Regular Article

Synthesis of a Carbon Analogue of Scytonemin

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The synthesis of a carbon analogue of scytonemin was accomplished on the basis of molybdenum-mediated intramolecular double Pauson–Khand type reaction of bis(allenyne), followed by the double aldol condensation of the formed double Pauson–Khand type adduct.

Key words scytonemin; allene; [2+2+1] cycloaddition; alkyne; molybdenum; aldol condensation

Scytonemin (**1**) is the cyanobacterial dimeric alkaloid pigment, whose chemical structure has been elucidated by Gerwick and co-workers in 1993,[1] over 100 years after its discovery. Scytonemin has an intriguing novel structural feature, which consists of a two 1,1′-linked cyclopent[*b*]indole-2(1*H*)-one framework possessing 4-hydroxybenzylidenes at the 3-positions of the fused tricyclic systems. The biosynthetic studies of scytonemin have been recently made by Walsh and Balskus.[2,3] In 2011, Mårtensson and colleagues achieved the first total synthesis of scytonemin by taking advantage of the tandem Heck carbocyclization/Suzuki–Miyaura coupling and a bioinspired oxidative dimerization.[4] Of particular interest is its interesting biological features. Scytonemin is a UV-absorbing pigment that protects important cellular components in a cyanobacteria against harmful UV radiation.[5–8] Besides this important function, scytonemin exhibits a biological activity as a small molecule inhibitor of *polo*-like kinase 1[9] and possesses anti-inflammatory and antiproliferative properties.[10] During our studies on the syntheses of various kind of alkaloids,[11–19] we became very interested in the highly conjugated and characteristic dimeric structure of scytonemin as well as its biological activity. We postulated that the origin of the biological activity of scytonemin (**1**) might be elucidated by comparison with its carbon analogue, in which two nitrogen atoms are replaced by two carbon atoms. Therefore, our endeavor was directed toward the synthesis of **2**, a carbon analogue of scytonemin (**1**) (Chart 1).

In 2005, Liu and Datta developed the efficient synthesis of 1*H*-cyclopent[*a*]inden-2-one (**4a**) from 1-ethynyl-2-(1,2-propadienyl)benzene (**3a**) through the $Mo(CO)_3(MeCN)_3$-mediated carbonylative [2+2+1] ring-closing reaction at 25°C in a stoichiometric manner[20] (Chart 2). They also reported the catalytic version of that transformation in the presence of 5 mol% of $[RhCl(CO)_2]_2$ at 90°C to furnish **4a** in 62% yield along with the by-production of 2-methylnaphthalene (**5**), the latter of which should be arisen from the Myers–Saito cycloaromatization[21–25] of **3a**. We have independently reported that treatment of 3-(2-ethynylphenyl)prop-2-ynyl benzenesulfinate (**6**) with 2.5 mol% of $[RhCl(CO)_2]_2$ at 40°C in an atmosphere of CO effected the successive 2,3-sigmatropic rearrangement and carbonylative [2+2+1] ring-closing reaction of the resulting allenyne species **3b** to afford the 8-(phenylsulfonyl)-1*H*-cyclopent[*a*]inden-2-one (**4b**) in a high yield.[26] In this case, the formation of 2-methylnaphthalene could not be detected in the reaction mixture.

We now report the short-step synthesis of **2**, a carbon analogue of scytonemin (**1**), by taking advantage of the intramolecular double carbonylative [2+2+1] cycloaddition of the bis(allenyne) derivative **7**,[27,28] which should provide the central linked two tricyclic framework, namely the dimeric 1*H*-cyclopent[*a*]inden-2-one **8**, in one operation. The outline of our synthetic plan is depicted in Chart 3. The double Pauson–Khand type reaction (PKTR) of bis(allenyne) **7** would proceed under the conditions shown in Chart 2 as is the case of **3** to afford **8**. The successive aldol condensation of **8** with the suitably protected 4-hydroxybenzaldehyde **9** and several manipulations would lead to **2**.

