NEW SYNTHETIC APPROACH IN THE PROSTAGLANDIN FIELD

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The aim of this work was to devise a practical synthesis of new prostaglandin analogs and to evaluate them with regard to their biological activity. A secondary purpose was the total synthesis of known prostaglandins. Portions of our work have been described previously(Collins et al, 1968).

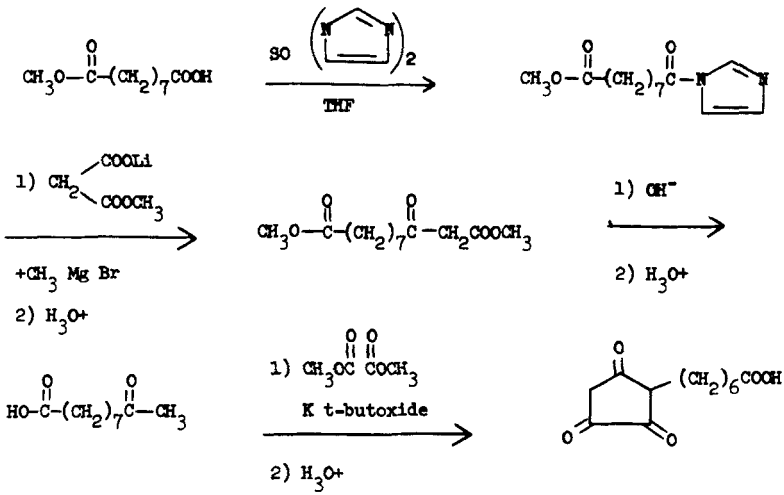


Figure 1.

Fig.1 depicts the synthesis of the trione-acid(I). A similar preparation of the corresponding ester was described recently(Yura & Ide,1969). It is of interest to note the novel preparation of 9-oxodecanoic acid,which was patterned after the work of Bram and Vilkas(1964). A distinct practical improvement over their method was the use of the lithium salt of monomethyl malonate,instead of the corresponding free acid,since the former is a stable,crystalline solid that could be purified easily.

In Fig.2,3 we see the sequence of steps used in our total synthesis of dl-PGB_1. Analogous syntheses appeared

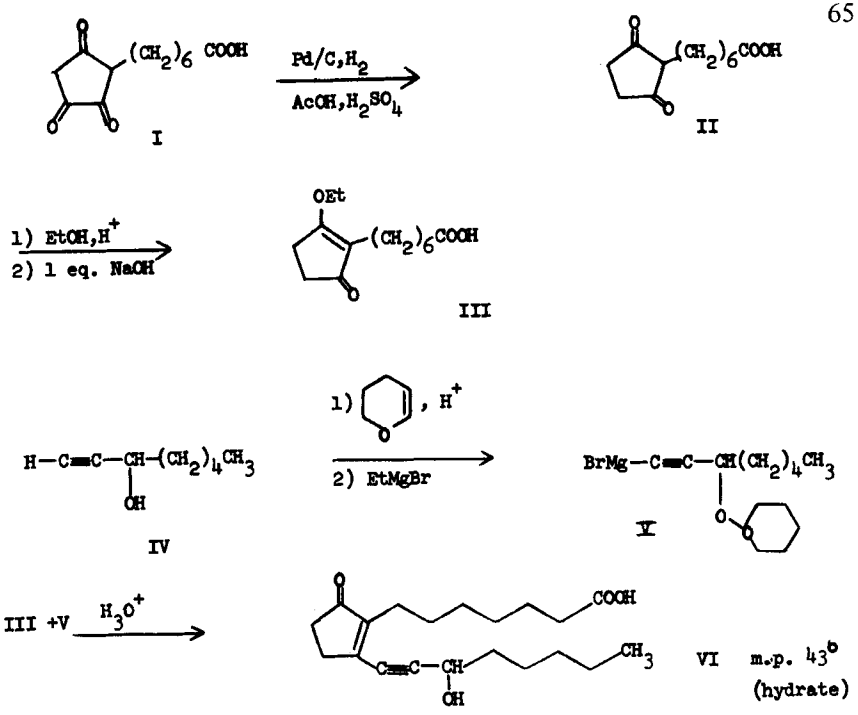


Figure 2.

