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INTRAMOLECULAR WITTIG REACTIONS APPLIED TO THE SYNTHESIS OF MEDIUM SIZED α,β-UNSATURATED LACTONES AND DILACTONES.

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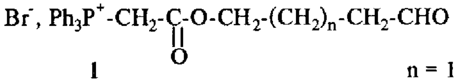
Abstract : A systematic study of the intramolecular Wittig reactions of ω-aldehydophosphoranes 5 has been performed and indicates that the amounts of monounsaturated lactones 6 and dilactones 7 is dependent on chain length.

Intramolecular Wittig type reactions have often been used in synthesis especially for the preparation of five and six membered rings [2]. They also represent one of the most useful methods of ring closure for the synthesis of macrocycles and their use in the preparation of macrolides, for instance, is well documented [3,4]. To the best of our knowledge, however, there is no report of studies of these reactions for the synthesis of medium sized rings. Consequently, this note describes a short and facile synthesis of ω-aldehydophosphonium salts 1 and reports the results from a systematic study of the intramolecular Wittig reactions of the phosphoranes obtained from 1.

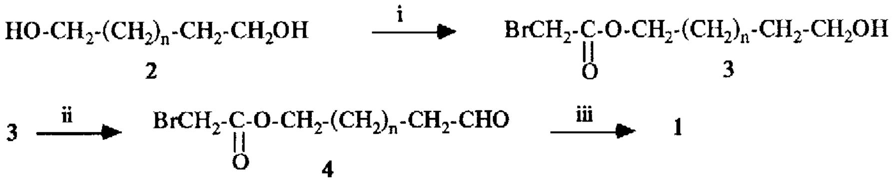


$$Br^-, Ph_3P^+\text{-}CH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}O\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_2\text{-}CHO$$

1 n = 1 to 7

Synthesis of the phosphonium salts 1

Bestmann and Schobert have reported an elegant approach to such salts, using cumulated ylid chemistry, during their synthesis of α, β-unsaturated monocyclic lactones [4]. We have studied a short (only 3 steps) synthesis of compounds 1 starting from commercially available ω-diols 2 (scheme 1).



$$\underset{2}{HO\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_2\text{-}CH_2OH} \xrightarrow{i} \underset{3}{BrCH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}O\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_2\text{-}CH_2OH}$$

$$3 \xrightarrow{ii} \underset{4}{BrCH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}O\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_2\text{-}CHO} \xrightarrow{iii} 1$$

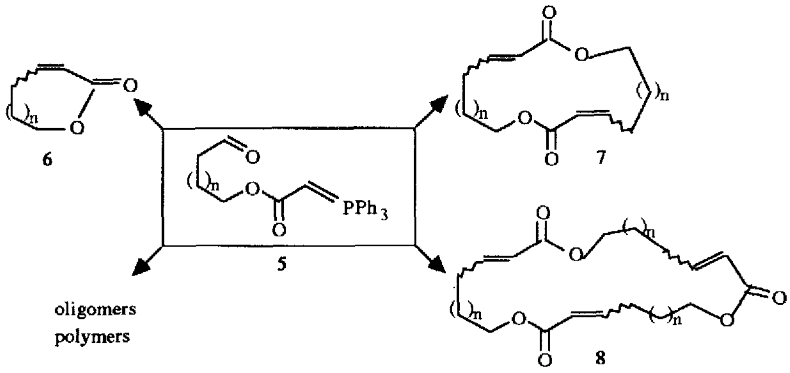
i : NaH then $BrCOCH_2Br$, THF, 40-68 %
ii : PCC, AcONa, CH_2Cl_2, 68-79 %
iii : Ph_3P, CH_3CN, R.T., 81-98 %

Scheme 1

The monoesterification of **2** is possible using the methodology first described by McDougal for their monoprotection [5]: the sodium monoalcoxide salt of **2** reacts with bromoacetylbromide (1 eq.) to give **3**, contaminated in most cases by only small amounts of the diesterified derivatives which are easily separated by chromatography. Oxidation of **3** using PCC and sodium acetate [6] gives aldehydes **4** which, after reaction with PPh$_3$, lead to the desired phosphonium salts in good overall yields (36-51 % from **2**).

Intramolecular Wittig reactions

The phosphoranes **5** can, in principle, show several types of Wittig reactivity (scheme 2) leading not only to the α, β-unsaturated lactones **6** but also to the dimeric species **7** or to the trimeric lactones **8**. For all these compounds E and Z isomers have to be considered and oligomerization or polymerization may also occur. Many factors including solvent, temperature, base used for the preparation of **5**, and concentration of the reactants, play a role in these reactions. After considerable experimentation, it has been found that the best overall yields (78-86 %) are obtained using Et$_3$N in refluxing acetonitrile under high dilution conditions [7,8].



Scheme 2

In each case, the mixture of lactones which is obtained is separated by flash chromatography and characterized by physical and spectroscopical data. In the case of **7e**, the assigned structure was confirmed by an X-ray analysis [9]. The isolated yields of the different products are given in table 1 and several points are worthy of note :

- The intramolecular Wittig reaction is more difficult in the medium size range (n = 2 to 5) *though there is still an appreciable amount (10 to 28 %) of the monomeric (Z) derivative.* This is somewhat unexpected, not only because of the known difficulties in the synthesis of these rings but also because reaction of stabilized ylids is usually E-stereoselective. Also in those cases (n = 2 to 5) the amount of dimers and trimers is higher (see diagram 1).

