

Novel natural products from marketed plants of eastern and southern Africa*

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Abstract: Marketed plants are an important but a vulnerable group of plants whose investigations as well as conservation should be considered with priority. The chemistry, and in some cases biological activities of novel isoflavonoids, nor-lignans, anthracene and naphthalene derivatives and poly prenylated flavonoids isolated and characterized from *Hagenia abyssinica*, *Salsola somalensis*, *Hypoxis* spp., *Taverniera abyssinica*, *Aloe* spp., *Bulbine capitata*, *Rhamnus prinoides* and *Dorstenia* spp. are discussed.

INTRODUCTION

Different strategies have been developed by various research groups to determine a sound and practical basis for the selection of plants for scientific examination. One of the strategies followed by groups involved in drug discovery programs is to use bioassay guided fractionation to isolate and identify substances that have positive activity. Other approaches employ ethnomedical information as leads. More recently combinatorial chemistry and high throughput robotic screening techniques have been employed as viable strategies for drug discovery programs in many countries. But many of our institutions or countries do not have drug discovery programs, a point that should not be forgotten when defining objectives and strategies for research in natural products.

The selection of plant material for investigation in our research group has been guided by the belief that plants that have acquired the status of a marketed commodities have already been screened by traditional methods. Marketed plants have a variety of uses. The most common ones are the medicinal plants, and those that are used as flavor and fragrance materials. Some may be regarded as non conventional foods because their use as food may be restricted to specific communities only. There are also those that are psychoactive like *khat* (*Catha edulis*). Still others are those that are used as poisons and insecticides and those that are used for fumigation purposes. Many of these plants are of such widespread acceptance that the users do not need the advice of a specialist—but rather proceed to use many of the plants in much the same way as one uses the common health and cosmetic aids and ‘over-the-counter’ drugs. Our experience with this strategy has given us an exciting experience in the study of these important plants. 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 anti-parasitic, 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. 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

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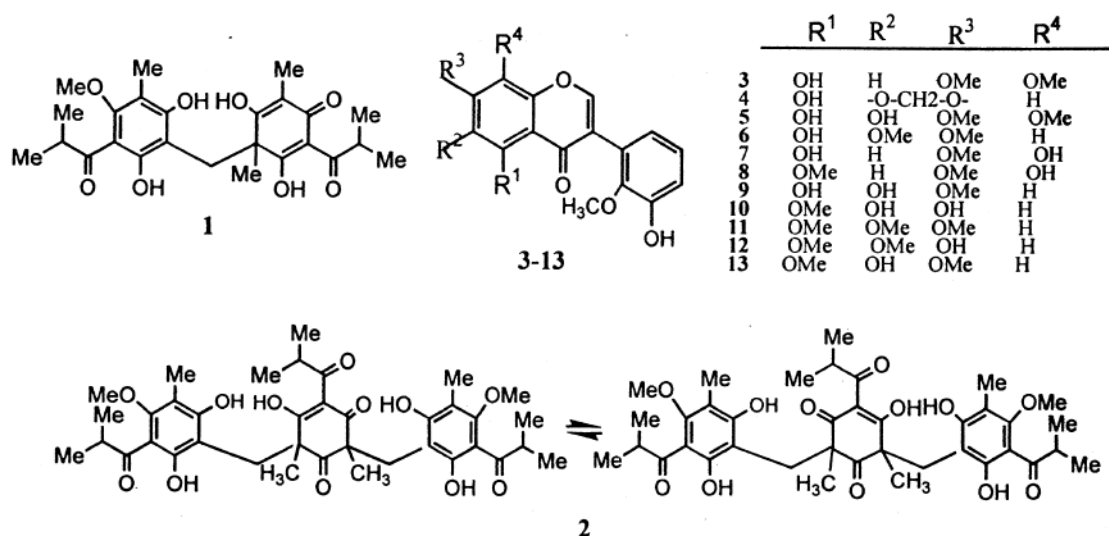
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conservation issues are very important. It is therefore important to draw attention to the need to introduce the cultivation and sustainable use of these plants as an integral part of the investigation of marketed plants.

