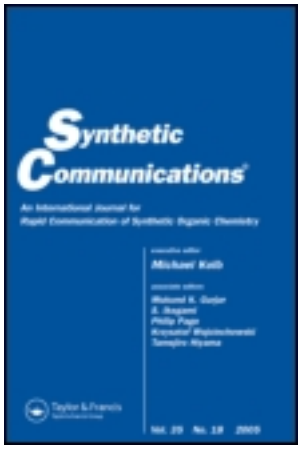

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Synthesis and Characterization of Novel Acyclic Enediynes

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SYNTHESIS AND CHARACTERIZATION OF NOVEL ACYCLIC ENEDIYNES

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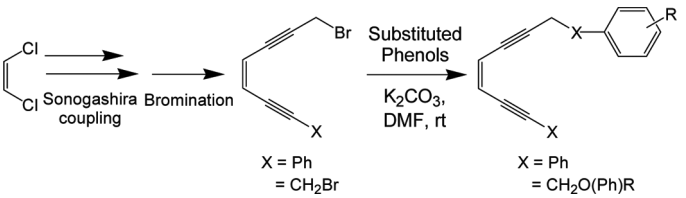
GRAPHICAL ABSTRACT



Abstract *A novel group of symmetrical and asymmetrical acyclic enediynes has been synthesized by using Sonogashira coupling conditions and characterized spectroscopically.*

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Keywords Acyclic enediynes; Bergman cyclization; Sonogashira coupling

INTRODUCTION

Ever since the initial reports of enediyne anticancer antibiotics in the late 1980s, researchers from a number of disciplines have been devoting increasing attention to their chemistry, biology, and potential medical applications. Origins of enediynes have come from various marine and terrestrial plant sources, and they are a potent class of antitumor and antimicrobial agents and high cytotoxic activity. Natural product enediynes (viz., calichemicin,[1] esperamicins,[2] dynemicin,[3] neocarzinostatin,[4] kedarcidin,[5] uncialamycin,[6] etc.) are known for spectacular biological profiles and proven clinical efficacy.[7,8] The antitumor activity of these compounds is due to the presence of the highly unsaturated 1,5-diyne-3-ene unit, which undergoes Bergman cyclization (BC) under physiological conditions to generate a benzene-1,4-diradical intermediate. This radical intermediate abstracts hydrogen atom from the DNA backbone and causes cell death.[9,10] To control BC, different approaches have been explored and used.[11–14] Furthermore, recent studies revealed that even thermally stable enediynes exert biological activities,[15] which indicates that enediynes can

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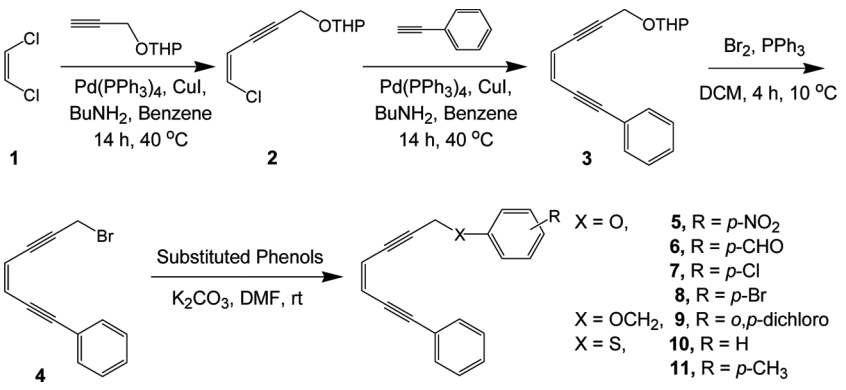
have potential in the treatment of many infectious diseases apart from their role in anticancer drug discovery.[16,17] Therefore, the aim is to synthesize enediynes and evaluate their biological activities. To this end, we have already explored the synthesis and biological activity of enediynes,[18,19] and this article deals with the syntheses and characterization of novel groups of O-, N-, and S-substituted symmetrical and asymmetrical acyclic enediynes.

