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**SYNTHESIS OF ISOCOUMARIN COMPOUNDS,
8-HYDROXY-6-METHOXY-3-PENTYL-1*H*-ISOCHROMEN-1-ONE AND
FUSARIUMIN ANALOG USING PALLADIUM-CATALYZED
CARBONYLATION TRAPPING WITH *O*-ENOLATE**

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Abstract – Concise synthesis of 6,8-dialkoxyisocoumarin framework was achieved using Pd-catalyzed carbonylation trapping with *O*-enolate. This methodology was applied to the synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one isolated from *Tessmannia densiflora* and fusariumin analog.

INTRODUCTION

Isocoumarin compounds are natural products which are isolated from wide range of natural sources such as microorganism, plants and insects and so on. These compounds have significant biological activities such as cytotoxic, antifungal, antiallergic and antimalarial activities.¹ Most of natural isocoumarin compounds have 3-alkyl side chain and 6,8-dioxygenated functional groups. In 1962, Huneck isolated 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) from dried powder of *Lecidea confluens* after treatment with CH₂N₂.² This compound was also isolated by Nkunya and co-workers from *Tessmannia densiflora* in 2009.³ Compound **1** showed insecticidal activity against mosquito larvae. In 2011, Laatsch and co-workers isolated fusariumin (**2**) which showed significant growth inhibitory activity against the brine shrimp from *Fusarium* sp.⁴ As to the examples of the synthesis of isocoumarin compounds, heating of homophthalic acid⁵ and preparation from homophthalic anhydride⁶ were reported. These methods often suffered from low yield. In 2009, Willis and co-workers synthesized isocoumarin compound thunberginol A using Pd-catalyzed carbonylation-intramolecular *O*-enolate acylation.⁷ We also reported concise

synthesis of legioliulin using this strategy and Heck reaction.⁸ Here, we wish to report the synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) and 6,8-dimethylfusariumin (**3**), the analog of fusariumin (**2**), using Pd-catalyzed carbonylation trapping with *O*-enolate as a key step (Figure 1).

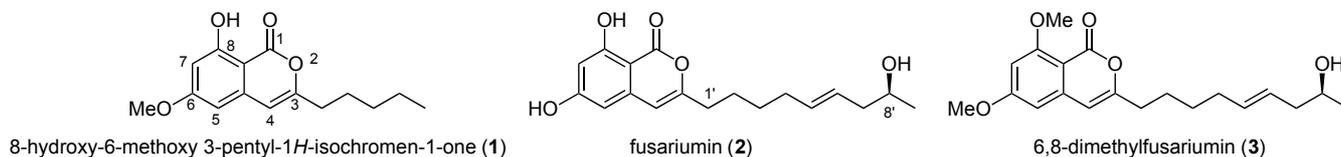
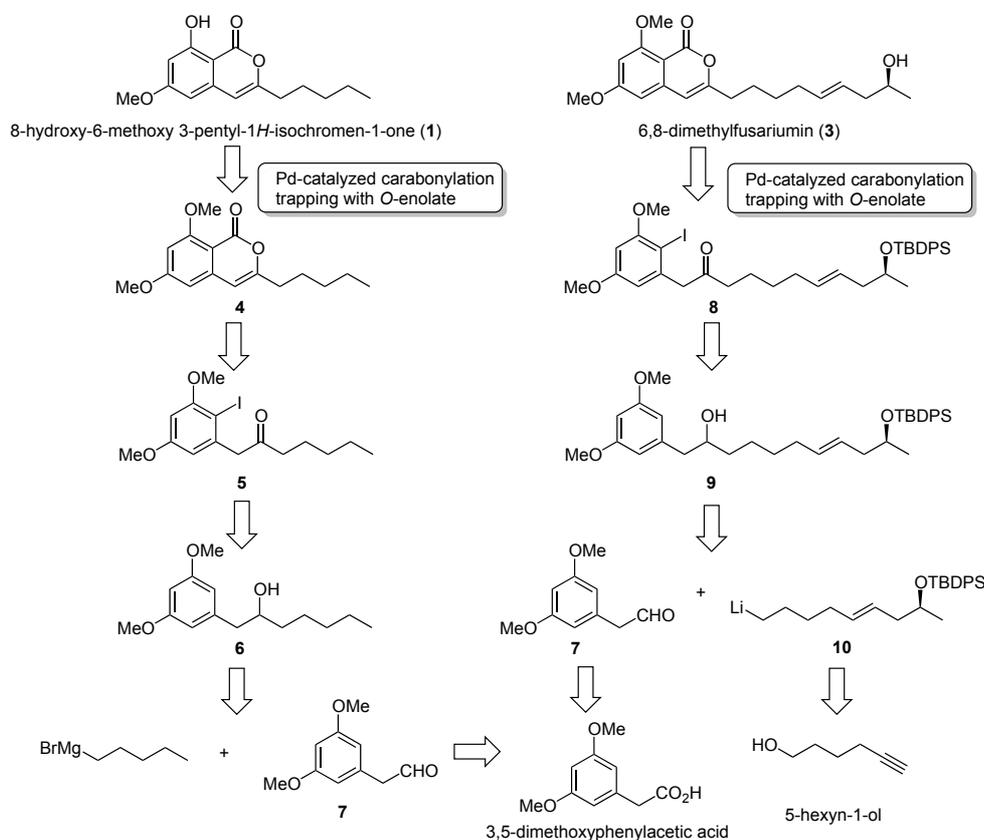


