

## Fatty Acids and Terpenoids from *Trigonía fasciculata*

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A fração lipídica do extrato hexânico das raízes de *Trigonía fasciculata* foi analisada por CG/EM sob a forma de seus ésteres metílicos, identificando-se dezessete ácidos graxos, sendo o ácido oléico (38,8%) o principal componente. A análise por CG/EM da fração menos polar da parte insaponificável do extrato hexânico das raízes permitiu identificar quinze sesquiterpenos não oxigenados, sendo o  $\alpha$ -santaleno (28,4%) o componente majoritário. Cromatografia em gel de sílica da fração mais polar permitiu o isolamento de dois triterpenos conhecidos, ácido betulínico e friedelina, e o diterpeno inédito 7-(2-hidroxiacetil)-10-hidroxitetradecaidro-1-metileno-4b,7,10a-trimetilfenantreno (6 $\alpha$ -hidroxil-15-oxo-allodevadarool). Todas as substâncias isoladas e identificadas são inéditas para a espécie. A determinação estrutural foi realizada por derivatização química, comparação com dados da literatura, análise espectral, incluindo RMN 2D (COSY, HETCOR e COLOC), e cristalografia de raios X.

The fatty portion of the hexane extract from roots of *Trigonía fasciculata* has been determined by GC/MS analysis of the methyl ester mixture. Seventeen fatty acids were identified and oleic acid (38.8%) was the major component. The GC/MS analysis of the less polar fraction of the non-saponifiable part of the root hexane extract allowed the identification of fifteen sesquiterpenes and  $\alpha$ -santalene (28.4%) was the major component. Chromatography over silica gel of the more polar fraction allowed the isolation of two known compounds: betulinic acid and friedelin, and a novel diterpene 7-(2-hydroxy-acetyl)-10-hydroxy-tetradecahydro-1-methylene-4b,7,10a-trimethylphenantrene (6 $\alpha$ -hydroxy-15-oxo-allodevadarool), all unknown for the species. Structure determination was accomplished by chemical derivatization, comparison to literature data and spectral analysis, including 2D NMR (COSY, HETCOR, COLOC) and X-ray crystallography.

**Keywords:** *Trigonía fasciculata*, Trigonaceae, terpenoids, 6 $\alpha$ -hydroxy-15-oxo-allodevadarool, fatty acids

## Introduction

In our search for *Bredemeyera* species of plants in the Northeast of Brazil because of its pharmacological properties,<sup>1,2</sup> we have collected another liana like plant later identified as *Trigonía fasciculata* Griseb. (Trigonaceae).

According to Barroso,<sup>3</sup> the Trigonaceae family consists of two genera comprising 33 species. Only the *Trigonía* genus occurs in Brazil. A literature survey in the Chemical and Biological Abstracts revealed no phytochemical study of *T. fasciculata*, a shrub well dispersed through Bahia

and Minas Gerais States. Thus, it was chosen for phytochemical analysis.

## Results and Discussion

TFRH, the clear viscous brownish extract obtained after hexane extraction of ground roots of *T. fasciculata*, yielded a precipitate after standing at room temperature. Silica gel chromatography column of the precipitate allowed the isolation of friedelin and betulinic acid. Coarse chromatography of the mother liquor yielded a non-polar fraction after elution with hexane designated TFRH(1). Hydrolysis with KOH/EtOH 1:1 solution, yielded the free fatty acids mixture (TFRH(1)/FA) and a unsaponifiable

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portion (TFRH(1)/NS) after usual work up. Methylation of an aliquot of TFRH(1)/FA with  $\text{BF}_3/\text{MeOH}$  14% solution followed by GC/MS analysis of the methyl ester mixture allowed the identification of the fatty acids listed in the Experimental Section. Silica gel chromatography of TFRH(1)/NS yielded a yellowish fraction by elution with hexane.  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis indicated its terpenoid character. GC/MS analysis of this fraction, followed by comparison of the mass spectra obtained for each compound with a computer library data bank,<sup>4</sup> and literature data<sup>5</sup> in addition to Kovats' Indices comparison<sup>6</sup> allowed the identification of the sesquiterpenes listed in the Experimental Section.

