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STUDIES TOWARD THE SYNTHESIS OF PERFORATUMONE: SYNTHESIS OF THE 7-OXABICYCLO[4.2.1]NONANE-8,9-DIONE CORE

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This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

Abstract – Construction of the unique bridged bicyclic skeleton, 7-oxabicyclo[4.2.1]nonane-8,9-dione, of perforatumone was achieved. Key steps included a Dieckmann-type condensation, a Claisen rearrangement, and an intramolecular Michael reaction.

More than 100 derivatives of polycyclic polyprenylated acylphloroglucinols (PPAPs) have been isolated from the Guttiferae family of plants and are reported to possess a variety of biological activities.[1] PPAPs often contain highly oxygenated, multisubstituted bicyclo[3.3.1]nonane-2,4,9-trione cores. Many chemists have been interested in the structure and biological activity of PPAPs. One of the most widely studied PPAPs is hyperforin (**1**) (Figure 1), which was isolated from *Hypericum perforatum* (Saint John's wort) and is responsible for an antidepressant effect.[2] Due to its complex structure, total synthesis of **1** has been challenging for chemists, but the first total synthesis was achieved by Shibasaki, Kanai, and colleagues in 2010.[3] Subsequently, several elegant total syntheses of **1** have been reported by Shair and colleagues,[4] Uwamori and Nakada,[5] Bellavance and Barriault,[6] and Ting and Maimone.[7]

Perforatumone (**2**) was also isolated from *H. perforatum* by Harrison and colleagues in 2004.[8] The hypothetical biosynthesis indicated that **2** is derived from **1**. The structure of **2** was originally reported to include a 7-oxabicyclo[4.2.1]nonane-8,9-dione skeleton, which is a novel structure in nature.[9] Total synthesis of **2** has not been achieved, and only two synthetic studies have been reported, by Nicolaou et al.[10] and our group.[11] However, the structure of perforatumone was recently revised to the congener hyphenrone A (**3**) by Xu and colleagues.[12] Although our targeted structure was consequently wrong, we were interested in the unique bridged bicyclic structure and unknown biological activities of **2**. Here, we describe the synthesis of model compound **4** for the 7-oxabicyclo[4.2.1]nonane-8,9-dione core of **2**. Compound **4** could be also converted into the skeleton of **3** through a ring-expansion reaction. Therefore, the development of synthesizing **4** is a worthwhile study for research on PPAPs.

