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A NEW NITRILE OXIDE BASED SYNTHESIS OF THE ANTITUMOR AGENT GEIPARVARIN

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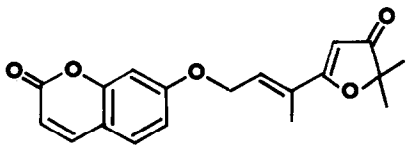
Abstract: Geiparvarin **1** has been synthetized utilizing the 3,5-disubstituted isoxazole **8** as protected synthon for the 3(2H)furanone system, the desired α'-hydroxy-1,3-diketone precursor being eventually revealed by $Mo(CO)_6$ promoted reductive cleavage.

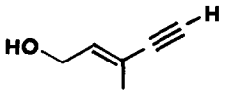
A large amount of synthetic work has recently been directed at the development of new methods for the preparation of the 3(2H)-furanone ring system, a central structural element common to an increasing number of antitumor agents, including jatrophone, lychnophorolide, eremantholides and geiparvarin **1**. The last compound in particular has become a popular target for many synthetic investigations[1] since its isolation from the leaves of Geijera parviflora Lindl.[2]



1

We describe in this paper a new route to **1** which utilizes three readily available precursors; namely: (E)-3-methylpent-2-en-4-yn-1-ol **2**, which possesses the required configuration about the double bond, umbelliferone **3**, both commercially available, and 2-trimethylsilyloxy-2-methyl--1-nitropropane **4**, readily accessible via Henry reaction between nitromethane and acetone followed by silylation. Central to our strategy is the well-known fact that acid-induced cyclodehydration of an α'-hydroxy-1,3-diketone provides a highly efficient route to the substituted 3(2H)-furanone ring system.[1a]

Since the ability of the isoxazole ring to serve as a masked 1,3-diketone has also been amply demonstrated[3], the 3,5-disubstituted isoxazole 8 appeared the most logical precursor for our synthetic strategy.



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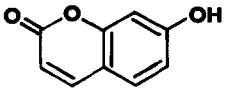

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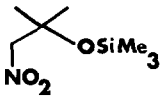
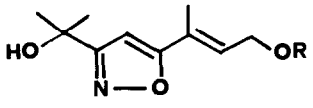


4

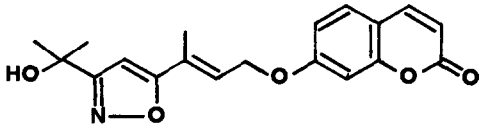
Its preparation began with a regio- and chemo-selective cycloaddition of the nitrile oxide generated from the nitro-compound 4 under the Mukaiyama[4] conditions into the acetyl derivative of 2, producing after acid work-up[5] an essentially quantitative yield of the isoxazole 5[6]. Successive treatment with LiOH effected the removal of the acetyl group to give excellent overall yields of 6[7]. Selective mesylation of the primary alcoholic function of 6 under standard conditions ($MeSO_2Cl$; Et_3N; CH_2Cl_2) gave the crude mesylate 7 (60-70% yield), which reacted with umbelliferone 3 in the presence of LiBr to give quantitatively the key intermediate 8.[8]



5 R=Ac

6 R=H

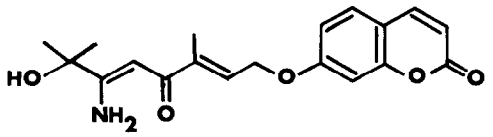
7 R=SO_2Me



8

The next operation, namely the unmasking of the isoxazole nucleus to reveal a ß-enamino-ketone, called for a chemical reduction which secures the survival of the double bond. It is well known that isoxazole derivatives played a variety of fascinating roles in the preparation of new molecular systems. Much of their chemistry stems from the lability of the nitrogen-oxygen bond under catalytic conditions, which in our case are prohibited due to the presence of the double bond. However heating 8 with molybdenum hexacarbonyl in wet acetonitrile[9] accomplished reductive cleavage of the isoxazole ring, furnishing a quantitative yield of the expected ena-

minone 9.[10]



9

Completion of the synthetic plan involved the exposure of 9 to acetic acid at 0°C for 4h which induced easy cyclodehydration to afford a 96% yield of 1 (mp 159-160°C, lit[1a], mp 160-161°C), whose IR and ^{1}H NMR spectral data are identical with those reported in the literature[1a]. This work stresses once more the utility of nitrile oxide cycloaddition as a tool in natural product chemistry[11] as well as the enhanced versatility of the isoxazole derivatives offered by reductive cleavage of the heterocyclic ring under non-hydrogenolytic conditions.

Acknowledgement.
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References and Notes.

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3. B.J. Wakefield and D.J. Wright, Adv.Heterocycl.Chem., 1979, 25, 147.
4. T. Mukaiyama and T.Hoshino, J.Am.Chem.Soc., 1960, 82, 5339.
5. All new compounds gave satisfactory analyses. Selected spectral data are given. All ^{1}H NMR spectra are at 80MHz in $CDCl_3$.
6. 5, Oil; IR (neat): 3470, 1740, 1570 cm^{-1}; ^{1}H NMR: δ 1.6 (s, 6H), 2.07 (d, 3H, J=1.2Hz), 2.1 (s, 3H), 3.35 (brs, 1H), 4.8 (d, 2H, J=6.5Hz), 6.27 (s, 1H), 6.35 (brt, 1H, J=6Hz).

7. **6**, Oil; IR (neat): 3350, 1580 cm^{-1}; ^1H NMR: δ 1.6 (s, 6H), 1.95 (d, 3H, J=1.2Hz), 3.25 (br, 1H), 3.6 (brs, 1H), 4.35 (d, 2H, J=6Hz), 6.22 (s, 1H), 6.42 (brt, 1H, J=6Hz).

8. **8**, m.p. 128-130°C (diethyl ether); IR ($CHCl_3$): 3430. 1730, 1620, 1615 cm^{-1}; ^1H NMR: δ 1.62 (s, 6H), 2.12 (d, 3H, J=1.2Hz), 2.32 (brs, 1H), 4.85 (d, 2H, J=6Hz), 6.3 (d, 1H, J=9Hz), 6.32 (s, 1H), 6.55 (brt, 1H, J=6Hz), 6.8-7 (m, 2H), 7.42 (d, 1H, J=8.5Hz), 7.67 (d, 1H, J=9Hz).

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10. **9**, m.p. 149-151°C (AcOEt:petroleum ether, 1:2); IR ($CHCl_3$): 3480, 1730, 1620, 1560, 1520 cm^{-1} ^1H NMR: δ 1.5 (s, 6H), 1.97 (d, 3H, J=1.2Hz), 2.35 (brs, 1H), 4.8 (d, 2H, J=6Hz), 5.4 (s, 1H), 6.27 (d, 1H, J=9Hz), 6.45 (brt, 1H, J=6Hz), 6.75-7 (m, 2H), 7.4 (d, 1H, J=8.5Hz), 7.65 (d, 1H, J=9Hz), 9.7 (br, 2H).

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