Tetrahedron Letters,Vol.24,No.40,pp 4327-4330,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

ON THE ROLE OF THE PHOSPHATE RESIDUES IN GERANYL PYROPHOSPHATE BIOSYNTHESIS

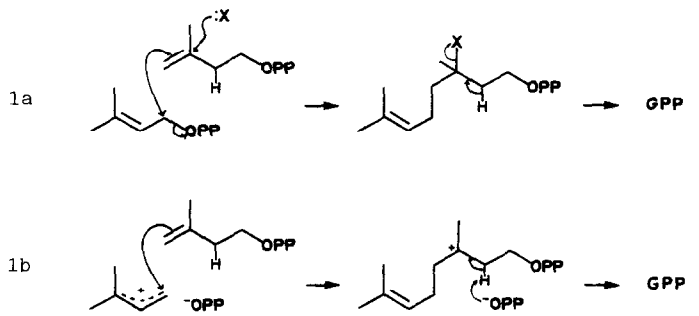
L. Jacob, M. Julia *, B. Pfeiffer and C. Rolando.

Ecole Normale Supérieure, Laboratoire de Chimie,
24, rue Lhomond, 75231 Paris Cedex 05. FRANCE.

Abstract : *Phosphoric esters bearing a sulfonium group in the γ position are converted under basic conditions into allylic phosphates.*

In the biosynthesis of geranyl pyrophosphate (GPP), one mole of dimethylallyl pyrophosphate (DMAPP) is attached, through C-1, to one mole of isopentenyl pyrophosphate (IPP), through C-4, the C-2 proton on the same side of IPP as the attacking molecule being lost. This makes a concerted process unlikely (1).

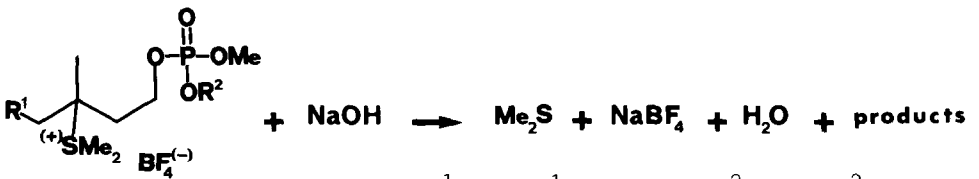
In order to account for the stereochemical results, it has been proposed that a nucleophilic group becomes attached to C-3 during the prenylation step and is eliminated with the H_R on C-2 in a second step (2)(Scheme 1a). Alternatively, evidence has been presented in favour of attack of IPP by an ion-pair (DMA^+, OPP^-) and abstraction by the pyrophosphate anion OPP^- of H_R (scheme 1b)(3).



Scheme 1

The problem of the regioselectivity of the proton abstraction has not been extensively investigated. It is not "chemically obvious" that this should lead selectively to GPP. In fact it is known (4) that the acid-catalysed dehydration of 1,3-glycols leads predominently to the formation of β,γ- but not α,β- unsaturated alcohols. Participation of the hydroxyl group as a base has been invoked (5) (scheme 2a).

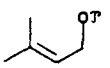
Scheme 4 : Basic elimination of sulfonium phosphates.



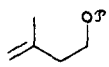
1 a,b ; 2 a,b (R^1=H, 1 ; R^1=prenyl, 2 ; R^2=H, a ; R^2=Me, b)

products

R^1=H

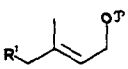


3 a,b

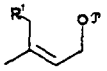


4 a,b

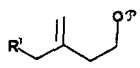
R^1=prenyl



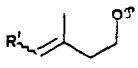
5 a,b



6 a,b



7 a,b



E: 8 a,b ; Z: 9 a,b

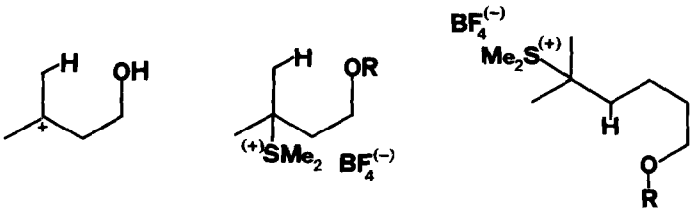
"natural isomers" "retro isomers"

($\mathcal{P}$ = $\overset{O}{\overset{\|}{P}}$(OMe) ONa, a ; $\mathcal{P}$ = $\overset{O}{\overset{\|}{P}}(OMe)_2$, b)