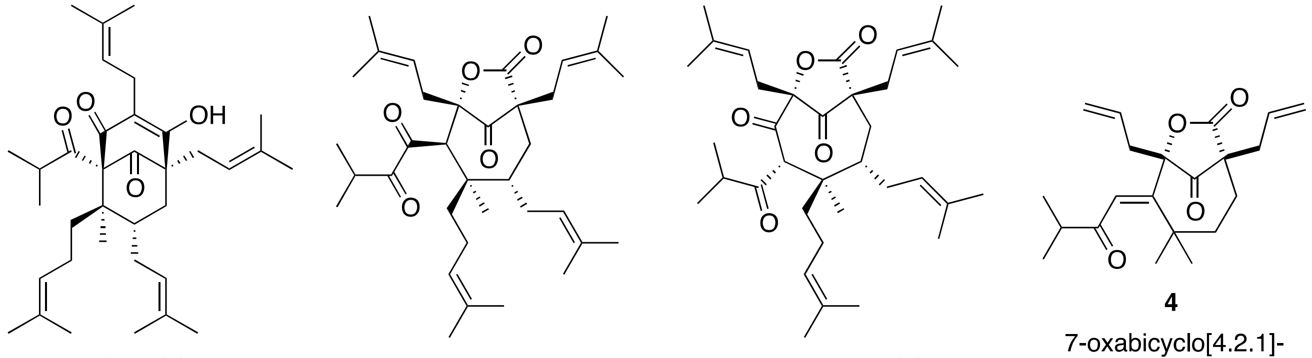
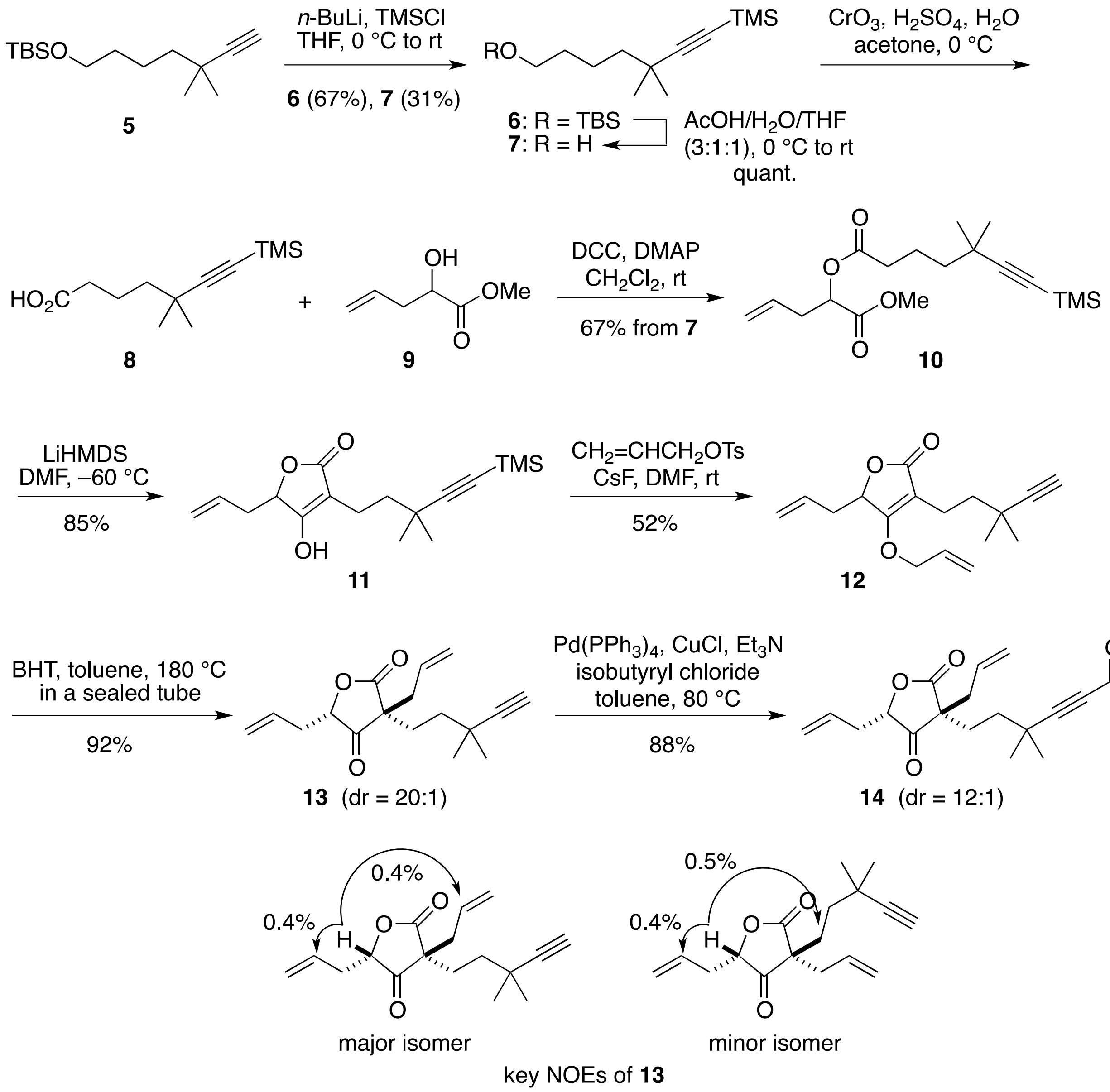

hyperforin (**1**) perforatumone (**2**) hyphenrone A (**3**) **4** 7-oxabicyclo[4.2.1]-nonane-8,9-dione

Figure 1. Structures of hyperforin, perforatumone, hyphenrone A, and model compound **4**

