Tetrahedron Letters,Vol.27,No.48,pp 5885-5888,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NOVEL BIOSYNTHESIS OF IRREGULAR SESQUITERPENE ARTEMONE IN ARTEMISIA PALLENS

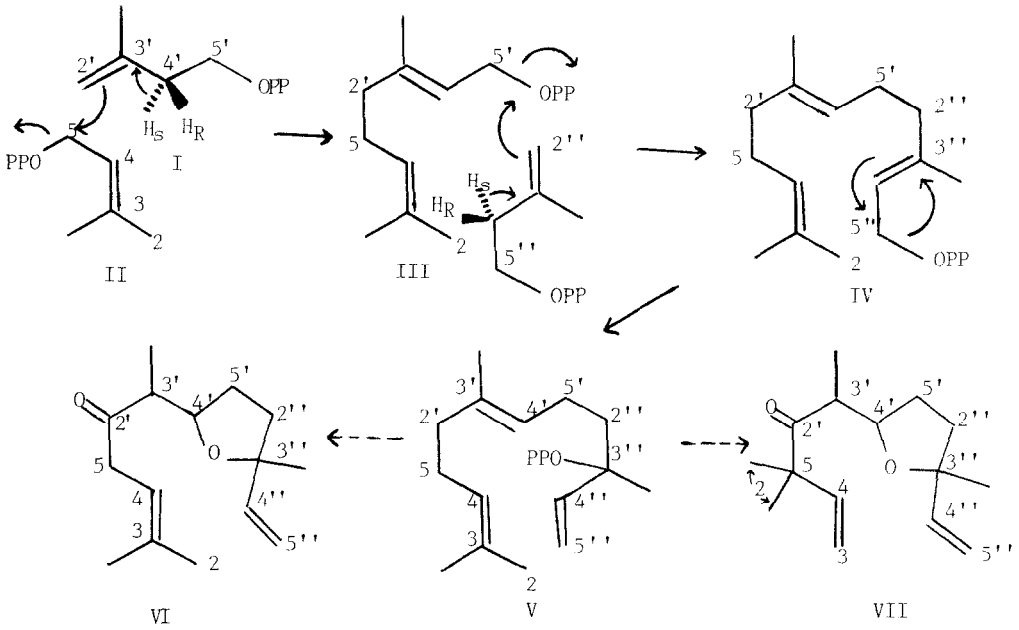
A. AKHILA*, P. K. SHARMA AND R. S. THAKUR

Central Institute of Medicinal and Aromatic Plants
Lucknow India 226 016

ABSTRACT - A novel condensation between two isoprene units, isopentenylpyrophosphate (IPP) and dimethylvinylcarbinylpyrophosphate (DMVCPP) is being reported here for the first time within the plant system to produce artemone, an iregular sesquiterpene.

IPP (I) and dimethylallylpyrophosphate (DMAPP) , the two isoprene units join in a "Head to Tail" fashion to biosynthesise terpenoids and steroids [1-3]. Several times these units join in "H & T" fashion and then the fission and rearrangement of various bonds and organic groups gives rise to a compound that does not seem to be formed by usual "H & T" linkage [4-5]. Such compounds are kown as irregular terpenoids. Artemone (VII), isolated from Artemisia pallens, is an irregular sesquiterpene [6] whereas davanone (VI) is another sesquiterpene present as the chief constituent in the essential oil of this plant [7,8].

