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# Determination of the Absolute Configuration of (+)- Surinamensin's via Diastereomeric O-Methylmandelic Esters

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A configuração absoluta da (+)-surinamensina **1a**, uma neolignana 8.0.4', foi determinada baseado em seus esteres do ácido *O*-metilmandélico.

The absolute configuration of (+)-surinamensin **1a**, a 8.0.4' neolignan, has been determined based on its *O*-methylmandelates esters.

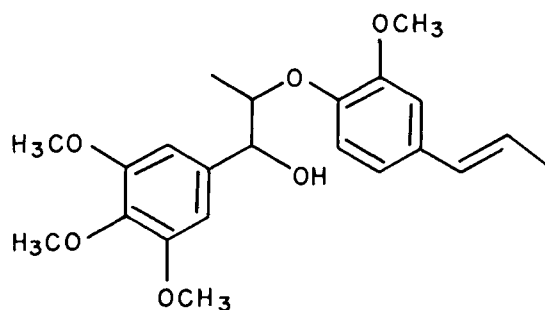
**Key words:** *surinamensin, O-methylmandelate, absolute configuration*

## Introduction

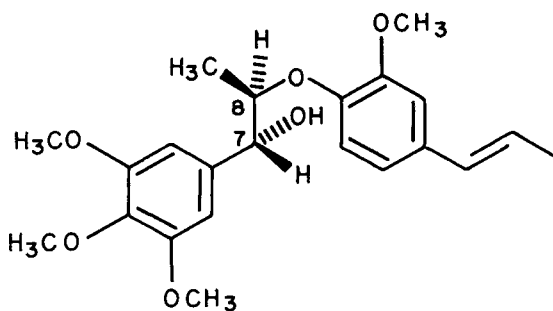
While working on the leaves of *Virola surinamensis* (Rol.) Warb. a typical Amazonian tree, the hexane crude extract was submitted to biological essays revealing a strong activity against *Schistosoma mansoni* cercariae infestation<sup>1</sup>. A careful monitoring of the chromatographic fractions activity led to the isolation of a 8.0.4' neolignan, named surinamensin **1a** which was the secondary metabolite responsible for the above mentioned activity.

Synthetic work supported the structural proposal and the C-7/C-8 relative configuration was assigned as *threo* based on <sup>1</sup>H-nmr<sup>2</sup> and <sup>13</sup>C-nmr<sup>3</sup>. The absolute configuration, though, remained undetermined.

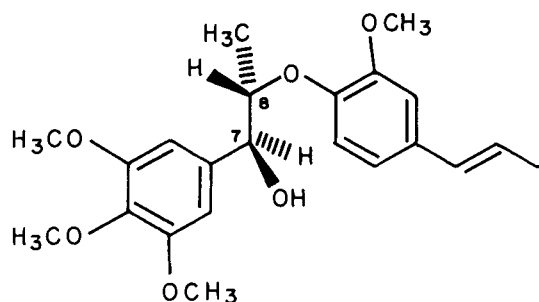
In this paper we report the absolute configuration of (+)-surinamensin **1a** using the method of *O*-methylmandelate derivatives<sup>4</sup>.



**1 - threo**



**1b**



**1a**

Table 1. <sup>1</sup>H-NMR spectra of diastereomeric esters **2a** and **2b**<sup>a</sup>

