

A ROUTE TO PROSTAGLANDIN PRECURSORS FROM 1-(PHENYLTHIO)-2-OCTENYL LITHIUM.

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Summary: The enolates generated by the conjugate addition of 1-(phenylthio)-2-octenyllithium to 4-tert-butoxycyclopent-2-en-1-one and γ -crotonolactone react with methyl 7-halohept-5-ynoates in the presence of Ph_3SnCl to deliver products which may be converted into prostaglandin precursors.

Carbanions derived from simple allylic sulfides undergo conjugate addition to cyclopent-2-en-1-one in the presence of HMPA in THF at -78° to give allylic sulfides in good yields.¹ As we now report, the reaction may be extended to the anion of an octenyl sulfide in a synthetically useful manner.

Reaction of commercially available 1-octen-3-ol with PBr_3 in ether at 0° gave a mixture of (E)-1-bromo-2-octene and 3-bromo-1-octene (1:1, 91%), which was quantitatively converted by sodium benzenethiolate in methanol at 0° into the corresponding sulfide mixture. Irradiation (sunlight, or tungsten lamp, 600w, 12h) of this mixture in dichloromethane containing a trace of thiophenol converted the 3-(phenylthio)-1-octene therein quantitatively into the other component of the mixture, (E)-1-(phenylthio)-2-octene 2.² Deprotonation of 2 at -78° in THF containing HMPA (1.5 eq) by butyllithium gave the orange red anion 2⁻, which was treated at -78° with 4-tert-butoxycyclopent-2-en-1-one 1³ (ca. 1 eq) until disappearance of the colour of the anion. If the reaction was quenched at this stage with aqueous NH_4Cl , then the addition product 3 was isolated in 86% yield after flash chromatography, as a 1:1 mixture of diastereomers. If, however, the reaction mixture was treated with methyl 7-iodohept-5-ynoate,⁴ low and variable yields (to 44%) of the vicinally-dialkylated cyclopentanone 4 in addition to other unidentified products were obtained. Notably, very little of the simple addition product 3 could be isolated from such reactions, which contrasts with the high yield of this product obtained on direct aqueous quenching of the enolate produced by the addition of 2⁻ to 1. It thus appears likely that decomposition of the enolate, perhaps by an equilibration initiated by the neutral product 4, competes with its alkylation. Mindful of the notable success achieved by Posner and Lentz in suppressing enolate equilibration through use of copper(I) salts,⁵ we treated the enolate with a number of trans-metallating agents - CuCN , CuI , Bu_3SnCl ,⁶ Ph_3SnCl - prior to addition of the electrophile. Whereas the use of the copper(I) salts surprisingly led to formation of mixtures of vicinally-dialkylated products in which de-tert-butylation had

taken place,⁷ use of Ph_3SnCl resulted in an exceptionally clean formation of the dialkylated product 4 in an isolated yield of 70%. Use of Bu_3SnCl resulted in inferior yields of 4. Presumably the intermediate - either an enol stannane⁶ or enolate "ate" complex⁹ - displays no tendency to enter into the side reactions characteristic of the lithium enolate.

