Available online at www.sciencedirect.com

SCIENCE DIRECT®

Phytochemistry 66 (2005) 1100–1107

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Mexicanolide limonoids from the Madagascan Meliaceae *Quivisia papinae*

Philip H. Coombes [a,*], Dulcie A. Mulholland [a], Milijaona Randrianarivelojosia [a,b]

[a] *School of Chemistry, University of KwaZulu-Natal, Howard College Campus, Durban 4041, South Africa*
[b] *Malaria Research Group, BP 1274 – Antananarivo (101) – Institut Pasteur de Madagascar*

Received 5 December 2004; accepted 2 March 2005
Available online 16 April 2005

Abstract

An investigation of the seeds of the Madagascan Meliaceae *Quivisia papinae* has yielded five mexicanolide group limonoids, together with two known mexicanolide limonoids and two known triterpenoids. Quivisianolide A **9** possesses a hitherto unreported 9α,11α-epoxide ring, quivisianolide B **10** the corresponding $\Delta^{9(11)}$ double bond, and quivisianone **11** is a 17-keto *seco*-ring D compound.

Keywords: *Quivisia papinae*; Meliaceae; Madagascar; Seeds; Isolation; Mexicanolide limonoids; Melianol; Melianone; Swietenolide; Proceranolide; 2α-Hydroxyswietenolide; 7-Angeloyl-7-detigloylruageanin B; Quivisianolide A; Quivisianolide B; Quivisianone

---

1. Introduction

Quivisia papinae Baillon ex Grandidier is an endemic Madagascan species originally placed in the genus *Trichilia*, tribe Trichilieae, subfamily Melioideae by Harms (1940), who thought it to be very similar to the genus *Ekebergia*. Pennington and Styles (1975) subsequently considered the fruit and seed sufficiently distinctive to warrant the creation of a new subfamily, the Quivisianthiodeae, in which it is currently the sole species. It is known locally in Southern Madagascar as "hompy", but no information at present is available about its medicinal properties.

A previous study (Mulholland and Taylor, 1988) on the wood and stembark of this species yielded a limonoid tentatively identified as the 3-keto analogue of *Ekebergia pterophylla* compound 1 (Taylor and Taylor, 1984) from the bark, and the coumarin 5-methoxy-6,7-methylenedioxycoumarin from the wood. A more recent investigation (Coombes et al., 2004) of the seed afforded two azadiradione derivatives and the novel evodulone group limonoid quivisianthone.

Further investigation of the seed of *Q. papinae* has now furnished two known triterpenoids, melianone **1** and melianol **2**, two known mexicanolide group limonoids, swietenolide **3** and proceranolide **4**, and five novel mexicanolide limonoids **5**, **8**–**11**.

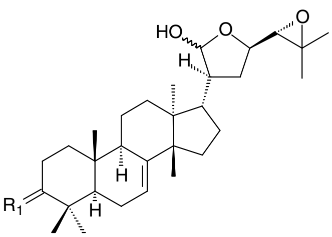
2. Results and discussion

The triterpenoids melianone **1** and melianol **2** were identified by comparison with literature data (Nakanishi et al., 1986). Both compounds displayed the characteristic signal "doubling" in the ^{13}C NMR spectrum, which occurs when rapid equilibration in solution of the five-membered hemiacetal ring that

---

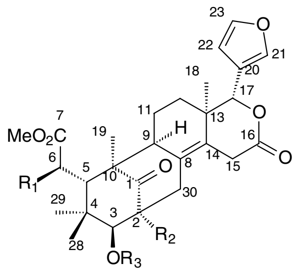
[*] Corresponding author. Tel.: +27 31 260 1395; fax: +27 31 260 3091.
E-mail address: coombesp@ukzn.ac.za (P.H. Coombes).

0031-9422/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2005.03.002



(**1**) $R_1 = O$ melianone

(**2**) $R_1 =$ -H, -OH melianol



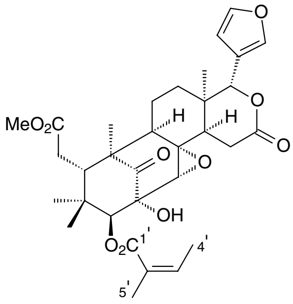
(**3**) $R_1 = OH$, $R_2 = H$, $R_3 = H$

(**4**) $R_1 = H$, $R_2 = H$, $R_3 = H$

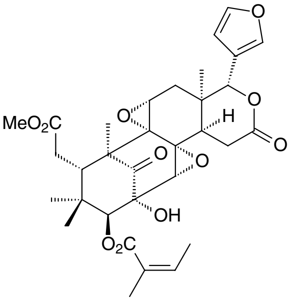
(**5**) $R_1 = OH$, $R_2 = OH$, $R_3 = H$

(**6**) $R_1 = OH$, $R_2 = H$, $R_3 = Ac$

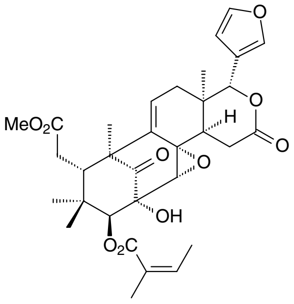
(**7**) $R_1 = OH$, $R_2 = OH$, $R_3 = Ac$



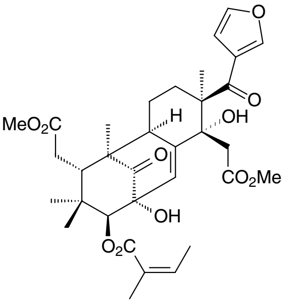
(**8**)



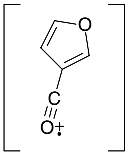
quivisianolide A (**9**)



quivisianolide B (**10**)



quivisianone (**11**)



A

characterises these compounds gives rise to two C-21 epimeric forms (Polonsky et al., 1977). The identities of the mexicanolide group limonoids swietenolide **3** and proceranolide **4** were confirmed in similar fashion (Kadota et al., 1989, 1990).