PROTON	COMPOUND	
	<b>2a</b>	<b>2b</b>
CH <sub>3</sub> - 9	0.98(d, J=7.0)	1.11(d, J=7.0)
CH <sub>3</sub> - 9'	1.88(d, J=5.0)	1.88(d, J=5.0)
OCH <sub>3</sub> - (OMMA)	3.39(s, 1 OCH <sub>3</sub> )	3.33(s, 1 OCH <sub>3</sub> )
OCH <sub>3</sub> Ar (A) (B)	3.78(s, 3OCH <sub>3</sub> ) 3.82(s, 1 OCH <sub>3</sub> )	3.62(s, 1 OCH <sub>3</sub> ) 3.78(s, 2 OCH <sub>3</sub> ) 3.82(s, 1 OCH <sub>3</sub> )
H - 7	5.91(d, J=6.0)	5.88(d, J=6.0)
H - 8	4.30-4.70(m)	4.30-4.70(m)
OCH <sub>3</sub> -C-H(Ph) <sup>b</sup>	4.81(s)	4.62(s)
H - 7'	6.37(d, J=16.0)	6.37(d, J=16.0)
H - 8'	6.00-6.30(m)	6.00-6.30 (m)
H - Ar (A)	6.57(s)	6.30(s)
H - Ar (B)	6.70-6.90(m)	6.89 (br s)
H - Ar (C)	7.10-7.60(m)	7.30(s)

<sup>a</sup> Chemical shifts were determined at 80 MHz in CDCl<sub>3</sub>. δ values are in ppm downfield in relation to TMS. The J values are given in Hz. <sup>b</sup>Proton of the O-methylmandelic portion.

## Experimental

Optical rotations were measured with a Polamat polarimeter. The IR spectra were obtained on a Perkin Elmer 399B spectrophotometer. <sup>1</sup>H-NMR spectra were recorded in CDCl<sub>3</sub>, using TMS as internal standard, employing a Bruker AW-80 NMR spectrometer. Low resolution mass spectra were obtained with Varian MAT 311A instrument, operating at 70 eV. Analytical and preparative TLC were carried out on precoated Merck silica gel F 254 plates. Compounds were visualized by uv light or spraying with anisaldehyde followed by heating.

(*S*)-OMMA-7*S*,8*S*-surinamensin **2a** and (*S*)-OMMA-7*R*,8*R*-surinamensin **2b**: (*S*)-O-methylmandelic acid (0.24 g, 1.54 mmol) was added to a white suspension prepared by the slow addition of oxalyl chloride (0.14 mL, 1.6 mmol) to dry DMF (0.18 mL, 2.17 mmol) in dry acetonitrile (5 mL) at 0 °C under nitrogen. After 10 min, a solution of *threo*-(±)-surinamensin (0.20 g, 0.51 mmol) in dry pyridine (0.26 mL, 3.2 mmol) was slowly added during 3-min and the resulting mixture was stirred at 0 °C for 1 hr. The reaction mixture was diluted with diethylether (25 mL) and the organic phase washed twice with a saturated aqueous cupric sulfate solution and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a pale yellow oil. Purification by flash column chromatography on silica gel (hexane: diethylether, 2:8) gave 0.244g (90% yield) of two diastereomeric esters **2a** (less polar) and **2b** (more polar) in 1:1 ratio by HPLC analysis. The diastereomers were separated by preparative thin layer chromatography (hexane: diethylether, 4: 6) with continuous elution.

**2a**: colorless oil, [α]<sub>D</sub><sup>22</sup> + 17.8° (c 0.30, CHCl<sub>3</sub>); IR (film) ν<sub>max</sub> 2940, 2880, 1750 (C=O, ester), 1600, 1515, 1465, 1455, 1330, 1260, 1130, 1010, 910, 830 cm<sup>-1</sup>; <sup>1</sup>H-NMR (80 MHz (CDCl<sub>3</sub>)) see Table 1.

**2b**: colorless oil, [α]<sub>D</sub><sup>22</sup> - 14.8° (c 0.53, CHCl<sub>3</sub>). IR (film) ν<sub>max</sub> 2920, 2825, 1758, (C=O, ester), 1595, 1515, 1510,

1465, 1335, 1265, 1130, 1010, 915, 830 cm<sup>-1</sup>; <sup>1</sup>H-NMR (80 MHz (CDCl<sub>3</sub>)) see Table 1.