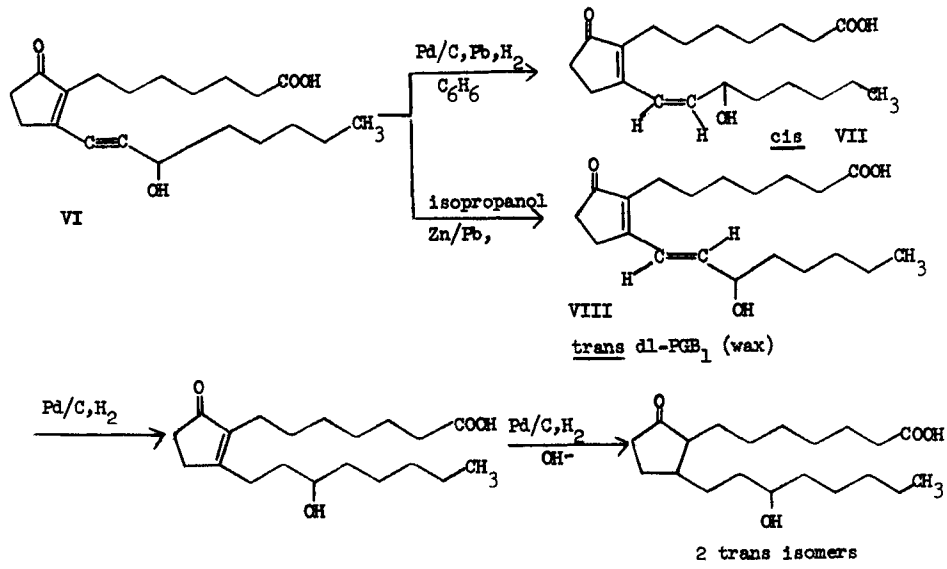


Figure 3.

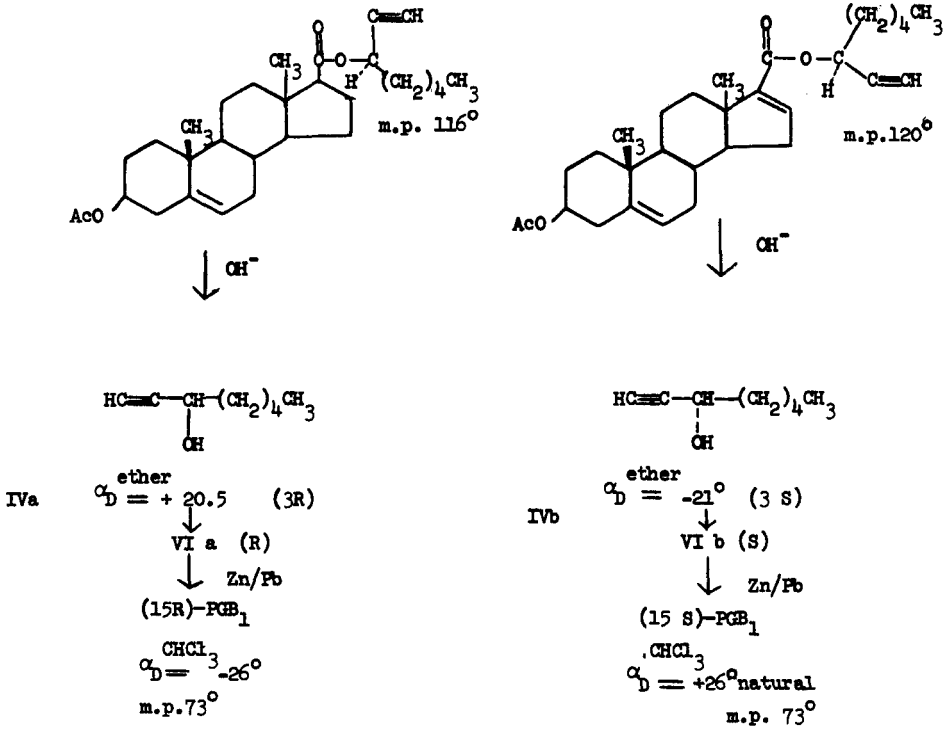


Figure 4. Resolution of 1-octyn-3-ol and synthesis of (+) and (-) PGB$_1$.

subsequently in the literature (Yura & Ide, 1969; Katsube & Matsu, 1969). However, there are some significant differences between our work and the other published methods. For instance, the acid-catalyzed hydrogenolysis of II to III in good yield is a novel process that was found to be quite general. Moreover, the selective hydrolysis of the ethyl ester corresponding to III proceeded in excellent yield, leading to the key enol ether acid III. This compound is a much more useful intermediate than its ester, since it was found that the carboxyl function, unlike the carboethoxy function, does not react with the Grignard reagent V, thus allowing a selective addition to the enol ether carbonyl. The acetylenic analog of dl-PGB$_1$ (VI) was thus obtained in good yield.