An HREIMS of compound **5** gave an $[M]^+$ at m/z 502.2195, corresponding to the molecular formula $C_{27}H_{34}O_9$ and a difference, relative to swietenolide **3**, of an additional single oxygen atom. Comparison of the ^1H and ^{13}C NMR spectra revealed them to be very similar, with the major difference being the disappearance of the 1H signal at δ_H 3.01, assigned to H-2 in **3**, and downfield shift of the corresponding C-2 resonance from δ_C 50.2(*d*) in **3** to δ_C 79.6(*s*) in **5**. This suggested that the additional oxygen atom occurred at C-2, and therefore that **5** is the novel compound 2α-hydroxyswietenolide. Comparison of the ^{13}C NMR spectra of the 3-acetyl analogues 3-acetylswietenolide **6** and 2α-hydroxy-3-acetylswietenolide **7** revealed that hydroxylation at C-2 shifts both of the C-3 and C-30 resonances downfield from δ_C 79.9(*d*) and δ_C 33.9(*t*) in **6** to δ_C 86.9(*d*) and δ_C 44.6(*t*) in **7** (Kadota et al., 1989, 1990; Khalid et al., 1998); C-3 and C-30, at δ_C 78.8(*d*) and δ_C 34.0(*t*) in **3**, occur in **5** at δ_C 87.1(*d*) and δ_C 44.7(*t*), respectively. A similar comparison of the C-2 signals in **6** and **3** reveals a downfield shift of $\delta_C \sim 2$ ppm from δ_C 47.9(*d*) to δ_C 50.0(*d*) on deacetylation at C-3 (Kadota et al., 1989, 1990); our value, at δ_C 79.6(*s*), bears the same relationship to the δ_C 77.8(*s*) recorded for C-2 in **7** (Inada et al., 1994).

An HREIMS of compound **8** gave an $[M]^+$ at m/z 584.2634, corresponding to the molecular formula $C_{32}H_{40}O_{10}$ and thirteen double bond equivalents. Inspection of the ^1H and ^{13}C NMR spectra revealed resonances attributable to a furan ring (δ_H 7.44*s*, δ_C 141.1(*d*), H-21; δ_H 7.40*s*, δ_C 143.4(*d*), H-23; δ_H 6.40*s*, δ_C 110.4(*d*), H-22; and δ_C 120.4(*s*), C-20), C-7 carbomethoxy ester (δ_H 3.70*s*, 3H, δ_C 52.7(*q*); δ_C 174.0(*s*), C-7), and four quaternary methyl singlet resonances characteristic of the mexicanolide group limonoids. Compound **8** differed significantly from **3**–**5**, however, in that the fully substituted olefinic resonances at $\delta_C \sim$ 126–129 and $\delta_C \sim$131–133, attributed to C-8 and C-14, respectively, of the $\Delta^{8(14)}$ double bond are absent. An angeloyl ester (δ_C 166.7(*s*), C-1′; δ_C 126.7(*s*), C-2′; δ_H 6.21*qq*, $J = 7.3$, 1.5 Hz, H-3′, δ_C 141.4(*s*), C-3′; δ_H 2.03*d*, 3H, $J = 7.3$ Hz, 3H-4′, δ_C 16.4(*q*), C-4′; δ_H 2.07*d*, 3H, $J = 1.5$ Hz, 3H-5′, δ_C 21.2(*q*), C-5′) was placed at C-3 on the basis of a correlation in the HMBC spectrum between H-1′ and C-3 at δ_C 84.7(*d*), with the corresponding 1H singlet resonance at δ_H 5.13, ascribed to H-3, displaying a correlation in the HMBC spectrum to a fully substituted oxygenated resonance at δ_C 78.5, assigned to C-2. The remaining ester carbonyl resonance at δ_C 171.6(*s*) must then be C-16, which correlates in the HMBC spectrum to a one proton singlet signal at δ_H 5.12, ascribed to H-17, and a pair of one proton signals, coupled in the COSY spectrum, at δ_H 2.82 (*dd*, $J = 16.1$, 5.3 Hz, H-15β, by correlation in the NOESY spectrum to H-17) and δ_H 3.51 (*m*, H-15). These, in turn, are coupled in the COSY spectrum to a signal at δ_H 1.56 (1H, *dd*, $J = 13.9$, 5.3 Hz), ascribed to H-14, with C-14 occurring at δ_C 45.5(*d*). A correlation in the HMBC spectrum between the H-14 resonance and a fully substituted signal at δ_C 63.6 designates this as C-8, and a further correlation in the HMBC spectrum between the C-8 signal and a 1H singlet resonance at δ_H 3.52 assigns this as H-30, with C-30 occurring at δ_C 67.5(*d*). The multiplicities and significantly downfield shifts of both C-8 and C-30 suggest that **8** possesses an 8,30-epoxide ring, which then accounts for both the tenth and final oxygen atom, and thirteenth and final double bond equivalent.

Further support for this assumption is provided by a correlation in the HMBC spectrum between the resonances of H-30 and C-2, while correlations in the NOESY spectrum between the H-14 and 3H-18 signals, and between those of H-30 and 3H-5′ establish their stereochemistry as α and β, respectively. Compound **8** is thus the novel angeloyl analogue of ruageanin B from *Ruagea glabra* Triana et Planchon (Mootoo et al., 1996), and as such is an epoxy derivative of swietenine, where the double bond occurs at $\Delta^{8(30)}$, rather than of swietenolide **3**, where it occurs at $\Delta^{8(14)}$.

