Synthesis of a Natural Chromenoquinone *via* the Diels–Alder Reaction of Pyranobenzyne and Furan

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We describe the total synthesis of angular chromenoquinone 1 isolated from *Conospermum* plants. Iodophenol, a precursor of pyranobenzyne, was prepared by Claisen rearrangement of an iodoresorcinol derivative. Diels–Alder reaction of the pyranobenzyne and a substituted furan proceeded in low regioselectivity to afford desired 1 and its regioisomer.

Key words naphthoquinone; Diels–Alder reaction; furan; benzyne; total synthesis

Quinones are widely found in plants and microorganisms, and show various properties, such as anti-human immunodeficiency virus (HIV),[1] antitumor, and antibiotic activities.[2,3] Angular chromenoquinones, such as teretifolione B[4] and its trimeric derivative, conocurvone,[5] are unique naphthoquinone compounds produced by *Conospermum* plants. Conocurvone possesses anti-HIV activity. We have reported a simple route for constructing the naphthoquinone core *via* the Diels–Alder reaction (DAR) of benzyne and a functionalized furan.[6] This led us to investigate the construction of more complex quinone skeletons, which frequently appear in natural products, using unsymmetrical benzyne substrates. In this Note, we describe the application of the DAR approach to constructing the angular chromenoquinone core and the total synthesis of natural chromenoquinone **1**. The total synthesis of **1** starting from naphthalene-2,7-diol was reported as part of the structural elucidation.[4]

Retrosynthetic analysis in this study is shown in Chart 1. The benzochromene core **1** would be constructed by the DAR of pyranobenzyne **2** and substituted furan **3**. Benzyne precursor **4** would be accessible by Claisen rearrangement of propargyl ether **5**.[7] Regioselective iodination[8] and introduction of the propargyl moiety to commercially available resorcinol monobenzoate (**6**) would provide **5**.

Our attempts at the iodination of **6** could not reproduce reported regioselectivity, which furnished a 2 : 1 regioisomeric mixture of iodophenols **7** and **8**. The structures of **7** and **8** were determined by two dimensional (2D)-NMR analysis. After separation, propargyl group was introduced to **7** in the presence of Cu(II) catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[9,10] by using propargyl ester **9**, derived from alcohol **10** and trifluoroacetic anhydride (TFAA) *in situ*, to afford propargyl ether **5**. The regioselectivity of the thermal Claisen rearrangement of **5** was unexpectedly low and a mixture of the desired product **11** and the regioisomer **12** was obtained in a 2 : 1 ratio,[11] estimated from the ^{1}H-NMR integrals. The inseparable mixture of chromenes **11** and **12** was hydrolyzed to afford the corresponding phenols **13**[12] and **14**, which were separated by column chromatography. Desired chromene **13** was treated with Tf_2O to give benzyne precursor **4** (Chart 2).

The DAR of the pyranobenzyne, derived from **4**, with furan **3**[6] gave a 1 : 2 isomeric mixture of the desired hydroquinone **15** and the undesired **16**. The structures of **15** and **16** were determined by 2D-NMR analysis. The solvents used (Et_2O, tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME)) did not affect the product ratio. Hydroquinone **15** was oxidized with $FeCl_3$[13] to quinone **17** and then debenzylated with BCl_3 to give **1**. The spectroscopic data for **1** were identical to the literature data.[14] The oxidation of its regioisomer **16** in the same manner gave a complex mixture. Application of (diacetoxyiodo)benzene (DIB)-oxidation in methanol[15] gave quinone monoacetal **18**. Subsequent debenzylation and deacetalization with BCl_3 gave **19**, the corresponding regioiso-

