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Sonogashira Coupling Reactions of Bromomaleimides: Route to Alkyne/*cis*-Alkene/Alkyl Maleimides: Synthesis of Luffarin X and Cacospongionolide C

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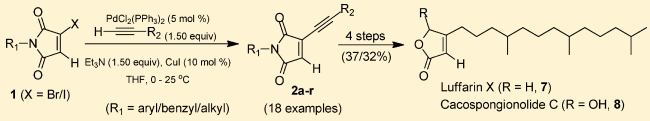
Supporting Information

ABSTRACT: Palladium-catalyzed Sonogashira coupling reaction of bromomaleimides with a diverse range of terminal alkynes has been demonstrated to furnish the corresponding alkynylmaleimides in very good yields. This coupling reaction followed by selective reduction of the triple bond to single bond have been utilized as the decisive steps to accomplish the first total synthesis of natural products (±)-luffarin X and (±)-cacospongionolide C.



A large number of alkyl- and dialkyl-substituted maleic anhydrides, the corresponding lactols and γ-lactones (butenolides), have been isolated as the natural products with an array of promising bioactivities (Figure 1).[1−7] Many new

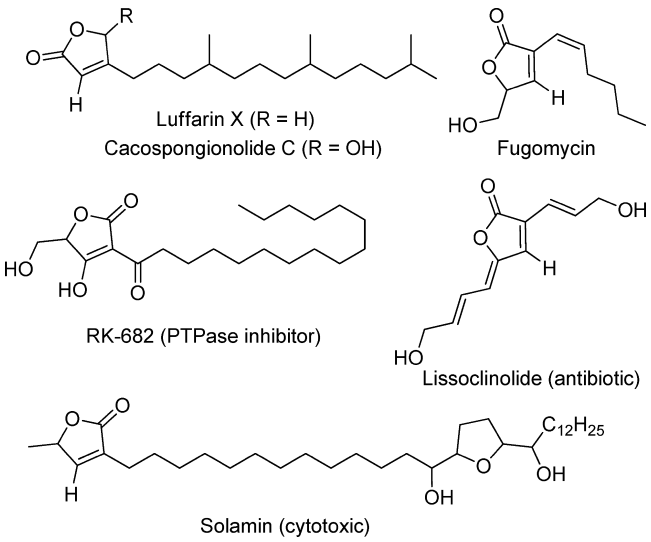


Figure 1. Naturally occurring butenolides.

routes have been devised in recent times to synthesize the essential dialkyl-substituted maleic anhydrides[8−12] and butenolides.[13−18] To the best of our knowledge, only a few practical routes have been known for the synthesis of alkylmaleic anhydrides.[19−21] They have been based on condensation of glyoxylic acid with aldehydes/esters bearing the active α-hydrogens[19] and also Heck reaction using palladium-catalyzed dicarbonylation of terminal acetylenes with carbon monoxide.[20] Our own recent approach based on isomaleimide intermediate involves more synthetic steps.[21] The Sonogashira coupling is one of the most important carbon−carbon bond-forming reactions for the introduction of an alkyne segment.[22−27] The synthetic utility of this reaction has been demonstrated on a broad assortment of vinylic, aromatic, and heteroaromatic substrates to accomplish the effective synthesis of many exotic bioactive natural and unnatural products.[28−34] Although the Sonogashira coupling with halomaleimides has not been previously described, several palladium-catalyzed cross-coupling reactions with them have been reported.[35−37] In continuation of our studies on carbon−carbon and carbon−heteroatom coupling reactions,[13,15,38−40] we realized that Sonogashira coupling of bromomaleic anhydrides/bromomaleimides would be useful to develop a new general route to alkyne/alkene/alkyl-substituted maleic anhydrides and several analogous natural products. In this context, we herein report our results on the synthesis of a variety of alkylmaleimides/maleic anhydrides and their applications in the synthesis of (±)-luffarin X and (±)-cacospongionolide C (Tables 1−5 and Scheme 1).

The initially attempted Sonogashira coupling reaction of reactive bromomaleic anhydride with 1-hexyne resulted in decomposition. Relatively more stable corresponding multifunctional halomaleimides **1**[41] were therefore preferred as the potential precursors for our systematic studies on Sonogashira coupling reactions. As depicted in Table 1, the reaction between bromomaleimide and 1-hexyne was performed employing three different palladium catalysts in THF. Two of these catalysts selectively furnished the desired coupled product **2b** in ∼90% yields (entries 2 and 4). However, the bromomethylmaleimide and dibromomaleimide under similar set of reaction conditions failed to deliver the corresponding desired mono/double coupling products, leading to decomposition (entries 5−8). The corresponding chloromaleimide and dichloromaleimide also failed to deliver the coupling products and remained unreacted at room temperature, while

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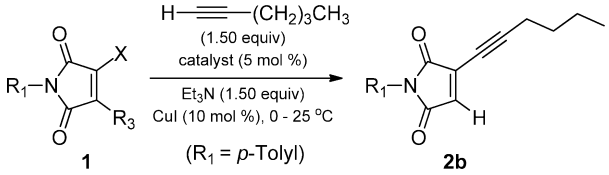
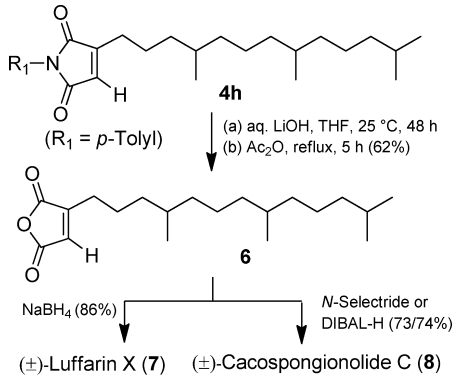
Table 1. Sonogashira Coupling Reactions of Bromomaleimides and Chloromaleimides



entry	X	R_3	catalyst	solvent	time (h)	% yield
1	Br	H	$Pd(PPh_3)_4$	THF	6.0	NR[a]
2	Br	H	$PdCl_2(PPh_3)_2$	THF	1.0	90
3	Br	H	$PdCl_2(PPh_3)_2$	DMF	1.0	67
4	Br	H	$PdCl_2(CH_3CN)_2$	THF	1.0	89
5	Br	Me	$PdCl_2(PPh_3)_2$	THF	6.0	NR[a]
6	Br	Me	$PdCl_2(CH_3CN)_2$	THF	6.0	NR[a]
7	Br	Br	$PdCl_2(PPh_3)_2$	THF	6.0	NR[a]
8	Br	Br	$PdCl_2(CH_3CN)_2$	THF	6.0	NR[a]
9	Cl	H	$PdCl_2(PPh_3)_2$	THF	6.0	NR[b]
10	Cl	Cl	$PdCl_2(PPh_3)_2$	THF	6.0	NR[b]

