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Synthesis of naturally occurring polyacetylenes via a bis-silylated diyne

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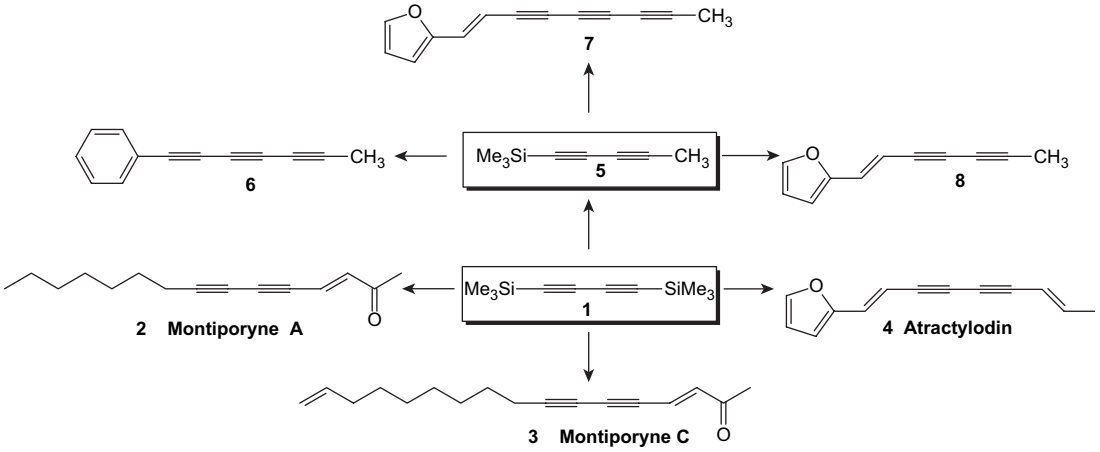
Abstract—A straightforward synthesis of a series of naturally occurring polyacetylenes has been developed, including the montiporynes A and C, possessing cytotoxic activity against several human solid tumor cells, the atractylodin, with antibiotic activity against *Escherichia coli*, and triynes, which display insecticidal activities, starting from the readily available 1,4-bis(trimethylsilyl)-1,3-butadiyne.

1. Introduction

Polyynes and acetylenic arrays are readily found in a series of natural products and exhibit a broad distribution in plant species[1] and stony corals[2] and display a wide range of biological activity for their antibacterial,[3] antifungal,[3,4] and pesticidal properties.[5] In particular the montiporynes,[6] possessing cytotoxic activity against human solid tumor cells, have been isolated from stony corals *Montipora* sp., whereas atractylodin, isolated from the roots of *Atractylis cancellata*,[7] is phototoxic and antibiotic against *Escherichia coli*.[8] Moreover, other acetylenic products, with a conjugated triyne structure,[1,8] isolated from various plant species, revealed to be extremely phototoxic toward mosquito larvae. Consequently, the search for improved synthetic methodologies for well-defined polyynes continues to expand.

We have recently reported successfully the applications of our methodology,[9] which led to the synthesis of a variety of unsymmetrically substituted conjugated diynes, to the preparation of a series of natural diacetylenic compounds, such as xerulins,[10] which are potent inhibitors of the biosynthesis of cholesterol, montiporic acids,[11] possessing antibacterial and cytotoxic properties, and virol C and 1-dehydroxyvirol A,[12] congeners of cicutoxin and isolated from *Cicuta virosa*. In connection with our ongoing work, we now wish to report the total synthesis of a series of naturally occurring polyacetylenes.

As reported in Scheme 1, we have devised a common strategy for the preparation of all these naturally occurring acetylenes. In particular the synthesis of the montiporynes A, C (**2**, **3**)[6] and the atractylodin **4**[8] can be realized starting



Scheme 1.

Keywords: Silicon and compounds; Polyacetylenes; Coupling reactions; Bioactive products.
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directly from the same bis-silylated diyne **1**, whereas the precursor for the synthesis of compounds **6**–**8**[8] can be achieved from the mono-silylated pentadiyne **5**.

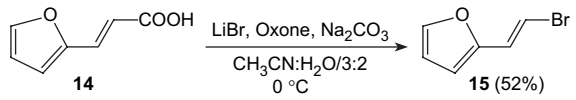
2. Results and discussion

The synthetic approach leading to the montiporynes **2**, **3** and to atractylodin **4** was based upon the selective and sequential substitution of the two silyl groups of the diyne **1**. Indeed, the montiporynes A **2** and C **3** differ in the aliphatic chain linked to the diyne moiety, a *n*-heptyl group for montiporyne A and a 8-nonenyl group for montiporyne C, and, therefore, the same strategy has been devised for the synthesis of both the montiporynes.

