

CHEMISTRY OF MARKETED PLANTS OF EASTERN AND SOUTHERN AFRICA

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ABSTRACT:

Different strategies have been developed by various research groups to determine a sound and practical basis for the selection of plants for scientific examination. Groups involved in drug discovery programs often use bioassay-guided fractionation to track, isolate and identify substances that have positive activity. Others employ ethno-medical information as leads. More recently combinatorial chemistry and high throughput robotic screening techniques have been employed mostly by the big multinational pharmaceutical companies. Each one of these approaches has its benefits and disadvantages and the selection depends upon the goals of the project and the resources available to the researchers. The selection of plant material for investigation by our research group has been guided by the belief that plants that have acquired the status of marketed commodities have already been screened by traditional methods. This approach has led us to examine a number of plants and the results obtained in the course of training students has been stimulating and exciting. This paper will deal with examples of marketed plants from a number of countries in eastern, central and southern Africa. It will be selective rather than comprehensive. Reference will be made to the historically important Ethiopian anti-parasitic plant *Hagenia abyssinica*, and other marketed plants of current interest like Aloe, the devil's claw (*Harpagophytum procumbens*), *Hypoxis* spp. In addition results from our own laboratories will be presented. *Scilla nervosa* (Burch) Jessop sub-species *rigidifolia* (Hyacinthaceae) is used in Zulu medicine to treat rheumatic fever and as purges for children. In Botswana the plant is alleged to enhance female fertility and to treat infections. The tubers yielded thirteen homoisoflavonoid (nine of which are new) and three-stilbene derivatives. *Bulbine capitata* V Poellen (syn. *B. stenophylla* Verdoorn) is used in Botswana as antibiotic. This plant is a rich source of furanonaphthoquinones, anthraquinones including knipholone type compounds which show interesting biological properties. We have investigated several species of *Dorstenia* (Moraceae): *D. manji*, *D. kameruniana*, *D. psiliris* and *D. poinsettifolia*. They are rich sources of prenylated flavonoids, which undergo various cyclizations to yield furano-, pyrano-, and dihydropyrano derivatives. *Rhamnus prinoides* L'Herit occurs widely in Africa and is commonly known as Gesho in Ethiopia and dogwood in southern Africa. We have reported several quinones, flavonoids and naphthalenic compounds from various parts of this plant and have established that geshoidine may be the flavoring principle of the plant responsible for the characteristic bitter tastes of the domestic beverages, *Tella* and *Tej*. Further examinations of the more polar fractions of (Rhamnaceae) have yielded acylated glycosides of emodin and emodin anthrone. *Rhus pyroides* (Anacardiaceae) is a plant whose leaves are carefully avoided by the corn cricket. Examination of this plant has yielded novel bichalcones, which may have potential insecticidal properties. Marketed plants that are collected from the wild run a great risk of extinction. This lecture will urge the need to developed sustainable use of these important plants.

INTRODUCTION

Different strategies have been developed and used by various research groups to determine a sound and practical basis for the selection of plants for scientific examination. Phytochemical studies are generally driven by the desire to discover beneficial compounds in order to add value to the plant resources that are investigated. Groups involved in drug discovery programs often use bioassay guided fractionation to track down, isolate and identify substances that have positive activity. Over the years several tests have been developed to serve such purposes. Simple antibacterial and antifungal assays, the brine shrimp assay, etc. are examples of this type. The brine-shrimp assay is regarded as a very simple test and can be carried out even by natural product chemists as a way of monitoring the biological activity of extracts and pure substances. Although this test was introduced 17 years ago, there is no report assessing its true utility or how reliable this test is for those researchers who only have this assay to rely on. Other biological bioassay techniques that are employed are not simple and require experts of the corresponding disciplines to be involved and can only be used in collaborative work.

Many scientists in Africa do not have access to good biological evaluation programs. As a result most phytochemical research efforts have been confined to the publication of articles detailing the isolation, separation and characterization of

secondary metabolites. Efforts to examine the biological activities of these substances through cooperation with laboratories overseas have not proceeded expediently probably due to the legal, financial and other complexities that would be associated with the discovery of a commercially exploitable material. Many of our African colleagues are probably involved in frustrating cooperation with laboratories in the North and it is possible that the existing relationships do not guarantee equitable benefit to them should commercialization be possible. It is now becoming increasingly clear for us to seriously address such issues and hope that we will be able to devote our panel discussion, at least in part, to such a topic.

