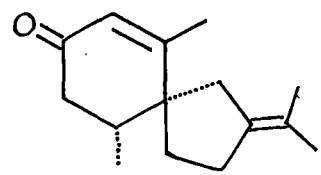
P R E F A C E

The thesis entitled "Synthetic studies in Sesquiterpenes" incorporates the results of the investigations carried out by the author as a Teacher fellow under the Faculty Improvement Programme of the University Grants Commission, New Delhi during the period March 14, 1978 through March 13, 1982 in the Organic Chemical Laboratories of the University of North Bengal. The investigations were undertaken to exploit $Ar_1^{(-)}$-5 participation reaction discovered independently by Dreiding and Winstein for the synthesis of spiro sesquiterpenes in general and beta-vetivone in particular.

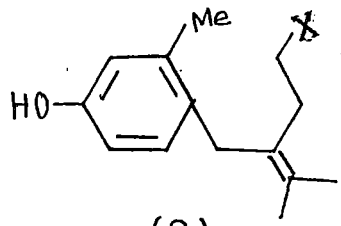
At the outset, a brief review of the Chemistry of beta vetivone (1) leading to the currently accepted structure is presented. Inter alia a note on the biogenesis of the sesquiterpenes is incorporated. It is followed by a detailed review of the various synthetic methods available at present for the synthesis of (4.5) spiro decane carbo cyclic compounds. The review covers the methods reported in literature upto December 1981.



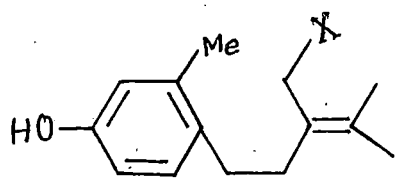
(1)

After the correct structural assignment, there had been a flood of syntheses of beta vetivone and related sesquiterpenes, each method differing in its approach to the spiro system. A review of the various syntheses that have appeared, clearly bringing out the wide array of methods, is included in the main body of the thesis.

The review underlines the fact that aryl participation reaction has not been fully exploited so far. One of the reasons, perhaps, is difficult accessibility of appropriately substituted phenolic tosylates (2) or (3).



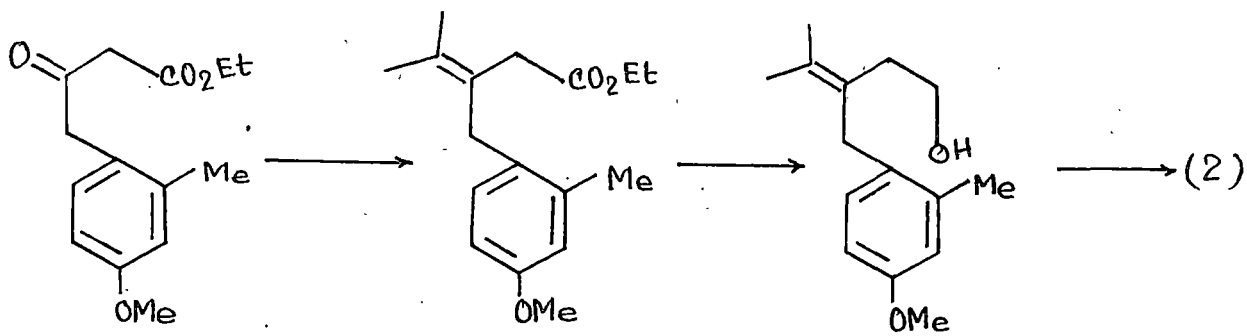
(2)



(3)

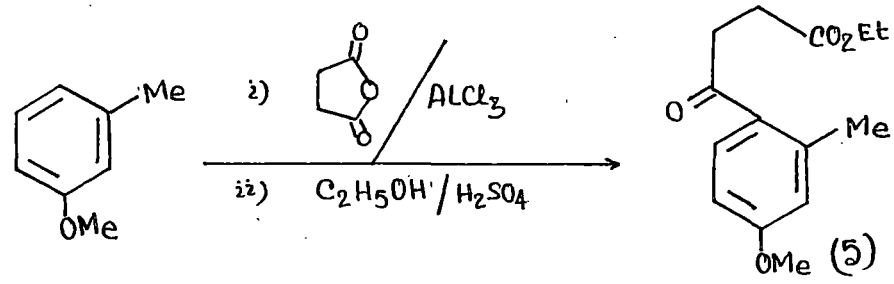
X = OTs, or any leaving group.