Figure 1. Structure of isocoumarins

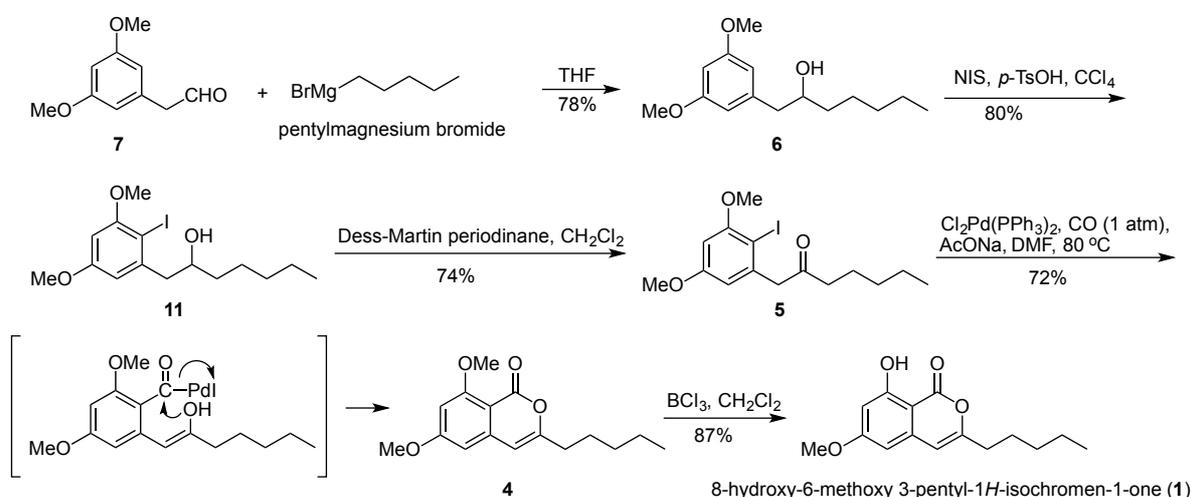
RESULTS AND DISCUSSION

The synthetic strategy is shown in Scheme 1. As to the synthetic strategy of **1**, isocoumarin ring would be constructed using Pd-catalyzed carbonylation trapping with *O*-enolate⁹⁻¹³ from iodoketone **5**. Iodoketone **5** would be synthesized *ortho* iodination followed by oxidation of alcohol **6**. Compound **6** would be prepared from aldehyde **7**¹⁴ and pentylmagnesium bromide. Aldehyde **7** would be synthesized from commercially available 3,5-dimethoxyphenylacetic acid. As to the synthetic strategy of **3**, isocoumarin ring would be constructed from iodoketone **8**. Iodoketone **8** would be prepared *ortho* iodination followed by oxidation of alcohol **9**. Alcohol **9** would be synthesized from aldehyde **7** and organolithium compound **10**. Compound **10** would be prepared from 5-hexyn-1-ol.



Scheme 1. Synthetic strategy of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) and 6,8-dimethylfusariumin (**3**)

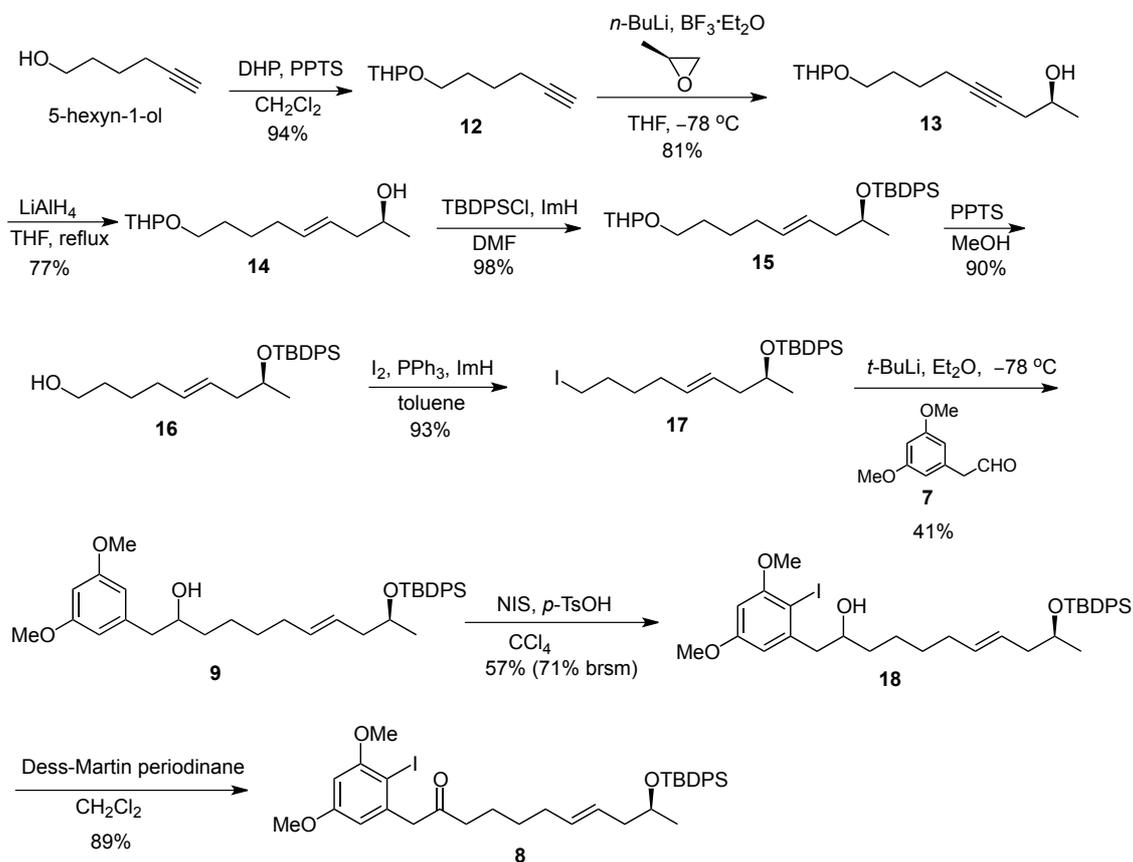
Scheme 2 shows the synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) (Scheme 2).^{2,3} Grignard reaction of pentylmagnesium bromide with aldehyde **7**¹⁴ afforded alcohol **6**. Iodination at C-2 position of the benzene ring using NIS in the presence of *p*-TsOH gave **11**. Oxidation of the secondary hydroxy group of **11** using Dess-Martin periodinane afforded **5**. Pd-Catalyzed carbonylation trapping with *O*-enolate of **5** using $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ as a catalyst and AcONa as a base under the 1 atm of CO atmosphere at 80 °C furnished isocoumarin **4** in 72% yield.⁶ When this reaction was performed at 50 °C, the yield was almost same as that of 80 °C. By comparison with mono-oxygenated isocoumarin, which was synthesized by us before,⁸ the chemical yield was much higher. The reason might be that the additional methoxy group enhanced the reactivity of oxidative addition of the Pd catalyst due to electron donating effect. Finally, selective deprotection of the C-8 methyl group due to the coordination of BCl_3 at the *ortho* carbonyl group gave 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) in good yield.¹⁵ The lactone carbonyl absorption in the IR spectrum showed 1672 cm^{-1} by forming hydrogen bond with C-8 hydroxy group.¹⁶ The spectral data of synthetic **1** were in good agreement with those of the reported values.³ As to the melting point value, our synthetic sample (57-58 °C) was consistent with that of the reported value (57-57.5 °C) by Huneck et al.,² although Nkunya and co-workers reported much higher value (79-80 °C).³



