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STUDIES ON REDUCTIVE ALKYLATION:

SYNTHESIS OF WIELAND-MIESCHER KETONE ANALOGUES BEARING AN OXYGENATED ANGULAR SUBSTITUENT

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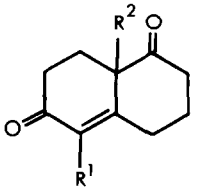
SUMMARY: Wieland-Miescher analogues 2a and 2b have been prepared in good yield by a sequence utilising reductive alkylation of the dihydro aromatic ester enolate 7d, which functions as a synthetic equivalent of the dioxo ester 5 anion; these analogues are envisaged as intermediates in a projected synthesis of bruceantin.

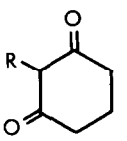
The Wieland-Miescher ketone 1a[1] or its homologue 1b[2] have been used extensively in the synthesis of a wide variety of terpenoids[3] and steroids.[4]

With recent interest shifting to the preparation of more highly functionalised terpene derivatives, there appears to be considerable synthetic potential in analogues of 1a or 1b



a, R^1 = H; b, R^1 = Me

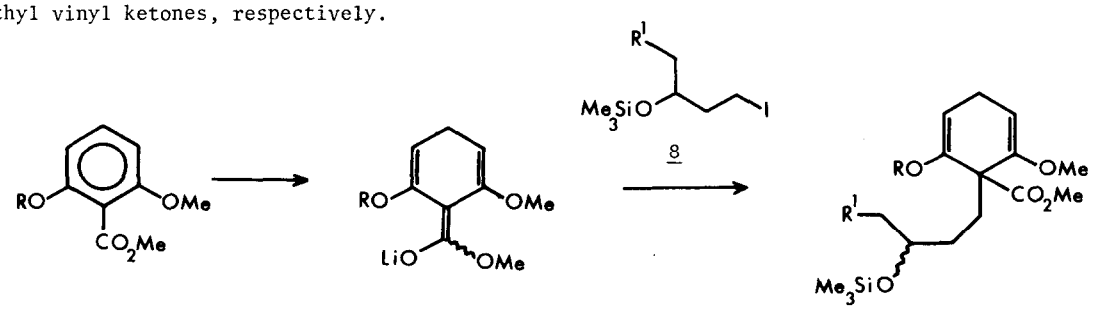
1 R^2 = Me
2 R^2 = CO_2Me
3 R^2 = CH_2OR



4 R = Me
5 R = CO_2Me

in which the angular substituent is functionalised. Our own special interest, for example, was centered on the possibility of utilising 2b or 3b as potential precursors to the B and C rings of the anti-neoplastic quassinoid, bruceantin.[5] It appeared that the facile preparation[1] of 1a and 1b by Robinson annulation of dione 4 could not readily be extended to dione 5[6] or another suitable substrate, however. For example, even if 2-acyl derivatives could be induced to undergo alkylation or Michael addition, the adducts would be especially prone to acyl cleavage by nucleophiles.

In this Letter we describe a successful solution to this dilemma, based on the utilisation of the dihydroaromatic ester enolates 7c and 7d as operational equivalents of the dioxo-ester 5 anion.[7] The side chains required in the annulations were introduced by alkylation with iodides[8] 8 (R^1 = H, Me) which serve as useful new equivalents to methyl and ethyl vinyl ketones, respectively.

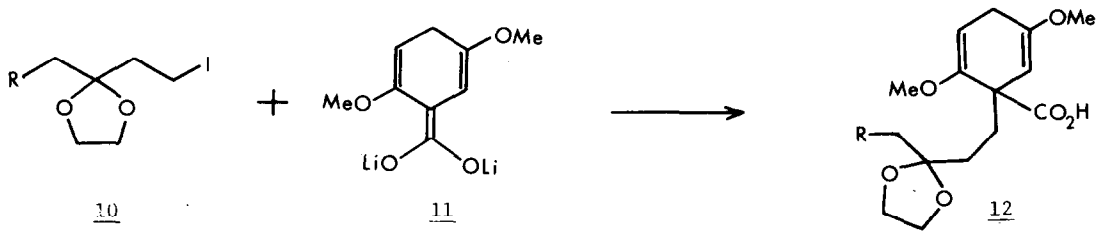


6 7 8 9

c, R = Me; d, R = $Si(^tBu)Me_2$

Scheme 1

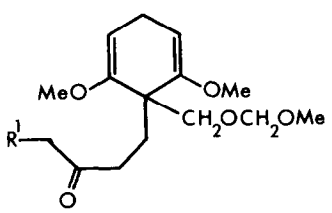
Thus, reduction of ester 6c by potassium metal in liquid ammonia at -78°C (THF, *t*-BuOH, 1 eq. N_2 atmosphere, 15 min), then addition of anhydrous LiBr, followed by either iodide 8 (R^1 = H) or 8 (R^1 = Me), furnished adducts 9c (R^1 = H and Me, respectively) in almost quantitative yields (Scheme 1); alkylation of the *lithium* enolate is vital (no useful products were obtained from the potassium enolate). Although a great variety of reagents[9] are, in principle, available for the introduction of the 3'-oxobutyl and 3'-oxopentyl side chains, the choice was severely proscribed by our intention to reduce the ester function in 9c subsequently (to minimise the risk of retrograde Claisen processes, following the liberation of the keto groups from the enol ether functions). Iodoketals 10 (R = H, Me)[10] were obvious choices, but although the dilithium enediolate 11 derived from reduction of 2,5-dimethoxybenzoic acid [7a] was successfully alkylated (Scheme 2) to furnish acid 12 (R = Me), m.p. 105-110° in 67% yield, neither the equivalent 2,6-isomer nor the ester derived 7c gave useful products (only E2 elimination of iodide was observed).