RESULTS AND DISCUSSION

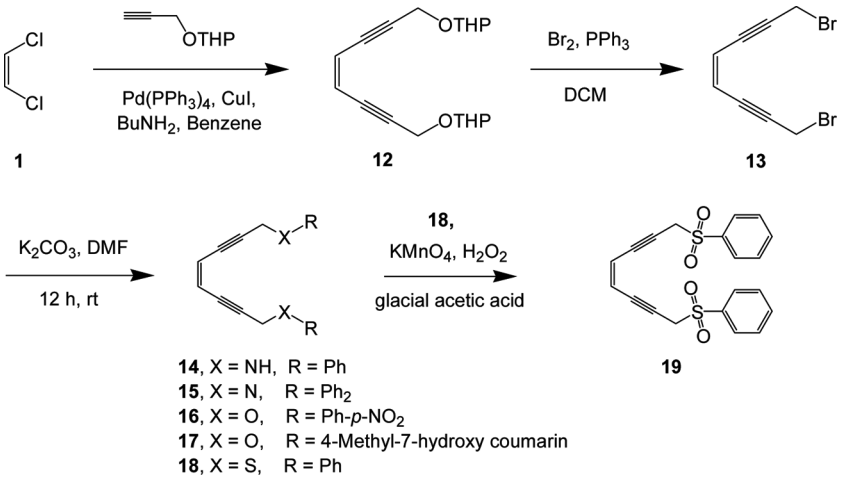
Intermediate (7-bromohept-3-ene-1,5-diynyl)benzene (**4**) was synthesized using two standard Sonogashira coupling reactions followed by bromination of 2-(7-phenylhept-4-ene-2,6-diynyloxy)tetrahydropyran **3**[20] in the presence of PPh_3/Br_2. Then intermediate **4** (1.0 equiv) reacted with various substituted phenol derivatives (1.0 equiv), in the presence of K_2CO_3 (dry, 5.0 equiv) and dimethylformamide (DMF) (dry) as a solvent, leading to the formation of asymmetrical acyclic enediynes (**5–11**, Scheme 1).

At the same time intermediate 1,8-dibromo-oct-4-ene-2,6-diyne (**13**)[21] was synthesized by using one standard Sonogashira coupling reaction followed by bromination in the presence of PPh_3/Br_2. Intermediate **13** (1.0 equiv) reacted with various substituted phenol, thiophenol, and aromatic amines (2.1 equiv) in the presence of K_2CO_3 (dry, 10.0 equiv) and DMF (dry) as a solvent, leading to the formation of symmetrical acyclic enediynes (**14–18**, Scheme 2). Oxidation of 1,1′-[(4Z)-oct-4-ene-2,6-diyne-1,8-diylbis(thio)]dibenzene (**18**, 1.0 equiv) in the presence of $KMnO_4$ (4.0 equiv), 2 mL of H_2O_2 (30%), and glacial acetic acid as a solvent led to the formation of 1,1′-[(4Z)-oct-4-ene-2,6-diyne-1,8-diyldisulfonyl]dibenzene (**19**, Scheme 4). The overall yields of all the enediynes are very good to excellent.

These all enediynes were characterized spectroscopically. Asymmetrical acyclic enediyne 1-nitro-4-(7-phenylhept-4-ene-2,6-diynyloxy) benzene (**5**) shows six signals in the ^1H NMR spectrum. The peak appears at δ 5.01 as a singlet and was assigned to two -OCH_2 proton, whereas the peaks at δ 5.86 (J = 10.8 Hz) and δ 6.09 (J = 10.8 Hz) as doublets were assigned to two vinylic protons. The aromatic peak



Scheme 1. Synthesis of asymmetrical enediynes.



Scheme 2. Synthesis of symmetrical enediynes.

downfield at δ 7.29–7.33 as a multiplet was assigned to acetylenic linked aryl five protons, whereas peaks at δ 7.05 ($J = 9.0$ Hz) and δ 8.08 ($J = 9.0$ Hz) as doublets were assigned to two set of protons (2H each) attached to the nitrobenzene ring. The ^{13}C NMR spectrum of enediynes **5** showed 15 signals in the spectrum. Asymmetry in the enediyne can be easily seen for all the four acetylenic carbon atoms separately, at δ 85.72, 86.40, 90.03, and 97.78, whereas peak at δ 57.16 was assigned to the OCH_2 carbon. The peaks at δ 128.41, 128.99 were assigned to two asymmetric alkene carbon atoms. All the aromatic carbons at δ 115.00, 117.85, 121.57, 122.57, and 131.65, whereas the peaks appeared at δ 125.83, 142.20, and 162.55 were assigned to three quaternary carbon atoms. On the other hand symmetrical acyclic enediyne 1,1′-[(4Z)-oct-4-ene-2,6-diyne-1,8-diylbis(oxy)]bis(4-nitrobenzene) (**16**) shows only four signals in the ^{1}H NMR spectrum. The peak at δ 4.98 as a singlet was assigned to four protons of -OCH_2, whereas peak the at δ 5.90 as a singlet was assigned to two symmetrical alkene protons. The two sets of aromatic protons (4H each) appeared at δ 7.07 and 8.23 as a doublet each. The ^{13}C NMR spectrum of enediyne **16** showed eight signals in the spectrum. The peaks at δ 84.88 and 90.25 were assigned to the two set of acetylenic carbon atoms, while peak appear at δ 56.88 was assigned for two symmetrical -OCH_2 carbon atoms. The peak at δ 125.77 was assigned to two symmetric alkene carbon atoms. The peaks at δ 114.98, 119.91 were assigned to two sets of phenyl carbon atoms, whereas the peaks at δ 142.07 and 162.34 were assigned to two sets of quaternary carbon atoms.

