

Terpenoid Constituents from Leaves of *Guarea kunthiana*

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Das folhas de *Guarea kunthiana* foram obtidos um novo diterpeno com esqueleto do tipo caurano (*ent*-caur-16-eno-2-ona), além de oito diterpenos (*ent*-caur-16-eno, *ent*-3 α - e 3 β -hidroxicaur-16-eno, kolavelool, kolavenol, kolavenal, *ent*-13-*epi*- δ -óxido de manófila e (-)-neftenol), quatro sesquiterpenos (alismol, alismóxido, espatulenol e 4 β ,10 α -aromadendranediol), poliprenol-12 e α - e δ -tocoferóis. Kolavenal está sendo relatado pela primeira vez como produto natural, assim como a ocorrência de diterpenos do tipo cembrano e *ent*-caurano na família Meliaceae.

From leaves of *Guarea kunthiana* one new kaurene diterpene (*ent*-kaur-16-en-2-one) was isolated along with eight known diterpenes (*ent*-kaur-16-ene, *ent*-3 α - and 3 β -hydroxykaur-16-ene, kolavelool, kolavenol, kolavenal, *ent*-13-*epi*-manoyloxide and (-)-nephthenol), four sesquiterpenes (alismol, alismoxide, spathulenol and 4 β ,10 α -aromadendranediol), polyprenol-12 and α - and δ -tocopherols. Kolavenal is reported for the first time as a natural product, as well as the occurrence of cembrane- and *ent*-kaurane-type diterpenes in the Meliaceae.

Keywords: *Guarea kunthiana*, Meliaceae, diterpenes, sesquiterpenes, *ent*-kaur-16-en-2-one

Introduction

In our continuing interest on the chemical constituents of plants of the Meliaceae family which are widely distributed in the central-western region of Brazil¹ we have investigated the leaves of *Guarea kunthiana* A. Juss. A previous chemical study of the aerial parts of a specimen of *Guarea kunthiana* found in Ecuador resulted in the isolation of the limonoid ecuadorin.² No limonoids were detected in the leaves of the specimen investigated in the present work which provided, on the other hand, one new, *ent*-kaur-16-en-2-one (**3**) and three known, *ent*-kaur-16-ene (**1**), *ent*-3 β - and 3 α -hydroxykaur-16-ene (**2**, **4**) kaurenoids, three known *ent*-clerodane diterpenes, kolavelool (**5**), kolavenol (**6**) and kolavenal (**7**), the cembranoid (-)-nephthenol (**8**) and *ent*-13-*epi*-manoyloxide (**9**) in addition to four known sesquiterpenes, spathulenol (**10**) alismol (**11**), alismoxide (**12**), and (-)-4 β ,10 α -aromadendranediol (**13**), polyprenol-12 (**14**) and α - and δ -tocopherols (**15**, **16**). Kolavenal has now been

reported for the first time from nature, while it was known earlier as a derivative by synthesis from kolavenol.³ (-)-Nephthenol was previously obtained only from marine organisms.^{4,5} These diterpenes and sesquiterpenes, except for kolavelool and spathulenol, are described for the first time in the Meliaceae.

