CHAPTER SEVEN

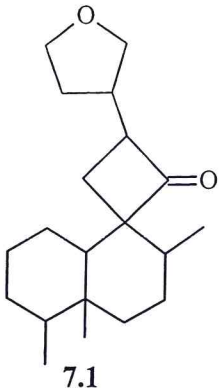
CONCLUSION AND RECOMMENDATIONS

The phytochemical investigations and biological assay results described in this Thesis were carried out following a synergistic research approach involving an interdisciplinary team of collaborators. This has facilitated achievement of the objectives of the research. Thus, bio-prospecting for mosquito larvicidal, mosquitocidal, mosquito repellent and antimicrobial constituents of different plant species that was undertaken yielded bioactive and other natural products, some of which were novel compounds. During these studies, some extracts from the leaves, stem and root barks of sixteen Tanzanian plant species, namely *Annona squamosa*, *Asteranthe asterias*, *Croton sylvaticus*, *Hoslundia opposita*, *Lettowianthus stellatus*, *Polyalthia tanganyikensis*, *Tessmannia densiflora*, *T. martiniana* var *pauloi*, *T. martiniana* var *martiniana*, *Uvaria lungonyana*, *U. scheffleri*, *U. faulknerae*, *U. leptocladon*, *U. kirkii*, *Uvariodendron usambaranse*, and *U. pycnophyllum* showed activity against *An. gambiae* mosquito larvae. The investigations formed part of long term phytochemical studies to search for botanical insecticides for the control of malaria transmitting mosquitoes, which would be affordable to the local community and environmentally friendly, being carried out in the Department of Chemistry at the University of Dar es Salaam, in collaboration with the International Centre of Insect Physiology and Ecology (ICIPE) in Nairobi, Kenya and the Tanzanian National Institute for Medical Research (NIMR). Collaboration with the Institute of Traditional Medicine at MUCHS was also pursued, in establishing antimicrobial activity of the compounds, as reported in this Thesis. Some of the extracts from *Annona squamosa*, *Polyalthia tanganyikensis*, *Tessmannia densiflora*, *T. martiniana*

new clerodanoid *cis*-kolavenolic acid (**4.1**) and (9-*epi*)-*ent*-(18-hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.4**). *T. densiflora* yielded a series of *nor*-halimanoids and isocoumarins, while *T. martiniana* var *martiniana* also yielded a series of *ent*-clerodanoid diterpenes. Compounds from the former species were tessmannic acid (**3.1**), methyltessmannoate (**3.2**), 2-methylpropyltessmannoate (**3.12**), 1-methylbutyltessmannoate (**3.13**), 8-hydroxy-6-methoxy-3-pentylisocoumarin (**3.14**), chlotessmin (**3.15**) and 5-pentyl-3-methoxy-*N*-butylaniline (**3.16**). Those from the latter plant species were *ent*-(18-hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.3**), 2-oxo-*ent*-cleroda-3,13(*Z*)-dien-15-oic acid (**4.5**), *cis*-2-oxo-*ent*-cleroda-13(*Z*)-dien-15-oic acid (**4.6**) and *O*-(3-hydroxy-4-hydroxycarbonyl-5-pentylphenyl)-3-chloro-4-methoxy-5-pentyl-2-oxybenzoic acid (**4.7**). The *ent*-clerodanoids and *nor*-halimanoids are related diterpenoids whose biosynthetic relationship would be conceived to involve cyclization of the side chain alkanoyl unit and the exocyclic propenyl moiety in the halimanoids, followed by methyl migration and then opening of the furanoid ring.

Although the three *Tessmannia* species are not used in traditional medicine, the larvicidal and antimicrobial activity shown by the extracts and the type of compounds isolated (*nor*-halimanoids and *ent*-clerodanoids) revealed the potential of this genus as a source of natural products that could influence the behaviour, development, reproduction and fitness of insects in various ways. Most of the diterpenes such as those reported in this Thesis have been reported to possess a number of bioactivities, including insecticidal, antitrypanosomal and antifeedant activity. Of particular interest among the biological activities that were observed in these investigations when mosquito larvae were exposed to the methanol extract of *T. martiniana* var

pauloi is larvae developing deformities by forming tail like-structures. The compound or compounds responsible for the observed deformities was not obtained, as the particular chromatographic fraction that exhibited the activity when further worked up only led to decomposition. However, these larval deformities could be envisioned to have been caused by some of the clerodane diterpenes occurring in the plant species, such as the ajugarins like **7.1**, that have been reported in several other studies to exhibit such biological activity.[212]