It will not be possible to present in this report a full coverage of the chemistry of marketed plants. Only a few representative ones have been selected. For historical reasons, the anthelmintic plant *Hagenia abyssinica* will be described first and the section will conclude with our own work on one of the anthelmintic plants that we have studied, namely *Salsola somalensis*. Then, a short synopsis of other people's work on *Hypoxis* spp., *Taverniera abyssinica* and *Aloe* spp. is given followed by our own work on *Bulbine capitata*, *Rhamnus* and *Dorstenia* spp.

HAGENIA ABYSSINICA AND SALSOLA SOMALENSIS

Historically one of the most famous African plant that was included in the European pharmacopoeia in the last century was the Ethiopian plant *Hagenia abyssinica* Gmel. (Rosaceae). Lemordant [1] claims that it was Godinho, a Portuguese priest who in 1645 described the use of the plant as a vermifuge by Ethiopians. The first scientific description of this plant was provided in a five-volume book written in 1790 by the Scottish explorer James Bruce [2]. Volume 5 of Bruce's book provides an artistic illustration provided by the Italian artist L. Bulgani who apparently accompanied Bruce in his travels in Ethiopia but unfortunately met his demise in Gondar in 1770. Bruce, very much aware of the pervasive parasitic afflictions in Europe was hopeful that this plant would develop as a drug. Additional observations and attributes of this plant were provided by the physician Brayer and the Botanist Kunth in 1822 [3], although Johnston [4] who traveled in 1844 was more cautious about the possibilities of toxicological manifestations. In 1870 Merck of Germany produced the first crystalline substances, called Kosins from the female flowers of this dioecious plant. Kosso soon became incorporated in European Pharmacopoeia. More scientific papers were published by Fluckiger and Buri in 1874 [5], then by Leichsenring in 1894 [6], who isolated a toxic substance, which he named kossotoxin. Scientific interest on kossotoxin [1], protokosin [2] and the kosins (α -, and β) continued slowly over the years with eminent scientists like Sir A. Todd and A. J. Birch [7] getting close to but not quite to the currently accepted structure of these elusive substances which were published in 1974 by Finnish workers [8] (Scheme 1).



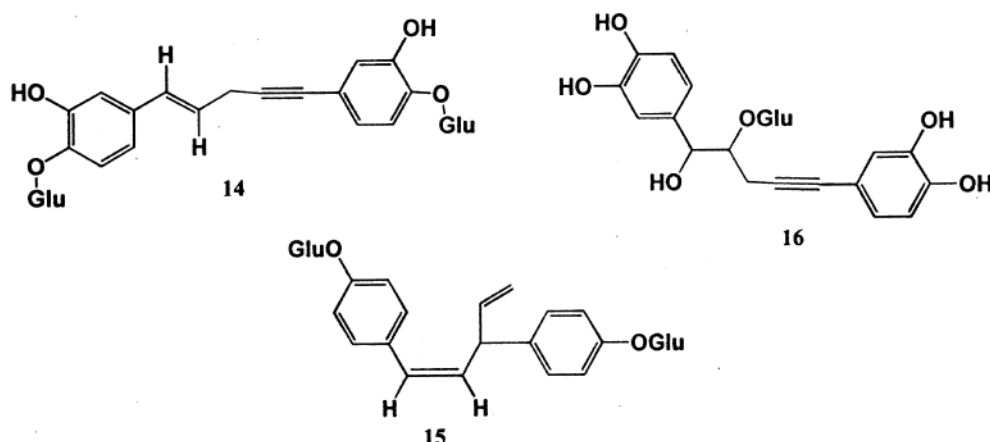
Scheme 1

The toxicity of this plant is now well recognized and although the plant is no longer used in Europe, one still occasionally encounters the Kosso vendor in the city streets of Addis Ababa with the characteristic stick over his shoulder and two enormous bundles of the attractive orange flowers hanging at the end of the long stick. Tapeworm infestation is such a common phenomenon arising from the dietary habit of consuming raw meat that there are scores of plants used as taenicides. We have studied two of

these plants, *Glinus lotoides* (Aizoaceae) and *Salsola somalensis* (Chenopodiaceae). Our work on *G. lotoides* led to the characterization of a novel triterpenoid glycoside [9]. The residues from the chloroform and ethyl acetate extracts of the roots of *S. somalensis* showed strong activity against freshly excysted tape worms. These residues were found to contain the novel isoflavonoids **3–13**, in addition to the common compounds lupeol, β -sitosterol and β -amyrin. The structures of these isoflavonoids are curious indeed to those that are biosynthetically oriented since they lack oxygenation at the 4'-position. It is, however, possible to propose an equally plausible biosynthetic mechanism for these isoflavonoids which proceeds through a dienone intermediate where the keto-function resides at the 2'-, instead of at the 4'-position [10].