The hydrogenation of VI to the corresponding cis-dihydro compound VII could be accomplished using a variety of conditions. An unusual catalyst was used here for the first time: a lead coated palladium-on-carbon catalyst, obtained by the hydrogenation of an aqueous solution of lead nitrate in the presence of the commercial catalyst. The isomerization of cis-VII to trans-dl-PGB$_1$ was possible but could not be made to proceed in good yield. However, applying a new reaction we had discovered previously in the steroid field, we

found that it was possible to reduce directly the propargylic alcohol VI to trans-dl-PGB_1(VIII) using a zinc-lead couple in isopropanol. The product could be obtained directly in a high state of purity. It appears that the reduction of propargylic alcohols to the corresponding allylic alcohols is quite general, with a zinc-lead or a zinc-copper couple in a variety of hydroxylic solvents.

At about the time this work was completed, the description of another successful approach to this problem was published by two different groups (Hardegger et al, 1967; Klok et al, 1968).

The stepwise reduction of dl-PGB_1(VIII) to the dihydro and tetrahydro ketone proceeded smoothly. This last ketone was assigned the trans configuration, since it resulted from a hydrogenation in the presence of sodium hydroxide. However, the existence of 2 trans-isomers is possible, even though the product appeared to be pure.

For a rational stereospecific synthesis of PGB_1 it is obvious that it would be necessary to resolve the intermediate 1-octyn-3-ol(IV). After several attempts we found the reaction of IV with 3β-acetoxy-5,16-etiadienic acid chloride gave a crystalline ester which, after purification and hydrolysis led to(-)-(3S)-1-octyn-3-ol(IVb). On the other hand, the crystalline ester derived from 3β-acetoxy-5-etienic acid, after purification and hydrolysis, led to(+)-(3R)-1-octyn-3-ol(IVa). In Fig.4 we see these transformations and the conversion of IVa and IVb to(15R)-PGB_1 and (15S)-PGB_1, respectively, by the methods described previously in Fig.2,3. The purity of the alcohols IVa and IVb was determined by the method of Dale et al(1969), which consists of N.M.R. analysis of the corresponding(-)-α-methoxy-α-trifluoromethylphenylacetic acid(MTPA) esters, as illustrated in Fig.5,6,7.

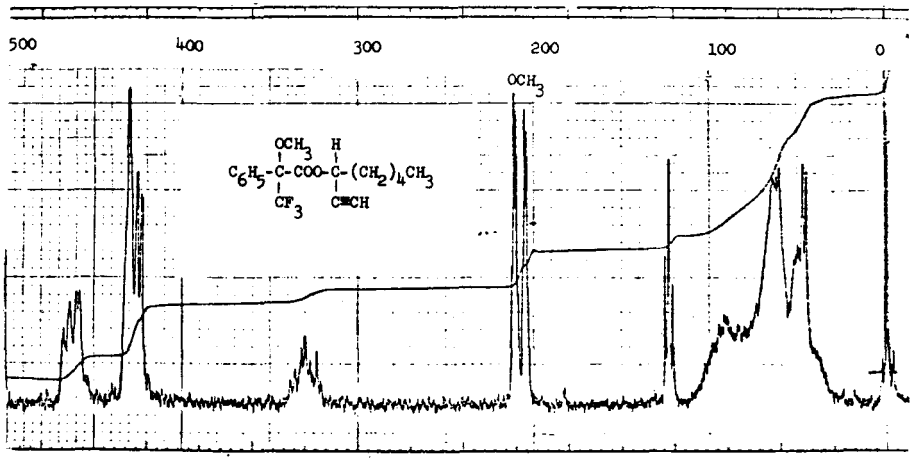


Figure 5. 60 MHZ proton NMR spectrum of the 2 diastereomeric esters from racemic 1-octyn-3-ol and(-) MTPA chloride. C_6D_6 solvent, TMS.