7.1

Furthermore, the series of compounds isolated from *T. martiniana* var *martiniana*, namely *ent*-(18-hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.3**), 2-oxo-*ent*-cleroda-3,13(*Z*)-dien-15-oic acid (**4.5**) and *cis*-2-oxo-*ent*-cleroda-13(*Z*)-dien-15-oic acid (**4.6**) that exhibited larvicidal and antimicrobial activity, tend to suggest that the active site in these compounds could have been the α, β-unsaturated carbonyl moiety, as previously reported in other studies, thereby indicating the importance of α, β-unsaturated carbonyl groups as bioactive sites in natural products. However, other diterpenoids as well as the isocoumarins from *T. densiflora* and *T. martiniana* var *pauloi* were not tested for bioactivity due to the paucity of the isolated samples.

Hence, at this stage the structure activity relationship for all the isolated compounds may not be conclusively stated.

Chemical investigations of the pet ether extract of the root bark of *Polyalthia tanganyikensis* yielded a new aromadendrane sesquiterpenoid that has been named tanganyikenol (**5.78**) whose isolation and structural determination is described in Chapter 5 of this Thesis. In addition to this compound polycarpol (**5.81**) which seems to be exclusively found in the family Annonaceae was also obtained. The compounds exhibited mosquitocidal activity against *An. gambiae* larvae and adult mosquitoes. The mosquitocidal activity of polycarpol (**5.81**) would suggest that the compound, just as for its antitumour efficacy, acts through interference with oxidative phosphorylation in insect cells by binding to complex I of the mitochondrial electron transport system, as previously reported for annonaceous acetogenins.

A new *ent*-kaurane diterpenoids, 17-acetoxy-*ent*-kauran-19-al (**5.83**), and a known compound *ent*-kaur-en-19-oic acid (**5.82**) were obtained from the chloroform extract of the root bark of *Annona squamosa* that showed activity and the isolated compounds exhibited larvicidal activity against *An. gambiae* mosquito larvae. Although *A. squamosa* is known to be a rich source of annonaceous acetogenins, in these investigations such acetogenins were not found, probably this being a result of either seasonal of geographical variation in the metabolism of these compounds by the investigated plant species.

Until now *Uvaria lungonyana* and *Uvariodendron pycnophyllum* are reported to be found only in Tanzania, the former at Lungonya valley within the Selous Game Reserve in Rufiji district and the latter at Kisiwani village, within the Amani Nature

Reserve in Muheza district. Chemical investigations of *Uvaria lungonyana* and *Uvariodendron pycnophyllum* yielded the usual compounds reported to occur in the genera *Uvaria* and *Uvariodendron*, these being flavonoids in the former and phenylalkenes (eugenol derivatives) in the latter plant species respectively. However, *Uvaria lungonyana* also yielded the heptanolides melodorinol (**5.85**) and acetylmelodorinol (**5.86**). These findings are interesting because the occurrence of the heptanolides has never been reported from the genus *Uvaria*, and as such the phytochemical results tend to indicate a (chemo) taxonomical relationship between the genera *Sphaerocoryne*, *Cleistochlamys* and some species of the genus *Uvaria*.

Apparently, it has been established in these studies that the occurrence of *Uvaria faulkenerae* in Tanzania is not restricted to Pangani District, Tanga Region, as it was previously reported, but the distribution of the plant also extends to Handeni and in Kimboza forest reserve in Morogoro District, respectively.

The bioassay results in Chapter 2 indicate that some of the crude extracts exhibited good larvicidal activity, and this was the basis for choosing the extracts for further analysis in order to isolate the constituent compounds, some of which were expected to be responsible for the observed activity. The biological activities of the crude extracts from the sixteen plant species as discussed in Chapter 2 have given clues on the insecticidal potency of the traditional use of the plant species in the crude form. The high activity shown by some extracts conforms to the suggestion that plants never defend themselves against insects with a mono-component system. Normally, for this purpose plants are said to use numerous constituent compounds, whether biosynthetically related or unrelated. Individual plant species are known to produce a variety of biosynthetically distinct metabolites and usually insects would perceive

and react to these compounds as mixtures rather than as individual compounds. This could also be supported by some other evidence that natural mixtures do act synergistically. However, the high bioactivities shown by some pure compounds as discussed in Chapter 6 also tend to suggest that the natural products were in fact the active components in the crude extracts. However, where the crude extracts were less active than the pure compounds, such phenomenon could be explained by assuming that the activity of the pure compounds in the crude mixtures was masked by the other, less active or completely inactive minor constituents. These studies have therefore considered these findings as challenges which have to be clarified when considering using a particular plant in crude form or as semi purified fractions.