The uses of plants as poisons, medicinals and spices have been known since ancient times. It is possible to classify the empirical information on these plants into two broad categories.

The first is where the information about the use of a given plant is guarded in a proprietary manner by herbalists or traditional doctors. Ethno-medical information is used as leads by many researchers. This strategy is complex to those who are sensitive to the intellectual property rights issues of our people. Many scientists, pharmaceutical companies and western organizations appear to have ignored these issues and treated the genetic materials as well as the ethno-medical information as free-for-all. This situation is fortunately changing in the post Rio era and the awareness of various stakeholders to intellectual property issues is very much

heightened. However one observes the development of sound policies addressing intellectual issues from our countries has been far too slow. On the other hand, the mechanisms that have emerged recently for acquisitions of plant materials, extracts and compounds from the South by North institutions, particularly pharmaceutical and other multinational companies have become very sophisticated and the transfer of biological materials and information is, if any, even more intensified than before.

The second refers to cases where the uses of the plants are generally known by the community and the people go to markets and purchase these plants in much the same way as a person in the developed countries goes to a drugstore and purchases over-the-counter drugs, cosmetics, insecticides etc. Although there is some degree of scepticism about the efficacy of plants used traditionally, it should be pointed out that plants that are sold in markets are generally those that have attained broad acceptability and thus, have become established items of commerce.

Each one of the above strategies has its benefits and disadvantages and the selection depends upon the goals of the project and the resources available to the researchers. The selection of plant material for investigation by our research group has been guided by the belief that plants that have acquired the status of marketed commodities have already been screened by traditional methods. This approach has led us to examine a number of plants and the results obtained in the course of training students has been stimulating and exciting. In the case of many plants, the sale is based on the collection of wild plants and in cases where the roots or tubers are sold, then conservation issues are very important. It is, therefore, important to draw attention to the need to introduce the cultivation and sustainable use of these plants as an integral part of the investigation of marketed plants. Our concern for conservation has convinced us of the importance of maintaining an Experimental Garden in our Department. We have found that many of the sterile samples sold in markets are in fact viable for planting and have been grown successfully in our garden. This effort has enabled us to obtain botanical specimens for establishing the taxonomic names of plants whose identity has been in doubt previously. Our efforts to identify and document the scientific names of plants sold in markets have enabled taxonomists to identify plants, which have not been described in the literature. We have also been able to identify many novel structures and biological properties - such as antiparasitic, cytotoxic and a few with interesting flavor and fragrance properties. From first hand knowledge in visiting markets in Botswana, Ethiopia, Kenya, Tanzania and Uganda it is observed that the informal trade in marketed plants is much broader than may have been imagined. *Harpagophytum procumbens*, a medicinal plant popularly known as "Devils claw" is harvested from the wild in southern Africa (Botswana, South Africa, etc.) and is marketed in Europe. This plant is one of many that are traded in such manners. Marketed plants may be classified into the following categories:

1. Medicinal and Toxic Plants:

Ajuga remota, *Albizzia anthelmintica*, *Aloe* spp., *Asparagus africanus*, *Berberis holstii*, *Carissa edulis*, *Clerodendron myricoides*, *Croton machrostachys*, *Cucumis* spp., *Cyphostemma adencaule*, *Echinops kebericho*, *Embelia schimperi*, *Glinus lotoides*, *Hagenia abyssinica*, *Lathyrus sativus*, *Leonotis ocyimifolia*, *Lepidium sativum*, *Myrsine africana*, *Ocimum lamiiifolium*, *Phytolacca dodecandra*, *Rubus apetalus*, *Rumex abyssinicus*, *Salsola somalensis*, *Taverniera abyssinica*, *Verbascum sinaiticum*, *Verbena officinalis*, *Withania somnifera*.