EXPERIMENTAL

All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and were used as such. Thin-layer chromatography (TLC) was used to monitor the progress of the reactions. All of the compounds were purified over a silica-gel column (60–120 mesh). Solvents were distilled prior to use. Melting points (mp) were

determined on a Glassco melting-point apparatus (Cat. No. 514.303.01). Infrared Infrared (IR) (KBr) spectra were recorded using a Perkin-Elmer Fourier transform (FT)–IR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a Jeol (Japan) JMS-DX303 and micromass LCT, mass spectrometer/data system. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Spectrospin spectrometer at 300 and 75.5 MHz, tetramethylsilane respectively using (TMS) as an internal standard. The chemical shift values are recorded on δ (ppm) scale and the coupling constants (*J*) are in hertz (Hz). Elemental analysis for all compounds were performed on a Carlo Erba model EA-1108 elemental analyzer and data of C, H, and N are within ±0.4% of calculated values. Differential scanning calorimetry (DSC) traces were recorded on a Pyris 6 differential scanning calorimeter of Perkin-Elmer as a peak value at a heating rate of 10 °C min^{-1}.

General Procedure for the Synthesis of Compounds 2 and 12

2-Prop-2-ynyloxy-tetrahydro-pyran (1.0 equiv) was added dropwise to a stirred solution of $Pd(PPh_3)_4$ (0.04 equiv), CuI (0.02 equiv), and *n*-butylamine (5.0 equiv) in benzene at 40 °C. Then, *cis*-dichloroethylene (**1**, 1.0/0.5 equiv) was added to the reaction mixture after 15 min, and the reaction mixture continued to stir for 13 h at the same temperature. The progress of the reaction was monitored by TLC. The excess solvent was evaporated under vacuo. Residue was purified over SiO_2 column using ethyl acetate/hexane as an eluent.

2-(5-Chloro-pent-4-en-2-ynyloxy)-tetrahydro-pyran (2).[22] Yellow liquid; yield 60%; IR (KBr, cm^{-1}): 2933, 2852, 2207, 1428, 1341, 1195, 1062, 1019. ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (d, $J = 10.3$ Hz, 1H), 5.85 (d, $J = 10.3$ Hz, 1H), 4.81–4.78 (t, $J = 3.4$ Hz, 1H), 4.37 (s, 2H), 3.80–3.74 (m, 1H), 3.48–3.44 (m, 1H), 1.70–1.35 (m, 6H); MS *m/z* (%) 202 (M + 2, 31), 200 (M+, 99), 117 (48), 115 (13).

1,8-Bis-(tetrahydropyran-2-yloxy)-oct-4-ene-2,6-diyne (12).[21] Yellow liquid; yield 62%; DSC 151.57 °C; (peak value); IR (KBr, cm^{-1}): 2942, 2870, 2210, 1440, 1389, 1344, 1201, 1119, 1078, 1023. ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (s, 2H), 4.88–4.86 (t, $J = 3.4$ Hz, 2H), 4.45 (s, 4H), 3.88–3.81 (m, 2H), 3.56–3.52 (m, 2H) 1.85–1.42 (m, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 119.00 (C=C), 96.30 (C≡C), 92.60 (C≡C), 82.60 (O−C−O), 61.60 (O−CH_2), 54.30 (O−CH_2), 30.00 (−CH_2), 25.10 (−CH_2), 18.60 (−CH_2); MS *m/z* (%) 304 (M+, 100), 136 (56), 104 (32).

Synthesis of 2-(7-Phenyl-hept-4-ene-2,6-diynyloxy)-tetrahydro-pyran (3)[20]

Phenylacetylene (1.1 equiv) was added dropwise to a stirred solution of $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.02 equiv), and *n*-butylamine (5.0 equiv) in benzene (40 mL) at 40 °C. Then 2-(5-chloro-pent-4-en-2-ynyloxy)-tetrahydro-pyran (**2**, 1.0 equiv) was added to the reaction mixture after 15 min, and the reaction mixture was stirred for 13 h at the same temperature. The progress of the reaction was monitored by TLC. The excess solvent was evaporated in vacuo. Residue was purified over an SiO_2 column using ethyl acetate/hexane as an eluent. Yellow oil; yield

70%; DSC: 158.56 °C (peak value); IR (KBr, cm^{-1}): 3054, 2943, 2852, 2190, 1598, 1489, 1441, 1344, 1201, 1116, 1054, 1023.^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50–7.46 (m, 2H), 7.33–7.30 (m, 3H), 6.06 (d, 1H, $J = 10.8$ Hz), 5.91 (d, 1H, $J = 10.8$ Hz), 4.92–4.90 (t, $J = 3.3$ Hz, 1H), 4.50 (s, 2H), 3.87–3.80 (m, 1H), 3.54–3.50 (m, 1H), 1.73–1.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 131.72 (C_{quart}), 128.51 (C=C), 128.23 (C=C), 122.90 (C_{Ar}), 119.82 (C_{Ar}), 118.94 (C_{Ar}), 96.67 (C≡C), 94.67 (C≡C), 93.39 (C≡C), 86.81 (C≡C), 83.33 (O−C−O), 54.70 ($-CH_2O$), 30.63 ($-OCH_2$), 30.29 ($-CH_2$), 25.40 ($-CH_2$), 25.33($-CH_2$); MS m/z (%) 266 (M+, 99), 190 (22), 182 (29), 166 (54), 106 (21).