Generally, the bioactivity trends in plant extracts versus the constituent natural products is a subject of many phenomena. Thus, apart from the masking effects discussed above the activity and hence the presence of the active constituents would also be determined by the plant part investigated, the nature of the test organism, the method and time of collection of plant materials, the method of extraction and the solvent used, and geographic location of the plant. In this regard, therefore, proper screening methods are of paramount importance in obtaining promising insecticides from plants.

As it has been observed before, Chapter two indicates that plant ecotypes in different geographical regions may differ in the accumulation of their active ingredients. For instance the extracts of the plant materials of *H. opposita* collected around the University of Dar es Salaam Main Campus were strongly active against *An. gambiae* mosquito larvae, while the extracts from the same plant species collected from Kwamngumi forest reserve in Muheza district were not active. Furthermore, different

collection seasons may also yield different constituents, as it could be deduced from the fact that plant materials of *T. densiflora* collected in January 2004 from Kichi Hills in Rufiji district, had the chloroform extract constituting only two major compounds, tessmannic acid (**3.1**) and methyltessmannoate (**3.2**), while extracts from the same plant species collected from the same locality in April 2007 were found to constitute different compounds, namely 2-methylpropyltessmannoate (**3.12**), 1-methylbutyltessmannoate (**3.13**), 8-hydroxy-6-methoxy-3-pentylisocoumarin (**3.14**), chlotessmin (**3.15**), 5-pentyl-3-methoxy-*N*-butylaniline (**3.16**), lupeol (**3.17**) and heptacosanoic acid (**3.18**). Therefore, in bioprospecting initiatives for active plant constituents, it is important to take the seasonal variations of the constituents into consideration in order to maximize the yield of such compounds at the time when they are metabolized in abundance. Consideration must also be given to the fact that most active principles in plants would show low stability, and as such they are usually lost during the extraction and purification process. Therefore, again this factor needs to be recognised when embarking onto bioprospecting ventures for bioactive compounds.

In general, plant species of the same or closely related genera would contain the same or similar active principles. Consequently, a screening system which was successful with one species should also be attempted with closely related species. This applied, for instance, for the genus *Tessmannia*, which in these investigations was represented by three species, namely *T. densiflora*, *T. martiniana* var *pauloi* and *T. martiniana* var *martiniana*. The three *Tessmannia* species were found to be a rich source of diterpenoids, especially *nor*-halimanoid and *ent*-clerodanoid diterpene. As such it

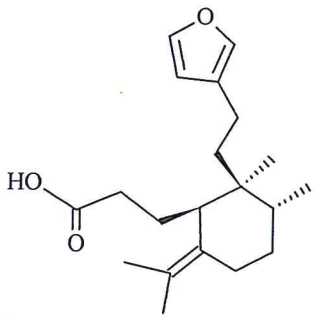
proved useful to invoke the same separation techniques for compounds from each of the three species.

Several other major challenges were encountered when conducting these studies, that included the isolation of small amounts of pure compounds which were not sufficient to conduct bioassay tests. Such compounds included some of the natural products that had novel chemical structures, like 2-methylpropyltessmannoate (**3.12**), 1-methylbutyltessmannoate (**3.13**), 8-hydroxy-6-methoxy-3-pentylisocoumarin (**3.14**), 7-chloro-8-hydroxy-6-methoxy-3-pentylisocoumarin (**3.15**), 5-pentyl-3-methoxy-*N*-butylaniline (**3.15**), *cis*-kolavenolic acid (**4.1**) and 18-oxocleroda-3,13(*E*)-dien-15-oic acid (**4.5**). Likewise, limits in the availability of essential facilities hampered the ability to carry out spectroscopic experiments such as one- and two-dimensional NMR spectroscopy, and MS and X-ray diffraction analysis for structural elucidation and stereochemical and conformational assignments, particularly of enantiomeric structures such as *ent*-(18-hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.3**) and (9-*epi*)-*ent*-(18-hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.4**).