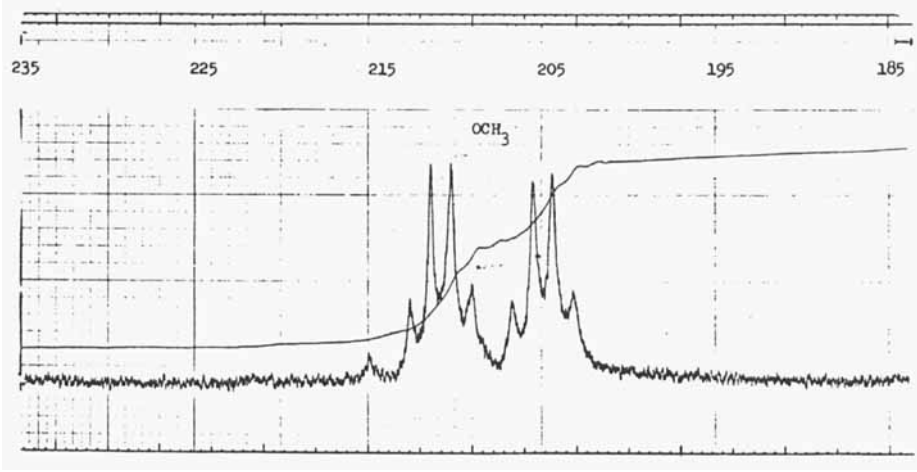


Figure 6. Expansion of Figure 5 NMR.

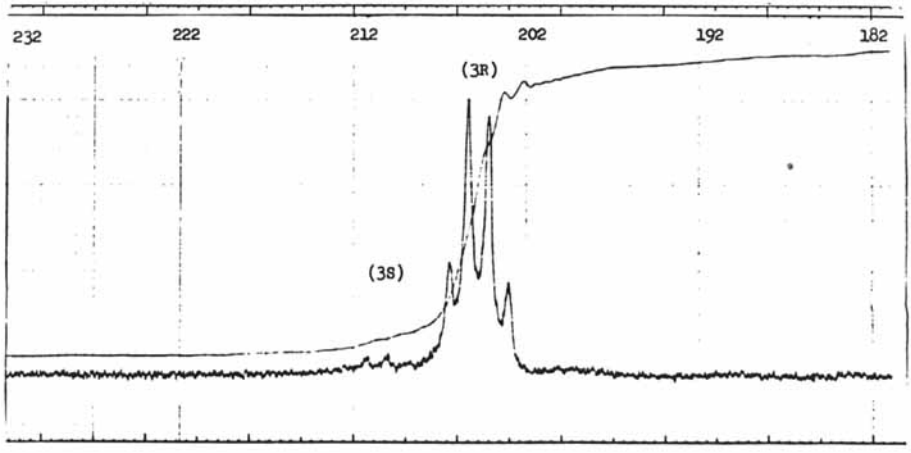


Figure 7. 60 MHZ proton NMR spectrum of the ester derived from(3R)-1-octyn-3-ol and(-)-MTPA chloride. C_6D_6 solvent,TMS. Note about 5% of corresponding(3S)-ester.

With benzene as a solvent,the 60 MHZ proton NMR spectrum of the(-) MTPA ester of racemic IV indicates two different quartets for the MTPA methoxyl,separated by 5 cps. Fig.7 shows an expansion of the NMR of the(-) MTPA

ester of(3R)-1-octyn-3-ol(IVa). One can see that in the methoxyl region it is quite easy to determine the presence of small amounts of the 3S ester.

The synthetic(15S)-PGB_1 was found to be identical with the naturally derived product kindly supplied by Dr. John Pike,of The Upjohn Company. Moreover,(15R)-PGB_1 had O.R.D. curve which was the mirror image of that of(15S)-PGB_1.

An interesting consequence of our total synthesis of optically active PGB_1 was the possibility of independent confirmation of the absolute configuration of naturally derived PGB_1 and,therefore,of all known prostaglandins, by applying the method of Horeau and Kagan(1964)to the intermediate propargylic alcohols IVa and IVb.