Synthesis of (7-Bromohept-3-ene-1,5-diynyl)benzene (4)

PPh_3 (1.6 equiv) was added to a mixture of 2-(7-phenylhept-4-ene-2,6-diynyloxy)tetrahydropyran (**3**) in dichloromethane (40 mL) and stirred for 10 min. Then the reaction mixture was cooled to 10 °C, followed by the slow addition of bromine (1.6 equiv) for 20 min. Then the reaction was allowed to stir at 10 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, excess solvent was removed under high vacuum. Then the crude mixture was washed several times with cold hexane. The solvent was removed again under high vacuum. Then the crude mixture was purified using SiO_2 column chromatography with 5% ethyl acetate/hexane as an eluent. Yellow liquid; yield 98%; IR (KBr, cm^{-1}): 2952, 2878, 2209; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.34–7.32 (m, 3H), 6.10 (d, $J = 10.8$ Hz, 1H), 5.91 (d, $J = 10.8$ Hz, 1H), 4.16 (s, 2H); MS m/z (%) 246, 244 (M^+, 70, 100), 166 (45).

General Procedure for the Syntheses of Asymmetrical Acyclic Enediynes (5–11)

A solution of (7-bromohept-3-ene-1,5-diynyl)benzene (**4**) (1.0 equiv) in 5 mL DMF to a stirred solution of substituted phenols (1.0 equiv), K_2CO_3 (5.0 equiv) in dry DMF (20 mL), was added dropwise. The reaction mixture was stirred at ambient temperature for 13 h under a nitrogen atmosphere. The reaction mixture was extracted with $CHCl_3$ (6×25 mL), and the combined organic layer was washed with water (6×250 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under high vacuum. The crude product was purified over SiO_2 column using ethyl acetate/hexane as an eluent.

1-Nitro-4-(7-phenylhept-4-ene-2,6-diynyloxy)benzene (5). Yellow solid powder; yield 90%; mp 74–78 °C; DSC 134.39 °C (peak value); IR (KBr, cm^{-1}): 3081, 2924, 2190, 1592, 1513, 1494, 1342, 1262, 1228, 1111, 1005; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, $J = 8.9$ Hz, 2H), 7.32–7.26 (m, 5H), 7.08 (d, $J = 8.9$ Hz, 2H), 6.13 (d, $J = 10.8$ Hz, 1H), 5.89 (d, $J = 10.8$ Hz, 1H), 5.01 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.55 (C_{quart}), 142.00 (C_{quart}), 131.65 (C_{Ar}), 128.99 (C=C), 128.41 (C=C), 125.83 (C_{Ar}), 122.57 (C_{Ar}), 121.57 (C_{Ar}), 117.85 (C_{Ar}), 115.00 (C_{quart}), 97.78 (C≡C), 90.03 (C≡C), 86.40 (C≡C), 85.72 (C≡C), 57.16 ($-CH_2$); MS m/z (%) 303 (M^+, 100), 258 (32), 182 (27), 166 (35). Anal. calcd. for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62; O, 15.82. Found: C, 75.29; H, 4.34; N, 4.58.

4-(7-Phenylhept-4-ene-2,6-diynyloxy)benzaldehyde (6). Yellow liquid; yield 77%; DSC 138.52 °C (peak value); IR (KBr, cm^{-1}): 3052, 2922, 2851, 2194, 1693, 1599, 1507, 1222, 1161, 1007; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 2H), 7.35–7.26 (m, 5H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.12 (d, $J = 10.8$ Hz, 1H), 5.90 (d, $J = 10.8$ Hz, 1H), 5.01 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.73 (CHO), 162.49 (C_{quart}), 131.82 (C_{Ar}), 131.64 (C_{Ar}), 130.30 (C_{quart}), 128.76 (C=C), 128.29 (C=C), 122.00 (C_{quart}), 121.14 (C_{Ar}), 117.92 (C_{Ar}), 115.10 (C_{Ar}), 97.56 (C≡C), 90.50 (C≡C), 86.41 (C≡C), 85.23 (C≡C), 56.69 ($-CH_2$); MS m/z (%) 286 (M^+, 100), 258 (54), 182 (21), 166 (28). Anal. calcd. for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93; O, 11.18. Found: C, 83.87; H, 4.99.