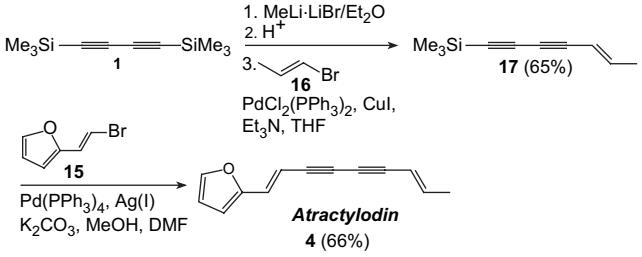
As depicted in Scheme 2, we started with a coupling reaction between the readily available iodides **9** or **10** and the lithium salt of the mono-silylated terminal diyne, obtained by selective desilylation of the diyne **1** with MeLi–Libr complex.[13] The coupling products were desilylated with K_2CO_3 in MeOH leading to the diyne **11** in 69% yield or to the enediyne **12** in 57% yield. Finally, a Sonogashira[14] cross-coupling reaction of the diyne **11** with the bromovinyl ketone **13**[15] of *E*-configuration led to the montiporyne A in 77% yield, whereas the reaction of the enediyne **12** with the same halide **13** led to the montiporyne C in 71% yield.

Following the same synthetic approach, in order to prepare atractylodin **4**, it was necessary to form the appropriate halovinyl intermediate possessing a furyl moiety. Thus, (Scheme 3), the bromoderivative **15** was synthesized, through modification of literature procedures,[16–18] in 52% yield (*E*:*Z*≥85:15) by halodecarboxylation of commercially available (2*E*)-3-(2-furyl)acrylic acid **14**.

Therefore, (Scheme 4), we began from diyne **1**, which was selectively desilylated with the MeLi–LiBr complex. The mono-silylated diyne was isolated and reacted with (*E*)-1-bromopropene **16** in the presence of a Pd(II) catalyst, leading to compound **17** in an overall 65% yield.[10] A further and



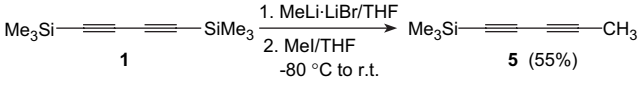
Scheme 3.



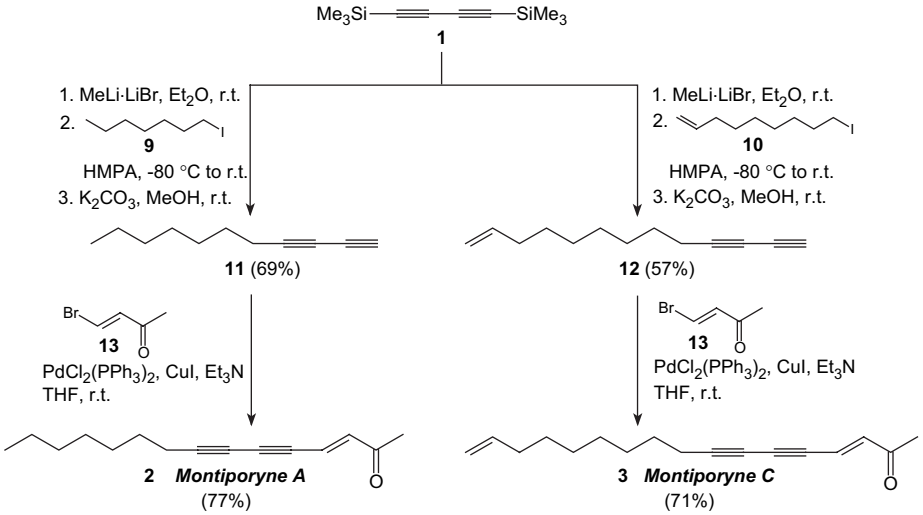
Scheme 4.

direct cross-coupling reaction[9,12,19] of the silylated enediyne **17** with the bromoderivative **15** in the presence of a Pd(0) catalyst led to atractylodin **4** in 66% yield. It is noteworthy that, notwithstanding the ≥85:15 mixture of compound **15**, essentially all *E* product **4** was isolated by chromatography.

As reported in Scheme 1, the key intermediate for the synthesis of triynes **6**, **7**, and enediyne **8**, a potential mosquito larvicidal agent, is mono-silylated pentadiyne **5**. This intermediate was readily prepared[20,21] in 55% yield (Scheme 5) by a coupling reaction between the lithium salt of the diyne **1** and methyl iodide.