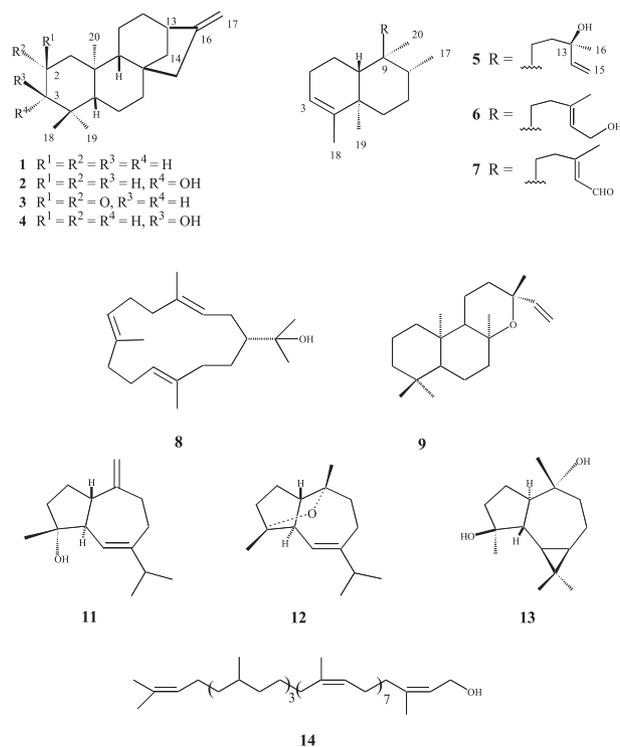
Results and Discussion

A crude ethanol extract of the leaves of *Guarea kunthiana* was partitioned between methanol-H₂O (9:1) and hexane. The hydromethanolic solution was further partitioned with ethyl acetate. Compounds **1-10** and **14-16** were isolated from the hexane soluble fraction while compounds **11-13** and further amounts of **5**, **6** and **10** were obtained from the ethyl acetate soluble fraction, after a combination of column chromatography on silica gel, gel filtration and preparative TLC separations. The known compounds were identified by comparison of their physical and spectroscopic (IR, ¹H and ¹³C NMR, MS) data with those of authentic samples and/or reported in the literature.

Compounds **1** and **2** were found to be identical with

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ent-kaur-16-ene and *ent*-3 β -hydroxykaur-16-ene, respectively, on the basis of their specific rotation and spectral (^1H , ^{13}C NMR, MS) data, which in turn were in



accordance with those published.⁶⁻⁸ Although widely distributed in a number of plants, no records related to the isolation of kaurane-type diterpenes have hitherto been reported in the Meliaceae.

The molecular formula of **3**, obtained as an amorphous solid, was established as $\text{C}_{20}\text{H}_{30}\text{O}$ from HREIMS data ($[\text{M}^+]$ m/z 286.2296). Its IR spectrum was consistent with the presence of a carbonyl (1714 cm^{-1}) and an exomethylene (881 cm^{-1}) group, while the ^1H NMR spectrum (Table 1), displaying the characteristic pair of broad singlets due to the exocyclic methylene group, was very similar to that of **1** (*ent*-kaur-16-ene). The only significant difference referred to the presence of two double doublets at δ 2.50 ($\text{H}-1_{\text{eq}}, J$ 12.6 and 1.9 Hz) and δ 2.15 ($\text{H}-3_{\text{eq}}, J$ 13.6 and 1.9 Hz) and two broad doublets at δ 1.90 ($\text{H}-1_{\text{ax}}, J$ 12.6 Hz) and δ 2.24 ($\text{H}-3_{\text{ax}}, J$ 13.6 Hz). The ^{13}C NMR spectrum (Table 1) showed, in addition to the signals at δ 155.1 (C) and 103.4 (CH_2) attributed to the exocyclic double bond at C-16 in a kaurane skeleton, a ketone carbon signal at δ 212.0. Accordingly, the molecular ion observed in the HREIMS at m/z 286.2296 was 14 mass units higher than that of **1**. Comparison of ^{13}C NMR data of **1** and **3** indicated that they had identical constituting rings B, C and D, therefore indicating that the carbonyl was located on the A ring of compound **3**. The deshielding of the A-ring methylene carbons in **3** when compared to those of **1** ($\Delta\delta$ 14-15)

Table 1. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectral data of compounds **3**, **4** and **7** in CDCl_3 ^{a,b}