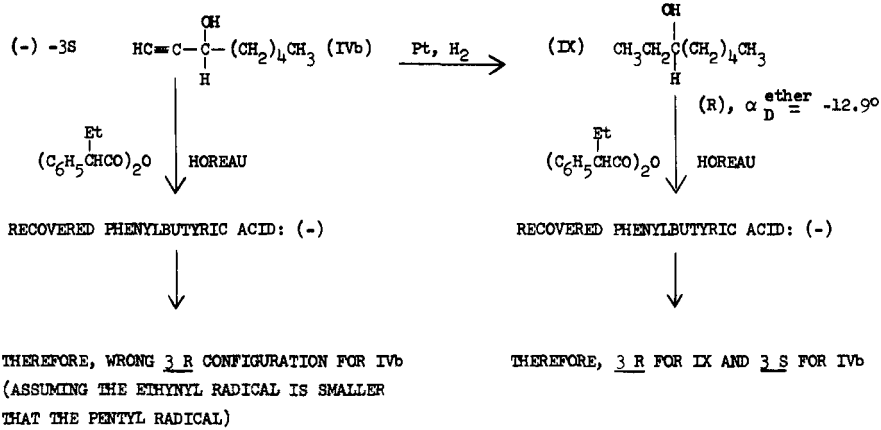


Figure 8. Independent confirmation of absolute configuration of prostaglandins. Same sequence for(+) IVa gave results confirming above absolute configurations.

The results,as described in Fig.8,do not confirm the established configurations(Nugteren et al,1966)of(+)-(15S)-PGB_1. Therefore,one is forced to conclude that,surprisingly in Horeau's order of precedence,the ethynyl radical should be considered larger than an alkyl radical. However,the difficulty was resolved easily by hydrogenating IVa and IVb to the corresponding saturated alcohols. Thus,(3S)-1-octyn-3-ol(IVb)led to(3R)-3-octanol(IX)which,when analyzed by Horeau's method,gave results which were consistent with the 3S configuration for IVb and the 15S configuration for the naturally derived(+)PGB_1.

A similar series of results were obtained with IVa, confirming the 15R configuration for(-)-PGB_1.

Parallel to our efforts in the PGB_1 series,work was also initiated in the 11-hydroxyprostanoic acid series. Theoretically,an approach similar to the one described in

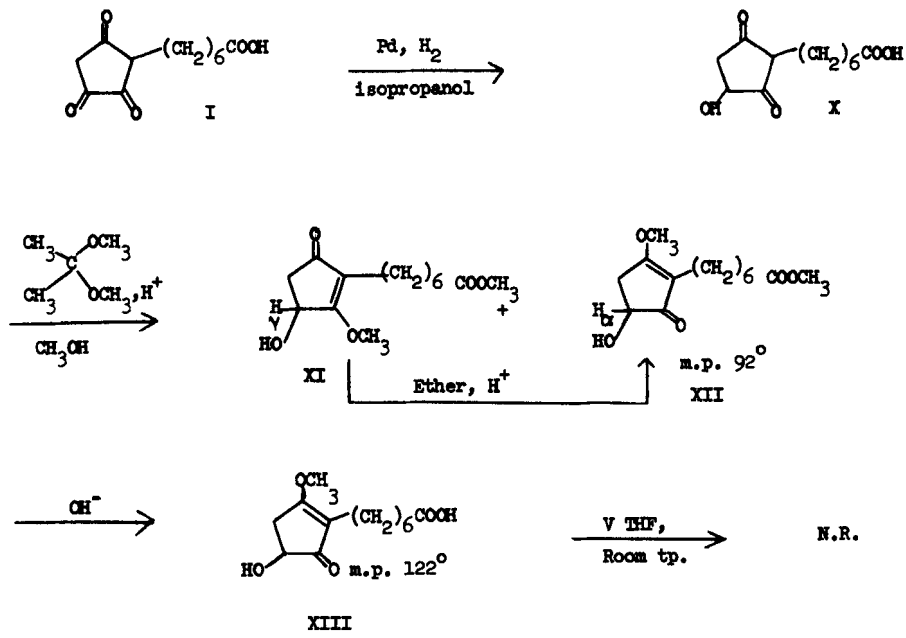


Figure 9. 11-hydroxy series.