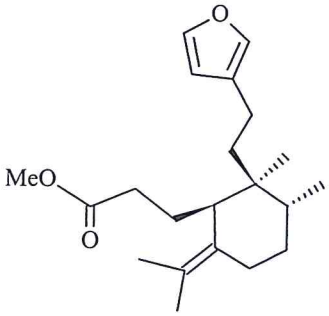
In summary, as investigations in natural products research continue to develop and proceed towards the discovery of novel natural products with pesticidal or other activities, future studies should aim at examining and evaluating the influence of the bioactive compounds on a variety of biological screens and improve strategies of evaluating extracts, re-collect, re-isolate and/or synthesize authentic samples of natural product(s) and their derivatives to afford gram quantities for follow-up bioassay screens so as to update the available chemical and biological data.

COMPOUNDS ISOLATED IN THESE INVESTIGATIONS

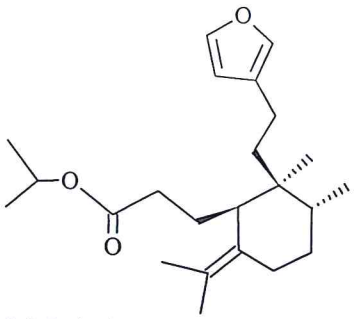
A. COMPOUNDS FROM *TESSMANNIA DENSIFLORA*



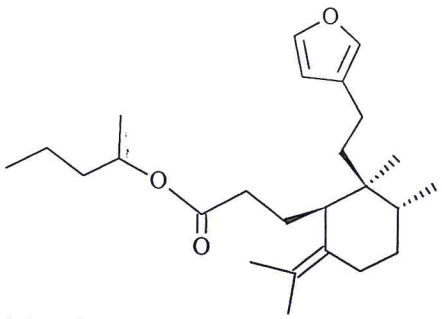
Tessmannic acid (**3.1**, NEW)



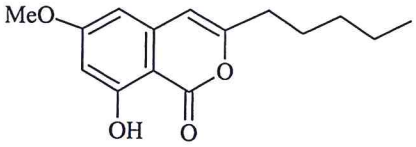
Methyltessmannoate (**3.2**, NEW)



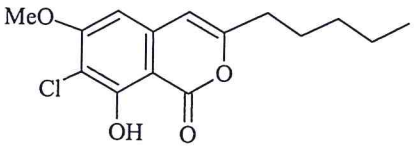
2-Methylpropyltessmannoate (**3.12**, NEW)



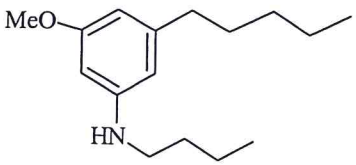
1-Methylbutyltessmannoate (**3.13**, NEW)



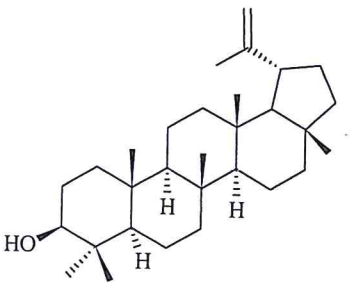
8-Hydroxy-6-methoxy-3-pentylisocoumarin (**3.14**)



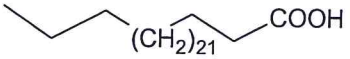
Chlotessmin or 7-Chloro-8-Hydroxy-6-methoxy-3-pentylisocoumarin (**3.15**, NEW)



5-Pentyl-3-methoxy-*N*-butylaniline (**3.16**, NEW)

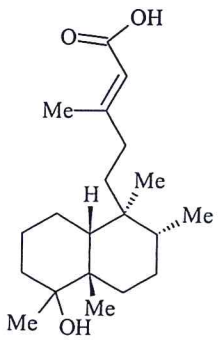


Lupeol (**3.17**)

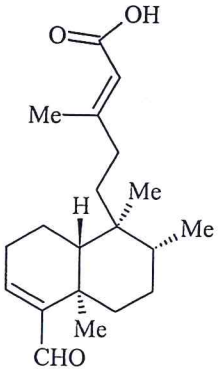


Heptacosanoic acid (**3.18**)

