Tetrahedron Letters No. 51/52, pp 4451 - 4454, 1974. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 11-OXAPROSTAGLANDINS

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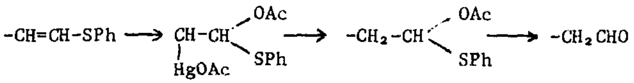
(Received in USA 11 September 1974; received in UK for publication 5 November 1974)

In a previous communication we reported the synthesis of 9-thiaprostaglandins[1], as part of our program to prepare prostaglandin analogs in which C_9 or C_{11} are replaced by a heteroatom. A recent publication on the synthesis of 11-desoxy-11-oxaprostaglandin-E_1[2] prompts us to report our synthesis of the corresponding 11-desoxy-11-oxaprostaglandin-E_2 13.

The tetrahydrofuranone 2[3] (70%; bp. 123-126°/0.5 mm, $\nu_{max}^{CH_2Cl_2}$ 1770, 1730 cm^{-1}) was prepared by reaction[4] of the methyl 4,4-diethoxycrotonate 1 with methyl sodium glycolate. Reduction of 2 ($NaBH_4$/EtOH/-70°) gave a mixture of the two epimeric alcohols 3. The major epimer (65%) was purified by column chromatography on silica gel and reacted with dihydropyran to give the ester 4[3] ($\nu_{max}^{CH_2Cl_2}$ 1725 cm^{-1}). Reduction of the ester 4 [$HAl(iBu)_2/\phi CH_3/-70°$] followed by reaction of the resulting aldehyde 5 ($\nu_{max}^{CH_2Cl_2}$ 2730, 1715 cm^{-1}) with triphenylphosphoranylidene-phenylmercaptomethane in DMSO gave a mixture of the cis and trans vinylthioethers 6[5]. Treatment of 6 with mercuric acetate in acetonitrile, followed by reductive cleavage of (Al/Hg/THF) the resulting



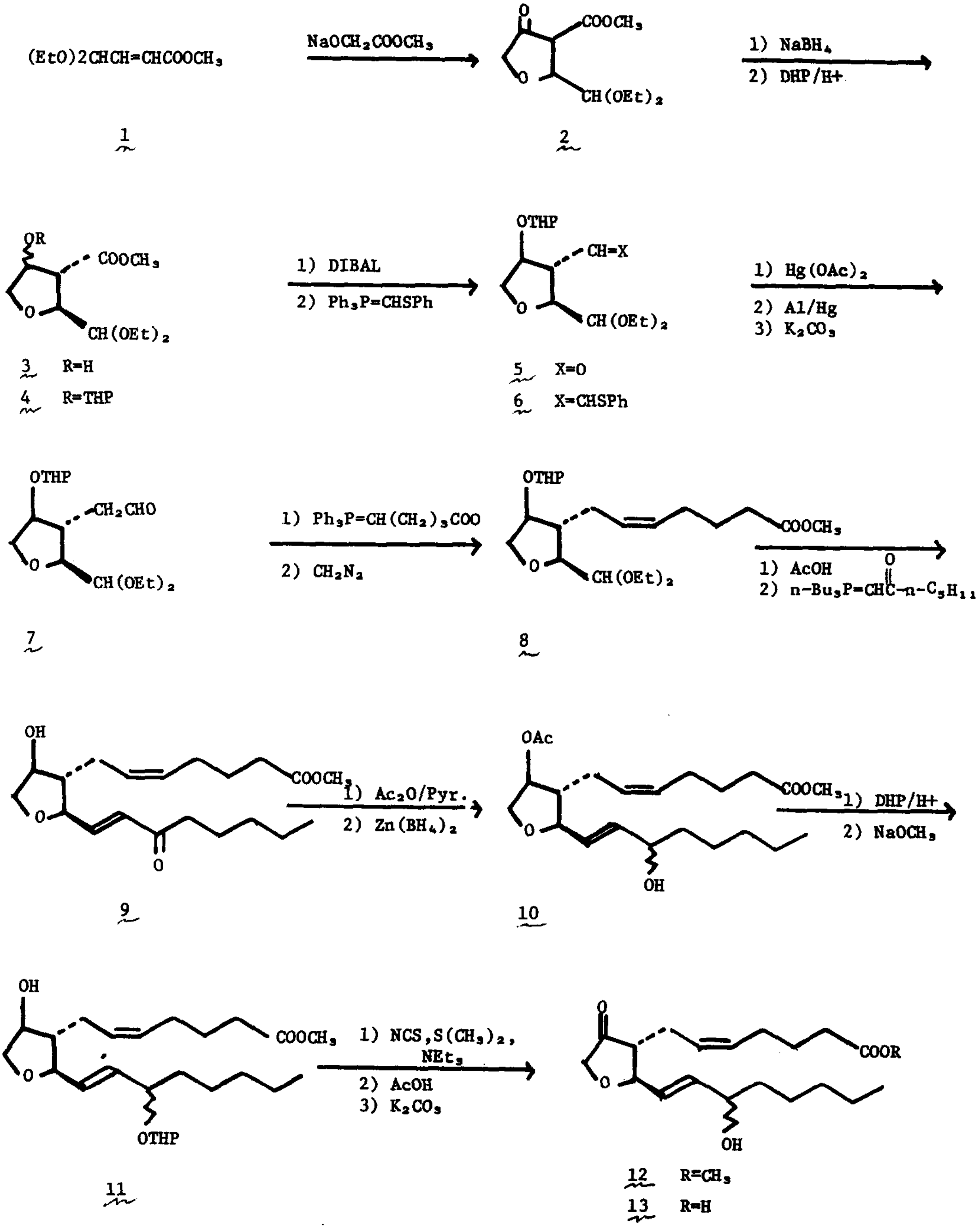
$$-CH{=}CH{-}SPh \longrightarrow \underset{HgOAc}{CH}{-}CH\begin{smallmatrix}OAc\\SPh\end{smallmatrix} \longrightarrow -CH_2{-}CH\begin{smallmatrix}OAc\\SPh\end{smallmatrix} \longrightarrow -CH_2CHO$$