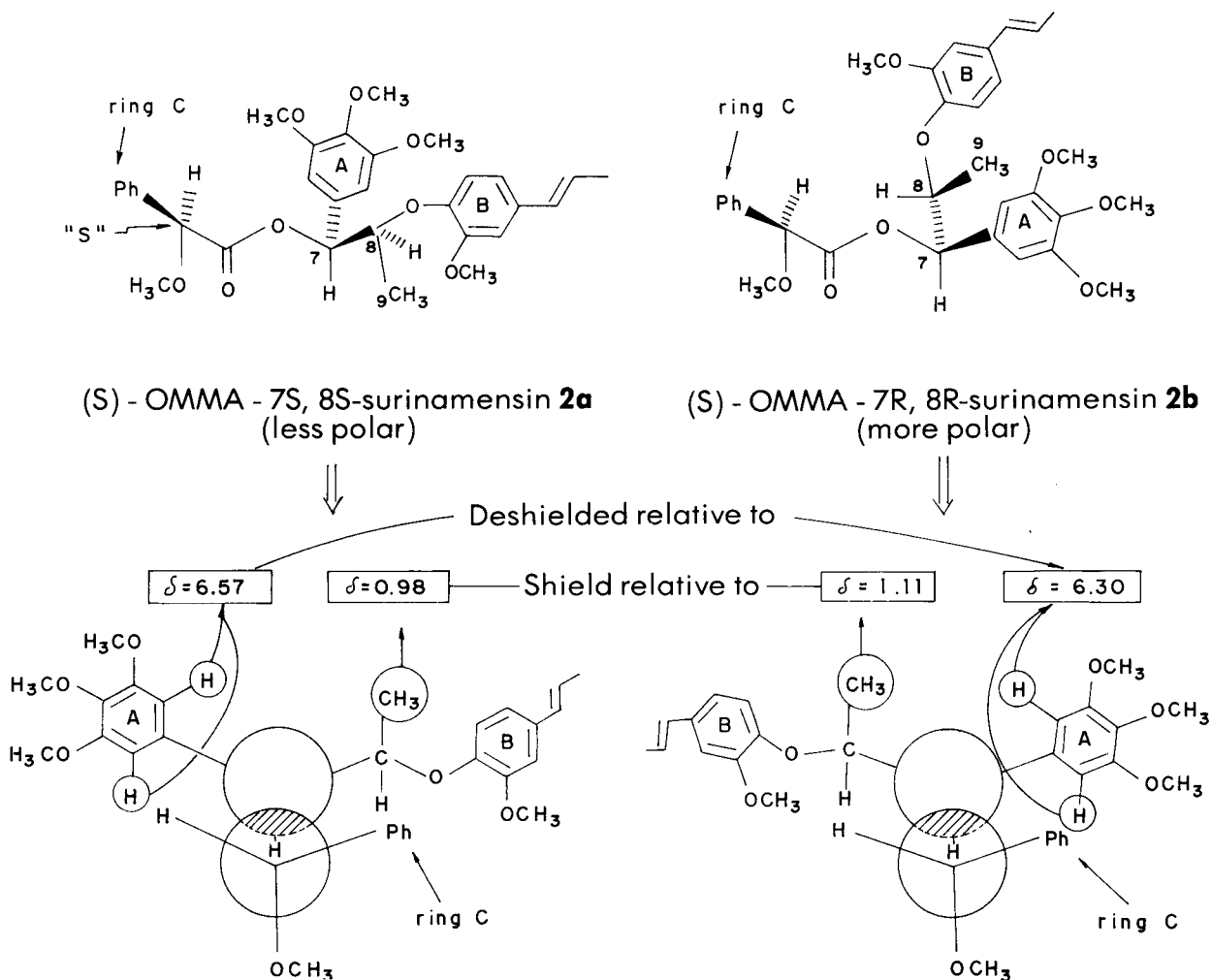
(+)-7*S*,8*S*-surinamensin **1a**: To a solution of **2a** (0.080g, 0.15 mmol) in methanol (1.0 mL) were added K<sub>2</sub>CO<sub>3</sub> (anhydrous powder) (0.084 g, 0.6 mmol) and enough H<sub>2</sub>O to obtain a nearly homogeneous solution. After 1 h at room temperature the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x 5mL). The organic layer was washed with H<sub>2</sub>O (1x 5mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude extract was purified by preparative TLC (hexane: diethylether, 4: 6) using continuous elution and gave 0.058g (98% yield) of (+)-7*S*,8*S*-surinamensin **1a**, [α]<sub>D</sub><sup>22</sup> + 101.2° (c 0.43, CHCl<sub>3</sub>), <sup>1</sup>H-NMR, IR and ms data were in accordance with those previously reported<sup>2</sup>.