[a]No reaction, decomposition after 24 h. [b]No reaction from 25 to 65 °C.

Scheme 1. Synthesis of Luffarin X and Cacospongionolide C



slowly undergoing decomposition under the reflux conditions (entries 9 and 10). As described in Table 2, the reactions of bromomaleimides with several aliphatic and aromatic alkynes were performed in the presence of $PdCl_2(PPh_3)_2$/CuI in THF, and the desired products **2a**–**r** were obtained in very good yields (entries 1–18). We also obtained the coupling products **2b**, **2k**, and **2n** from the corresponding iodomaleimide in similar yields (Table 2, entries 19–21). In these multifunctional maleimides **2a**–**r**, a variety of chemoselective transformations would be possible on carbon–carbon triple bond to obtain the corresponding alkenyl/alkyl/acyl/1,2-dicarbonyl-substituted maleimides/maleic anhydrides as potential building blocks.[42−45] As indicated in Table 3, chemoselective and controlled hydrogenation of carbon–carbon triple bond in product **2b** was performed employing several catalysts. The reduction of imide **2b** in the presence of Wilkinson catalyst and Pearlman catalyst were futile. While the former reaction did not proceed at all, the latter resulted in decomposition (entries 1 and 3). As shown in entry 4, the transfer hydrogenation conditions also resulted in decomposition. The selective reduction of imide **2b** in the presence of Lindlar catalyst was feasible, and it was dependent on both the solvent used and the presence/absence of quinoline.[45] As described in entry 2, the acetylene segment of imide **2b** in the presence of Lindlar catalyst in ethyl acetate did not undergo reduction and remained unreacted. The reaction of **2b** in the presence of Lindlar catalyst in methanol reduced both the triple bond and internal double bond to provide alkylsuccinimide **5b** in 74% yield (entry 6). However the same reaction in methanol–acetone (1:1) in the presence of quinoline (1.00 equiv) selectively reduced only the carbon–carbon triple bond to the single bond furnishing the alkylmaleimide **4b** in 68% yield (entry 8). The reaction of **2b** in the presence of Lindlar catalyst in solvent acetonitrile/acetone and quinoline (1.50 equiv) yielded the desired monoreduction product *cis*-alkenylmaleimide **3b** in 56/57% yields along with the ∼6% of **4b** (entries 9 and 10). The reaction of imide **2b** in the presence of Pd–C in ethyl acetate provided completely reduced product **5b** in 78% yield (entry 5). The same reaction in methanol in the presence of quinoline (1.50 equiv) was also selective and gave the alkylmaleimide **4b** in 63% yield (entry 7). Finally, as depicted in Tables 4 and 5, the aliphatic alkyne-substituted maleimides were selectively reduced to the corresponding *cis*-alkenylmaleimides in 61–66% yields and alkylmaleimides in 68–75% yields. The *cis*-geometry of the products **3** was confirmed on the basis of NOE studies and the comparison with reported data.[4] Thus, the present protocol provides a facile new route to both the alkylmaleimides and the alkylmaleic anhydrides. Further conversion of alkylmaleimides to the corresponding dialkylmaleic anhydrides has been recently reported from our group.[21] However the alkyne-substituted maleimides with aromatic rings led to decomposition under present reduction conditions (Tables 4 and 5, entry 5).

The terpenoids luffarin X and cacospongionolide C have been isolated, respectively, from the marine sponge *Luffariella geometrica*[46] and *Fasciospongia cavernosa*.[47] To date, no synthesis of these natural products has been reported in the literature. The present protocol was extended for the first synthesis of the above-mentioned natural products. The appropriate precursor **4h** on base-catalyzed hydrolysis followed by the acetic anhydride induced ring-closure provided the corresponding alkylmaleic anhydride **6** in 62% yield[41] (Scheme 1). The regioselective reduction of anhydride **6** was studied using the five different reducing agents.[48] In the sodium borohydride reduction of unsymmetrical anhydride **6**, boron atom complexes with the unhindered carbonyl group and delivers the hydride to the hindered carbonyl group to exclusively yield the desired butenolide (±)-luffarin X (**7**) in

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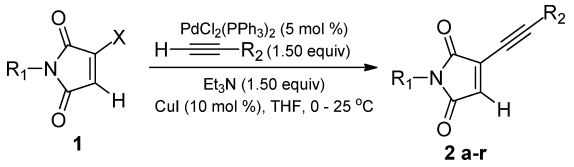
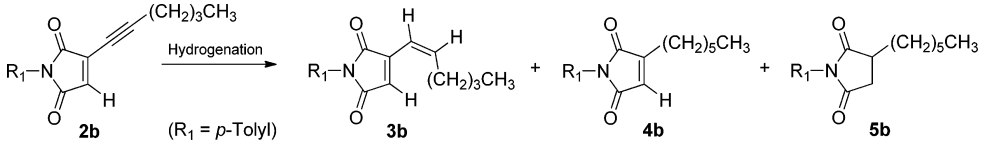
Table 2. Sonogashira Couplings of Bromomaleimides and Iodomaleimides: Synthesis of Alkynylmaleimides