Carbon No.	3			4 ^{13}C	7 ^{13}C
	^1H	^{13}C	HMBC		
1	2.50 dd (12.6, 1.9) [1_{eq}] 1.90 brd (12.6) [1_{ax}]	56.1	20- H_3	33.3	18.3
2	-	212.0	$1_{\text{ax}}\text{-H}, 1_{\text{eq}}\text{-H}, 3_{\text{ax}}\text{-H}, 3_{\text{eq}}\text{-H}$	25.3	26.9
3	2.24 brd (13.6) [3_{ax}] 2.15 dd (13.6, 1.9) [3_{eq}]	56.3	18- $\text{H}_3, 19\text{-H}_3$	76.1	120.4
4	-	38.8		37.5	144.5
5	1.40 - 1.49 m	55.4	$3_{\text{ax}}\text{-H}, 18\text{-H}_3, 19\text{-H}_3$	49.0	38.2
6	1.55 - 1.70 m	20.7	$1_{\text{eq}}\text{-H}, 3_{\text{eq}}\text{-H}, 18\text{-H}_3, 19\text{-H}_3, 20\text{-H}_3$	19.8	36.8
7	1.55 - 1.70 m	40.5		41.0	27.4
8	-	44.3	14- H_2	44.1	36.3
9	1.30 brd (6.0)	55.1	$1_{\text{eq}}\text{-H}, 1_{\text{ax}}\text{-H}, 15\text{-H}$	55.7	38.8
10	-	44.5	$1_{\text{ax}}\text{-H}, 6\text{-H}_2, 9\text{-H}, 11\text{-H}_2, 20\text{-H}_3$	39.1	46.5
11	1.40 - 1.49 m	18.3		18.1	36.0
12	1.40 - 1.49 m	32.9	9-H	33.3	34.4
13	2.63 br s	43.7	17- H_2	44.0	165.5
14	1.90 brd (12.6) 1.12 dd (12.6, 3.0)	39.3	9-H	39.7	127.2
15	2.08 brs	48.7	17- $\text{H}_2, 14\text{-H}_2$	49.1	191.3
16	-	155.1	14- H_2	156.0	17.8
17	4.79 brs 4.73 brs	103.4		102.9	15.9
18	1.03 s	33.7	$3_{\text{ax}}\text{-H}, 19\text{-H}_3$	28.5	18.0
19	0.87 s	23.2	$3_{\text{ax}}\text{-H}, 18\text{-H}_3$	22.1	19.8
20	1.00 s	18.8	$1_{\text{ax}}\text{-H}, 9\text{-H}$	17.4	18.3

^a Chemical shifts in δ from TMS; ^b Coupling constants (J in Hz) are given in parentheses.

suggested that the carbonyl group was located at the C-2 position. This proposal was in agreement with the chemical shifts and multiplicities of H-1 and H-3 as aforementioned. Accordingly, the ^1H - ^1H COSY spectrum of **3** showed the geminal coupling between H-1_{ax} and H-1_{eq} as well as between H-3_{ax} and H-3_{eq}. Likewise, this spectrum depicted the long-range couplings between H-1_{eq} and H-3_{eq}, H-1_{ax} and H-20 and H-3_{ax} and H-19. Unambiguous assignment of H-1 and H-3 was also achieved by the long-range correlations observed in the HMBC spectrum between H-1 and C-9, C-10, C-20 and between H-3 and C-4, C-18 and C-19 (Table 1). On the other hand, the cross-peak correlations in the HMQC spectrum of H-1 and H-3 with the carbon signals at δ 56.1 and δ 56.3, respectively, as well as the long range connectivities shown by the HMBC spectrum between the signal ascribed to H-20 (δ 1.00) and δ 56.1 and between H-18 (δ 1.03) and δ 56.3 confirmed the assignments of C-1 and C-3, respectively. The significant HMBC correlations noticed between the signals of H-1 and H-3 and that of the carbonyl carbon further supported the location of this group at C-2. The remaining quaternary carbons in the structure of **3** were assigned according to the ^1H - ^{13}C long range correlation data provided in Table 1. On the basis of its negative $[\alpha]_D$ value, it is suggested that **3** belongs to the *ent* series, similarly to other analogous kaurenoid diterpenes.^{8,9} Thus **3** was characterized as *ent*-kaur-16-en-2-one.