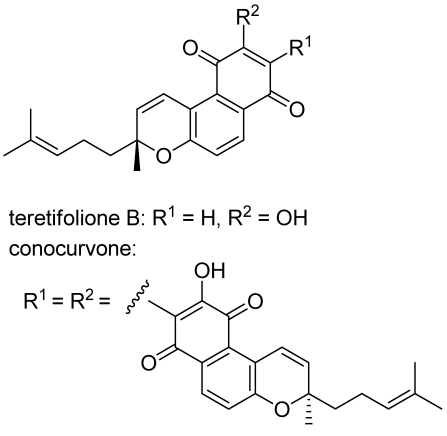

Fig. 1. Representative Natural Chromenoquinones

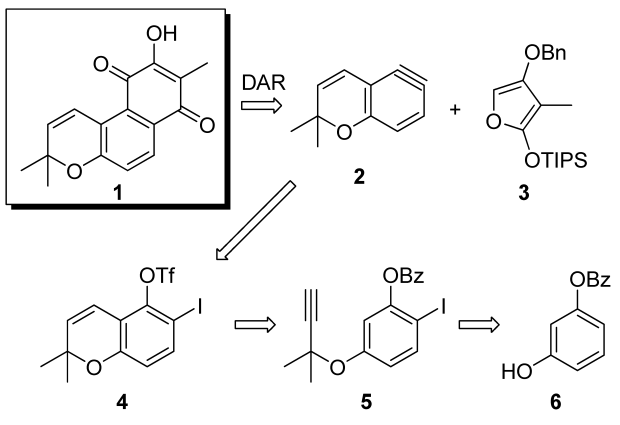

Chart 1. Retrosynthetic Analysis of **1**

The authors declare no conflict of interest.

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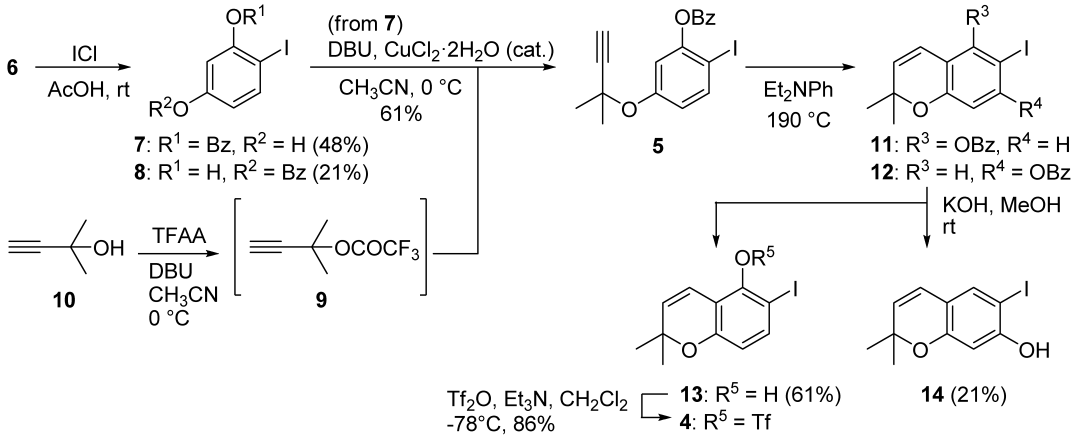

Chart 2. Synthesis of Benzyne Precursor **4**

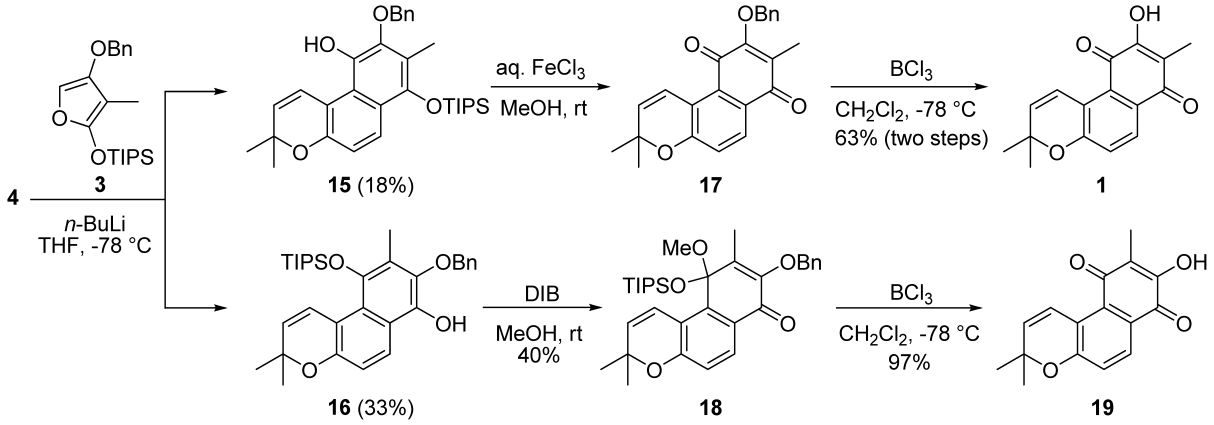

Chart 3. Synthesis of Chromenoquinones **1** and **19**

mer of **1** (Chart 3).