entry	X	R_1	R_2	time (h)	**2** (% yield)
1	Br	*p*-C_6H_4-CH_3	$Si(Me)_3$	3.0	**2a** (52)
2	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_2CH_3$	1.0	**2b** (90)
3	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_4CH_3$	1.0	**2c** (90)
4	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_6CH_3$	1.0	**2d** (93)
5	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{11}CH_3$	0.5	**2e** (93)
6	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{12}CH_3$	0.5	**2f** (95)
7	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_{13}CH_3$	0.5	**2g** (95)
8[a]	Br	*p*-C_6H_4-CH_3	$C_{14}H_{29}$	1.0	**2h** (56)
9	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_7CH_2OH$	2.0	**2i** (67)
10	Br	*p*-C_6H_4-CH_3	$CH_2(CH_2)_7COOH$	2.0	**2j** (63)
11	Br	*p*-C_6H_4-CH_3	C_6H_5	1.0	**2k** (75)
12	Br	*p*-C_6H_4-CH_3	*p*-C_6H_4-CH_3	1.0	**2l** (78)
13	Br	*p*-C_6H_4-CH_3	*o*-C_6H_4-OCH_3	1.5	**2m** (67)
14	Br	*p*-C_6H_4-CH_3	*p*-C_6H_4-OCH_3	1.0	**2n** (72)
15	Br	C_6H_5	$CH_2(CH_2)_2CH_3$	1.0	**2o** (91)
16	Br	$CH_2C_6H_5$	$CH_2(CH_2)_2CH_3$	1.0	**2p** (86)
17	Br	CH_3	C_6H_5	1.0	**2q** (81)
18	Br	$(CH_2)_2CO_2CH_3$	$CH_2(CH_2)_2CH_3$	1.5	**2r** (74)
19	I	*p*-C_6H_4-CH_3	$CH_2(CH_2)_2CH_3$	1.0	**2b** (86)
20	I	*p*-C_6H_4-CH_3	C_6H_5	1.0	**2k** (77)
21	I	*p*-C_6H_4-CH_3	*p*-C_6H_4-OCH_3	1.0	**2n** (69)

[a]$C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$ (diastereomeric mixture).

Table 3. Selective Hydrogenation of Alkynylmaleimides



			% yield		
entry	catalyst	reaction conditions	**3b**	**4b**	**5b**
1	Wilkinson	H_2, DCM, reflux, 5 h		NR[a]	
2	Lindlar	H_2, quinoline, EtOAc, 25 °C, 24 h		NR[a]	
3	Pearlman	H_2, MeOH, 25 °C, 5 h		D[b]	
4		$TsNHNH_2$, DME aq NaOAc, reflux, 5 h		D[b]	
5	Pd–C	H_2, EtOAc, 25 °C, 1 h			78
6	Lindlar	H_2, MeOH, 25 °C, 5 h			74
7	Pd–C	H_2, quinoline, MeOH, 25 °C, 1.5 h		63	
8	Lindlar	H_2, quinoline MeOH + acetone (1:1), 25 °C, 6 h		68	
9	Lindlar	H_2, quinoline, CH_3CN, 25 °C, 5 h	56	6	
10	Lindlar	H_2, quinoline, acetone, 25 °C, 5 h	57	6	

[a]No reaction. [b]Decomposition.

86% yield. The reduction reactions of anhydride **6** with $NaBH(OAc)_3$ and Li(*t*-BuO)$_3$AlH were less selective and provided the column chromatographically separable mixture of products **7** and **8** in 81/70% yields (**7**:**8** = ~1:3). The reduction reactions of anhydride **6** with the $NaB[CH(CH_3)C_2H_5]_3H$ and DIBAL-H at −78 °C were also completely regioselective and reduced the hindered carbonyl group to the corresponding lactol to provide yet another desired natural product (±)-cacospongionolide C (**8**) in 73/74% yields, respectively. Such compounds containing hemiketal/lactol/lactamol unit display the ring−chain tautomerism and are prone to racemize.[39] The analytical and spectral data obtained for both the natural products **7** and **8** were in complete agreement with reported data.[46,47] Thus, starting from imide **1** the natural products **7** and **8** were obtained in five linear steps with 21% and 18% overall yields, respectively.

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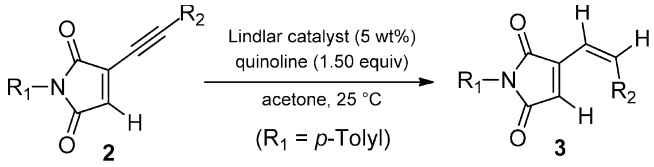
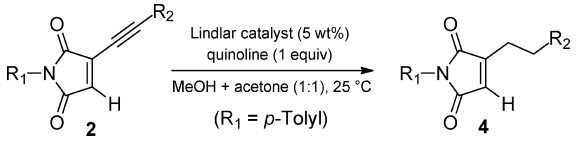
Table 4. Stereoselective Reduction of Alkynylmaleimides



entry	R_2	time (h)	3 (% yield)
1	$CH_2(CH_2)_2CH_3$	5.0	**3b** (63)[a]
2	$CH_2(CH_2)_6CH_3$	5.0	**3d** (61)[a]
3	$CH_2(CH_2)_{12}CH_3$	5.0	**3f** (65)
4[b]	$C_{14}H_{29}$	5.0	**3h** (66)
5	C_6H_5	12.0	**3k** D[c]

[a]The products were contaminated with traces of overreduced products **4b** and **4d**. [b]$C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$. [c]Decomposition.

Table 5. Synthesis of Alkylmaleimides



entry	R_2	time (h)	4 (% yield)
1	$CH_2(CH_2)_2CH_3$	6.0	**4b** (68)
2	$CH_2(CH_2)_6CH_3$	5.0	**4d** (70)
3	$CH_2(CH_2)_{12}CH_3$	6.5	**4f** (75)
4[a]	$C_{14}H_{29}$	6.5	**4h** (70)
5	C_6H_5	12.0	**4k** D[b]

[a]$C_{14}H_{29}$: $CH_2CHCH_3(CH_2)_3CHCH_3(CH_2)_3CH(CH_3)_2$. [b]Decomposition.