An HREIMS of quivisianolide A **9** gave an $[M]^+$ at *m*/*z* 598.2424, corresponding to the molecular formula $C_{32}H_{38}O_{11}$ and the possession, relative to **8**, of an additional double bond equivalent and an additional oxygen atom. A comparison of the spectra of compounds **8** and **9** revealed them to be very similar in structure, with **9** also displaying the furan ring, four quaternary methyl singlet resonances, C-7 carbomethoxy ester, and D ring lactone (δ_H 4.97*s*, 1H, H-17; δ_C 82.8(*d*), C-17; δ_C 169.0(*s*), C-16; δ_H 2.76*dd*, 1H, J = 18.5, 7.0 Hz, H-15α; δ_H 3.62*dd*, 1H, J = 18.5, 12.5 Hz, H-15β; δ_C 29.0(*t*), C-15; δ_H 1.64*dd*, 1H, J = 12.5, 7.0 Hz; H-14; δ_C 38.7(*d*), C-14) signals characteristic of a mexicanolide group limonoid. Additionally, in common with **8**, **9** also possesses a ketone at C-1, an 8α,30α-epoxide ring, a hydroxy group at C-2α, and an angeloyl ester at C-3β. A correlation in the HMBC spectrum between C-17 and a 3H quaternary methyl singlet resonance at δ_H 1.07 established this as 3H-18; the corresponding C-18 resonance at δ_C 23.6(*q*) displays a further correlation in the HMBC spectrum to an unusual pair of coupled doublets at δ_H 1.98 (*d*, 1H, J = 15.2 Hz, H-12α, by correlation in the NOESY spectrum to 3H-18) and δ_H 2.39 (*d*, 1H, J = 15.2 Hz, H-12β, by correlation in the NOESY spectrum to H-15β), with the corresponding methylene C-12 resonance occurring at δ_C 27.7. A correlation in the HMBC spectrum between the C-12 resonance and a 1H broad singlet at δ_H 3.25, ascribed to H-11, is supported by a correlation in the NOESY spectrum between the signals of H-11 and 2H-12, while assignment of the corresponding methine resonance at δ_C 56.7 to C-11 is supported by the absence of the characteristic upfield methylene resonance at $\delta_C \sim 20$ normally attributable to this carbon. The assignment of a fully substituted oxygenated resonance at δ_C 62.4 to C-9 is made on the basis of correlations in the HMBC spectrum between this signal and the resonances of H-14, H-12α, and H-30β, and supported further by additional correlations in the HMBC spectrum to a 3H quaternary methyl singlet resonance at δ_H 0.90, assigned (by correlation in the HMBC spectrum to C-1) to 3H-19, and a double doublet at δ_H 3.21 (1H, J = 7.7, 5.7 Hz) assigned (by correlation in the HMBC spectrum to C-7) to H-5. The multiplicities and significant downfield shifts of both C-9 and C-11 in **9** suggest that it possesses a second epoxide ring at C-9,C-11 in addition to that at C-8α,C-30α, thereby accounting for both the additional oxygen atom and double bond equivalent. The stereochemistry of this ring is assigned as α on the basis of the $J_{11,12}$ coupling constants. In the β conformation, H-11 and H-12 are virtually co-planar, with an H-11,H-12α dihedral angle of 0°, which would give rise to a $J_{11,12}$ value of ~10–15 Hz; an α-oriented epoxide ring, on the other hand, results in H-11 bisecting the geminal 2H-12 bond angle, giving rise to $J_{11,12}$ values of 3–4 Hz, which present themselves in this compound as the observed broad singlet. It should be noted, however, that the observed doublets for both H-12α and H-12β would then be expected to be double doublets; it is difficult to explain why this is not observed. The use of correlations in the NOESY spectrum in this compound is inconclusive, as most of those observed can arise in either conformation. However, the β-epoxide conformation should lead to correlations of different intensities; although both distances are sufficiently small for NOESY correlations to occur, the H-11,H-12β distance is much larger than that between H-11 and H-12α. The α-epoxide conformation, however, leads to virtually identical H-11,H-12 distances and therefore equivalent NOESY correlations, as observed in our spectrum. Construction of a model with a $\Delta^{9(11)}$ double bond, in an attempt to predict a favoured side from which epoxidation might occur, is equally unhelpful. From a steric perspective 3H-18, 3H-19, H-14 and the carbonyl group at C-1 all favour the formation of a β-oriented epoxide ring, but this argument could then be applied equally to epoxidation of the $\Delta^{8(30)}$ double bond, which gives rise exclusively to swietenine derivatives possessing 8α,30α-epoxide rings.

This is the first report, to our knowledge, of a limonoid with either a 9,11-epoxide ring or two epoxide rings. Even within the terpenoids as a whole there are only three examples of such compounds; a fusidane derivative from the fungi *Fusidium coccineum* Fuckel (Gotfredson et al., 1979) and two epimeric fernene epoxides from *Cyathea lepifera* (J.Sm. ex Hooker) Copel (Arai et al., 1995).

An HREIMS of quivisianolide B **10** gave an $[M]^+$ at *m*/*z* 582.2474, corresponding to molecular formula $C_{32}H_{38}O_{10}$ and the possession, relative to **9**, of one oxygen atom less, but the same number of double bond equivalents. Comparison of the spectra of **10** and **9**, as before, revealed much similarity; **10** displayed the furan ring, four quaternary methyl singlet resonances, C-7 carbomethoxy ester and D ring lactone signals characteristic of a mexicanolide group limonoid, together with the C-1 ketone, C-2α hydroxy group, C-3β angeloyl ester, and 8α,30α-epoxide ring found in **9**. The ADEPT spectrum of **10** showed the additional double bond, whose carbon resonances appeared at δ_C 127.1(*d*) and δ_C 136.9(*s*), to be trisubstituted. This was placed at $\Delta^{9(11)}$

by the same chain of reasoning used to assign the 9,11-epoxide ring in **9**, with correlations in the HMBC and HSQC spectra visible from the resonances of C-17 at δ_C 82.2(*s*) to 3H-18 at δ_H 1.02*s*, from C-18 at δ_C 23.5(*q*) to 2H-12 at δ_H 2.56 (*dd*, 1H, $J = 18.9$, 2.7 Hz, H-12β, by correlation in the NOESY spectrum to H-15β) and δ_H 2.14*m* (H-12α, by correlation in the NOESY spectrum to 3H-18), and finally from both 2H-12 and C-12 at δ_C 32.0(*t*) to a 1H multiplet at δ_H 5.84, ascribed to H-11. The corresponding olefinic methine resonance at δ_C 127.1, assigned to C-11, has again replaced the missing characteristic upfield methylene resonance at $\delta_C \sim 20$ normally attributable to this carbon. A correlation in the HMBC spectrum between the H-14 signal at δ_H 1.81 (*dd*, 1H, $J = 12.1$, 7.0 Hz) and the remaining fully substituted olefinic carbon resonance at δ_C 136.9, which, in turn, displays correlations in the HMBC spectrum to 2H-12, H-30, 3H-19 (δ_H 1.26*s*, 3H, by correlation in the HMBC spectrum to C-1), and H-5 (δ_H 2.95*m*, 1H, by correlation in the HMBC spectrum to C-7), establishes this as C-9. Quivisianolide B **10** is the first example of a mexicanolide group limonoid (or any other, for that matter) possessing both a $\Delta^{9(11)}$ double bond and an epoxide ring at 8α, 30α. (In Yadav et al. (1999), a compound isolated from *Chisocheton paniculatus* Hiern is claimed to be the first reported possessing both a $\Delta^{9(11)}$ double bond *and* a 7β,8β-epoxide ring. The authors cite cneorin NP_{38} from *Cneorum tricoccon* (Mondon et al., 1982), which possesses a "normal" 7α,8α epoxide ring, as a basis for comparison, but do not explain why they assign their ring as β, nor why they place the double bond at $\Delta^{9(11)}$.)