HYPOXIS SPP

Among one of the most widely available medicinal plants sold in various markets in Southern Africa is the rhizomes of plants belonging to the genus *Hypoxis* (Hypoxidaceae). They are used for the treatment of various infectious diseases, prostatic hypertrophy, and internal cancer. Five species *H. interjecta*, *H. multiceps* [11] *H. nyasica* [12,13], *H. obtusa* and *H. rooperi* [14–16] have been examined from various countries in southern Africa—Mozambique, Malawi and South Africa by Drewes *et al.* in South Africa and Italian workers. What is typical and characteristic in this genus is the presence of the rather unusual nor-lignan structure containing a C6-C5-C6 skeleton. These include hypoxoside **14** [17] first isolated from *H. obtusa*, nyasoside **15** [18] nyasicoside **16** [12] and various derivatives from *H. nyasica*. The aglycone from hypoxoside (**14**), named rooperol was patented in the US as an anti-cancer agent. Considerable data is now available on the pharmacological properties of rooperol and also the potential of hypoxoside as an oral prodrug for cancer therapy [19]. A phytomedicine based on *Hypoxis* has been sold in Germany for many years for regenerating the prostate gland. It is important to mention the availability of two drugs, Moducare and Prostone, already in the European market whose *Hypoxis* derived sterols are claimed to boost the immune system (Scheme 2).



Scheme 2

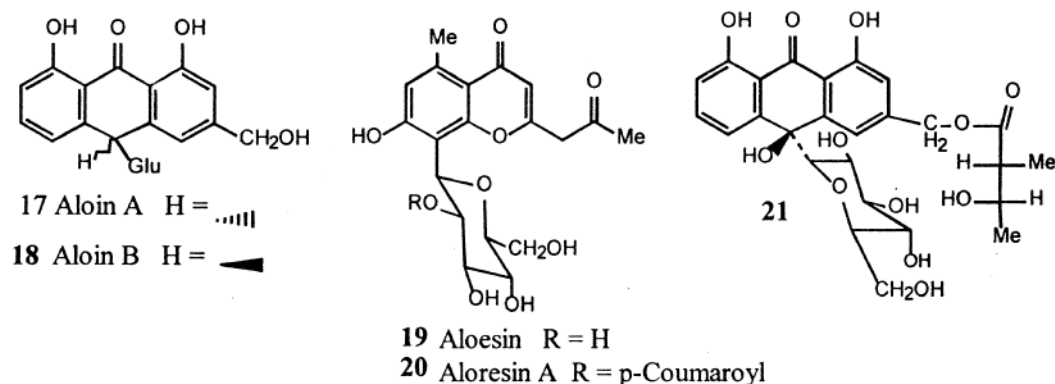
TAVERNIERA ABYSSINICA

Taverniera abyssinica A. Rich (Leguminosae) is a plant belonging to a small genus of 15 taxa and known to occur in north-east Africa and south-west Asia. It is sold in markets in Ethiopia as an all-purpose analgesic. The Ethiopian vernacular name of the plant, *Dingetegna*, tells the full story since it means 'cure for sudden illness'. A small bundle of the roots is chewed and the juice swallowed for immediate relief of fever, discomfort and pain. The roots of this plant have yielded [20] four isoflavonoid derivatives and a new pterocarpan: 3,4-dihydroxy-9-methoxypterocarpan. Pharmacological studies were conducted on rats made hyperthermic with yeast injections [21]. The aqueous extract of the roots was shown to antagonize the contractile responses of guinea-pig ileum to acetyl cholin and histamine [22]. At least some of the analgesic properties of the roots have been attributed to

the isoflavonoids. This plant is so widely used that steps should be taken to produce standardized phytomedicines and formulate dosages. At the same time it is necessary to look into the conservation and cultivation aspects of the plant.