Results and Discussion

The Sonogashira coupling reaction of 1-bromo-2-iodobenzene (**10**) with trimethylsilylacetylene produced 1-bromo-2-[2-(trimethylsilyl)ethynyl]-benzene (**11**) in quantitative yield. Treatment of **11** with butyllithium was followed by iodination to afford **12**, which was then used for the second Sonogashira coupling reaction with propargyl alcohol resulting in the formation of the cross-coupling adduct **13** in 84% overall yield from **11**. The exposure of **13** to $Cu(OAc)_2 \cdot H_2O$ effected the consecutive removal of the trimethylsilyl (TMS) group and homo-coupling of the terminal alkyne moiety[29] to afford the tetrayne **14** in 89% yield. The Mitsunobu reaction of **14** with diisopropyl azodicaroboxylate (DIAD) and *N*-isopropylidene-

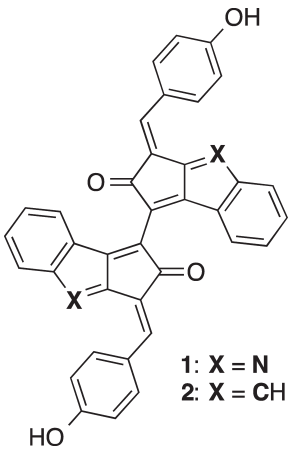

Chart 1. Structures of Scytonemin (**1**) and Its Carbon Analogue (**2**)

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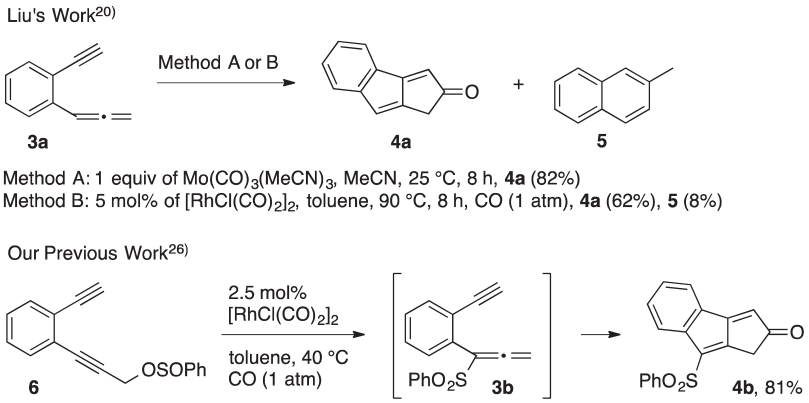


Chart 2. Synthesis of 1*H*-Cyclopent[*a*]inden-2-one Derivatives **4** by PKTR of Allenynes **3**

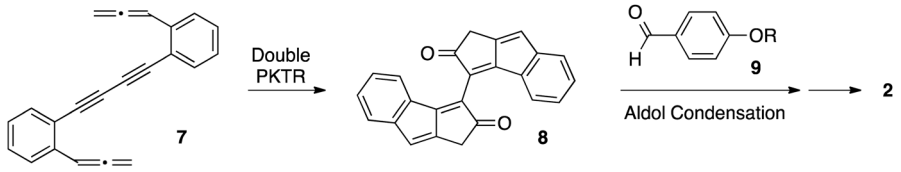


Chart 3. Strategy for the Synthesis of **2**

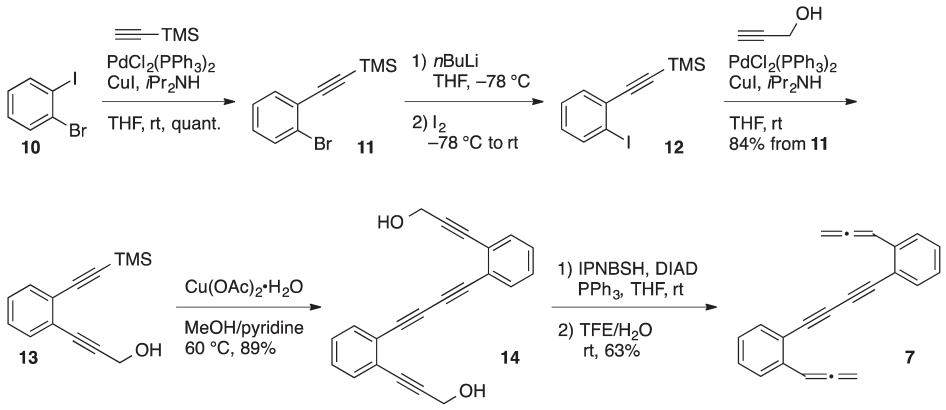
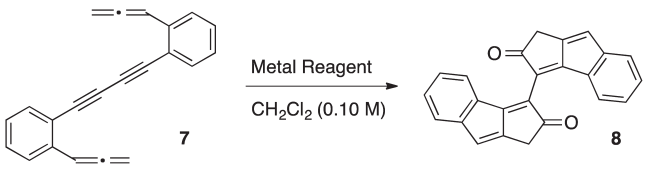


Chart 4. Synthesis of Bis(allenyne) **7**

N′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) was followed by hydrolysis under trifluoroethanol (TFE)/water conditions[30] to produce the bis(allenyne) **7**, a substrate of PKTR, in 63% yield (Chart 4).

