^{1}H and ^{13}C NMR of Synthetic Macrocyclic Lactones and Their Precursors

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Atribuição dos deslocamentos químicos de hidrogênio e carbono-13 de lactonas macrocíclicas (**12, 13**) e diméricas (**14, 15**) obtidas de produtos (**7, 9**) preparados (**5, 8, 10**) de ácido anacárdico (**4**) isolado de cascas de castanha de caju, utilzando-se inclusive experiências bidimensionais de correlação homonuclear ($^{1}Hx^{1}H$-COSY) e heteronuclear [$^{1}Hx^{13}C$-COSY-$^{1}J_{CH}$ e $^{1}Hx^{13}C$-COSY-$^{n}J_{CH}$ (n= 2 e 3, COLOC) e NOE por subtração de espectros ($^{1}H\{^{1}H\}$-NOE) de RMN. As estruturas de produtos secundários (**6, 16**) foram também definidas.

Assignment of ^{1}H and ^{13}C NMR spectra of macrocyclic (**12, 13**) and dimeric (**14, 15**) lactones synthesized from the products (**7, 9**) prepared (**5, 8, 10**) from anacardic acid (**4**), the major constituent of cashew nut-shell liquid (CNSL), including 2D-NMR methods and NOE difference spectra. The structures of secondary products (**6, 16**) were also established.

Key words: *lactones; anacardic acid; cashew nut.*

Introduction

Macrolides are attractive compounds because of their fascinating chemistry and therapeutical activities. Several members of naturally ocurring macrocyclic lactones possessing diverse and significant biological activities have been prepared by many workers.

Lasiodiplodin (**1**), a potent antileukemic drug isolated from the stems and leaves of *Euphorbia splendens*[1] and *Annona dioica*,[2] resorcylide (**2**), a plant growth inhibitor from an unidentified species of penicillium,[3] and zearalenone (**3**), another structurally related macrolide with anabolic and uterotropic activity obtained from the mycelia of the fungus *Gibberella zeae* (*Fusarium graminearum*),[4] are some exemples of this class of compounds.

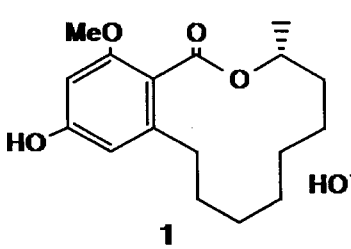
Recently, a variety of synthetic approaches to macrocyclic lactones involving mainly intramolecular esterification have been developed.[5-8]

During the course of our studies to prepare lasiodiplodin (**1**), four new members of macrocyclic lactones (**12-15**) were synthesized besides several acyclic precursors (**5, 7, 9**) and their derivatives (**8, 10**), along with secondary products formed during the preparation of these compounds.

The main purpose of this paper is the structural characterization of these compounds employing mainly one- and two-dimensional ^{1}H and ^{13}C NMR. The publication of these data, containing assignments of ^{1}H and ^{13}C chemical shifts confirmed by 2D experiments, is considered to be quite interesting for workers in the fields of natural products and synthetic chemistry.

Results and Discussion

Compound **5**, obtained by ozonolysis of anacardic acid (**4**) after methylation of the phenolic hydroxyl group and esterification of the carboxyl function (methyl ester), was identified, as antecipated, as an aldehyde by signals at δ 9.72 (t,J=1.8 Hz, H-14), 2.37 (td,J=1.8 and 7.4, 2H-13), 202.86 (d, C-14), 43.62 (t, C-13) and 23.30 (t, C-12) observed in the ^{1}H (Table 1) and ^{13}C (Table 2) NMR spectra. The multiplicities of the carbon signals of all compounds were determined by DEPT experiments. The presence of derivatives **6** (oxidation of **5**) and **16** (cyclic trimer of **5**, analogous to paraldehyde **17**)



