Novel Routes to Furan-3(2*H*)-ones. New Syntheses of Bullatenone and Geiparvarin

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New convenient versatile routes to the furan-3(2*H*)-one nucleus are described as exemplified by the synthesis of the two natural products bullatenone (1) and geiparvarin (2). The key step involves the hydration and cyclisation of the corresponding readily accessible acetylenic ketones which are best made by a Pd(II)–Cu(I)-catalysed coupling process.

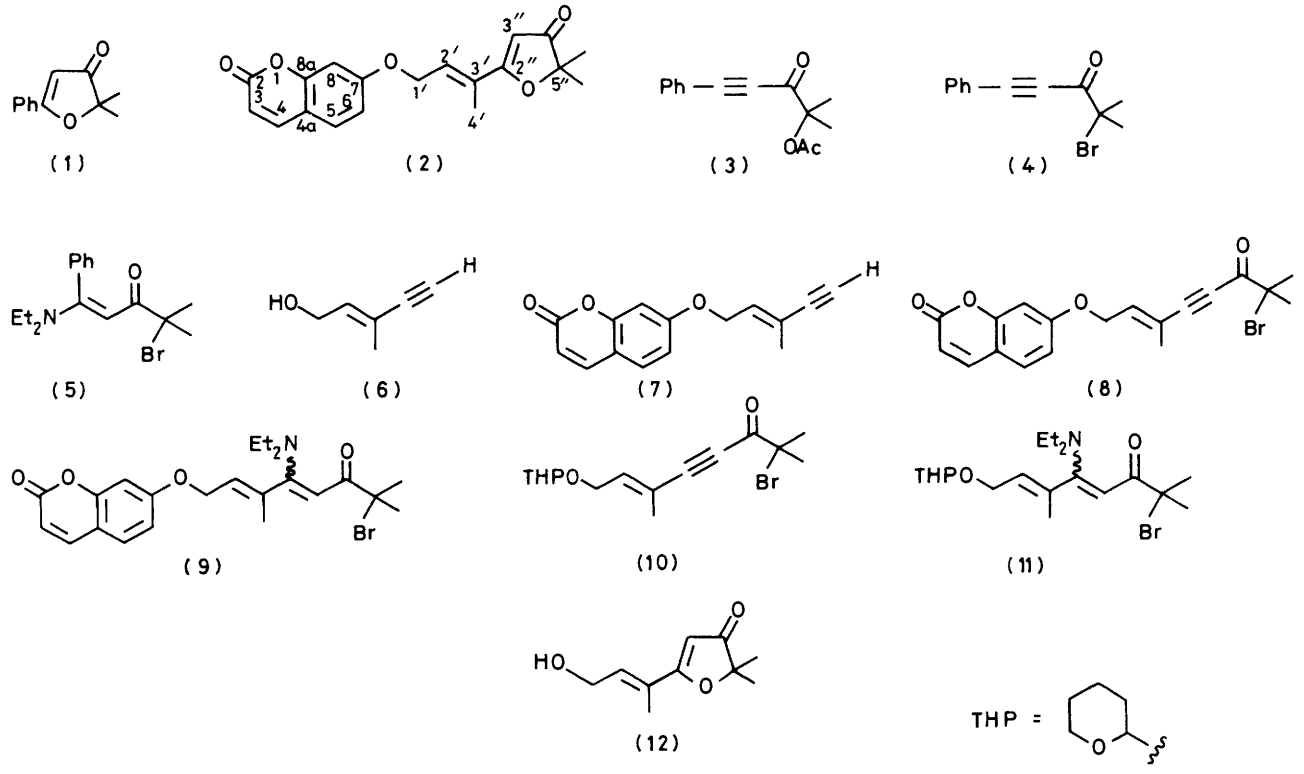
Since our original establishment of the structure (1) for bullatenone and its synthesis [1] there has been continual interest in alternative synthetic approaches [2] to the furan-3(2*H*)-one system in this and other natural products such as the antitumour agent geiparvarin (2). We now describe flexible new routes to compounds (1) and (2) which are highly convenient and readily applicable to large-scale operation.