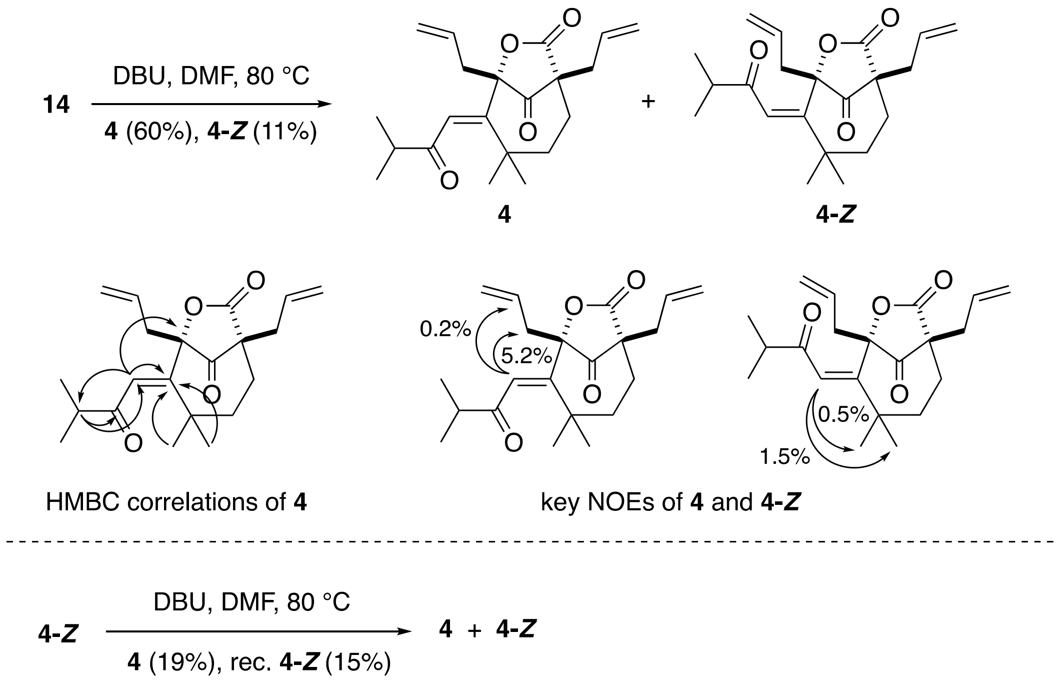
There are few synthetic studies of the 7-oxabicyclo[4.2.1]nonane-8,9-dione structure and these are based on a ring-expansion reaction.[13] Our synthetic plan for **4** relied on an intramolecular Michael reaction to assemble the bridged bicyclic skeleton. The synthesis of substrate **14** is shown in Scheme 1. Protection of known terminal alkyne **5**[14] with a trimethylsilyl (TMS) group furnished **6** and deprotected alcohol **7**. The *tert*-butyldimethylsilyl (TBS) group of **6** was selectively removed under mild acidic conditions to give more **7**. Jones oxidation of **7** provided carboxylic acid **8**, which was used for condensation with readily prepared racemic α-hydroxyester **9**.[15,16] Dicyclohexylcarbodiimide (DCC) condensation of **8** and **9** provided diester **10**. Dieckmann-type condensation of **10** with lithium bis(trimethylsilyl)amide (LiHMDS) formed a five-membered ring to afford a tetronic acid derivative **11**.[11] Subsequent allylation with allyl bromide (LiHMDS /DMF, –60 °C to rt) furnished not only *O*-allylated product **12**, but also *C*-allylated product **13**, with a diastereomeric ratio of 1:1. Using CsF as a base and allyl *p*-toluenesulfonate (OTs) as an allylation reagent, *O*-selective allylation and removal of the TMS group proceeded to provide *O*-allylated product **12** predominantly. Claisen rearrangement of **12** produced *C*-allyl **13** in high yield with a diastereomeric ratio of 20:1. The stereochemistry of **13** was determined by NOE experiments. The high diastereoselectivity would be useful in the asymmetric synthesis.[16] Desired ynone **14** was obtained by Sonogashira-type coupling of **13** with isobutyryl chloride, accompanied by slight epimerization (diastereomeric ratio = 12:1).