Scheme 5.



Scheme 2.

The strategy employed for the synthesis of the triynes **6** and **7** was based upon the conversion of this mono-silylated diyne **5** into the 1-bromo-1,3-pentadiyne, which was subjected to a coupling reaction with the appropriate acetylenic intermediates, the phenylacetylene for the synthesis of compound **6** and the 2-[(1*E*)-but-1-en-3-ynyl]furan for the synthesis of compound **7**. The furyl intermediate was prepared according to Scheme 6, through a coupling reaction of bromovinylfuran **15** with trimethylsilylacetylene, in the presence of a Pd(II) catalyst, which led to the mono-silylated enyne **18**, and subsequently, after a desilylation reaction with K_2CO_3 in MeOH, to the desired enyne **19**.

Therefore, the synthesis of all acetylenic products **6**–**8** is outlined in Scheme 7.

Both triynes **6** and **7** were obtained following the same reaction sequence. In particular the diyne **5** was converted by NBS, in the presence of AgF in acetonitrile,[22] to the corresponding bromoderivative, which, without isolation, was directly coupled with phenylacetylene **20**, in the presence of a Pd(0) catalyst, to afford the triyne **6** in an overall 60% yield, or with the enyne **19** to lead to triyne **7** in an overall 72% yield. Finally, the enediyne **8** was obtained in 65% yield by a direct coupling reaction between the silylated diyne **5** and the bromovinyl derivative **15** in the presence of a Pd(0) catalyst.

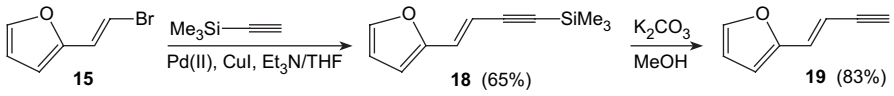
In summary, our synthetic approach to naturally occurring acetylenes compares favorably with other procedures. A special advantage of our strategy is represented by the possibility of preparing different acetylenes starting from the same compound and following the same reaction sequence. Moreover, the simplicity of the operations involved and the ready availability of the starting materials are additional features making the procedure useful.

3. Experimental

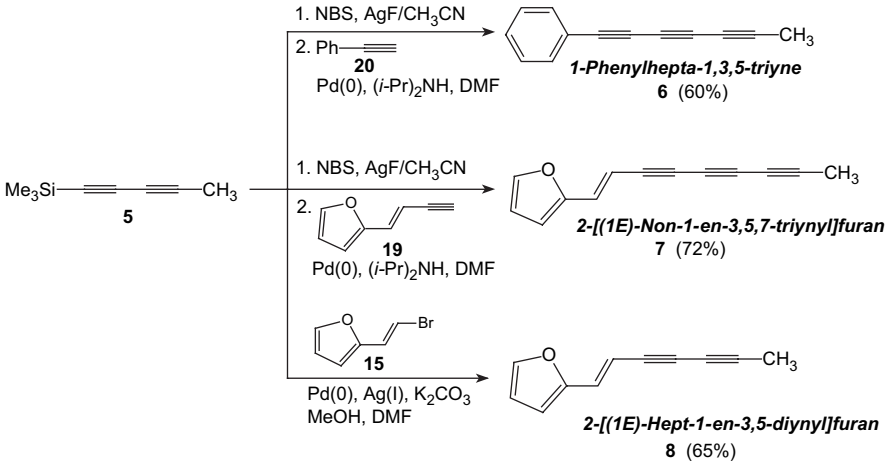
Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a J & W capillary column (DB-1301, 30 m×0.25 mm i.d.). GC/mass spectrometry analysis was performed on a Shimadzu GCMS-QP5000 gas chromatograph–mass spectrometer equipped with a Zebron capillary column (methyl polysiloxane, 30 m×0.25 mm i.d.). ^{1}H NMR spectra were recorded in deuterochloroform or CD_3OD on a Bruker AM 500 spectrometer at 500 MHz. ^{13}C NMR spectra were recorded in deuterochloroform or CD_3OD on a Bruker AM 500 spectrometer at 125.7 MHz. IR spectra were recorded on a Perkin–Elmer FTIR—Spectrum One and on a Shimadzu IR Prestige 21 spectrometers. Solvents were dried before use as follows: tetrahydrofuran was distilled from sodium, *N*,*N*-dimethylformamide and acetonitrile were distilled over molecular sieves. Melting points (uncorrected) were determined on a Reichert Microscope. The halide 9-iodonon-1-ene **10** was synthesized from commercial 1,9-nonandiol using literature procedures.[23,24]

3.1. General procedure for the synthesis of montiporynes A 2 and C 3

MeLi–LiBr complex (1.5 M) in ether (1.1 equiv) was added, under nitrogen, to a THF (0.5 M) solution of 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.0 equiv) at room temperature. After complete monodesilylation (3–5 h), the reaction mixture was cooled to −80 °C. A solution of 1-iodoheptane **9** or 9-iodonon-1-ene **10** (1.1 equiv) in THF (1.1 M) and HMPA (2.0 equiv) were slowly dropped at the same temperature, then the mixture was slowly brought to room



Scheme 6.