We felt that the tosylate (2) could be synthesized from the beta keto ester (4) by way of Wittig reaction followed by the reduction of the ester function, demethylation and tosylation as shown below:



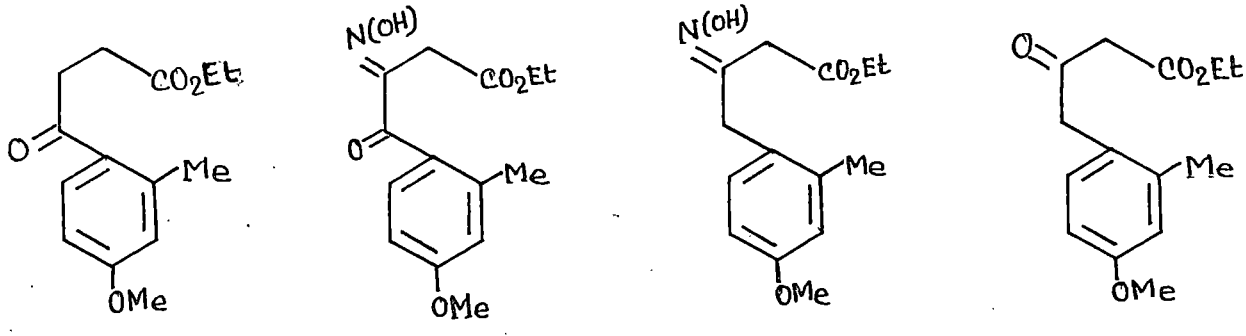
(4) (5) (6)

We planned to synthesize (4) from the keto ester (5) which could be easily prepared from m - Cresyl methyl ether and succinic anhydride. We hoped to achieve this transformation (5 ⟶ 4) by



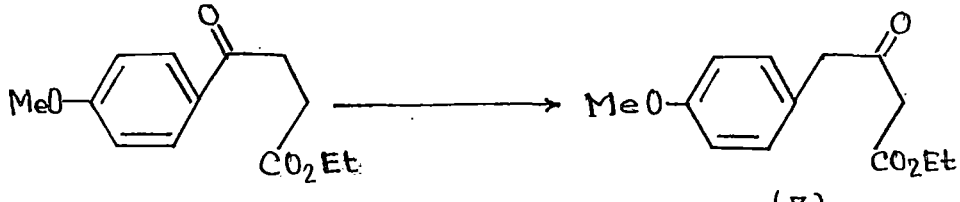
(5)

way of oximination and modified Wolff-Kishner reduction followed by hydrolysis of the oximinofunction.



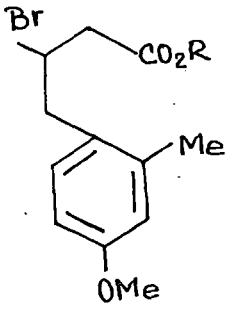
(5) (4)

We felt that a detailed study of this carbonyl transposition reaction on simpler systems would be rewarding and accordingly chose the anisoyl propionate (6) for this study. Though we could successfully transform (6) to the keto ester (7) we discarded the approach as the over all yields were not very much encouraging. The oximino keto ester was very labile and moisture sensitive.



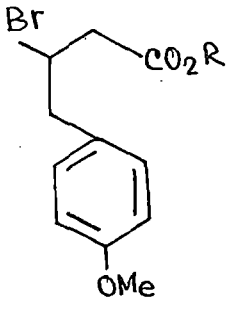
(6) (7)

Other approaches for the conversion of (5) to (4) like oxidation with selenium dioxide followed by the selective reduction of carbonyl group linked to the aryl system; bromination of the ketone followed by the removal of carbonyl function were made with limited success. The compounds (8) and (9) could be, however, prepared from (5) and (6) respectively by way of bromination and Clemmenson reduction



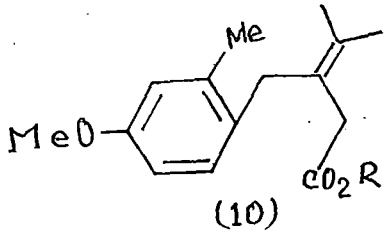
(8)

R = H, Et.



(9)

The bromo ester (8) was converted to the Wittig reagent which on reaction with acetone gave (10).