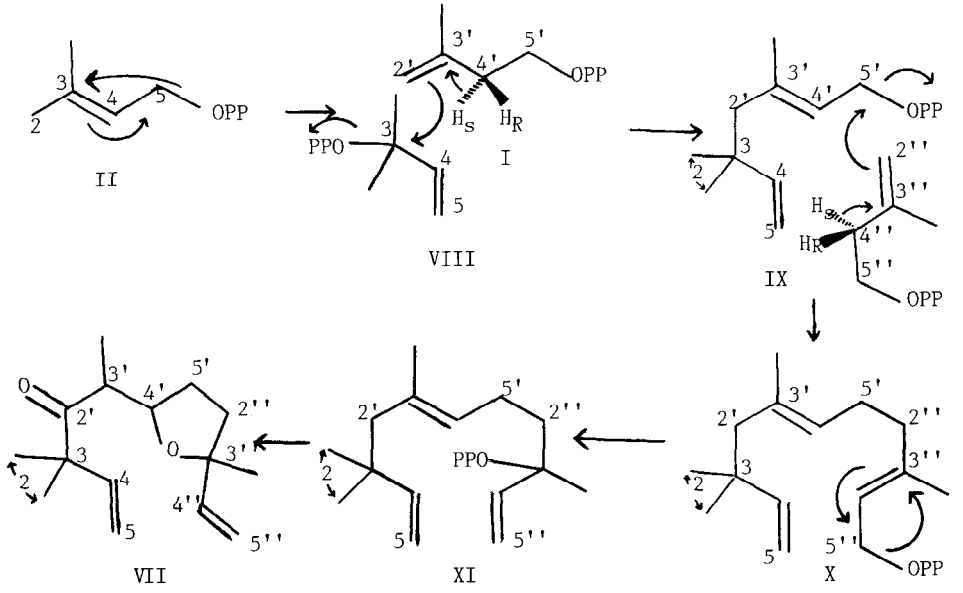
I condenses with II to give geranylpyrophosphate (III) which further condenses with another molecule of I to produce farnesylpyrophosphate (FPP,IV), the traditional precursor of sesquiterpenes (Scheme 1). It is well established now that FPP isomerises to nerolidylpyrophosphate (V) to metabolise many acyclic and cyclic sesquiterpenoids [9]. In this case -OPP from C-5" of IV would shift to C-3" to give V (analogy to geraniol - linalool interconversion) [10]. V is expected to undergo cyclisation and oxidation at C-2' to metabolise VI. In the case of artemone (VII) biosynthesis, the two gem-methyls from C-3 of V or VI must shift to C-5 to give the desired product (Scheme 1).



Scheme 1: Possible biosynthetic pathway to VI and VII from C-5 units. The numbering system follows that of the mevalonic acid. The C-1 of MVA being lost during the decarboxylation and formation of IPP, DMAPP and DMVCPP.

In order to find out whether the two gem-methyls at C-3 of V or VI have shifted to C-5 or some other biogenetic pathway has taken place, the twigs of A. pallens were fed with [2-$^{3}H_2$,2-^{14}C] and [5-$^{3}H_2$,2-^{14}C]-MVA in separate set of experiments. The isotope ratios (^{3}H : ^{14}C) in VI and VII and the degraded product (XII) (Exp.1,Table 1) suggest that C-3 of VII is in fact C-5 of MVA which has been lost during degradation. Had the two methyls from C-3 of V or VI shifted to C-5 the two ^{3}H at C-5 would have been lost in VII. However the isotope ratio in VII (^{3}H : ^{14}C ; 2 : 1) is the same as in the precursor (MVA) (^{3}H : ^{14}C ; 2 : 1) suggesting no loss of ^{3}H. Later on when it was degraded to XII it lost four ^{3}H atoms, obviously from the two terminal methylenes [C-5" and C-3 (actually C-5)].

The results from Exp.2 (Table 1) suggest that only one ^{3}H is lost from V during the course of cyclisation and oxidation to VI and VII. The ^{3}H at C-2 and C-2" seem to be unaffected from Scheme 1 during the course of biogenesis. This suggests that one ^{3}H from C-2' of VI or VII has shifted to some other carbon and this can well be explained by the X-group mechanism suggested for cyclisation and oxidation of NPP (V) to VI or VII (Scheme 3).

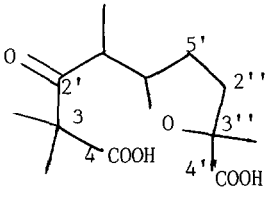


Scheme 2: Biosynthetic scheme to artemone from DMVCPP and IPP

VII was subjected to known conditions (as checked by blanks using $^{2}H_2O$-exchange and monitored by ^{1}H-NMR) to allow exchange of tracer at carbons alpha to carbonyl group. 40 to 50% of tracer was exchanged in the presence of base [11] suggesting that ^{3}H was present at C-3' of VII.

The isotope ratios in VI, VII and XII suggest that artemone (VII) can only be biosynthesised in the plant system if DMVCPP (VIII) condenses with IPP(I) (Scheme 2) and the biosynthesis proceeds via the following sequence. (I + VIII → IX + I → X → XI → VII). To the authors knowledge this is the first report that DMAPP has isomerised to DMVCPP within the plant system and DMVCPP produced <u>in vivo</u> has actively taken part in terpene biosynthesis.