1-Chloro-4-(7-phenylhept-4-ene-2,6-diynyloxy)benzene (7). Yellow liquid; yield 85%; IR (KBr, cm^{-1}): 3055, 2919, 2865, 2191, 1596, 1489, 1288, 1220, 1171, 1093, 1008; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H), 7.19 (d, $J = 9.0$ Hz, 2H), 6.95 (d, $J = 9.0$ Hz, 2H), 6.09 (d, $J = 10.8$ Hz, 1H), 5.89 (d, $J = 10.8$ Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.14 (C_{quart}), 131.63 (C_{Ar}), 129.20 (C=C), 128.67 (C_{Ar}), 128.24 (C=C), 126.13 (C_{quart}), 122.54 (C_{quart}), 120.71 (C_{Ar}), 118.08 (C_{Ar}), 116.08 (C_{Ar}), 97.45 (C≡C), 91.33 (C≡C), 86.52 (C≡C), 84.73 (C≡C), 56.67 ($-CH_2$); MS m/z (%) 295, 292 (M^+, 88, 100), 258 (41), 182 (30), 166 (44). Anal. calcd. for $C_{19}H_{13}ClO$: C, 77.95; H, 4.48; Cl, 12.11; O, 5.47. Found: C, 77.99; H, 4.45.

1-Bromo-4-(7-phenylhept-4-ene-2,6-diynyloxy)benzene (8). Yellow liquid; yield 85%; IR (KBr, cm^{-1}): 3055, 2921, 2851, 2190, 1579, 1487, 1287, 1221, 1173, 1072, 1014; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 7H), 6.91 (m, $J = 8.6$ Hz, 2H), 6.10 (d, $J = 10.8$ Hz, 1H), 5.89 (d, $J = 10.8$ Hz, 1H), 4.89 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.79 (C_{quart}), 132.41 (C_{quart}), 132.27 (C_{Ar}) 131.75 (C_{Ar}), 128.77 (C=C), 128.36 (C=C), 122.68 (C_{quart}), 120.89 (C_{Ar}), 118.15 (C_{Ar}), 116.73 (C_{Ar}), 113.67 (C_{Ar}), 97.53 (C≡C), 91.23 (C≡C), 86.51 (C≡C), 84.86 (C≡C), 56.78 ($-CH_2$); MS m/z (%) 339, 337 (M^+, 94, 100), 258 (32), 182 (18), 166 (38). Anal. Calcd. for $C_{19}H_{13}BrO$: C, 67.67; H, 3.89; Br, 23.70; O, 4.74. Found: C, 67.63; H, 3.93.

2,4-Dichloro-1-(7-phenylhept-4-ene-2,6-diynyloxymethyl)benzene (9). Dark brown liquid; yield 79%; IR (KBr, cm^{-1}): 3057, 2921, 2851, 2191, 1582, 1478, 1439, 1024; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.16 (m, 8H), 6.11 (d, $J = 10.8$ Hz, 1H), 5.93 (d, $J = 10.8$ Hz, 1H), 4.71 (s, 2H), 4.49 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 151.28 (C_{quart}), 150.99 (C_{quart}), 131.63 (C_{Ar}), 128.60 (C_{quart}) 128.26 (C=C), 128.21 (C=C), 126.93 (C_{Ar}), 122.68 (C_{quart}), 120.26 (C_{Ar}), 118.52 (C_{Ar}), 97.74 (C≡C), 92.61 (C≡C), 86.68 (C≡C), 84.42 (C≡C), 67.97 ($-CH_2Ph$), 58.60 ($-CH_2$); MS m/z (%) 344, 341 (M^+, 96, 100), 306 (17), 272 (25), 182 (30), 166 (46). Anal. calcd. for $C_{20}H_{14}Cl_2O$: C, 70.40; H, 4.14; Cl, 20.78; O, 4.69. Found: C, 70.43; H, 4.19.

{[(4Z)-7-Phenylhept-4-ene-2,6-diyne-1-yl]thio}benzene (10).[20] Dark brown liquid; yield 75%; IR (KBr, cm^{-1}): 3057, 2921, 2851, 2191, 1582, 1478, 1439, 1024; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.49 (m, 4H), 7.44–7.27 (m, 6H), 5.98 (d, $J = 10.8$ Hz, 1H), 5.83 (d, $J = 10.8$ Hz, 1H), 3.65 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 141.21 (C_{quart}), 132.41 (C_{Ar}), 132.27 (C_{Ar}), 130.75 (C_{Ar}),

128.77 (C=C) 128.36 (C=C), 122.68 (C_{quart}), 120.89 (C_{Ar}), 118.15 (C_{Ar}), 116.73 (C_{Ar}), 113.67 (C_{Ar}), 97.53 (C≡C), 91.23 (C≡C), 86.51 (C≡C), 80.99 (C≡C), 56.78 ($-CH_2$); MS m/z (%) 275 (M^+, 100), 198 (52), 166 (31). Anal. calcd. for $C_{19}H_{14}S$: C, 83.17; H, 5.14; S, 11.69. Found: C, 83.11; H, 5.18.