An HREIMS of quivisianone **11** gave an $[M]^+$ at *m*/*z* 614.2735, corresponding to the molecular formula $C_{33}H_{42}O_{11}$ and thirteen double bond equivalents. The ADEPT spectrum displayed the four quaternary methyl group singlet resonances characteristic of a mexicanolide group limonoid.

Inspection of the ^1H and ^{13}C NMR spectra of **11** revealed the upfield carbonyl signal at δ 201.9(*s*) and downfield furanyl ring resonances (δ_H 8.13*s*, δ_C 148.5(*d*), H-21; δ_H 7.38*s*, δ_C 142.9(*d*), H-23; δ_H 6.82*s*, δ_C 110.8(*d*), H-22; and δ_C 124.5(*s*), C-20) characteristic of a *seco*-ring D 17-keto limonoid (Coombes et al., 2003). No direct support for this assumption could be obtained directly by correlation in the HMBC spectrum between H-21 and/or H-22 and C-17, but the appearance of a peak at *m*/*z* 95.0141 in the HREIMS, corresponding, as before, to fragment **A** provided sufficient indirect evidence. A 3H quaternary methyl singlet resonance at δ_H 1.46, ascribed to 3H-18 by a correlation in the HMBC spectrum to C-17 and correlations in the NOESY spectrum to both H-21 and H-22, showed further correlations in the HMBC spectrum to a methylene resonance at δ_C 33.7, ascribed to C-12 (δ_H 1.74*m*, 1H, H-12α, by a correlation in the NOESY spectrum to 3H-18; δ_H 2.40*m*, 1H, H-12β, by correlations in the NOESY spectrum to H-21 and H-22), a fully substituted signal at δ_C 55.2, assigned to C-13, and another fully substituted oxygenated resonance at $\delta_C \sim 77$ (obscured by solvent), which can then only be C-14. The C-14 resonance displayed a correlation in the HMBC spectrum to a doublet at δ_H 2.62 (1H, $J = 12.1$ Hz), assigned to H-15b (δ_H 2.52, H-15a, by coupling in the COSY spectrum; δ_C 42.4(*t*), C-15), from which further correlations in the HMBC spectrum established the C-16 carbomethoxy carbonyl resonance at δ_C 170.2(*s*) and attached methyl ester (δ_H 3.56*s*, 3H; δ_C 51.8(*q*)). The 2H-15 signals displayed a correlation in the HMBC spectrum to a fully substituted olefinic resonance at δ_C 140.1, which can only be C-8. A coupling in the COSY spectrum between 2H-12 and a second pair of 1H multiplets at δ_H 1.60 and δ_H 1.45, coupled in the COSY spectrum, designated these as 2H-11 (δ_C 22.4(*t*), C-11), and between 2H-11 and a 1H multiplet at δ_H 2.42 established this as H-9, with C-9 occurring at δ_C 55.0(*d*). The C-9 resonance correlated in the HMBC spectrum to a 3H quaternary methyl signal at δ_H 1.15, assigned to 3H-19, a doublet at δ_H 3.16 (1H, $J = 9.2$ Hz), whose assignment as H-5 (δ_C 40.5(*d*), C-5) was confirmed by coupling in the COSY spectrum to 2H-6 (δ_C 33.1(*t*)) at δ_H 2.35*m*, and a correlation in the HMBC spectrum to C-7 at δ_C 172.9(*s*), and to a 1H singlet signal at δ_H 5.80, assigned to H-30. With C-30 at δ_C 127.7(*d*), **11** possesses the $\Delta^{8(30)}$ double bond which characterises the swietenine type mexicanolide limonoids. The remaining downfield carbonyl signal at δ_C 214.3(*s*) was then assigned to C-1, and the singlet resonance at δ_H 4.82 to H-3 (δ_C 85.6(*d*), C-3) by correlations in the HMBC spectrum to the signals of both C-5 and C-30. That H-3 and H-30 are both singlets is accounted for, as in **8**, by the correlations of these signals in the HMBC spectrum of these signals to a second fully substituted oxygenated resonance obscured by the solvent, which was assigned to C-2.

The stereochemistry of C-14 in the 17-keto *seco*-ring D phragmalin group limonoids leandreanins A and B (Coombes et al., 2003) was determined as α by virtue of a correlation in the NOESY spectrum between the resonances of H-14 and 3H-18. A similar correlation is observed in the NOESY spectrum of **11** between the 3H-18 signal and a resonance at δ_H 4.81*br s*, assigned to the proton of a hydroxy group at C-14 by correlations in the HMBC spectrum to the signals of both C-14 and C-15, and a correlation in the NOESY spectrum to the resonance of H-15b. The hydroxy group at C-14 is thus α, and quivisianone has structure **11**.

17-Keto *seco*-ring D limonoids are relatively uncommon in the Meliaceae, with only three examples previously reported. These comprise the previously mentioned leandreanin A, phragmalin congener pseudrelone B from *Pseudocedrela kotschyii* (Schweinf.) Harms (Taylor, 1979; Niven and Taylor, 1988), and utilin type limonoid febrinolide from *Soymida febrifuga* A.

Juss (Mallavarapu et al., 1985). They are also found in the Rutaceae, with *Oriciopsis glaberrima* Engl. yielding the obacunone group limonoid oriciopsin (Ayafor et al., 1982), and in the genus *Harrisonia* (Simaroubaceae), with 5,6-didehydrooriciopsin isolated from *H. abyssinica* Oliv. (Balde et al., 1988), and a number of highly rearranged limonoids from *H. brownii* Juss. (Koike et al., 1993; Mitsunaga et al., 1994a,b) *H. perforata* (Blanco) Merr. (Thu et al., 2000; Chiaroni et al., 2000; Khuong-Huu et al., 2001) and *H. abyssinica* (Hassanali et al., 1987). None of these compounds, however, possess a hydroxy group at C-14, and only in febrinolide is the C–O bond α, where it forms part of the 8,9,14-orthoacetate linkage that characterises limonoids of the utilin type. In all of the other compounds in which the C and D rings are still recognisable, the C–O bond is β, and usually forms part of the 14β,15β-epoxide ring that often accompanies the D ring lactone.

