

# **SYNTHETIC STUDIES IN HEMITERPENOIDS**

*by*

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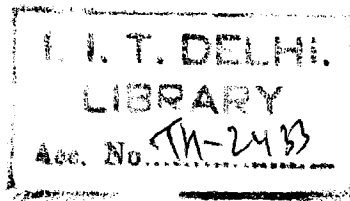
***THESIS SUBMITTED  
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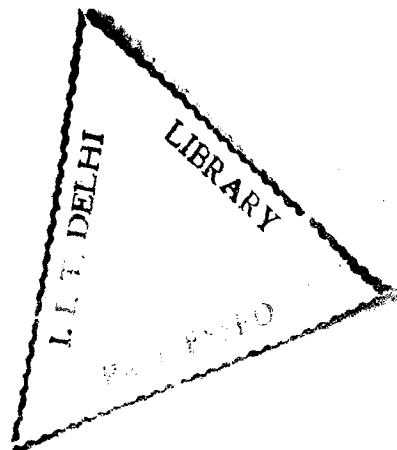
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## CERTIFICATE

This is to certify that the thesis entitled "**Synthetic Studies in Hemiterpenoids**", being submitted by Mr. N. Selvapalam 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. Selvapalam 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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(N. SELVAPALAM)

## ABSTRACT

The thesis embodies results of investigations towards the synthesis of following hemiterpenoids.

- (a) Glycocitrine-II
- (b) Acronycine and Des-N-Methyl-Acronycine
- (c) (*R*)-(+)-Lunacridine and (*S*)-(+)-Lunacrine

An efficient and regiospecific synthesis of glycocitrine-II has been accomplished. The synthesis is based on a highly useful observation that 3,5-dimethoxy-acetanilide can be prenylated at 2-position regioselectively in excellent yield using 2-methyl-3-buten-2-ol, boron trifluoride diethyl etherate in dioxane (no rearranged or demethylated or 4-substituted product could be detected). The amine obtained from this versatile intermediate (may also lead to a possible entry into regiospecific synthesis of biologically active prenylated coumarins) was condensed with diphenyl-iodonium-2-carboxylate to give the corresponding 2-[3,5-dimethoxy-2-(3'-methyl-2'-butenyl)-phenylamino] benzoic acid in high yield and specificity in the displacement of iodobenzene (the usual substitution of copper catalysed *o*-halobenzoic acid furnished only moderate yield of the product). Cyclization of the N-substituted anthranilic acid with phosphorus oxytrichloride, trifluoroacetic anhydride and polyphosphate ester under literature reported conditions afforded poor yield of the cyclic product because the prenyl group does not survive under the reaction conditions.

However, the reaction of N-substituted anthranilic acid with polyphosphate ester under rigorously anhydrous conditions followed by quenching of the reaction mixture through slow addition to the cold sodium bicarbonate solution rendered a high yield of the 1,3-dimethoxy-4-(3-methyl-2-butenyl) 9-acridone. Methylation of 10-amino-group with methyl iodide using benzyltriethyl ammonium chloride-sodium hydroxide system followed by de-O-methylation of the resulting N-methylated product through sodium ethanethiolate in anhydrous N,N-dimethylformamide at ambient temperature furnished glycocitrine-II in good overall yield.

Prior to the above synthesis, attempts were also made to carry out a regiospecific synthesis of glycocitrine-II through tandem Michael-Claisen condensation reaction of 3-acetyl-1-methyl 4-quinolinone with the preformed enolate of ethyl 5-methyl-4-hexenoate and tandem Michael-Michael reaction of 3-ethoxycarbonyl-1-methyl 4-quinolinone with 1-methoxy-7-methyl 1,6-octadien-3-one but without any success.

The possibility of a regioselective synthesis of the key intermediate, 3,5-dimethoxy-2-(3-methyl-2-butenyl) aniline, was also explored through a Diels-Alder reaction (with inverse electron demand) between a heterodiene (1-methoxy-7-methyl-1,6-octadien-3-one) and diethyl keteneacetal, tandem Michael-Claisen condensation between 1-methoxy-7-methyl 1,6-octadien-3-one and diethyl malonate and a tandem Claisen-Claisen condensation between the ketal of diethyl 1,3-acetone-dicarboxylate and the preformed carbanion of

2-methyl-5-(4-methyl-phenyl-sulphonyl) 2-pentene. These reactions failed to secure the desired product. However, 3,5-dimethoxy-2-(3-methyl-2-butenyl) aniline could be prepared in one pot in low yield via Thorpe-Ziegler intramolecular cyclization of the suitably positioned carbanion and nitrile function in a molecule. This precursor was prepared by Claisen condensation of the anion of acetonitrile with the enolate of  $\beta$ -oxoester, ethyl 3-oxo-7-methyl 6-octenoate, followed by generation of dianion *insitu* with lithium diisopropylamide at low temperature. The cyclization through yet another dianion from 5-oxo-3-methoxy-9-methyl 3,8-decadienenitrile did not materialize.