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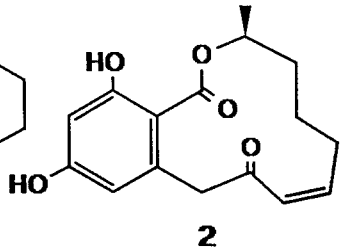

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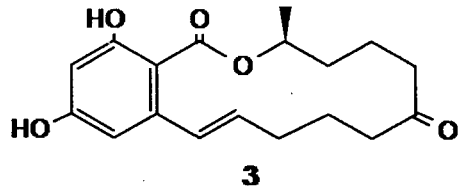

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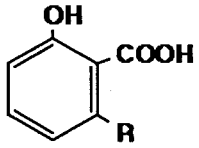
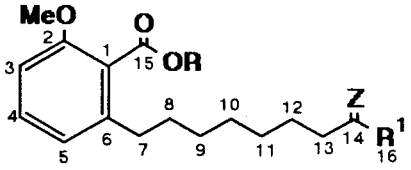
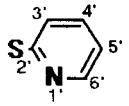
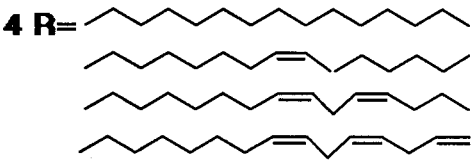
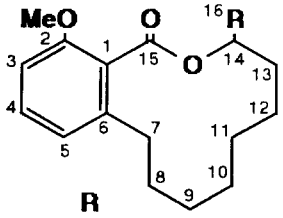




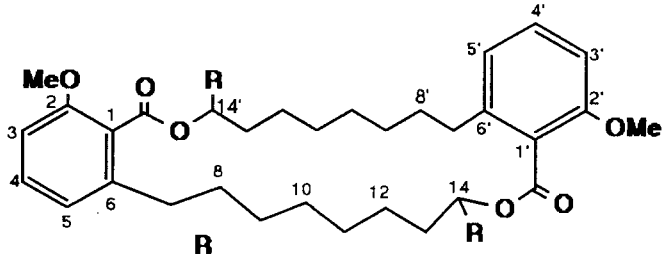
	Z	R	R¹
5	O	Me	H
6	O	Me	OH
7	OH,H	H	H
8	OH,H	Me	H
9	OH,H	H	Me
10	OH,H	Me	Me
11	H,H	Me	

4 R=

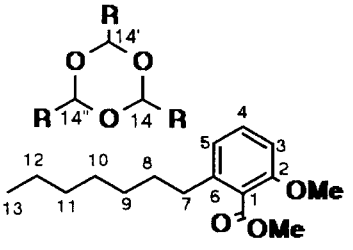




	R
12	H
13	Me

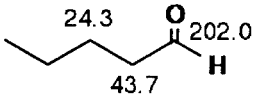


	R
14	H
15	Me



16

17 **Me**(paraldehyde)



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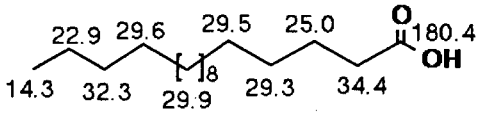

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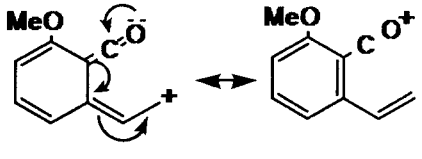
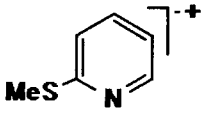
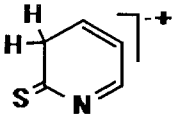


20 m/z 161



21 m/z 125



22 m/z 111

Table 1. *^{1}H NMR spectral data of* **5-10** *and* **16** *(200 MHz, $CDCl_3$, TMS as internal standard). The chemical shifts are recorded in* δ (ppm) and coupling constants (J, in parenthesis) in Hz.*

