

CYCLOPENTENONE SYNTHESIS VIA ALDOL CONDENSATION.

SYNTHESIS OF A KEY PROSTAGLANDIN INTERMEDIATE

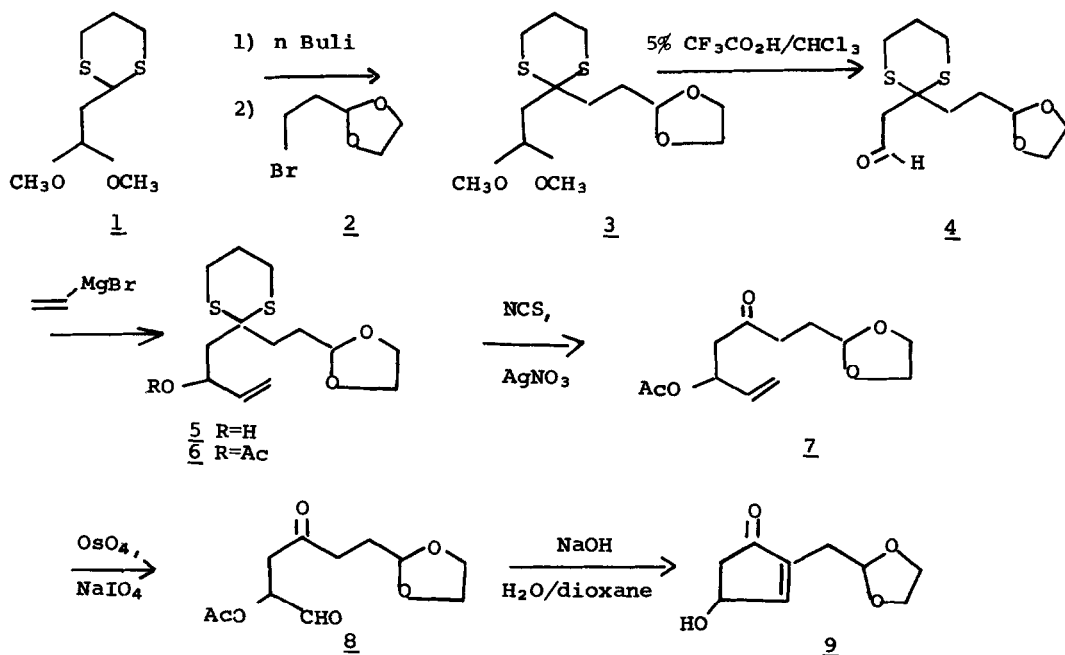
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We wish to report a continuation of our work directed toward the synthesis of hydroxycyclopentenones<sup>1</sup> suitable for elaboration into prostaglandins. General synthetic approaches to cyclopentenones have been reviewed<sup>2</sup> and several more recent routes have subsequently appeared<sup>3</sup>. The approach described here was based on the assumption that the desired cyclopentenones ought to be obtainable by condensation of the corresponding  $\gamma$ -keto aldehyde under appropriate conditions.<sup>4</sup>

The starting material (1) was prepared according to a previous procedure<sup>5</sup> by



exposure of malonaldehyde-bis-dimethylacetal to propanedithiol in methanolic hydrogen chloride. The bromoacetaldehyde ethylene ketal (2) was prepared by reaction of acrolein with ethylene glycol in the presence of hydrogen bromide at  $0-5^{\circ}$ .

Metalation of 1 was effected with n-butyllithium in tetrahydrofuran at  $-70^{\circ}$  for 30 min. Condensation product 3 was obtained in 90% yield (based on recovered starting material) by exposure of 2 to the above anion for 1 hr. at  $-70^{\circ}$  followed by chromatography on silica gel: nmr ( $\text{CDCl}_3$ )  $\delta$  1.90 (m, 6H), 2.13 (d,  $J=4.5$  Hz, 2H), 2.6-3.0 (m, 4H), 3.29 (s, 6H), 3.87 (m, 4H), 4.58 (t,  $J=4.5$  Hz, 1H), 4.82 (t,  $J=4.0$  Hz, 1H).<sup>7</sup>