With substrate **14** in hand, we examined the intramolecular Michael reaction. After extensive trial and error, we found that treatment of **14** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide (DMF) formed the 7-oxabicyclo[4.2.1]nonane-8,9-dione core (Scheme 2).



Scheme 1. Synthesis of ynone **14**

Cyclized product **4** was obtained as the major isomer in 60% yield along with 11% yield of geometrical isomer **4-*Z***. The ^{1}H and ^{13}C NMR spectra of **4** showed that it was a single diastereomer, indicating that compound **4** was not a dimerized product because substrate **14** was a racemate; thus, a dimerized product would be a 1:1 diastereomeric mixture. HMBC and NOE experiments also confirmed the structure of **4**. Minor isomer **4-*Z*** isomerized to **4** under the same conditions (DBU/DMF, 80 °C) for the Michael reaction, which suggests that the two isomers are reversible, but that **4** is thermodynamically stable.



Scheme 2. Intramolecular Michael reaction of ynone **14**

In conclusion, we have constructed the unique bridged bicyclic skeleton, 7-oxabicyclo[4.2.1]nonane-8,9-dione, of perforatumone (**2**). The five-membered ring was formed by a Dieckmann-type condensation of diester **10**. Claisen rearrangement of *O*-allyl **12** created a quaternary stereocenter with high diastereoselectivity. The seven-membered ring was constructed by an intramolecular Michael reaction of ynone **14**, giving model compound **4**. This research provides a new method for constructing a 7-oxabicyclo[4.2.1]nonane-8,9-dione structure.

EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded at 300 MHz or 400 MHz with tetramethylsilane as an internal standard on a JEOL JNM-LA300 or JEOL JNM-ECS400 spectrometer. ^{13}C NMR spectra were recorded at 125 MHz on a JEOL JNM-ECA500 spectrometer. High-resolution mass spectra (HRMS) were measured by the ESI mode on a Waters LCT premier XE spectrometer. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates. The crude reaction mixtures and extracted materials were purified by chromatography on Silica gel 60N (Kanto Chemical). Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from the reaction mixture and the combined organic extracts by concentration under reduced pressure using an evaporator with bath at 35–45 °C.

7-(*tert*-Butyldimethylsilyloxy)-3,3-dimethyl-1-(trimethylsilyl)hept-1-yne (6) and 5,5-dimethyl-7-(trimethylsilyl)hept-6-yn-1-ol (7). The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **5** (2.50 g, 9.82 mmol) in THF (50 mL) was added *n*-BuLi (2.6 M solution in hexane, 5.3 mL, 14 mmol). The mixture was stirred at 0 °C for 1 h and TMSCl (3.8 mL, 30 mmol) was added. After being stirred at 0 °C for 2 h and at room temperature for 1 h, the mixture was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with EtOAc (100 mL × 3). The combined extracts were washed with saturated brine (300 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:80) to provide 2.15 g (67%) of **6** and 654 mg (31%) of **7**. Compound **6** was obtained as a colorless oil: TLC R_f 0.81 (EtOAc/hexane, 1:8); IR (neat) 2958, 2160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.17 (s, 6H), 1.39–1.56 (m, 6H), 3.63 (t, 2H, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2 (2C), 0.3 (3C), 16.4, 21.6, 26.0 (3C), 29.2 (2C), 31.8, 33.3, 43.1, 63.2, 83.1, 114.9. Compound **7** was obtained as a colorless oil: TLC R_f 0.13 (EtOAc/hexane, 1:8); IR (neat) 3356, 2964, 2158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.18 (s, 6H), 1.36–1.61 (m, 6H), 3.67 (t, 2H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.3 (3C), 21.4, 29.1 (2C), 31.8, 33.1, 42.9, 62.9, 83.3, 114.7.