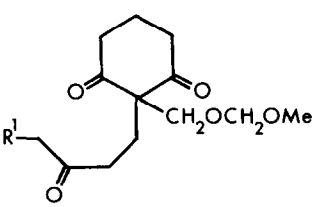
10 11 12

Scheme 2

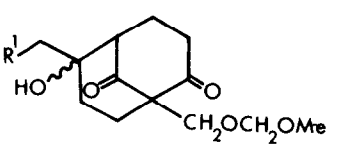
The desired oxopentyl derivative 13, m.p. 43-45°, was readily obtained from 9c (R^1 = Me) in 59% overall yield, however, by $LiAlH_4$ reduction, hydroxyl protection ($MeOCH_2Cl$, $^iPr_2NEt$), KF induced silyl ether cleavage, and then Pfitzner-Moffat oxidation.[11] Hydrolysis[12] of the



13 R^1 = Me
14 R^1 = H



15 R^1 = Me

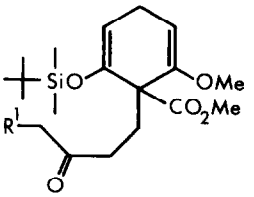


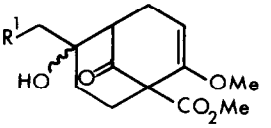
16 R^1 = Me
17 R^1 = H

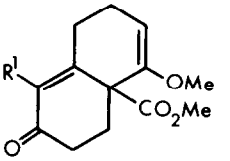
enol ether functions [$Hg(NO_3)_2$, CH_3CN, H_2O, 24°, 48 h] in 13 then furnished a mixture of 15 with the "wrong" epimeric ketols[13] 16, but all efforts to convert these compounds into the target keto enone 3b (R = CH_2OMe) by treatment with a range of bases failed. Attempts to prepare 3a (R = CH_2OMe) from the lower homologue 14, m.p. 57-59°, were also unsuccessful, resulting in the undesired aldol product 17 (major epimer, m.p. 110-112°).[14]

Our objectives were finally achieved by maintaining one of the enol ether functions through the aldol process. Thus, reductive alkylation (as for 6c) of the *t*-butyldimethylsilyl ether 6d,[15] m.p. 30-32°, with iodide 8 (R^1 = Me) furnished 9d (R^1 = Me) in 88% yield. Selective hydrolysis of the trimethyl silyl ether function by brief exposure to aqueous acetic acid (this was best carried out during work-up of the alkylation reaction mixture)

followed by oxidation[11] furnished 18 (m.p. 30-32°, 65% yield). Hydrolysis[16] (n-$Bu_4\overset{+}{N}F^-$, THF,







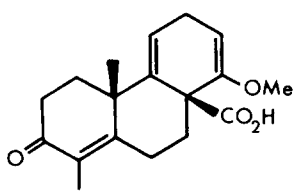
18 R^1 = Me
19 R^1 = H

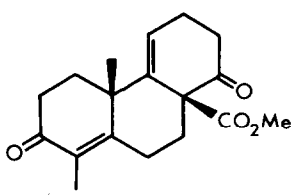
20 R^1 = Me
21 R^1 = H

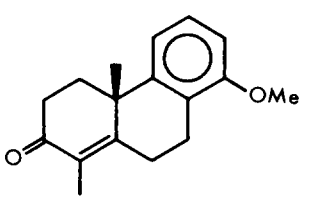
22 R^1 = Me
23 R^1 = H

0°, 0.5 h, N_2, 90% yield) then gave a 2:1 mixture of ketols 20 (major epimer, m.p. 137-139°), and this time, base treatment (K_2CO_3-MeOH, N_2) furnished enone 22, m.p. 84-85°, in 75% yield. The analogous sequence beginning with iodide 8 (R^1 = H) afforded 19, m.p. 50-51°, diastereomers 21 (1.5:1, m.p. 139-140°, m.p. 95-97°, respectively) and then 23, m.p. 53-54°, in comparable yields.

Enol ethers 22 and 23 were efficiently hydrolysed in the presence of $Hg(NO_3)_2$ (0.3 eq. 72 h) to the interim target keto enone 2b (m.p. 39-40°, 91% yield) and its nor-homologue 2a (oil, 78% yield). For the purpose of synthesising larger molecules, however, it was advantageous to postpone hydrolysis of the enol ether function. Thus, 22 was annulated with 1-chloro-pentan-3-one (NaOMe, MeOH, Δ, 3 h) to give tricyclic acid 24. Hydrolysis [$Hg(NO_3)_2$] of the derived methyl ester, m.p. 134-136°, furnished diketo ester 25, m.p. 155-7°, while attempted hydrolysis of 24 under similar conditions led to the known[17] aromatic derivative 26.







24 25 26

Studies on the elaboration of 25 into bruceantin are continuing, but the greatest immediate value of the present study stems from the successful development of a practical route to 2a and 2b, and from the demonstration of the considerable potential in aromatic esters such as 6c and 6d to serve as precursors of complex cyclohexane-1,3-dione derivatives. The introduction of the new vinyl ketone equivalents 8 (R^1 = Me and H) should also prove to be a useful contribution to annulation methodology. Although the need to carry out an oxidation of the introduced side chain may be limiting in some applications, the preparations of 13, 14, 18, and 19 provide a severe test of the procedure. The dihydroaryl moiety in these compounds undergoes very rapid oxidation with Cr(VI) based reagents, for example, and success was obtained only with activated dimethyl sulfoxide reagents. Without this limitation, even higher yields than those reported above should be readily attainable.

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