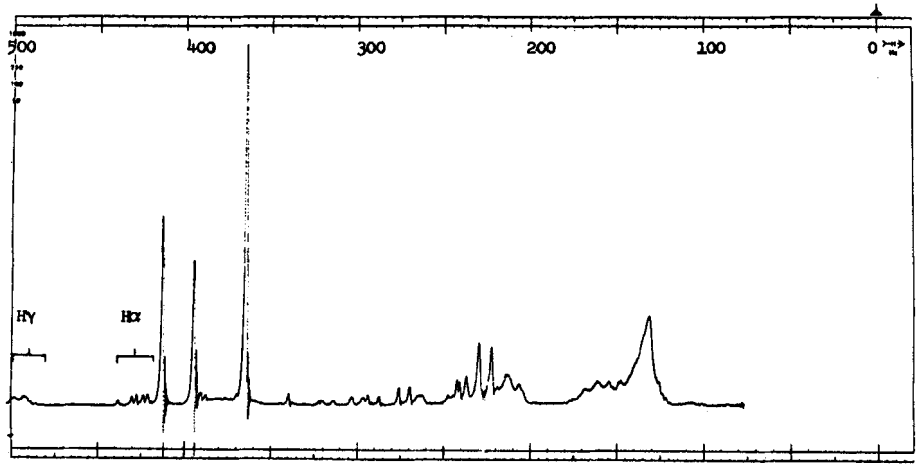


Figure 10. The 100 MHZ proton NMR spectrum of the crude reaction mixture(XI and XII). $CDCL_3$ solvent, TMS.

Fig.2,3 should be possible. As we can see in Fig.9,the first obstacle was the conversion of the readily available

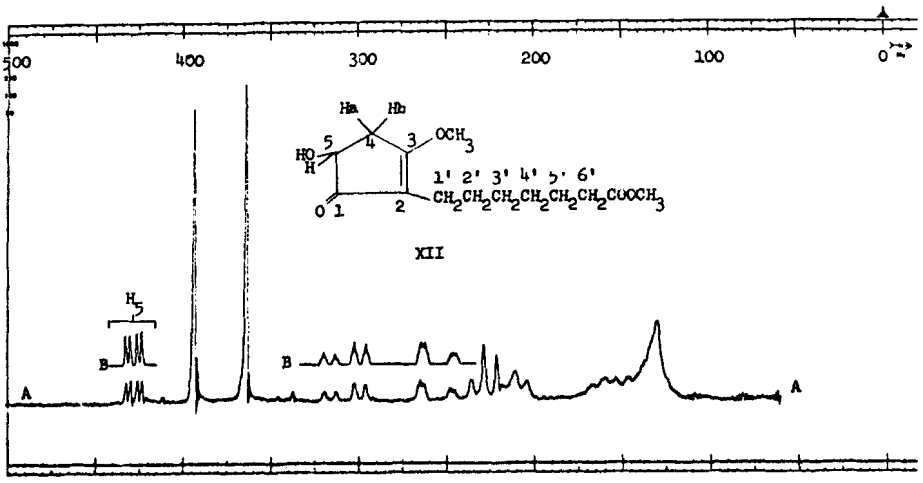


Figure 11. A)Proton NMR spectrum 100 MHZ of pure XII, $CDCl_3$ solvent, TMS, B)computer calculated spectrum

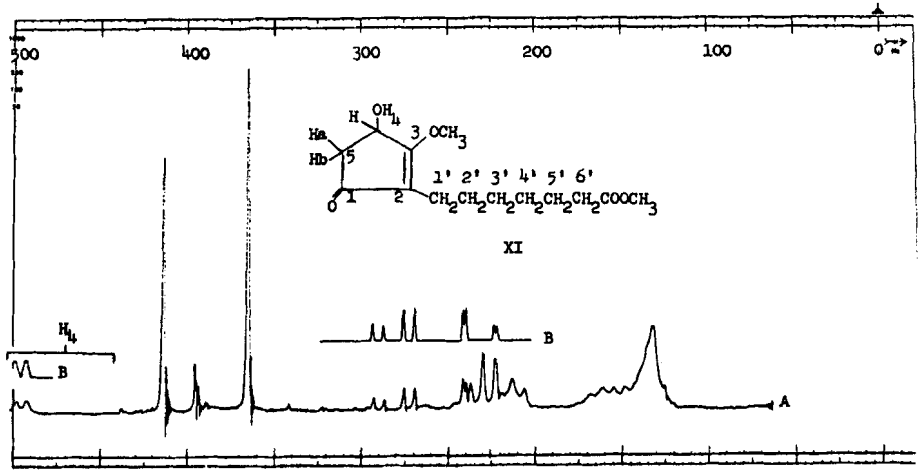
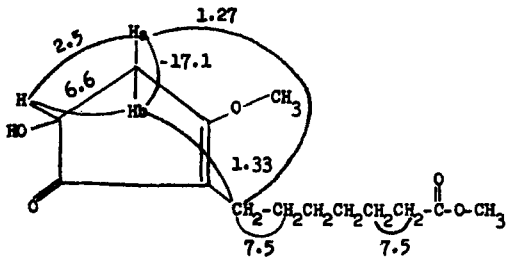


Figure 12. A)100 MHZ proton NMR spectrum of crude XI. $CDCl_3$ solvent, TMS, B)computer calculated spectrum.

hydroxy-dione(X)to the corresponding enol ether. As expected, regardless of the method used, diazomethane or acid catalyzed esterification, a mixture of 2 enol ethers XI and XII was obtained.