ALOE SPP

The genus *Aloe* (Asphodelaceae) consisting of more than 360 species is indigenous to eastern, southern Africa and Madagascar and includes herbs, shrubs and trees. *Aloe* species are sold commercially for a variety of uses. They are used as sources of laxative drugs, as additives to shampoo, shaving and skin care creams, for skin disorders and treatment of burns. The botany and chemistry of *Aloes* have been the subject of two excellent reviews recently [23,24]. *Aloes* are rich sources of secondary metabolites—alkaloids, benzene, naphthalene, anthracene and bianthracene derivatives, chromones, coumarins and pyrones. About 20% of *Aloe* species are reported to contain alkaloids, many of which are piperidine and related hemlock alkaloids, and thus can be poisonous, an aspect that should be noted in considering such plants as medicinal agents. The roots of aloes contain two main types of anthraquinones: 1,8-dihydroxylated ones (e.g. chrysophanol) and 1-hydroxy-8-methylanthraquinones like aloesaponarin. The distribution of these substances in several species of aloes has been studied and important chemotaxonomic conclusions presented [24]. By far the most important constituents of commercial aloe drug are the anthrones aloin A and B (**17**, **18**) (the mixture of the two is commonly known as barbaloin), and the chromones aloesin (**19**) and aloeresin A (**20**). The aloins are two diastereomeric C-glucosides and are the purgative and bitter principles present in the commercial aloe drug which is obtained from the leaf exudates of *A. ferox* and *A. vera* [24]. The true natural product is believed to be aloin B which has the glucose moiety in α -orientation (i.e. 10R, 1'S) and it has also been shown that aloin A is derived from it [25]. These studies have also shown that aloin B is formed by attachment of glucose to aloe-emodinanthrone. Dagne *et al.* [26] have recently reported a novel nilate ester of 10-hydroxyaloins B (**21**) from *A. littoralis* with the glucose unit in the α -configuration also indicating that hydroxylation at C-10 occurs prior to epimerization of the natural aloin B. It is interesting to note that 6-hydroxyanthraquinones (emodin, physcion) are not found in aloes (Scheme 3).

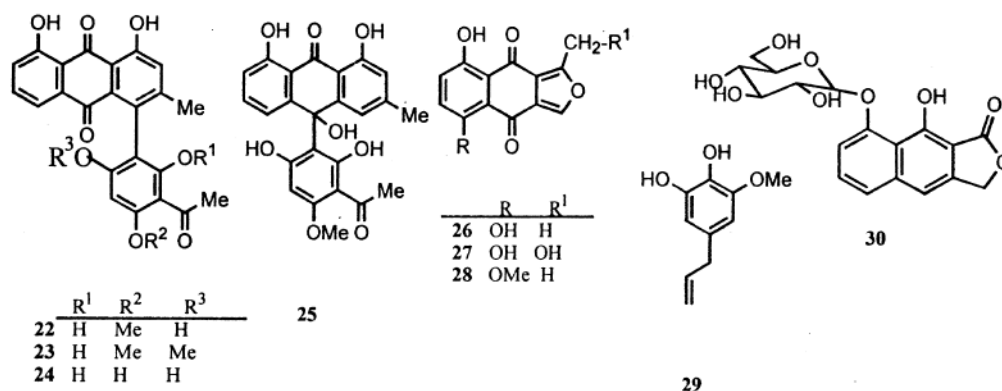


Scheme 3

BULBINE CAPITATA

The distribution of the genus *Bulbine* (Asphodelaceae) is centered in southern Africa where the occurrence of 41 species is recorded [27]. *B. capitata* is an important medicinal plant widely used in Botswana for the treatment of a wide range of ailments. Only *B. abyssinica* [28], *B. annua*, *B. asphodeloides* [29], *B. frutescens* and *B. latifolia* [30] have been investigated for secondary metabolites prior to our work on *B. capitata*. The earlier reports indicated the presence of common anthraquinones and islandicin, knipholone (**22**) and knipholone anthrone [28,30]. Our studies on the roots [31] and aerial [32] parts of *B. capitata* purchased from a market in Gaborone yielded 10 metabolites including foliosone (**25**) two novel derivatives of knipholone (**23**, **24**), the isofuranonaphthoquinones (**26**, **27**, **28**) and the allyl substituted pyrogallol derivative (**29**).

Isosufuranonaphthoquinones have very limited distribution, with few reported earlier from *Aloe ferox* [33], *Ventilago* spp. [34–36] and the fungus *Nectria haematococca* [37] (Scheme 4).



