SYNTHETIC STUDIES IN TERPENOIDS

By
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CERTIFICATE

This is to certify that the thesis entitled "Synthetic Studies in Terpenoids", being submitted by Mr. Harish Ranjan 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 him. Mr. Ranjan 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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A B S T R A C T

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

(a) 4-Nerolidylcatechol dimethyl ether
(b) 2,2-Dimethyl-5-hydroxy-3-(3-oxo-butyl)-7-n-pentyl-4-chromanone
(c) ∝-cuparenone
(d) Dihydrojasmone
(e) ar-trans-Atlantone.

Synthesis of 4-nerolidylcatechol dimethyl ether has been accomplished for the first time. Wittig reaction has been utilized for the introduction of vinylic substituent at the quaternary carbon. Attempts to synthesize 4-nerolidylcatechol dimethyl ether through [3,3] sigmatropic rearrangement or using 1-(3', 4'-dimethoxy-phenyl)-5,9-dimethyl-4,8-decadienone as the key intermediate were not successful.

A synthesis of 2,2-dimethyl-5-hydroxy-3-(3-oxo-butyl)-7-n-pentyl-4-chromanone, a cannabinoid, has been carried out starting from olivetol and thus corroborated its structure. An interesting observation in this synthesis is that alkylation and deformylation of 2,2-dimethyl-3-hydroxymethylene-5-hydroxy-7-n-pentyl-4-chromanone have taken place in the same step.

A practical synthesis of olivetol has also been developed. The advantages of the present synthesis are (i) an overall yield of 55 percent (ii) the intermediates isolated are solid crystalline compounds and are easier to purify (iii) deprotection of the masked hydroxyl groups under mild reaction conditions.

An attempt to prepare olivetol, by coupling of n-butyl magnesium bromide with 3,5-dimethoxy-benzyl bromide, resulted in the formation of 3,5-dimethoxy-toluene. The proposed pathway for this unusual observation (hydrogenolysis of 3,5-dimethoxy-benzyl bromide with n-butyl magnesium bromide) has been supported experimentally.

In view of potential of tetrahydrocannabinol derivatives as therapeutic agents, an isoxazole analogue of THC has been synthesized utilizing an intermediate of 2,2-dimethyl-5-hydroxy-3-(3-oxo-butyl)-7-n-pentyl-4-chromanone's synthesis.

During the synthesis of α-cuparenone, the present studies have resulted in the development of a new synthetic route for substituted 2-cyclopentenone (a moiety present in several biologically important compounds) through the cyclisation of 1,4-diketone. The approach involves elaboration of easily accessible conjugated ketone into 1,4-diketone through the sequence of following reactions. (i) Methylene transfer to the double bond (ii) nucleophilic ring opening by thiophenoxide anion (iii) chlorination-dehydrochlorination of thioether (iv) generation of carbonyl group from enol thioether.

α-cuparenone has also been synthesized through an extension of the route, established earlier in our laboratory, for substituted 2-cyclopentenone.

An attempt to synthesize α-cuparenone, through [3,3] sigmatropic rearrangement as the key reaction, did not materialize.

Dihydrojasmone, an important perfume constituent, has been synthesized to illustrate the generality of the new approach for substituted 2-cyclopentenone, developed during the synthesis of α-cuparenone.

ar-trans-Atlantone has been synthesized through two approaches. The first pathway makes use of 6-methyl-6-p-tolyl-4-ethoxy-5,6-dihydro-pyran-2-one as an important intermediate and the second route involves copper catalysed conjugate addition of an alkyl group to α,β-unsaturated ketone.

During the synthesis of ar-trans-atlantone following unprecedent experimental results were also observed.

(i) Acid catalysed hydrolysis of enol ether of β-keto-δ-lactone (6-methyl-6-p-tolyl-4-ethoxy-5,6-dihydro-pyran-2-one) resulted in the formation of only an unsaturated ketone (4-p-tolyl-3-penten-2-one) instead of expected β-keto-δ-lactone. The structure of the isolated product has been confirmed through its unambiguous synthesis. The mode for the present acid catalysed decarboxylative-elimination of 6-methyl-6-p-tolyl-4-ethoxy-5,6-dihydro-pyran-2-one has been proposed. (ii) Allylic rearrangement-oxidation reaction with 6-p-tolyl-4-hepten-2,6-diol using Jones reagent or pyridinium chlorochromate-sodium acetate resulted in carbon-carbon bond cleavage to afford p-methyl acetophenone as the only reaction product.

CONTENTS