Evaluation of the optimum procedures was carried out with bullatenone as the initial target. The simplest method involved addition of lithium phenylacetylide to 2-acetoxy-2-methylpropanoyl chloride at −70 °C to give the acetylenic ketone (3) which, without purification, was heated under reflux with a suspension of potassium carbonate in methanol to give bullatenone (1) in 35% overall yield from phenylacetylene. A better yield was obtained using a stepwise sequence involving the acetylenic bromoketone (4) as intermediate. We first prepared this compound by interaction of trimethyl(phenylethynyl)silane and 2-bromo-2-methylpropanoyl bromide in the presence of aluminium chloride (77% yield).[3] A much more convenient preparation of the bromoketone (4) comprised the reaction of the bromide with phenylacetylene itself employing bis(triphenylphosphine)-palladium(II) chloride–copper(I) iodide as catalyst (75%).[4] A much lower yield of compound (4) was obtained by low-temperature interaction of lithium phenylacetylide and the bromoacid bromide (50%), the main by-product being the corresponding diacetylenic tertiary alcohol. Reaction of compound (4) with diethylamine gave a quantitative yield of a homogeneous enaminone, probably the (*E*)-isomer (5). Hydrolysis of (5) with aqueous acetic acid resulted also in subsequent *in situ* cyclisation to yield directly bullatenone (1) (63%). Similar sequences were employed for the synthesis of geiparvarin. An efficient and highly convenient starting material was (*E*)-3-methylpent-2-en-4-yn-1-ol (6) which was not only readily available as the starting point for an industrial synthesis of vitamin A [5] but also possessed the required configuration about the double bond. This alcohol (6) was converted into the corresponding ether (7) of umbelliferone (7-hydroxycoumarin) either directly by means of triphenylphosphine–diethyl azodicarboxylate [6] or *via* the derived bromide in the presence of potassium carbonate. Coupling of compound (7) with 2-bromo-2-methylpropanoyl bromide in the presence of $(PPh_3)_2PdCl_2$–Cu_2I_2 catalyst gave the expected acetylenic ketone (8) (55%). Addition of diethylamine gave a mixture of (*E*)- and (*Z*)-enaminones (9) which were hydrolysed–cyclised with aqueous oxalic acid to give geiparvarin (2) (22%). The unexpectedly low yield in this last step was due to the ready acid-catalysed cleavage of the umbelliferone ether linkage. To obviate this an alternative sequence was used. The tetrahydropyranyl derivative [7] of (6) was coupled with 2-bromo-2-methylpropanoyl bromide by $(PPh_3)_2PdCl_2$–Cu_2I_2 catalysis to give the corresponding acetylenic ketone (10). Addition of diethylamine to (10) followed by aqueous acetic acid hydrolysis–cyclisation of the resulting enaminone (11) then produced the furan-3(2*H*)-one (12) in 38% overall yield from the tetrahydropyranyl derivative of (6), with no necessity for purification of intermediates. Conversion of compound (12) into the corresponding mesylate and reaction of this derivative with umbelliferone in acetone in the presence of potassium carbonate–lithium bromide then gave geiparvarin (2) (95%), identical with a sample of the natural product. It was noticed that geiparvarin was light sensitive; exposure in chloroform solution converted it into an isomeric mixture from which the (*Z*)-isomer, isogeiparvarin, could be readily isolated.

Experimental

M.p.s were determined on a Kofler hot-stage. Spectrometric measurements were obtained on the following instruments in the indicated solvents: i.r., Perkin-Elmer 297 ($CHCl_3$); u.v., Pye Unicam SP 1800 (95% EtOH); ^1H n.m.r., Varian EM 390 ($CDCl_3$; internal standard $SiMe_4$) or Bruker WM 250 ($CDCl_3$; internal deuterium lock); ^{13}C n.m.r., Bruker WM 250; mass spectrometry, MS30. Thin-layer chromatography (t.l.c.) and preparative t.l.c. (p.l.c.) were performed on plates coated with Merck Kieselgel 60 F_{254} silica. Column chromatography was performed with Merck Kieselgel 60, 70—230 mesh silica. Dry THF refers to tetrahydrofuran dried by distillation from potassium benzophenone ketyl in a recycling still. Dichloromethane was distilled from phosphorus pentaoxide. Triethylamine was distilled from calcium hydride.