	6	7 (Z,E)	7 (E,E)	8 (E,E,E)
1a (n = 1)	70 % (Z)*	-	15 %	-
1b (n = 2)	28 % (Z)	2 %	41 %	7 %
1c (n = 3)	10 % (Z)	4 %	47 %	21 %
1d (n = 4)	15 % (Z)	4 %	51 %	11 %
1e (n = 5)	25 % (Z)	5 %	51 %	5 %
1f (n = 6)	55 % (E)	-	28 %	-
1g (n = 7)	62 % (E)	-	20 %	-

* mixture of the conjugated **6a** and non-conjugated derivative **6'a**.

Table 1. Isolated yields from the reaction of phosphoranes **5**.

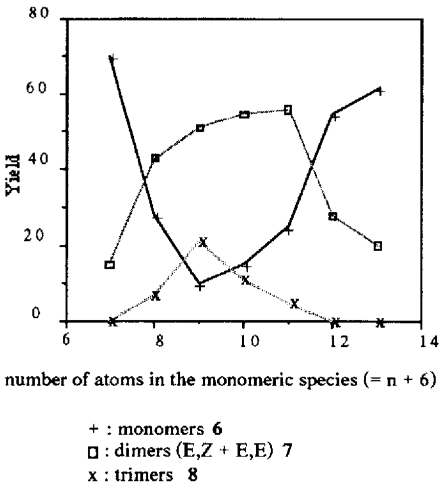
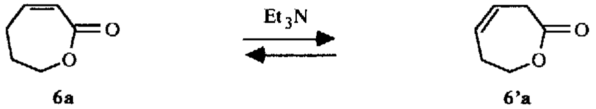


Diagram 1

- The seven membered lactone has been isolated as a 1/1 mixture (which could be separated by chromatography) of **6a** and **6'a**. These are in equilibrium under the basic conditions used for



the reactions [10].

- Monomers **6a**-**6e** were found to exist as their Z-isomers whilst **6f** and **6g** had the E-configuration. Dimers **7** were predominantly the E,E isomers whilst for trimers **8**, only the E,E,E derivatives could be isolated.

In conclusion, this approach appears very useful for the preparation of seven membered lactones and for those lactones with n ≥ 5. Although the yields of the intramolecular Wittig reactions are lower, this route gives a valuable entry into the medium sized derivatives [10] since the starting phosphonium salts **1** are easily and quickly obtained. This method is also particularly useful for the preparation of the dimeric lactones having 18 to 22 atoms. Another approach to the 14 to 16 atom-dimers, which are interesting as macrodiolide models, will be described in the following paper.

References and notes

1 - URA CNRS D0704

2 - The "non classical" Wittig reaction has already been used in its intramolecular version for the synthesis of 5 or 6 membered derivatives ; see Le Corre M. Janssen Chimica Acta, 1985, 3, 4 and ref. therein ; see also Brennan J., Murphy P.J., Tetrahedron Lett., 1988, 29, 2063.

3 - Stork G., Nakamura E., J. Org. Chem., 1979, 44, 4010 ; Roush W.R., J. Org. Chem., 1979, 44, 4011.

4 - Bestmann H.J., Schobert R., Angew. Chem. Int. Ed., 1983, 22, 780 and Synthesis, 1989, 419.

5 - Mc Dougal P.G., Rico J.G., Oh V., Condon B.D., J. Org. Chem., 1986, 51, 3388.

6 - Overman L.E., Thompson A.S., J. Am. Chem. Soc., 1988, 110, 2248.

7 - General procedure used for the Intramolecular Wittig reactions : A solution of the phosphonium salt **1** (0.5 mmol) in acetonitrile (50 ml) is slowly added (over 34 hours) under nitrogen to a refluxing solution of triethylamine (4 mmol) in acetonitrile (20 ml). After completion of the addition, the reaction mixture is left under reflux for seven days. After concentration *in vacuo*, the monomeric, dimeric, or trimeric species are separated by flash-chromatography using mixtures of light boiling petroleum ether (40-60 °C) and ether as eluents.

8 - Other bases such as DBU or imidazole [12], or other solvents (CH_2Cl_2,CH_3NO_2) give lower yields. High dilution also plays a critical role : for instance, under standard 9.2×10^{-2} M conditions, **1g** gives a **6/7** ratio of 9:80 instead of 62:20 obtainable at high dilution.

9 - Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Center. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW,UK.
7f : $C_{20}H_{32}O_4$: Mr = 336.4 , triclinic , P-1 , a = 5.256(2) , b =9.041(4), c = 11.074(4) Å , α= 105.06(3), β= 91.02(3), γ = 103.48(4), V = 492.5(6) $Å^{-3}$, Z = 1 , D_x = 1.14 $Mg.m^{-3}$, $\lambda(MoK\alpha)$ = 0.71069Å , μ = 0.72 cm^{-1} , F(000) = 368 , T = 296 K . Structure solved with direct methods. Final R = 0.036 for 1120 observations and 158 variables .

10 - A similar deconjugation process has already been reported : Hirao T., Fujihara Y., Kurokawa K., Oshiro Y., Agawa T., J. Org. Chem., 1986, 51, 2830.

11 - After completion of this work, we were informed of a new iterative procedure for the synthesis of such compounds, developped recently by Pr J. Seyden Penne's group : E. Fouque, PhD Thesis, University of Paris Sud, Orsay, September 1989.

12 - Bestmann H.J., Schmidt M., Angew. Chem. Int. Ed., 1987, 26, 79.

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