An Alternative Synthesis of the Corey Prostaglandin Aldehyde†

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Summary Efficient four-pot syntheses from norbornadiene of the γ-lactones (**7**), (**8**), and (**2**), which are useful as prostaglandin precursors, are described.

AMONGST the large variety of synthetic approaches to the prostaglandins,[1] the aldehyde[2] (**1**) stands out as an intermediate allowing the ready preparation of a variety of prostaglandins and analogues. We here report an alterna-

† This work was presented as a lecture at the 3rd International Symposium on Organic Synthesis at Oxford on 12th July 1973. On that occasion Professor E. J. Corey kindly informed us that his group had prepared the acid (**11**) by a similar route and converted it into prostaglandins by routes different from ours.

tive synthesis of (**1**) and some related intermediates starting with the Prins reaction[3] of norbornadiene and paraformaldehyde in formic acid‡ which yielded the mixture of epimeric diformates (**9**) (67%), τ 1·96 (2H, s), 5·20 (0·5H, m), 5·27 (0·5H, m), and 6·00 (2H, m). Hydrolysis of (**9**) gave the diols (**10**) (87%) τ 6·19 (1H, m), 6·52 (dd, J 8 and 2 Hz), 6·26 (1H, m), and 6·67 (d, J 7 Hz). Oxidation of either

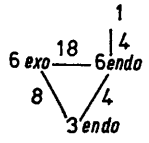
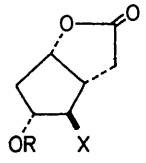


FIGURE. H–H Couplings for (**13**) in Hz.

(**9**)[4] or (**10**) with Jones' reagent gave the crystalline acid§ (**11**) (65 and 70% respectively). The structure of this acid was established by its Wolff–Kishner reduction to the known nortricyclyl-2-carboxylic acid.[5]



(1) (R=COC_6H_4Ph; X=CHO)

(2) (R=H; X=CO_2H)

(3) (R=H; X=$CO_2CH_2COC_6H_4Br$)

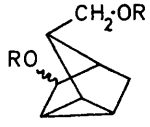
(4) (R=COC_6H_4Ph; X=$CO_2CH_2COC_6H_4Br$)

(5) (R=COC_6H_4Ph; X=CO_2H

(6) (R=COC_6H Ph; X=CH_2OH)

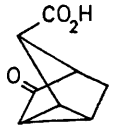
(7) (R=Ac; X=CO_2H)

(8) (R=COC_6H_4Ph; X=CO_2Me)

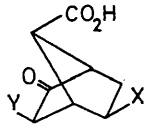


(9) (R=H·CO)

(10) (R=H)



(11)



(12) (Y=H; X=Br)

(13) (Y=Br; X=Br)

(14) (Y=H; X=Cl)

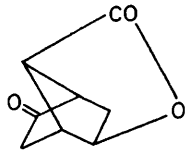
(15) (Y=H; X=OAc)

(16) (Y=H; X=OH)

(17) (Y=H; X=$OSO_2C_7H_7$)

The direction(s) of electrophilic ring-opening of the cyclopropyl ketone system in (**11**) could not be predicted unambiguously; however, in the event, reaction with 48% HBr in AcOH yielded (**12**) (92%),¶ τ 5·62 ($W_{\frac{1}{2}}$ 14 Hz).

The structure and stereochemistry of (**12**) was established by bromination to (**13**), the n.m.r. spectrum of which contained the coupled system shown in the Figure which is consistent only with (**13**). That no drastic rearrangements had occurred in this series of reactions was demonstrated by reduction (Zn–AcOH) of (**13**) to (**12**) and dehydrohalogena-



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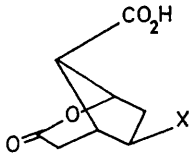
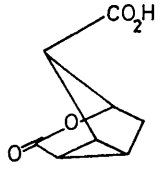


(19) (X=Br)

(20) (X=$OSO_2C_7H_7$)

(21) (X=Cl)



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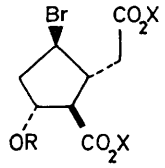

(23) (R=Ac; X=H)

(24) (R=H; X=Me)