Scheme 2. Synthesis of 8-hydroxy-6-methoxy-3-pentyl-1*H*-isochromen-1-one (**1**) isolated from *Tessmannia densiflora*

Next, we began to synthesize 6,8-dimethylfusariumin (**3**) (Scheme 3). Scheme 3 shows the preparation of cyclization precursor **8** of the 6,8-dimethylfusariumin (**3**). Protection of the hydroxy group as a THP ether of 5-hexyn-1-ol afforded **12**.¹⁷ Reaction of lithium acetylide of **12** with (*S*)-2-methyloxirane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave alcohol **13**.¹⁸ Reduction of the triple bond to *E*-double bond using LiAlH_4 under reflux in THF afforded **14**. Protection of the secondary hydroxy group of **14** with TBDPSCl in the presence of imidazole afforded **15**. Selective deprotection of the THP group of **15** using PPTS gave **16**

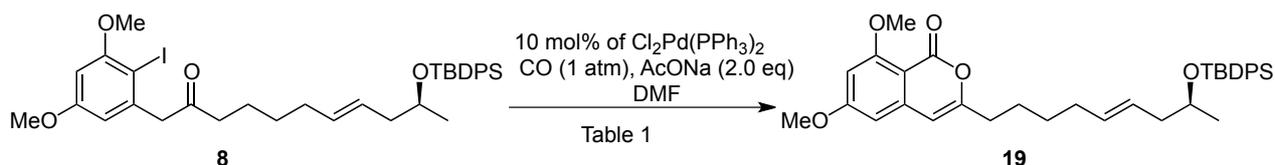
followed by iodination using I_2 and PPh_3 in the presence of imidazole furnished primary iodide **17** in good yield. Lithium-halogen exchange of **17** using $t\text{-BuLi}$ followed by reaction with aldehyde **7** afforded **9**. Regioselective iodination of **9** using NIS in the presence of $p\text{-TsOH}$ gave **18**. Oxidation of the secondary hydroxy group using Dess-Martin periodinane afforded cyclization precursor **8**.



Scheme 3. Synthesis of cyclization precursor **8** of 6,8-dimethylfusariumin (**3**)

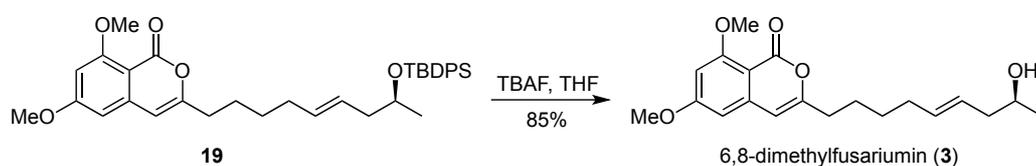
The cyclization precursor **8** was in hand, we investigated Pd-catalyzed carbonylation trapping with *O*-enolate to construct isocoumarin ring (Table 1). As shown in Table 1, the reaction temperature was important. We found that 50 °C was optimized reaction temperature.

Table 1. Pd-catalyzed carbonylation trapping with *O*-enolate **8**



Entry	Temp (°C)	Time (h)	Yield of 19 (%)
1	50	96	89
2	80	24	76
3	100	3	55

As whole carbon skeleton of **3** was constructed, we deprotected the TBDPS group of **19** using TBAF to afford 6,8-dimethylfusariumin (**3**) in good yield. As to the absolute configuration at C-8' position of natural fusariumin (**2**), Laatsch and co-workers determined to be *S* by comparison of the positive sign of the optical rotation of the known compounds, (+)-(*S*)-3-hydroxybutyl benzoate and (+)-(*S*)-dichlorodiaportin, respectively. However, because the specific rotation value of natural **2** is very small $\{[\alpha]_D + 1.01 (c 0.2, \text{MeOH})\}$,⁴ it is difficult to determine the absolute configuration by specific rotation. The specific rotation value of our synthetic 6,8-dimethylfusariumin (**3**) showed $-6.60 (c 2.05, \text{CHCl}_3)$. If 6,8-dimethylfusariumin (**3**) could be prepared from natural fusariumin (**2**), the absolute configuration at C-8' position would be determined definitely by comparison with our synthetic **3**.