Successive column chromatography over silica gel of the more polar fraction obtained by ethyl acetate elution from TFRH followed by rotational planar chromatography yielded **1**, a colorless solid, homogenous by TLC. The BB  $^{13}\text{C}$  NMR spectrum of **1** showed 20 spectral lines. Comparison of the BB spectrum with the DEPT 135° and DEPT 90° spectra revealed the presence of 3 methines, 9 methylenes, 3 methyls and consequently 5 non-hydrogenated carbons. A closer analysis of the  $^{13}\text{C}$  NMR data allowed the identification of a ketone carbonyl ( $\delta$  215.2, C-15), a  $\text{sp}^2$  methylene ( $\delta$  102.9, C-18) and a non-hydrogenated  $\text{sp}^2$  carbon ( $\delta$  157.4, C-4), very characteristic of an exocyclic double bond, an

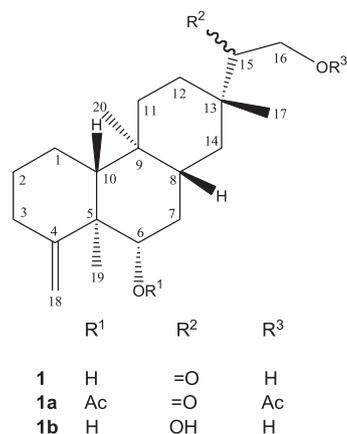
oxygenated methylene ( $\delta$  63.8, C-16) and an oxygenated methine ( $\delta$  74.5, C-6). All other signals indicated non-functionalized, saturated carbons. The FT-IR spectrum confirmed the ketone moiety ( $1723\text{ cm}^{-1}$ ), its carbinolic character ( $3300$  and  $1020\text{ cm}^{-1}$ ) and the exocyclic double bond [ $3100$  ( $\nu_{\text{C-H}}$ ),  $1642$  ( $\nu_{\text{C=C}}$ ) and  $900\text{ cm}^{-1}$  ( $\delta_{\text{C-H}}$ )]. The EI-Mass spectrum showed the molecular ion  $[\text{M}]^+$  at  $m/z$  320 compatible with the molecular formula  $\text{C}_{20}\text{H}_{32}\text{O}_3$  corresponding to a tricyclic structure if a carbonyl and a carbon-carbon bond have already been characterized. The  $^1\text{H}$  NMR spectrum clearly showed 3 angular methyl groups as singlets at  $\delta$  0.73, 1.06 and 1.21, a carbinolic methine at  $\delta$  3.99 (1H, dd,  $J$  9.9 and 4.9 Hz, H-6), a carbinolic methylene at  $\delta$  4.36 (2H, s, H-16), and two  $\text{sp}^2$  hydrogens at  $\delta$  4.64 (1H, br s) and  $\delta$  4.70 (1H, br s).

Direct one bond attached hydrogen-carbon correlations were established by  $^1\text{H}$ ,  $^{13}\text{C}$ -COSY (HETCOR) NMR experiment. Thus, the methyls at  $\delta$  0.73, 1.06 and 1.21 correlate with carbons at  $\delta$  12.0, 15.7 and 20.5, respectively. The carbinolic carbons at  $\delta$  74.5 and 63.8 correlate with hydrogens at  $\delta$  3.99 and 4.36, respectively. The hydrogens at  $\delta$  4.64 and 4.70 correlate both with the carbon at  $\delta$  102.9. All observed direct C, H correlations are depicted in Table 1. The more downfield character of the carbinolic methylene protons relative to the carbinolic methine