An unambiguous and facile synthesis of the antitumour alkaloid, acronycine, has been carried out by utilizing an intermediate from the synthesis of glycocitrine-II. The approach is quite flexible and has provision for modifications in ring A (through condensation of the prenylated aniline with any  $\beta$ -ketoester), angular pyran ring (via cleavage of prenyl group at the olefin) and variations in the substituents at N and O atoms to prepare its analogues. The aforementioned intermediate, 1,3-dimethoxy-4-(3-methyl-2-butenyl) 9-acridone, was transformed into acronycine through a sequence of reactions, i.e. de-O-methylation with sodium ethanethiolate, cyclization via 2,3-dichloro-5,6-dicyanobenzoquinone and methylation under phase transfer catalyst successively, in 59.6 percent overall yield. In an alternate strategy, the de-O-methylated product was cyclized by oxymercuration and demercuration (through iodine) followed by methylation using phase transfer catalyst to give acronycine. Des-N-methyl acronycine has been prepared from an intermediate, 6-hydroxy-

3,3-dimethyl-3,12-dihydro-7H-pyrano[2,3-c] acridin-7-one, of acronycine synthesis. It was chemoselectively O-methylated in preference to -NH- using diazomethane in the presence of boron trifluoride diethyl etherate.

(*R*)-(+)-Lunacridine and (*S*)-(+)-lunacrine have been synthesized enantioselectively using chiron approach resulting in the confirmation of their absolute configurations. The key intermediate, (*S*)-1,2-oxido-3-methyl butane, was prepared from (*S*)-(+)-valine through a series of transformations, i.e. hydroxy-acid  $\rightarrow$  hydroxy-ester  $\rightarrow$  THP-ester  $\rightarrow$  THP-carbinol  $\rightarrow$  THP-tosylate  $\rightarrow$  hydroxy-tosylate  $\rightarrow$  epoxide. In an alternative pathway, D-mannitol was elaborated to the desired chiral epoxide *via* 1,2:5,6-di-O-cyclohexylidene derivatization, sodium metaperiodate oxidation, methylmagnesium iodide treatment, tosylation, lithium dimethylcuprate treatment, diol regeneration, monotosylation and epoxidation as the reaction steps sequentially. The chiral epoxide was tailored to the natural product through two routes. In the first pathway, it was reacted with lithiated 2,4,8-trimethoxy quinoline and the resulting product was selectively de-O-methylated at 2-position followed by N-methylation to procure (*R*)-(+)-lunacridine (> 97 percent e.e.). In the second approach, the epoxide was converted into chiral lactone, (*R*)-(-)- $\gamma$ -isopropyl  $\gamma$ -butyrolactone, by its alkylation with the carbanion of dimethyl malonate and subsequent decarbomethoxylation of the resulting  $\beta$ -ketoester. The chiral lactone was elaborated into (*R*)-(-)-5-methyl-4-tetrahydropyranyloxy hexanoic acid through a sequence of reactions, namely transesterification, THP formation and THP-ester hydrolysis successively. The THP-acid was condensed with methyl

3-methoxy-2-amino benzoate through mixed anhydride coupling followed by cyclization, of the amide thus acquired, with a base to afford 4-hydroxy-8-methoxy-3-(2-tetrahydropyranyloxy-3-methyl-butyl) 2-quinolinone. Methylation at 1- and 4-positions and subsequent cleavage of the THP in the methylated compound furnished (*R*)-(+)-lunacridine (>97 percent e.e.). The conversion of (*R*)-(+)-lunacridine into (*S*)-(+)-lunacrine has already been achieved by intramolecular nucleophilic substitution of the tosyl derivative of chiral lunacridine with a base involving complete inversion of configuration.

During the present synthetic studies, a new methodology has been developed to transform hydroxyacids and lactones into corresponding hydroxyesters at room temperature in high yield and purity. It involves keeping of the substrates in methanol or ethanol over Amberlyst-15 at room temperature. No racemization has been detected in chiral compounds. The generality of the procedure has been demonstrated through a number of compounds including the intermediates of (*R*)-(+)-lunacridine and (*S*)-(+)-lunacrine synthesis.

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