A literature survey conducted to ascertain the extent of oxygenation at C-14 and its accompanying stereochemistry revealed interesting results. Some one hundred compounds to date have been reported which possess both the D ring lactone and 14β,15β-epoxide ring, compared to perhaps twenty which possess the lactone and Δ^{14} double bond. This suggests that the oxidative biosynthetic pathway in which the five-membered D ring undergoes Baeyer–Villiger oxidation to give the D ring lactone is responsible also for epoxidation of the Δ^{14} double bond, and therefore that these compounds are the most likely precursors for oxygenation at C-14. The isolation of the 14β,15β-epoxy *seco*-ring D compounds such as oriciopsin, as mentioned above, would appear to support this hypothesis, as the formation of these compounds occurs via further oxidative cleavage of the ring D epoxylactone. If the hydroxy group at C-14 then arises from subsequent opening of the epoxide ring, it can only be β.

However, opening of the epoxide ring in this in this way would also result in the oxygenation of C-15. The isolation of a 14,15-dihydroxy compound has yet to be announced, while only eleven compounds have been isolated with oxygenation at both C-14 and C-15; these without exception have a 1α,14β-oxide ring and β oxygenation at C-15, and presumably arise by nucleophilic attack of the hydroxy group at C-1 on the epoxide C-14 position. This hypothesis is supported by the fact that no compound has yet been isolated that is oxygenated at C-15 but not at C-14. As quivisianone **11** is not oxygenated at C-15, its C-14 hydroxy group cannot have come about in this fashion.

What remains, then, is oxygenation of C-14 either by direct oxidation or nucleophilic attack on a Δ^{14} double bond. Again a literature survey is revealing. Intramolecular nucleophilic substitution yields almost exclusively oxide rings that are C-14β, but of the twelve compounds possessing an oxygen functionality at C-14 that is *not* part of a ring – and hence could not have formed by an intramolecular route – C-14 has the β configuration in five compounds and α in seven. This suggests that intramolecular substitution occurs more easily than oxidation, with the observed β configuration predominance presumably arising from the different steric constraints of the two faces of the molecule, and that only when this does not occur can oxidation at C-14 give rise to the carbocation necessary for inversion to occur.

3. Experimental

3.1. General

NMR spectra were recorded at room temperature on a 400 MHz Varian UNITY-INOVA spectrophotometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as internal standard and coupling constants are given in Hz. ^{1}H NMR spectra were referenced against the $CHCl_3$ signal at δ 7.27, and ^{13}C NMR spectra to the corresponding signal at δ 77.0. IR spectra were recorded on a Nicolet Impact 400D Fourier-Transform Infrared (FT-IR) spectrometer, using NaCl windows with $CHCl_3$ as solvent against an air background. Melting points were determined on a Kofler micro-hot stage melting point apparatus and are uncorrected. HREIMS were acquired on a Kratos 9/50 or a VG 70-SE HRMS instrument. Optical rotations were measured at room temperature in $CHCl_3$ on an Optical Activity AA-5 Polarimeter, using a series A2 (4 × 200 mm) stainless steel unjacketed flow tube.

3.2. Plant material

Quivisia papinae was collected in April 1999 in the Bezaha Mahafaly area in southern Madagascar. Plant identification was confirmed by Dr. Harison Rabarison of the Department of Botany at the Parc Zoologique et Botanique de Tsimbazaza, where a voucher specimen (02/99-Mj/Mdul, TAN) is retained.

3.3. Extraction and isolation of compounds

The air-dried, milled seed (701 g) was extracted successively for 24 h each in a Soxhlet apparatus with hexane, CH_2Cl_2, ethyl acetate and methanol, yielding extracts of masses 19.47, 27.99, 20.28 and 189.15 g, respectively. Only the hexane and CH_2Cl_2 extracts were examined during the course of this investigation, while the ethyl acetate and methanol extracts have been stored for future study. Melianone **1** (16.1 mg), melianol **2** (12.2 mg), swietenolide **3** (12.8 mg), proceranolide **4** (9.2 mg), 2α-hydroxyswietenolide **5** (9.3 mg), 3-angeloyl-3-detigloylruageanin B **8** (17.3 mg), quivisianolide

A **9** (9.4 mg) and quivisianone **11** (6.8 mg) were isolated from the $\mathrm{CH_2Cl}$ extract, and quivisianolide B **10** (7.8 mg) from the hexane extract. Compounds were isolated using a combination of gravity column and PTLC; Merck 7734 and 9385 silica gels were employed for column chromatography, while final separation was achieved using analytical Merck 1.05553 TLC plates, using a variety of hexane, $\mathrm{CH_2Cl}$ and methanol solvent systems.

3.3.1. 2α-Hydroxyswietenolide **5**

Pale yellow gum. $[\alpha]_D = -110°$ (*c*, 0.16 in $\mathrm{CHCl_3}$); ν_{max} (NaCl) $\mathrm{cm^{-1}}$ 3462, 2941, 1724, 1461, 1385, 1256; HREIMS (70 eV) *m*/*z* (rel. int.) 502.2195 (4) (calc. for $\mathrm{C_{27}H_{34}O_9}$ 502.2203), 484.2099 (22) $[\mathrm{M-H_2O}]^+$, 413.1852 (8), 406.1976 (24), 378.2017 (27), 360.1930 (22), 342.1806 (12), 317.1741 (23), 299.1649 (27), 271.1686 (50), 223.0977 (30), 195.1018 (33), 166.0992 (51), 153.0911 (100), 119.0858 (69), 95.0501 (86); ^{1}H NMR spectral data (400 MHz, $\mathrm{CDCl_3}$) Table 1; ^{13}C NMR spectral data (100 MHz, $\mathrm{CDCl_3}$) Table 2.