In summary, we have demonstrated a new general approach to alkyne/alkene/alkyl substituted maleimides/anhydrides by performing the palladium-catalyzed Sonogashira coupling reactions on the multifunctional bromomaleimides with a variety of terminal alkynes using CuI as the cocatalyst. The present protocol has been utilized to accomplish the total synthesis of natural products luffarin X and cacospongionolide C. The present Sonogashira coupling reactions of bromomaleimides and the chemo- and regioselective reductions are of general interest. We foresee their usefulness to obtain several complex bioactive natural and unnatural products for SAR studies.

EXPERIMENTAL SECTION

General Description. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz, and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 (50 MHz), 400 (100 MHz), and 500 NMR spectrometer (125 MHz). Mass spectra were taken on an MS-TOF mass spectrometer. HRMS were taken on ESI mass spectrometer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60−120 and 200−400 mesh). Commercially available $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, CuI, alkynes, Lindlar catalyst (5 wt %), Pd on charcoal (10 wt %), synthetic quinoline, $NaBH_4$, $NaBH(OAc)_3$, DIBAL-H, *N*-Selectride, and Super-Hydride were used. The halomaleimides were prepared by using known procedure.[41] The required alkynes were also prepared by using known procedure.[49]

General Procedure for Sonogashira Coupling Reaction of 3-Bromo-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione. A round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (13 mg, 5 mol %) and bromomaleimide (100 mg, 0.37 mmol) in THF (7 mL). The alkyne (0.55 mmol), triethylamine (0.077 mL, 0.55 mmol), and CuI (0.70 mg, 10 mol %) were added successively at 0 °C, and reaction mixture was stirred at 25 °C under argon atmosphere. After completion of the reaction (by TLC), ethyl acetate (10 mL) and water (5 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether−ethyl acetate as an eluent to furnish the desired coupling product **2**. Alternatively, the reaction mixture was filtered through a Celite, concentrated under vacuum, and then directly subjected to silica gel column chromatographic purification. All the reactions were performed using bromomaleimides (100 mg) to obtain the desired products **2a−g,i−r**. For the preparation of natural products precursor **2h**, the reaction was performed on a 1 g scale of 3-bromo-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione.

1-(*p*-Tolyl)-3-((trimethylsilyl)ethynyl)-1*H*-pyrrole-2,5-dione (2a): yellow solid (55 mg, 52%); mp 89−92 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.30 (s, 9H), 2.39 (s, 3H), 6.79 (s, 1H), 7.15−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 0.7, 21.1, 92.9, 115.2, 125.9, 128.5, 129.8, 130.4, 132.3, 138.1, 166.1, 169.0; ESIMS (*m*/*z*) 306 [M + Na]$^+$, 322 [M + K]$^+$; HRMS (ESI) calcd for $C_{16}H_{18}NO_2Si$ [M + H]$^+$ 284.1107, found 284.1110; IR ($CHCl_3$) ν_{max} 2311, 1713, 1393 cm^{-1}.

3-(Hex-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2b): yellow solid (90 mg, 90%); mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, *J* = 8 Hz, 3H), 1.35−1.70 (m, 4H), 2.38 (s, 3H), 2.54 (t, *J* = 8 Hz, 2H), 6.67 (s, 1H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 19.9, 21.1, 22.0, 30.0, 70.9, 110.3, 125.9, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (*m*/*z*) 290 [M + Na]$^+$, 306 [M + K]$^+$; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ [M + H]$^+$ 268.1338, found 268.1339; IR ($CHCl_3$) ν_{max} 2230, 1721, 1715 cm^{-1}.

3-(Oct-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2c): yellow solid (100 mg, 90%); mp 74−75 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, *J* = 6 Hz, 3H), 1.20−1.52 (m, 6H), 1.60 (quintet, *J* =

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8 Hz, 2H), 2.37 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.10−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 20.2, 21.1, 22.4, 27.9, 28.5, 31.2, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (m/z) 366 $[M + K + MeOH]^+$; HRMS (ESI) calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$ 296.1651, found 296.1649; IR ($CHCl_3$) ν_{max} 2224, 1723, 1715 cm^{-1}.

3-(Dec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2d): yellow solid (113 mg, 93%); mp 52−53 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.28 (br s, 8H), 1.35−1.53 (m, 2H), 1.64 (quintet, J = 6 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.13−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.6, 27.9, 28.9, 29.0, 29.1, 31.8, 70.9, 110.4, 125.9, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (m/z) 394 $[M + K + MeOH]^+$; HRMS (ESI) calcd for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964, found 324.1975; IR ($CHCl_3$) ν_{max} 2225, 1724, 1715 cm^{-1}.

3-(Pentadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2e): yellow solid (137 mg, 93%); mp 59−60 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.25 (br s, 18H), 1.30−1.50 (m, 2H), 1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.13−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.57, 29.61 (3 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (m/z) 426 $[M + H + MeOH]^+$; HRMS (ESI) calcd for $C_{26}H_{36}NO_2$ $[M + H]^+$ 394.2746, found 394.2737; IR ($CHCl_3$) ν_{max} 2218, 1721, 1713 cm^{-1}.

3-(Hexadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2f): yellow solid (145 mg, 95%); mp 61−62 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 8 Hz, 3H), 1.26 (br s, 20H), 1.35−1.55 (m, 2H), 1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.66 (s, 1H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.6 (5 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (m/z) 440 $[M + H+MeOH]^+$; HRMS (ESI) calcd for $C_{27}H_{38}NO_2$ $[M + H]^+$ 408.2903, found 408.2899; IR ($CHCl_3$) ν_{max} 2224, 1718, 1608 cm^{-1}.