Scheme 4. Synthesis of 6,8-dimethylfusariumin (**3**)

CONCLUSION

Concise synthesis of 6,8-dialkoxyisocoumarin frame work was achieved using Pd-catalyzed carbonylation trapping with *O*-enolate. This methodology was applied to the synthesis of natural products, 8-hydroxy-6-methyl-3-pentyl-1*H*-isochromen-1-one (**1**) isolated from *Tessmannia densiflora* and 6,8-dimethylfurariumin (**3**) which is an analog of furariumin (**2**).

EXPERIMENTAL

General. ¹H and ¹³C NMR spectra were measured with a Bruker DRX 500 FT-NMR spectrometer in CDCl₃ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on JEOL GC-mate II and Shimadzu LCMS-IT-TOF mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

1-(3,5-Dimethoxyphenyl)heptan-2-ol (6). To a suspension of Mg (122 mg, 5.0 mmol) was added small amount of I₂ and one drop of 1,2-dibromoethane in THF (1.0 mL) under an argon atmosphere. To the mixture prepared as described above, 1-bromoheptane (516 μL, 4.17 mmol) was added. The mixture was diluted with THF (7.0 mL) and aldehyde **7** (250 mg, 1.39 mmol) was added. After being stirred for 30 min at 0 °C, the reaction was quenched with 1M HCl (5.0 mL). The mixture was extracted with EtOAc (5.0 mL x 3), and the organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and

concentrated. The residue was purified with silica gel column chromatography (hexane:EtOAc = 5:1) to afford **6** (274 mg, 78%) as a colorless oil; IR (film) ν_{\max} cm^{-1} : 3423, 2998, 2931, 2858, 1596, 1463, 1429, 1343, 1322, 1294, 1206, 1150, 1069, 935, 829, 701; ^1H NMR (500 MHz, CDCl_3) δ : 6.37 (2H, d, $J = 2.0$ Hz), 6.34 (1H, d, $J = 2.0$ Hz), 3.82-3.74 (1H, m), 3.79 (3H, s), 3.78 (3H, s), 2.77 (1H, dd, $J = 13.5, 4.0$ Hz), 2.57 (1H, dd, $J = 13.5, 9.0$ Hz), 1.63 (1H, br., -OH), 1.54-1.42 (3H, m), 1.40-1.25 (5H, m), 0.90 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 160.8, 141.0, 107.3, 98.3, 72.5, 55.2, 44.4, 36.8, 31.9, 25.4, 22.6, 14.0 ppm. HRMS-EI $[\text{M}]^+$: Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_3$ 252.1726, Found 252.1721.

1-(2-Iodo-3,5-dimethoxyphenyl)heptan-2-ol (11). To a solution of **6** (240 mg, 0.95 mmol) in CCl_4 was added NIS (214 mg, 0.95 mmol) and small amount of *p*-TsOH \cdot H $_2$ O. After the resulting mixture had been stirred for 1 h, the reaction was quenched with saturated aqueous NaHCO_3 (5 mL) and aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). The mixture was extracted with EtOAc (20 mL x 2), and the organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 5:1) to give **11** (289 mg, 80%) as a colorless solid. Mp 46-47 $^\circ\text{C}$; IR (KBr) ν_{\max} cm^{-1} : 3415, 3001, 2953, 2929, 2856, 1580, 1454, 1413, 1375, 1324, 1280, 1205, 1162, 1081, 1010, 939, 828, 720 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 6.49 (1H, d, $J = 2.5$ Hz), 6.33 (1H, d, $J = 2.5$ Hz), 3.93-3.90 (1H, m), 3.88 (3H, s), 3.80 (3H, s), 3.06 (1H, dd, $J = 13.5, 4.0$ Hz), 2.77 (1H, dd, $J = 13.5, 9.0$ Hz), 1.60-1.51 (4H, m), 1.43-1.25 (5H, m), 0.90 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 160.7, 159.0, 143.6, 107.8, 97.1, 82.2, 71.2, 56.4, 55.5, 48.7, 37.0, 31.8, 25.3, 22.6, 14.1 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{15}\text{H}_{23}\text{IO}_3$; 378.0692, Found 378.0695.

1-(2-Iodo-3,5-dimethoxyphenyl)heptan-2-one (5). To a solution of **11** (245 mg, 0.65 mmol) in CH_2Cl_2 (2.0 mL) was added Dess-Martin periodinane (331 mg, 0.78 mmol) at 0 $^\circ\text{C}$. After being stirred for 30 min at room temperature, the reaction was quenched with saturated aqueous NaHCO_3 (5 mL) and aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) at 0 $^\circ\text{C}$ and the mixture had been stirred until the organic layer was cleared. The mixture was extracted with EtOAc (20 mL x 2), and the organic layer was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 7:1) to give **5** (182 mg, 74%) as a colorless oil. IR (film) ν_{\max} cm^{-1} : 3002, 2955, 2932, 2870, 1716, 1581, 1454, 1434, 1418, 1334, 1281, 1205, 1163, 1080, 1011, 932, 830, 730 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 6.43 (1H, d, $J = 2.5$ Hz), 6.34 (1H, d, $J = 2.5$ Hz), 3.94 (2H, s), 3.87 (3H, s), 3.81 (3H, s), 2.49 (2H, t, $J = 7.0$ Hz), 1.64-1.58 (2H, m), 1.34-1.23 (4H, m), 0.88 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 207.4, 160.9, 159.1, 140.3, 107.6, 97.5, 82.6, 56.4, 55.4, 55.0, 42.6, 31.3, 23.4, 22.4, 13.9 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{15}\text{H}_{21}\text{IO}_3$; 376.0536, Found 376.0532.