Bullatenone (1).—n-Butyl-lithium (1.6M in hexane; 3.5 ml) was added dropwise to a cooled (−70 °C) solution of phenylacetylene (0.51 g, 5 mmol) in dry THF (20 ml) under nitrogen. After being stirred for 15 min the solution was transferred *via* a cannula to a dropping funnel and was added dropwise during 40 min to a cooled (−70 °C), stirred solution of 2-acetoxy-2-methylpropanoyl chloride [8] (0.92 g, 5.6 mmol) in dry THF (25 ml) under nitrogen. The cooling bath was removed and, after the mixture had attained room temperature and THF had been removed under reduced pressure, the residue was partitioned between water (30 ml) and ethyl acetate (30 ml). The aqueous layer was extracted with more ethyl acetate (30 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was dissolved in methanol (30 ml) and anhydrous potassium carbonate (0.7 g, 5 mmol) was added. The suspension was stirred and heated at reflux for 25 min. Methanol was then removed under reduced pressure and the residue was partitioned between water (30 ml) and ethyl acetate (30 ml). The aqueous layer was re-extracted with ethyl acetate (30 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to



column chromatography (adsorbent 30 g) using dichloromethane–ethyl acetate (20 : 1) as eluant to yield bullatenone (1) (0.33 g, 35%). A sample was recrystallised from light petroleum (b.p. 60—80 °C), m.p. 65—67 °C (lit.,[1] 67.5—68.5 °C) (Found: C, 76.3; H, 6.35. Calc. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4%); $\nu_{max.}$ 1 685 (C=O) and 1 620 cm^{-1} (C=C); $\lambda_{max.}$ 303.5 (ε 15 700), 242.5 (7 900), 219.5 (9 400), and 202 nm (13 400); δ_H (90 MHz) 1.48 (6 H, s, Me_2), 6.00 (1 H, s, 4-H), 7.5—7.7 (3 H, m, ArH), and 7.8—8.0 (2 H, m, ArH); *m/z* 188 (M^+, 11%), 105 (22), and 102 (100).

4-Bromo-4-methyl-1-phenylpent-1-yn-3-one (4).—A solution of trimethyl(phenylethynyl)silane (1.74 g, 10 mmol) and 2-bromo-2-methylpropanoyl bromide [9] (2.30 g, 10 mmol) in dry dichloromethane (2 ml) was added dropwise, during 10 min, to a stirred suspension of aluminium trichloride (1.34 g, 10 mmol) in dry dichloromethane (30 ml) cooled to −70 °C. The reaction mixture was stirred at −70 °C for 60 min and then allowed to warm to room temperature before being poured onto ice–water (30 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 30 ml). The combined organic extracts were washed in turn with saturated aqueous sodium hydrogen carbonate and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was subjected to Kugelrohr distillation to yield the *acetylenic ketone* (4) (1.94 g, 77%), oven temperature 85—90 °C/0.25 mmHg. A sample was recrystallised from hexane at −15 °C, m.p. 40 °C (Found: C, 57.15; H, 4.4; Br, 32.1. $C_{12}H_{11}BrO$ requires C, 57.4; H, 4.4, Br, 31.9%); $\nu_{max.}$ 2 210 (C≡C), 1 665 (C=O), and 610 cm^{-1} (C–Br); $\lambda_{max.}$ 293 (ε 10 800), 280sh, 220 (8 400), and 202 nm (12 800); δ_H (90 MHz) 1.95 (6 H, s, Me_2), 7.35—7.55 (3 H, m, ArH), and 7.55—7.75 (2 H, m, ArH); *m/z* 252, 250 [M^+ (^{79}Br), 1.65%], 211, 209 (6), and 129 (100).

When 2-acetoxy-2-methylpropanoyl chloride was subjected to the same conditions, the product purified by column chromatography using dichloromethane–ethyl acetate (20 : 1) as eluant proved to be *4-acetyl-2,2-dimethyl-5-phenylfuran-3-(2H)-one* (25%). A sample was recrystallised from hexane, m.p. 90.5—91.5 °C (Found: C, 73.1; H, 6.35. $C_{14}H_{14}O_3$ requires C, 73.05; H, 6.1%); $\nu_{max.}$ 1 700 (C=O), 1 695 (C=O), and 1 640 cm^{-1} (C=C); $\lambda_{max.}$ 266 (ε 13 700), 253 (14 100), and 204 nm (11 100); δ_H (250 MHz) 1.48 (6 H, s, Me_2), 2.54 (3 H, s, CH_3CO), 7.43 (2 H, dd, *J* 7 and 8 Hz, aryl 3- and 5-H), 7.55 (1 H, tt, *J* 7 and 1.5 Hz, aryl 4-H), and 7.74 (2 H, dd, *J* 8 and 1.5 Hz, aryl 2- and 6-H); δ_C (62.5 MHz) 17.48 (CH_3CO), 22.83 (Me_2), 89.74 (C-2), 114.37 (C-4), 127.92 (aryl C-2 and -6), 129.24 (aryl C-3 and -5), 132.69 (aryl C-4), 137.75 (aryl C-1), 189.79 (C-5), 194.39 (CH_3CO), and 200.41 p.p.m. (C-3); *m/z* 230 (M^+, 63%), 229 (52), and 105 (100).

