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A NEW METHOD FOR THE SYNTHESIS OF STRUCTURALLY SPECIFIC OLEFINS FROM ENOLATE ANIONS

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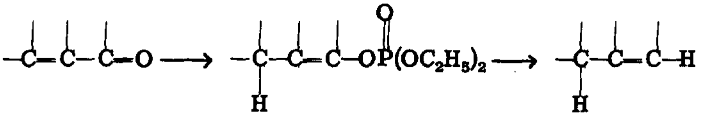
During the course of a current synthetic program under investigation in these laboratories, we had need of an efficient synthesis of the ketal 3. In an effort to avoid what might be a tedious separation of the isomeric olefins that would probably result from a dehydration process, we sought a synthetic scheme that would generate the ketal 3 in a structurally selective manner from readily available intermediates.

One such scheme was suggested by deoxygenation (1) of phenols through lithium-ammonia reduction of the derived diethyl aryl phosphates. If diethyl enol phosphates behaved in a similar manner, the structurally related olefin should result. Formation of the required diethyl enol phosphate might logically result from the interaction of an enolate anion and a suitable phosphorylating agent such as diethyl phosphorochloridate (2). The desired structural selectivity would depend then on the generation of the enolate anion. The answer for this requirement appeared available from the recent work of Stork and co-workers (3) who have shown that the lithium-ammonia reduction of α,β-unsaturated ketones is an ideal source of such enolate anions. In its general form, the complete project appeared then to require the transformations suggested by Equation 1.



$$-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O \longrightarrow -\underset{H}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-O\overset{O}{\overset{\|}{P}}(OC_2H_5)_2 \longrightarrow -\underset{H}{\overset{|}{C}}-\overset{|}{C}=\overset{|}{C}-H$$

(Equation 1)

The ketone ketal 1 (4) required as the starting material for this sequence was readily prepared by ketalization of the annellation product from 2-methylcyclohexane-1, 3-dione and ethyl vinyl ketone. Reduction of this α,β-unsaturated ketone 1 with two equivalents of lithium

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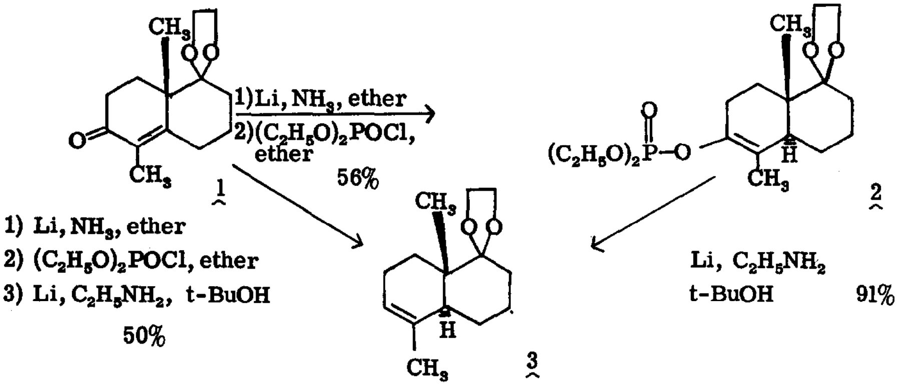
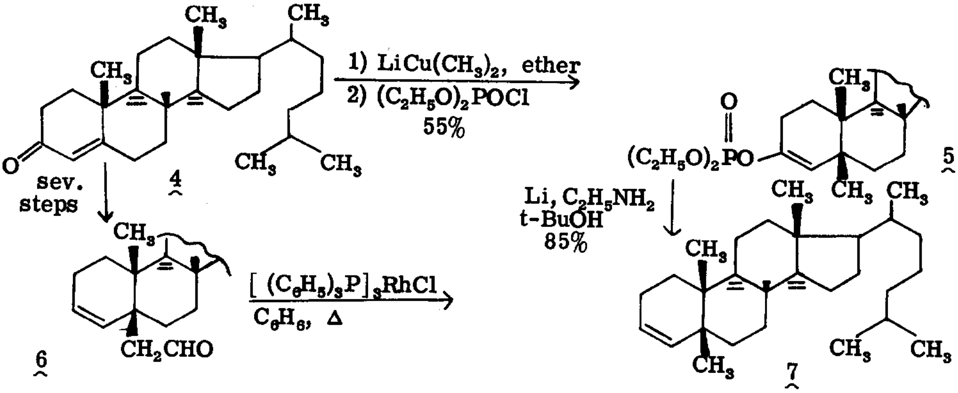
in ammonia-ether solution was followed by evaporation of the ammonia and phosphorylation of the resulting lithium enolate in ethereal solution with diethyl phosphorochloridate. After chromatography of the crude phosphate on silica gel there was obtained a 56% yield of the diethyl enol phosphate 2 (5) as an oil. This material was characterized by infrared [max. ($CHCl_3$) 1680 cm^{-1} ($>C=C<$) 1260, 1025 and 960 cm^{-1} (trialkyl phosphate)] and nmr[$\delta(CDCl_3)$ 0.99 (s, 3, C10-CH_3), 1.35 (t, 2x3, J=7Hz, $(C\underline{H}_3CH_2O)_2PO_2$-), 1.60 (s, 3, C1-$CH_3$), 3.90 (s, 4, C5-$OCH_2C\underline{H}_2O$-) and 4.10 (m, 2x2, $(CH_3C\underline{H}_2O)_2PO_2$-)] spectroscopy. Further reduction of the diethyl enol phosphate 2 with excess lithium in a mixture of ethyl amine and t-butyl alcohol did indeed lead to a high yield of the desired olefinic ketal 3 (5). The reduction was quite specific and no isomeric olefins could be detected by either vapor phase chromatography or nmr [$\delta(CDCl_3)$ 0.99 (s, 3, C10-CH_3), 1.60 (s, 3, C1-CH_3), 3.90 (s, 4, C5-$OCH_2C\underline{H}_2O$-) and 5.25 (m, 1, C2-H)] spectroscopy of the crude reduction product.