6,8-Dimethoxy-3-pentylisocoumarin (4). To a solution of **5** (125 mg, 0.33 mmol) in DMF (7.0 mL) was added AcONa (54 mg, 0.66 mmol) and $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ (23 mg, 33 μmol) under 1 atm of CO atmosphere. After the resulting mixture had been stirred for 20 h at 80 °C, the reaction was quenched with saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc (20 mL x 3) and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc = 3:1) to afford **4** (65 mg, 72%) as a colorless solid. Mp 83-84 °C, IR (KBr) ν_{max} cm^{-1} : 3088, 2931, 2859, 1725, 1664, 1599, 1570, 1511, 1456, 1426, 1374, 1243, 1214, 1164, 1120, 1102, 1057, 996, 837 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 6.42 (1H, d, $J = 2.0$ Hz), 6.32 (1H, d, $J = 2.0$ Hz), 6.09 (1H, s), 3.96 (3H, s), 3.89 (3H, s), 2.46 (2H, t, $J = 7.5$ Hz), 1.69-1.65 (2H, m), 1.35-1.29 (4H, m), 0.90 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 165.2, 163.1, 159.7, 159.1, 142.4, 102.9, 99.4, 98.1, 56.2, 55.5, 33.2, 31.1, 26.4, 22.3, 13.9 ppm. These NMR spectra were identified with those of the reported values.⁶

8-Hydroxy-6-methoxy-3-pentyl-1H-isochromen-1-one (1). To a solution of **4** (60 mg, 0.22 mmol) in CH_2Cl_2 (4.4 mL) was added BCl_3 (1.0 M in heptane, 330 μL , 0.33 mmol) at 0 °C. After being stirred for 20 h at 0 °C, the reaction was quenched with saturated aqueous NaHCO_3 . The mixture was extracted with EtOAc (20 mL x 2), and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc = 4:1) to afford **1** (50 mg, 87%) as a colorless solid. Mp 56-57 °C (lit, 57-57.5 °C,² 79-80 °C³). IR (KBr) ν_{max} cm^{-1} : 3079, 3001, 2945, 2867, 1672, 1637, 1568, 1511, 1454, 1391, 1346, 1294, 1249, 1207, 1196, 1159, 1077, 953, 880, 761 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 11.12 (1H, s), 6.44 (1H, d, $J = 2.0$ Hz), 6.30 (1H, d, $J = 2.0$ Hz), 6.17 (1H, s), 3.86 (3H, s), 2.48 (2H, t, $J = 7.0$ Hz), 1.71-1.65 (2H, m), 1.36-1.31 (4H, m), 0.91 (3H, t, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 166.7, 166.4, 163.5, 158.0, 139.4, 103.8, 100.9, 100.1, 99.9, 55.6, 33.2, 31.1, 26.4, 22.3, 13.9 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4$; 262.1205, Found 262.1207. These NMR spectra were identified with those of the reported values.³

(S)-9-[(Tetrahydro-2H-pyran-2-yl)oxy]-4-nonyl-2-ol (13). To a solution of **12** (2.0 g, 11.0 mmol) in THF (44 mL) was added $n\text{-BuLi}$ (2.5 mol/L in hexane, 2.9 mL, 7.3 mmol) at -78 °C. Then, $\text{BF}_3 \cdot \text{OEt}_2$ (0.92 mL, 7.3 mmol) was added to the solution. After being stirred for 10 min, (S)-2-methyloxirane (0.51 mL, 7.3 mmol) was added. After being stirred for 1 h, the reaction was quenched with saturated aqueous NaHCO_3 . The mixture was extracted with EtOAc (100 mL x 3), and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 3:1) to afford **13** (1.42 g, 81%) as a colorless oil. IR (film)

ν_{\max} cm^{-1} : 3420, 2941, 2869, 2658, 1454, 1441, 1372, 1352, 1323, 1284, 1261, 1201, 1137, 1119, 1076, 1034, 941, 905, 868, 814; ^1H NMR (500 MHz, CDCl_3) δ : 4.59-4.57 (1H, m), 3.93-3.84 (2H, m), 3.79-3.74 (1H, m), 3.52-3.48 (1H, m), 3.43-3.39 (1H, m), 2.42-2.21 (4H, m), 2.08 (1H, br., -OH), 1.85-1.51 (10H, m), 1.24 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 98.9, 82.9, 76.4, 67.0, 66.5, 62.3, 30.7, 29.4, 28.9, 25.8, 25.5, 22.2, 19.6, 18.6 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_3$; 240.1726, Found: 240.1721.