Scheme 7.

temperature. After reaction completion (18 h), MeOH (10 mL) and K_2CO_3 (1.2 equiv) were added, then the reaction mixture was stirred for 1 h at room temperature. A saturated aqueous solution of NH_4Cl (100 mL) was added and then the reaction mixture extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (3×50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography leading to the compounds **11** or **12**. A solution of diyne **11** or **12** (1.0 equiv) in THF (0.2 M) was added at room temperature, under nitrogen, to a stirred mixture of **13** (1.0 equiv), $PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.04 equiv), and Et_3N (1.5 equiv) in THF (0.2 M). After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography leading to title compounds **2** and **3**.

3.1.1. Undeca-1,3-diyne (11).[25] Compound **11** was prepared from 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.00 g, 5.16 mmol) and 1-iodoheptane **9** (1.28 g, 5.67 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) gave compound **11** (0.527 g, 69% yield) as a pale yellow oil. ν_{max} (neat) 3310, 2955, 2930, 2857, 2297, 2224, 1458, 1425, 1375, 1244, 613; δ_H (500 MHz, $CDCl_3$) 2.22 (td, J=7.0, 1.1 Hz, 2H), 1.92 (t, J=1.1 Hz, 1H), 1.51 (quintet, J=7.0 Hz, 2H), 1.39–1.32 (m, 2H), 1.31–1.20 (m, 6H), 0.86 (t, J=6.9 Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 78.5, 68.5, 64.6, 64.4, 31.6, 28.7, 28.7, 28.0, 22.6, 19.0, 14.0; MS *m/z* 133 (1), 119 (5), 105 (29), 91 (68), 79 (30), 78 (31), 77 (18), 67 (14), 65 (16), 63 (31), 55 (48), 51 (24), 43 (62), 41 (100%).

3.1.2. Tridec-12-en-1,3-diyne (12). Compound **12** was prepared from 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (1.00 g, 5.16 mmol) and 9-iodonon-1-ene **10** (1.429 g, 5.67 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) gave compound **12** (0.512 g, 57% yield) as a pale yellow oil. [Found: C, 89.50; H, 10.43. $C_{13}H_{18}$ requires C, 89.59; H, 10.41%]; ν_{max} (neat) 3308, 3076, 2974, 2928, 2855, 2297, 2224, 1640, 1458, 1425, 1246, 995, 910, 617; δ_H (500 MHz, $CDCl_3$) 5.78 (ddt, J=17.1, 10.2, 6.7 Hz, 1H), 4.97 (ddt, J=17.1, 2.2, 1.6 Hz, 1H), 4.91 (ddt, J=10.2, 2.2, 1.2 Hz, 1H), 2.23 (td, J=7.1, 1.1 Hz, 2H), 2.05–1.99 (m, 2H), 1.93 (t, J=1.1 Hz, 1H), 1.51 (quintet, J=7.1 Hz, 2H), 1.41–1.32 (m, 4H), 1.31–1.25 (m, 4H); δ_C (125.7 MHz, $CDCl_3$) 139.0, 114.2, 78.4, 68.5, 64.7, 64.4, 33.7, 28.9, 28.8, 28.8, 28.7, 27.9, 18.9; MS *m/z* 145 (3), 131 (11), 117 (19), 105 (15), 91 (51), 79 (24), 78 (15), 77 (16), 67 (22), 65 (14), 63 (23), 55 (35), 51 (20), 41 (100%).