Synthesis of 7 from 6. To a cooled (0 °C) stirred solution of **6** (2.15 g, 6.59 mmol) in THF (21 mL) were added AcOH (64 mL) and H_2O (21 mL). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 1.41 g (quant) of **7** as a colorless oil.

5,5-Dimethyl-7-(trimethylsilyl)hept-6-ynoic acid (8). To a cooled (0 °C) stirred solution of **7** (2.00 g, 9.42 mmol) in acetone (30 mL) was added Jones reagent (2.67 M CrO_3 in 30 vol% aqueous H_2SO_4, 5.4 mL, 14 mmol). After being stirred at 0 °C for 10 min, the mixture was quenched with 2-propanol (16 mL) and concentrated under reduced pressure. The residue was diluted with H_2O (340 mL) and extracted with EtOAc (170 mL × 5). The combined extracts were washed with saturated brine (340 mL), dried and concentrated under reduced pressure to provide 2.13 g of crude **8**, which was used in the next step without further purification.

Methyl 2-[5,5-dimethyl-7-(trimethylsilyl)hept-6-ynoyloxy]pent-4-enoate (10). To a cooled (0 °C) stirred solution of crude **8** (2.13 g) obtained above in CH_2Cl_2 (40 mL) were added a solution of **9** (1.23 g, 9.45 mmol) in CH_2Cl_2 (20 mL), DMAP (115 mg, 0.941 mmol), and DCC (1.94 g, 9.40 mmol). After being stirred at room temperature for 20 h, the mixture was diluted with EtOAc (110 mL), washed with saturated brine (90 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:80) to provide 2.13 g (67% from **7**) of **10** as a colorless oil: TLC R_f 0.70 (EtOAc/hexane, 1:3); IR (neat) 2965, 2159, 1745, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.18 (s, 6H), 1.40–1.44 (m, 2H), 1.76–1.84 (m, 2H), 2.43 (t, 2H, J = 7.6 Hz), 2.57–2.65 (m, 2H), 3.74 (s, 3H), 5.09–5.18 (m, 3H), 5.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.3 (3C), 20.7, 29.1 (2C), 31.6, 34.2, 35.5, 42.4, 52.2, 71.5, 83.6, 114.2, 118.7, 132.0, 170.2, 173.0; HRMS (ESI) calcd for $C_{18}H_{31}O_4Si$ $[M+H]^+$ m/z 339.1992, found 339.1987.

3-[3,3-Dimethyl-5-(trimethylsilyl)pent-4-ynyl]-4-hydroxy-5-(2-propenyl)-2(5*H*)-furanone (11). The following reaction was carried out under Ar. To a cooled (–60 °C) stirred solution of **10** (96.2 mg, 0.284 mmol) in DMF (2 mL) was added LiHMDS (1.0 M solution in THF, 0.50 mL, 0.50 mmol). After being stirred at –60 °C for 20 min, the mixture was quenched with 0.1 M aqueous HCl (10 mL) and extracted with EtOAc/hexane (1:1, 10 mL × 3). The combined extracts were washed with saturated brine (10 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to provide 73.7 mg (85%) of **11** as a reddish oil: TLC R_f 0.36 (EtOAc/hexane, 1:1); IR (neat) 3340, 2963, 2160, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.21 (s, 6H), 1.55–1.59 (m, 2H), 2.31–2.45 (m, 3H), 2.72 (m, 1H), 4.75 (dd, 1H, *J* = 6.6, 4.3 Hz), 5.13 (dd, 1H, *J* = 10.4, 1.0 Hz), 5.18 (dd, 1H, *J* = 17.0, 1.0 Hz), 5.75 (ddt, 1H, *J* = 17.0, 10.4, 7.0 Hz), 8.00 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.2 (3C), 17.4, 29.2 (2C), 32.3, 35.6, 40.5, 77.1, 85.0, 102.6, 115.4, 119.4, 130.9, 173.9, 175.5; HRMS (ESI) calcd for $C_{17}H_{27}O_3Si$ $[M+H]^+$ *m/z* 307.1729, found 307.1717.