3.3.2. 3-Angeloyl-3-detigloylruageanin B **8**

Pale yellow gum. $[\alpha]_D = -67.0°$ (*c*, 0.298 in $\mathrm{CHCl_3}$); ν_{max} (NaCl) $\mathrm{cm^{-1}}$ 3468, 2965, 2929, 1724, 1467, 1391, 1262, 1233, 1134, 1034; HREIMS (70 eV) *m*/*z* (rel. int.) 584.2634 (9) (calc. for $\mathrm{C_{32}H_{40}O_{10}}$ 584.2621), 566.2557 (1) $[\mathrm{M-H_2O}]^+$, 485.2148 (3) $[\mathrm{M-HOAng}]^+$, 467.2078 (8) $[\mathrm{M-HOAng-H_2O}]^+$, 449.1974 (3), 425.1952 (4), 407.1871 (3), 224.1053 (11), 197.1164 (7), 196.1098 (8), 164.0837 (13), 137.0972 (11), 122.0733 (13), 95.0502 (17), 83.0494 (100), 55.0551 (57); ^{1}H NMR spectral data (400 MHz, $\mathrm{CDCl_3}$) Table 1; ^{13}C NMR spectral data (100 MHz, $\mathrm{CDCl_3}$) Table 2.

3.3.3. Quivisianolide A **9**

Pale yellow gum. $[\alpha]_D = -99°$ (*c*, 0.15 in $\mathrm{CHCl_3}$); ν_{max} (NaCl) $\mathrm{cm^{-1}}$ 2918, 1742, 1233, 1145, 1046; HREIMS (70 eV) *m*/*z* (rel. int.) 598.2424 (2) (calc. for $\mathrm{C_{32}H_{38}O_{11}}$

Table 1
^{1}H NMR spectral data for compounds **5**, **8**–**11** ($\mathrm{CDCl_3}$, 400 MHz)

Proton	**5**	**8**	**9**	**10**	**11**
1	–	–	–	–	–
2	–	–	–	–	–
3	3.44 (*s*)	5.13 (*s*)	5.08 (*s*)	5.05 (*s*)	4.82 (*s*)
4	–	–	–	–	–
5	3.13 (*br s*)	3.15 (*dd*, 8.5, 2.6)	3.21 (*dd*, 7.7, 5.7)	2.95 (*m*)	3.16 (*d*, 9.2)
6	4.49 (*br s*)	2.32 (*m*)	a 2.35 (*dd*, 16.5, 7.7)	2.30 (*m*)	2.35 (*m*)
7	–	–	b 2.47 (*dd*, 16.5, 5.7)	–	–
8	–	–	–	–	–
9	2.03 (*m*)	1.89 (*m*)	–	–	2.42 (*m*)
10	–	–	–	–	–
11	a 1.81 (*m*) b 1.84 (*m*)	a 1.81 (*m*) b 1.85 (*m*)	3.25 (br *s*)	5.84 (*m*)	α 1.60 (*m*) β 1.45 (*m*)
12	α 1.14 (*m*) β 1.70 (*m*)	α 1.20 (*m*) β 1.98 (*m*)	α 1.98 (*d*, 15.2) β 2.39 (*d*, 15.2)	α 2.14 (*m*) 2.56 (*dd*, 18.9, 2.7)	α 1.74 (*m*) β 2.40 (*m*)
13	–	–	–	–	–
14	–	1.56 (*dd*, 13.9, 5.3)	1.64 (*dd*, 12.5, 7.0)	1.81 (*dd*, 12.1, 7.0)	1.81 (*dd*, 12.1, 7.0)
15	α 3.43 (*m*) β 4.02 (*d*, 21.1)	α 2.82 (*dd*, 16.1, 5.3) β 3.51 (*m*)	α 2.76 (*dd*, 18.5, 7.0) β 3.62 (*dd*, 18.5, 12.5)	α 3.02 (*dd*, 18.5, 12.1) β 2.74 (*dd*, 18.5, 7.0)	a 2.52 (*m*) b 2.62 (*d*, 12.1)
16	–	–	–	–	–
17	5.43(*s*)	5.12 (*s*)	4.97 (*s*)	5.06 (*s*)	–
18	0.97 (*s*)	0.98 (*s*)	1.07 (*s*)	1.02 (*s*)	1.46 (*s*)
19	1.48 (*s*)	1.14 (*s*)	0.90 (*s*)	1.26 (*s*)	1.15 (*s*)
20	–	–	–	–	–
21	7.46 (*s*)	7.44 (*s*)	7.29 (*s*)	7.33 (*s*)	8.13 (*s*)
22	6.37 (*s*)	6.40 (*s*)	6.16 (*s*)	6.24 (*s*)	6.82 (*s*)
23	7.39 (*s*)	7.40 (*s*)	7.38 (*s*)	7.40 (*s*)	7.38 (*s*)
28	0.86 (*s*)	0.78 (*s*)	0.90 (*s*)	0.80 (*s*)	0.74 (*s*)
29	0.92 (*s*)	0.97 (*s*)	0.81 (*s*)	0.83 (*s*)	0.77 (*s*)
30	α 3.43 (*m*) β 1.62 (*m*)	3.52 (*s*)	3.49 (*s*)	3.47 (*s*) –	5.80 (*s*)
7-C*H*$_3$O$_2$C	3.81 (*s*)	3.70 (*s*)	3.72 (*s*)	3.72 (*s*)	3.49 (*s*)
16-C*H*$_3$O$_2$C	–	–	–	–	3.56 (*s*)
3′	–	6.21 (*qq*, 7.3, 1.5)	6.24 (*m*)	6.24 (*m*)	6.20 (*dd*, 7.3, 1.5)
4′	–	2.03 (*d*, 7.3)	2.05 (*m*)	2.05 (*m*)	2.05 (*m*)
5′	–	2.07 (*d*, 1.5)	2.07 (*m*)	2.07 (*m*)	2.09 (*m*)
2-O*H*	–	–	4.05 (*br s*)	4.05 (*br s*)	4.10 (*br* s)
14-O*H*	–	–	–	–	4.81 (*br* s)

Table 2
^{13}C NMR spectral data for compounds **5**, **8**–**11** ($CDCl_3$, 100 MHz)