The ketone (4) was also prepared directly from phenylacetylene by two methods. (a) n-Butyl-lithium (1.6M in hexane; 3.5 ml) was added dropwise to a solution of phenylacetylene (0.51 g, 5 mmol) in dry THF (10 ml) under nitrogen at −70 °C. After being stirred at this temperature for 10 min, the solution of lithium phenylacetylide was added dropwise, using a syringe, to a solution of 2-bromo-2-methylpropanoyl bromide (1.23 g, 5.35 mmol) in dry THF (5 ml), so that the temperature of the reaction mixture at no time exceeded −60 °C. The reaction mixture was stirred for a further 30 min at −70 °C and then allowed to warm to room temperature during a further 60 min. Saturated aqueous ammonium chloride (20 ml) was then added, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 30 ml). The combined organic extracts and mother liquor were washed in turn with saturated aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was chromatographed (adsorbent 30 g) with hexane–dichloromethane (1 : 1) as eluant to yield the acetylenic ketone (4) (0.63 g, 50%), R_F 0.39, together with *1,1-bis(phenylethynyl)-2-bromo-2-methylpropan-1-ol* (0.18 g), R_F 0.17. A sample of the alcohol was recrystallised from hexane, m.p. 64—66 °C (Found: C, 68.15; H, 4.7; Br, 22.7.

$C_{20}H_{17}BrO$ requires C, 68.0; H, 4.8; Br, 22.65%); $\nu_{max.}$ 3 580, 3 540 (OH), and 2 240 cm^{-1} (C≡C); δ_H (90 MHz) 2.13 (6 H, s, Me_2), 3.27 (1 H, br s, OH), and 7.3—7.7 (10 H, m, ArH); *m/z* 354, 352 [M^+ (^{79}Br)], 353, 351 ($M^+ - H$, 0.6%), 232 (52), 231 (100), and 129 (70).

(b) Phenylacetylene (1.02 g, 10 mmol) and 2-bromo-2-methylpropanoyl bromide (2.30 g, 10 mmol) were dissolved in dry triethylamine (20 ml) under nitrogen. Bis(triphenylphosphine)palladium(II) chloride (10 mg) and dry copper(I) iodide (10 mg) were added and the mixture was mechanically stirred for 23 h. Methanol (30 ml) was then added and the solvent was evaporated under reduced pressure. The residual solid was partitioned between dichloromethane (50 ml) and water (50 ml) and, after separation of the organic layer, the aqueous layer was extracted with more dichloromethane (50 ml). The combined organic phases were washed in turn with 1M hydrochloric acid (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and brine (20 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was subjected to Kugelrohr distillation to yield the acetylenic ketone (4) (1.88 g, 75%).

4-*Bromo*-1-*diethylamino*-4-*methyl*-1-*phenylpent*-1-*en*-3-*one* (5).—The acetylenic ketone (4) (1.44 g, 5.75 mmol) was dissolved in hexane (30 ml) and diethylamine (0.49 ml, 6.7 mmol) was added. The solution was stirred for 24 h and then hexane and excess of diethylamine were removed under reduced pressure to yield the *enaminone* (5) (1.86 g, 100%). A sample was recrystallised from hexane, m.p. 69—70 °C (Found: C, 59.45; H, 6.85; Br, 24.9; N, 4.4. $C_{16}H_{22}BrNO$ requires C, 59.25; H, 6.8; Br 24.7; N, 4.3%); $\nu_{max.}$ 1 630 cm^{-1} (C=O); $\lambda_{max.}$ 328 (ε 23 350) and 203.5 nm (16 750); δ (90 MHz) 1.10 (6 H, t, *J* 7 Hz, NCH_2CH_3), 1.80 (6 H, s, Me_2CBr), 3.20 (4 H, q, *J* 7 Hz, NCH_2), 5.90 (1 H, s, 2-H), 7.10—7.30 (2 H, m, ArH), and 7.30—7.50 (3 H, m, ArH); *m/z* 325, 323 [M^+ (^{79}Br), 1.8%], 244 (29), and 202 (100).