Our endeavor then focused on the intramolecular double carbonylative [2+2+1] cycloaddition of **7** (Table 1). Treatment of **7** with 10 mol% of $[RhCl(CO)_2]_2$, which was effective for the PKTR of allenynes **3**[20,26] (Chart 2), in toluene at 70°C produced the desired product **8** in 22% yield along with the formation of unidentified by-products[31] (entry 1). Lowering the reaction temperature for suppression of the undesired reactions was not effective. The reaction at 30°C in CH_2Cl_2 led to a result similar to entry 1 with a prolonged reaction time (entry 2), while no reaction occurred at 0°C (entry 3). The reaction with 2 equiv of $Mo(CO)_3(MeCN)_3$,[32] being effective for the PKTR of allenynes **3**[20] (Chart 2), at room temperature afforded **8** in 19% yield (entry 4). A slightly higher yield was recorded when treated at 0°C (entry 5). Dimethyl sulfoxide (DMSO) was found to be an effective additive.[33] Indeed, the reaction in the presence of 4 equiv of $Mo(CO)_3(MeCN)_3$ and

Table 1. Optimization of Reaction Conditions for Double Carbonylative [2+2+1] Cycloaddition of **7**



Entry	Metal reagent (eq)	CO (atm)	Temp. (°C)	Time (h)	Yield (%)[a]
1[b]	$[RhCl(CO_2)]_2$ (0.10)	1	70	4	22
2	$[RhCl(CO_2)]_2$ (0.20)	1	30	23	18
3	$[RhCl(CO_2)]_2$ (0.10)	1	0	19	nr
4	$Mo(CO)_3(MeCN)_3$ (2.0)	—	rt	1	19
5	$Mo(CO)_3(MeCN)_3$ (2.0)	—	0	5.5	28
6[c]	$Mo(CO)_3(MeCN)_3$ (4.0)	—	0	8	44
7[c]	$Mo(CO)_3(MeCN)_3$ (4.0)	1	0	24	59
8[b,c]	$Mo(CO)_3(MeCN)_3$ (4.0)	1	0	24	61

a) Yield of the isolated product. *b*) Reaction was performed in toluene. *c*) Reaction was carried out with 8 eq of DMSO. nr=no reaction.

DMSO (8 eq) afforded **8** in 44% yield (entry 6). The reaction in a CO atmosphere increased the yield to 59% (entry 7). The highest yield of **8** (61%) was attained when the reaction was performed in toluene (entry 8).

The next task was the introduction of 4-hydroxybenzylidene moieties to the α-positions of the two carbonyl groups of **8** (Chart 5). Treatment of **8** with 4-benzoyloxybenzaldehyde (**9a**) in the presence of sodium hydroxide resulted in an intractable mixture. The reaction with 4-acetoxybenzaldehyde (**9b**) gave a similar result. Gratifyingly, the MOM-protected 4-hydroxybenzaldehyde **9c** (MOM: methoxymethyl) was shown to afford the desired condensation product **15**[34] in 51% yield. Finally, the exposure of **15** to acidic conditions resulted in the removal of the MOM group to provide **2**, the carbon analogue of scytonemin (**1**), in 91% yield.[35]

In summary, we have completed the short-step synthesis of a carbon analogue of scytonemin from the commercially available 1-bromo-2-iodobenzene (**10**). The significant features of this synthesis are (i) the intramolecular double PKTR of bis(allenyne), which enabled us to straightforwardly construct the 3,3′-linked dimeric 1*H*-cyclopent[*a*]inden-2-one skeleton, and (ii) the stereoselective introduction of the arylidene moiety by aldol condensation. The biological studies of **2** are now in progress.

