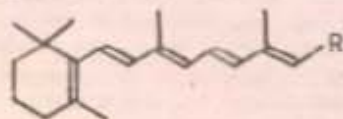


**S.a.c.7. JOSE DAVID, P.-Studies on the synthesis of Vitamin-A and related compounds-1989-Dr. Paul A. Vatakencherry**

In the first chapter an overview of retinoid research with special reference to the synthesis of retinoids is presented. The review though not exhaustive highlights the important achievements in the field of retinoid synthesis including the industrial aspects.

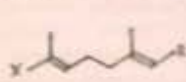
The importance of retinoids and their isomers, because of their biological activities and possible therapeutic applications, calls for developing new methodologies for their syntheses. Vitamin A or Retinol (1) a prominent member among retinoids and its simple derivatives like retinoic acid (1a) gained importance, after their role in the process of vision and therapeutic applications mainly in cancer therapy, was established. The other equally important derivative of Vitamin A is Vitamin A aldehyde or Retinal (1c). In this regard, devising practical new approaches for syntheses or improvements in the existing methods for the synthesis of these class of biologically important compounds is of more than academic interest. In the second chapter the scope of the present work is presented with synthetic schemes envisaged.



- 1, R = CH<sub>2</sub>OH    2 - R - CH<sub>2</sub>OH  
 1a, R = COOH    2a - R - CHO  
 1b, R = CHO

Considering the above, the synthetic strategy planned are presented. The starting materials geraniol (2) and/or citral (2a) are considered because of their easy availability. Since different modes of coupling using most of the fragments are known, stress is given on the synthesis of intermediates which can act as synthons for Vitamin A synthesis. Different approaches for the necessary functionalisation for the required intermediates are presented.

C<sub>10</sub> + C<sub>10</sub> approach is one of the important modes of building the C<sub>20</sub> skeleton. Different methods of allylic functionalisation, and further elaboration to synthesise the fully conjugated C<sub>10</sub> unit are described.



3

X-CH<sub>2</sub>OH, CHO



4

X-CH<sub>2</sub>OH, CHO



5

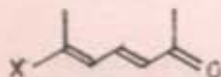


6

R = CH<sub>2</sub>OAc

Allylic functionalisation using  $\text{SeO}_2$ , NBS, epoxide opening,  $\text{PhSeCl}$  and singlet oxygen to get 3 are described. Introduction of double bond to get 4 using reagents  $(\text{PhSe})_2/\text{NaBH}_4$ ,  $\text{I}_2/\text{Cu}(\text{OAc})_2$ ,  $\text{PhSeCl}$ ,  $t\text{BuOOH}/\text{PDC}$ , NBS, and an electrochemical method are described. The necessary functionalisation to synthesise the cyclic  $\text{C}_{10}$  part of Vitamin A 5 is described employing sulfone cyclization,  $\text{PhSeCl}$  and  $\text{PhSeCl}$  reagents. Novel method for cyclization to cyclooctal starting from geranic acid together with the classical approach is also presented.

A method for the preparation of  $\text{C}_7$  synthon 6 for Vitamin A synthesis is presented. Similarly a short approach for the synthesis of  $\text{C}_9$  unit 7 derived from methyl heptenone is also presented. Another versatile industrial  $\text{C}_9$  intermediate 8 for Vitamin A synthesis was prepared and functionalised to get 7.



7

$\text{X} = \text{CH}_2\text{OH}$  or  $\text{CHO}$



8

Synthetic approaches to the  $\text{C}_{10}$  unit 9 derived from Levulinic acid and 2-Acetyl butyrolactone is also described.

The coupling schemes involving  $\text{C}_{10} + \text{C}_{13}$  and  $\text{C}_{13} + \text{C}_7$  approach are described using Wittig, Wittig-Horner and sulfone alkylation. Double elimination variation of sulfone alkylation is also described.

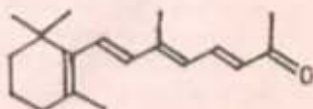
Synthesis of the  $\text{C}_{18}$  ketone (10) - a key intermediate - in the synthesis of Vitamin A is effected through  $\text{C}_{13} + \text{C}_5$  and  $\text{C}_{13} + \text{C}_8$  routes. Here also Wittig, Wittig-Horner variation and sulfone alkylation mode of coupling are used. The double elimination variation of sulfone alkylation is also attempted.

Since the conversion of this  $\text{C}_{18}$  ketone to Vitamin A is known, this convergent approach constitutes a formal synthesis of Vitamin A. The  $\text{C}_{13} + \text{C}_7$  approach too is a novel method for Vitamin A synthesis.

In the third chapter the results are discussed analysing the various aspects of the synthetic schemes. In chapter four is given the experimental details, and the list of references cited are given at the end of the thesis.



9



10