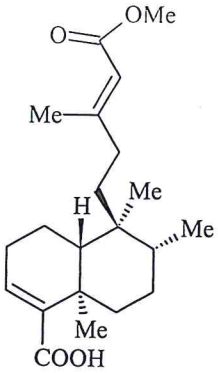
B. COMPOUNDS FROM *TESSMANNIA MARTINIANA* VAR *PAULOI*



cis-Kolavenolic acid (**4.1**, NEW)

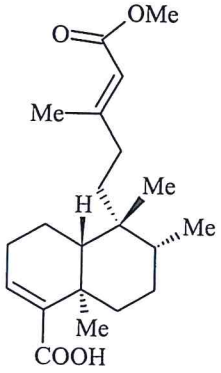


18-Oxocleroda-3,13(*E*)-dien-15-oic acid (**4.2**)

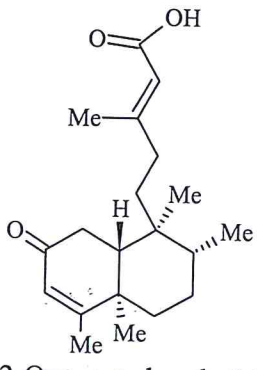


(9-*epi*)-*ent*-(18-Hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.4**, NEW)

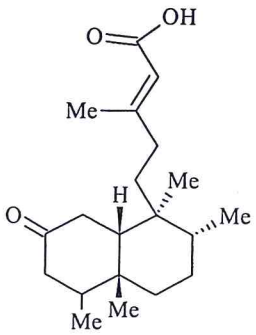
C. COMPOUNDS FROM *TESSMANNIA MARTINIANA* VAR *MARTINIANA*



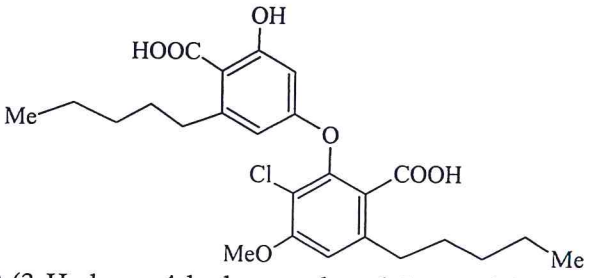
ent-(18-Hydroxycarbonyl)-cleroda-3,13(*E*)-dien-15-oate (**4.3**, NEW)



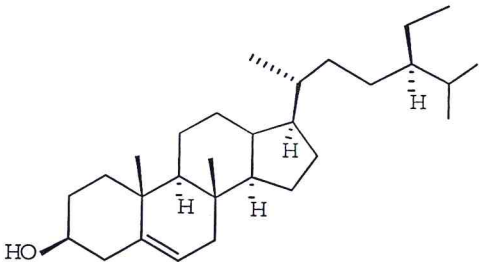
2-Oxo-*ent*-cleroda-3,13(*Z*)-dien-15-oic acid (**4.5**)



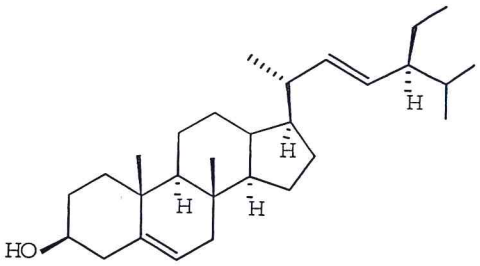
cis-2-Oxo-*ent*-cleroda-13(*Z*)-en-15-oic acid (**4.6**)



O-(3-Hydroxy-4-hydroxycarbonyl-5-pentylphenyl)-3-chloro-4-methoxy-5-pentyl-2-oxybenzoic acid (**4.7**, NEW)

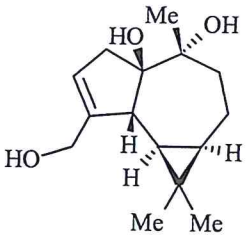


β-Sitosterol (**4.8**)

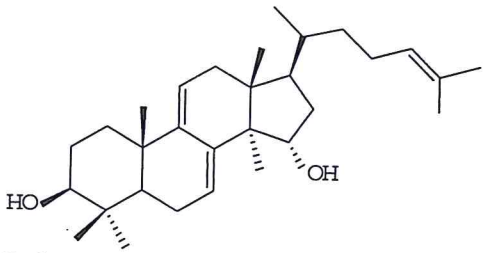


Stigmasterol (**4.9**)