Experimental

General Melting points were measured with Yanagimoto (Tokyo, Japan) micro melting point apparatus, and were uncorrected. Infrared spectra were measured with a Shimadzu FTIR-8700 spectrometer (Kyoto, Japan) for samples in $CHCl_3$. ^{1}H-NMR spectra were measured with JNM-ECS400 or JNM-ECA600 spectrometers for samples in $CDCl_3$. Tetramethylsilane (0.00 ppm) for compounds with a phenyl group or $CHCl_3$ (7.26 ppm) were used as an internal reference. ^{13}C-NMR spectra were measured with JNM-ECS400 or JNM-ECA600 spectrometers for samples in $CDCl_3$. $CDCl_3$ (77.00 ppm) was used as an internal reference. High-resolution mass spectra (HR-MS) and MS were measured with JMS-SX102A (FAB) or JMS-T100TD (Direct Analysis in Real Time: DART) mass spectrometers. UV visible absorption spectra were measured with UV-3150 (Shimadzu). Commercially available anhydrous tetrahydrofuran (THF), CH_2Cl_2, and toluene were employed for reactions. DMSO was distilled from $CaSO_4$. $[RhCl(CO)_2]_2$ was purchased from Kanto Chemical Co. (Tokyo, Japan). Other reagents were commercially available and used without further purification. All reactions were carried out under a nitrogen atmosphere. Silica gel (silica gel 60, 230–400 mesh) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

1-Bromo-2-[2-(trimethylsilyl)ethynyl]-benzene (11) To a solution of 1-bromo-2-iodobenzene (**10**, 1.0 mL, 8.0 mmol) in THF (50 mL) were added $PdCl_2(PPh_3)_2$ (112 mg, 0.16 mmol), CuI (15 mg, 0.080 mmol), trimethylsilylacetylene (1.4 mL, 8.8 mmol) and iPr$_2$NH (7.8 mL, 56 mmol) at room temperature. After being stirred for 5 h, the mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with hexane. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane to give **11** (2.28 g, quantitative yield) as a pale yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, 1H, J=8.1 Hz), 7.53 (dd, 1H, J=7.8, 1.4 Hz), 7.28 (dd, 1H, J=7.8, 7.8 Hz), 7.19 (dd, 1H, J=8.1, 7.8 Hz), 0.32 (s, 9H). NMR data is identical to literature data.[36]

3-[2-(2-(Trimethylsilyl)ethynyl)phenyl]-2-propyn-1-ol (13) To a solution of **11** (2.03 g, 8.0 mmol) in THF (42 mL) was added butyllithium (1.61 M in hexane, 7.0 mL, 11 mmol) at −78°C. After being stirred for 30 min, I_2 (3.0 g, 12 mmol) was added to the reaction mixture at –78°C. The mixture was stirred for 2 h at room temperature, quenched by addition of saturated aqueous $Na_2S_2O_3$ and extracted with hexane. The extract was washed with water and brine, dried and concentrated to dryness. To a solution of the residue in THF (50 mL) were added $PdCl_2(PPh_3)_2$ (109 mg, 0.16 mmol), CuI (15 mg, 0.078 mmol), propargyl alcohol (0.70 mL, 12 mmol) and iPr$_2$NH (7.7 mL, 55 mmol) at room temperature. After being stirred for 25 h, the mixture was quenched by addition of saturated aqueous NH_4Cl, and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (5 : 1) to give **13** (1.53 g, 84% yield from **11**) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.48–7.41 (m, 2H), 7.27–7.24 (m, 2H), 4.54 (br s, 2H), 0.27 (s, 9H). NMR data is identical to literature data.[37]

2,2′-(Buta-1,3-diyne-1,4-diyl)bis[(3-hydroxypropynyl)benzene] (14) To a solution of **13** (2.20 g, 9.6 mmol) in MeOH (30 mL) and pyridine (30 mL) was added $Cu(OAc)_2 \cdot H_2O$ (3.9 g, 19 mmol) at room temperature. After stirring for 9 h at 60°C, the reaction was quenched by addition of 10% aqueous HCl, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2 : 1) to afford **14** (1.32 g, 89% yield) as a pale brown solid: mp 105–106°C; IR 3601, 3420, 2399, 1522, 1475, 1448, 1383, 1022, 951, 930 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.51 (d, 2H, J=6.9 Hz), 7.42 (d,