(-)-7*R*,8*R*-surinamensin **1b**: obtained from **2b** by the same procedure with 96% yield. [α]<sub>D</sub><sup>22</sup> - 97.4° (c 0.49, CHCl<sub>3</sub>). <sup>1</sup>H-NMR, IR and ms data are identical with those of **1a**.

Extraction of (+)-surinamensin **1a** from leaves: The compound **1a** was isolated from the leaves of *Virola surinamensis* (Rol.) Warb collected in Belém-Pará-Brazil following the procedure reported by Barata *et al*<sup>2</sup>. The last purification step however was realized by preparative TLC continuously eluted with hexane: diethylether 4:6. **1a** (natural) was a viscous colorless oil [α]<sub>D</sub><sup>23</sup> + 131.2° (c 0.21, CHCl<sub>3</sub>) and <sup>1</sup>H-NMR, IR and ms data are in accordance with those reported in the literature<sup>2</sup>.

## Results and Conclusions

Synthetic *threo*-(±)-surinamensin<sup>2,3,6</sup> was treated with o-methylmandelic acid (OMMA) following Trost's method<sup>4</sup>, leading to a diastereomeric mixture which was resolved by preparative thin layer chromatography, continuously eluted with hexane-diethylether 4:6. The "less polar" component **2a** was dextrorotatory, [α]<sub>D</sub><sup>22</sup> + 17.8° (c 0.30, CHCl<sub>3</sub>) and had the C-9 methyl group resonating at 0.98 ppm, while compound **2b** was "more polar", levorotatory, [α]<sub>D</sub><sup>22</sup> - 14.8° (c 0.53, CHCl<sub>3</sub>) and its C-9



**Figure 1** - Configurational correlation model for diastereomeric esters **2a** and **2b**

methyl group absorbed at lower field, 1.11 ppm. Based on the model proposed by Trost and coworkers<sup>4</sup> we deduced that the C-9 methyl of **2a** is on the same side as the aromatic moiety of the *O*-methylmandelate portion (ring C), showing an upfield shift in comparison to the corresponding signal of **2b**, due to the anisotropic shielding by ring C (Fig. 1).

Additionally, ring A of **2b** has to be located on the same side as ring C because its aromatic protons absorbed at a higher field (6.30ppm) than the corresponding ones of **2a** (6.57ppm).

Consequently the absolute configuration at carbon 7 of **2a** should be (S) and at that of **2b** should be (R). Ultimately as **2a** and **2b** are *threo* isomers we have deduced that **2a** is (S)-OMMA-7S, 8S-surinamensin and **2b** is (S)-OMMA-7R, 8S-surinamensin.

A mild basic hydrolysis<sup>5</sup> of **2a** and **2b** led to the chiral alcohols **1a**, (+)-7S, 8S-surinamensin [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 101.2° (c 0.43, CHCl<sub>3</sub>) and **1b** (-)-7R, 8R-surinamensin [ $\alpha$ ]<sub>D</sub><sup>25</sup> - 97.4° (c 0.49, CHCl<sub>3</sub>).

Comparison of the optical rotations of the resolved alcohols to that of the natural product which was reisolated in a purer form, from the leaves of *Virola surinamensis* [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 131.2° (c 0.21, CHCl<sub>3</sub>) led us to the conclusion that surinamensin, is (+)-7S-8S, **1a**.

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