We have achieved the total synthesis of natural chromenoquinone **1** *via* the DAR of pyranobenzyne and furan as a key step. The regioselectivity of several steps in this series of transformation is low, which will be improved by further examination. Regioisomer **19** will be useful as a candidate for exploring the structure–activity relationship of this series of chromenoquinones.

Experimental

General Commercially available reagents and anhydrous solvents were used without further purification. Flash chromatography was carried out with Silica gel 60N (40–50 μm) from Kanto Chemical Co. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer with Attenuated Total Reflectance Unit ATR PRO450-S. Electron ionization (EI)-MS and electrospray ionization (ESI)-MS were recorded on a JEOL GC-Mate II and a Thermo Scientific Orbitrap in positive mode, respectively. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR spectra were recorded with JEOL ECX 400 spectrometer with deuterated chloroform as a solvent and tetramethylsilane as an internal reference otherwise noted. Chemical shifts were reported in ppm and *J* in Hz.

5-Hydroxy-2-iodophenyl Benzoate (7) To a suspension of **6** (23.0 g, 107 mmol) in AcOH (108 mL), ICl (7.0 mL, 140 mmol) was added at rt. After the solution was stirred at rt for 1 h, H_2O (215 mL) and Na_2SO_3 (4.33 g, 34.4 mmol) were added. The whole was filtered and the precipitates were washed with H_2O until the filtrate indicates neutral pH and dried in air. The crude (32.3 g) was recrystalized from benzene to yield **7** (12.9 g, colorless powder, 35%). After the mother liquid was concentrated *in vacuo*, the residue was purified over SiO_2 column chromatography (AcOEt–$CHCl_3$=5 : 95) to give two fractions. Polar fraction (7.64 g) which included **7** mainly was recrystalized from benzene to give **7** (4.91 g, colorless needles, 13%) and less polar fraction (10.7 g) was also recrystalized from benzene to give **8** (7.70 g, colorless powder, 21%)

mp: 163–165°C. IR: 3330, 1708 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 10.07 (1H, s), 8.15 (2H, dd, *J*=7.7, 1.3 Hz), 7.76 (1H, tt, *J*=7.7, 1.3 Hz), 7.64 (1H, d, *J*=8.7 Hz), 7.62 (2H, t, *J*=7.7 Hz), 6.77 (1H, d, *J*=2.7 Hz), 6.59 (1H, dd, *J*=8.7, 2.7 Hz). ^{13}C-NMR (DMSO-d_6) δ: 163.7, 158.8, 151.6, 138.9, 134.3, 129.9, 129.1, 128.7, 115.9, 111.0, 77.4. High resolution (HR)-EI-MS: *m/z* 339.9593 (Calcd for $C_{13}H_9IO_3$: 339.9597).

2-Iodo-5-(1,1-dimethyl-2-propynyloxy)phenyl Benzoate (5) To a solution of **10** (0.22 mL, 2.27 mmol) and DBU (0.40 mL, 2.67 mmol) in CH_3CN (1.0 mL) at 0°C, TFAA (0.32 mL, 2.30 mmol) was added and stirred for 1 h to prepare a solution of **9**. In another flask, a solution of **7** (680.4 mg, 2.00 mmol) and $CuCl_2·2H_2O$ (1.0 mg, 0.006 mmol) in CH_3CN (1.5 mL) was treated with DBU (0.40 mL, 2.67 mmol) at 0°C for 5 min. To this solution, the above mixture of **9** was added at 0°C and stirred at 0°C for 75 min. The whole was poured

into H_2O (7.5 mL) and extracted with AcOEt (3×15 mL). The combined organic layer was washed with 1 N HCl, 1 N KOH and brine (each 1×5 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane=5 : 95) to give **5** (491.7 mg, a colorless oil, 61%).