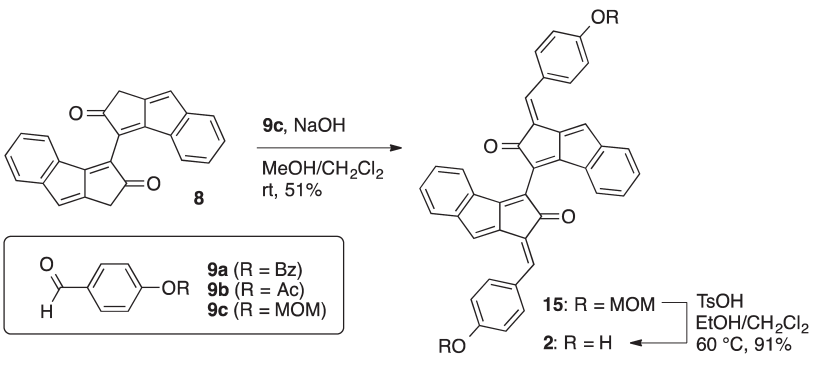


Chart 5. Completion of the Synthesis of **2**

2H, J=7.2 Hz), 7.31–7.26 (m, 4H), 4.58 (d, 4H, J=5.8 Hz), 2.97 (t, 2H, J=5.8 Hz); ^{13}C-NMR (151 MHz, $CDCl_3$) δ: 132.7, 131.8, 128.9, 128.1, 126.3, 124.3, 92.3, 83.7, 81.2, 77.5, 51.5; DART MS m/z 311 (M^++1, 29.0); DART HR-MS Calcd for $C_{22}H_{15}O_2$ 311.1072, Found 311.1077.

2,2′-(Buta-1,3-diyne-1,4-diyl)bis[(1,2-propadienyl)benzene] (7) To a solution of **14** (151 mg, 0.49 mmol) in THF (4.9 mL) were successively added PPh_3 (498 mg, 1.9 mmol), IPNBSH (490 mg, 1.9 mmol), and DIAD (0.40 mL, 1.9 mmol) at 0°C. After stirring for 5 h at room temperature, TFE–H_2O (1 : 1, 5.0 mL) was added to the reaction mixture. After stirring for 1 h at room temperature, the reaction was quenched by addition of water, and the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane to afford **7** (57 mg, 51% yield) as a pale yellow solid: mp 68°C (decomposed); IR 1940, 1481, 1447, 854, 667 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.51–7.47 (m, 4H), 7.31 (br s, 2H), 7.16 (br s, 2H), 6.74 (br s, 1H), 5.21–5.20 (m, 5H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ: 210.7, 137.1, 133.3, 129.3, 126.64, 126.61, 119.4, 92.0, 80.7, 79.1, 78.3; DART MS m/z 279 (M^++1, 42.9); DART HR-MS Calcd for $C_{22}H_{15}$ 279.1174, Found 279.1188.

[3,3′-Bi(cyclopent[*a*]inden)]-2,2′(1*H*,1′*H*)-dione (8) To a solution of **7** (29 mg, 0.10 mmol) in toluene (1.0 mL) were added $Mo(CO)_3(MeCN)_3$ (126 mg, 0.42 mmol) and DMSO (59 μL, 0.83 mmol). The reaction mixture was stirred at 0°C for 24 h under CO (1 atm). The reaction mixture was chromatographed with hexane–CH_2Cl_2–AcOEt (8 : 1 : 1) to afford **8** (21 mg, 61% yield) as a red solid: mp over 300°C; IR 1713, 1607, 1443, 1327, 1306, 1277, 1207, 1177, 1150 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.28 (dd, 2H, J=7.6, 7.6 Hz), 7.19 (d, 2H, J=7.2 Hz), 7.11 (d, 2H, J=7.2 Hz), 6.98 (dd, 2H, J=7.6, 7.2 Hz), 6.56 (s, 2H), 3.43 (s, 4H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ: 203.2, 168.6, 148.2, 140.6, 132.2, 130.0, 129.1, 127.1, 125.6, 124.2, 121.8, 35.5; DART MS m/z 335 (M^++1, 100); DART HR-MS Calcd for $C_{24}H_{15}O_2$ 335.1072, Found 335.1065.

