of compound **4** showed signals due to a methine proton attached to a carbonyl group at δ 4.46 ppm (ddd, J = 10.8, 10.8, 5.4 Hz) and a methine proton on the benzylic position at 3.30 (ddd, J = 11.4. 11.4, 5.4 Hz), whereas compound **14** showed signals of a proton of carbonyl group at δ 4.52 (ddd, J = 10.8, 10.8, 4.8 Hz) and a methine proton on the benzylic position at 3.24 (ddd, J = 10.8, 10.8, 5.4 Hz). The spectral data of the synthetic material **4** was the same as those reported in the literature.[9]

The total synthesis of crinatusins C_1 (**5**) and C_2 (**6**) was next investigated starting from the commercially available 2,4-dihydroxy-6-methoxyacetophenone (**15**), as shown in Scheme 3. Treatment of compound **15** with 1 equivalent of methoxymethyl chloride and *N*,*N*-diisopropylethylamine in methylene chloride at room temperature for 2 h gave product **16** in 87% yield, whereas treatment with 2.2 equivalents of methoxymethyl chloride in refluxing methylene chloride for 24 h afforded the diprotected product **17** in 84% yield. Condensation of compound **16** with benzaldehyde (**10**) in ethanolic KOH at room temperature for 48 h afforded chalcone **18** in 83% yield, whereas treatment of compound **17** with benzaldehyde (**10**) produced chalcone **19** in 94% yield. The thermal reaction of the chalcone **18** with myrcene in benzene in a sealed tube at 220 °C for 24 h followed by the cleavage of MOM ether with conc-HCl at room temperature for 2 h gave two natural products **5** and **6** (67%, 2 steps) as a 67:33 ratio. Reaction of the chalcone **19** with myrcene followed by the cleavage of two MOM ethers



compound	yield (**4**+**14**)	ratio (**4**:**14**)
from **11**	65%	69:31
from **12**	76%	79:21

Scheme 2



compound	yield (**5**+**6**)	ratio (**5**:**6**)
from **18**	67%	67:33
from **19**	76%	80:20

Scheme 3

afforded two natural products **5** and **6** as a 80:20 mixture of regioisomers in 76% yield (2 steps). The spectral data of the synthetic materials **5** and **6** were the same as those reported in the literature.[12]

In conclusion, the efficient and concise total syntheses of biologically interesting dihydrochalcone natural products nicolaioidesin C (**4**), crinatusin C_1 (**5**), and crinatusin C_2 (**6**) have been described. The key strategy in the synthetic procedures involved aldol reactions and Diels-Alder reactions. Further synthetic approaches for the other dihydrochalcone natural products, panduratin A (**1**), nicolaioidesin A (**2**), and nicolaioidesin B (**3**), are currently underway.

Experimental

All the experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ using δ = 7.24 and 77.0 ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer.

1-(2-Hydroxy-4-methoxy-6-methoxymethoxyphenyl) ethanone (8). Methoxymethyl chloride (162 mg, 2.0 mmol) was added to a solution of **7** (364 mg, 2.0 mmol) and diisopropylethylamine (1.292 g, 10.0 mmlo) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 8 h, and then water (30 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 20 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ ethyl acetate (10:1) afforded **8** (398 mg, 88%) as a soild: mp 60-61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ6.07 (1H, d, J = 2.2 Hz), 6.00 (1H, d, J = 2.2 Hz), 5.17 (2H, s), 3.73 (3H, s), 3.45 (3H, s), 2.57 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 166.9, 163.5, 162.9, 106.4, 96.1, 93.8, 91.1, 56.2, 55.4, 32.8; IR (KBr) 3113, 2949, 1620, 1591, 1429, 1271, 1225, 1167, 1082, 1030, 928, 833, 790 cm^{-1}.

1-(4-Methoxy-2,6-bismethoxymethoxyphenyl)ethanone (9). Methoxymethyl chloride (354 mg, 4.4 mmol) was added to a solution of **7** (364 mg, 2.0 mmol) and diisopropylethylamine (1.292 g, 10.0 mmlo) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was refluxed for 24 h, and then water (30 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 30 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethylacetate (5:1) afforded **9** (459 mg, 85%) as a soild: mp 54-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ6.32 (2H, s), 5.04 (4H, s), 3.71 (3H, s), 3.40 (6H, s), 2.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 161.8, 155.3, 115.6, 94.8, 94.6, 56.1, 55.4, 32.4; IR (KBr) 2959, 1699, 1609, 1450, 1394, 1352, 1251, 1217, 1155, 1113, 1051, 1006, 922, 826 cm^{-1}.