1-Methyl-4-(7-phenylhept-4-ene-2,6-diynylsulfanyl)benzene (11). Dark brown liquid; yield 66%; IR (KBr, cm^{-1}): 3022, 2920, 2851, 2190, 1597, 1478, 1490, 1232, 1017; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, $J = 8.2$ Hz, 2H), 7.40–7.23 (m, 5H), 7.06 (m, $J = 7.9$ Hz, 2H), 6.03 (d, $J = 10.8$ Hz, 1H), 5.87 (d, $J = 10.8$ Hz, 1H), 3.80 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 136.99 (C_{quart}), 131.67 (C_{Ar}), 131.26 (C_{Ar}), 130.83 (C_{Ar}), 129.57 (C_{Ar}), 128.41 (C=C) 128.12 (C=C), 122.12 (C_{quart}), 119.50 (C_{Ar}), 118.99 (C_{Ar}), 96.78 (C≡C), 93.89 (C≡C), 86.86 (C≡C), 80.90 (C≡C), 53.36 ($-CH_2$); MS m/z (%) 288 (M^+, 99), 274 (59), 198 (52), 166 (31). Anal. calcd. for $C_{20}H_{16}S$: C, 83.29; H, 5.59; S, 11.12. Found: C, 83.33; H, 5.64.

Synthesis of 1,8-Dibromooct-4-ene-2,6-diyne (13)[20]

PPh_3 (1.6 equiv) was added to a stirred solution of 1,8-bis-(tetrahydropyran-2-yloxy)-oct-4-ene-2,6-diyne (**12**, 1.0 equiv) in dichloromethane (40 mL) and stirred for 10 min. Then the reaction mixture was cooled to 10 °C, followed by the slow addition of bromine (1.6 equiv) for 20 min. Then the reaction was allowed to stir at 10 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, excess solvent was removed under high vacuum. Then the crude mixture was washed several times with cold hexane. The solvent was removed again under high vacuum. Then the crude mixture was purified over SiO_2 column chromatography using 5–10% ethyl acetate/hexane as an eluent. Light yellow liquid; yield 82%; IR (KBr, cm^{-1}): 3400, 3051, 2924, 2854, 2211, 2161, 2172, 1602, 1504, 1436, 1314, 1259, 1154, 1059. ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 2H), 4.14 (s, 4H); MS m/z (%) 266 (M + 4, 58), 264 (M + 2, 94), 262 (M+, 37), 104 (29).

General Proceedure for the Synthesis of Symmetrical Acyclic Enediynes (14–18)

A solution of 1,8-dibromooct-4-ene-1,6-diyne (**13**, 1.0 equiv) in 5 mL of DMF was added to a stirred solution of substituted phenols (2.1 equiv) and K_2CO_3 (10.0 equiv) in dry DMF (25 mL), dropwise. The reaction mixture was stirred at ambient temperature for 13 h under nitrogen atmosphere. The reaction mixture was extracted with $CHCl_3$ (6 × 25 mL), and the combined organic layer was washed with water (6 × 250 mL). The organic layer was dried over anhydrous. Na_2SO_4, and the solvent was removed under high vacuum. The crude product was purified over a silica-gel column using 10% ethyl acetate/hexanes as an eluent.

(4Z)-N,N′-Diphenyloct-4-ene-2,6-diyne-1,8-diamine (14). Dark red crystal; yield 85%; mp 128–135 °C; DSC 155.31 °C (peak value); IR (KBr, cm^{-1}): 3400, 3051, 2924, 2854, 2211, 1602, 1504, 1436, 1314, 1259, 1154, 1059; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.15 (m, 4H), 6.77–6.66 (m, 6H), 5.76 (s, 2H), 4.02 (s, 4H), 3.89 (brs, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.81 (C_{quart}), 129.07 (C_{Ar}),

119.28 (C_{Ar}), 118.25 (C=C) 114.89 (C_{Ar}), 113.34 (C_{Ar}), 94.23 (C≡C), 80.05 (C≡C), 53.38 ($-CH_2$); MS m/z (%) 286 (M^+, 100), 134 (39), 104 (19). Anal. calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.91; H, 6.30; N, 9.71.

(4Z)-N,N′-Tetraphenyloct-4-ene-2,6-diyne-1,8-diamine (15). Brown solid; yield 90%; mp 158–163 °C; IR (KBr, cm^{-1}): 2926, 2857, 2208, 1611, 1517, 1448, 1341, 1165, 1042; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.10 (m, 12H), 6.99–6.94 (m, 8H), 5.96 (s, 2H), 4.30 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.98 (C_{quart}), 142.49 (C_{quart}), 129.17 (C_{Ar}), 123.57 (C_{Ar}), 119.28 (C=C) 118.25 (C_{Ar}), 114.99 (C_{Ar}), 113.14 (C_{Ar}), 95.21 (C≡C), 82.05 (C≡C), 54.33 ($-CH_2$); MS m/z (%) 439 (M^+, 100), 286 (35), 134 (39), 104 (19). Anal. calcd. for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.60; H, 5.92; N, 6.33.