IR: 1739 cm^{-1}. ^{1}H-NMR δ: 8.27 (2H, dif. d, J=8.4 Hz), 7.72 (1H, d, J=8.8 Hz), 7.67 (1H, tt, J=7.6, 1.1 Hz), 7.54 (2H, t, J=7.6 Hz), 7.19 (1H, d, J=2.7 Hz), 6.94 (1H, dd, J=8.8, 2.7 Hz), 2.61 (1H, s), 1.67 (6H, s). ^{13}C-NMR δ: 164.1, 156.8, 151.4, 138.7, 133.8, 130.5, 129.2, 128.6, 120.5, 116.3, 85.2, 81.6, 74.7, 72.9, 29.5. HR-EI-MS: *m/z* 406.0082 (Calcd for $C_{18}H_{15}IO_3$: 406.0066).

6-Iodo-2,2-dimethyl-2*H*-chromen-5-ol (13) **5** (396.8 mg, 0.977 mmol) was dissolved in *N*,*N*-diethylaniline (0.39 mL) and heated at 190°C for 30 min. The whole was diluted with AcOEt (15 mL) and washed with 5% HCl (1×1.5, 1×1.0 mL) and brine (1×1.0 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give a residue (450.5 mg). A portion of the residue (231.0 mg) was dissolved in methanolic KOH (0.54 M, 2.0 mL, 1.08 mmol) and stirred at rt for 50 min. The reaction mixture was evaporated and the residue was dissolved in H_2O (1.0 mL) and washed with *n*-hexane (1.0 mL). The organic layer was extracted with 1 N KOH (0.5 mL) and the combined aqueous layer was acidified with 5% HCl and extracted with AcOEt (3×10 mL). The combined organic layer was washed with brine (1×3 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane= 1 : 99–15 : 85) to give **13** (92.3 mg, a colorless oil, 61%) and **14** (31.8 mg, colorless solids, 21%).

IR: 3438 cm^{-1}. ^{1}H-NMR δ: 7.32 (1H, d, J=8.5 Hz), 6.66 (1H, d, J=10.0 Hz), 6.26 (1H, dd, J=8.5, 0.7 Hz), 5.59 (1H, d, J=10.0 Hz), 5.22 (1H, s), 1.42 (6H, s). ^{13}C-NMR δ: 154.6, 150.1, 136.5, 129.8, 117.1, 111.5, 109.7, 76.2, 74.9, 27.8. Low resolution (LR)-EI-MS: *m/z* (%) 302 (M^+, 22), 287 (100), 252 (52), 250 (32), 235 (25), 233 (16), 219 (16), 217 (10), 160 (41), 105 (33).

6-Iodo-2,2-dimethyl-2*H*-chromen-5-yl Trifluoromethanesulfonate (4) To a solution of **13** (1.80 g, 5.95 mmol) and Et_3N (1.70 mL, 12.2 mmol) in CH_2Cl_2 (14.0 mL), Tf_2O (1.25 mL, 7.43 mmol) was added at −78°C. After the solution was stirred at −78°C for 1.5 h, H_2O (6.0 mL) was added and the mixture was warmed to rt. The whole was poured into H_2O (6.0 mL) and extracted with Et_2O (1×100, 2×50 mL). The combined organic layer was washed with brine (1×10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane=1 : 99–3 : 97) to give a pale yellow oil (2.42 g), which was dissolved in pentane. The solution was cooled to −78°C. The precipitates were collected by filtration and dried under reduced pressure to give **4** (2.21 g, colorless needles, 86%).

mp: 49–50°C. IR: no characteristic absorption. ^{1}H-NMR δ: 1.45 (6H, s), 5.77 (1H, d, J=10.1 Hz), 6.56 (1H, d, J=10.1 Hz), 6.61 (1H, dd, J=8.6, 0.8 Hz), 7.57 (1H, d, J=8.6 Hz). ^{13}C-NMR δ: 27.5, 76.7, 77.4, 116.4, 117.4, 118.4, 118.5 (q, J_{C-F}=321.1 Hz), 133.0, 139.4, 145.2, 154.6. HR-EI-MS: *m/z* 433.9299 (Calcd for $C_{12}H_{10}F_3IO_4S$: 433.9297).

