Tetrahedron Letters Vol. 21, pp 711-714 0040-4039/80/0215-0711$02.00/0

SYNTHESIS OF GEIPARVARIN: A NOVEL ANTITUMOR AGENT POSSESSING A 3(2H)-FURANONE RING

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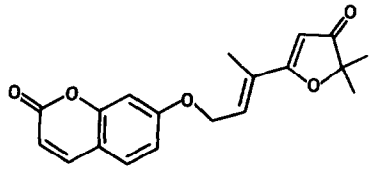
Summary: The first synthesis of geiparvarin as well as assignment of configuration of the previously undefined trisubstituted olefinic bond has been achieved.

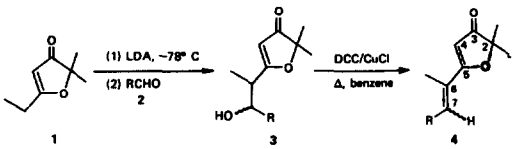
During the past two years, a major effort in our laboratory has been directed towards the development of a viable synthetic approach to jatrophone,[2] an architecturally interesting diterpenoid antitumor agent. This synthetic venture has led to a general exploration of the chemistry of the 3(2H)-furanone ring system, a central structural element of the jatrophone molecule. In particular, we have encountered several novel features of this system,[3] not the least of which is the proclivity of the lithium dienolate derived from 5-alkyl derivatives to undergo efficient γ-alkylation with a wide variety of electrophilic reagents.[4,5] This observation recently led in our laboratory to the first total synthesis of geiparvarin,[6] a novel 3(2H)-furanone also known to possess significant antitumor properties.[7] In this letter we wish to report the details of this synthesis as well as the determination of the stereochemistry of the trisubstituted olefinic bond.

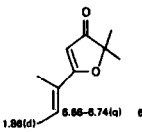
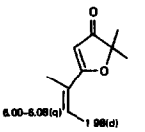
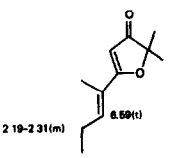
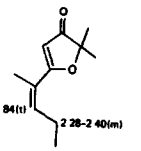
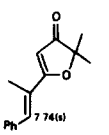
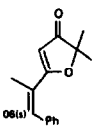
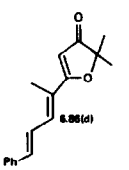
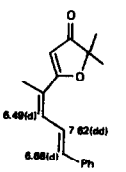
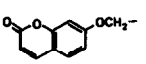
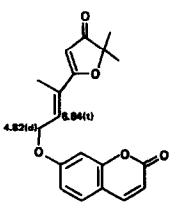
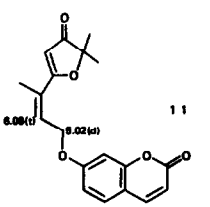


Geiparvarin

At the outset the undefined stereochemistry of geiparvarin demanded that our synthetic strategy not only allow for elaboration of geiparvarin but also for its configurational isomer. With this constraint in mind, we initiated study by examination of the low temperature aldol condensation of the lithium dienolate derived from 3(2H)-furanone 1 (i.e. LDA/THF/-78° C) with a variety of simple model aldehydes (2a-d). Our results are illustrated in Table I. As expected, alkylation in each case took place solely at the γ-position to afford a diastereomeric mixture of alcohols (i.e. 3);[8] the isolated yields in general were good.[9] Interestingly, when the aldol condensation of 1 with benzaldehyde was conducted at 0° C a 2:3 mixture of γ and α[10] adducts was obtained. This result was

Table 1. Synthesis of 3(2H)-Furandienones and Related Systems[a]



Entry	R	Yield aldol (percent)[a]	Dehydration product		E Z ratio	Yield (percent)[b]
			E	Z		
a.	CH_3	54			1 1	64
b.	CH_3CH_2	69			1 2	73
c	C_6H_5	76			1 2	59
d	$C_6H_5CH{=}CH{-}$ (t)	40			3 2	55
e		53	 Mp 157–158° C	 Mp 149–150° C	1 1	30

unique to benzaldehyde.

With condensation at the γ-position assured, at least at low temperature, we turned next to defining dehydration conditions which could be adjusted to afford either the E or Z isomer. Initially, we explored a variety of acid catalyzed conditions including: (a) pTsOH in benzene with azeotropic removal of H_2O; (b) pTsOH/$CuSO_4$ in benzene at reflux; (c) the Burgess reagent[11] (Et_3NSO_2N-CO_2Me) in benzene at 65 °C; and (d) the Stork-Kraus dehydration protocol[12] (MsCl/Et_3N followed by chromatography on silica gel). In each case only a single olefin, the E isomer (vide infra), was obtained; yields at best were modest (ca. 20-50%). Assuming that the above acidic conditions afforded the thermodynamically more stable E isomer,[13] we next examined the mild, neutral dehydration conditions of Alexandre and Rouessac.[14] Treatment of (3a-d) with dicyclohexylcarbodiimide and a catalytic amount of CuCl at the reflux point of benzene led to mixtures of the E and Z olefins (4), which could easily be separated by TLC (silica gel); in each case the isomer which corresponded to the product derived from the acid catalyzed dehydration protocols (later shown to be the E isomer) possessed the lower R_f value.