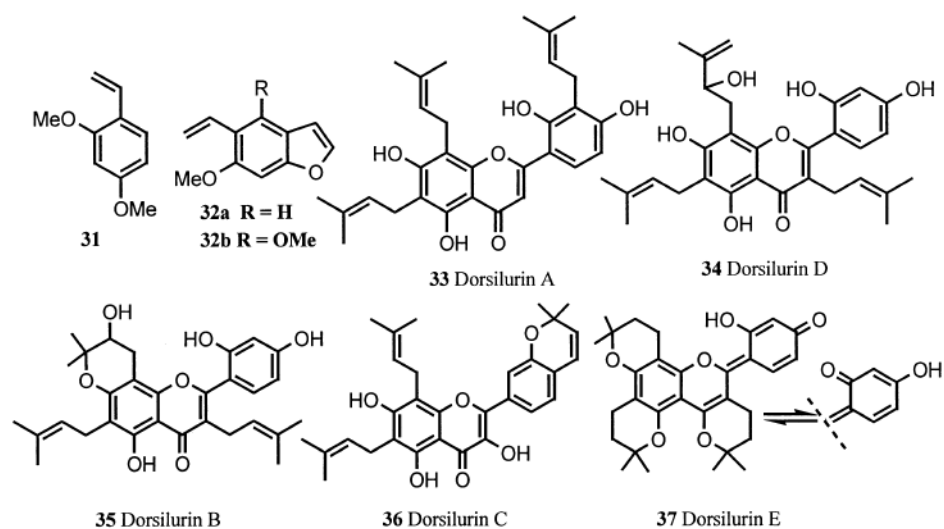
Scheme 4

RHAMNUS PRINOIDES

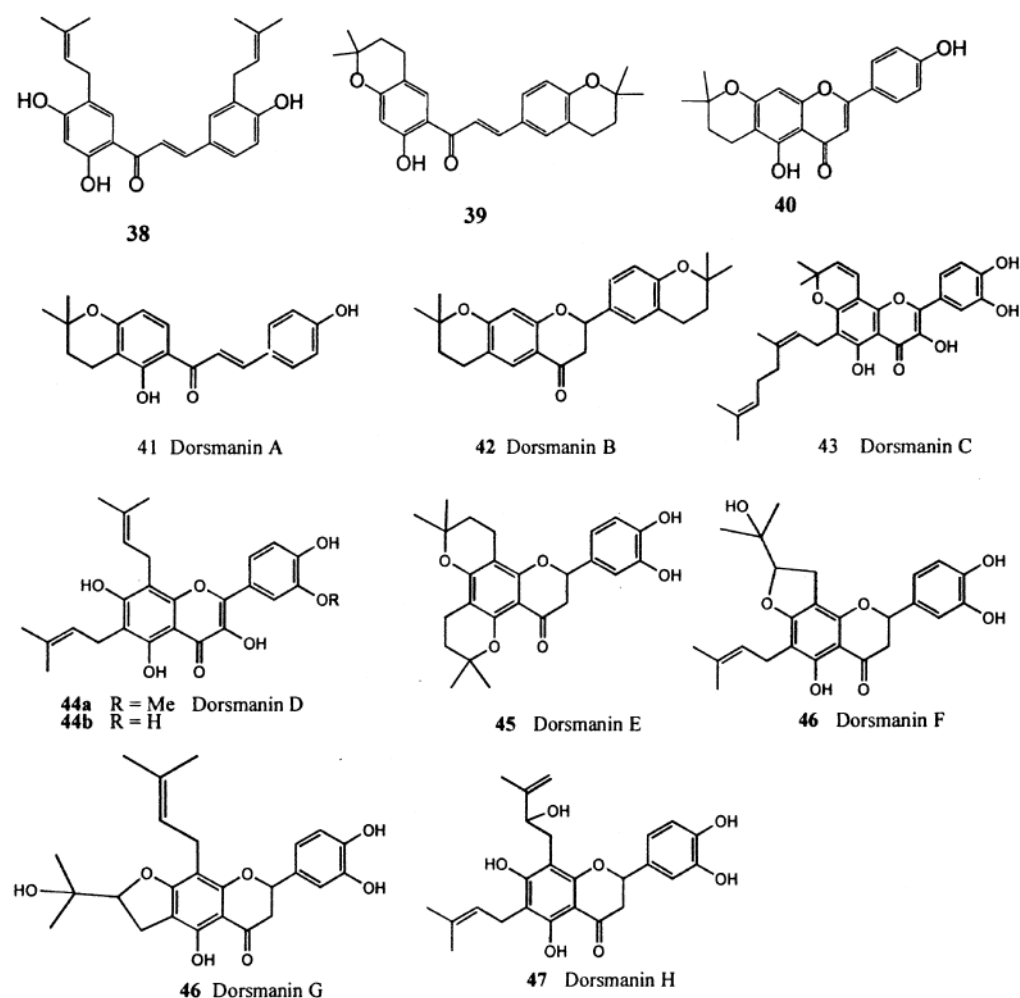
R. purshiana and *R. frangula* (Rhamnaceae) are well known sources of the commercial drugs popularly known as Cascara and Frangula. These species do not occur in Africa. The only two *Rhamnus* species that occur in Africa are *R. staddo* and *R. prinoides*. *R. prinoides* L'herit is a very interesting plant. It is widespread in many parts of eastern and central Africa. In South Africa it is known as dogwood and is referred to as a drought and frost resistant plant. In Ethiopia it is a widely cultivated multipurpose plant. The fruits are used for the treatment of ringworm infections. The leaves and stems are used as a bittering principle in the preparation of domestic beverages. Recent studies have shown that it can serve as a commercial hopping agent in the brewery industries. We have studied the above ground parts of this plant and have isolated and characterized 20 compounds consisting of seven glycosides of emodin anthrone, five flavonoids and three naphthalenic derivatives [38–40]. Organoleptically the most important substance is the naphthalenic glucoside, geshoidin (**30**), which is responsible for the characteristic bitter flavor of the beverages derived from this plant.

