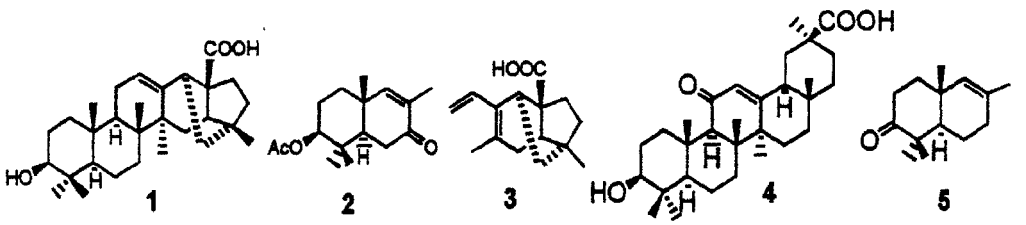
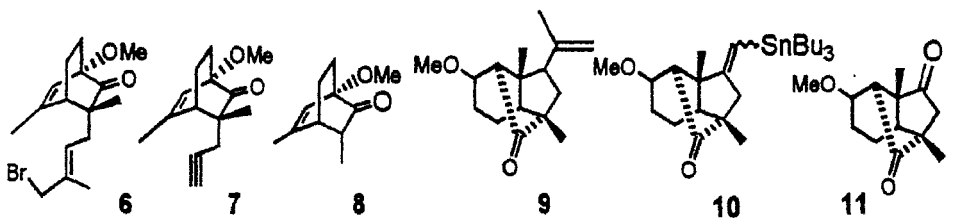
Synopsis

The thesis entitled **"Synthetic Investigations on Terpenoids''** consists of 4 chapters, each chapter begins with an introduction to the respective class of compounds in particular to its isolation, biological properties, structure elucidation, biosynthetic and synthetic background reported in the literature followed by the current work and the experimental details.

Chapter 1 deals with the synthetic studies towards pfaffic acid **1**, a hexacyclic nortriterpene isolated from the Brazilian plant *Pfaffia paniculata kuntze* with highly promising anti-tumor activities. The enone acetate **2** and the tricyclic diene **3** were identified as the two basic fragments for a key Diels-Alder reaction approach. The synthesis of AB ring synthon was achieved in chirally pure form from the commercially available naturally occurring glycyrrhetinic acid **4.** Under high temperature pyrolytic conditions, the 3-keto acid of **4** underwent a retro Diels-Alder fragmentation into the bicyclic ketone **5**, which was transformed into the required dienophile **2** through straight forward reactions.

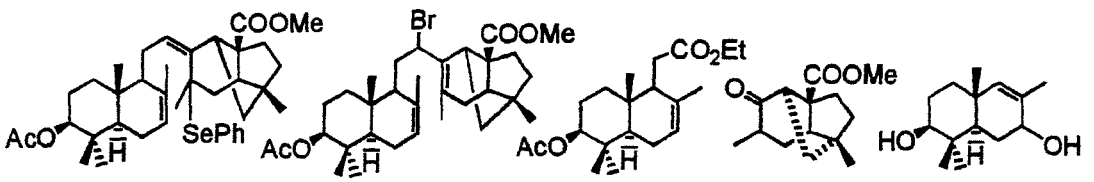


The synthetic strategy towards the DEF ring fragment **3** involves a novel tandem 5-*exo-trig*-allyl-radical, 3-*exo*-radical cyclization rearrangement reaction and also its vinyl radical analogue as key steps. The two key intermediates for the radical cyclization, the bicyclic allyl bromide **6** and the acetylenic compound **7** were obtained from the ketone **8** through kinetic alkylation with 1,4-dibromo-2-methylbut-2-ene and propargyl bromide



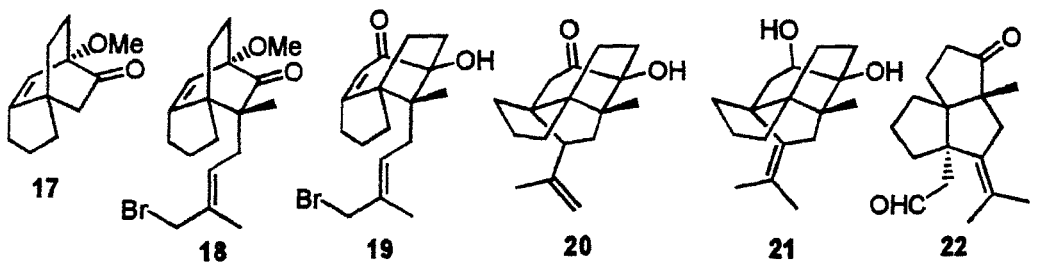
respectively. Treatment of the bicyclic bromide **6** and the acetylenic ketone **7** with tributyltinhydride gave the tricyclic systems **9** & **10** with the required DEF ring carbon framework, which was transformed into the tricyclic diketone **11**.