H	**5**	**6**	**16**	**7**[a]	**8**	**9**	**10**
3	6.72 d(8.3)	6.72 d(8.3)	6.72 d(8.3)	6.83 d(7.6)	6.73 d(8.2)	6.74 d(7.8)	6.69 d(8.1)
4	7.24 t(8.3)	7.24 t(8.3)	7.24 t(8.3)	7.26 dd(7.6,8.4)	7.24 t(8.2)	7.24 t(7.8)	7.20 t(8.1)
5	6.78 d(8.3)	6.78 d(8.3)	6.78 d(8.3)	6.85 d(8.4)	6.79 d(8.2)	6.80 d(7.8)	6.75 d(8.1)
7	2.50 t(7.3)	2.50 t(7.3)	2.50 t(7.3)	2.6-2.5	2.51 ~t(7.4)	2.63 t(6.8)	2.47 ~t(8.2)
8	1.7-1.5 (m)	1.7-1.5 (m)	1.7-1.5 (m)	1.58 (m)	1.60 (m)	1.7-1.5 (m)	1.60 (m)
9-11	1.28 (m)	1.28 (m)	1.28 (m)	1.4-1.2 (m)	1.28 (m)	1.5-1.0 (m)	1.4-1.2 (m)
12	1.7-1.5 (m)	1.7-1.5 (m)	1.28 (m)	1.4-1.2 (m)	1.40 (m)	1.5-1.0 (m)	1.24) (m)
13	2.37 td(1.8,7.4)	2.30 t(7.5)	1.7-1.5 (m)	1.48 (m)	1.50 (m)	1.5-1.0 (m)	1.50 (m)
14	9.72 t(1.8)	-	4.79 t(5.6)	3.52 t(6.3)	3.59 t(6.5)	3.9-3.7[b]	3.8-3.6[b]
16	-	-	-	-	-	1.16 d(6.2)	1.10 d(6.2)
MeO-2	3.72 (s)	3.72 (s)	3.72 (s)	3.79 (s)	3.79 (s)	3.61 (s)	3.74 (s)
MeO-15	3.87 (s)	3.87 (s)	3.87 (s)	-	3.88 (s)	- (s)	3.87 (s)

** Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2,3; COLOC)] 2D NMR spectra were also used for these assignments. The chemical shifts and coupling constants were deduced of the 1D NMR spectra.*

[a] *Spectra recorded in $CDCl_3$+CD_3COCD_3.*

[b] *Overlapped with the methoxyl signals.*

in the ^{1}H and ^{13}C NMR spectra of **5** was determined by the presence of signals at δ 2.30 (t,J=7.5 Hz, 2H-13 of **6**), 4.79 (t,J=5.6 Hz, C-14, 14', 14'' of **16**), 178.61 (s, C-14 of **6**), 33.82 (t, C-13 of **6**), 24.42 (t, C-12 of **6**), 101.38 (d, C-14, 14', 14'' of **16**), 31.92 (t, C-13, 13', 13' of **16**) and 25.00 (t, C-12, 12', 12'' of **16**). Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2 and 3, COLOC] 2D shift-correlated spectra,[9,10] comparison with literature data for models **18**[10] and **19**[11] and application of the usual chemical shift parameters[10] were used in the assignment of these signals, along with those corresponding to benzene ring 1-carbomethoxy-2-methoxy-6-alkil and polymethylenic chain (Tables 1 and 2). Additional confirmation of this analysis was obtained through a ^{1}H NMR spectrum of the same sample after two months and eleven days (May 31, 1993 to July 20, 1993), when it was observed a modification in the ratio of compounds **5** (17.6%), **6** (58.0%) and **16** (24.4%) to 10.4%, 71.4% and 18.2%, respectively, revealing the oxidation of **5** to **6**.