DORSTENIA SPP

The genus *Dorstenia* (Moraceae) is represented by about 170 species world-wide and is relatively unstudied with only one taxon mentioned in the chemical literature [41] before we reported our first paper on the *Dorstenia* series [42]. A number of taxa belonging to this genus are important medicinal plants in Africa. In Addis Ababa *D. barnimiana* is sold for the treatment of gout and also for various skin diseases. In Cameroon, a decoction of the leaves of *D. psilurus* is used to treat rheumatism, snake bites, headache and stomach disorders. Interest in this genus is now on the rise and there are different groups in Africa and elsewhere working on this genus [43,44]. The chloroform and ethyl acetate extracts of *D. barnimiana* contained copious amounts of polymeric material and small quantities of the styrene (**31**) and benzofuran derivatives (**32**) in addition to known furocoumarins and triterpenes. The Cameroonian plant *D. psilurus* also contained furocoumarins and benzofuran derivatives, but was also found it to be a very rich source of tri-prenylated flavonoids [45]. These include the relatively simple derivatives dorsilurin A (**32**) and D (**33**), the hydroxy chroman (**35**) and chromen (**36**) derivatives dorsilurin B and C, respectively, and the unusual terchromanodienone dorsilurin E (**37**). All five flavonoids are novel compounds with the last one representing a hitherto undescribed class where ring B has been modified to a dienone moiety. The double bond connecting rings B and C presents a possibility for two E or Z regio isomers, which was established by the application of NOESY experiments. NOE experiments also revealed the existence of an alternative dienone arrangement with the hydroxy function at C-4' and the ketone group at 2' [46]. In chloroform solution a slow equilibrium of these two structures appears to exist as is evidenced by the broadened NMR signals of the aryl protons of ring B. However, these signals are sharpened very much in DMSO solution indicating the probable existence of fast exchange process (Scheme 5).



Scheme 5



Scheme 6

The leaves of *D. kameruniana* from Cameroon yielded mono-, and di-prenylated chalcones and flavonoids [47]. Two of the chalcones 4-hydroxyisocordoin and stipulin (**38**) were reported previously from the legumes *Cordia piaca* and *Dalbergia stipulacea*, respectively [48,49]. The former was also reported by other workers from callus culture of *Glycyrrhiza uralensis* and named isobavachalcone. Also found was the known 6-prenyl apigenin [50]. It is interesting to note that the last two compounds were tested against growth profiles and viability of HL-60 promyelocytic cells and found to be extremely toxic [51]. *D. kameruniana* also furnished the novel dichromanochalcone (**39**) and the monochromanoflavone (**40**). The nonpolar extract of this plant was also found to contain large quantities of β -sitosterol glucoside.