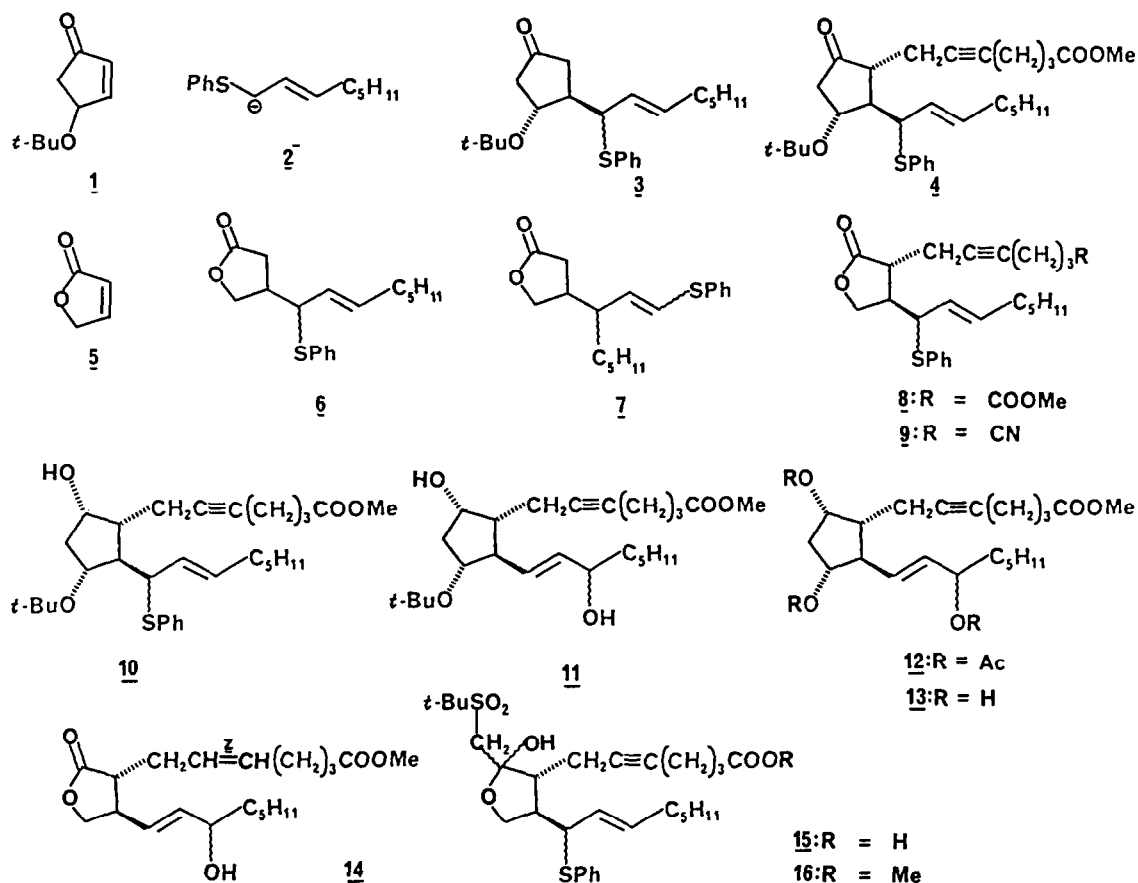
γ -Crotonolactone 5 reacted in similar fashion with 2^- at -78° in THF, provided that HMPA (1.5 eq) was present, to give after aqueous quenching, the simple addition product 6 as a 1:1 mixture of diastereomers in 90% yield. In the absence of HMPA, conjugate addition was still the exclusive reaction pathway, but a substantial quantity (22%) of the vinylic sulfide (7) in addition to the allylic sulfide 6 (62%) was now formed. When the reaction mixture of 2 and 5 in the presence of HMPA was treated with either methyl 7-bromohept-5-ynoate⁴ or 7-bromo-5-heptynenitrile at -40° and then at -15° after 10h with aqueous NH_4Cl the respective enolate trapped products 8 (50%) and 9 (55%) in addition to the simple addition product 6 (19-20%) were obtained. Treatment of the enolate generated in the addition with Ph_3SnCl prior to its reaction with the first electrophile gave 8 in 63% yield. Attempts to alter the diastereochemical outcome of the addition process by utilizing the cis isomer of 2^- or carbanions related to 2^- in which the phenyl group was replaced by alkyl groups (tert-butyl, methyl), or by polar groups [Me_2NCO^- , $(\text{Me}_2\text{N})_2\text{PO}^-$] were not successful.