Carbon	**5**	**8**	**9**	**10**	**11**
1	219.0 (C)	213.2 (C)	208.9 (C)	210.2 (C)	214.3 (C)
2	79.6 (C)	78.5 (C)	78.5 (C)	79.2 (C)	77 (C)[b]
3	87.1 (CH)	84.7 (CH)	84.6 (CH)	84.8 (CH)	85.6 (CH)
4	40.2 (C)	40.2 (C)	39.2 (C)	39.5 (C)	39.6 (C)
5	44.3 (CH)	42.8 (CH)	43.3 (CH)	47.6 (CH)	40.5 (CH)
6	73.5 (CH)	33.4 (CH_2)[a]	32.1 (CH_2)	31.4 (CH_2)	33.1 (CH_2)
7	175.8 (C)	174.0 (C)	173.6 (C)	173.1 (C)	172.9 (C)
8	126.8 (C)	63.6 (C)	62.1 (C)	61.4 (C)	140.1 (C)
9	52.8 (CH)	55.5 (CH)	62.4 (C)	136.9 (C)	55.0 (CH)
10	53.1 (C)	49.5 (C)	50.8 (C)	51.7 (C)	50.3 (C)
11	18.9 (CH_2)	19.8 (CH_2)	56.7 (CH)	127.1 (CH)	22.4 (CH_2)
12	29.2 (CH_2)	33.5 (CH_2)[a]	27.7 (CH_2)	32.0 (CH_2)	33.7 (CH_2)
13	38.2 (C)	36.6 (C)	34.4 (C)	35.4 (C)	55.2 (C)
14	132.5 (C)	45.5 (CH)	38.7 (CH)	39.2 (CH)	77 (C)[b]
15	33.5 (CH_2)	33.8 (CH_2)	29.0 (CH_2)	29.2 (CH_2)	42.4 (CH_2)
16	171.1 (C)	171.6 (C)	169.0 (C)	169.5 (C)	170.2 (C)
17	80.6 (CH)	79.3 (CH)	82.8 (CH)	82.2 (CH)	201.9 (C)
18	18.1 (CH_3)	26.8 (CH_3)	23.6 (CH_3)	23.5 (CH_3)	19.2 (CH_3)
19	18.1 (CH_3)	16.4 (CH_3)	24.0 (CH_3)	14.5 (CH_3)	15.8 (CH_3)
20	120.9 (C)	120.4 (C)	122.0 (C)	120.1 (C)	124.5 (C)
21	141.3 (CH)	141.1 (CH)	140.8 (CH)	140.8 (CH)	148.5 (CH)
22	110.0 (CH)	110.4 (CH)	109.5 (CH)	109.6 (CH)	110.8 (CH)
23	143.2 (CH)	143.4 (CH)	143.9 (CH)	143.9 (CH)	142.9 (CH)
28	23.7 (CH_3)	22.3 (CH_3)	10.9 (CH_3)	20.7 (CH_3)	22.6 (CH_3)
29	22.8 (CH_3)	21.1 (CH_3)	21.5 (CH_3)	23.7 (CH_3)	20.6 (CH_3)
30	44.7 (CH_2)	67.5 (CH)	64.8 (CH)	64.4 (CH)	127.7 (CH)
7-CH_3O_2C	53.6 (CH_3)	52.7 (CH_3)	52.9 (CH_3)	52.50 (CH_3)	52.2 (CH_3)
16-CH_3O_2C	–	–	–	–	51.8 (CH_3)
1′	–	166.7 (C)	166.4 (C)	166.4 (C)	167.6 (C)
2′	–	126.7 (C)	126.4 (C)	126.5 (C)	127.7 (C)
3′	–	141.4 (CH)	141.9 (CH)	141.9 (CH)	141.1 (CH)
4′	–	16.4 (CH_3)	16.3 (CH_3)	16.3 (CH_3)	16.3 (CH_3)
5′	–	21.2 (CH_3)	21.2 (CH_3)	21.2 (CH_3)	20.8 (CH_3)

[a] Values within column interchangeable.
[b] Obscured by solvent.

598.2414), 497.1816 (7) $[M - HOAng]^+$, 421.1655 (9), 403.1581 (4), 175.0755 (3), 83.0497 (100), 55.0548 (43); ^1H NMR spectral data (400 MHz, $CDCl_3$) Table 1; ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 2.

3.3.4. *Quivisianolide B* ***10***

Pale yellow gum. $[\alpha]_D = -120$ °C (*c*, 0.12 in $CHCl_3$); ν_{max} (NaCl) cm^{-1} 3462, 2929, 1736, 1461, 1443, 1390, 1227, 1145, 1046; HREIMS (70 eV) *m*/*z* (rel. int.) 582.2474 (10) (calc. for $C_{32}H_{38}O_{10}$ 582.2465), 564.2338 (3) $[M - H_2O]^+$, 483.1987 (10), 482.1926 (14) $[M - HOAng]^+$, 472.2435 (7), 444.2460 (12), 423.1804 (7), 344.1675 (7), 311.1268 (7), 251.1089 (5), 197.1143 (8), 175.0759 (17), 95.0502 (62), 83.0496 (100); ^1H NMR spectral data (400 MHz, $CDCl_3$) Table 1; ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 2.

3.3.5. *Quivisianone* ***11***

Pale yellow gum. $[\alpha]_D = -240°$ (*c*, 0.10 in $CHCl_3$); ν_{max} (NaCl) cm^{-1} 3468, 2959, 1742, 1654, 1461, 1443, 1237, 1163, 1046; HREIMS (70 eV) *m*/*z* 614.2735 (calc. for $C_{33}H_{42}O_{11}$ 614.2727), 572.2169, 542.2340, 514.2208; ^1H NMR spectral data (400 MHz, $CDCl_3$) Table 1; ^{13}C NMR spectral data (100 MHz, $CDCl_3$) Table 2.

Acknowledgements

We thank Dr. Harison Rabarison for the collection and identification of plant material, Mr. Dilip Jagjivan, Dr. Philip Boshoff, and Mr. John Hill for the running of NMR and mass spectra, respectively, Mr. Bret Parel and Mr. Ernest Makhaza for their technical assistance, and the University of Natal, the Foundation for Research Development and the Wellcome Trust, under Grant No. 05 2451, for financial support.

References

Arai, Y., Hirohara, M., Matsuhira, M., Toyosaki, K., Ageta, H., 1995. Fern constituents: triterpenoids isolated from leaflets of *Cyathea lepifera*. Chem. Pharm. Bull. 43, 1849–1852.