As antecipated, the absorptions corresponding to the hydrogen and carbon atoms with identical number of aryl moieties in all compounds (**5** - **16**) were observed with very similar chemical shifts (Tables 1-4): δ_H 6.69-6.83 (d,J=7.6-8.3 Hz, H-3), 7.20-7.26 [t or dd (**7** and **12**), J=7.6-8.3 Hz, H-4] and 6.75-6.85 (d,J=7.6-8.3 Hz, H-5); d_C 122.89-124.80 (s, C-1), 155.41-157.00 (s, C-2), 107.72-108.44 (d, C-3), 129.90-130.27 (d, C-4), 120.87-121.82 (d, C-5) and 140.37-141.46 (s, C-6). The ambiguity promoted by small differences (Tables 1 and 3) between the chemical shifts of H-3 (δ 6.69-6.85) and H-5 (6.75-6.85) was eliminated with the help of $^1Hx^{13}C$-COSY 2D heteronuclear correlation via one bond ($^1Hx^{13}C$-COSY-$^1J_{CH}$) and through long-range coupling [$^1Hx^{13}C$-COSY-$^nJ_{CH}$ (n=2 and 3, COLOC)] spectra. The chemical shift of C-3 (δ 107.72-108.44) is significantly different from C-5 (δ 120.87-121.87), reflecting two different interactions involving the electron-releasing methoxy group at C-2 increasing the electron density: one with C-3 (*ortho* effect, Δδ= -14.4 ppm, included γ effect of the methyl group) and another one with C-5 (*para* effect, Δδ= -7.8 ppm).[10] Furthemore, in the $^1Hx^{13}C$-COSY-$^nJ_{CH}$ (n=2 and 3) spectrum of *e. g.* **14** CH_2-7 methylenic protons signal at δ 2.55 (~t,J=7.4) showed an interaction due to long-range coupling with sp^2 carbon C-5 at δ 121.51 (d). Thus, the accurate assignments (Tables 1-4) of the signals of the aryl system were confirmed.

The triplet signals of the benzylic methylene CH_2-7 of all compounds (**5** - **16**) had chemical shifts between δ_H 2.4-2.8 (anisotropic effect of the benzene ring) and the corresponding carbon signals [δ_C 32.70-33.70 (**5** - **11**, **14** - **16**), 30.12 (**12**)

Table 2. *^{13}C NMR spectral data of **5-10** and **16** (50.3 MHz, $CDCl_3$, TMS as internal standard). The chemical shifts are given in* δ (ppm) and the multiplicity of the signals was deduced by comparative analysis of the proton-noise decoupled (PND) and DEPT spectra.*

C	**5**	**6**	**16**	**7**[a]	**8**	**9**	**10**
1	123.18	123.18	123.18	123.20	123.20	122.89	123.00
2	155.99	155.99	155.99	155.41	156.11	156.08	156.11
3	108.15	108.15	108.15	107.72	108.25	108.33	108.23
4	130.07	130.07	130.07	129.27	130.17	130.27	130.12
5	121.27	121.24	121.27	120.87	121.36	121.61	121.33
6	141.04	140.95	141.04	140.37	141.16	141.46	141.16
7	33.21	33.21	33.21	32.70	33.32	33.41	33.31
8	30.88	30.82	30.82	30.43	30.97	30.95	30.94
9	29.03	29.03	29.03	28.58	29.24	29.06	29.33
10	29.14	28.78	29.14	28.72	29.21	29.06	29.19
11	28.88	28.70	28.70	28.45	29.14	28.91	30.94
12	24.42	23.30	21.75	25.00	25.57	25.36	25.57
13	43.62	33.82	34.17	31.94	32.59	38.75	39.16
14	202.86	178.61	101.38	61.44	62.76	68.24	67.91
15	168.76	168.76	168.76	168.51	168.92	171.82	168.84
16	-	-	-	-	-	22.96	23.31
MeO-2	55.59	55.59	55.59	54.96	55.73	55.78	55.71
MeO-15	51.92	51.92	51.92	-	52.06	-	52.01

** Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2,3; COLOC)] 2D NMR experiments were also used for these assignments. Signals in the same column corresponding to C-9 to C-11 in all these compounds are interchangeable.*
[a] *In $CDCl_3$ + CD_3COCD_3.*

Table 3. *^1H NMR spectral data of **12-15** (200 MHz, $CDCl_3$, TMS as internal standard). The chemical shifts are reported in* δ (ppm) and coupling constants (J, in parenthesis) in Hz.*

H	**12**	**13**	**14**	**15**
3/3'	6.72(d, 8.2)	6.73(d, 8.1)	6.75(d, 8.1)	6.74(d, 8.0)
4/4'	7.24(dd, 8.2,7.6)	7.24(t, 8.1)	7.25(t, 8.1)	7.24(t, 8.0)
5/5'	6.80(d, 7.6)	6.81(d, 8.1)	6.79(d, 8.1)	6.79(d, 8.0)
7/7'	2.55(t, 7.3)	2.8-2.5	2.55(t, 7.4)	2.7-2.4
8/8'	1.66 (m)	1.8-1.5	1.62 (m)	1.8-1.4
9/9'-11/11'	1.5-1.3	1.6-1.2	1.6-1.2	1.29
12/12'	1.56 (m)	1.7-1.0	1.6-1.2	1.29
13/13'	1.85 (m)	2.1-1.9	1.72 (m)	1.8-1.4
		1.8-1.5		
14/14'	4.5-4.4	5.23 (m)	4.34(t, 6.1)	5.19 (m)
16/16'	-	1.34(d, 6.2)	-	1.34(d, 6.2)
MeO-2/2'	3.79 (s)	3.79 (s)	3.80 (s)	3.79 (s)

** Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2,3; COLOC)] 2D NMR experiments were also used for these assignments.*

Table 4. *^{13}C NMR spectral data of* **12-15** *(50 MHz, $CDCl_3$, TMS as internal standard). The chemical shifts are described in* δ (ppm). The multiplicity of the signals was deduced by comparative analysis of the proton-noise decoupled and DEPT spectra.*

C	12	13	14	15
1/1'	124.36	124.80	123.72	124.00
2/2'	155.65	156.01	156.09	157.00
3/3'	107.99	108.19	108.34	108.44
4/4'	129.94	129.90	130.06	129.92
5/5'	121.63	121.82	121.51	121.54
6/6'	141.22	141.24	141.05	140.89
7/7'	30.12	30.19	33.66	33.70,33.53
8/8'	29.79	30.09	31.79	32.00,31.73
9/9'	25.87	26.41	29.99	30.25,30.00
10/10'	25.58	25.38	29.60	29.91
11/11'	24.73	24.07	29.58	29.79,29.68
12/12'	23.67	21.04	26.42	25.63,25.58
13/13'	26.30	32.26	28.89	36.04
14/14'	66.57	72.18	65.27	72.15
15/15'	168.66	168.14	168.59	168.29
16/16'	-	19.29	-	19.96
MeO-2/2'	55.72	55.77	55.78	55.72

** Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2,3; COLOC) were also used for these assignments. Signals in the same column corresponding to C-9 to C-11 in all these compounds are interchangeable.*