3.1.3. (3*E*)-Pentadec-3-en-5,7-diyn-2-one (2) (Montiporyne A).[6] Compound **2** was prepared from undeca-1,3-diyne **11** (0.423 g, 2.86 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 5% ethyl acetate/petroleum ether) gave compound **2** (0.476 g, 77% yield) as a yellow oil. ν_{max} (neat) 2955, 2928, 2857, 2228, 2139, 1694, 1676, 1589, 1466, 1424, 1360, 1248, 1171, 957; δ_H (500 MHz, CD_3OD) 6.76 (dt, J=16.1, 1.0 Hz, 1H), 6.61 (d, J=16.1 Hz, 1H), 2.44 (td, J=7.0, 1.0 Hz, 2H), 2.31 (s, 3H), 1.61 (quintet, J=7.0 Hz, 2H), 1.50–1.42 (m, 2H), 1.41–1.31 (m, 6H), 0. 96 (t, J=6.9 Hz, 3H); δ_C (125.7 MHz, CD_3OD) 199.3, 141.6, 124.5, 90.8, 85.3, 73.0, 65.9, 33.2, 30.2, 30.2, 29.5, 27.8, 24.0, 20.5, 14.7; MS *m/z* 216 (M^+, <1), 187 (1), 173 (2), 159 (2), 145 (4), 131 (6), 117 (4), 115 (4), 105 (3), 103 (3), 91 (7), 77 (5), 63 (4), 62 (3), 55 (7), 43 (100), 41 (17%).

3.1.4. (3*E*)-Heptadeca-3,16-dien-5,7-diyn-2-one (3) (Montiporyne C).[6] Compound **3** was prepared from tridec-12-en-1,3-diyne **12** (0.341 g, 1.96 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 5% ethyl acetate/petroleum ether) gave compound **3** (0.337 g, 71% yield) as a yellow oil. ν_{max} (neat) 3075, 2928, 2855, 2228, 2139, 1694, 1676, 1638, 1589, 1458, 1424, 1360, 1248, 1234, 1171, 957, 910; δ_H (500 MHz, CD_3OD) 6.76 (dt, J=16.1, 1.1 Hz, 1H), 6.61 (d, J=16.1 Hz, 1H), 5.85 (ddt, J=17.1, 10.2, 6.7 Hz, 1H), 5.03 (ddt, J=17.1, 2.2, 1.5 Hz, 1H), 4.96 (ddt, J=10.2, 2.2, 1.2 Hz, 1H), 2.44 (td, J=7.1, 1.1 Hz, 2H), 2.31 (s, 3H), 2.13–2.07 (m, 2H), 1.61 (quintet, J=7.1 Hz, 2H), 1.50–1.41 (m, 4H), 1.41–1.35 (m, 4H); δ_C (125.7 MHz, CD_3OD) 199.3, 141.5, 140.3, 124.5, 115.1, 90.8, 85.3, 73.0, 65.9, 35.1, 30.3, 30.3, 30.3, 30.2, 29.5, 27.8, 20.5; MS *m/z* 199 (2), 185 (1), 159 (2), 145 (4), 143 (3), 131 (5), 129 (5), 117 (5), 115 (4), 105 (3), 103 (3), 95 (3), 91 (8), 79 (5), 77 (6), 67 (6), 55 (10), 43 (100), 41 (29%).

3.2. Synthesis of the intermediates 15, 18, 19

3.2.1. 2-[(*E*)-2-Bromovinyl]furan (15).[16–18] Lithium bromide (3.74 g, 43.48 mmol) and sodium carbonate (1.54 g, 14.49 mmol) were added to a stirred solution of carboxylic acid **14** (2 g, 14.49 mmol) in 50 mL of CH_3CN–H_2O (3:2 v/v) at 0 °C, and then followed by the addition in one portion of a solution of Oxone (4.45 g, 7.25 mmol) in 24 mL of H_2O. After reaction completion (5 min), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with a saturated aqueous solution of NaOH (10%, 3×50 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by percolation on a florisil column (petroleum ether) affording 0.65 g (52% yield) of compound **15** as a yellow oil. ν_{max} (neat) 3078, 1629, 1477, 1014, 926, 788, 771, 737, 689; δ_H (500 MHz, $CDCl_3$) (*E*+*Z* isomer): (*E* isomer) 7.37 (d, J=1.8 Hz, 1H), 6.89 (d, J=13.9 Hz, 1H), 6.72 (d, J=13.9 Hz, 1H), 6.38 (dd, J=3.3, 1.8 Hz, 1H), 6.26 (d, J=3.3 Hz, 1H), (*Z* isomer)[26] 7.44 (d, J=1.8 Hz, 1H), 7.10 (d, J=3.3 Hz, 1H), 7.06 (d, J=8.3 Hz, 1H), 6.50–6.47 (m, 1H), 6.31 (d, J=8.3 Hz, 1H); δ_C (125.7 MHz, $CDCl_3$) 151.1, 142.6, 125.4, 111.3, 108.6, 105.3; MS *m/z* 174 (M^{+2}, 55), 172 (M^+, 58), 145 (10), 143 (10), 119 (3), 117 (3), 93 (12), 87 (7), 86 (7), 65 (100), 64 (15), 63 (34), 62 (15), 61 (8), 50 (8%).