Hydrolysis of the Enaminone (5) *to give Bullatenone*.—The enaminone (1.30 g, 4 mmol) was dissolved in a mixture of acetic acid (10 ml) and water (5 ml) and the solution was heated at reflux for 2 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was partitioned between water (20 ml) and ethyl acetate (20 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (20 ml). The combined organic extracts were washed in turn with saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml), and dried ($MgSO_4$). The residue was chromatographed (30 g) with dichloromethane–ethyl acetate (20 : 1) as eluant to yield bullatenone (1) (0.47 g, 63%).

7-[(E)-3-*Methylpent*-1-*en*-4-*ynyloxy*]*coumarin* (7).—Umbelliferone (9.48 g, 58.5 mmol) was added to a suspension of potassium carbonate (10 g, 72.5 mmol) in distilled acetone (200 ml). (*E*)-5-Bromo-3-methylpent-3-en-1-yne [10] (9.5 g, 60 mmol) was then added and the mixture was heated at reflux for 16 h. After the solution had cooled, acetone was removed under reduced pressure and ammonia (10% aqueous solution; 200 ml) was added. The solid product was filtered off and dried *in vacuo* to yield the *ether* (7) (13.5 g, 96%). A sample was recrystallised from methanol, m.p. 108—109 °C (Found: C, 75.05; H, 5.1. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%); $\nu_{max.}$ 3 310 (C≡CH), 1 730 (C=O), and 1 615 cm^{-1} (C=C); $\lambda_{max.}$ 323 (ε 9 900) and 222.5 nm (11 100); δ (250 MHz) 1.92 (3 H, d, *J* 1.2 Hz, Me), 2.89 (1 H, s, 5-H), 4.66 (2 H, d, *J* 6.4 Hz, 1-H_2), 6.12 (1 H, br t, *J* 7 Hz, 2-H), 6.25 (1 H, d, *J* 9.5 Hz, aryl 3-H), 6.78 (1 H, d, *J* 2 Hz, aryl 8-H), 6.83 (1 H, dd, *J* 8.5 and 2 Hz, aryl 6-H), 7.37 (1 H, d, *J* 8.5 Hz, aryl 5-H), and 7.63 (1 H, d, *J* 9.5 Hz, aryl 4-H); *m/z* 240 (M^+, 7%), 162 (67), 134 (40), and 79 (100).

This compound was also prepared directly from (*E*)-3-methylpent-2-en-4-yn-1-ol (6) as follows. (*E*)-3-Methylpent-2-en-4-yn-1-ol (0.48 g, 5 mmol), triphenylphosphine (1.31 g, 5 mmol) and umbelliferone (0.81 g 5 mmol) were dissolved in dry THF (100 ml) under nitrogen. Diethyl azodicarboxylate (0.87 g, 5 mmol) was added and the solution was stirred for 16 h. The solvent was then removed under reduced pressure. and triphenylphosphine oxide was removed by filtration through silica gel (90 g) using diethyl ether as eluant. Evaporation gave the ether (7) as a solid (0.99 g, 83%).

7-[(E)-7-*Bromo*-3,7-*dimethyl*-6-*oxo*-*oct*-2-*en*-4-*ynyloxy*]-*coumarin* (8).—The acetylenic coumarin (7) (4.8 g, 20 mmol) and 2-bromo-2-methylpropanoyl bromide (7.44 g, 32.3 mmol) were dissolved in a mixture of dry dichloromethane (40 ml) and dry triethylamine (40 ml). Bis(triphenylphosphine)palladium(II) chloride (20 mg) and dry copper(I) iodide (20 mg) were added and the reaction mixture was then stirred for 6 h. Methanol (10 ml) was then added and the solvent was removed under reduced pressure. The residue was partitioned between water (100 ml) and diethyl ether (100 ml) and, after separation of the organic layer, the aqueous layer was extracted with more diethyl ether (100 ml). The combined organic extracts were washed with brine (50 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue (adsorbent 200 g), using ethyl acetate–light petroleum (b.p. 60—80 °C) (1 : 2) as eluant, yielded the *acetylenic ketone* (8) (3.62 g, 55%). A sample was recrystallised from methanol as plates, m.p. 133—136 °C (Found: C, 58.3; H, 4.5; Br, 20.55. $C_{19}H_{17}BrO_4$ requires C, 58.6; H, 4.35; Br, 20.6%); $\nu_{max.}$ 2 200 (C≡C), 1 730 (OC=O), 1 665 (C=C–C=O), and 1 605 cm^{-1} (C=C); $\lambda_{max.}$ 319 (ε 18 500), 292 (16 500), and 215 nm (24 500); δ_H (250 MHz) 1.93 (6 H, s, CMe_2), 2.00 (3 H, d, *J* 1.3 Hz, 3-Me), 4.73 (2 H, d, *J* 6 Hz, 1-H_2), 6.27 (1 H, d, *J* 9.5 Hz, aryl 3-H), 6.39 (1 H, br t, *J* 6 Hz, 2-H), 6.79 (1 H, d, *J* 2.3 Hz, aryl 8-H), 6.83 (1 H, dd, *J* 8.5 and 2.5 Hz, aryl 6-H), 7.38 (1 H, d, *J* 8.5 Hz, aryl 5-H), and 7.64 (1 H, d, *J* 9.5 Hz, aryl 4-H); *m/z* 390, 388 [M^+ (^{79}Br), 2%], 309 (5), 308 (2), 267 (12), and 162 (100).