1,1′-[(4Z)-Oct-4-ene-2,6-diyne-1,8-diylbis(oxy)]bis(4-nitrobenzene) (16). White solid powder; yield 88%; mp 119–122 °C; IR (KBr, cm^{-1}): 2923, 2123, 1589, 1493, 1339, 1109; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (m, $J = 10.8$ Hz, 4H), 7.07 (m, $J = 10.8$ Hz, 4H), 5.90 (s, 2H), 4.89 (s, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.34 (C_{quart}), 142.07 (C_{quart}), 125.77 (C_{Ar}), 119.91 (C=C), 114.98 (C_{Ar}), 90.25 (C≡C), 84.88 (C≡C), 56.88 ($-CH_2$); MS m/z (%) 378 (M^+, 100), 288 (51), 136 (65), 104 (17). Anal. calcd. for $C_{20}H_{14}N_2O_6$: C, 63.49; H, 3.73; N, 7.40; O, 25.37. Found: C, 63.44; H, 3.70; N, 7.44.

1,1′-[(4Z)-Oct-4-ene-2,6-diyne-1,8-diylbis(oxy-7)]bis(4-methyl-chromen-2-one) (17). Brown solid powder; yield 78%; mp 140–145 °C; IR (KBr, cm^{-1}): 2924, 2854, 2211, 1722, 1612, 1462, 1376, 1278, 1138, 1069, 1013; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J = 8.6$ Hz, 2H), 6.97–6.90 (m, 4H), 6.13 (s, $J = 1.0$ Hz, 2H), 5.90 (s, 2H), 4.92 (s, 4H), 2.39 (d, $J = 1.0$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.10 (C_{quart}), 160.51 (C_{quart}), 154.94 (C_{quart}), 152.49 (C_{quart}), 125.57 (C_{Ar}), 119.98 (C=C), 114.99 (C_{quart}), 112.84 (C_{Ar}), 112.23 (C_{Ar}), 102.03 (C_{Ar}), 90.71 (C≡C), 84.67 (C≡C), 56.89 ($-CH_2$), 18.63 ($-CH_3$); MS m/z (%) 452 (M^+, 100), 424 (13), 368 (11), 288 (47), 136 (27), 104 (52). Anal. calcd. for $C_{28}H_{20}O_6$: C, 74.33; H, 4.46; O, 21.22. Found: C, 74.38; H, 4.53.

1,1′-[(4Z)-Oct-4-ene-2,6-diyne-1,8-diylbis(thio)]dibenzene (18). Yellow liquid; yield 60%; DSC 169.78 °C (peak value); IR (KBr, cm^{-1}): 3056, 2960, 2925, 2854, 2202, 1582, 1479, 1439, 1260, 1089, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 3H), 7.24–7.14 (m, 7H), 5.75 (s, 2H), 3.73 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.80 (C_{quart}), 129.07 (C_{Ar}), 120.29 (C_{Ar}), 118.23 (C=C), 113.11 (C_{Ar}), 95.21 (C≡C), 81.09 (C≡C), 52.29 ($-CH_2$); MS m/z (%) 321 (M^+, 100), 168 (56), 104 (18). Anal. calcd. for $C_{20}H_{16}S_2$: C, 74.96; H, 5.03; S, 20.01. Found: C, 75.00; H, 5.05.

Synthesis of 1,1′-[(4Z)-Oct-4-ene-2,6-diyne-1,8-diyldisulfonyl] dibenzene (19)

$KMnO_4$ (610 mg, 0.38 mmol) was added to a mixture of 1,1′-[(*4Z*)-oct-4-ene-2,6-diyne-1,8-diylbis(thio)]dibenzene (**18**) (310 mg, 0.09 mmol) in glacial acetic acid (15 mL) and stirred at room temperature for 45 min. Excess of $KMnO_4$ was decomposed by addition of 2 mL of H_2O_2 (30%). The crude product was then

extracted with $CHCl_3$ (4×25 mL) and washed with H_2O (5×30 mL), and then the resulting solution was dried over anhydrous Na_2SO_4 and excess solvent was removed under high vacuum. The crude product was then purified by SiO_2 column chromatography using 40% ethyl acetate/hexane as an eluent. Yellow liquid; yield 78%; DSC 221.57 °C (peak value); IR (KBr, cm^{-1}): 2956, 2872, 2211, 1732, 1455, 1442, 1251, 1122, 1077, 1027; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.89 (m, 4H), 7.63–7.60 (m, 4H), 7.52–7.48 (m, 2H), 5.76 (s, 2H), 4.06 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.67 (C_{quart}), 130.10 (C_{Ar}), 122.26 (C_{Ar}), 118.93 (C=C), 114.71 (C_{Ar}), 98.67 (C≡C), 84.73 (C≡C), 60.20 ($-CH_2$); MS m/z (%) 384 (M, 100), 230 (12), 104 (22). Anal. calcd. for $C_{20}H_{16}O_4S_2$: C, 62.48; H, 4.19; O, 16.65; S, 16.68. Found: C, 62.45; H, 4.22.

Further details are available online in the Supplemental Materials.

CONCLUSIONS

Thus, a novel group of symmetrical and asymmetrical acyclic enediynes has been synthesized and characterized spectroscopically, using standard Sonogashira coupling conditions.