9-(Benzyloxy)-3,3,8-trimethyl-7-(triisopropylsilyloxy)-3*H*-benzo[*f*]chromen-10-ol (15) and 8-(Benzyloxy)-3,3,9-trimethyl-10-(triisopropylsilyloxy)-3*H*-benzo[*f*]chromen-7-ol (16) To a solution of **4** (138.3 mg, 0.319 mmol) and furan **3** (138.0 mg, 87% w/w purity as a mixture with TIPSOH, 0.333 mmol) in THF (4.0 mL), *n*-BuLi (1.11 M in *n*-hexane, 0.49 mL, 0.544 mmol) was added at −78°C. After the solution was stirred at −78°C for 15 min, further *n*-BuLi (0.09 mL, 0.100 mmol) was added and stirred at same temperature for further 20 min. The H_2O (4.0 mL) was added and the mixture was warmed to rt. The whole was extracted with AcOEt (3×10 mL) and the combined organic layer was washed with H_2O and brine (each 1×2 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane= 1 : 99–15 : 85) to give **15** (29.3 mg, a reddish brown oil, 18%) and **16** (53.8 mg, a yellow oil, 33%).

15: IR: 3380 cm^{-1}. ^{1}H-NMR δ: 1.11 (18H, d, J=7.6 Hz), 1.33–1.41 (3H, m), 1.47 (6H, s), 2.39 (3H, s), 4.89 (2H, s), 5.56 (1H, d, J=10.2 Hz), 5.94 (1H, s), 6.93 (1H, d, J=9.2 Hz), 7.39–7.45 (3H, m), 7.48 (2H, dd-like, J=7.9, 1.7 Hz), 7.78 (1H, d, J=10.2 Hz), 7.84 (1H, d, J=9.2 Hz). ^{13}C-NMR δ: 11.6, 14.2, 18.1, 27.4, 74.9, 75.7, 114.1, 1115.1, 17.2, 119.2, 122.3, 122.9, 124.0, 127.1, 128.2, 128.6, 128.9, 136.8, 139.5, 141.9, 144.3, 151.2. HR-EI-MS *m/z*: 518.2828 (Calcd for $C_{32}H_{42}O_4Si$: 518.2852).

16: IR: 3357 cm^{-1}. ^{1}H-NMR δ: 0.85–0.96 (21H, m), 1.43 (3H, s), 1.49 (3H, s), 1.95 (3H, s), 5.11 (2H, s), 5.69 (1H, d, J=10.5 Hz), 6.90 (1H, dd, J=8.6, 0.7 Hz), 7.18 (1H, brs), 7.29–7.36 (4H, m), 7.45 (2H, dd-like, J=7.9, 1.7 Hz), 7.96 (1H, d, J=8.6 Hz). ^{13}C-NMR δ: 11.4, 13.6, 17.8, 18.0, 27.9, 28.6, 73.8, 76.5, 101.4, 118.5, 120.5, 125.3, 128.2, 128.3, 128.4, 128.8, 130.5, 137.2, 137.4, 141.1, 149.0, 158.2, 179.5. HR-ESI-MS: *m/z* 517.2772 [$(M-H)^+$, Calcd for $C_{32}H_{41}O_4Si$: 517.2774].

9-Hydroxy-3,3,8-trimethyl-7,10-dihydro-3*H*-benzo[*f*]-chromene-7,10-dione (1) To a solution of **15** (28.9 mg, 0.0557 mmol) in methanol (1.1 mL), aqueous $FeCl_3$ (0.82 M, 0.15 mL, 0.123 mmol) was added at rt and the whole was stirred at rt for 50 min. The mixture was poured into H_2O (2 mL) and extracted with CH_2Cl_2 (1×10, 2×5 mL). The combined organic layer was washed with H_2O and brine (each 1×2 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give crude **17** (30.9 mg). A portion of the crude **17** (30.2 mg) was dissolved in CH_2Cl_2 (2.7 mL) and cooled to −78°C. BCl_3 in heptane (1.0 M, 0.28 mL, 0.28 mmol) was added to the solution and stirred at −78°C for 20 min. H_2O (2.0 mL) was added and the mixture was warmed to rt. The whole was extracted with CH_2Cl_2 (1×10, 2×5 mL). The combined organic layer was washed with H_2O and brine (each 1×2 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane=5 : 95–15 : 85) to give **1** (9.3 mg, orange solids, 63%).