The Diels-Alder reaction of the dienophile **2** with some of the readily available dienes was investigated under different reaction conditions, which proved to be unsuccessful. The synthetic strategy was redesigned, where in a 6-*exo*-*trig*-allyl radical cyclization was opted as one of the key reactions to construct the pfaffane framework. The two key compounds for the 6-*exo*-*trig*-allyl radical cyclization, either the seleno compound **12** or the bromo compound **13** can be made from the bicyclic ester **14** and tricyclic ketone **15**. The bicyclic ester **14** was prepared from the enone acetate **2**, through the allylic alcohol **16** using the Johnson's orthoester Claisen rearrangement reaction.



12 **13** **14** **15** **16**

Chapter 2 describes the synthetic studies towards the polyquinane natural products by a new methodology, which is described for the synthesis of linear and angular triquinanes. The synthetic strategy towards angular triquinanes starts with the tricyclic ketone **17**, which is transformed to the allylic bromide **18** via two consecutive alkylation

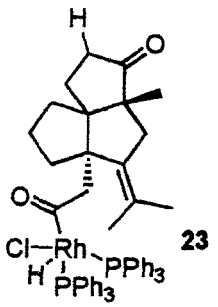


17 **18** **19** **20** **21** **22**

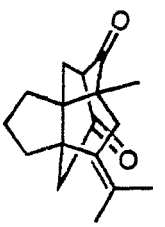
reactions under kinetic conditions. The bromide **18** was converted to the hydroxy-enone **19** through an acid catalysed rearrangement. The key intermediate, the tetracyclic hydroxy

ketone **20** was obtained from the hydroxy-enone **19** through a 5-*exo*-*trig*-allyl radical cyclization and was transformed into the diol **21**. The angular triquinic keto-aldehyde **22** was obtained through periodic acid cleavage of the 1,2-diol **21.**

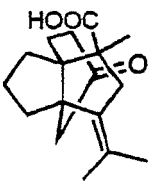
During decarbonylation of the triquinic aldehyde **22**, using the Wilkinson catalyst, a novel C-C bond formation was observed, which resulted in the formation of a tetracyclic 1,3-diketone **24**. A mechanism was proposed which involves the intermediate acyl-rhodium complex **23**, through an intramolecular C-H insertion of the CO-Rh bond to the weakly acidic **CO-C-H** bond. The tetracyclic 1,3-diketone **24** was converted to tricyclo[4.3.3]propellane **25** and the triquinic acid **26** through a retro-aldol reaction. The synthetic utility of this reaction was further extended to the substrate **27** which resulted in the diketone **28**, an important intermediate for the synthesis of the natural product 2-isocyanoallopupukeanane **29**. A similar strategy was extended towards the synthesis of linear triquinanes. The key compound, the tricyclic system **31** was prepared from the known ketone **30** through the sequence of reactions described for the compound **21**. The diol **32** was converted to the diquinane **33**, which was transformed into the corresponding tri-ketone through ozonolysis and further to the linear triquinane **34** through an aldol reaction.