3-(Heptadec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2g): yellow solid (150 mg, 95%); mp 65−66 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (br s, 22H), 1.30−1.52 (m, 2H), 1.64 (quintet, J = 8 Hz, 2H), 2.38 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.66 (s, 1H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 20.2, 21.1, 22.7, 28.0, 28.9, 29.0, 29.3, 29.4, 29.57, 29.63, 29.7 (4 carbons), 31.9, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.4; ESIMS (m/z) 444 $[M + Na]^+$; HRMS (ESI) calcd for $C_{28}H_{40}NO_2$ $[M + H]^+$ 422.3059, found 422.3078; IR ($CHCl_3$) ν_{max} 2361, 1717 cm^{-1}.

1-(*p*-Tolyl)-3-(4,8,12-trimethyltridec-1-yn-1-yl)-1*H*-pyrrole-2,5-dione (2h, diastereomeric mixture): thick oil (860 mg, 56%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.75−1.60 (m, 26H), 1.70−1.92 (m, 1H), 2.25−2.65 (m, 2H), 2.39 (s, 3H), 6.67 (s, 1H), 7.15−7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5, 19.6, 21.1, 22.6, 22.7, 24.4, 24.7, 27.5, 27.6, 27.9, 32.5, 32.7, 36.5, 37.1, 37.2, 37.3, 39.3, 71.8, 109.5, 125.9, 128.6, 129.7, 130.3, 131.5, 137.9, 166.6, 169.4; ESIMS (m/z) 430 $[M + Na]^+$; HRMS (ESI) calcd for $C_{27}H_{38}NO_2$ $[M + H]^+$ 408.2903, found 408.2903; IR ($CHCl_3$) ν_{max} 2220, 1721, 1606 cm^{-1}.

3-(11-Hydroxyundec-1-yn-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2i): yellow solid (89 mg, 67%); mp 70−72 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20−1.75 (m, 14H), 2.38 (s, 3H), 2.54 (t, J = 8 Hz, 2H), 3.64 (t, J = 6 Hz, 2H), 6.68 (s, 1H), 7.15−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.1, 25.6, 27.9, 28.8, 28.9, 29.28, 29.33, 32.7, 63.0, 70.9, 110.4, 126.0, 128.6, 129.7, 130.5, 131.5, 138.0, 166.6, 169.5; ESIMS (m/z) 376 $[M + Na]^+$; HRMS (ESI) calcd for $C_{22}H_{28}NO_3$ $[M + H]^+$ 354.2069, found 354.2066; IR ($CHCl_3$) ν_{max} 2359, 1721, 1715, 1697 cm^{-1}.

11-(2,5-Dioxo-1-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrol-3-yl)undec-10-ynoic acid (2j): yellow solid (87 mg, 63%); mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20−1.75 (m, 12H), 2.35 (t, J = 8 Hz, 2H), 2.37 (s, 3H), 2.53 (t, J = 8 Hz, 2H), 6.67 (s, 1H), 7.12−7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.2, 21.1, 24.6, 27.9, 28.7, 28.8, 28.9, 29.0, 33.9, 70.9, 110.3, 126.0, 128.6, 129.8, 130.6, 131.5, 138.0, 166.7, 169.5, 179.7; ESIMS (m/z) 390 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 2359, 1721, 1715, 1697 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.65; H, 6.84; N, 3.76.

3-(Phenylethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2k): yellow solid (81 mg, 75%); mp 138−139 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H), 6.82 (s, 1H), 7.15−7.33 (m, 4H), 7.33−7.52 (m, 3H), 7.62 (d, J = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 79.0, 106.8, 121.0, 126.0, 128.6, 129.8, 130.4, 130.7, 130.8, 132.4, 138.1, 166.3, 169.1; ESIMS (m/z) 342 $[M + Na + MeOH]^+$; HRMS (ESI) calcd for $C_{19}H_{14}NO_2$ $[M + H]^+$ 288.1025, found 288.1028; IR ($CHCl_3$) ν_{max} 2212, 1717 cm^{-1}.

1-(*p*-Tolyl)-3-(*p*-tolylethynyl)-1*H*-pyrrole-2,5-dione (2l): yellow solid (88 mg, 78%); mp 133−134 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 6H), 6.78 (s, 1H), 7.15−7.32 (m, 6H), 7.51 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 21.7, 78.8, 107.4, 117.9, 125.9, 128.6, 129.4, 129.7, 130.2, 130.8, 132.4, 138.0, 141.1, 166.4, 169.2; ESIMS (m/z) 356 $[M + Na + MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_2$ $[M + H]^+$ 302.1181, found 302.1181; IR ($CHCl_3$) ν_{max} 2212, 1721, 1715 cm^{-1}.

3-((2-Methoxyphenyl)ethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2m): yellow solid (80 mg, 67%); mp 127−129 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (s, 3H), 3.94 (s, 3H), 6.82 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 6.99 (dt, J = 8 and 2 Hz, 1H), 7.20−7.32 (m, 4H), 7.43 (dt, J = 8 and 2 Hz, 1H), 7.57 (dd, J = 8 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 55.9, 83.1, 103.9, 110.3, 110.8, 120.6, 126.0, 128.6, 129.7, 130.1, 130.9, 132.2, 134.3, 138.0, 160.7, 166.4, 169.3; ESIMS (m/z) 372 $[M + Na + MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_3$ $[M + H]^+$ 318.1130, found 318.1119; IR ($CHCl_3$) ν_{max} 2359, 1717 cm^{-1}.

3-((4-Methoxyphenyl)ethynyl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (2n): yellow solid (86 mg, 72%); mp 140−141 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3H), 3.85 (s, 3H), 6.75 (s, 1H), 6.87−6.95 (m, 2H), 7.17−7.32 (m, 4H), 7.50−7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.1, 55.4, 78.8, 107.8, 113.0, 114.3, 126.0, 128.7, 129.4, 129.7, 131.0, 134.3, 138.0, 161.3, 166.5, 169.4; ESIMS (m/z) 372 $[M + Na + MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{16}NO_3$ $[M + H]^+$ 318.1130, found 318.1131; IR ($CHCl_3$) ν_{max} 2212, 1721, 1715 cm^{-1}.