7-[(2E)-7-*Bromo*-4-*diethylamino*-3,7-*dimethyl*-6-*oxo*-*octa*-2,4-*dienyloxy*]*coumarin* (9).—The acetylenic ketone (8) (1.0 g, 2.57 mmol) was dissolved in dry dichloromethane (15 ml) and diethylamine (0.37 g, 5 mmol) was then added. After the solution had been stirred for 16 h the solvent was removed under reduced pressure to yield enaminone (9) (1.17 g, 98%) as a mixture of isomers, $\nu_{max.}$ 1 730 (O–C=O) and 1 620 cm^{-1} (C=C); δ_H (90 MHz) 1.16 and 1.50 (each 3 H, t, *J* 7 Hz, NCH_2CH_3), 1.90 (6 H, s, CMe_2), 2.00 (3 H, s, 3-Me), 3.10 and 3.30 (each 2 H, q, *J* 7 Hz, NCH_2), 4.80 (2 H, d, *J* 6 Hz, 1-H_2), 5.60 (1 H, br t, *J* 6 Hz, 2-H), 5.66 (1 H, s, 5-H), 6.25 (1 H, d, *J* 9 Hz, aryl 3-H), 6.8—7.0 (2 H, m, aryl 6- and 8-H), 7.46 (1 H, d, *J* 9 Hz, aryl 5-H), and 7.75 (1 H, d, *J* 9 Hz, aryl 4-H); *m/z* 381 (M^+ – HBr, 3%), 340 (9), 220 (100), and 206 (58). No attempt was made to purify this compound and it was used directly in the next step.

Geiparvarin (2).—The enaminone (9) (1.17 g) was dissolved in THF (15 ml) and saturated aqueous oxalic acid (10 ml) was added. The homogeneous solution was heated at reflux for 45 min and then, after being cooled, was evaporated under reduced pressure. The residue was partitioned between water (20 ml) and dichloromethane (20 ml) and, after separation of the organic layer, the aqueous layer was extracted with more dichloromethane (20 ml). The combined organic extracts were washed in turn with ammonia (5% aqueous solution; 3 ×

20 ml) and then brine (20 ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (25 g) using dichloromethane–ethyl acetate (10 : 1) as eluant to yield geiparvarin (2) (0.18 g, 22%). Recrystallisation from methanol yielded prisms, m.p. 158—159 °C (lit.,[11] 160—161 °C) (Found: C, 69.8; H, 5.3. Calc. for $C_{19}H_{18}O_5$: C, 69.95; H, 5.5); $\nu_{max.}$ 1 735, 1 700, 1 620, and 1 570 cm^{-1}; $\lambda_{max.}$ 312 (ε 27 200), 300sh, 236 (14 000), and 216 nm (18 500); δ_H (250 MHz) * 1.40 (6 H, s, 5″-Me_2), 2.01 (3 H, d, *J* 1 Hz, 4′-H_3), 4.82 (2 H, d, *J* 6 Hz, 1′-H_2), 5.61 (1 H, s, 3″-H), 6.27 (1 H, d, *J* 9 Hz, 3-H), 6.74 (1 H, br t, *J* 6 Hz, 2′-H), 6.81 (1 H, d, *J* 2.5 Hz, 8-H), 6.86 (1 H, dd, *J* 8.5 and 2.5 Hz, 6-H), 7.40 (1 H, d, *J* 8.5 Hz, 5-H), and 7.64 (1 H, d, *J* 9 Hz, 4-H); δ_C (62.5 MHz) 13.73 (q, C-4′), 23.08 (q, 5″-Me), 65.23 (t, C-1′), 88.64 (s, C-5″), 100.31 (d, C-8), 101.64 (d, C-3″), 112.49 (s, C-4a), 112.93 (d) and 113.54 (d) (C-3 and C-6), 128.82 (s, C-3′), 128.95 (d, C-5), 130.45 (d, C-2′), 143.21 (d, C-4), 155.88 (s, C-8a), 160.90 (s, C-2), 161.42 (s, C-7), 182.85 (s, C-2″), and 207.17 p.p.m. (s, C-4″); *m/z* 326 (M^+, 28%), 165 (70), and 65 (100).