**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data assignment for **1**, **1a** and **1b**

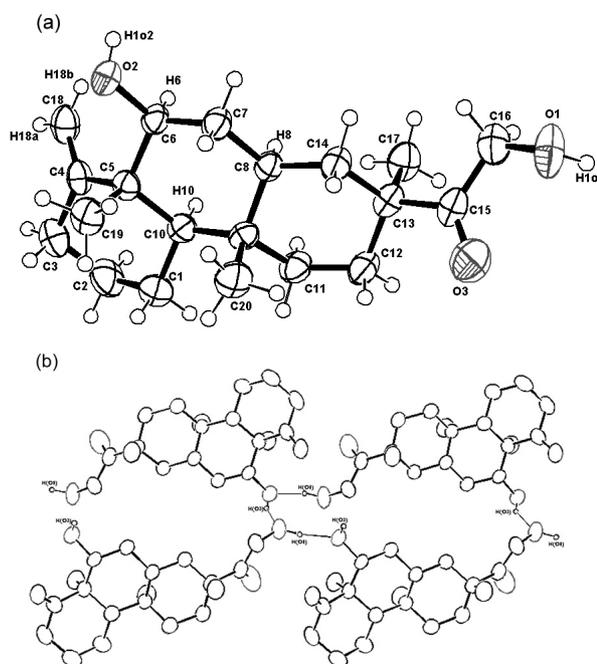
#C	<b>1</b>				<b>1a</b>		<b>1b</b>	
	HETCOR		COLOC		$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$
	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$^2J_{\text{C-H}}$	$^3J_{\text{C-H}}$				
1	20.6	1.20 & 1.60			20.5		21.0	
2	28.7	-			27.8		29.9	
3	33.3	1.40-1.50		H-18	33.2		35.3	
4	157.4	-		H-19	156.0		157.4	
5	46.8	-	H-19		46.2		47.5	
			H-18					
6	74.5	3.99		H-19	77.0	5.06	74.5	4.26
7	33.2	1.50 & 2.10			30.6		33.9	
8	38.8	-			38.6		39.8	
9	37.0	-	H-20		36.8		37.2	
10	55.7	0.95			56.0		56.2	
11	34.0	1.50		H-20	34.1		36.2	
12	27.9	-		H-17	28.5		29.2	
13	45.4	-	H-17		45.2		37.5	
14	34.7	-		H-17	34.4		36.2	
15	215.2	-		H-17	207.8		81.5	3.95
16	63.8	4.36			64.5	4.82	63.0	3.72
								4.13
17	20.5	1.21			20.5	1.20	20.0	1.32
18	102.9	4.70			102.9	4.50	104.8	5.40
		4.64				4.30		4.89
19	15.7	1.06			16.6	1.14	16.1	1.11
20	12.0	0.73			12.0	0.74	12.3	0.76
C=O (Ac)					170.9			
C=O (Ac)					170.4			
CH <sub>3</sub> (Ac)					21.3	2.13		
CH <sub>3</sub> (Ac)					20.5	1.98		

protons is indicative of its neighboring position to an anisotropic deshielding group such as the carbonyl or the carbon-carbon double bond. Acetylation of **1** yielded a colorless solid, designated **1a**,  $[M]^+$   $m/z$  404 ( $C_{24}H_{36}O_5$ ). The  $^1H$  NMR spectrum of **1a**, showed two extra methyl groups at  $\delta$  2.13 and 1.98 (3H each, s), confirming the dihydroxy character of **1a**. It also showed a more deshielded carbinolic methine ( $\delta$  5.06) with respect to the carbinolic methylene ( $\delta$  4.82) in an opposite relationship relative to the non-acetylated compound. These features are indicative of the presence of an  $\alpha$ -hydroxy-acetyl moiety in **1a**. The upfield shift of the carbonyl ( $\delta$  207.8, for **1a**) due to the loss of the chelation through the five member ring hydrogen bonding is also in agreement with the ketone carbonyl bearing the carbinolic hydrogen. Reduction of **1** with  $NaBH_4$ /ethanol yielded a colorless solid, designated **1b**,  $[M]^+$   $m/z$  322 ( $C_{20}H_{34}O_3$ ). The BB  $^{13}C$  NMR spectrum of **1b** showed a signal at  $\delta$  81.5 related to a carbinolic methine carbon and the absence of the signal at  $\delta$  215.2 which confirmed the presence of the ketone carbonyl in **1**. A search in the literature for tricyclic diterpene skeletons that could accommodate three angular methyls, an exocyclic double bond and an  $\alpha$ -hydroxy-acetyl moieties, yielded three possible diterpene general structure types: cassane, cleistanthane and erythroxyllane.<sup>7-9</sup>