3-(Hex-1-yn-1-yl)-1-phenyl-1*H*-pyrrole-2,5-dione (2o): yellow solid (91 mg, 91%); mp 67−68 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, J = 8 Hz, 3H), 1.37−1.73 (m, 4H), 2.55 (t, J = 8 Hz, 2H), 6.68 (s, 1H), 7.30−7.53 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 19.9, 22.0, 29.9, 70.8, 110.5, 126.0, 127.9, 129.1, 130.5, 131.3, 131.5, 166.5, 169.3; HRMS (ESI) calcd for $C_{16}H_{16}NO_2$ $[M + H]^+$ 254.1181, found 254.1182; IR ($CHCl_3$) ν_{max} 2231, 1719 cm^{-1}.

1-Benzyl-3-(hex-1-yn-1-yl)-1*H*-pyrrole-2,5-dione (2p): thick oil (86 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 8 Hz, 3H), 1.45 (sextet, J = 8 Hz, 2H), 1.60 (quintet, J = 8 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 4.67 (s, 2H), 6.53 (s, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 19.8, 21.9, 29.9, 41.8, 70.9, 109.8, 127.8, 128.4, 128.6, 130.6, 131.4, 136.0, 167.4, 170.1; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$ 268.1338, found 268.1328; IR ($CHCl_3$) ν_{max} 2228, 1773, 1714 cm^{-1}.

1-Methyl-3-(phenylethynyl)-1*H*-pyrrole-2,5-dione (2q): yellow solid (90 mg, 81%); mp 74−75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.07 (s, 3H), 6.70 (s, 1H), 7.35−7.48 (m, 3H), 7.59 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 79.0, 106.3, 121.1, 128.6, 130.3, 130.8, 131.0, 132.4, 167.5, 170.3; HRMS (ESI) calcd for $C_{13}H_{10}NO_2$ $[M + H]^+$ 212.0712, found 212.0711; IR ($CHCl_3$) ν_{max} 2200, 1775, 1713 cm^{-1}.

Methyl 3-(3-(hex-1-yn-1-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoate (2r): thick oil (74 mg, 74%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J = 8 Hz, 3H), 1.35−1.75 (m, 4H), 2.52 (t, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 3.68 (s, 3H), 3.84 (t, J = 8 Hz, 2H), 6.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 19.9, 22.0, 30.0, 32.6, 34.0, 51.9, 70.8, 110.0, 130.6, 131.6, 167.3, 170.0, 171.0; HRMS (ESI) calcd for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1236, found 264.1238; IR ($CHCl_3$) ν_{max} 2220, 1775, 1734, 1716 cm^{-1}.

General Procedure for Hydrogenation of Alkynylmaleimides (2b,d,f,h) to Alkenylmaleimides (3b,d,f,h). To a solution of alkynylmaleimide **2** (0.10 mmol) in CH_3CN or acetone (2 mL)

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were added quinoline (19.4 mg, 0.15 mmol) and Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was then stirred at 25 °C under balloon pressure hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether−ethyl acetate as an eluent to yield the desired (*Z*)-alkene **3**. All the reactions were performed using alkynylmaleimides **2b,d,f,h** (0.10 mmol) to obtain the desired products **3b,d,f,h**.

(*Z*)-3-(Hex-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3b): yellow solid (17 mg, 63%); mp 81−83 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (t, J = 8 Hz, 3H), 1.25−1.75 (m, 4H), 2.40 (s, 3H), 2.40 (t, J = 8 Hz, 2H), 6.30−6.50 (m, 2H), 6.57 (s, 1H), 7.17−7.35 (m, 4H); ^{1}H NMR (benzene-d_6, 400 MHz) δ 0.80 (t, J = 8 Hz, 3H), 1.05−1.20 (m, 4H), 1.80−1.90 (m, 2H), 2.05 (s, 3H), 5.82 (dt, J = 12 and 8 Hz, 1H), 6.08 (s, 1H), 6.36 (d, J = 12 Hz, 1H), 6.98 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 21.1, 22.5, 30.5, 30.9, 115.5, 123.9, 125.9, 128.8, 129.7, 137.7, 140.7, 147.5, 170.4, 170.5; ^{13}C NMR (benzene-d_6, 125 MHz) δ 14.0, 20.9, 22.5, 30.4, 31.0, 115.9, 124.1, 125.9, 129.6, 130.0, 137.1, 140.3, 146.4, 169.8, 170.3; ESIMS (m/z) 292 $[M + Na]^+$; HRMS (ESI) calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1494, found 270.1507; IR ($CHCl_3$) ν_{max} 1777, 1714, 1620 cm^{-1}.

(*Z*)-3-(Dec-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3d): yellow solid (20 mg, 61%); mp 77−78 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82 (t, J = 8 Hz, 3H), 1.21 (br s, 10H), 1.40−1.60 (m, 2H), 2.20−2.40 (m, 2H), 2.31 (s, 3H), 6.20−6.40 (m, 2H), 6.48 (s, 1H), 7.10−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.6, 28.8, 29.2, 29.36, 29.42, 30.9, 31.8, 115.5, 124.0, 125.9, 128.8, 129.7, 137.8, 140.8, 147.6, 170.49, 170.54; ESIMS (m/z) 380 [M + Na + MeOH]$^+$; HRMS (ESI) calcd for $C_{21}H_{28}NO_2$ $[M + H]^+$ 326.2120, found 326.2121; IR ($CHCl_3$) ν_{max} 1709, 1621 cm^{-1}.

