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NEW SYNTHESES OF BULLATENONE AND GEIPARVARIN

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Abstract:- New convenient syntheses of two 3(2H)-furanone natural products bullatenone (1) and geiparvarin (2) are described involving the hydration of the corresponding readily accessible acetylenic ketones. These 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 3(2H)-furanone system in this and other natural products such as the antitumour agent geiparvarin (2). We now describe new routes to (1) and (2) which are both highly convenient and readily applicable to large scale operation.

Addition of lithium phenylacetylide to α-acetoxyisobutyryl chloride in tetrahydrofuran at - 70°C gave 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 by carrying out the following stepwise sequence.

Room temperature treatment of a triethylamine solution of phenylacetylene with α-bromoisobutyryl bromide in the presence of dichlorobis(triphenylphosphine) palladium and copper (I) iodide[3] gave the acetylenic ketone (4; 75%). Reaction of (4) with diethylamine in hexane at room temperature gave a quantitative yield of the enamine (5). Hydrolysis of (5) with oxalic acid in aqueous dioxan resulted also in subsequent in situ cyclisation to yield directly bullatenone (1; 64%).

A similar sequence was employed in the synthesis of geiparvarin (2). A highly convenient starting point was (E)-3-methylpent-2-en-4-yn-1-ol (6) which was not only readily available[4] as the starting point for an industrial synthesis of Vitamin A but also possessed the required configuration about the double bond. The corresponding tetrahydropyranyl ether[5] (95%) was treated in triethylamine/methylene chloride with α-bromoisobutyryl bromide at room temperature in the presence of $Pd(PPh_3)_2Cl_2/Cu_2I_2$ catalyst. The resulting acetylenic ketone (7) was converted into the enamine (8) by diethylamine treatment. Hydrolysis/cyclisation of (8) with aqueous acetic acid produced the 3(2H)-dihydrofuranone (9). The overall yield of (9) from the tetrahydropyranyl derivative of (6) without purification of intermediates was 38%. Conversion of (9) to its mesylate ($MeSO_2Cl$, NEt_3, CH_2Cl_2; 0^oC; 95%) and treatment with umbelliferone in refluxing acetone solution in the presence of excess potassium carbonate and lithium bromide produced geiparvarin (2; 95%) m.p. 158 - 159^oC identical in every respect with the natural product.[6]

Confirmatory analytical and spectroscopic data were obtained for all the above new compounds.

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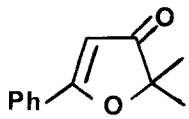
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O

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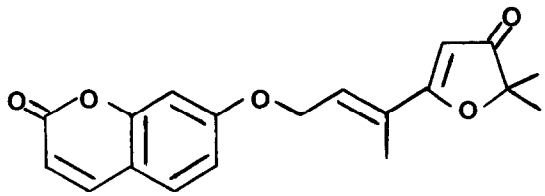
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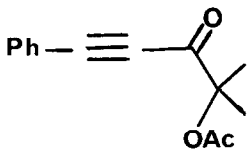
O
O

2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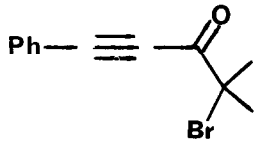
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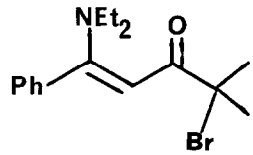
4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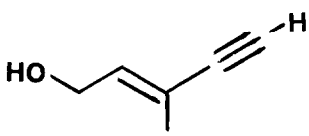
5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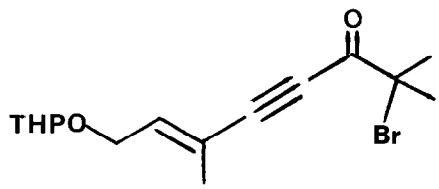
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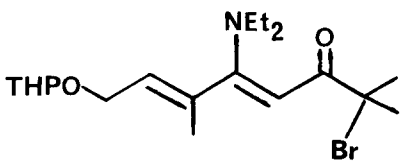
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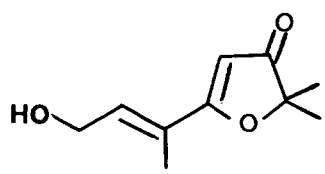
O
HO
O

9

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4. We thank Hoffmann-La Roche, AG, Basel, for a generous supply of this starting material.
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6. We thank Professor A. B. Smith III for kindly providing full spectroscopic details for geiparvarin.

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