2. Flavour plants:

Carum carvi, *Coriandrum sativum*, *Lippia adoensis*, *Melilotus officinalis*, *Rhamnus prinoides*, *Thymus schimperi*.

3. Fragrance Plants:

Artemisia rehan, *Cymbopogon citratus*, *Myrtus communis*, *Ocimum* spp.

4. Fumigants:

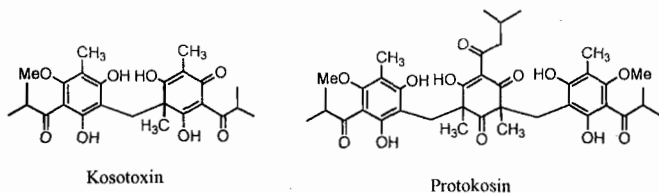
Capparis tomentosa, *Indigofera caerulea*, *Inula confertifolia*, *Otostegia integrifolia*, *Silene macrosalen*.

This lecture deals with a few examples of marketed plants beginning with a historical as well as scientific discussion of the plant *Hagenia abyssinica* J. F. Gumel. (Rosaceae) a plant with a long history and one that is still used by quite a number of people in Ethiopia as a vermifuge to rid of intestinal flat worms from the body. This will be followed by a comprehensive review of the chemistry of the genus *Dorstenia* with particular reference to the secondary metabolites obtained from several taxa. Many members of this genus are sold in a number of countries in Africa as important medicinal plants.