The dimethylacetal was selectively hydrolyzed by stirring in a mixture of chloroform and 50% aqueous trifluoroacetic acid (2:1) at  $0^{\circ}$  for 90 min. The resulting oily product was reacted with vinyl magnesium bromide<sup>8</sup> in tetrahydrofuran at  $-70^{\circ}$  for 30 min. at which time the reaction mixture was treated with acetic anhydride. After warming to room temperature the recovered product mixture was chromatographed on silica gel to give the vinyl acetate 6 in 57% yield overall from 3: ir ( $\text{CHCl}_3$ ) 1743,  $1640\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ ) 1.7-2.2 (m, 9H), 1.95 (s, 3H), 3.6-4.0 (m, 4H), 3.86 (m, 4H), 4.82 (t,  $J=4.0$  Hz, 1H), 4.9-6.0 (m, 4H).

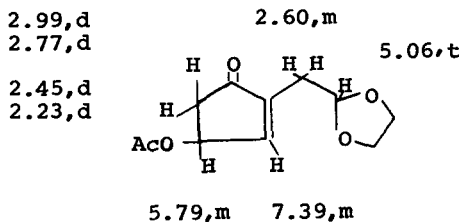
For verification, the aldehyde 4 could be isolated in 96% yield: ir ( $\text{CHCl}_3$ )  $1713\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  9.86 (bs, 1H). The remainder of the nmr spectrum was identical to that of 3 minus the signals at  $\delta$  3.29 and 4.6.

The dithiane blocking group was removed by reaction with N-chlorosuccinimide and silver nitrate in acetonitrile-water (4:1)<sup>9</sup> at room temperature for 10 min. The sole product isolated was the oily ketone 7 (97% yield): ir ( $\text{CHCl}_3$ ) 1743, 1720,  $1657\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  2.01 (s, 3H), 2.6-2.9 (m, 6H), 3.88 (m, 4H), 4.92 (t,  $J=4.0$  Hz, 1H), 5.0-6.1 (m, 4H).<sup>7</sup>

Aldehyde 8 was smoothly generated by dissolution in dioxane-water (3:1) and exposure to a trace of osmium tetroxide in the presence of sodium metaperiodate which was added over a period of 1.5 hr. The reaction mixture was kept in the refrigerator for 14 hr. whereupon 8 was isolated as an oil in 77% yield: ir ( $\text{CHCl}_3$ )  $1743\text{cm}^{-1}$  (broad); nmr ( $\text{CDCl}_3$ )  $\delta$  2.07 (s, 3H), 2.6-3.2 (m, 6H), 3.92 (m, 4H), 4.93 (t,  $J=4.0$  Hz, 1H), 5.30 (t,  $J=5.5$  Hz, 1H), 9.73 (s, 1H). Again, the

product was sufficiently pure to be used directly in the subsequent condensation.

Ketoaldehyde **8** was dissolved in a mixture of dioxane and 1N aqueous sodium hydroxide (15:1) at 10° and stirred under a nitrogen atmosphere for 30 min. The oily product mixture was chromatographed on silica gel to give pure hydroxycyclopentenone **9** in 37% yield: ir (CHCl<sub>3</sub>) 1740, 1713 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>) δ 2.2-3.0 (m, 4H), 4.34 (m, 4H), 4.91 (m, 1H), 5.06 (t, J=4.0 Hz, 1H), 7.93 (m, 1H).<sup>7</sup>



The structure of **9** was verified by pmr decoupling experiments at 90 MHz on the corresponding acetate. Thus, irradiation of the olefinic proton at 7.39 δ resulted in a noticeable decrease in the bandwidth of the multiplet at 5.79 δ and an improvement in the resolution of the multiplet at 2.60 δ. Irradiation at 5.79 δ sharpened the signal at 7.39 δ and collapsed the signals for the ring methylene protons to a pair of doublets (J=19.5 Hz). In the hydroxy derivative (**9**), the signal at 5.79 δ is absent and is replaced by a multiplet at 4.98 δ which is partly superimposed on the side-chain methine triplet.

#### References

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