(*E*)-1-(2-Hydroxy-4-methoxy-6-methoxymethoxyphenyl)-3-phenylpropenone (11). To a solution of **8** (300 mg, 1.3 mmol) in ethanol (10 mL) was added potassim hydroxide (364 mg, 6.5 mmol) and benzaldehyde (**10**) (170 mg, 1.6 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2N-HCl solution (30 mL) and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (15:1) gave **11** (319 mg, 78%) as a solid: mp 75-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.07(1H, s), 7.92 (1H, d, J = 15.6 Hz), 7.76 (1H, d, J = 15.6 Hz), 7.60-7.56 (2H, m), 7.42-7.33 (3H, m), 6.13 (1H, s), 6.12 (1H, s), 5.26 (2H, s), 3.77 (3H, s), 3.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 167.8, 165.9, 159.7, 142.2, 135.3, 130.0, 128.8, 128.2, 127.3, 106.6, 94.9, 94.7, 93.8, 56.5, 55.5; IR (KBr) 2962,

1634, 1564, 1449, 1346, 1223, 1159, 1086, 1026, 976, 932, 835, 795, 746 cm^{-1}.

(*E*)-1-(4-Methoxy-2,6-bismethoxymethoxyphenyl)-3-phenylpropenone (12). To a solution of **9** (270 mg, 1.0 mmol) in ethanol (10 mL) was added potassim hydroxide (280 mg, 5.0 mmol) and benzaldehyde (**10**) (127 mg, 1.2 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2 N-HCl solution (30 mL) and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (5:1) gave **12** (351 mg, 98%) as a solid: mp 79-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.47 (2H, m), 7.36-7.30 (4H, m), 6.95 (1H, d, J = 15.6 Hz), 6.41 (2H, s), 5.08 (4H, s), 3.78 (3H, s), 3.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 161.9, 155.9, 144.8, 134.7, 130.3, 129.0, 128.8, 128.2, 113.5, 94.8, 94.4, 56.1, 55.4; IR (KBr) 2991, 1642, 1609, 1491, 1451, 1393, 1300, 1271, 1231, 1217, 1152, 1115, 1049, 924, 912, 808, 777 cm^{-1}.

Nicolaioidesin C (4) and its regioisomer 14. From compound **11**: To a sealed tube was added **11** (189 mg, 0.6 mmol) in benzene (2 mL), followed by myrcene (817 mg, 6.0 mmol) at room temperature. The tube was then sealed and heated at 220 °C for 24 h. After cooling to room temperature, the solvent and myrcene were evaporated under reduced pressure to give residue. Then, methanol (10 mL) and c-HCl (5 drops) were added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) to give **4** and **14** (159 mg, 65%) as a mixture of 69: 31 ratio.

Compound **4**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26-7.18 (4H, m), 7.09-7.05 (1H, m), 5.84 (2H, s), 5.50 (1H, br s), 5.11 (1H, t, J = 6.8 Hz), 4.46 (1H, ddd, J = 10.8, 10.8, 5.4, Hz), 3.70 (3H, s), 3.30 (1H, ddd, J = 11.4. 11.4, 5.4 Hz), 2.57-2.54 (1H, m), 2.27-2.08 (7H, m), 1.67 (3H, s), 1.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 165.5, 145.4, 137.5, 131.6, 128.3, 127.2, 126.0, 124.1, 119.2, 105.4, 94.4, 55.5, 50.0, 42.7, 38.3, 37.3, 30.7, 26.4, 25.7, 17.7.

Compound **14**: ^{1}H NMR (600 MHz, $CDCl_3$) 7.26-7.18 (4H, m), 7.09-7.05 (1H, m), 5.84 (2H, s), 5.50 (1H, br s), 5.09 (1H, t, J = 6.8 Hz), 4.52 (1H, ddd, J = 10.8, 10.8, 4.8 Hz), 3.70 (3H, s), 3.24 (1H, ddd, J = 10.8, 10.8, 5.4 Hz), 2.57-2.08 (1H, m), 2.44 (1H, dd, J = 16.2, 4.8 Hz), 2.38-2.34 (1H, m), 2.27-1.99 (5H, m), 1.67 (3H, s), 1.59 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 163.1, 145.3, 136.6, 131.5, 128.2, 127.2, 126.0, 124.1, 120.3, 105.3, 94.4, 53.0, 50.2, 42.4, 37.4, 35.1, 34.0, 26.4, 25.7, 17.7.