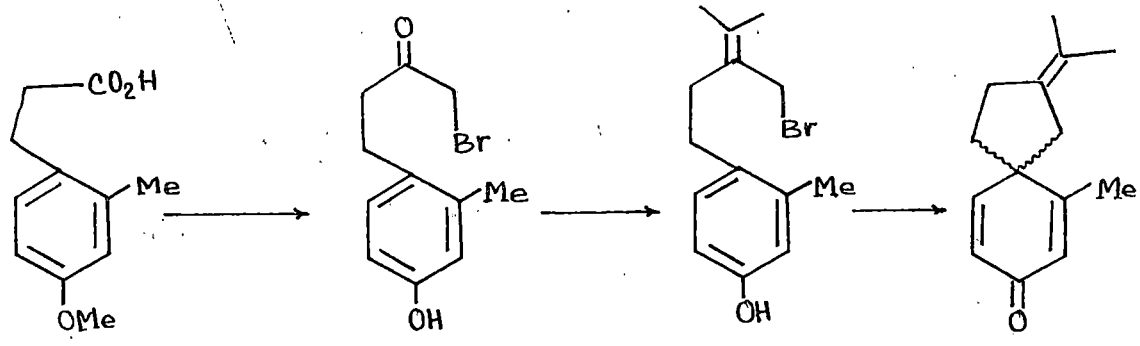


(10)

R = H, Et.

As the amount of the isopropylidine compound (10) we have prepared in our laboratory was insufficient to complete the formal synthesis more material is being prepared.

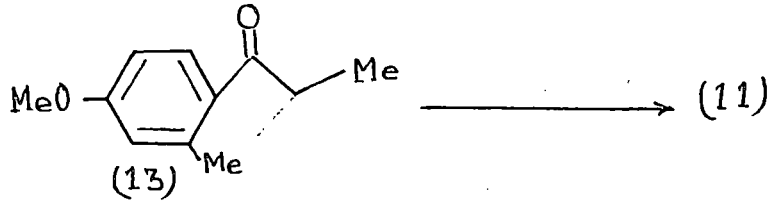
In a different approach, we felt that the synthesis of the key intermediate (12) may be worth attempting. The compound can be theoretically constructed from the acid (11).



(11) (12)

The acid (11) has been described in literature. But we chose a different route for the synthesis of the same.

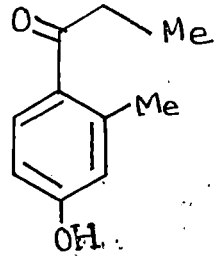
We expected the propiophenone (13) to undergo Willgerodt reaction to give the acid (11). The propiophenone (13)



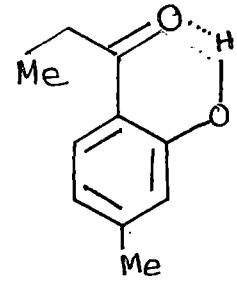
has been described in literature.

As the method described in the literature makes use of chemicals not easily accessible we wanted to prepare compound (13) by the acylation of m-cresyl methyl ether with propionic anhydride or propionyl chloride. We felt ~~that~~ the acylation procedure of Kosolapoff most attractive. However, the yields were found far from satisfactory. Though we considered Fries rearrangement as an

alternative approach we did not persue because of the reported low yields in even simpler systems. Interestingly the most obvious method of preparing the compound (13) by Friedel-Crafts' acylation using m-Cresyl methyl ether and propionic anhydride/or propionyl chloride is not reported in literature. When we carried out the reaction, apart from the desired propiophenone (13), the demethylated product (14) and the undesired isomeric phenol (15) were obtained.



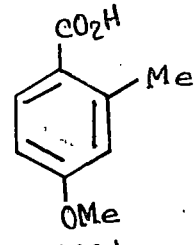
(14)



(15)

The structures of the compounds have been unambiguously established by chemical degradation and spectral studies.

The Willgerodt reaction of (13) gave not only the desired acid (11) but also the undesired benzoic acid (16).



(16)

The separation of the acids (11 and 16) either by chromatography or repeated crystallization was not successful. However we could separate the acids via the chromatography of their methyl esters. The process is very tedious and time consuming. We are contacting sister laboratories within the country and also abroad for a seperation of the esters by G.L.C. We hope to complete the synthesis in due course.