3-[3,3-Dimethylpent-4-ynyl]-5-(2-propenyl)-4-(2-propenyloxy)-2(5*H*)-furanone (12). To a cooled (0 °C) stirred solution of **11** (442 mg, 1.44 mmol) in DMF (15 mL) were added $CH_2=CHCH_2OTs$ (1.0 mL, 8.7 mmol) and CsF (696 mg, 4.58 mmol). After being stirred at room temperature for 21 h, the mixture was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc/hexane (1:1, 30 mL × 3). The combined extracts were washed with saturated brine (10 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50) to provide 212 mg (52%) of **12** as a yellow oil: TLC R_f 0.52 (EtOAc/hexane, 1:3); IR (neat) 3301, 2969, 1753, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.57–1.64 (m, 2H), 2.11 (s, 1H), 2.36 (m, 1H), 2.47–2.55 (m, 2H), 2.69 (m, 1H), 4.68 (dd, 1H, *J* = 6.8, 4.4 Hz), 4.82 (ddt, 1H, *J* = 12.4, 5.2, 1.2 Hz), 4.86 (ddt, 1H, *J* = 12.4, 5.2, 1.2 Hz), 5.14 (dq, 1H, *J* = 10.4, 1.2 Hz), 5.17 (dq, 1H, *J* = 17.2, 1.2 Hz), 5.34 (dq, 1H, *J* = 10.4, 1.2 Hz), 5.40 (dq, 1H, *J* = 17.2, 1.2 Hz), 5.73 (ddt, 1H, *J* = 17.2, 10.4, 6.8 Hz), 5.97 (ddt, 1H, *J* = 17.2, 10.4, 5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 28.8 (2C), 31.1, 36.0, 42.7, 68.3, 71.7, 76.9, 91.2, 103.1, 118.6, 119.2, 131.0, 131.8, 171.5, 174.3; HRMS (ESI) calcd for $C_{17}H_{23}O_3$ $[M+H]^+$ *m/z* 275.1647, found 275.1646.

(3*S,5*S**)-3-[3,3-Dimethylpent-4-ynyl]-3,5-di(2-propenyl)-2,4(3*H*,5*H*)-furandione (13).** A solution of **12** (212 mg, 0.773 mmol) and BHT (25.5 mg, 0.102 mmol) in toluene (8 mL) was stirred at 180 °C for 1.5 h in a sealed tube. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 195 mg (92%) of **13** (dr = 20:1) as a colorless oil: TLC R_f 0.69 (EtOAc/hexane, 1:3); IR (neat) 3298, 2972, 1800, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.23–1.48 (m, 2H), 1.91–2.04 (m, 2H), 2.10 (s, 1H), 2.38–2.58 (m, 3H), 2.66 (m, 1H), 4.61 (dd, 1H, *J* = 8.0, 4.4 Hz), 5.13–5.25 (m, 4H), 5.66 (m, 1H), 5.81 (m, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 28.7 (2C), 29.8, 30.7, 34.6, 37.4, 40.3, 53.8, 68.8, 83.7, 90.0, 120.0, 121.4, 130.0, 130.9, 175.6, 211.7; HRMS (ESI) calcd for $C_{17}H_{23}O_3$ $[M+H]^+$ *m/z* 275.1647, found 275.1646.

(3*S,5*S**)-3,5-Di(2-propenyl)-3-(3,3,7-trimethyl-6-oxooct-4-ynyl)-2,4(3*H*,5*H*)-furandione (14).** The following reaction was carried out under Ar. To a cooled (0 °C) mixture of CuCl (14.8 mg, 0.149 mmol) and $Pd(PPh_3)_4$ (164 mg, 0.142 mmol) were added a solution of **13** (195 mg, 0.711 mmol) in toluene (8 mL), Et_3N (0.20 mL, 1.4 mmol), and isobutyryl chloride (0.15 mL, 1.4 mmol). After being stirred at 80 °C for 4 h, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60) to provide 215 mg (88%) of **14** (dr = 12:1) as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:3); IR (neat) 2971, 2206, 1799, 1754, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 6H, *J* = 6.9 Hz), 1.24 (s, 6H), 1.27–1.46 (m, 2H), 1.86–1.99 (m, 2H), 2.42–2.56 (m, 3H), 2.58–2.72 (m, 2H), 4.55 (dd, 1H, *J* = 7.6, 4.6 Hz), 5.15–5.24 (m, 4H), 5.65 (ddt, 1H, *J* = 16.5, 10.5, 7.1 Hz), 5.87 (ddt, 1H, *J* = 17.0, 10.1, 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0 (2C), 28.0, 28.2, 29.5, 31.3, 34.5, 37.1, 40.5, 43.1, 53.7, 79.9, 83.7, 99.2, 120.2, 121.5, 129.8, 130.8, 175.4, 192.2, 211.4; HRMS (ESI) calcd for $C_{21}H_{29}O_4$ $[M+H]^+$ *m/z* 345.2066, found 345.2053.