3.2.2. 2-[(1*E*)-4-Trimethylsilylbut-1-en-3-ynyl]furan (18). A solution of trimethylsilylacetylene (0.445 g, 4.528 mmol) in THF (5 mL) was added at room temperature, under nitrogen, to a stirred mixture of bromovinylfuran **15** (0.649 g, 3.773 mmol), $PdCl_2(PPh_3)_2$ (0.053 g,

0.075 mmol), CuI (0.0287 g, 0.151 mmol), and Et_3N (0.573 g, 5.660 mmol) in THF (7 mL). After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with H_2O (3×20 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.47 g of compound **18** (65% yield) as a pale yellow oil. [Found: C, 69.50; H, 7.36. $C_{11}H_{14}OSi$ requires C, 69.42; H, 7.41%]; ν_{max} (neat) 2959, 2897, 2115, 1481, 1251, 1086, 1065, 1015, 944, 844, 760, 738; δ_H (500 MHz, $CDCl_3$) 7.35 (d, J=1.8 Hz, 1H), 6.72 (d, J=16.0 Hz, 1H), 6.37 (dd, J=3.4, 1.8 Hz, 1H), 6.30 (d, J=3.4 Hz, 1H), 6.05 (d, J=16.0 Hz, 1H), 0.2 (s, 9H); δ_C (125.7 MHz, $CDCl_3$) 152.0, 143.1, 129.3, 111.8, 110.3, 106.1, 104.3, 97.7, –0.1; MS m/z 190 (M^+, 78), 175 (100), 160 (12), 147 (45), 145 (48), 131 (16), 116 (26), 115 (82), 105 (16), 91 (21), 88 (51), 75 (25), 73 (24), 67 (16), 59 (20), 53 (45), 45 (81), 43 (78%).

3.2.3. 2-[(1*E*)-But-1-en-3-ynyl]furan (19). K_2CO_3 (0.358 g, 2.589 mmol) was added to a MeOH solution (4 mL) of silylated compound **18** (0.41 g, 2.158 mmol). The reaction mixture was stirred for 1 h at room temperature, then quenched with H_2O (30 mL), and extracted with ethyl acetate (30 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum leading to compound **19** as a pale yellow oil; 0.212 g, yield 83%. [Found: C, 81.38; H, 5.10. C_8H_6O requires C, 81.34; H, 5.12%]; ν_{max} (neat) 3294, 2095, 1624, 1479, 1373, 1246, 1045, 1016, 947, 741; δ_H (500 MHz, $CDCl_3$) 7.36 (d, J=1.8 Hz, 1H), 6.75 (d, J=16.0 Hz, 1H), 6.49 (dd, J=3.4, 1.8 Hz, 1H), 6.33 (d, J=3.4 Hz, 1H), 6.01 (dd, J=16.0, 2.5 Hz, 1H), 3.07 (dd, J=2.5, 0.6 Hz, 1H); δ_C (125.7 MHz, $CDCl_3$) 151.7, 143.2, 130.1, 111.8, 110.4, 105.0, 82.8, 80.0; MS m/z 118 (M^+, 75), 90 (67), 89 (100), 64 (19), 63 (64), 62 (23), 59 (12), 51 (27), 50 (25), 45 (24), 40 (11%).

3.3. Synthesis of the atractylodin 4

3.3.1. (5*E*)-1-Trimethylsilyl-hept-5-en-1,3-diyne (17).[10] MeLi–LiBr complex (1.5 M) in ether (20.6 mL, 30.93 mmol) was added to an ether solution (40 mL) of 1,4-bis(trimethylsilyl)-1,3-butadiyne **1** (4 g, 20.57 mmol) at room temperature. After reaction completion (4 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl ether (3×20 mL). The organic extracts were washed with water (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The mono-silylated diyne 1-trimethylsilyl-1,3-butadiyne **1a** was purified by distillation (2.0 g, 79% yield). A THF solution (20 mL) of diyne **1a** (1.21 g, 9.92 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*E*)-1-bromopropene **18** (1.0 g, 8.26 mmol), Et_3N (1.25 g, 12.40 mmol), CuI (0.063 g, 0.33 mmol), and $Pd(PPh_3)_2Cl_2$ (0.116 g, 0.165 mmol) in THF (12 mL). After reaction completion (12 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with water (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography (petroleum ether) led to the title compound **17** as a yellow oil (1.1 g, 82% yield).