2-*Bromo*-2,6-*dimethyl*-8-(*tetrahydropyran*-2′-*yloxy*)*oct*-6-*en*-4-*yn*-3-*one* (10).—(*E*)-3-Methyl-5-(tetrahydropyran-2′-yloxy)-pent-3-en-1-yne (1.80 g, 10 mmol) and 2-bromo-2-methylpropanoyl bromide (2.30 g, 10 mmol) were dissolved in a mixture of dry triethylamine (10 ml) and dry dichloromethane (10 ml) under nitrogen. Bis(triphenylphosphine)palladium(II) chloride (10 mg) and copper(I) iodide (10 mg) were then added and the solution was stirred for 4 h. Methanol (5 ml) was then added and the solution was stirred for a further 5 min. The solvent was evaporated under reduced pressure and the residue was partitioned between hexane (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with more hexane (100 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent was then removed under reduced pressure to yield the crude acetylenic ketone (10) (3.18 g) as a red oil. Attempted distillation of this compound led to extensive decomposition and chromatography yielded very poor recovery of material. It was therefore used without purification in the next step. The i.r. spectrum indicated some ester, formed by attack of 2-bromo-2-methylpropanoyl bromide on the tetrahydro-2-pyranyloxy group, $\nu_{max.}$ (film) 2 200 (C≡C), 1 735m (O–C=O), 1 665 (C=O), and 1 620 cm^{-1} (C=C); δ_H (90 MHz; C_6D_6) 1.25—1.70 (9 H, m, 3 × THP CH_2 and 6-Me), 1.77 (6 H, s, Me_2), 3.3—4.3 (4 H, m, THP CH_2 and 8-H_2), 4.55 (1 H, br s, THP 2′-H), and 6.35 (1 H, br t, *J* 7 Hz, 7-H); *m/z* 330, 328 [M^+ (^{79}Br), 0.1%], 315, 313 (M^+ – Me, 1), and 207 ($M^+ - C_3H_6Br$, 40).

This compound was also prepared by a different method as follows. (*E*)-3-Methyl-5-(tetrahydropyran-2′-yloxy)pent-3-en-1-yne (3.60 g, 20 mmol) was dissolved in dry THF (35 ml) and the solution was cooled to −70 °C under nitrogen. n-Butyl-lithium (1.6M solution in hexane; 13.5 ml) was added dropwise and the resulting solution was stirred for 15 min. The solution was transferred, using a cannula, to a dropping funnel and was then added to a solution of 2-bromo-2-methylpropanoyl bromide (4.60 g, 20 mmol) in dry THF (100 ml) under nitrogen so that the temperature of the solution at no point exceeded −65 °C. The solution was stirred at −70 °C for 60 min and then allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was filtered through Florisil (60 g) using dichloromethane as eluant to yield, after evaporation of solvent, the crude acetylenic ketone (10) (6.60 g). This material was used without purification in the following process.

* Numbering scheme as shown in formula (2).

5-(3′-*Hydroxy*-1′-*methylprop*-1′-*enyl*)-2,2-*dimethylfuran*-3(2H)-*one* (12).—Crude bromoacetylenic ketone (10) (3.18 g) was dissolved in hexane (40 ml) and diethylamine (2.4 ml, 32.8 mmol) was added. The solution was stirred for 16 h and then the solvent was removed under reduced pressure to yield crude enaminone (11) as an oil, which was used in the next step without purification.