and 30.19 (**13**) were distinguished by $^1Hx^{13}C$-COSY-$^1J_{CH}$ spectra (Tables 1-4). The chemical shifts of CH_2-8 were deduced by $^1Hx^1H$-COSY spectra, which showed cross peaks due to the spin-spin interaction with the hydrogen atoms at CH_2-7; after these assignments, the $^1Hx^{13}C$-COSY-$^1J_{CH}$ spectra were consequently used to determine the chemical shift of the carbon atom CH_2-8. The easiness of attribution of the chemical shifts of the hydrogen and carbon atoms of the hydroxylated C-14 methylene [**7**: δ_H 3.52 (t,J=6.3 Hz), δ_C 61.44 (t); **8**: δ_H 3.59 (t,J=6.5 Hz), δ_C 62.76 (t)] and methine groups [**9**: δ_H 3.9-3.7, δ_C 68.24 (d); **10**: δ_H 3.8-3.6 (m), δ_C 67.91 (d)] allowed to recognize the signals of the protons ($^1Hx^1H$-COSY) and carbon ($^1Hx^{13}C$-COSY-$^1J_{CH}$) of the methylene CH_2-13 and methyl CH_3-16 (Tables 1-4). The presence of a methyl group at C-14 [9: δ_H 1.16 (d,J=6.2 Hz), dc 22.96 (q); **10**: δ_H 1.10 (d,J=6.2 Hz),δdc 23.31 (q)] was also revealed a- and b-effects at C-14 and C-13, respectively, when compared with the analogous spectral data for **7** and **8** (Tables 1-4). The chemical shifts of the CH_2-12 were also assigned by $^1Hx^1H$-COSY in combination with $^1Hx^{13}C$-COSY-$^1J_{CH}$ spectra.

The formation of macrocyclic lactones **12** and **13** together with the dimers **14** and **15** was clearly indicated by downfield shifts observed in the comparative analisys of the chemical shifts of the carbinolic methylene hidrogens and carbons of **7** (CH_2-14: δ_H 3.52; δ_C 61.44) or **8** (CH_2-14: δ_H 3.59; δ_C 62.76), **12** (CH_2-14: δ_H 4.5-4.4, $\Delta\delta_H$=1.0 ppm; δ_C 66.57, $\Delta\delta_C$=5.13 and 3.81 ppm) and **14** (CH_2-14: δ_H 4.34, $\Delta\delta_H$=ca 0.8 ppm; δ_C 65.27, $\Delta\delta$=3.83 and 2.71 ppm). Analogous

Table 5. *^1H (200 MHz) and ^{13}C (50.3 MHz) NMR spectral data of* **11** *($CDCl_3$, TMS as internal standard. The chemical shifts are described in* δ (ppm) and coupling constants (J) in Hz (in parenthesis).

	$^1Hx^{13}C$-COSY-$^1J_{CH}$		$^1Hx^{13}C$-COSY-$^nJ_{CH}$ (n=2,3)		
C	δ_C	δ_H	$^2J_{CH}$	$^3J_{CH}$	$^1Hx^1H$-COSY
1	123.33	-		H-3,H-5,2H-7	
2	156.11	-		MeO-2,H-4	
3	108.23	6.72(d, 8.3)		H-5	
4	130.12	7.23(t, 8.3)			
5	121.36	6.78(d, 8.3)		H-3,2H-7	
6	141.16	-	2H-7	H-4	
7	33.37	2.51(t, 7.4)			2H-8
8	30.97	1.57			2H-7,2H-9
9	28.94[a]	1.31			2H-8
10	29.27[a]	1.6-1.2			
11	28.79[a]	1.6-1.2			
12	29.27[a]	1.44			2H-13
13	29.16	1.67	2H-14		2H-14,2H-12
14	29.97	3.12(t, 7.2)			2H-13
15	168.81	-		MeO-15	
MeO-2	55.72	3.78 (s)			
MeO-15	52.02	3.86 (s)			
2'	159.00	-		2H-14	
3'	121.99	7.13(d, 7.5)			H-4'
4'	135.68	7.42(td, 7.5, 1.9)			H-3',H-5'
5'	119.03	6.92(dd, 7.5, 4.7)		H-3'	H-4',H-6'
6'	149.29	8.38(br d, 4.7)			H-5'

[a] *Signals in the same column with the same superscript are interchangeable.*

Table 6. *^1H {^1H}-NOE difference spectral data of 11 (200 MHz, $CDCl_3$, TMS as internal standard). The chemical shifts are described in* δ (ppm) and the relative NOE was based in the intensity attributed (100%) for the irradiated hydrogen atom.