The efficiency of the second stage of this reduction process suggested that the entire sequence might be carried out without isolation of the intermediate diethyl enol phosphate 2. This proved to be the case, for if the crude reaction mixture from the initial reduction and phosphorylation of the ketone ketal 1 was reduced directly with lithium in ethyl amine-t-butyl alcohol, 50% overall yield of the desired olefinic ketal 3 was isolated after chromatography on silica gel. While the yield in this phosphorylation step leaves something to be desired, the efficiency of the subsequent reductive cleavage of the diethyl enol phosphate is quite satisfactory, and the ability to telescope the two steps makes the synthetic process quite useful.

Intrigued by these results, we applied the same techniques to the enolate anion that is generated by the conjugate addition of organometallic reagents to α,β-unsaturated ketones. The ability to trap such enolate anions with acylating agents has been amply demonstrated by

House and co-workers (6), and it was not surprising to find that the addition of excess diethyl phosphorochloridate to a mixture of lithium dimethyl copper and 4-cholesten-3-one (4) resulted in a 55% yield of the desired diethyl enol phosphate 5 (5) after silica gel chromatography. The structure of this material was confirmed by infrared [max. ($CHCl_3$) 675 cm^{-1} (>C=C<); 1250, 1025 and 975 (trialkyl phosphate)] and nmr [δ($CDCl_3$) 1.33 (t, 2x3, J=7Hz, $(C\underline{H}_3CH_2O)_2PO_2$-), 4.10 (m, 2x2, $(CH_3C\underline{H}_2O)_2PO_2$-) and 5.10 (m, 1, C4-H)] spectroscopy.



On further reduction of this enol phosphate with lithium in ethyl amine-t-butyl alcohol solution again led in high yield to a single (vpc, nmr) olefinic product. From the previous experience, together with satisfactory analytical and spectral data, this olefin was assigned the structure 7 (5).

Confirmation of this assignment was possible as a result of the recently reported (7) method for the angular methylation of α,β-unsaturated ketones by the decarbonylation of the angular acetaldehyde residues that result from the Claisen rearrangement of the derived vinyl ethers. Thus, formation of the aldehyde 6 from 4-cholesten-3-one (1) proceeded as expected (8) in 45% overall yield, and then decarbonylation was effected in 80% yield in benzene solution with tristriphenylphosphine rhodium chloride. The 5-methyl-3-coprostene (7)(5) prepared in this manner had identical spectral physical properties to that which resulted from the phosphate reduction and established with certainty the structure of the material from the former process. The overall yield of the olefin 7 from the enone 4 was 47% in two operations by the phosphate reduction method and 36% in four operations through the aldehyde 6.

While this work was in progress, a report appeared by Fetizon and co-workers (9) on the preparation of some steroidal Δ^2-olefins by lithium-ammonia reduction of the corresponding diethyl enol phosphates, generated by the action of triethyl phosphite on the 2-bromo-3-ketones. To contrast our work with that of the French workers and to test our phosphorylation procedure in the absence of extraneous by-products, we prepared the diethyl enol phosphate **4** from the enolate anion formed by treatment of 5-methyl-3-coprostanone (10) with sodium hydride in dimethoxyethane. The expected enol phosphate **5** was again generated, and this time in high yield (95%). Thus, it appears that both methods for the preparation of the requisite diethyl enol phosphate intermediates are equally satisfactory, and the lower yields we experienced in the phosphorylation of the enolate anions from conjugated addition may be due to the more complex reaction mixtures involved. Further work on this phase of the sequence, as well as a program to investigate the generality of the method, is being undertaken.

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(10) This ketone (5) was prepared in 50% yield by the addition of lithium dimethyl copper to 4-cholesten-3-one.