The residue was dissolved in a mixture of acetic acid (20 ml) and water (10 ml) and heated at reflux for 40 min. The solvent was then removed under reduced pressure and the residue was partitioned between ethyl acetate (100 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic layer was washed in turn with more sodium hydrogen carbonate solution (50 ml) and brine (50 ml) before being dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (80 g) using ethyl acetate–dichloromethane (1 : 1) as eluant to yield the *furanone* (12) [0.69 g, 38% from the THP derivative of (6)]. A sample was recrystallised from diisopropyl ether, m.p. 76—78 °C (Found: C, 65.7; H, 7.5. $C_{10}H_{14}O_3$ requires C, 65.95; H, 7.7%); $\nu_{max.}$ 3 350 (OH), 1 695 (C=O), 1 645 (C=C), and 1 565 cm^{-1} (C=C); $\lambda_{max.}$ 292 (ε 26 200) and 243.5 nm (12 500); δ_H (250 MHz) 1.39 (6 H, s, 5-Me_2), 1.68 (1 H, br s, OH), 1.91 (3 H, d, *J* 1.2 Hz, 1′-Me), 4.42 (2 H, d, *J* 6 Hz, 3′-H_2), 5.55 (1 H, s, 4-H), and 6.68 (1 H, br t, *J* 6 Hz, 2′-H); δ_C (62.5 MHz) 13.22 (1′-Me), 23.00 (2-CH_3), 59.42 (C-3′), 88.46 (C-2), 99.58 (C-4), 126.45 (C-1′), 136.27 (C-2′), 184.07 (C-5), and 207.48 p.p.m. (C-3); *m/z* 182 (M^+, 100%).

5-(3′-*Mesyloxy*-1′-*methylprop*-1′-*enyl*)-2,2-*dimethylfuran*-3(2H)-*one*.—The furanone (12) (0.31 g, 1.65 mmol) was dissolved in dry dichloromethane (15 ml) and cooled to 0 °C. Triethylamine (0.25 g, 2.48 mmol) was added to the solution followed by methanesulphonyl chloride (0.21 g, 1.83 mmol) added dropwise. After being stirred for 5 min at 0 °C the solution was allowed to warm to room temperature during 15 min. The solution was washed in turn with hydrochloric acid (1M; 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml), and brine (10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the mesylate (0.41 g, 95%), $\nu_{max.}$ 1 690 (C=O), 1 645 (C=C), and 1 560 cm^{-1} (C=C); δ_H (90 MHz) 1.40 (6 H, s, 2-Me_2), 2.03 (3 H, s, 1′-Me), 3.15 (3 H, s, $MeSO_3$), 5.05 (2 H, d, *J* 7 Hz, 3′-H_2), 5.70 (1 H, s, 4-H), and 6.70 (1 H, br t, *J* 7 Hz, 2′-H); *m/z* 260 (M^+, 28%), 181 ($M^+ - MeSO_2$, 20), and 123 (100).

Geiparvarin (2).—The mesylate (0.41 g) was dissolved in acetone (30 ml), umbelliferone (0.267 g, 1.65 mmol), potassium carbonate (0.228 g, 1.65 mmol), and lithium bromide (0.03 g) were added, and the suspension was heated at reflux for 2.5 h. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (50 ml) and ammonia (10% aqueous solution; 30 ml). The organic layer was separated and the aqueous layer was extracted with more dichloromethane (20 ml). The combined organic layers were washed in turn with aqueous ammonia (20 ml) and brine (20 ml) and dried ($MgSO_4$). The solvent was removed to yield geiparvarin (2) (0.48 g, 95%), identical with the material prepared by the alternative route.

Isogeiparvarin.—Geiparvarin (2) (45 mg) was dissolved in chloroform (1 ml) and the solution was kept for 4 d in the light. The solvent was then removed under reduced pressure and the residue was purified by p.l.c. using ethyl acetate–dichloromethane (1 : 9) as developer (double development) to yield geiparvarin (26 mg recovery) and isogeiparvarin (11 mg). Isogeiparvarin was recrystallised from methanol, m.p.

149—151.5 °C (lit.,[2] 149—150 °C); $\nu_{max.}$ 1 710 (C=O), 1 690 (C=O), 1 620 (C=C), 1 610 (C=C), and 1 550 cm^{-1} (C=C); δ_H (250 MHz) 1.45 (6 H, s, 5″-Me_2), 2.05 (3 H, d, *J* 1.5 Hz, 4′-H_3), 5.02 (2 H, d, *J* 5 Hz, 1′-H_2), 5.57 (1 H, s, 3″-H), 6.06 (1 H, br t, *J* 5 Hz, 2′-H), 6.26 (1 H, d, *J* 9.5 Hz, 3-H), 6.78 (1 H, d, *J* 2.5 Hz, 8-H), 6.83 (1 H, dd, *J* 8.5 and 2.5 Hz, 6-H), 7.38 (1 H, d, *J* 8.5 Hz, 5-H), and 7.64 (1 H, d, *J* 9.5 Hz, 4-H); *m/z* 326 (M^+, 28%), 165 (55), and 65 (100).

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