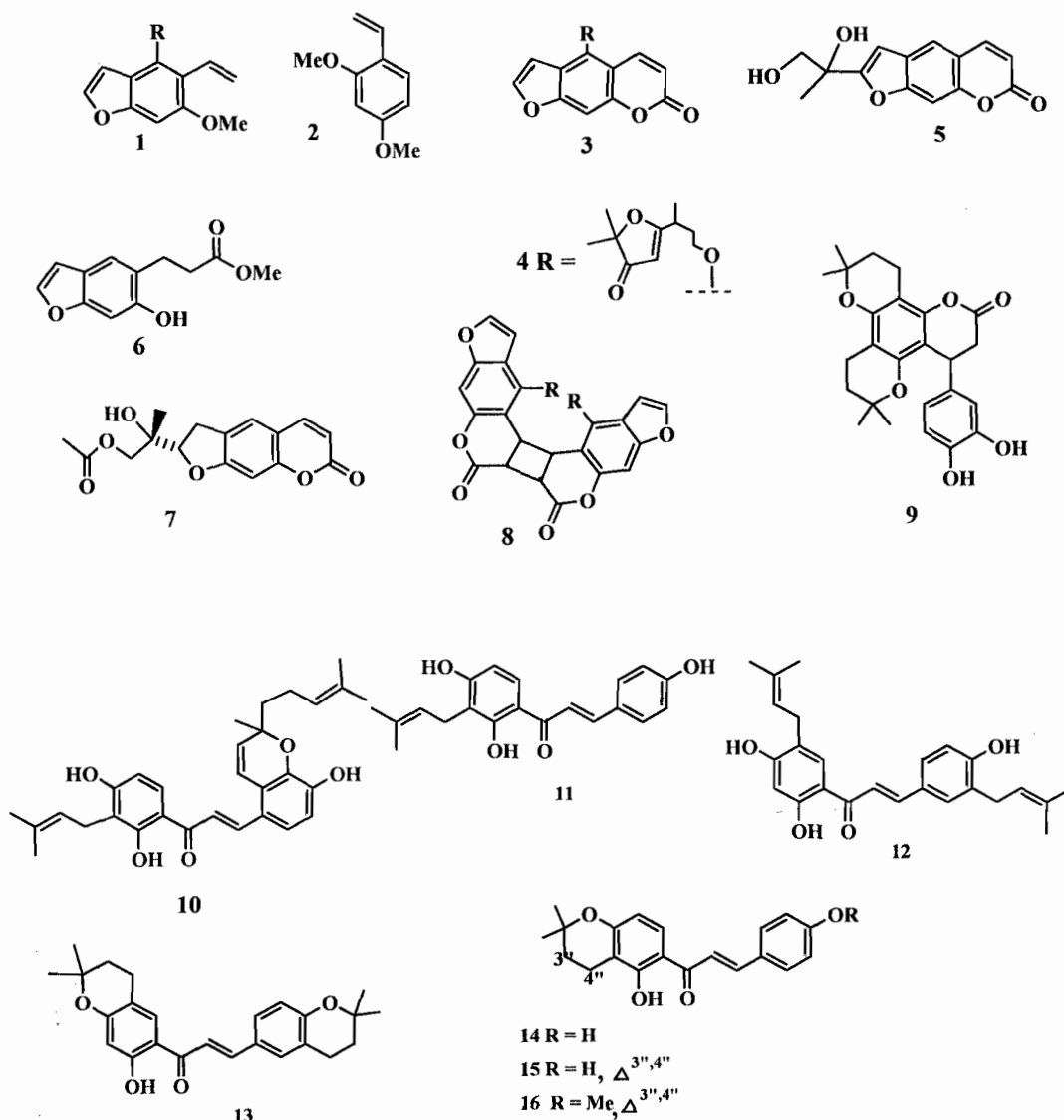
HAGENIA ABYSSINICA

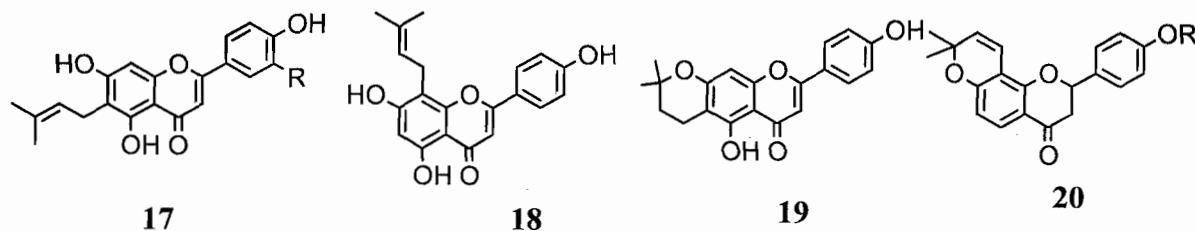
Hagenia abyssinica is a plant, known in Ethiopia by the name of Kosso and is sold in markets for use as a taeniacide. According to Lemordant (1972) [1] who wrote a detailed account on the "History and Ethnobotany of Kosso", it was in 1645 that the Portuguese Jesuit Father Godinho brought the merits of Kosso to the attention of the World. James Bruce, the Scottish adventurer who came to Ethiopia (1768-1773) to learn the source of the Nile also encountered the use of this plant in Ethiopia. Bruce provided a scientific description of the plant and also advocated the desirability of this plant for use in his country for the same purpose [2]. Nearly a hundred years later, Merck from Darmstadt in Germany came up with a mixture of crystalline substances isolated from the female flowers as an anthelmintic drug. A publication that appeared quite early in this regard is one by Fluckiger and Buri (1874) [3]. This was followed by another in 1894 by Leichsenring [4] who described the isolation of a toxic substance called kosotoxin. Efforts continued intermittently with notable

scientists like Sir Alexander Todd and A. J. Birch (1952) making significant contributions but not quite arriving at the correct chemical structures of the active constituents until 1974, when Finnish workers published the currently accepted structures of kossotoxin, protokosin, kosidin and kosin [5].



In Addis Ababa *D. barnimiana* is sold for the treatment of gout and also for various skin diseases. Samples bought from market in Addis Ababa as well as tubers of the plant collected from a site just south of the city led to the isolation of the first examples of natural styrenes (**1**, R=H, and **1**, R=OMe), which contain furan moiety. These as well as **2** were found to be devoid of any significant antimicrobial activity when tested against a variety of organisms [7]. Also isolated were the furocoumarin bergapten (**3**, R = OMe), glutinol and β -amyrin acetate. *D. cayapiaa* yielded the unusual furocoumarin **4** [14] which was subsequently found in other *Dorstenia* species by other workers. *D. brasiliensis* is used in Brazil for treating malaria, typhoid fever, and against snake bites. Kuster *et al.* identified bergapten (**3**, R = OMe), psoralen (**3**, R = H), **4** and traces of a compound, which from ms data was concluded to be a dihydroderivative of **4** [8]. *D. contrajerva* is a medicinal plant used by the Kuna Indians of Panama as a remedy for





