SYNTHETIC STUDIES IN FURANOTERPENOIDS

by

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CERTIFICATE

This is to certify that the thesis entitled **"Synthetic Studies in Furanoterpenoids"**, being submitted by **Miss Vibha Singh** to the Indian Institute of Technology, Delhi, for the award of the degree of Doctor of Philosophy in Chemistry, is a record of bonafide research work carried out by her. Miss Vibha has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge, has reached the requisite standard.

The results contained in this thesis have not been submitted, in part or in full, to any other university or institute for the award of any degree or diploma.

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ABSTRACT

The thesis embodies results of investigations towards the syntheses of following furanoterpenoids.

1. Myoporone
2. Furoixiolal
3. Bilobanone

An enantioselective synthesis of myoporone has been accomplished in 91 percent enantiomeric excess. The key intermediate 5,5-ethylenedioxy-3(S),7-dimethyl-octanoic acid was synthesized through diastereoselective conjugate addition of methylcuprate complex to 1,5 (S)-dimethyl-4(R)-phenyl-3-(5',5'-ethylenedioxy-7'-methyl-2'-octenoyl)-2-imidazolidone followed by hydrolysis of the resulting imide. The α,ß-unsaturated imide was prepared by base catalysed acylation of 1,5(S)-dimethyl-4(R)-phenyl-2-imidazolidone [obtained by condensation of (1R,2S)-(-)-ephedrine and urea] with 5,5-ethylenedioxy-7-methyl-2-octenoyl chloride. The acid chloride in turn has been synthesized from carbethoxylated isobutylmethyl ketone through a sequence of reactions, i.e. ketalisation with ethylene glycol, reduction, oxidation, Wadsworth Emmon's phosphonate ester olefination, hydrolysis and acid chloride derivation successively.

The ester of the chiral acid obtained above was transformed into next higher homologue via reduction, tosylation, substitution by cyanide ion, hydrolysis and

esterification as the reaction steps sequentially. The ester was then submitted to base catalysed condensation with 3-carbethoxy-furan followed by decarbethoxylation of the resulting ß-keto-ester (acidic workup) to afford (R)-(+)-myoporone. Prior to this condensation, some experiments were also carried out to (a) develop a simple and convenient pathway for the synthesis of 3-carbethoxy-furan, (b) synthesize racemic ethyl 6,6-ethylenedioxy-4,8-dimethyl-nonaoate in substantial quantity in order to optimize conditions for the condensation.

(a) 3-carbethoxy-furan has been synthesized starting from ethyl 2-hydroxyethyl acrylate which in turn was acquired by Reformatsky reaction in aqueous medium with ethyl 2-bromomethyl acrylate with formalin. Michael reaction of acrylate with thiophenol followed by masking of formyl function, obtained on oxidation of carbinol, resulted in the formation of ethyl 4,4-ethylenedioxy-2-phenylthiomethyl-butanoate. This intermediate was transformed into 3-carbethoxy-furan through two routes: (i) generation of phenylthioether into aldehyde followed by acid catalysed cyclisation; (ii) oxidation of phenylthioether into sulphoxide and then Pummerer rearrangement and cyclization in acidic medium with the deprotected aldehyde group.

(b) (±) Ethyl 6,6-ethylenedioxy-4,8-dimethyl-nonaoate was prepared by elaboration of the carbethoxy group of ethyl

3,3-ethylenedioxy-5-methyl-hexanoate through a series of transformations, i.e. acid --> methyl ketone --> conjugated ester ---> saturated carbinol ---> tosylate ---> nitrile --> carboxylic acid ---> ester. An alternative procedure to have the desired ester by ketalization of ethyl 4-keto-2,6-dimethyl-heptanoate did not succeed.

Furoixiolal has been synthesized enantioselectively and for the first time. During the synthesis of this natural product, some model experiments were performed on benzaldehyde in order to devise an efficient and facile synthesis of 2-substituted-4-functionalized furan in view of the presence of this structural moiety in a number of naturally occurring furanoterpenoids.

The synthetic stratagem involves (i) Reformatsky reaction of ethyl 2-bromomethyl-acrylate on an aldehyde in aqueous medium and then oxidation of the resulting hydroxy ester to provide γ-keto-ester, (ii) 1,4-addition of thiophenol to acrylate olefin and transformation of phenylthioether function into formyl group followed by acid catalysed cyclization. In an alternate procedure, the phenylthioether was converted into corresponding sulphoxide which undergoes Pummerer rearrangement and cyclisation in the same step to provide 2-substituted-4-carbethoxy-furan.

Utilizing above synthetic pathway, furoixiolal was synthesized through (S)-3-p-tolyl-butanal. This aldehyde was prepared in more than 91 percent enantiomeric excess by a four step reaction sequence, i.e, (i) conjugate addition of p-tolylcuprate complex to 1,5(S)-dimethyl-4(R)-phenyl-3-(2'-butenoyl)-2-imidazolidone, (ii) hydrolysis, (iii) reduction and (iv) oxidation. For the synthesis of corresponding (R)-enantiomer, a conjugate addition of methylcuprate to 1,5(S)-dimethyl-4(R)-phenyl-3-(3'-p-tolyl-2'-propenoyl)-2-imidazolidone gave the product in 85 percent enantiomeric excess.

In view of higher optical purity of (S)-isomer, this chiral aldehyde was subjected to the synthetic sequence of reactions developed for 2-substituted-4-carbethoxy-furan (mentioned above) to procure 2-(2'-p-tolyl-propyl)-4-carbethoxy-furan. The ester group was then smoothly transformed into aldehyde to have (S)-(-)- furoixiolal.

In the synthesis of bilobanone, the key intermediate, 2-isobutyl-4-hydroxymethyl-furan, has been synthesized in good yield. The approach is based on the synthetic plan, developed during the present studies, for 2-substituted-4-carbethoxy-furan thereby exhibiting the generality of the route.

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