(1*S,6*S**)-4,4-Dimethyl-5-[(*E*)-3-methyl-2-oxobutylidene]-1,6-di(2-propenyl)-7-oxabicyclo[4.2.1]-nonane-8,9-dione (4) and (*Z*)-isomer (4-*Z*).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **14** (299 mg, 0.869 mmol) in DMF (9 mL) was added DBU (0.19 mL, 1.3 mmol). After being stirred at 80 °C for 7 h, the mixture was quenched with saturated aqueous NH_4Cl (9 mL), diluted with H_2O (5 mL), and extracted with EtOAc/hexane (1:1, 9 mL × 3). The combined extracts were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:80) to provide 178 mg (60%) of **4** and 32.3 mg (11%) of **4-*Z***. Compound **4** was obtained as a white amorphous solid: TLC R_f 0.61 (EtOAc/hexane, 1:4); IR (neat) 2931, 1798, 1755, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3H, *J* = 6.8 Hz), 1.16 (d, 3H, *J* = 6.8 Hz), 1.18 (s, 3H), 1.21 (s, 3H), 1.45 (dt, 1H, *J* = 15.6, 3.3 Hz), 1.80 (dd, 2H, *J* = 8.2, 3.3 Hz), 2.08 (dt, 1H, *J* = 15.6, 8.2 Hz), 2.49 (dd, 1H, *J* = 14.2, 7.4 Hz), 2.56 (dd, 1H, *J* = 14.2, 7.4 Hz), 2.71 (sept, 1H, *J* = 6.8 Hz), 2.79 (d, 2H, *J* = 7.1 Hz), 5.07–5.23 (m, 4H), 5.59 (ddt, 1H, *J* = 17.2, 10.1, 7.1 Hz), 5.73 (ddt, 1H, *J* = 17.2, 10.0, 7.4 Hz), 6.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 18.4, 28.5, 29.7, 31.8, 32.9, 33.9, 39.0, 39.6, 42.0, 57.7, 92.8, 119.7, 122.9, 129.8, 130.7, 131.7, 146.9, 174.3, 208.6, 209.0. Compound **4-*Z*** was obtained as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:4); ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.19 (d, 3H, *J* = 6.7 Hz), 1.20 (d, 3H, *J* = 6.7 Hz), 1.28 (s, 3H), 1.61 (dt, 1H, *J* = 15.1, 3.7 Hz), 1.78–1.87 (m, 2H), 2.04 (dt, 1H, *J* = 15.1, 4.3 Hz), 2.47 (dd, 1H, *J* = 14.0, 7.1 Hz), 2.54 (dd, 1H, *J* = 14.0, 7.1 Hz), 2.70 (d, 2H, *J* = 7.1 Hz), 2.87 (sept, 1H, *J* = 6.7 Hz), 5.07 (d, 1H, *J* = 9.9 Hz), 5.10 (d, 1H, *J* = 17.1

Hz), 5.11 (d, 1H, *J* = 9.9 Hz), 5.16 (d, 1H, *J* = 17.1 Hz), 5.43 (ddt, 1H, *J* = 17.1, 9.9, 7.1 Hz), 5.72 (ddt, 1H, *J* = 17.1, 9.9, 7.1 Hz), 6.38 (s, 1H).

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