Table 1 : Results of basic elimination of sulfonium phosphates

Substrate	conditions	total yield	natural/ retro [c]	natural [e]		retro [e]		
				E / Z		exo	/ E /	Z
				5	6	7	8	9
1a R^1=H, R^2=H	A[a]	85[c]	74 26	-	-	-	-	-
2a R^1=prenyl, R^2=H	A	100[c], 77[d]	84 16	27	59	14	0	0
1b R^1=H, R^2=Me	B[b]	77[c]	100 0	-	-	-	-	-
2b R^1=prenyl, R^2=Me	B	88[c], 68[d]	95 5	27	68	3.5	0.5	1

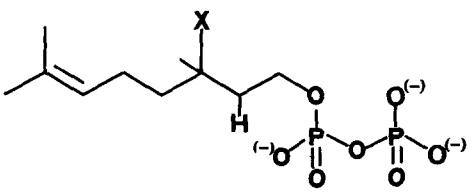
a : NaOH 4 eq, MeOH, 24h.
b : NaOH 3 eq, MeOH + CH_2Cl_2 (1/4), 0.5h.
c : by ^{1}H NMR (250 MHz).
d : isolated yield of alcohols after extraction in dichloromethane with tetrabutylammonium hydroxide, methylation with diphenyl methyl sulfonium tetrafluoroborate (9) and reduction with lithium aluminium hydride.
e : by G.L.C. on alcohols using capillary columns (50m X 0.3mm, SE52). The procedure has been checked with authentic samples (9,10).



2a 2b 2c

Scheme 2

A series of model compounds $Me_2^+SCMe_2(CH_2)_n$ OR, BF_4^- (accompanying letter) showed a high proportion of elimination involving the proton located in 1,6-position with respect to an alkoxide group (scheme 2b and 2c). The reference compound without oxygen gave almost exclusively the terminal olefin.In the biosynthetic intermediate (scheme 3) a basic phosphate oxygen atom is located as in scheme 2c and it has been suggested (6) that it is responsible for the elimination.



Scheme 3

The influence of a phosphoric ester group on the direction of elimination was investigated with the sulfonium salts 1a, 2a, (Scheme 4) chosen as models for Kosower's hypothesis. These were prepared as shown in note 7 and submitted to basic elimination conditions. They gave indeed large proportions of elimination in the natural direction (Table 1).

For comparison purposes, the corresponding triesters 1b, 2b were also submitted to basic conditions. The reaction was even faster and again high regioselectivity was observed, with formation of geranyl and neryl phosphates, the latter predominating in the mixtures.

It so appears that the phosphoric ester groups do strongly influence the position of the double bond formed in such eliminations. The reasons for this remarkable regioselectivity will be discussed in the full paper.

The financial support of CNRS (LA 32) is gratefully acknowledged.

References and Notes.

1 C.D. Poulter and H.C. Rilling in J.W. Porter and S.L. Spurgeon, Eds, Biosynthesis of isoprenoid compounds, Vol. 1, p. 161, Wiley, New-York, 1981, and references cited therein.

2 J.W. Cornforth, Angew. Chem., 80, 977 (1968), Angew. Chem. Int. Ed., 7, 903 (1968) ; Chem. Soc. Reviews, 2, 1 (1973).

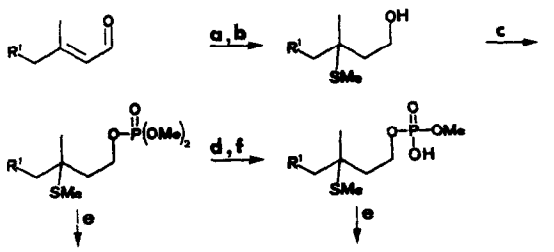
3 C.D. Poulter and H.C. Rilling, Acc. Chem. Res., 11, 307 (1978).

4 A. St. Pfau and Pl. Plattner, Helv. Chim. Acta, 15, 1250 (1932).

5 R.T. Arnold, Helv. Chim. Acta, 32, 134 (1949).

6 E.M. Kosower, Molecular Biochemistry, Mc Graw-Hill, New-York, 1962, p 57.

7



a : MeSH, piperidine ; b : $NaBH_4$, methanol ; c : $(MeO)_2POCl$, pyridine ; d : PhSK, DMF (8) ; e : $Me_3O^+ BF_4^-$, CH_2Cl_2 ; f : aqueous HCl.

All new compounds gave analytical results (NMR ^1H, ^{13}C, ^{31}P, IR, MS and microanalysis) in agreement with their structures.

8 P. Savignac, G. Lavielle, Bull. Soc. Chim. Fr., 1974, 1506.

9 B. Badet, M. Julia, C. Rolando, Synthesis, 1982, 291.

10 H. Mestdagh, M. Julia, C. Rolando, to be published.

(Received in France 3 July 1983)