^1H Irradiated		NOE enhancements		
H	δ_H	H	δ_H	NOE (%)
7	2.51	5	6.78	5
		8	1.57	5
		9	1.31	2
MeO-2	3.78	3	6.72	7
14	3.12	3	7.13	3
		13	1.67	6

results were observed in the comparison involving the chemical shifts of the carbinolic methine of **9** (CH-14: δ_H 3.9-3.7; δ_C 68.24) or **10** (CH-14: δ_H 3.8-3.6; δ_C 67.91), **13** (CH-14: δ_H 5.34, $\Delta\delta_H$=ca 1.5 ppm; δ_C 72.18, Δδ=ca 4.0 ppm) and **15** (CH-14: dH 5.19, ΔδH=ca 1.4 ppm; δ_C 72.15, $\Delta\delta_C$=ca 4.0 ppm). These downfield shifts are highly consistent with the modifications antecipated by esterification of the primary and secondary hydroxy groups.[12] Additional evidence for the esterification of these hydroxyl groups was revealed by upfield shifts observed in the comparison (**7** or **8** with **12** and **14**; **9** or **10** with **13** and **15**) of the chemical shifts of the methylenic carbon CH_2-13 signals due γ-effect (protection)[10] ascribed to the carbonyl carbon of the ester function: **7** (CH_2-13: δ_C 31.94) or **8** (CH_2-13: δ_C 32.59) compared with **12** [CH_2-13: δ_C 26.30, $\Delta\delta_C$=26.30-31.94= -5.66 and Δδ=26.30-32.59= -6.29 ppm) and **14** (CH_2-13: d_C 28.89, Dd_C=28.89-31.94= -3.05 ppm and Dd_C=28.89-32.59= -3.70 ppm); **9** (CH_2-13: d_C 38.75) or **10** (CH_2-13: 39.16) in comparative analysis with **13** [CH_2-13: d_C 32.26, Dd_C=32.26-38.75 (**9**)= -6.49 and Dd_C=32.26-39.16 (**10**)= -6.90 ppm] and **15** [CH_2-13: d_C 36.04, Dd_C=36.04-38.76 (**9**)= -2.72 ppm and Dd_C=36.04-39.16 (**10**)= -3.12 ppm]. The assignments of all these signals were also confirmed by $^1Hx^1H$-COSY (cross peaks due to the spin-spin interaction between CH_2-13, CH_2-14 and CH_2-12), $^1Hx^{13}C$-COSY-$^1J_{CH}$ (connectivity of C-13 and H-13 due the spin-spin interaction between hidrogen and carbon-13 through one bond) and $^1Hx^{13}C$-COSY-$^nJ_{CH}$ [n=2 and 3, COLOC; long-range coupling between C-15 and 2H-14 (**12, 14**)] spectra. The spin-spin interaction of C-15 and 2H-14 observed in the $^1Hx^{13}C$-COSY-$^nJ_{CH}$ (n=2, 3) spectra of **12** and **14** was also used as an additional confirmation of the macrocyclic lactone (**12**) and of the dimer (**14**).

The mass spectra of **12** [M^+262 (57%)] and **14** [M^+ 524 (59%)] were used to confirm the molecular formules $C_{16}H_{22}O_3$ and $C_{32}H_{44}O_6$ of these synthetic products, respectively. The base peak at m/z 161 (100%) observed in the mass spectra of these two compounds can be attributed to the fragment ion 20.[13]

The comparative analysis of the ^{13}C NMR spectra of **12** and **13** revealed the presence of a methyl group at C-14 experiencing α, β and γ-effects of 5.61 ppm [$\Delta\delta_C$ (C-14)=72.18 (**13**) - 66.57 (**12**)], 5.96 ppm [$\Delta\delta_C$ (C-13)= 32.26 (**13**)-26.30 (**12**)] and -2.63 ppm [$\Delta\delta_C$ (C-12)= 21.04 (13)-23.67 (**12**)], respectively. Similar results were also observed in the comparison between **14** and **15**: 6.88 (α), 7.15 (β) and -0.79 ppm (γ). This smaller (-0.79 ppm) γ-effect (protection) can be ascribed to conformational modification and/or stereochemical influence of the chiral carbons C-14 and C-14' (**15**), which also justify the appearance of the additional signals observed in the ^{13}C NMR of **15** (Table 4).