Compound **4** which showed a molecular ion at m/z 288 in EIMS and a negative specific rotation value, was assumed to be a C-3 epimeric derivative of **2** on the basis of the close resemblance of their ^1H and ^{13}C NMR spectra, except for the chemical shift and coupling constant of H-3 and in some resonance values of A-ring carbons. In the ^1H NMR spectrum of **4**, a broad singlet at δ 3.39, instead of a double doublet at δ 3.18 (J 10.2, 5.8 Hz) ascribed to H-3 in **2**, determined the equatorial nature of H-3 and the resulting axial orientation of the C-3 hydroxyl group. As expected, an upfield shift of the C-3 resonance (δ 76.1) was observed in **4** when compared to that of **2** (δ 79.1). Likewise, the axial orientation of the hydroxyl accounted for the γ -effect on C-1 and C-5 which were shielded by 5.4 and 6.2 ppm, respectively. Therefore, compound **4** was determined to be *ent*-3 α -hydroxy-kaur-16-ene, which is described for the first time in the Meliaceae, yet previously reported from *Annona senegalensis* (Annonaceae)¹⁰ and as a reduction product of *ent*-kaur-16-en-3-one.⁷ Identity was further confirmed by comparison with literature data (^1H and EIMS).⁷ The ^{13}C NMR spectral data of **4**, not previously reported in literature, are now presented in Table 1. The unambiguous assignment of the carbon resonances of **4**, mainly those of C-18, C-19 and C-20 methyls, was

based on information provided by HMQC, HMBC and NOESY experiments.

Diterpenes **5** and **6** were characterized as *ent*-clerodane derivatives with a Δ^3 double bond, in addition to a hydroxyl group and a double bond in the C-9 side chain. The optical rotation values and spectral characteristics (^1H and ^{13}C NMR, MS and IR) of **5** and **6** agreed with those of kolavelool^{8,11} and kolavenol,^{8,12} respectively. The first was already obtained from *Guarea trichilioides*¹³ while kolavenol was hitherto unreported in the Meliaceae.

The ^1H and ^{13}C NMR spectra of **6** and **7** were almost identical, except for the presence of an aldehyde (δ_{H} 9.95 *d*, 7.6 Hz; δ_{C} 191.3) in **7** in place of the hydroxymethylene group at C-15. The carbon resonances at δ 127.2 and 165.5 together with a carbonyl absorption band at 1675 cm^{-1} in the IR spectrum also confirmed this assumption. Therefore compound **7** was characterized as *ent*-(*E*)-cleroda-3,13-dien-15-al whose spectroscopic properties (IR and ^1H NMR) and optical rotation value were very similar to those described for kolavenal, a compound obtained by MnO_2 oxidation of **6**.³ Thus compound **7** is reported for the first time as a genuine natural product. Its ^{13}C NMR data, not reported before now and presented in Table 1, readily support the assignment of the double bond configuration in the side chain as (*E*), on the basis of the chemical shifts of C-12 (δ 34.4) and C-16 methyl group (δ 17.8). In similar 13-en-15-al *ent*-clerodane derivatives, e. g., 3R*,4R*-dihydroxyclerod-13E-en-15-al and the corresponding (*Z*) isomer, the presence of a carbonyl at C-15 accounts for the γ -effect observed at C-12 methylene carbon in the (*Z*) isomer (δ 26.9) with respect to the corresponding resonance in the (*E*) isomer (δ 34.5). On the other hand, the same effect is observed at the C-16 methyl group in the (*E*) isomer (δ 17.1) when compared to the corresponding resonance of the (*Z*) isomer (δ 24.7).¹⁴

The ^1H and ^{13}C NMR spectral data of compound **8**, in addition to the cross-peak correlations and the long-range connectivities observed in the HMQC and HMBC spectra, respectively, defined **8** as a carbomonocyclic diterpene of the cembrane class, characterized as a cembra-3,7,11-triene-15-ol. These results, together with the negative optical rotation value of **8**, agreed with those reported earlier for (-)-nephthenol, (1R,3E,7E,11E)-cembra-3,7,11-triene-15-ol.^{4,8} The great majority of cembranoids of plant origin occurs in tobacco (*Nicotiana tabacum*, Solanaceae) and in Coniferae species, although they are widely distributed in marine organisms and insects.^{5,8} However, (-)-nephthenol was only described in marine invertebrates (e.g. soft corals).^{4,5} Thus, this is, to the best of our knowledge, the first report of the isolation of a cembrane-type diterpene from Meliaceae, as well as of the occurrence of (-)-nephthenol in a plant taxon.

The structure of **9** was shown to be of a labdane-type diterpenoid from its ^1H and ^{13}C NMR spectral data, which showed striking resemblance with those of (+)-13-*epi*-manoyl oxide,¹⁵ a compound which differs from **9** by having a specific rotation of opposite sign.¹⁵ The latter diterpene was then characterized as *ent*-13-*epi*-manoyl oxide, which was previously isolated from members of other plant families, e.g. Cistaceae and Flacourtiaceae¹⁶ but, until now, not yet reported in the Meliaceae.