Ayafor, J.F., Sondengam, B.L., Kimbu, S.F., Tsamo, E., Connolly, J.D., 1982. Oriciopsin, a new ring-D cleaved tetranortriterpenoid, and flindersiamine from *Oriciopsis glaberrima*. Phytochemistry 21, 2602–2603.

Balde, A.M., Vanhaelen, M., Daloze, D., 1988. 5-Dehydrooriciopsin, a ring-D cleaved tetra-nortriterpenoid from *Harrisonia abyssinica*. Phytochemistry 27, 942–943.

Chiaroni, A., Riche, C., Khuong-Huu, Q., Nguyen-Ngoc, H., Nguyen-Viet, K., Khuong-Huu, F., 2000. New limonoids from *Harrisonia perforata* (Blanco). Merr. Acta Crystallogr., Sect. C: Cryst. Struct. Commun. 56, 711–713.

Coombes, P.H., Mulholland, D.A., Randrianarivelojosia, M., 2003. Phragmalin limonoids from the Madagascan Meliaceae *Neobeguea leandreana*. J. Nat. Prod. 66 (6), 735–738.

Coombes, P.H., Mulholland, D.A., Randrianarivelojosia, M., 2004. Quivisianthone, an evodulone limonoid from the Madagascan Meliaceae *Quivisia papinae*. Phytochemistry 65, 377–380.

Gotfredson, W.O., Rastrup-Anderson, N., Vangedal, S., 1979. Metabolites of *Fusidium coccineum*. Tetrahedron 35, 2419–2431.

Harms, H., 1940, second ed. In: Engler, A., Prantl, K. (Eds.), Die Natürlichen Pflanzenfamilien, 19bI, pp. 1–172.

Hassanali, A., Bentley, M.D., Slawin, A.M.Z., Williams, D.J., Shephard, R.N., Chapya, A.W., 1987. Pedonin, a *spiro*-tetranortriterpenoid insect antifeedant from *H arrisonia abyssinica*. Phytochemistry 26, 573–575.

Inada, A., Konishi, M., Murata, H., Nakanishi, T., 1994. Structures of a new limonoid and a new triterpenoid derivative from pericarps of *Trichilia connaroides*. J. Nat. Prod. 57, 1446–1449.

Kadota, S., Marpaung, L., Kikuchi, T., Ekimoto, H., 1989. Tetrahedron Lett. 30, 1111–1114.

Kadota, S., Marpaung, L., Kikuchi, T., Ekimoto, H., 1990. Chem. Pharm. Bull. 38, 639–651.

Khalid, S.A., Friedrichson, G.M., Kharazami, A., Theander, T.G., Olsen, C.E., Christensen, S.B., 1998. Limonoids from *Khaya senegalensis*. Phytochemistry 49, 1769–1772.

Khuong-Huu, Q., Chiaroni, A., Riche, C., Nguyen-Ngoc, H., Nguyen-Viet, K., Khuong-Huu, F., 2001. New rearranged limonoids from *Harrisonia perforata*. III. J. Nat. Prod. 64, 634–637.

Koike, K., Mitsunaga, K., Ishii, K., Ohmoto, T., Kawakami, Y., Ikemori, M., Sato, T., 1993. Brownins A and B: novel rearranged limonoids from *Harrisonia brownii*. Tetrahedron 49, 2209–2216.

Mallavarapu, G.R., Muralikrishna, E., Connolly, J.D., 1985. Three tetranortriterpenoids from fruits of *Soymida febrifuga*. Phytochemistry 24, 305–307.

Mitsunaga, K., Koike, K., Ishii, K., Ohmoto, T., 1994a. Rearranged limonoids from *Harrisonia brownii*. Phytochemistry 35, 451–454.

Mitsunaga, K., Koike, K., Ohmoto, T., 1994b. Brownins F and H: new limonoids from *Harrisonia brownii*. Phytochemistry 37, 1443–1446.

Mondon, A., Epe, B., Oelbermann, U., 1982. Zur kenntnis der bitterstoffe aus Cneoraceen, XVI. Tetrahedron Lett. 23, 3551–3554.

Mootoo, B.S., Ramsewak, R., Khan, A., Tinto, W.F., Reynolds, W.F., McLean, S., Yu, M., 1996. Tetranortriterpenoids from *Ruagea glabra*. J. Nat. Prod. 59, 544–547.

Mulholland, D.A., Taylor, D.A.H., 1988. Limonoid extractives from the genera *Capuronianthus*, *Neobeguea* and *Quivisianthe*. Phytochemistry 27, 1741–1743.

Nakanishi, T., Inada, A., Lavie, D., 1986. A new tirucallane-type triterpenoid derivative, lipomelianol from fruits of *Melia toosendan* Sieb. et Zucc. Chem. Pharm. Bull. 34, 100–104.

Niven, M.L., Taylor, D.A.H., 1988. Revision of the structure of limonoid pseudrelone B from *Pseudocedrela kotschyii*. Phytochemistry 27, 1542.

Pennington, T.D., Styles, B.T., 1975. A generic monograph of the Meliaceae. Blumea 22, 419–540.

Polonsky, J., Varon, Z., Rabanal, R.M., 1977. 20,21-Anhydromelianone and melianone from *Simarouba amara* (Simaroubaceae); carbon-13 NMR spectral analysis of Δ^7-tirucallol-type triterpenes. Isr. J. Chem. 16, 16–19.

Taylor, A.R.H., Taylor, D.A.H., 1984. Limonoids from *Ekebergia pterophylla*. Phytochemistry 23, 2676–2677.

Taylor, D.A.H., 1979. A limonoid, pseudrelone B, from *Pseudocedrela kotschyii*. Phytochemistry 18, 1574–1576.

Thu, H.D.T., Tri, M.V., Ngoc, N.B., Sévenet, T., Païs, M., Martin, M-T., 2000. Foritin, a new limonoid from *Harrisonia perforata*. Nat. Prod. Lett. 14, 191–195.

Yadav, R.D., Kataky, J.C.S., Mathur, R.K., 1999. New protolimonoids and limonoids: Part III – arunachalin, a new tetranortriterpenoid from *Chisocheton paniculatus* Hiern. (Meliaceae). Ind. J. Chem., Sect. B 38B, 243–245.