The long-range heteronuclear correlation spectrum (COLOC) of **1** showed a correlation between the angular methyl at  $\delta$  1.21 with the carbonyl carbon at  $\delta$  215.2 ( $^3J_{H-17, C-15}$ ). The same angular methyl also correlated with two methylenes at  $\delta$  34.7 ( $^3J_{H-17, C-14}$ ) and  $\delta$  27.9 ( $^3J_{H-17, C-12}$ ) and the quaternary carbon at  $\delta$  45.4 ( $^2J_{H-17, C-13}$ ). The COLOC spectrum also showed correlations of the angular methyl at  $\delta$  1.06 to the non-hydrogenated  $sp^2$  carbon at  $\delta$  157.4 ( $^3J_{H-19, C-4}$ ), the quaternary carbon at  $\delta$  46.8 ( $^2J_{H-19, C-5}$ ), and the carbinolic methine carbon at  $\delta$  74.5 ( $^3J_{H-19, C-6}$ ). Moreover, the exocyclic double-bond hydrogens at

$\delta$  4.70 and 4.64 correlated to a methylene at  $\delta$  33.3 ( $^3J_{H-18, C-3}$ ) and to the same quaternary carbon at  $\delta$  46.8 ( $^3J_{H-18, C-5}$ ). Thus, **1** was suggested to be the 6 $\alpha$ -hydroxy-15-oxo-allodevadarool. This carbon skeletal-pattern, also designated by dolabrane, has been observed for compounds from *Erythroxyllum* species.<sup>10-13</sup> The junction of the A/B ring is *trans*, since the  $^{13}C$  NMR spectra did not show any signal referent to a methyl group at approximately  $\delta$  32.0.<sup>14</sup> Finally, the X-ray analysis of a crystal obtained from MeOH confirmed the structure of **1** as 7-(2-hydroxy-acetyl)-10-hydroxy-tetradecahydro-1-methylene-4b,7,10a-trimethylphenantrene. Figure 1a shows an ORTEP three-dimensional structural drawing of the relative stereochemistry of **1**, whereas Figure 1b highlights the intermolecular hydrogen bonding among the molecules, further stabilizing the molecular structure arrangement. The absolute stereochemistry shown in Figure 1 is arbitrary.



**Figure 1.** Three-dimensional structural drawing of the relative stereochemistry of **1**, with hydrogens in idealized positions (a), and intermolecular hydrogen bonding structure spatial arrangement (b).

## Experimental

### General

mps.: uncorr.; IR: KBr pellets;  $^1H$  NMR: 200 and 400 MHz;  $^{13}C$  NMR: 50 and 100 MHz, Bruker AC-200 or Varian Unit Plus, respectively; GC/MS Low resolution EIMS: (70 eV) Hewlett-Packard HP-5995-A.

### X-ray analysis

A single crystal of **1** was mounted on an Enraf-Nonius CAD-4 diffractometer equipped with graphite monochromated MoK $\alpha$  radiation. Unit cell parameters and intensity data were obtained at room temp. The structure was solved by SIR and refined by full matrix least squares. Figure 1a is an ORTEP view of the molecule, with hydrogens on idealized position and Figure 1b shows the intermolecular hydrogen bonds between O(1)-O(2)\* ( $d_{\text{o-o}} = 2.679(4)\text{\AA}$ , \* -x,y,z), and O(2)-O(1)# ( $d_{\text{o-o}} = 2.682(5)\text{\AA}$ , # 2-x, 1/2+y, 2-z).