organomercury adduct and hydrolysis of the acetoxy phenylmercaptoacetal with aq. K_2CO_3 in methanol, gave the aldehyde 7 (70%; $\nu_{max}^{CHCl_3}$ 2730, 1720 cm^{-1}). The above transformation represents a novel method of converting vinyl sulfides to the corresponding carbonyl compounds under mildly basic conditions. Reaction of **7** with sodium 5-triphenylphosphoranylidene-pentanoate[6] followed by diazomethane esterification of the resulting carboxylic acid, gave the ester **8**[3] (70%; $\nu_{max}^{CH_2Cl_2}$ 1725 cm^{-1}). Hydrolysis of **8** (H_2O/AcOH) and reaction of the resulting hydroxy aldehyde with 1-tributylphosphoranylidene-2-heptanone[7] gave the enone **9**[3] (50%; $\nu_{max}^{CH_2Cl_2}$ 3585, 1725, 1690, 1670, 1630 cm^{-1}). Acetylation of **9** (Ac_2O/pyridine) followed by reduction of the C_{15}-carbonyl with zinc borohydride gave the C_{15}-epimeric alcohols **10**a,b[3] which were separated by prep. tlc (SiO_2,AcOEt/CH_2Cl_2, 30:70, R_{f_a} = 0.28, R_{f_b} = 0.39; $\nu_{max}^{CH_2Cl_2}$ 3595, 1725 cm^{-1}).

To conclude the synthesis, each isomer **10** was reacted with dihydropyran followed by methanolysis ($CH_3OH/NaOCH_3$) of the C_9-acetoxy group to give the alcohols **11** ($\nu_{max}^{CH_2Cl_2}$ 3580, 1725 cm^{-1}). Oxidation of **11** ($NCS/CH_3SCH_3/NEt_3$)[8] and hydrolysis of the tetrahydropyranyl group with aqueous acetic acid gave the ketones **12**[3] ($\nu_{max}^{CH_2Cl_2}$ 3600, 1755, 1730 cm^{-1}). Hydrolysis of the esters **12** with 10% aqueous potassium carbonate in methanol produced the corresponding C_{15}-epimeric 11-desoxy-11-oxa-E_2 prostaglandins **13**a,b(35% from **9**; $\nu_{max}^{CH_2Cl_2}$ 3590, 3480, 1750, 1705 cm^{-1}; m/e 320 ($M-H_2O$), 249 ($M-C_5H_{11}$), 221, 195).

Acknowledgment

The invaluable advice and encouragement of Drs. H. Gschwend and N. Finch are gratefully acknowledged. We also wish to thank Mr. L. Dorfman and his staff for preparative thin-layer chromatographies, microanalyses and spectra.


(EtO)2CHCH=CHCOOCH$_3$
1
NaOCH$_2$COOCH$_3$
O
COOCH$_3$
CH(OEt)$_2$
2
1) NaBH$_4$
2) DHP/H+
OR
COOCH$_3$
CH(OEt)$_2$
3 R=H
4 R=THP
1) DIBAL
2) Ph$_3$P=CHSPh
OTHP
CH=X
CH(OEt)$_2$
5 X=O
6 X=CHSPh
1) Hg(OAc)$_2$
2) Al/Hg
3) K$_2$CO$_3$
OTHP
CH$_2$CHO
CH(OEt)$_2$
7
1) Ph$_3$P=CH(CH$_2$)$_3$COO
2) CH$_2$N$_2$
OTHP
COOCH$_3$
CH(OEt)$_2$
8
1) AcOH
2) n-Bu$_3$P=CHC(=O)-n-C$_5$H$_{11}$
OH
COOCH$_3$
O
9
1) Ac$_2$O/Pyr.
2) Zn(BH$_4$)$_2$
OAc
COOCH$_3$
OH
10
1) DHP/H+
2) NaOCH$_3$
OH
COOCH$_3$
OTHP
11
1) NCS,S(CH$_3$)$_2$, NEt$_3$
2) AcOH
3) K$_2$CO$_3$
O
COOR
OH
12 R=CH$_3$
13 R=H

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