Thus, ^1H and ^{13}C NMR data together with the results of 2D shift-correlated $^1Hx^1H$-COSY, $^1Hx^{13}C$-COSY-$^1J_{CH}$ and $^1Hx^{13}C$-COSY-$^nJ_{CH}$ (n=2 and 3, COLOC) experiments and mass spectra (**12** and **14**) allowed to establish the structures of macrocyclic lactones (**12, 13**) and dimers (**14, 15**). obtained through Gerlach method.[14]

During the first reaction used to preparation of macrocyclic lactone **12** also was obtained the secondary product **11**, along with the dimer **14**. The characterization of this compound **11** was relatively facilitaded by comparative analysis of its ^1H and ^{13}C NMR spectra and other products (Tables 1, 2 and 5). A significant difference was only observed in the chemical shifts of the hydrogens [δ_H 3.12 (t,J=7.2 Hz) and carbon [d_C 29.97 (t)] of the CH_2-14 methylene group, along with the additional signals corresponding to the pyridine 2-substituted unit (Table 5). Homonuclear $^1Hx^1H$-COSY and heteronuclear $^1Hx^{13}C$-COSY [$^1J_{CH}$ and $^nJ_{CH}$ (n=2,3)] 2D shift-correlated NMR was also used for the assignment of the chemical shifts of this pyridine unit and other moieties of compound **11** (Table 5). The ^1H {^1H}-NOE difference spectra (Table 6) confirmed this deduction. Furthermore, the molecular peak ($M^{+\cdot}$) at m/z 387 (55%, $C_{22}H_{29}O_3SN$) and the postulated fragments **20**, **21** and **22** corresponding to peaks at m/z 161 (40%), 125 (100%) and 111 (85%), respectively, were also in accordance with the structure **11**.

Experimental

One- (1D) and two-dimensional (2D) ^1H and ^{13}C NMR spectra were recorded in an AC-200 (^1H:200 MHz; ^{13}C: 50.3 MHz) Bruker spectrometer, a superconducting magnet that works with radiofrequency pulse sequences and Fourier transform (FT) methods. The samples were dissolved in $CDCl_3$ (**5, 6, 8 - 16**) or $CDCl_3$ + CD_3COCD_3 (**7**) containing TMS as internal standard and the soluction placed in a tube with 5mm of diameter. The pulse sequences used in the two-dimensional (2D) experiments are contained in the Bruker programs XHCORR-AU, for heteronuclear correlation of hydrogen and carbon-13 through one bond $^1Hx^{13}C$-COSY-$^1J_{CH}$ (D3=0.5/J_{CH} and D4=0.5/2J_{CH}, modulated with $^1J_{CH}$ 140.0 Hz) and long-range coupling $^1Hx^{13}C$-COSY-$^nJ_{CH}$ [D3=0.5/J_{CH} and D4=0.5/$^2J_{CH}$, modulated with $^nJ_{CH}$ 7.0 Hz (n=2, 3)], and COSY-AU, for homonuclear correlation $^1Hx^1H$-COSY. In the one-dimensional (1D) experiments of nuclear Overhauser effect (NOE) by difference spectra and distortionless enhancement by polarization transfer (DEPT) were utilized Bruker NOEDIFF.AU and DEPTVAR.AU (Ø=90°: only CH signals; Ø=135°: CH and CH_3 signals in an apposite plase of the CH_2 signals) programs, respectively.

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