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REFERENCES

1. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Border, D. B. Calichemicins, a novel family of antitumor antibiotics, 2: Chemistry and structure of chelichemicin λ. *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468.
2. Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. Esperamicins, a novel class of potent antitmor antibiotics, 2: Structure of esperamicin X. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462.
3. Konishi, M.; Ohkuma, H.; Tsuno, T.; van Duyne, G. D.; Clardy, J. Crystal and molecular structure of dynemicin A: A novel 1,5-diyne-3-ene antitumor antibiotic. *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716.
4. Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. Neocarzinostatin, an antitumor antibiotic of high molecular weight. *J. Antibiot.* **1965**, *18*, 68–76.
5. Lam, K. S.; Hesler, G. A.; Gustavson, D. R.; Crosswell, A. R.; Veitch, J. M.; Forenza, S.; Tomita, K. Kedarcidin, a new chromoprotein antitumor antibiotic, I: Taxonomy of producing organism, fermentation, and biological activity. *J. Antibiot.* **1991**, *44*, 472–478.
6. Davies, J. E.; Wang, H.; Taylor, T.; Warabi, K.; Huang, X.-H.; Andersen, R. J. Uncialamicin, a new enediyne antitumor antibiotic. *Org. Lett.* **2005**, *7*, 5233–5236.
7. Smith, A. L.; Nicolaou, K. C. The enediyne antibiotics. *J. Med. Chem.* **1996**, *39*, 2103–217.

8. Xi, Z.; Goldberg, I. H. DNA damaging enediyne compounds. In *Comprehensive Natural Products Chemistry*; D. S. Barton and K. Nakanishi (Eds.); Elsevier: New York, 1999; pp. 553–592.
9. Bergman, R. G. Reactive 1,4-dehydroaromatics. *Acc. Chem. Res.* **1973**, *6*, 25–31.
10. Jones, R.; Bergman, R. G. *p*-Benzyne: Generation as an intermediate in a thermal isomerization reaction and trapping evidence for the 1,4-benzenediyl structure. *J. Am. Chem. Soc.* **1972**, *94*, 660–661.
11. Rawat, D. S.; Zaleski, J. M. Geometric and electronic control of thermal bergman cyclization. *Synlett* **2004**, *3*, 393–421.
12. Nicolaou, K. C.; Dai, W.-M. Chemistry and biology of the enediyne anticancer antibiotics. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416.
13. Konig, B.; Pitsch, W.; Thondorf, I. Synthesis, structure, and reactivity of enediyne macrocycles. *J. Org. Chem.* **1996**, *61*, 4258–4261.
14. Basak, A.; Shain, J. C.; Khamari, U. K.; Rudra, K. R.; Basak, A. Nitrogen substituted cyclic enediynes: Synthesis, thermal reactivity, and complexation with metal ions. *J. Chem. Soc., Perkin Trans. 1* **2000**, *12*, 1955–1964.
15. Lu, Y.-J.; Yang, S.-H.; Chien, C.-M.; Lin, Y.-H.; Hu, X.-W.; Wu, Z.-Z.; Wu, M.-J.; Lin, S.-R. Induction of G2/M phase arrest and apoptosis by a novel enediyne derivative, THDB, in chronic myeloid leukemia (HL-60) cells. *Toxicol. in Vitro* **2007**, *21*, 90–98.
16. Liu, X.; He, H.; Feng, Y.; Zhang, M.; Ren, K.; Shao, R. Difference of cell cycle arrests induced by lidamycin in human breast cancer cells. *Anti-Cancer Drugs* **2006**, *17*, 173–179.
17. Lin, C.-F.; Hsieh, P.-C.; Lu, W.-D.; Chiu, H.-F.; Wu, M.-J. A series of enediynes as novel inhibitors of topoisomerase I. *Bioorg. Med. Chem.* **2001**, *9*, 1707–1711.
18. Joshi, M. C.; Bisht, G. S.; Rawat, D. S. Syntheses and antibacterial activity of phendioxy substituted cyclic enediynes. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3226–3230.
19. Sharma, M.; Joshi, M. C.; Kumar, V.; Malhotra, S. V.; Rawat, D. S. Synthesis and anticancer activity of 13-membered cyclic enediynes. *Archiv Pharma. Chem. Life Sci.* **2011**, *344*, 564–571.
20. Wu, H.-J.; Lin, C.-F.; Lee, J.-L.; Lu, W.-D.; Lee, C.-Y.; Chen, C.-C.; Wu, M.-J. Substituent effects on the cyclization mode of 7-sulfonyl-3-hepten-1,5-diynes and 11-sulfonylundeca-3,7-dien-1,5,9-triynes. *Tetrahedron* **2004**, *60*, 3927–3934.
21. Konig, B.; Pitsch, W.; Dix, I.; Jones, P. G. Synthesis of macrocyclic enediynes by twofold *C*-alkylation. *Syntheis* **1996**, *4*, 446–448.
22. Erdelyi, M.; Gogoll, A. Rapid homogeneous-phase Sonogashira coupling reactions using controlled microwave heating. *J. Org. Chem.* **2001**, *66*, 4165–4169.