From compound **12**: To a sealed tube was added **12** (179 mg, 0.5 mmol) in benzene (2 mL), followed by myrcene (681 mg, 5.0 mmol) at room temperature. The tube was then sealed and heated at 220 °C for 24 h. After cooling to room temperature, the solvent and myrcene were evaporated under reduced pressure to give residue. Then, methanol (10 mL) and c-HCl (5 drops) were added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) to give **4** and **14** (154 mg, 76%) as a mixture of 79: 21 ratio.

1-(2-Hydroxy-6-methoxy-4-methoxymethoxyphenyl) ethanone (16). Methoxymethyl chloride (145 mg, 1.8 mmol) was added to a solution of **15** (328 mg, 1.8 mmol) and diisopropylethylamine (1.118 g, 9.0 mmlo) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then water (30 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 20 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (10:1) afforded **16** (354 mg, 87%) as a soild: mp 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ6.13 (1H, d, J = 2.1 Hz), 5.97 (1H, d, J = 2.1 Hz), 5.12 (2H, s), 3.79 (3H, s), 3.42 (3H, s), 2.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 167.0, 165.8, 160.1, 106.1, 94.3, 93.8, 92.4, 56.5, 55.4, 32.7; IR (KBr) 3112, 2955, 1620, 1424, 1366, 1268, 1223, 1151, 1114, 1065, 937, 886, 834 cm^{-1}.

1-(2-Methoxy-4,6-bismethoxymethoxyphenyl)ethanone (17). Methoxymethyl chloride (282 mg, 3.5 mmol) was added to a solution of **15** (291 mg, 1.6 mmol) and diisopropylethylamine (1.292 g, 10.0 mmlo) in dry methylene chloride (20 mL) at room temperature. The reaction mixture was refluxed for 24 h, and then water (30 mL) was added. The reaction mixture was extracted with methylene chloride (3 × 30 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (20 mL), water (20 mL), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel using hexane/ethyl acetate (5:1) afforded **17** (363 mg, 84%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ6.41 (1H, d, J = 1.9 Hz), 6.26 (1H, d, J = 1.9 Hz), 5.11 (2H, s), 5.09 (2H, s), 3.74 (3H, s), 3.43 (3H, s), 3.41 (3H, s), 2.43 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 159.6, 157.7, 155.3, 115.6, 95.7, 94.6, 94.3, 93.7, 56.2, 56.1, 55.7, 32.4; IR (neat) 2957, 2829, 1701, 1607, 1462, 1427, 1400, 1352, 1231, 1152, 1121, 1080, 1024, 924, 824 cm^{-1}.

(*E*)-1-(2-Hydroxy-6-methoxy-4-methoxymethoxyphenyl)-3-phenylpropenone (18). To a solution of **16** (271 mg, 1.2 mmol) in ethanol (10 mL) was added potassim hydroxide (336 mg, 6.0 mmol) and benzaldehyde (**10**) (159 mg, 1.5 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2N-HCl solution (30 mL) and brine (30 mL), drying over

$MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (15:1) gave **18** (313 mg, 83%) as a solid: mp 73-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, J = 15.6 Hz), 7.74 (1H, d, J = 15.6 Hz), 7.60-7.52 (2H, m), 7.40-7.34 (3H, m), 6.24 (1H, s), 6.05 (1H, s), 5.16 (2H, s), 3.88 (3H, s), 3.45 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 167.6, 162.4, 159.6, 142.2, 135.3, 129.9, 128.7, 128.2, 127.3, 106.7, 96.3, 93.8, 91.6, 56.3, 55.7; IR (KBr) 2953, 1632, 1582, 1451, 1424, 1343, 1219, 1152, 1115, 1084, 1028, 978, 932, 828, 745 cm^{-1}.