(1*E*,1′*E*)-1,1′-Bis[4-(methoxymethyl)oxybenzylidene]-[3,3′-bi(cyclopent[*a*]inden)]-2,2′(1*H*,1′*H*)-dione (15) To a solution of **8** (54 mg, 0.16 mmol) in MeOH (1.5 mL) and CH_2Cl_2 (1.5 mL) were added NaOH (27 mg, 0.68 mmol) and 4-(methoxymethyl)oxy-benzaldehyde (**9c**, 108 mg, 0.65 mmol) at room temperature. The reaction mixture was stirred for 2 h, quenched by addition of ice-cold water, neutralized by aqueous solution of 10% HCl and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt–CH_2Cl_2 (8 : 1 : 1) to afford **15** (53 mg, 51% yield) as a dark brown solid: mp 242–244°C; IR 1701, 1634, 1603, 1508, 1242, 1153, 1080, 997, 835 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.74 (d, 4H, J=8.6 Hz), 7.51 (s, 2H), 7.30 (dd, 2H, J=7.6, 7.2 Hz), 7.24 (d, 4H, J=7.2 Hz) 7.17 (d, 4H, J=8.6 Hz), 7.11 (s, 2H), 7.06 (dd, 2H, J=7.6, 7.2 Hz), 5.27 (s, 4H), 3.53 (s, 6H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ: 194.6, 164.8, 158.3, 148.6, 139.6, 132.5, 132.0, 131.7, 130.7, 129.0, 127.5, 127.4, 126.6, 125.1, 124.3, 122.5, 116.3, 94.2, 56.2; DART MS m/z 631 (M^++1, 4.66); DART HR-MS Calcd for $C_{42}H_{31}O_6$ 631.2121, Found 631.2128.

(1*E*,1′*E*)-1,1′-Bis(4-hydroxybenzylidene)-[3,3′-bi(cyclopent[*a*]-inden)]-2,2′(1*H*,1′*H*)-dione (2) To a solution of **15** (86 mg, 0.14 mmol) in EtOH (1.5 mL) and CH_2Cl_2 (1.5 mL) was added *p*-TsOH·H_2O (156 mg, 0.82 mmol) at room temperature. After stirring for 4 h at 60°C, EtOH was evaporated off. The residue was dissolved in acetone, extracted with CH_2Cl_2, washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (4 : 3) to afford **2** (67 mg, 91% yield) as a dark brown solid: mp 261–262°C; IR (KBr) 1684, 1664, 1630, 1601, 1580, 1560, 1510, 1437, 1288, 1159, 1088, 1040 cm^{-1}; ^{1}H-NMR (600 MHz, acetone-d_6) δ: 9.15 (br s, 2H), 7.82 (d, 4H, J=8.6 Hz), 7.43 (s, 2H), 7.40–7.35 (m, 6H), 7.30 (d, 2H, J=7.6 Hz), 7.10 (dd, 2H, J=6.9, 6.5 Hz), 7.05 (d, 4H, J=8.6 Hz); ^{13}C-NMR (151 MHz, acetone-d_6) δ: 194.8, 165.2, 160.2, 149.7, 140.4, 133.5, 133.3, 133.1, 131.4, 128.22, 128.17, 127.5, 127.4, 125.3, 124.5, 123.6, 116.7; DART MS m/z 543 (M^++1, 100); DART HR-MS Calcd for $C_{38}H_{23}O_4$ 543.1596, Found 543.1607.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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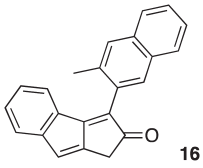
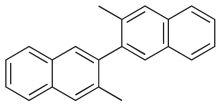
31) We presume that the naphthalene derivatives arisen from the undesired Myers–Saito cycloaromatization, such as **16** and **17**, might be formed.



16



17

32) $Mo(CO)_3(MeCN)_3$ was prepared by heating $Mo(CO)_6$ in refluxing MeCN for 10 h, see Al-Kathumi, K. M., Kane-Maguire, L. A. P., *J. Inorg. Nucl. Chem.*, **34**, 3759–3764 (1972).
33) It was reported that DMSO was an effective promoter in the molybdenum-mediated intramolecular PKTR of the allenynes. See ref. 20 and references cited therein.
34) The X-ray diffraction analysis of **15** unambiguously established its structure having the exocyclic double bonds with the 4-alkoxyphenyl groups oriented to the opposite side of the carbonyl groups (see Supplemental Information for details).
35) The UV-visible absorption spectrum of **2** (see Supplemental Information) showed strong absorbance peaks around 260 nm, which are different from those of scytonemin (**1**) exhibiting a characteristic strong absorbance peak around 400 nm (see ref. 1). The above observation might indicate that the nitrogen atoms affect the UV-visible absorption band of **1**.
36) Kashiki T., Shinamura S., Kohara M., Miyazaki E., Takimiya K., Ikeda M., Kuwabara H., *Org. Lett.*, **11**, 2473–2475 (2009).
37) Cheng X., Ma J., Zhi J., Yang X., Hu A., *Macromolecules*, **43**, 909–913 (2010).