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SYNTHETIC STUDIES ON PROSTANOIDS 1
SYNTHESIS OF METHYL 9-OXOPROSTANOATE

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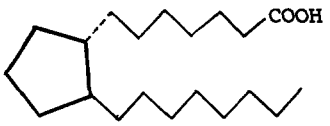
The prostaglandins, which have in common prostanoic acid skeleton (I), consist of a family of C_{20} acids of wide spread occurrences in animal tissues and of varied, extremely potent, biological activities.[1] The synthesis of, one of prostanoic acid derivatives, 15-deoxy-13,14-dihydroprostaglandin B_1 has been accomplished by Samuelsson[2] in connection with the structure elucidation of prostaglandin E_1. We wish to report two simple methods (A, B) for the preparation of methyl 9-oxoprostanoate (Va)[3], which are also applicable to the synthesis of other 2,3-disubstituted cyclopentanone derivatives.



I

(Method A) The Claisen rearrangement, in the presence of $Hg(OAc)_2$ at 120-130° for 10 hrs, of the mixture of the methoxyvinylether[4] (IIa) derived from oleic acid and the α,β-unsaturated alcohol (IIIa) obtained in a good yield by reduction of the α,β-unsaturated ester (VIII) with $LiAlH_4$-$AlCl_3$ afforded in 40% yield the rearrangement product 1-al-4-ene (IVa) which was shown by NMR spectroscopy to be an unseparable mixture of two stereoisomers.

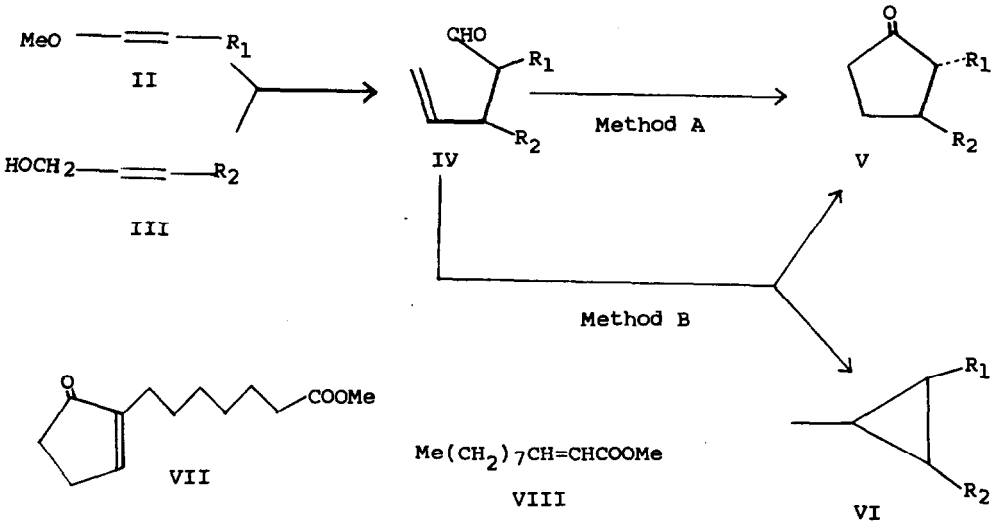


Table*2

	II, R_1	III, R_2	IV	Yield*1 (%) V (Method A)	V (Method B)	VI
a	$(CH_2)_6CO_2Me$	$(CH_2)_7Me$	40	42	30	30
b	$(CH_2)_3Me$ 6)	$(CH_2)_2Me$	52	37	29	35
c	$(CH_2)_6CO_2Me$	Me	30	38	-	-
d	$(CH_2)_6CO_2Me$	H	32	21	26	23
e	$(CH_2)_6CO_2Me$	$(CH_2)_2Me$	33	57	34	32
f	H	$(CH_2)_7Me$	45	0	30	32
g	$(CH_2)_6CO_2Me$	CH_2OMe	53	-	17	20
h	$(CH_2)_3Me$	$(CH_2)_7Me$	44	-	28	33

*1 All yield figures refer to chromatographically purified fractions.

*2 All compounds were characterized by NMR, IR and mass spectra.

IR (neat); 2700, 1740, 1640, 990, 910 cm^{-1}. NMR ($CDCl_3$); δ 3.72 (3H, s., COOMe), 4.8-6.0 (3H, m., vinyl protons), 9.65 (1H, a pair of doublets, J=3 Hz, -CHO). On the treatment of the 1-al-4-ene (IVa) with $SnCl_4$ in nitromethane at room temperature for 5 hrs under the argon atmosphere, oily methyl 9-oxo-protanoate (Va)[3], which is in a good agreement with the standard sample prepared in 10% yield by the reaction of octylmagnesium bromide with the cyclopentenone (VII) in the presence of CuI-Bu_3P complex[5], was obtained in 42% yield. A cyclopentenol, a possible intermediate, was not isolated.

To our knowledge, the above reaction is the first example on a direct cyclization of a 1-al-4-ene system to the five membered ring ketone. The reaction of compounds IV_{b-e} to the products V_{b-e} proceeded smoothly in a similar manner. On the contrary, the compound IV_f bearing no substituents at the α-position to the aldehyde function resulted in a complex mixture containing no cyclopentanone under the same conditions as described above.

(Method B) In the course of a study of cyclization reaction under milder conditions, we found a new reaction that tris(triphenylphosphine) chlororhodium converts 1-al-4-ene system into cyclopentanones and unexpected products, cyclopropane derivatives formed by the decarbonylation. The reaction of a 1-al-4-ene (IV) (1 eq.) with the rhodium complex (1 eq.) in $CHCl_3$, C_6H_6 or CH_3CN proceeded smoothly at room temperature, and two spots on TLC were observed in all runs carried out. The dark-red color of the reaction mixture in the early stages faded slightly into red at the end of the reaction. Two products were easily separated by column chromatography. The more polar product was characterized as a 2,3-dialkylcyclopentanone (V) by comparison with an authentic sample. The less polar one was elucidated as a cyclopropane derivative (VI), since its NMR spectrum showed a characteristic signal at δ 0.2-0.8 due to a cyclopropane ring protons and no olefinic signals. This elucidation was further confirmed by a partial synthesis. The comparison with the standard sample prepared from undecene-2 (a mixture of cis- and trans-) by the Simmons-Smith reaction indicated that the compound VIf consists of two stereoisomers. None of the compounds IVa-h afforded the normally

decarbonylated products expected from Tsuji reaction.[7] The compound Vg is important as a key intermediate for the synthesis of prostaglandin-like compounds. In the method A, we showed that IVf afforded no cyclopentanone derivatives in the reaction with $SnCl_4$-CH_3NO_2. The rhodium complex, on the other hand, was effective on the cyclization of such a compound. The mechanisms of these new reactions are under investigation.

Acknowledgment

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