The sesquiterpenes **10** - **12** obtained in the present work were found to be identical in their spectral data with spathulenol (data compared with those of an authentic sample), alismol^{17,18} and alismoxide,¹⁷ respectively. Direct comparison of the spectral data of **13** with those of 4 β ,10 α -aromadendranediol proved their identity.^{19,20} This sesquiterpene was first isolated as the dextrorotatory isomer from the soft coral *Sinularia mayi*¹⁹ and later obtained in the (-) form in only few plant species, e. g. *Brasilia sickii*.²⁰ On the basis of the negative sign of the specific rotation of **13**, its structure was therefore established as (-)-4 β ,10 α -aromadendranediol. Apart from **10**, these sesquiterpenes are described for the first time in the Meliaceae.

The polyprenol **14** was identified as ficaprenol-12 (also known as polyprenol-12) by comparison of its ^1H and ^{13}C NMR spectral data with literature.²¹ This compound, which has been obtained from leaves of several angiosperms, was also isolated from *Guarea jamaicensis*.²²

Although members of the Meliaceae, including those belonging to the genus *Guarea* that occur in Brazil, are well-known for the occurrence of sesqui-, di-, tri- and tetranortriterpenoids,^{1,13,23} the isolation for the first time of cembranoid and kaurenoid diterpenes in this family is noteworthy for its chemosystematic relevance. Also worthy of mention is the fact that, unlike the specimen of *G. kunthiana* found in Ecuador whose aerial parts yielded one limonoid as the only natural compound, no limonoids were detected in the leaves of the specimen collected in Brazil and investigated in the present work.

Experimental

General experimental procedures

IR spectra were recorded as KBr pellets on a Bomem-Hartmann & Braun FT IR spectrometer. ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-300 spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), using CDCl_3 as a solvent and internal reference. Standard pulse sequences were used for homo- and heteronuclear correlation experiments. EIMS data were obtained at 70 eV on a Shimadzu QP-5000 (Departamento de Química, UFMS,

MS, Brazil) and on a HP 5973 MSD spectrometer (Instituto de Química, UFBA, BA, Brazil). HREIMS data were obtained at 70 eV on a VG Autospec spectrometer (Instituto de Química, UNICAMP, SP, Brazil). Optical rotations were determined on a Perkin-Elmer 341 polarimeter (Na filter, $\lambda = 589$ nm).

Plant material

The leaves of *Guarea kunthiana* A. Juss. were collected in Campo Grande, MS, Brazil, in September 2000. The plant material was identified by one of the authors (U.R.) and Dr. Germano Guarin Neto (Universidade Federal de Mato Grosso, MT, Brazil). Voucher specimens (11536) are deposited at the CGMS Herbarium (UFMS), Campo Grande, MS, Brazil.

Extraction and isolation

Air-dried and powdered leaves (1450 g) were extracted at room temperature with EtOH. The residue obtained from the EtOH extract was partitioned between MeOH-H₂O 9:1 and hexane. The hydromethanolic solution was evaporated *in vacuo* and after removal of MeOH the aqueous phase was extracted with EtOAc. The hexane phase (59.5 g) was subjected to CC (Silica gel, 70-230 mesh, 200 g, hexane-CH₂Cl₂, CH₂Cl₂-EtOAc and EtOAc-MeOH gradients) to yield 19 fractions A→N (250 ml each). Fractions A and B gave **1** (3.5 g). Fraction D (7.4 g) was further separated by CC (Silica gel, 70-230 mesh, 115 g, hexane-CH₂Cl₂, CH₂Cl₂-EtOAc and EtOAc-MeOH gradients) and furnished 25 fractions. From these, fraction 8 consisted of **15**²⁴ (3.6 mg) while fraction 12 yielded after CC (Sephadex LH-20, 3x10 cm, hexane-CH₂Cl₂ 1:1) followed by prep. TLC (hexane-acetone 9:1) **5** (3.3 mg) and **14** (8.6 mg). Fraction E (7.6 g) was subjected to CC (Sephadex LH-20, 3x50 cm, 10 portions of 0.76g each, CHCl₃-MeOH 3:2). The fractions showing similar spots by TLC were combined and the residues from therein were subjected to rechromatography (Silica gel, 230-400 mesh, 70 g, hexane-EtOAc gradient) to give **3** (8.1 mg), **4** (44.2 mg), **5** (1.26 g), **6** (14.4 mg), **8** (75.0 mg), **9** (7.6 mg), **10** (21.4 mg), **16**²⁴ (22.5 mg) and phytol (22.5 mg). Fraction G (2.3 g) afforded, after CC (Sephadex LH-20, 3x50 cm, CHCl₃-MeOH 3:2) followed by a second CC (Silica gel, 230-400 mesh, 70 g, hexane-acetone gradient) **2** (10.1 mg), **6** (16.1 mg) and **7** (4.7 mg). Further amounts of **6** (0.9 g) were obtained from fraction H (2.2 g) after CC (Sephadex LH-20, 3x50 cm, CHCl₃-MeOH 3:2).