3.3.2. 2-[(1*E*,7*E*)-Nona-1,7-dien-3,5-diynyl]furan (4) (Atractylodin).[8] To a solution of bromovinylfuran **15** (0.238 g, 1.389 mmol) in anhydrous DMF (3.5 mL) at room temperature, under nitrogen, were successively added $Pd(PPh_3)_4$ (0.08 g, 0.0694 mmol), AgCl (0.0398 g, 0.278 mmol), and K_2CO_3 (1.533 g, 11.11 mmol). The resulting mixture was stirred for 5 min, then MeOH (0.355 g, 11.11 mmol) was added followed by a solution of mono-silylated enediyne **17** (0.225 g, 1.39 mmol) in anhydrous DMF (3.5 mL). The reaction mixture was warmed to 40 °C and stirred at same temperature. After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.17 g of compound **4** (66% yield) as a yellow solid (mp 49–51 °C). ν_{max} (KBr) 3133, 2964, 2929, 2852, 2194, 2126, 1616, 1475, 1440, 1261, 1096, 1016, 943, 802, 742; δ_H (500 MHz, $CDCl_3$) 7.37–7.35 (m, 1H), 6.77 (d, J=16.0 Hz, 1H), 6.40 (dd, J=3.4, 1.8 Hz, 1H), 6.35 (dd, J=3.4, 0.5 Hz, 1H), 6.31 (dq, J=15.8, 6.9 Hz, 1H), 6.09 (d, J=16.0 Hz, 1H), 5.61–5.50 (m, 1H), 1.81 (dd, J=6.9, 1.8 Hz, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.9, 143.6, 143.5, 130.7, 112.1, 111.1, 109.9, 104.8, 81.9, 80.2, 77.2, 72.5, 18.9; MS m/z 182 (M^+, 100), 181 (14), 153 (46), 152 (89), 151 (21), 139 (15), 127 (13), 126 (13), 115 (12), 113 (8), 102 (9), 98 (8), 91 (7), 89 (8), 87 (14), 86 (10), 77 (21), 76 (55), 75 (23), 74 (22), 64 (26), 63 (36), 62 (14), 52 (11), 51 (32), 50 (18%).

3.4. Synthesis of compounds 5–8

3.4.1. 1-Trimethylsilyl-1,3-pentadiyne (5).[20,21] MeLi–LiBr complex (1.5 M) in ether (18.9 mL, 28.350 mmol) was slowly dropped, under nitrogen, to a THF solution (50 mL) of 1,4-bis(trimetilsilyl)-1,3-butadiyne **1** (5 g, 25.773 mmol) at room temperature. After complete monodesilylation (5 h), the reaction mixture was cooled to a −80 °C and a solution of methyl iodide (4 g, 28.350 mmol) in THF (40 mL) was slowly dropped at the same temperature, then the mixture was slowly brought to room temperature. After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl ether (3×30 mL). The organic extracts were washed with water (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 1.93 g of compound **5** (55% yield) as a pale yellow oil. ν_{max} (neat) 2961, 2232, 2113, 1251, 1196, 870, 844, 760; δ_H (500 MHz, $CDCl_3$) 1.92 (s, 3H), 0.17 (s, 9H); δ_C (125.7 MHz, $CDCl_3$) 88.5, 82.2, 75.5, 64.7, 4.0, −0.5; MS m/z 136 (M^+, 14), 121 (100), 107 (3), 105 (3), 93 (9), 91 (7), 79 (7), 77 (15), 53 (20), 43 (22%).

3.4.2. 1-Phenylhepta-1,3,5-triyne (6).[8,27] To a solution of the mono-silylated diyne **5** (0.345 g, 2.537 mmol) in anhydrous CH_3CN (4 mL) were added NBS (0.542 g, 3.044 mmol) and AgF (0.383 g, 3.044 mmol) in the dark. The resulting mixture was stirred for 1 h at room temperature; after reaction completion (1 h), the mixture was directly percolated on a florisil column with DMF (30 mL)

as eluent. To this mixture of bromodiyne in DMF, were added at room temperature, under nitrogen, $Pd(PPh_3)_4$ (0.147 g, 0.127 mmol) and *i*-Pr_2NH (0.51 g, 5.073 mmol) followed by a solution of phenylacetylene **20** (0.26 g, 2.537 mmol) in anhydrous DMF (3 mL). After reaction completion (70 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3×30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×30 mL) dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.25 g of compound **6** (overall 60% yield) as a white solid (mp 56–58 °C). ν_{max} (KBr) 2957, 2924, 2853, 2219, 1490, 1440, 1425, 1024, 756, 689, 525; δ_H (500 MHz, $CDCl_3$) 7.51–7.47 (m, 2H), 7.39–7.34 (m, 1H), 7.33–7.28 (m, 2H), 1.99 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 132.9, 129.5, 128.4, 121.1, 78.3, 75.2, 74.6, 67.4, 64.9, 58.9, 4.6; MS *m/z* 164 (M^+, 100), 163 (63), 138 (48), 137 (15), 110 (8), 98 (7), 88 (7), 87 (11), 86 (13), 82 (50), 74 (6), 69 (16), 67 (8), 63 (11), 55 (9), 51 (6), 50 (6%).

