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UNUSUAL REGIOSPECIFICITY IN THE ENOLIZATION OF A KETONE AS THE RESULT OF DIFFERENCES IN ENERGY TO ACHIEVE THE BEST OVERLAP OF AN ALPHA HYDROGEN

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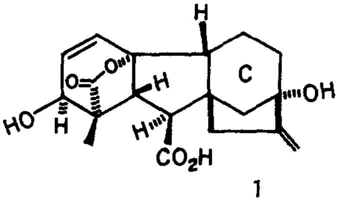
A case of ketone enolization which seems governed by geometry is discussed.

In connection with the study of reactions suggested by possible routes to gibberellic acid (1)[1] we made the remarkable observation that kinetic enolization of tricyclic ketone 2 (5.5 equiv. lithium diisopropylamide, -20°C in THF containing 30% of hexamethylphosphoramide) takes place regioselectively to produce, after trapping of the enolate with chlorotrimethylsilane, the enol silyl ether 3. The structure of 3 was strongly suggested by the NMR spectrum which had absorption at ∂ 4.48 as a singlet with $W\frac{1}{2}$ = 4 Hz. The structure was further supported by carbonation (ether saturated with dry CO_2 at -78°C) of the lithium enolate regenerated from the silyl ether 3 with methyllithium[2] (1.1 equiv., -5°C in glyme) to the corresponding β-keto acid.



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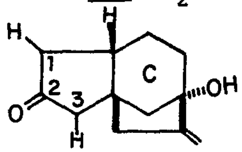

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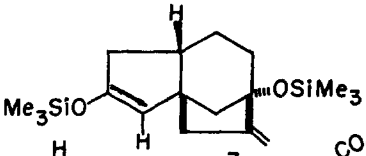

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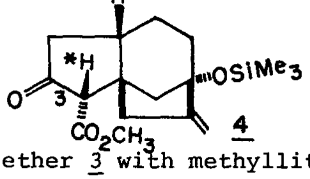

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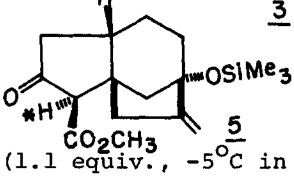

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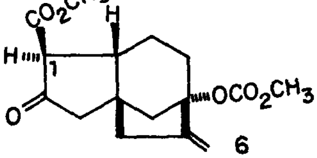

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Esterification (CH_2N_2) gave, in 60-70% yield from the ketone 2, a mixture of the two epimeric methyl esters 4 and 5 from which 4, mp 90-94°C was isolated by fractional crystallization from ether-pentane. Crystalline 4 was reconverted (90% recovery) into the equilibrium mixture (∿1:1) of 4 and 5 upon silica gel chromatography. The most important difference between 4 and 5 in the NMR spectrum was the position of the starred C_3-H which was at δ 3.23 in 4 and at δ 3.0 in 5. In both cases, the hydrogen was a 1H *singlet*, in agreement with the suggested structure.

Complete confirmation of the structure and relative stereochemistry of 4 was provided by an X-ray analysis [2] which also established the α-configuration of the carboxyl function in 4.

In attempting to rationalize this remarkably regioselective enolization, we noticed that a Dreiding model of 2 *seemed* to indicate a strong preference for a boat conformation of the ring labelled C. This appeared quite plausible since X-ray structure determination of gibberellic acid (1) itself has shown that its corresponding ring is, indeed, held in a boat conformation. It became clear, however, that when ring C in the Dreiding model of 2 was progressively transformed from a boat to a chair, the C_1 methylene hydrogen flanking the carbonyl on the accessible β-face of the molecule became less and less able to achieve perpendicularity to the carbonyl plane. The reverse was true of the C_3β-hydrogen. An X-ray structure determination on 2 served to support this view: The stereo drawings of the X-ray structure shown in fig. 1 [3] demonstrate that the ring labelled C is actually in a flattened chair conformation.

fig. 1

The remarkable regiospecificity observed in the kinetic formation of 3 thus appears to be due to the greater ease with which the C_3β hydrogen can achieve overlap with the carbonyl group in the enolization transition state. Not surprisingly, with rapidly interconverting enolates (dimethylcarbonate, sodium hydride, benzene), the major product of carbomethylation was the methyl ester 6 δ3.25 1H, d J = 12 Hz). The fact that 4 has a carboxyl in the same position as in gibberellic acid suggests its possible usefulness for the construction of 1.

References and Notes

(1) Stork, G.: Boeckman, Jr., R.K.; Taber, D.F.; Still, W.C.; Singh, J. *J. Am. Chem. Soc.* 1979, 101, 0000.

(2) Dewan, J.C. *Acta Cryst.*, submitted for publication.

(3) This structure has been published: Harlow, R.L. Simonsen, S.H. Cryst Struct. Comm. 1977, 6, 689-693.

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