Turning next to the synthesis of geiparvarin, the requisite aldehyde (2e)[15] was conveniently prepared in three steps from 7-hydroxycoumarin; the overall yield was 54%. To our delight dehydration of the derived γ-aldol mixture (3e) employing the Stork-Kraus protocol afforded a single crystalline olefin (mp 157-158 °C) in 50% yield, which was identical in all respects to geiparvarin (i.e. mp and direct comparison of the 60 MHz NMR spectra).[16] On the other hand, dehydration employing the Alexandre-Rouessac conditions led to an easily separable mixture (1:1, TLC) of geiparvarin and its configurational isomer (mp 149-150 °C).

With synthetic geiparvarin, its configurational isomer and the E and Z isomers of 4a-d in hand, there remained only assignment of configuration of the trisubstituted olefinic bond in each case to complete the study. Two NMR observations allowed us to make tentative assignments. First, the C(7) proton of the E isomer was found to resonate significantly downfield (Δ δ 0.4-0.6 ppm) relative to that of the corresponding protons in the Z isomer (see Table I). Similarly, protons at C(8) in the Z isomer, when present, appeared downfield from those of the E isomer (Δ δ 0.1-0.2 ppm). These shifts are presumably due to deshielding by the furanone oxygen.[17] Second, nuclear Overhauser experiments on carefully degassed samples demonstrated that the C(7) olefinic proton of the Z isomer experienced enhancement of signal strength when the C(6) methyl group was simultaneously irradiated; the enhancements ranged from 10-33%. Finally, to confirm rigorously both the E stereochemistry of geiparvarin and in turn to place the above empirical NMR correlations on a firm basis, we completed an X-ray crystallographic analysis of synthetic geiparvarin.[18]

Acknowledgements. It is a pleasure to acknowledge support of this investigation by the National Institutes of Health (The National Cancer Institute) through Grant No. CA-22807. In addition we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR Facility (NIH #RR542) at the University of Pennsylvania where the 220 and 360 MHz NMR spectra were recorded.

References and Footnotes

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8. The structure assigned to each new compound was in accord with its infrared and 220 or 360 MHz NMR spectra. Analytical samples of all new compounds, obtained by recrystallization or chromatography (TLC or LC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high resolution mass spectrometry.

9. All yields recorded here are based on isolated material which was > 97% pure.

10. The α-alkylation product was shown to be 4-phenylhydroxymethyl-5-ethyl-3(2H)-furanone.

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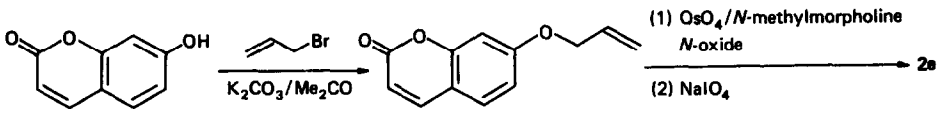
15. Aldehyde 2e was prepared as illustrated by a modified procedure of R. C. Esse and B. E. Christensen, J. Org. Chem., 25, 1565 (1960) employing the cis-hydroxylation protocol of VanRheenen, Kelly and Cha; see V. VanRheenen, R. C. Kelley and D. Y. Cha, Tetrahedron Letters, 1973 (1976).



16. Synthesis of 3e: To a flask which had been flamed dried was added under nitrogen 85 μL (0.6 mmol) diisopropylamine in 10 mL THF. After cooling to -15°, 0.25 mL (0.6 mmol, 2.4 M) n-butyllithium was added and stirred 5 min. The temperature was then lowered to -78° and a solution of 91.7 mg (0.66 mmol) of (1) in 2 mL THF was added dropwise. After stirring 30 min a solution of 187.4 mg (0.92 mmol) of (2e) in 8 mL THF was added very slowly over a 30 min period. Stirring was continued for 1 hr at -78°. Without removing the cooling bath, the solution was warmed to 10° over 1.5 hr. The mixture was then poured into ethylacetate, washed with sat. NH_4Cl, brine and dried over $MgSO_4$. Preparative TLC (20% Et_2O -CH_2Cl_2) afforded 92 mg of 3e. Synthesis of geiparvarin: To a solution consisting of 30.5 mg (0.09 mmol) of 3e, 2.5 mL THF, and 90 uL (0.62 mmol) Et_3N and cooled to 0° was added dropwise 13 uL (0.168 mmol) CH_3SO_2-Cl in 1 mL THF. The reactant mixture was then stirred at 0° for 1 hr, after which it was passed through a silica gel column (6" x 0.5"), and eluted with ether. Preparative TLC (20% Et_2O-CH_2Cl_2) afforded 42.6 mg (50%) geiparvarin.

17. Similar chemical shift correlations for related 3(2H)-furanones were recently observed by Ito; see M. Ito, M. Ohno, E. Takano, Y. Oda and K. Tsukida, Heterocycles, 12, 505 (1979).

18. Unpublished results of B. H. Toder and D. Boschelli of this laboratory.

(Received in USA 5 October 1979)