(*Z*)-3-(Hexadec-1-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (3f): yellow solid (27 mg, 65%); mp 76−77 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (br s, 22H), 1.45−1.65 (m, 2H), 2.30−2.45 (m, 2H), 2.38 (s, 3H), 6.27−6.45 (m, 2H), 6.55 (s, 1H), 7.17−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.1, 22.7, 28.8, 29.3, 29.4, 29.5, 29.6, 29.7 (5 carbons), 30.9, 31.9, 115.5, 124.0, 125.9, 128.8, 129.7, 137.8, 140.8, 147.6, 170.5, 170.6; ESIMS (m/z) 464 [M + Na + MeOH]$^+$; HRMS (ESI) calcd for $C_{27}H_{40}NO_2$ $[M + H]^+$ 410.3059, found 410.3052; IR ($CHCl_3$) ν_{max} 1712, 1625 cm^{-1}.

(*Z*)-1-(*p*-Tolyl)-3-(4,8,12-trimethyltridec-1-en-1-yl)-1*H*-pyrrole-2,5-dione (3h, diastereomeric mixture): thick oil (27 mg, 66%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.75−1.45 (m, 24H), 1.45−1.60 (m, 1H), 1.65−1.75 (m, 1H), 2.15−2.30 (m, 1H), 2.30−2.40 (m, 2H), 2.38 (s, 3H), 6.35−6.48 (m, 2H), 6.57 (s, 1H), 7.20−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 19.6, 19.7, 19.8, 21.1, 22.6, 22.7, 24.5, 24.8, 28.0, 29.4, 29.7, 31.9, 32.7, 33.3, 37.2, 37.4, 38.2, 38.3, 39.3, 116.1, 124.0, 125.9, 128.9, 129.7, 137.8, 140.8, 146.6, 170.5, 170.6; ESIMS (m/z) 464 [M + Na + MeOH]$^+$; HRMS (ESI) calcd for $C_{27}H_{40}NO_2$ $[M + H]^+$ 410.3059, found 410.3061; IR ($CHCl_3$) ν_{max} 1712, 1604 cm^{-1}.

General Procedure for Hydrogenation of Alkynylmaleimides (2b,d,f,h) to Alkylmaleimides (4b,d,f,h). *Method A.* To a solution of alkynylmaleimide **2** (0.10 mmol) in methanol (2 mL) were added quinoline (19.4 mg, 0.15 mmol) and palladium on activated charcoal (5 mg, 10 wt %). The reaction mixture was then stirred at 25 °C under balloon pressure hydrogen atmosphere for 1.5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether−ethyl acetate as an eluent to yield the desired monoalkyl-substituted maleimide **4**.

Method B. To a solution of alkynylmaleimide **2** (0.10 mmol) in methanol (2 mL) plus acetone (2 mL) were added quinoline (13 mg, 0.10 mmol) and Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was then stirred at 25 °C under balloon pressure hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether−ethyl acetate as an eluent to yield the desired monoalkyl-substituted maleimide **4**. All of the reactions were performed using alkynylmaleimides **2b,d,f** (0.10 mmol) to obtain the desired products **4b,d,f**. For the preparation of natural product precursor **4h** the reaction was performed using a 1.00 mmol scale of **2h**.

3-Hexyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4b):.[21] yellow solid (19 mg, 68%); mp 70−72 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.25−1.52 (m, 6H), 1.65 (quintet, J = 6 Hz, 2H), 2.38 (s, 3H), 2.51 (dt, J = 8 and 2 Hz, 2H), 6.41 (t, J = 2 Hz, 1H), 7.15−7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.5, 25.5, 27.0, 28.9, 31.4, 125.9, 126.2, 128.9, 129.7, 137.7, 150.3, 169.9, 170.6; ESIMS (m/z) 294 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1713, 1637 cm^{-1}.

3-Decyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4d):.[21] yellow solid (23 mg, 70%); mp 60−61 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 6 Hz, 3H), 1.26 (br s, 14H), 1.63 (quintet, J = 8 Hz, 2H), 2.36 (s, 3H), 2.49 (dt, J = 8 and 2 Hz, 2H), 6.40 (t, J = 2 Hz, 1H), 7.10−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 25.5, 27.1, 29.21, 29.24, 29.27, 29.46, 29.54, 31.9, 125.9, 126.3, 129.0, 129.7, 137.7, 150.3, 169.9, 170.6; ESIMS (m/z) 350 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1713, 1675 cm^{-1}.

3-Hexadecyl-1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (4f): yellow solid (31 mg, 75%); mp 66−67 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 8 Hz, 3H), 1.25 (br s, 26H), 1.63 (quintet, J = 8 Hz, 2H), 2.36 (s, 3H), 2.49 (dt, J = 8 and 2 Hz, 2H), 6.39 (t, J = 2 Hz, 1H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 21.1, 22.7, 25.5, 27.1, 29.3, 29.4, 29.5, 29.7 (8 carbons), 31.9, 125.9, 126.3, 128.9, 129.7, 137.7, 150.3, 170.0, 170.5; ESIMS (m/z) 444 [M + H +MeOH]$^+$; HRMS (ESI) calcd for $C_{27}H_{42}NO_2$ $[M + H]^+$ 412.3216, found 412.3213; IR ($CHCl_3$) ν_{max} 1713, 1635 cm^{-1}.

1-(*p*-Tolyl)-3-(4,8,12-trimethyltridecyl)-1*H*-pyrrole-2,5-dione (4h, Diastereomeric Mixture): thick oil (290 mg, 70%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80−0.93 (m, 12H), 0.95−1.75 (m, 19H), 2.36 (s, 3H), 2.48 (dt, J = 8 and 2 Hz, 2H), 6.40 (t, J = 2 Hz, 1H), 7.15−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.5, 19.55, 19.64, 19.7, 21.1, 22.6, 22.7, 24.4, 24.7, 24.8, 25.8, 28.0, 32.5, 32.8, 36.55, 36.64, 37.2, 37.4, 39.3, 125.9, 126.3, 128.9, 129.7, 137.6, 150.3, 169.9, 170.6; ESIMS (m/z) 434 $[M + Na]^+$; HRMS (ESI) calcd for $C_{27}H_{42}NO_2$ $[M + H]^+$ 412.3216, found 412.3216; IR ($CHCl_3$) ν_{max} 1710, 1635 cm^{-1}.