D. mannii was by far the richest source of mono-, and di-prenylated as well as geranylated chalcones and flavones and flavanones of considerable complexity in the modification of the substituent prenyl groups [52]. Several of these derivatives were identified (**41–47**) including the geranylated flavonol Dorsmanin C (**43**). This same compound was the only flavonoid that we were able to identify in the organic extract of *D. tayloriana* from Tanzania. The structure of all these compounds were obtained by detailed spectroscopic analysis. Dorsmanin E (**45**) was synthesized from 6,8-di-prenylerydiol (**44b**) obtained from the same plant, by treatment with methanolic HCl (Scheme 6).

REFERENCES

- 1 D. Lemordant. *Journal d'Agriculture Tropicale et de Botanique Appliquee* **XIX**, 12 (1972).
- 2 J. Bruce. *Travels to Discover the Source of the Nile in the Years 1768–1773*, Vol. 5, 1st edn. Edinburgh (1790).
- 3 R. Pankhurst. *Eth. Med. J.* **14**, 29–34 (1978).
- 4 C. Johnston. *Travels in Southern Abyssinia through the Country of Adal to the Kingdom of Shoa*, II, pp. 271–273. J. Madden, London (1844).
- 5 F. A. Fluckiger, A. Buri. *Archiv der Pharmazie* **205**, 193 (1874).
- 6 M. Leichsenring. *Archiv der Pharmazie* **232**, 50–65 (1894).
- 7 A. J. Birch, A. R. Todd. *J. Chem. Soc.* 3102–3108 (1952).
- 8 M. Lounasmaa, C.-J. Widen, A. Hutchikangas. *Acta Chem. Scand. B* **28**, 1200–1208 (1974).
- 9 B. Abegaz, B. Tecle. *Phytochemistry* **19**, 1553–1554 (1980).
- 10 B. M. Abegaz, Y. Woldu. *Phytochemistry* **30**, 1281–1284 (1991).
- 11 G. B. Marini-Bettolo, C. Galeffi, G. Multari, G. Pallazimo, I. Messana. *Tetrahedron* **47**, 6717–6724 (1991).
- 12 C. Galeffi, G. Multari, J. D. Msonthi, M. Nicoletti, G. B. Marini-Bettolo. *Tetrahedron* **43**, 3519–3522 (1987).
- 13 I. Messana, J. D. Msonthi, Y. De Vicente, G. Multari, C. Galeffi. *Phytochemistry* **28**, 2807–2809 (1989).
- 14 S. E. Drewes, A. J. Hall, R. A. Learmonth, U. J. Upfold. *Phytochemistry* **23**, 1313–1316 (1984).
- 15 M. Potgieter, G. L. Wentler, S. E. Drewes. *Phytochemistry* **27**, 1101–1104 (1988).
- 16 S. E. Drewes, V. J. Scogings, E. L. Wenteler. *Phytochemistry* **28**, 153–156 (1989).
- 17 G. B. Marini-Bettolo, M. Patamia, M. Nicoletti, I. Messana. *Tetrahedron* **38**, 1683–1687 (1982).
- 18 G. B. Marini-Bettolo, M. Nicoletti, I. Messana, C. Galeffi, J. D. Msonthi, W. A. Chapya. *Tetrahedron* **41**, 665–670 (1985).
- 19 C. F. Albrecht, E. J. Theron, P. B. Kruger. *SAfr. Med. J.* **85**, 853–860 (1995).
- 20 H. Duddeck, A. Yenesew, E. Dagne. *Bull. Chem. Soc. Ethiop.* **1**, 36–41 (1987).
- 21 E. Dagne, A. Yenesew, F. Capasso, N. Mascolo, A. Pinto. *Ethiop. Med. J.* **28**, 155–161 (1990).
- 22 B. K. Noamesi, M. Bogale, E. Dagne. *J. Ethnopharmacol.* **30**, 107–113 (1990).
- 23 E. Dagne. *Bull. Chem. Soc. Ethiop.* **10**, 89–103 (1996).
- 24 S. Demissew. *Bull. Chem. Soc. Ethiop.* **10**, 74–88 (1996).
- 25 M. Grun, G. Franz. *Planta Med.* **39**, 288 (1980).
- 26 E. Dagne, B.-E. van Wyk, M. Mueller, W. Steglich. *Phytochemistry* **42**, 1683–1687 (1996).
- 27 C. Reid. *Plants of Southern Africa: Names and Distribution* (T. H. Arnold, B. C. De Wett, eds), p. 133. National Botanical Institute, Pretoria (1993).