cold, for the treatment of snake bites and muscle aches and for the treatment of rattle-snake bites in southeastern Mexico. Swain *et al.* (1991) [15] examined this plant and isolated a bergapten and a derivative of the same furocoumarin whose structure was subsequently revised as **4** and confirmed by X-ray [9]. This same plant also yielded a dihydrofurocoumarin, dorsteniol **5**. The structure and relative stereochemistry of dorsteniol was confirmed by total synthesis and X-ray data on the acetate [10].

In Cameroon, a decoction of the leaves of *D. psilurus* is used to treat rheumatism, snake bites, headache and stomach disorders. Examination of the roots of this plant led to the characterization of novel prenylated flavonoids (See below) in addition to psoralen, stearyl-p-coumarate, stearylferulate and the benzofuran derivative, **6** [13]. Rojas-Lima *et al.* (1999) [16] have recently investigated three *Dorstenia* spp. and also found known and novel furocoumarins. *D. excentrica* yielded prandiol acetate, **7**, **4**, psoralen (**3**, R=H), and 7-hydroxycoumarin. *D. drakena* also yielded **4** and bergapten (**3**, R = OMe). *D. lindeniana* furnished small quantities of psoralen and the dimeric compounds **8** (R=H, and R=OMe). *D. poinsettifolia* is used in Cameroon for the treatment of yaws and infected wounds. The twigs of this plant yielded the novel dihydro-4-phenylcoumarin, **9** [12], a compound belonging to a small group of dihydrocoumarins isolated earlier from *Pityrogramma calomelanos* [17,18] and *Calophyllum thwaitesii* [19].

Prenylated and geranylated chalcones

Three species have so far been found to contain eight chalcones. The novel prenylated and modified geranylated derivative poinsettifolin B **10** was isolated from *D. poinsettifolia* [20] together with isobavachalcone **11** (also called 4-hydroxyisocordoin and isolated from *Cordia piaca*) [21]. Geranylated chalcones are rather uncommon with only a few reported from the family Leguminosae [22].

Examination of the *D. kameruniana* and *D. mannii* from Cameroon yielded **11** and the diprenylated chalcone stipulin, **12** [23]. **12** have been reported earlier from the legume *Dalbergia stipulacea* by Bhatt *et al.* (1992) [24]. *D. kameruniana* also yielded the novel di-, dihydropyran derivative **13** [23] which is undoubtedly formed by cyclization of the diprenylated chalcone **12**. What is more uncertain is whether this cyclization is caused during the isolation process or takes place enzymatically in the plant. However, the occurrence of both dorsmanin A, **14**, and **15** in *D. mannii* [25] strongly suggest that such cyclization reactions may very well be enzymatic. The cyclization product undergoes subsequent

oxidation to furnish the dehydroderivative 4-hydroxyonchocarpin **15** [26]. The 4-methoxy derivative **16** that has been reported previously from *Milletia pachycarpa* and *Pongamia glabra* [27] was also found in *D. poinsettifolia* [12].