(2S,4E)-9-[(Tetrahydro-2H-pyran-2-yl)oxy]-4-nonen-2-ol (14). To a suspension of LiAlH_4 (420 mg, 11.1 mmol) in THF (74 mL) was added **13** (888 mg, 3.70 mmol) in THF (10 mL) at 0 °C. The mixture was then heated to reflux and stirred for 36 h. After the reaction had been completed, the mixture was cooled to 0 °C and H_2O (20 mL) in THF (20 mL) was added. After being stirred for 30 min, the mixture was filtered through a pad of Celite with EtOAc. The filtrate was concentrated and the residue was purified with silica gel column chromatography (hexane : EtOAc = 3:1) to afford **14** (689 mg, 77%) as a colorless oil. IR (film) ν_{\max} cm^{-1} : 3419, 2939, 2869, 1454, 1441, 1370, 1353, 1323, 1261, 1200, 1137, 1119, 1077, 1034, 971, 942, 905, 869, 814; ^1H NMR (500 MHz, CDCl_3) δ : 5.57-5.51 (1H, m), 5.45-5.39 (1H, m), 4.58-4.57 (1H, m), 3.89-3.84 (1H, m), 3.81-3.72 (2H, m), 3.51-3.48 (1H, m), 3.42-3.37 (1H, m), 2.25-2.17 (1H, m), 2.12-2.04 (3H, m), 1.74-1.42 (11H, m), 1.18 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 134.2, 126.1, 98.8, 67.4, 67.1, 62.3, 42.5, 32.4, 30.7, 29.2, 26.1, 25.4, 22.6, 19.6 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_3$; 242.1882, Found: 242.1879.

(2S,4E)-2-tert-Butyldiphenylsilyloxy-8-tetrahydropyran-2-yl-oxynon-4-ene (15). To a solution of **14** (647 mg, 2.67 mmol) in DMF (30 mL) was added imidazole (273 mg, 4.0 mmol) and TBDPSCl (0.77 mL, 2.94 mmol) at 0 °C. After the resulting mixture had been stirred for 39 h, the reaction mixture was diluted with Et_2O . The organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 10:1) to afford **15** (1.26 g, 98%) as a colorless oil. IR (film) ν_{\max} cm^{-1} : 3071, 3048, 2932, 2857, 1590, 1472, 1428, 1376, 1353, 1323, 1260, 1200, 1112, 1078, 1035, 1005, 971, 905, 869, 822; ^1H NMR (500 MHz, CDCl_3) δ : 7.68-7.67 (4H, m), 7.43-7.35 (6H, m), 5.38-5.29 (2H, m), 4.58-4.56 (1H, m), 3.88-3.81 (2H, m), 3.74-3.70 (1H, m), 3.50-3.47 (1H, m), 3.39-3.34 (1H, m), 2.19-2.06 (2H, m), 2.00-1.96 (2H, m), 1.85-1.79 (1H, m), 1.73-1.68 (1H, m), 1.62-1.50 (6H, m), 1.44-1.36 (2H, m), 1.09 (9H, s), 1.04 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 135.9, 134.8, 134.6, 132.6, 129.5, 129.4, 127.4, 126.7, 98.8, 69.6, 67.4, 62.3, 42.7, 32.4, 30.7, 29.2, 27.0, 26.1, 25.5, 22.9, 19.7, 19.3 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{30}\text{H}_{44}\text{O}_3\text{Si}$; 480.3060, Found: 480.3058.

(5E,8S)-8-tert-Butyldiphenylsilyloxynon-5-en-1-ol (16). To a solution of **15** (1.25 g, 2.60 mmol) in MeOH (26 mL) was added PPTS (65 mg, 0.26 mmol). After the resulting mixture had been stirred for 44 h, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL). The mixture was extracted with EtOAc (50 mL x 2), and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane : EtOAc = 5:1) to furnish **16** (929 mg, 90%) as a colorless oil. $[\alpha]_D^{19}$ -21.1 (*c* 1.03, CHCl₃); IR (film) ν_{\max} cm⁻¹: 3337, 3071, 3048, 2930, 2857, 1590, 1487, 1462, 1390, 1362, 1131, 1111, 1076, 1006, 971, 939, 892, 869, 822; ¹H NMR (500 MHz, CDCl₃) δ : 7.69-7.67 (4H, m), 7.43-7.35 (6H, m), 5.35-5.33 (2H, m), 3.86-3.82 (1H, m), 3.62 (2H, t, *J* = 6.5 Hz), 2.19-2.07 (2H, m), 2.00-1.96 (2H, m), 1.57-1.50 (2H, m), 1.41-1.35 (2H, m), 1.17 (1H, brs), 1.09 (9H, s), 1.04 (3H, d, *J* = 6.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ : 135.9, 135.7, 134.8, 134.6, 132.4, 129.4, 127.4, 126.8, 69.6, 62.9, 42.8, 32.3, 27.2, 27.0, 25.5, 22.9, 19.3 ppm. HRMS-ESI: *m/z* [M+Na]⁺: Calcd for C₂₅H₃₆O₂SiNa; 419.2377, Found: 419.2381.

(2S,4E)-9-Iodonon-4-ene-2-tert-butylidiphenyloxysilane (17). To a solution of **16** (929 mg, 2.34 mmol) in toluene (23 mL) were added imidazole (207 mg, 3.0 mmol), PPh₃ (797 mg, 3.0 mmol), and I₂ (652 mg, 2.57 mmol). After the resulting mixture had been stirred for 15 h, the reaction was quenched with aqueous Na₂S₂O₃ (20 mL) at 0 °C. The mixture was extracted with pentane and the organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel column chromatography (hexane) to afford **17** (1.10 g, 93%) as a pale yellow oil. This compound was used immediately for the next step. $[\alpha]_D^{19}$ -19.9 (*c* 1.23, CHCl₃); IR (film) ν_{\max} cm⁻¹: 3070, 3047, 2962, 2856, 1472, 1461, 1427, 1389, 1376, 1362, 1203, 1128, 1111, 1081, 997, 970, 892, 866, 822; ¹H NMR (500 MHz, CDCl₃) δ : 7.69-7.67 (4H, m), 7.43-7.35 (6H, m), 5.43-5.25 (2H, m), 3.87-3.81 (1H, m), 3.15 (2H, t, *J* = 7.0 Hz), 2.18-2.07 (2H, m), 2.04-1.96 (2H, m), 1.84-1.72 (2H, m), 1.44-1.34 (2H, m), 1.09 (9H, s), 1.04 (3H, d, *J* = 5.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ : 136.1, 135.9, 134.8, 134.5, 131.9, 129.5, 127.5, 127.2, 69.6, 53.5, 42.7, 33.0, 31.5, 30.2, 27.1, 23.0, 19.3 ppm.