- 28 B.-E. van Wyk, A. Yenesew, E. Dagne. *Biochem. Syst. Ecol.* **23**, 277–281 (1995).
- 29 M. C. B. van Rheede van Oudtshoorn. *Phytochemistry* **3**, 383–390 (1964).
- 30 L. F. van Staden, S. E. Drewes. *Phytochemistry* **35**, 685–686 (1993).
- 31 M. Bezabih, S. Motlhagodi, B. M. Abegaz. *Phytochemistry* **46**, 1063–1067 (1997).
- 32 M. Bezabih, B. M. Abegaz. *Phytochemistry* **48**, 1071–1073 (1998).
- 33 J. Koyama, T. Ogura, K. Tagahara. *Phytochemistry* **37**, 1147–1148 (1994).
- 34 T. Hanumaiah, G. S. R. Rao, C. P. Rao, K. V. J. Rao, H. J. Cowe, R. A. Howie, D. S. Marshall, R. H. Thomson. *Tetrahedron* **41**, 635–642 (1985).
- 35 S. R. Jammula, S. B. Peppala, H. Telikepalli, K. V. J. Rao, R. H. Thomson. *Phytochemistry* **30**, 2427–2429 (1990).
- 36 S. Ali, R. W. Read, S. Sotheeswaran. *Phytochemistry* **35**, 1029–1032 (1994).
- 37 D. Parisot, M. Devys, J.-P. Ferezou, M. Babier. *Phytochemistry* **12**, 1301–1303 (1983).
- 38 B. M. Abegaz, M. G. Peter. *Phytochemistry* **39**, 1411–1414 (1995).
- 39 B. M. Abegaz, T. Kebede. *Bull. Chem. Soc. Ethiop.* **9**, 107–114 (1995).
- 40 M.-T. Bezabih, B. M. Abegaz. *Bull. Chem. Soc. Ethiop.* **12**, 1–5 (1998).
- 41 C. Casagrande, F. Ronchetti, G. Russo. *Tetrahedron* **30**, 3587–3589 (1974).
- 42 Y. Woldu, B. Abegaz, B. Botta, G. Delle Monache, F. Delle Monache. *Phytochemistry* **27**, 1227–1228 (1988).
- 43 R. M. Kuster, R. R. Bernardo, A. J. R. Da Silva, J. P. Parente, W. B. Mors. *Phytochemistry* **36**, 221–223 (1994).
- 44 L. A. Swain, K. R. Downum. *Biochem. Syst. Ecol.* **18**, 153–156 (1990).
- 45 B. T. Ngadjui, E. Dongo, E. N. Happi, M.-T. Bezabih, B. M. Abegaz. *Phytochemistry* **48**, 733–737 (1998).
- 46 B. Abegaz, B. T. Ngadjui, T. Tabopda, E. Dongo, G. W. F. Kapche, P. Sandor. *Phytochemistry*, in press.
- 47 B. M. Abegaz, B. T. Ngadjui, E. Dongo, H. Tamboue. *Phytochemistry* **49**, 1147–1150 (1998).
- 48 G. Delle Monache, J. F. De Mello, F. Delle Monache, G. B. Marini-Bettolo, G. D. De lima, J. S. D. B. Coelho. *Gazz. Chim. Ital.* **104**, 861 (1974).
- 49 M. Kobayashi, H. Noguchi, U. Sankawa. *Chem. Pharm. Bull.* **333**, 3811–3816 (1985).
- 50 G. Delle Monache, R. Scurria, A. Vitali, B. Botta, B. Monacelli, G. Pasqua, C. Palocci, E. Cernia. *Phytochemistry* **37**, 893–898 (1994).
- 51 These tests were made by Dr Rolf Becker of the University of the North under the auspices of NABSA bioassay services.
- 52 B. T. Ngadjui, B. M. Abegaz, E. Dongo, H. Tamboue, K. Fogue. *Phytochemistry* **48**, 349–354 (1998).