mp: 163–165°C. IR: 3376, 1642 cm^{-1}. ^{1}H-NMR δ: 1.47 (6H, s), 2.06 (3H, s), 5.97 (1H, d, J=10.3 Hz), 7.07 (1H, d, J=8.5 Hz), 7.44 (1H, brs), 7.77 (1H, d, J=10.3 Hz), 7.98 (1H, d, J=8.5 Hz). ^{13}C-NMR δ: 8.5, 28.0, 76.8, 118.7, 119.7, 121.3, 122.0, 123.4, 127.1, 128.7, 135.9, 153.3, 157.7, 183.3, 184.5. HR-EI-MS *m/z*: 270.0888 (Calcd for $C_{16}H_{14}O_4$: 270.0892).

8-(Benzyloxy)-10-methoxy-3,3,9-trimethyl-10-(triisopropylsilyloxy)-7,10-dihydro-3*H*-benzo[*f*]chromen-7-one (18) Methanol (1.0 mL) was added to a mixture of **16** (107.9 mg, 0.208 mmol) and DIB (73.7 mg, 0.229 mmol) and stirred at rt for 1 h. Saturated aqueous $NaHCO_3$ (1.0 mL) was added and

the whole was poured into H_2O (1.0 mL). The whole was extracted with AcOEt (1×10, 2×5 mL). The combined organic layer was washed with H_2O and brine (each 1×2 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane=1 : 99–9 : 91) to give **18** (45.5 mg, a yellow oil, 40%).

IR: 1658 cm^{-1}. ^{1}H-NMR δ: 0.86–0.91 (21H, m), 1.43 (3H, s), 1.45 (3H, s), 1.89 (3H, s), 2.62 (3H, s), 5.07 (1H, d, J=11.2 Hz), 5.22 (1H, d, J=11.2 Hz), 5.65 (1H, d, J=10.5 Hz), 6.87 (1H, dd, J=8.6, 0.7 Hz), 7.35–7.28 (3H, m), 7.44–7.41 (3H, m), 7.95 (1H, d, J=8.6 Hz). ^{13}C-NMR δ: 11.3, 13.7, 17.9, 18.1, 27.9, 28.5, 50.2, 73.6, 76.5, 97.7, 118.2, 118.9, 121.0, 125.0, 128.1, 128.2, 128.4, 128.9, 130.0, 137.4, 137.8, 141.6, 148.3, 158.1, 179.6. HR-ESIM-S: 549.3042 [$(M+H)^+$, Calcd for $C_{33}H_{45}O_5Si$: 549.3036].

8-Hydroxy-3,3,9-trimethyl-7,10-dihydro-3*H*-benzo[*f*]-chromene-7,10-dione (19) **18** (21.3 mg, 0.0388 mmol) was subjected to debenzylation in the same condition from **17** to **1** (*vide supra*). The obtained residue was purified over SiO_2 column chromatography (AcOEt–*n*-hexane=5 : 95–20 : 80) to give **19** (10.2 mg, yellow solids, 97%).

mp: 208–210°C. IR: 3347, 1646 cm^{-1}. ^{1}H-NMR δ: 1.47 (6H, s), 2.05 (3H, s), 5.93 (1H, d, J=10.3 Hz), 7.00 (1H, dd, J=8.4, 0.7 Hz), 7.27 (1H, br s), 7.82 (1H, d, J=10.3 Hz), 7.95 (1H, d, J=8.4 Hz). ^{13}C-NMR δ: 8.8, 28.0, 77.1, 120.1, 120.2, 120.8, 121.4, 123.5, 127.5, 128.6, 134.6, 152.2, 160.2, 180.1, 187.9. HR-EIMS: 270.0887 (Calcd for $C_{16}H_{14}O_4$: 270.0892).

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