The EtOAc phase (19.8 g) upon CC over silanised silica gel (70-230 mesh, 150 g) eluted with MeOH-H₂O 7:3, MeOH and CH₂Cl₂ successively, afforded 3 main fractions A→C.

CC of fraction A (8.9 g) (Silica gel, 70-230 mesh, 120 g, hexane-CH₂Cl₂, CH₂Cl₂- EtOAc and EtOAc-MeOH gradients) yielded 66 fractions. The major constituents of fractions 7-8 (45.0 mg) and 14-15 (50.0 mg) were found to be **11** and **12**, respectively, which were not further purified. Fractions 23-28 yielded **13** (38.0 mg). CC of fraction B (7.3 g) (Silica gel, 70-230 mesh, 140 g, hexane-EtOAc and EtOAc-MeOH mixtures) gave 40 fractions. Fractions 10-12 consisted of **5** (50.0 mg) and fractions 15-16 were further separated on CC (Silica gel, 230-400 mesh, hexane-acetone 95:5) to afford **6** (6.0 mg), **10** (18.9 mg) and **11** (8.0 mg).

Ent-kaur-16-en-2-one, (**3**). Colorless amorphous solid. $[\alpha]_D^{23}$: -80.0° (CHCl₃; *c* 0.4). IR (KBr) ν_{\max} /cm⁻¹: 3068, 1656, 881 (unsaturation), 1714 (ketone carbonyl). HREIMS, *m/z*: 286.2296 [M]⁺ (C₂₀H₃₀O requires 286.2298). EIMS *m/z* (rel. int.): 286 [M]⁺ (13), 271 (14), 243 (35), 227 (29), 187 (39), 159 (42), 145 (49), 119 (41), 105 (58), 91 (100). ¹H and ¹³C NMR: see Table 1.

Ent-3 α -hydroxykaur-16-ene, (**4**). Colorless amorphous solid. $[\alpha]_D^{24}$: -43.0° (CHCl₃; *c* 0.4). IR, EIMS and ¹H NMR data are in agreement with those reported in literature.⁷ ¹³C NMR: see Table 1.

Kolavenal, (**7**). Colorless oil. $[\alpha]_D^{23}$: -50.0° (CHCl₃; *c* 0.05). IR and ¹H NMR data are in agreement with those reported in literature.³ EIMS *m/z* (rel. int.): [M]⁺ not detected, 272 (5), 257 (14), 229 (13), 147 (22), 119 (32), 105 (61), 91 (83), 69 (100). ¹³C NMR data: see Table 1.

(-)-Nephtenol, (**8**). Colourless oil; $[\alpha]_D^{23}$: -30.0° (CHCl₃; *c* 0.4). IR, EIMS, ¹H and ¹³C NMR data are in agreement with those reported in literature.⁴

(-)-4 β ,10 α -aromadendranediol, (**13**). Colorless amorphous solid; $[\alpha]_D^{23}$: -15.0° (CHCl₃; *c* 1.05). IR, ¹H and ¹³C NMR data are in agreement with those reported in literature.^{19,20}

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