### Plant material

*Trigonia fasciculata* was collected in Jacobina-BA, Brazil and identified by Dr. Afrânio G. Fernandes and Dr. Edson de Paula Nunes (Botanists, Universidade Federal do Ceará). A voucher specimen (#20366) representing the collection has been deposited at Herbário Prisco Bezerra, Departamento de Biologia, Universidade Federal do Ceará, Brazil.

### Extraction and isolation of constituents

After removal of the aerial part, the roots (4.0 Kg) were dried, ground and extracted exhaustively with hexane to yield, after solvent evaporation, 26.2 g of a yellowish viscous extract designated TFRH. After standing at room temperature, a precipitate was formed, which yielded 1.6 g of a yellowish solid upon filtration and was designated TFRH-p. Two-hundred mg of TFRH-p was chromatographed over silica gel to yield 57.6 mg of TFRH-1, as a colorless solid, and 33.4 mg of another colorless solid designated TFRH-2. TFRH-1 mp. 260.2-261.2 °C, showed all spectrometric (MS, IR, <sup>1</sup>H and <sup>13</sup>C NMR) data identical to friedelin (lit.<sup>15,16</sup> 263.0-263.5 °C). TFRH-2, mp. 273.3-276.4 °C, was identified as betulinic acid (lit.<sup>7</sup> 275.0-278.0 °C) after spectral (MS, IR, <sup>1</sup>H and <sup>13</sup>C NMR) comparison to literature data.<sup>7</sup>

### Fatty acids and sesquiterpenes

Coarse chromatography over silica gel of the mother liquor TFRH (24.5 g) yielded a fraction by elution with hexane (6.9 g). An aliquot (3.5 g) was hydrolyzed with KOH/EtOH 1:1 solution yielding 0.56 g of fatty acids and 2.18 g of unsaponifiable material after usual work-up. 100 mg of the fatty acids were methylated with BF<sub>3</sub>/MeOH 14% and the methyl ester mixture obtained after work-up was analyzed by GC/MS allowing the identification of

methyl esters of lauric (C<sub>12</sub>:O, 2.00%), miristic (C<sub>14</sub>:O, 2.63%), pentadecanoic (C<sub>15</sub>:O, 0.41%), pentadecadienoic (C<sub>15</sub>:2, 0.96%), 14-methylpentadecanoic (C<sub>16</sub>:O, 0.39%), palmitic (C<sub>16</sub>:O, 13.87%), palmitoleic (C<sub>16</sub>:1, 0.50%), margaritic (C<sub>17</sub>:O, 0.51%), 14-methyl-hexadecanoic (C<sub>17</sub>:O, 0.55%), stearic (C<sub>18</sub>:O, 4.20%), oleic (C<sub>18</sub>:1, 38.84%), linoleic (C<sub>18</sub>:2, 19.54%), arachydic (C<sub>20</sub>:O, 0.96%), gonic (C<sub>20</sub>:1, 1.58%), behenic (C<sub>22</sub>:O, 2.87%), tricosanoic (C<sub>23</sub>:O, 0.57%) and lignoceric acid (C<sub>24</sub>:O, 1.58%). The unsaponifiable portion (2.15 g) was chromatographed over silica gel to yield a clear viscous fraction, by elution with hexane, whose <sup>1</sup>H NMR spectrum showed its terpenoid features. GC/MS analysis, utilizing the method developed by Alencar,<sup>4</sup> allowed the identification of the sesquiterpenes: d-elemene (4.68%), cyclosativene (1.20%),  $\alpha$ -copaene (1.51%),  $\beta$ -elemene (11.64%),  $\alpha$ -santalene (28.40%),  $\alpha$ -bergamotene (7.71%), *epi*- $\beta$ -santalene (2.66%),  $\alpha$ -humulene (2.14%), *cis*- $\beta$ -farnesene (6.74%),  $\beta$ -santalene (3.78%),  $\gamma$ -muurolene (2.22%),  $\beta$ -selinene (1.37%),  $\beta$ -bisabolene (9.20%),  $\gamma$ -cadinene (8.14%), and  $\delta$ -cadinene (3.64%).