The preponderant product was the oily enol ether XI,

XII



XI

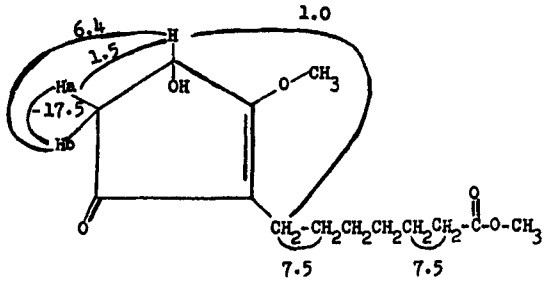


Figure 13.

which was obtained in the crude state from the mother-liquors of the crystallization of XII. Fortunately, since the desired isomer XII was crystalline, it was possible to obtain it in good yield. Thus, by treating a diethyl ether solution of XI, with a trace of methanolic hydrogen chloride the required crystalline XII precipitated out of solution, disturbing the equilibrium and allowing almost complete conversion of XI to XII.

Before we proceed any further in the description of our work it is of interest to mention how we assigned the structures of XI and XII. Analysis of their N.M.R. spectra (Fig.10,11,12) indicated interesting differences between the respective protons attached to the carbon 4 or 5 holding the hydroxyl grouping. Tentatively, we assigned structure XI to the compound whose N.M.R. spectrum of the secondary alcohol proton (Hγ at C_4) showed the greatest complexity, due to the long range coupling with the allylic methylene hydrogens at C_1.

Eventually, a more sophisticated analysis confirmed our preliminary assignments. Thus, decoupling and spin tickling experiments on XI and the crystalline isomer XII showed which protons were coupled and the relative signs of the

coupling constants. The LAOCN3 computer program was then used to calculate the chemical shifts and coupling constants of the protons at carbons 4 and 5 of both isomers, taking into account the long-range allylic couplings to the proton at carbon 1'. Plots of the computer calculated

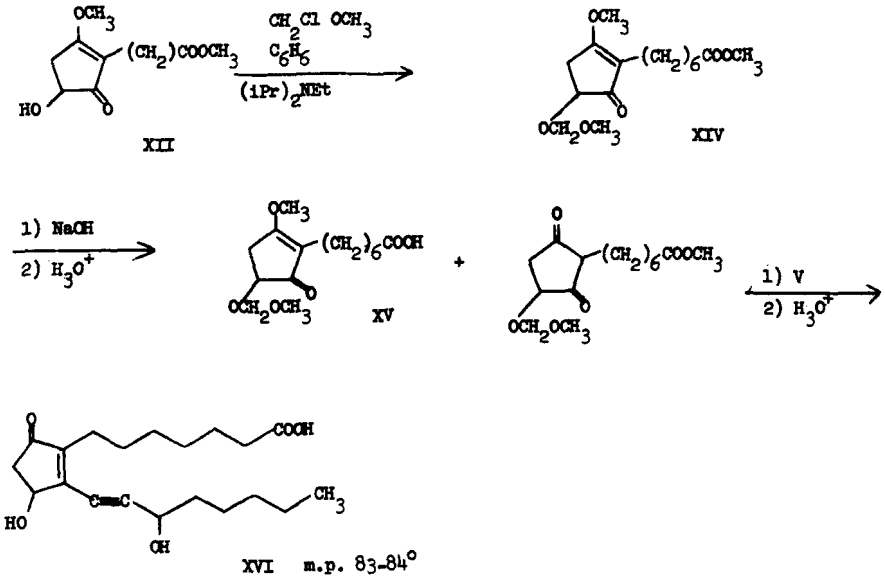


Figure 14.