(*E*)-1-(2-Methoxy-4,6-bismethoxymethoxyphenyl)-3-phenylpropenone (19). To a solution of **17** (297 mg, 1.1 mmol) in ethanol (10 mL) was added potassim hydroxide (308 mg, 5.5 mmol) and benzaldehyde (**10**) (138 mg, 1.3 mmol) at room temperature. The reaction mixture was stirred for 48 h at room temperature. Evaporation of ethanol and extraction with ethyl acetate (3 × 50 mL), washing with 2N-HCl solution (30 mL) and brine (30 mL), drying over $MgSO_4$ and removal of the solvent followed by flash column chromatography on silica gel using hexane/ethyl acetate (4:1) gave **19** (371 mg, 94%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.43 (2H, m), 7.33 (1H, d, J = 15.6 Hz), 7.28-7.24 (3H, m), 6.93 (1H, d, J = 15.6 Hz), 6.47 (1H, s), 6.32 (1H, s), 5.13 (2H, s), 5.04 (2H, s), 3.68 (3H, s), 3.43 (3H, s), 3.31 (3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 159.6, 158.2, 155.6, 144.4, 134.4, 130.0, 129.6, 128.5, 128.0, 113.2, 95.4, 94.2, 94.1, 93.6, 55.9, 55.8, 55.5; IR (neat) 2959, 1651, 1607, 1454, 1399, 1271, 1150, 1119, 1078, 1022, 924, 824, 775 cm^{-1}.

Crinatusins C_1 (5) and C_2 (6). From compound **18**: To a sealed tube was added **18** (157 mg, 0.5 mmol) in benzene (2 mL), followed by myrcene (749 mg, 5.5 mmol) at room temperature. The tube was then sealed and heated at 220 °C for 24 h. After cooling to room temperature, the solvent and myrcene were evaporated under reduced pressure to give residue. Then, methanol (10 mL) and c-HCl (5 drops) were added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) to give **5** and **6** (136 mg, 67%) as a mixture of 67: 33 ratio.

Compound **5**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18-7.13 (4H, m), 7.08-7.04 (1H, t, J = 7.0 Hz), 6.42 (1H, br s), 5.85 (1H, s), 5.82 (1H, s), 5.51 (1H, br s), 5.12 (1H, t, J = 6.8 Hz), 4.25 (1H, ddd, J = 10.2, 10.2, 4.8 Hz), 3.85 (3H, s), 3.26 (1H, ddd, J = 10.8, 10,8, 4.8 Hz), 2.48-2.42 (1H, m), 2.40-2.33 (1H, m), 2.27-2.08 (6H, m), 1.69 (3H, s), 1.61 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 166.9, 163.0, 162.9, 145.3, 137.3, 131.5, 128.2, 127.2, 125.9, 124.1, 119.3, 106.3, 96.4, 91.0, 55.8, 50.3, 42.9, 38.1, 37.2, 30.5, 26.3, 25.7, 17.7.

Compound **6**: ^{1}H NMR (600 MHz, $CDCl_3$) 7.18-7.13 (4H, m), 7.09-7.05 (1H, m), 5.85 (1H, s), 5.82 (1H, s), 5.51 (1H, br s), 5.12 (1H, t, J = 6.8 Hz), 4.30 (1H, ddd, J = 11.4, 11.4, 4.8 Hz), 3.85 (3H, s), 3.20 (1H, ddd, J = 11.4, 11.4, 5.4 Hz), 2.27-2.08 (8H, m), 1.69 (3H, s), 1.61 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 167.1, 163.0, 162.9, 145.2, 136.6, 131.6, 128.2, 127.2, 125.9, 124.0, 120.3, 106.2, 96.4, 91.0, 55.8, 50.6, 42.6, 37.4, 35.0, 33.3, 26.4, 25.7, 17.7.

From compound **19**: To a sealed tube was added **19** (143 mg, 0.4 mmol) in benzene (2 mL), followed by myrcene (545 mg, 4.0 mmol) at room temperature. The tube was then sealed and heated at 220 °C for 24 h. After cooling to room temperature, the solvent and myrcene were evaporated under reduced pressure to give residue. Then, methanol (10 mL) and c-HCl (5 drops) were added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and dried over $MgSO_4$. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane/ethylacetate (5:1) to give **5** and **6** (124 mg, 76%) as a mixture of 80: 20 ratio.

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