The cyclopentanone 4 was converted by diisobutylaluminium hydride-2,6-di-tert-butyl-4-methylphenol in toluene¹⁰ into the 9α -alcohol 10 (85%), and thence via the corresponding sulfoxide into the dialcohol 11 (60%). Deprotection of the 11α -hydroxyl group was carried out in two steps. Treatment of 11 with a catalytic amount of anhydrous FeCl_3 in freshly distilled acetic anhydride¹¹ at 0° rapidly converted it into the triacetate 12, which was hydrolysed by K_2CO_3 in methanol at 20° during 24h to triol 13 (90% from 11). Analysis of the product by HPLC indicated that it consisted of two diastereomers in a ratio of 1:1. As the sulfide 3 also consists of a 1:1 mixture of diastereomers, all reactions subsequent to the formation of the enolate of 3 in the conjugate addition step are stereospecific.^{12,13} A diprotected form of the 15(S) diastereomer of the triol 13 has been prepared previously¹⁴ and converted into prostaglandin $\text{F}_{2\alpha}$. Conversion of lactone 8 into the allylically-transposed alcohol, and subsequent hydrogenation furnished the 9-oxo-10-oxa prostaglandin analogue 14 (65% overall from 8). The lactone 8 was converted by sodium hydroxide (2.5M) in methanol: water (9:1) at 20° during 24h and then by aqueous acid into the free acid (95%), treatment of which with tert-butylsulfonyl-methylolithium¹⁵ (4.0 eq) in THF containing TMEDA (4 eq) at 0° gave the hemiacetal 15 (93%) as a mixture of diastereomers. 15 was quantitatively converted by diazomethane in ether at 0° into the ester 16. Surprisingly, however, attempted oxidation or tosylation of the primary alcohol which is present in the open-chain ketol form of 15 or 16 as a prelude to carbocyclization of 15 or 16 to natural prostaglandin precursors has so far been unsuccessful.¹⁶

Thus, the overall usefulness of these non-copper(I) mediated conjugate addition reactions has been demonstrated. Although we have not introduced the hydroxyl group at C-15 in a stereospecific manner, this is, in principle easily effected by its oxidation to the ketone,

followed by stereospecific reduction,¹⁰ a step which can be coupled with reduction of the C-9 carbonyl. Current work focusses on the use of stabilized carbanions which will serve as direct precursors of the lower side chain bearing a carbonyl at C-15.

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References and Notes

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- (3) This is readily prepared in three steps from cyclopentadiene: Schwartz, J.; Loots, M.J.; Kosugi, H. *J.Am.Chem.Soc.* 1980, 102, 1333.

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- (7) HPLC analyses indicated a complex mixture of products.
- (8) The enolate generated by addition of 2⁻ to 1 was treated at -40^o with Ph₃SnCl (1.0 eq). The mixture was warmed to -20^o, then cooled to -40^o prior to treatment with the electrophile. The resultant solution was stirred at -10^o for 15h prior to quenching.
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- (12) The de-tert-butylation-acylation reaction presumably proceeds via formation of an acylated oxonium ion followed by loss of the tert-butyl cation, or its equivalent.¹¹ An SN2 attack by acetate, which normally represents the alternative mode of cleavage of such oxonium ions and which, in this case, must take place at C-11, will be suppressed by the adjacent side chain attached to the β -face of the cyclopentane nucleus at C-12. Cleavage by an SN1 process would place a positive charge at C-11 which, for a similar reason, can only be quenched by acetate from the α -face of the cyclopentane nucleus. The use of the tert-butyl group as a protecting group is noteworthy as its introduction is inherent in the preparation of 1, and does not require a separate step.³
- (13) Initially, we wished to apply the deprotection reaction to the ketone 4 with the intention of generating the free C-9 hydroxyl group after the generation of those at C-11 and C-15 in protected forms. However, the FeCl₃-acetic anhydride reagent induced rapid, concomitant cleavage of the allylic thioether in 4 to deliver phenylthio acetate and an uncharacterized diene from 4.
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- (15) Use of phenylsulfonylmethyl lithium gave somewhat lower yields of product. In addition, the product could not be readily separated from unreacted methyl phenyl sulfone.
- (16) The ¹³C NMR spectra of 15 and 16 display signals due to hemiacetal carbons (105-110 ppm) but none due to ketone carbonyls.

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