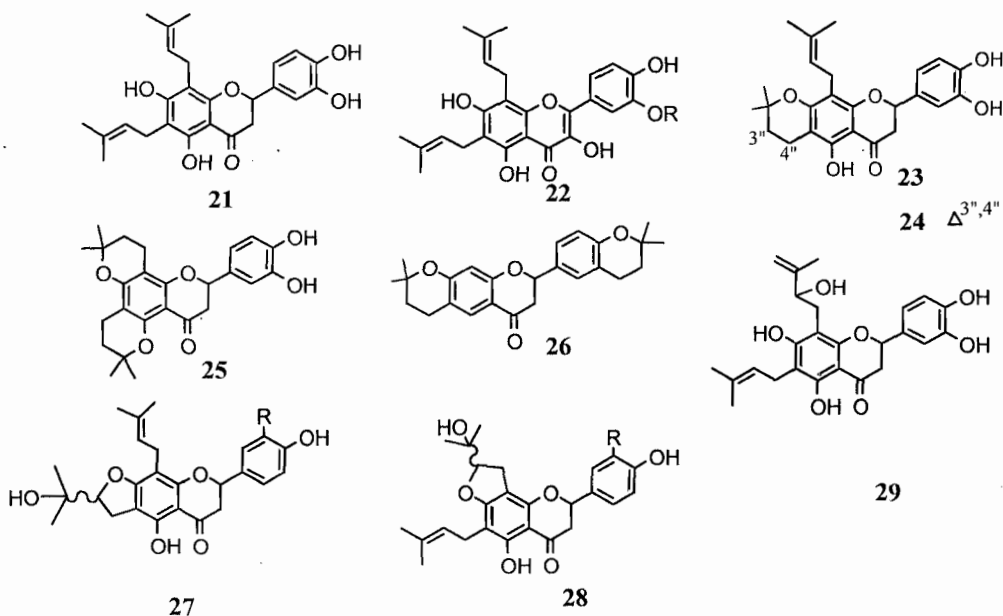
Prenylated flavanones and flavones and flavonols

Monoprenyl derivatives

A range of simple as well as complex prenylated flavonoids has been identified from a number of *Dorstenia* species. It is interesting to note that all the prenylated flavanones, flavones and flavonols reported so far appear to be only from African *Dorstenia* species. More data would have to be obtained to confirm if indeed this is truly so and if this observation has any chemotaxonomic significance. Four simple as well as modified prenylated flavonoids have been reported. The simple ones include 6-prenyl apigenin (**17**, R=H) and the 8-prenylated isomer (licoflavone C, **18**) from *D. kameruniana* [23] and *D. poinsettifolia* [20], respectively. 6-Prenylapigenin was isolated earlier from *Maclura pomifera* [28]. The simple dihydrochroman **19** and the chromen, dorspoinsettifolin (**20**, R=OMe) have so far been reported only from *D. kameruniana* [23], and *D. poinsettifolia*, [12] while the 4'-demethyl derivative of **20** has been isolated previously from *Milletia ferruginea* [29]. Compound **17**, R=OMe) was isolated from *D. mannii* [25] and was found to be identical to a compound found in *Cannabis sativa* [30].

Diprenylated derivatives

Eleven diprenylated derivatives have so far been isolated from *Dorstenia* and all of them are reported from *D. mannii*. All except dorsmanin D (**22**, R = OMe) are flavanones of which two (**21** and **22**) are simple diprenylated derivatives. 6,8-Diprenyleryodictyol **21** is a cytotoxic compound and was first reported by Harborne *et al.* in 1993 from *Vellozia coronata* and *V. namuzae* [31]. Broussonflavonol B, which is the demethyl derivative of dorsmanin D together with the 3-methoxy isomer have been reported from *Broussonetia papyfera* (Moraceae) [32]. The structure of Dorsmanin E **25** was arrived at from analysis of the spectroscopic data for the presumed natural product as well as by synthesizing it from 6,8-diprenyleryodictyol **21** upon treatment of the latter with methanolic HCl. Dorsmanin B (**26**) [12] lacks the 5-hydroxyl functionality that is common in most of the flavonoids isolated from *Dorstenia* spp and the range of compounds isolated from *D. mannii* is a good illustration of the diversity of structures that this taxon is capable of producing. The 5-hydroxy



derivative of **26** is in fact a known compound and has been found in *Paratocarpus venenosa*, a plant also belonging to the family Moraceae [33]. Both Dorsmanins F and epidorsmanin F (**28**, R=OH) occur as epimeric mixtures (*vide infra*), as do dorsmanin G and epidorsmanin G (**27**, R=OH) [34] which could not be separated by the usual chromatographic procedures. These compounds are recognized as the 3'-hydroxyl derivatives of lonchocarpols C (**28**, R=H) and D (**27**, R=H), respectively, reported from the legumes *Lupinus luteus* [35] and *Lonchocarpus minimiflorus* [36]. The clarifications of the structures of dorsmanins F and G with respect to which of the two possible prenyl groups at positions 6, and 8 is involved in the cyclization with the 7-OH group is of interest and is based on NMR spectroscopic evidence which is described here. Dorsmanin F **28** has an angular dihydrofuran ring and a prenyl substituent at C-6.