3.4.3. 2-[(1*E*)-Non-1-en-3,5,7-triynyl]furan (7).[8] To a solution of the mono-silylated diyne **5** (0.244 g, 1.797 mmol) in anhydrous CH_3CN (3 mL) were added NBS (0.384 g, 2.156 mmol) and AgF (0.272 g, 2.156 mmol) in the dark. The resulting mixture was stirred for 1 h at room temperature; after reaction completion (1 h), the mixture was directly percolated on a florisil column with DMF (21 mL) as eluent. To this mixture of bromodiyne in DMF, were added at room temperature, under nitrogen, $Pd(PPh_3)_4$ (0.104 g, 0.090 mmol) and *i*-Pr_2NH (0.363 g, 3.593 mmol) followed by a solution of the 2-[(1E)-but-1-en-3-ynyl]furan **19** (0.212 g, 1.797 mmol) in anhydrous DMF (2 mL). After reaction completion (70 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3×30 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.233 g of compound **7** (overall 72% yield) as a pale yellow solid (mp 59–62 °C). ν_{max} (KBr) 2955, 2913, 2852, 2219, 2203, 2166, 1613, 1479, 1282, 1261, 1051, 938, 927, 804, 740; δ_H (500 MHz, $CDCl_3$) 7.37 (d, *J*=1.6 Hz, 1H), 6.83 (d, *J*=15.9 Hz, 1H), 6.41 (dd, *J*=3.4, 1.6 Hz, 1H), 6.39 (dd, *J*=3.4, 0.5 Hz, 1H), 6.03 (dd, *J*=15.9, 0.5 Hz, 1H), 1.98 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.6, 143.8, 132.3, 112.2, 111.7, 103.8, 79.0, 77.6, 75.1, 68.6, 65.0, 59.2, 4.6; MS *m/z* 180 (M^+, 100), 179 (6), 152 (38), 151(67), 150 (35), 126 (33), 102 (8), 100 (8), 99 (16), 98 (20), 90 (19), 87 (14), 86 (14), 77 (13), 76 (31), 75 (30), 74 (38), 63 (56), 62 (22), 51 (25), 50 (24%).

3.4.4. 2-[(1*E*)-Hept-1-en-3,5-diynyl]furan (8).[8] To a solution of bromovinylfuran **15** (0.214 g, 1.244 mmol) in anhydrous DMF (3 mL) at room temperature, under nitrogen, were successively added $Pd(PPh_3)_4$ (0.072 g, 0.0622 mmol), AgCl (0.0357 g, 0.2488 mmol), and K_2CO_3 (1.373 g, 9.953 mmol). The resulting mixture was stirred for 5 min, then MeOH (0.318 g, 9.953 mmol) was added followed by a solution of mono-silylated diyne **5** (0.169 g, 1.244 mmol) in anhydrous DMF (3 mL). The reaction mixture was warmed to 40 °C and stirred at same temperature. After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether) leading to 0.126 g of compound **8** (65% yield) as a yellow oil. ν_{max} (neat) 3146, 3119, 3046, 2911, 2841, 2230, 2137, 1618, 1481, 1385, 1262, 1016, 941, 926, 883, 741; δ_H (500 MHz, $CDCl_3$) 7.36 (d, *J*=1.8 Hz, 1H), 6.76 (d, *J*=16.0 Hz, 1H), 6.39 (dd, *J*=3.4, 1.8 Hz, 1H), 6.33 (d, *J*=3.4 Hz, 1H), 6.03 (d, *J*=16.0 Hz, 1H), 1.99 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 151.9, 143.3, 130.7, 112.0, 110.8, 104.9, 81.4, 77.4, 73.8, 64.6, 4.7; MS *m/z* 156 (M^+, 100), 155 (19), 128 (32), 127 (51), 126 (18), 102 (40), 101 (12), 87 (8), 78 (27), 77 (25), 76 (17), 75 (25), 74 (20), 64 (21), 63 (39), 62 (17), 51 (82), 50 (57%).

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