(25) (R=COC_6H_4Ph; X=Me)

tion of (**12**) to (**11**) with 2N-NaOH. Chemical proof of the regio- and stereo-selectivity of the electrophilic ring-opening in this series resulted from reaction of (**11**) with AcOH–$HClO_4$ yielding the γ-lactone (**18**), τ 5·15 ($W_{\frac{1}{2}}$ 5 Hz), ν_{max} 1790 and 1760 cm^{-1} (30%) and the acetate (**15**) (24%), τ 4·97 ($W_{\frac{1}{2}}$ 12 Hz); both (**15**) and (**18**) could be hydrolysed to the alcohol (**16**), which, on sublimation, regenerated (**18**).

Baeyer–Villiger oxidation of (**12**) with peroxyacetic acid gave the lactone (**19**), τ 4·98 (1H, $W_{\frac{1}{2}}$ 9 Hz) and 5·40 (1H, $W_{\frac{1}{2}}$ 16 Hz) (71%), accompanied by *ca.* 20% of its isomer derived by the alternative mode of ring expansion. Baeyer–Villiger oxidation of (**11**) gave (**22**), τ 5·28 (1H, m), and its isomer in a superior ratio (7 : 1). Disappointingly, treatment of (**19**) with aqueous alkali formed (**22**), rather than (**2**); similar reaction of the methyl ester of (**20**) from (**17**) gave the methyl ester of (**22**). Reaction of the chlorolactone (**21**) [prepared from (**11**) *via* (**14**) as for the bromolactone] with aqueous alkali gave predominantly (**22**) but also some of the acid (**2**), τ (Me ester) 4·98 (1H, dt, J 2·5 and 6·5 Hz) and 5·50 (1H, q, J 4 Hz), ν_{max} 1770 and 1730 cm^{-1}. The predominance of elimination, rather than ring-opening

‡ Use of formic acid as solvent reduced the variety of products obtained in these reactions owing to formylation of the introduced primary hydroxymethyl group (R. Battaglia and J. K. Sutherland, unpublished work).

§ We thank Dr. G. F. Pratt for the initial preparation of this acid.

¶ The high regiospecificity of the reaction is probably due to the field effect of the carboxy-group rather than its direct participation since the methyl ester and epimeric acid also show this specificity.

with these bridged-lactones is undoubtedly due to the favourable geometry[6] for 1,3-elimination and the relatively high basicity of hydroxide ion compared to nucleophilicity for sp^2 carbon. Hydroxylamines are reagents where this differential is reduced and, indeed, reaction of (**19**) with hydroxylamine in collidine yielded the acid (**2**)** (52%), accompanied by the cyclopropyl lactone (**22**) (20%). The alternative solution for an efficient conversion of (**19**) into (**2**) is to destroy the highly favourable geometry for elimination before applying the basic conditions required for lactonisation; this was achieved by reaction of (**19**) with HBr in AcOH to give (**23**), τ[$(CD_3)_2CO$] 4·64 (1H, m) and 5·68 (1H, m), which on dissolution in aqueous NaOH yielded (**2**) [72% from (**19**)]. Reaction of (**23**) with $NaHCO_3$ (2 mol equiv.) yielded the acetate (**7**). The overall conversion of (**12**) into (**2**) could be carried out in a one-pot process by adding sulphuric acid to the Baeyer–Villiger reaction mixture and working up the product with alkali. Acid-catalysed methanolysis of (**19**) yielded (**24**) which, after *p*-phenylbenzoylation to (**25**) was converted into (**8**) by AgOAc in AcOH (72% overall).

The formal total synthesis of a number of PG's was completed by conversion of (**2**) into the *p*-bromophenacyl ester (**3**), *p*-phenylbenzoylation to (**4**), reduction (Zn–AcOH) to (**5**),[7] and diborane reduction to (**6**) which was identical with an authentic sample.

This work allows the simple preparation of the lactones (**2**), (**7**), and (**8**) and makes them attractive starting materials for synthesis of PG's.

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** Presumably after hydroxamic acid formation the carbonyl oxygen of this function displaces Br forming hydroximino-lactone which is then hydrolysed.

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