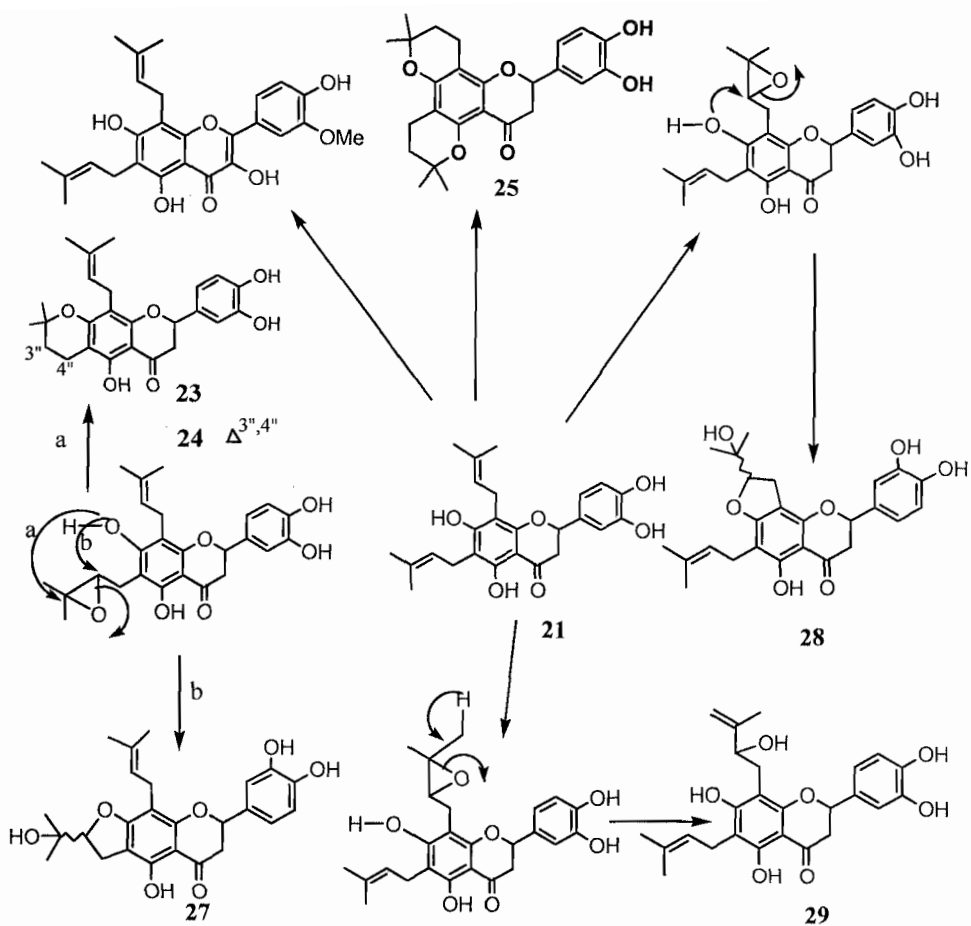
Tahara *et al.* [35,37] have shown that the chemical shift of the 5-OH signal is predictably influenced by the mode of cyclization to form the dihydrofurano ring, *i.e.* cyclization of the 8-prenyl group (8 \rightarrow 7 [O]) shifts the signal of 5-OH to lower field, whereas 6-prenyl cyclization (6 \rightarrow 7[O]) shifts it to higher field. In 6,8-diprenyleriodytyol **21** (uncyclized) the 5-OH is reported to occur at δ 12.30. In dorsmanin F the corresponding signal is at δ 12.74 consistent with the (8 \rightarrow 7[O]) cyclization and the attachment of the other prenyl group at C-6. The structure of dorsmanin F was determined to be 7,8-[2''-(1-hydroxy-1-methylethyl)-dihydrofurano]-6-prenyl-5,3',4'-trihydroxyflavanone **28**. It is possible to speculate the biosynthesis of most of the dorsmanins (**22-25**, **27**, **28** and **29**) from 6,8-diprenyleriodytyol **21**, which is in fact present in the plant in rather significant amount. Scheme 1 shows various epoxide intermediates arising from **21**, which undergo subsequent opening by phenolic hydroxyls to yield the various diprenylated dorsmannins.