D. COMPOUNDS FROM *POLYALTHIA TANGANYIKENSIS*

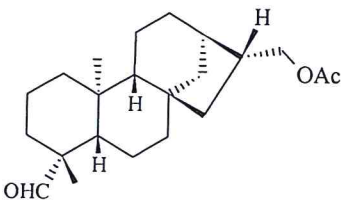


Tanganyikenol (**5.78**, NEW)

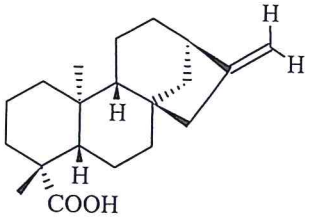


Polycarpol (**5.81**)

E. COMPOUNDS FROM *ANNONA SQUAMOSA*

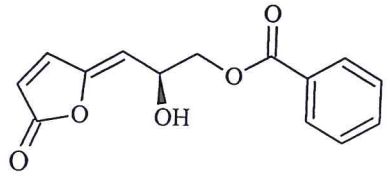


17-Acetoxy-*ent*-kauran-19-al (**5.83**, NEW)

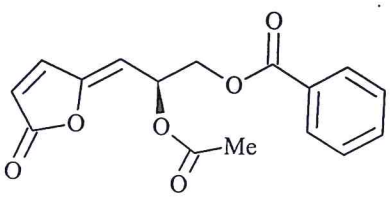


ent-Kaur-16-en-19-oic acid (**5.82**)

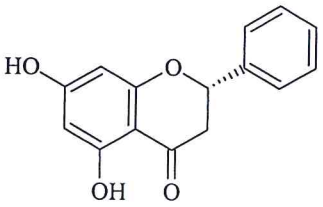
F. COMPOUNDS FROM *UVARIA LUNGONYANA*



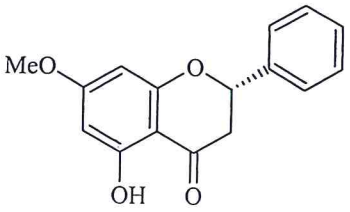
Melodorinol (**5.85**)



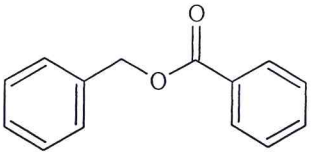
Acetylmelodorinol (**5.86**)



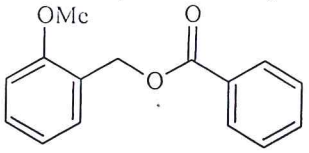
Pinocembrin (**3.1**)



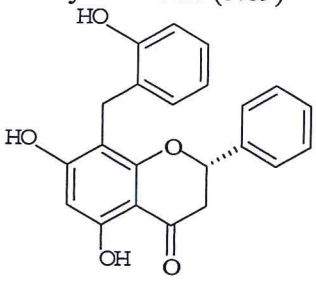
5–Hydroxy–7–methoxyflavanone (**3.1**)



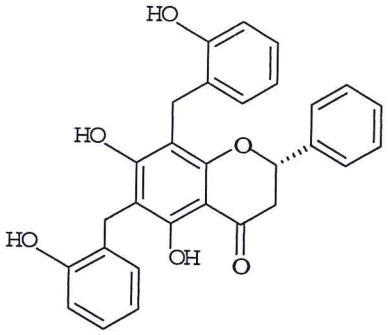
Benzyl benzoate (**5.89**)



2-Methoxybenzyl benzoate (**5.90**)

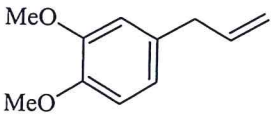


Chamanetin (**5.91**)

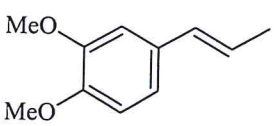


Dichamanetin (**5.92**)

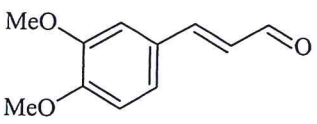
G. COMPOUNDS FROM *UVARIODENDRON PYCNOPHYLLUM*



O-Methyleugenol (**5.21**)



O-Methylisoeugenol (**5.93**)



2,3-Dimethoxycinnamaldehyde (**5.94**)

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