3-Hexyl-1-(*p*-tolyl)pyrrolidine-2,5-dione (5b). *Method A.* To a solution of alkynylmaleimide **2b** (27 mg, 0.10 mmol) in ethyl acetate (2 mL) was added palladium on activated charcoal (5 mg, 10 wt %). The reaction mixture was stirred at 25 °C under balloon pressure hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo, and the obtained residue was purified by silica gel flash column chromatography using petroleum ether−ethyl acetate (85:15) as an eluent to yield **5b**[50] as a white solid (21 mg, 78% yield).

Method B. To a solution of alkynylmaleimide **2b** (27 mg, 0.10 mmol) in methanol (2 mL) was added Lindlar catalyst (10 mg, 5 wt %). The reaction mixture was stirred at 25 °C under balloon pressure hydrogen atmosphere for 5 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (20 mL). The resulting solution was concentrated in vacuo and the obtained residue was purified by silica gel flash column chromatography using petroleum ether−ethyl acetate (85:15) as an eluent to yield **5b** as a white solid (20 mg, 74% yield): mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.20−1.55 (m, 8H), 1.55−1.75 (m, 1H), 1.90−2.10 (m, 1H), 2.39 (s, 3H), 2.45−2.72 (m, 1H), 2.87−3.10 (m, 2H), 7.16 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 21.1, 22.5, 26.5, 28.9, 31.4, 31.5, 34.4, 39.9, 126.2, 129.2, 129.7, 138.5, 175.8, 179.1; ESIMS (m/z) 296 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1705 cm^{-1}.

3-(4,8,12-Trimethyltridecyl)furan-2,5-dione (6, Diastereomeric Mixture). To a stirred solution of monoalkylmaleimide **4h** (1.20 g, 2.92 mmol) in THF (6 mL) was added 5% aq LiOH (3 mL) solution in a dropwise manner. The reaction mixture was stirred at 25

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°C for 48 h. The reaction mixture was acidified with 10% aq HCl (3 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue without any further purification was heated at 100 °C in acetic anhydride (10 mL) for 5 h. The acetic anhydride was distilled off in vacuo, and the obtained residue was purified by silica gel column chromatography using petroleum ether−ethyl acetate (9:1) as an eluent to yield the desired anhydride **6** as thick liquid (580 mg, 62% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80−0.93 (m, 12H), 1.00−1.80 (m, 19H), 2.51 (dt, J = 8 and 2 Hz, 2H), 6.60 (t, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 19.5, 19.6, 19.7, 22.6, 22.7, 24.4, 24.5, 24.8, 26.2, 28.0, 32.5, 32.7, 36.4, 36.5, 37.1, 37.15, 37.24, 37.29, 37.33, 39.3, 128.4, 153.8, 164.0, 165.9; ESIMS (m/z) 377 $[M + Na + MeOH]^+$; HRMS (ESI) calcd for $C_{20}H_{35}O_3$ $[M + H]^+$ 323.2586, found 323.2585; IR ($CHCl_3$) ν_{max} 1842, 1777, 1707, 1642 cm^{-1}.

4-(4,8,12-Trimethyltridecyl)furan-2(5*H*)-one (Luffarin X, 7, Diastereomeric Mixture). To a stirred solution of alkylmaleic anhydride **6** (50 mg, 0.15 mmol) in dry THF (3 mL) at 0 °C was added $NaBH_4$ (6.84 mg, 0.18 mmol) in three equal portions over a period of 10 min. The reaction mixture was allowed to reach room temperature (25 °C) and further stirred for 2 h. It was then quenched with dilute HCl (2 N, 3 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether−ethyl acetate (9:1) as an eluent to yield the desired product **7**[46] as a thick oil (41 mg, 86% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80−0.95 (m, 12H), 1.00−1.75 (m, 19H), 2.40 (t, J = 8 Hz, 2H), 4.75 (d, J = 2 Hz, 2H), 5.85 (t, J = 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 19.5, 19.6, 19.7, 22.6, 22.7, 24.4, 24.7, 27.9, 28.8, 32.5, 32.7, 36.5, 36.6, 37.1, 37.16, 37.19, 37.25, 37.29, 39.3, 73.0, 115.3, 170.6, 174.1; ESIMS (m/z) 331 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 1782, 1751, 1640 cm^{-1}.

5-Hydroxy-4-(4,8,12-trimethyltridecyl)furan-2(5*H*)-one (Cacospongionolide C, 8, Diastereomeric Mixture). To a stirred solution of alkylmaleic anhydride **6** (50 mg, 0.15 mmol) in dry THF (3 mL) at −20 °C was added DIBAL-H or *N*-Selectride (1 M in THF, 0.18 mL, 0.18 mmol) in a dropwise manner over 10 min. The reaction mixture was stirred at −20 °C for 1 h and then at 25 °C for 1 h. It was then quenched with water (3 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The obtained residue was purified by silica gel column chromatography using petroleum ether−ethyl acetate (8:2) to give desired product **8**[47] as a thick oil (37 mg, 74%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80−0.93 (m, 12H), 0.95−1.75 (m, 19H), 2.20−2.60 (m, 2H), 5.39 (br s, 1H), 5.83 (s, 1H), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.44, 19.50, 19.53, 19.6, 19.7, 22.6, 22.7, 24.2, 24.4, 24.8, 27.9, 28.0, 32.5, 32.8, 36.6, 36.7, 37.3, 37.4, 39.3, 99.2, 117.2, 170.4, 172.0; ESIMS (m/z) 347 $[M + Na]^+$; IR ($CHCl_3$) ν_{max} 3363, 1759, 1747, 1652 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **2a−r**, **3b,d,f,h**, **4b,d,f,h**, **5b**, and **6−8** and NOE of **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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