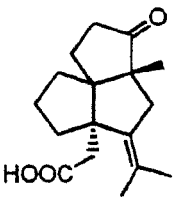
23



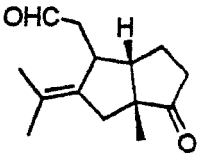
24



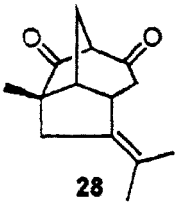
25



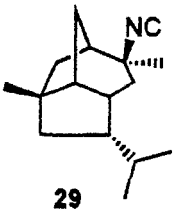
26



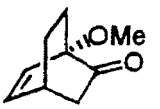
27



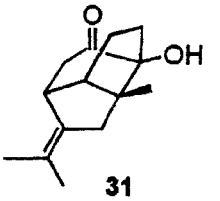
28



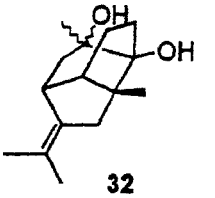
29



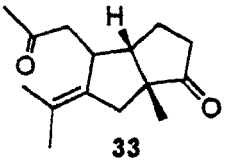
30



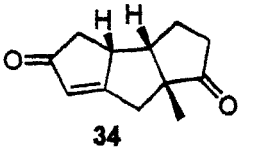
31



32

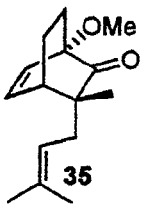


33

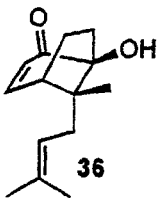


34

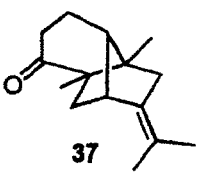
Chapter 3 describes a highly flexible route to tricyclo[4.3.1.$0^{3,7}$]-and tricyclo-[4.4.0.$0^{2,8}$]decane carbon framework, which was extended towards the synthesis of 2-pupukeanone **39**, the degradation product of the marine natural product 2-isocyanopupukeanane **41**. Two important strategies have been developed for the synthesis of the key intermediate, the tricyclic hydroxy ketone **31**.



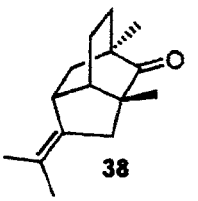
35



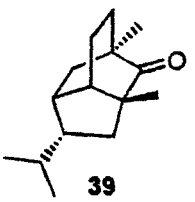
36



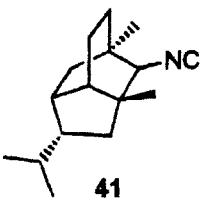
37



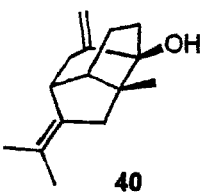
38



39



41



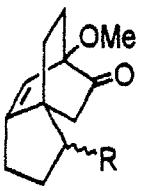
40

The first approach was a 5-*exo-trig*-allyl radical cyclization strategy, which was described in chapter II, where in the compound **31** is an intermediate in the linear trquinane synthesis. The second strategy involved a novel tandem acid catalysed rearrangement reaction of the ketone **35** to the enone **36** followed by an *ene* cyclization to afford the hydroxy-ketone **31**. Reaction of the ketone **31** with MeLi gave a separable mixture of *exo* and *endo* isomers in the ratio 4:1. The major *exo* alcohol and the minor *endo* alcohol was converted into the tricyclo[4.4.0.0]- and tricyclo[4.3.1.0]decane derivatives **37** & **38** through an acid catalysed rearrangement reaction involving perchloric acid. The 2-pupukeanone precursor **38** was also obtained from the hydroxy-olefin **40,** through the Lewis acid catalysed rearrangement reaction and constituted a formal synthesis of 2-pupukeanone.

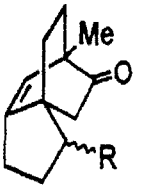
Chapter 4 deals with a general methodology for the stereospecific construction of the spiro centre in the spiro[4.5]decane sesquiterpenes from the readily available cyclohexadienes. This methodology was successfully demonstrated by achieving a formal synthesis of spiro[4.5]decane sesquiterpenes such as acorone, isoacorone and acoradienes.

The two important synthetic tranformations used are 1) the bridgehead substitution of a methoxyl group in the tricyclic ketones **42** & **43** by a methyl group to the

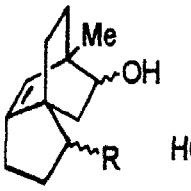
corresponding ketones **44** & **45** and 2) stereospecific construction of the spiro[4,5]decane via the oxidative cleavage of a tricyclo[5.2.2.0]undecane derivatives **46** & **47** to afford the spirohydroxy acid **48** & **49**. The two spiroketones synthesized are **50** and **51** from the corresponding spirohydroxy acid **48** & **49** through dehydrative decarboxylation reaction. The synthesis of spiroketone **51,** constituted a formal synthesis of acorone and acoradienes.



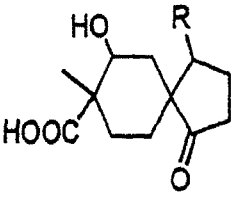
42 : R = Isopropyl
43 : R = Methyl.



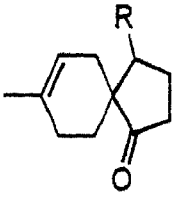
44
45



46
47



48
49



50; R = Isopropyl
51: R = Methyl

Publications:

1. A Highly Flexible Route to Tricyclo[4.3.1.$0^{3,7}$]-, and Tricyclo[4.3.0.$0^{4,10}$]decanes: A Short Synthesis of Pupukean-2-one. **P. J. Biju** and G. S. R. Subba Rao, *Tetrahedron Letters.*, **1999**, *40*, 181.
2. A New Strategy for the Synthesis of Spiro-[4,5]decanes: A Formal Total Synthesis of Acorone; **P. J. Biju** and G. S. R. Subba Rao, *Tetrahedron Letters.*, **1999**, *40*, 2405.