(7E,10S)-1-(3,5-Dimethoxyphenyl)-10-tert-butylidiphenylsilyloxyundec-7-en-2-ol (9). To a solution of **17** (82 mg, 0.16 mmol) in Et₂O (2.0 mL) was added *t*-BuLi (1.7 mol/L in pentane, 0.19 mL, 0.32 mmol) at -78 °C. After the mixture had been stirred for 30 min, aldehyde **7** (15 mg, 83 μ mol) in Et₂O (2.0 mL) was added to the mixture. After the resulting mixture had been stirred for 1 h, the reaction was quenched with saturated aqueous NH₄Cl (5.0 mL) at -78 °C. The mixture was extracted with EtOAc (10 mL x 3) and the organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified with preparative TLC (toluene : EtOAc = 5:1) to afford **9** (19 mg, 41%) as a pale

yellow oil. IR (film) ν_{\max} cm^{-1} : 3428, 3070, 2930, 2856, 1606, 1596, 1462, 1428, 1376, 1361, 1345, 1323, 1294, 1206, 1151, 1111, 1072, 998, 971, 823; ^1H NMR (500 MHz, CDCl_3) δ : 7.69-7.67 (4H, m), 7.42-7.34 (6H, m), 6.37 (2H, d, $J = 2.0$ Hz), 6.35 (1H, d, $J = 2.0$ Hz), 5.38-5.29 (2H, m), 3.92-3.81 (2H, m), 3.78 (6H, s), 2.76 (1H, dd, $J = 13.5, 4.0$ Hz), 2.55 (1H, dd, $J = 13.5, 9.0$ Hz), 2.19-2.07 (2H, m), 1.97-1.93 (2H, m), 1.60-1.34 (7H, m), 1.09 (9H, s), 1.04 (3H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 160.9, 140.9, 135.9, 134.8, 134.6, 132.6, 129.4, 127.4, 126.5, 107.3, 98.4, 72.4, 69.6, 55.3, 44.4, 42.8, 36.7, 32.6, 29.5, 27.0, 25.3, 22.9, 19.2 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{35}\text{H}_{48}\text{OSi}$; 560.3322, Found: 560.3320.

(7E,10S)-1-(2-Iodo-3,5-dimethoxyphenyl)-10-tert-butylidiphenylsilyloxyundec-7-en-2-ol (18). To a solution of **9** (49 mg, 87 μmol) in CCl_4 (1.7 mL) was added NIS (20 mg, 87 μmol). After the resulting mixture had been stirred for 1 h, the reaction was quenched with aqueous $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was extracted with EtOAc (20 mL x 2) and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with preparative TLC (toluene : EtOAc = 10:1) to afford **18** (34 mg, 57%) as a colorless oil. IR (film) ν_{\max} cm^{-1} : 3422, 3070, 2929, 2856, 1580, 1455, 1428, 1413, 1325, 1280, 1205, 1163, 1111, 1080, 1010, 971, 823; ^1H NMR (500 MHz, CDCl_3) δ : 7.69-7.67 (4H, m), 7.42-7.35 (6H, m), 6.48 (1H, d, $J = 2.5$ Hz), 6.33 (1H, d, $J = 2.5$ Hz), 5.37-5.30 (2H, m), 3.94-3.76 (2H, m), 3.86 (3H, s), 3.80 (3H, s), 3.05 (1H, dd, $J = 13.8, 4.0$ Hz), 2.76 (1H, dd, $J = 13.8, 9.0$ Hz), 2.19-2.07 (2H, m), 1.98-1.97 (2H, m), 1.68-1.31 (7H, m), 1.09 (9H, s), 1.04 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 160.8, 159.1, 143.6, 135.9, 134.8, 134.6, 132.7, 129.4, 127.4, 126.5, 107.9, 97.1, 82.2, 71.1, 69.6, 56.4, 55.5, 48.8, 42.7, 36.9, 32.6, 29.5, 27.0, 25.2, 22.9, 19.2 ppm. HRMS-EI: m/z $[\text{M}]^+$: Calcd for $\text{C}_{35}\text{H}_{47}\text{IOSi}$; 686.2289, Found: 686.2284.