Triprenylated derivatives

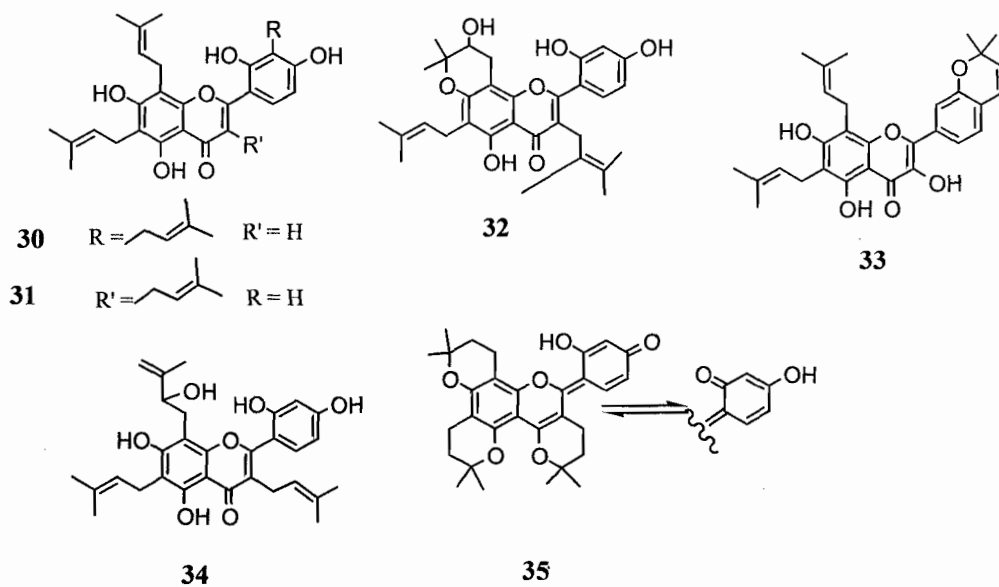
Five triprenylated flavonoids have been reported and all of them, from *D. psilurus* [13,38]. Dorsilurin A **30** is a labile compound. A chloroform solution that was kept in a NMR tube overnight, upon re-examination revealed that a number of decomposition products, probably arising by cyclisation of the prenyl groups had formed. An isomer of dorsilurin A, with a prenyl group at position 3 instead of in ring B, artelasticin **31** has been reported from *Artocarpus elasticus* [39]. The remaining members of this group have two prenyl groups in tact but the third one has undergone modification either to a hydroxychroman **32** or chromen **33** or to an allyl alcohol moiety **34**. It is quite conceivable that **32** is the biogenetic precursor to the corresponding chromen, which, however, has not been isolated. Compound **35** is a highly modified novel triprenylated derivative. The NMR spectroscopic evidence suggests that two tautomeric forms are possible. It is interesting that a triprenylated derivative like artelasticin **31** is a very probable biogenetic precursor for this compound.

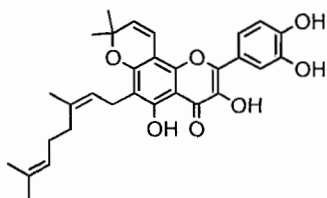
Geranylated flavonols

There are only two examples of such compounds isolated from *Dorstenia*. One of these is dorsmanin C **36**, a compound isolated from *D. mannii* and *D. tayloriana* from Cameroon and Tanzania, respectively. The second compound in this class is poinsettifolin A **37** and was reported from the Cameroonian herb *D. poinsettifolia*. Interestingly both geranylated compounds are isomeric differing only in the substitution pattern in ring A

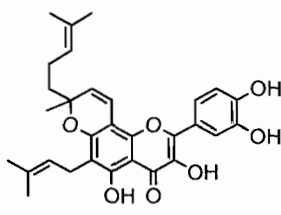


Scheme 1 Biosynthesis of Dorsmanins





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