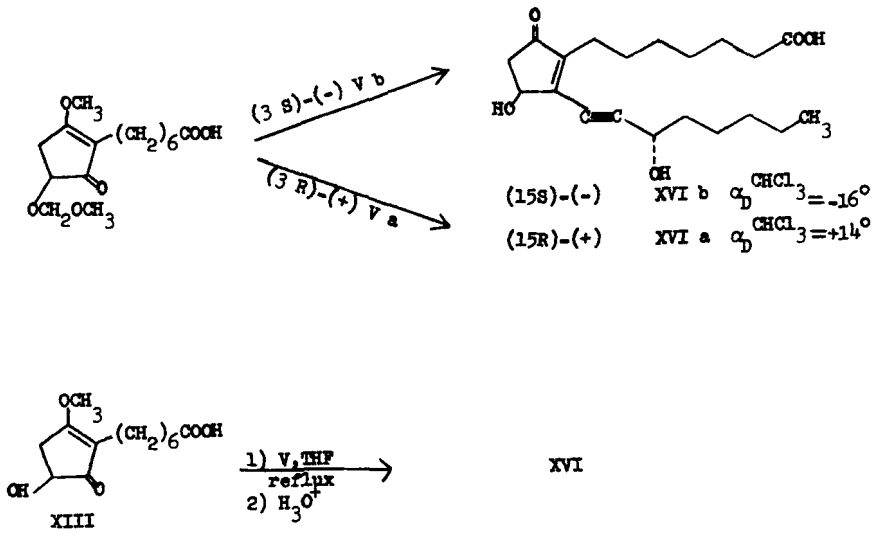


Figure 15.

spectra for the 4 and 5 protons gave good agreement with the actual spectra and were consistent with structure XII for the crystalline isomer and structure XI for the oily isomer.

The various coupling constants are summarized in Fig. 13.

The selective hydrolysis of XII to the corresponding enol ether and XIII proceeded in fair yield. This compound could be purified by crystallization. However,to our surprise,when XIII was treated at room temperature in THF with the Grignard reagent V,conditions that were successful in the 11-desoxy series,pure starting material was recovered, even after a prolonged reaction time.

On the assumption that alkoxide formation,by the 5-hydroxy adjacent to the carbonyl involved in the condensation,was responsible for our failure,we decided to protect the hydroxyl in question. In Fig.14 the conversions of XII to the corresponding methoxymethyl ether XIV using chloromethyl ether in the presence of diisopropylethylamine are illustrated. Selective alkaline hydrolysis of XIV to the carboxylic acid proceeded in fair yield. Pure XV could be obtained as an oil after chromatography on silica gel. However,it was possible to use the crude hydrolysis product in the Grignard addition with V. In this case,the reaction proceeded smoothly at room temperature. After prolonged acid hydrolysis followed by chromatography on silica gel,the required product was obtained as one isomer XVI in a crystalline form,mp 83-84°C.

The same series of reactions were performed with the Grignard reagent Va and Vb derived from(3R)-1-octyn-3-ol (IVa)and(3S)-1-octyn-3-ol(IVb),to yield the corresponding crystalline 15R and 15S isomer XVIa and XVIb(Fig.15).

It is interesting to note that we recently found that it was possible to use XIII successfully in the Grignard reaction with V,by the simple process of conducting the reaction at reflux temperature of the solvent in the presence of a large excess of V. Even under these seemingly drastic conditions,the side-chain carboxyl did not seem to react with the reagent. Therefore,should it be possible to resolve XIII,the way would be open for the stereospecific synthesis of all the 4 isomers of XVI.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Bible for stimulating discussions and for help in determining the structure of the isomers XI and XII,and the Special Synthesis group of G.D. Searle for invaluable assistance in the preparation of intermediates.

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DISCUSSION

Question: Is this lead reduction of the eneynol confined to this conjugated system or can you do this on an isolated ynol?

R. Pappo: You can do it with propargylic alcohols. You don't have to have a double bond,but you do need the hydroxylic function - any acetylenic alcohol will do that. The main danger here is you have to choose the right conditions, for if your conditions are too drastic you can lose the allylic alcohol,and if you use strong acidic conditions you get hydrogenolysis. So you do have to carefully control pH. If you don't have the alcohol,the reaction doesn't work.

D. A. van Dorp: Dr. Pappo, may I ask you the same question which I asked Dr. Corey? You have been working with the PGB compounds and you must have thought also about converting PGB to PGE. What about it?

R. Pappo: It is a good question. We actually haven't done any work along this line,but as you can see,I would be delighted to find a method that would do that,because most of our compounds are very suitable for this kind of work.