The authors are thankful to Dr. Akhtar Husain, Director CIMAP for keen interest he has shown during the course of this work and one of us PKS thanks to CSIR, New Delhi for financial assistance.

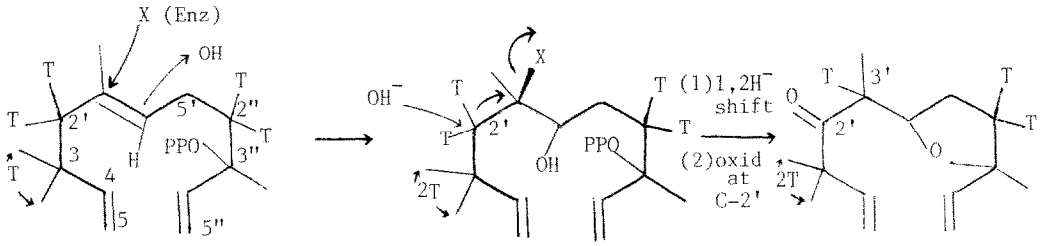


XII

TABLE 1 : Isotope ratio in Davanone (VI) and Artemone (VII) obtained from A.pallens after being fed with doubly labelled mevalonic acid.

Exp.	Precursor	Isotope ratio	% Incorporation	Isotope ratio (^3H : ^{14}C) Davanone (VI)	Artemone (VII)	Deg. Product (XII)
1.	[5-$^3H_2$,2-^{14}C]MVA	2 : 1	0.05	1.86 : 1	1.92 : 1	2.13 : 3
2.	[2-$^3H_2$,2-^{14}C]MVA	2 : 1	0.05	4.92 : 3	4.88 : 3	4.96 : 3

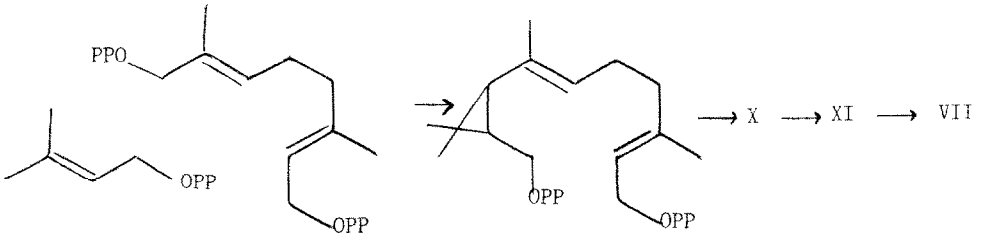
Scheme 3 : Postulated X-group mechanism for introduction of OH^- at C-2' during the biogenesis of artemone (VII). Same shall apply for davanone (VI). T denotes ^3H from [2-$^3H_2$]MVA



V VII

REFERENCES

1. O. WALLAC, Ann. Chem. (1887) 239, 1.
2. L. RUZICKA, A. ESCHENMOSER and H. HEUSSER; Experientia (1953) 9, 357.
3. R. CROTEAU and M. A. JOHNSON; Biology and chemistry of Plant Trichomes (1984), 133. Edited by Eloy Rodrignez, Patrick L. Healy and Indira Mehta.
4. G. R. WALLER, G. M. FROST and D. BURLESON; Phytochemistry (1968) 7, 213.
5. J. SHAW, T. NOBLE and W. W. EPSTEIN; J. Chem. Soc. Chem. Comm. (1975) 591.
6. P. NAEGELI, J. KLIMES and D. WEHER: Tett. Lett. (1970) 57, 5021.
7. G. SIMPA and B. VANDER WAL; Rec. Trav. Chem. Pay-Bas (1968) 87.
8. A. F. THOMAS and G. PITTON; Helv. Chim. Acta (1971) 54 , 1890.
9. D. E. CANE; Tetrahedron (1980) 36, 1109.
10. D. V. BANTHORPE and B. V. CHARLWOOD; Chemistry of Terpenes and Terpenoids (1972) 337. Edited by A. A. Newmann. Academic Press, London.
11. A. AKHILA and D. V. BANTHORPE; Phytochemistry (1980) 19, 1691.
12. Another hypothetical biogenetic route to artemone (VII), and this would also give the same isotope ratio in VII (as shown in Table 1). This route does not involve DMVCPP as precursor. To confirm this pathway some unequivocal experimental proof has to be given. (Scheme given below)
13. During the preparation of the manuscript all the carbons in the structures and all the H or ^3H are not represented to avoid congestion.



(Received in UK 22 September 1986)