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A CONVENIENT SYNTHESIS OF 11-DEOXY PROSTAGLANDIN INTERMEDIATES[1)]

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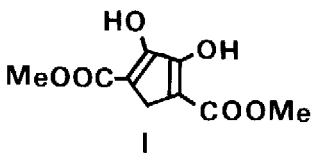
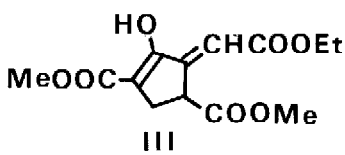
During the last few years, much effort has been concentrated on the synthesis of 11-deoxy prostaglandins[2)], which aroused our interest in a convenient synthesis of 11-deoxy PGs.

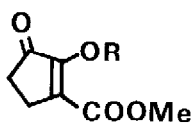
Wittig reaction of the dienol I (1eq.,) with the stable ylide II (1-2eq.,) in $CHCl_3$ under reflux proceeded to afford the desirable product III. However, the first step of this reaction is clearly different from usual Wittig reaction. Typical behavior of this reaction is that the dienol I (pka 5.85 and 9.97) disappeared rapidly at room temperature to form the very polar intermediate[3)] which is converted to the triester III[4)] under reflux [41.2%, mp. 73-75°; ir (KBr): 1745, 1705, 1670, 1620 cm^{-1}; nmr[5)]: 9.9 (1H, bs., OH) 6.37 (1H, d, J=3 >C=CH-) 3.06 (1H, dd, J=8 and 16 $-CH_2-$) 2.60 (1H, dd, J=3 and 16 $-CH_2-$); m/e: 284 (M^+)].



I

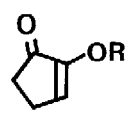


III



IXa. R= H

b. R= Me

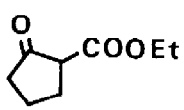


Xa. R= H

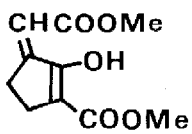
b. R=Me

$Ph_3P=CHCOOR$

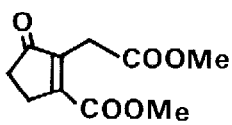
II (R=Me or Et)



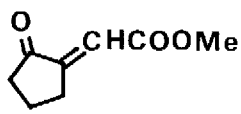
VIII



XI



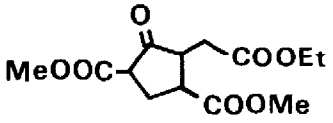
XII



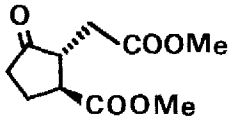
XIII

Similarly, the enolized α-diketone IXa and Xa yielded the corresponding product XI, XII[6)] and XIII via the formation of the polar intermediate prior to the Wittig reaction: XI, [67%, mp. 137.5°; ir (nujol): 1710, 1660, 1640, 1610 cm^{-1}; nmr: 9.6 (1H, bs., OH) 6.04 (1H, t, J=3 >C=CH-)] XII, [24%, oily, ir (neat): 1740, 1720, 1650 cm^{-1}; nmr: 3.56 (2H, m, $-CH_2-$)] XIII, [72%, mp. 38°; ir (nujol): 1710, 1650 cm^{-1}; nmr: 6.40 (1H, t, J=2 >C=CH-)].

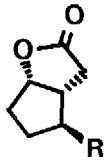
It is noteworthy that under the same conditions cyclopentanone and the β-ketoester VIII as well as the enol ether IXb and Xb do not afford the corresponding product. These facts suggest that the acidity of the enol diketone might be involved in this reaction.



IV



V



VI. R= COOMe
VII. R= CH_2OH

The triester III was easily converted to the key intermediate VII of 11-deoxy PGs as follows. Catalytic reduction of III with 10% Pd-C in methanol gave the saturated ester IV. By decarboxylation with hot c.HCl followed by treatment with CH_2N_2, the diester V [bp. 120-123°/0.85mmHg; ir (neat): 1740 cm^{-1}] was obtained in 80.2% yield from III. Stereospecific reduction of V with potassium tri-sec-butyl borohydride[7] gave the lactone ester VI [76%, mp. 52-53°; ir (nujol): 1755, 1740 cm^{-1}; nmr: 5.04 (1H, m, >CH-O-); m/e: 184 (M^+)]. Acid hydrolysis of VI by HCl afforded the crystallin acid lactone [mp. 102.5° (decomp.)] which was reduced into the key intermediate VII[8] via the acid anhydride ($ClCOOEt-Et_3N$, $NaBH_4$)[9].

This Wittig reaction will be applied to the synthesis of 11-substituted prostaglandins.

Acknowledgement: The authors thank Director Dr. K. Arima and Assistant Director Dr. Y. Kishida for their valuable help and advice.

REFERENCES AND FOOTNOTES

1) Synthetic Studies on Prostanoids XIII.
2) U.Axen, J.E.Pike and W.P.Schneider, The Total Synthesis of Natural Products, Vol I (ed, by J.ApSimon), Wiley, New York (1973).
3) The polarity on TLC suggests that this intermediate might be a phosphonium salt. NMR of the reaction mixture shows that olefinic proton of ylide disappeared rapidly and newly formed signal is observed as a overlapping signal with the acidic proton.
4) The geometrical configuration of the olefinic double bond of III, XI and XIII is not assigned.
5) NMR (δ) spectra were taken in $CDCl_3$ solution containing tetramethylsilane as internal standard.
6) This is clearly due to the rearrangement of the first formed exo double bond.
7) H.C.Brown and S.Krishnamurthy, J. Am. Chem. Soc., 94 7159 (1972).
8) P.Crabbé and A.Guzumán, Tetrahedron Letters, 1972 115.
9) K.Ishizumi, K.Koga and S.Yamada, Chem. Pharm. Bull., 16 492 (1968).