(7E,10S)-1-(2-Iodo-3,5-dimethoxyphenyl)-10-tert-butylidiphenylsilyloxyundec-7-en-2-one (8). To a solution of **18** (86 mg, 0.125 mmol) in CH_2Cl_2 (2.0 mL) was added Dess-Martin periodinane (68 mg, 0.16 mmol) at 0 $^\circ\text{C}$. After being stirred for 30 min at room temperature, the reaction was quenched with aqueous $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (1:1, 10 mL) at 0 $^\circ\text{C}$ and the mixture had been stirred until the organic layer was cleared. The mixture was extracted with EtOAc (20 mL x 2) and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with preparative TLC (toluene : EtOAc = 10:1) to afford **8** (76 mg, 89%) as a colorless oil. $[\alpha]_D^{19} -13.7$ (c 0.760, CHCl_3); IR (film) ν_{\max} cm^{-1} : 3070, 2961, 2930, 2856, 1717, 1581, 1455, 1428, 1375, 1362, 1335, 1306, 1281, 1205, 1163, 1111, 971, 823; ^1H NMR (500 MHz, CDCl_3) δ : 7.68-7.66 (4H, m), 7.42-7.34 (6H, m), 6.38 (1H, d, $J = 2.5$ Hz), 6.33 (1H, d, $J = 2.5$ Hz), 5.34-5.30 (2H, m), 3.88 (2H, s), 3.84 (3H, s), 3.83-3.79 (1H,

m), 3.78 (3H, s), 2.47 (2H, t, $J = 7.5$ Hz), 2.17-2.05 (2H, m), 1.95-1.92 (2H, m), 1.62-1.55 (2H, m), 1.34-1.26 (2H, m), 1.08 (9H, s), 1.04 (3H, d, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 207.1, 160.9, 159.1, 140.3, 135.8, 134.7, 134.5, 132.2, 129.4, 127.4, 126.7, 107.7, 97.5, 82.6, 69.6, 56.4, 55.4, 54.9, 42.7, 42.4, 32.4, 28.9, 27.0, 23.1, 22.8, 19.2 ppm. HRMS-ESI: m/z $[\text{M}+\text{Na}]^+$: Calcd for $\text{C}_{35}\text{H}_{45}\text{IOSiNa}$; 707.2024, Found: 707.2026.

(5'E,8'S)-8'-tert-Butyldiphenylsilyloxynon-5'-enyl-6,8-dimethoxy-1H-2-benzopyran-1-one (19). To a solution of **8** (54 mg, 0.079 mmol) in DMF (5.0 mL) was added AcONa (13 mg, 0.16 mmol) and $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ (5.5 mg, 7.9 μmol) under 1 atm of CO atmosphere. After the resulting mixture had been stirred for 96 h at 50 °C, the reaction was quenched with saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc (20 mL x 3) and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified with preparative TLC (hexane : EtOAc = 2:1) to afford **19** (41 mg, 89%) as a colorless oil. $[\alpha]_D^{19} -17.8$ (c 2.05, CHCl_3); IR (film) ν_{max} cm^{-1} : 3070, 3047, 2962, 2930, 2856, 1731, 1664, 1600, 1571, 1458, 1427, 1375, 1240, 1213, 1164, 1111, 1075, 997, 823; ^1H NMR (500 MHz, CDCl_3) δ : 7.68-7.66 (4H, m), 7.42-7.34 (6H, m), 6.42 (1H, d, $J = 2.5$ Hz), 6.30 (1H, d, $J = 2.5$ Hz), 6.06 (1H, s), 5.38-5.29 (2H, m), 3.96 (3H, s), 3.87 (3H, s), 3.86-3.83 (1H, m), 2.44 (2H, t, $J = 7.5$ Hz), 2.18-2.05 (2H, m), 2.00-1.96 (2H, m), 1.68-1.62 (2H, m), 1.41-1.37 (2H, m), 1.09 (9H, s), 1.04 (3H, d, $J = 5.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 165.3, 163.2, 159.7, 159.0, 142.4, 135.8, 134.8, 134.5, 132.2, 129.4, 127.4, 126.9, 103.0, 99.4, 98.1, 69.6, 56.2, 55.5, 42.7, 33.1, 32.3, 28.7, 27.0, 26.2, 22.9, 19.2 ppm. HRMS-ESI: m/z $[\text{M}+\text{Na}]^+$: Calcd for $\text{C}_{36}\text{H}_{44}\text{O}_5\text{SiNa}$; 607.2850, Found: 607.2845.

6,8-Dimethylfusariumin (3). To a solution of **19** (10 mg, 17 μmol) in THF (1.7 mL) was added TBAF (1.0 mol/L, 30 μL , 0.030 mmol) at 0 °C. After being stirred for 67 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl . The mixture was extracted with EtOAc (20 mL x 3) and the organic layer was washed with water, brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with preparative TLC (hexane : EtOAc = 1:3) to afford **3** (5 mg, 85%) as a colorless solid. Mp 114-115 °C; $[\alpha]_D^{19} -6.60$ (c 2.05, CHCl_3); IR (KBr) ν_{max} cm^{-1} : 3460, 2917, 2849, 1715, 1663, 1600, 1570, 1457, 1426, 1374, 1242, 1165, 1120, 1060, 993, 977, 846; ^1H NMR (500 MHz, CDCl_3) δ : 6.43 (1H, d, $J = 2.0$ Hz), 6.32 (1H, d, $J = 2.0$ Hz), 6.13 (1H, s), 5.55-5.40 (2H, m), 3.96 (3H, s), 3.89 (3H, s), 3.82-3.76 (1H, m), 2.47 (2H, t, $J = 7.5$ Hz), 2.23-2.02 (2H, m), 2.12-2.05 (3H, m), 1.72-1.55 (2H, m), 1.47-1.41 (2H, m), 1.06 (3H, d, $J = 6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ : 165.3, 163.2, 159.7, 158.9, 142.4, 133.9, 126.4, 103.1, 103.0, 99.5, 98.2, 67.2, 56.3, 55.6, 42.5, 33.1, 32.3, 28.7, 26.2, 22.7 ppm.

HRMS-EI: m/z $[M]^+$: Calcd for $C_{20}H_{26}O_5$; 346.1780, Found: 346.1782.

SUPPORTING INFORMATION

1H and ^{13}C NMR spectra of **1** and **3**.

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