*6 $\alpha$ -Hydroxy-15-oxo-allodevadarool (1)*. The most polar fraction obtained from column chromatography of TFRH after elution with EtOAc, 120 mg, was submitted to rotational planar chromatography (CHROMATOTRON<sup>®</sup>) with a mixture of hexane/EtOAc 3:2 to yield 31.2 mg of **1** as colorless crystals from MeOH. The next closest fraction, also eluted with EtOAc (1.6 g), was submitted to successive CC over silica gel to yield 120 mg more of **1**, mp. 140-144 °C,  $[\alpha]_D^{25} = +4.73^\circ$  (c. 0.5, CHCl<sub>3</sub>) FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3301, 3100, 2934, 2852, 1723, 1642, 1089, 1018, 890 (KBr). EI-MS m/z (rel. int.): 320 ([M]<sup>+</sup>, 14), 302 (13, M - H<sub>2</sub>O), 289 (28, M - CH<sub>2</sub>OH), 271 (6, 302 - CH<sub>2</sub>OH), 261 (89, M - O=C-CH<sub>2</sub>OH), 243 (73, 271 - CO or 261 - H<sub>2</sub>O), 109 (100). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): Table 1 <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): Table 1.

*6 $\alpha$ ,16-Acetoxy-15-oxo-allodevadarool (1a)*. 32 mg of **1** was acetylated by usual procedure with pyridine/Ac<sub>2</sub>O to yield 24 mg of the acetylated material **1a** after usual work-up and filtration of the reaction product over a small layer of silica gel. **1a**, a yellowish amorphous solid, mp. 114.0-116.0 °C.

EI-MS m/z (rel. int.): 404 ([M]<sup>+</sup>, 26), 362 (33, M<sup>+</sup>-CH<sub>2</sub>CO), 347 (11, 362-CH<sub>3</sub>), 344 (50, M<sup>+</sup>-CH<sub>3</sub>CO<sub>2</sub>H), 329 (36, 344-Me), 303 (58, 362-CH<sub>2</sub>OHCO), 261 (71, 303-CH<sub>2</sub>CO), 243 (100, 261-H<sub>2</sub>O). Supplementary material under author request. FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3093, 2932-2858, 1750, 1720, 1642, 1248, 889 (KBr). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): Table 1 <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): Table 1.

*6 $\alpha$ ,15-dihydroxy-allodevadarool (1b)*. 60 mg of **1** was treated with saturated solution of NaBH<sub>4</sub>/EtOH. After usual

work-up the reaction mixture was chromatographed over a small layer of silica gel to yield 29 mg of a white amorphous solid **1b**, mp. 184.5-187.5 °C.

EI-MS  $m/z$  (rel. int.): 322 ( $[M]^+$ , 32), 307 (26,  $M - CH_3$ ), 304 (14,  $M^+ - H_2O$ ), 291 (27,  $M - CH_2OH$ ), 273 (18, 291- $H_2O$ ), 109 (100). Supplementary material under author request. FT-IR  $\nu_{max}/cm^{-1}$ : 3386, 3106, 2932, 2858, 1642, 1095, 1068, 892 (KBr).  $^1H$ NMR (200 MHz,  $CDCl_3$ ): Table 1.  $^{13}C$  NMR (50 MHz,  $CDCl_3$ ): Table 1.

## Supplementary Information

Crystallographic data (excluding structure factors) for the structure **1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication on CCDC 176082. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

## Acknowledgements

The authors wish to acknowledge Dr. Afrânio G. Fernandes and Dr. Edson de Paula Nunes (Botanists, UFC-CE) for plant identification; Dr. R. Braz-Filho (UENF-RJ) for his helpful discussion about MS data; CNPq for the fellowships and CAPES/PADCT/FINEP/PRONEX/FUNCAP for financial support.

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Received: January 6, 2002

Published on the web: May 8, 2003

FAPESP helped in meeting the publication costs of this article.