



Sesquiterpene lactone glycosides from *Lapsana communis* L. subsp. *communis*.

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Received in revised form 10 October 1998

Abstract

From the latex of *Lapsana communis* L. subsp. *communis*, five guaianolide glycosides were identified: crepiside E, tectoroside and three new ones: 3-*O*-β-D-glucopyranosyl-8-*O*-β-acetyl-1αH,5αH,6βH,7αH-guai-4(15),10(14),11(13)-triene-6,12-olide, 3-*O*-β-D-glucopyranosyl-8-*O*-β-acetyl-1αH,5αH,6βH,7αH-guai-3(4),10(14), 11(13)-triene-15-methyl-6,12-olide, and 3-*O*-β-glucopyranosyl-8-*O*-β-(4-hydroxyphenyl)-lactyl-1αH,5αH,6βH,7αH-guai-3(4),10(14),11(13)-triene-15-methyl-6,12-olide. Their structures were established by spectroscopic methods. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Lapsana communis* subsp. *communis*; Asteraceae; Lactuceae; Sesquiterpene lactone glycosides; Guaianolides

1. Introduction

In previous studies on the chemical constituents of *Lapsana communis*, only inositol (Plouvier, 1970) and two polyphenols, chlorogenic acid (Bandyukova, Zemtsova, Sergeeva, & Frolova, 1970) and luteolin-7-*O*-glucoside (Bandyukova, Sergeeva, & Dzhumyrko, 1970) were reported. Recently, we isolated triterpene alcohols (in press). In spite of its closely related taxonomic classification to the Crepidinae (Pak, & Bremer, 1995), a sub-tribe rich in sesquiterpene lactones, no investigations have been published about these compounds in *L. communis*. The present paper describes the isolation of two known sesquiterpene lactone glycosides, crepiside E (**2**), tectoroside (**4**), from latex of young stems and the structural determination of three new compounds (**1**, **3** and **5**) named lapsanoside A, lapsanoside B and lapsanoside C, respectively.

2. Results and discussion

The acetone extract of the latex of the stems of *L. communis* subsp. *communis* was fractionated on silica gel

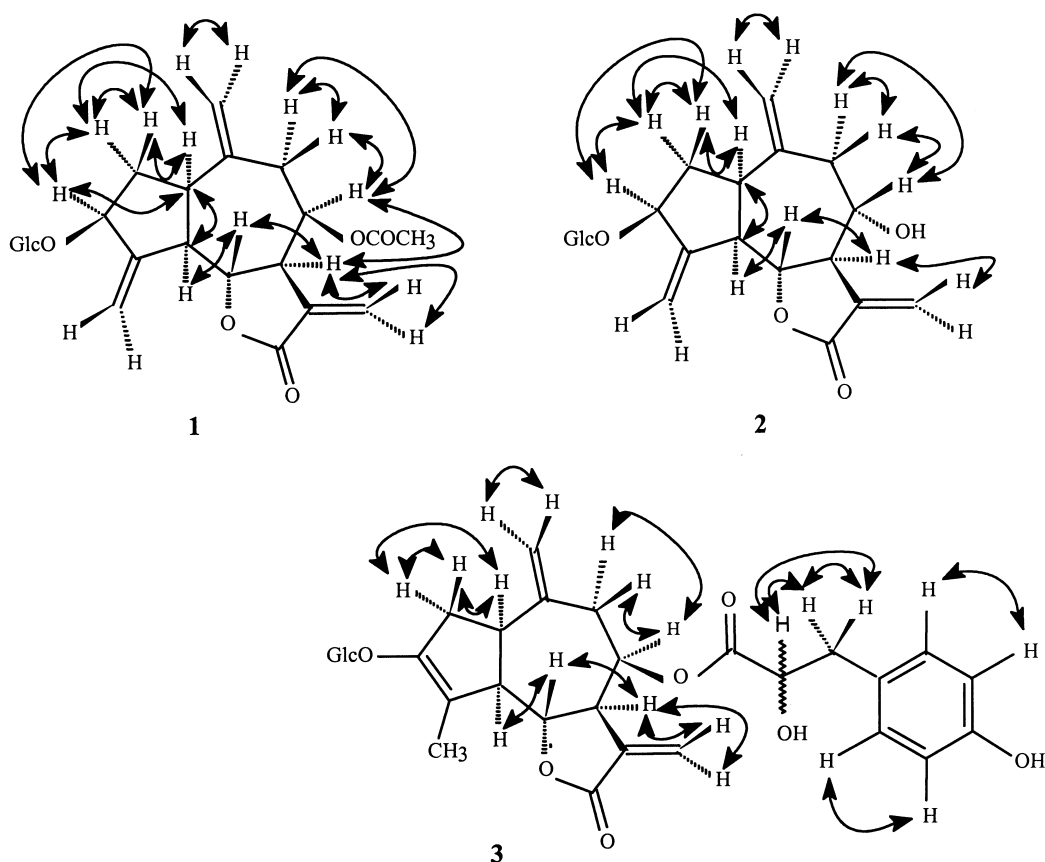
to allow the separation of lipids and sesquiterpene lactone glycosides fractions. No sesquiterpene lactone aglycone was detected in the latex. The sesquiterpene glycosides fraction showed four major spots on reversed-phase-TLC and was subjected to preparative-HPLC giving three guaianolides glycosides and two mixtures of two others.

Compound **1**, which represented the main guaianolide in the latex, was obtained as an amorphous powder. The structure of **1** was elucidated from ¹H NMR, COSY-DQF, NOE, NOESY, HOHAHA, ¹³C NMR and XHCORR. The ¹H NMR spectrum exhibited two doublets at δ 6.11 (1H, *J* = 3.3 Hz) and 5.64 (1H, *J* = 3.0 Hz), which are characteristic of exocyclic α-methylene-γ-lactone. Four other exocyclic methylene protons at δ 5.40, 5.39, 5.14 and 4.90 (each s) were observed. The spectrum also included a signal at δ 5.02 which was assigned to the proton on the carbon bearing an ester group and a three-proton singlet at δ 2.15 which corresponded to an acetate.

In the ¹³C NMR spectrum, 23 signals, including six signals due to a glucopyranosyl moiety, were observed, and the two signals at δ 167.3 and 171 confirmed the presence of a lactonic and ester functions Table 3.

The DQF-COSY spectrum data of **1** showing the coupled protons signals (Figure 1) clearly indicated that the ester group was at C-8 and O-function at C-3. The NOESY spectrum was particularly helpful in the assign-

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ment of the glycosylation site which is attached to C-3. The significant spatial interactions between the protons were confirmed by HOHAHA, in particular H-3 with H-15 and H-15', H-2 and H-2' with H-14 and H-14'.

The relative stereochemistry of compound **1** was investigated on the basis of the coupling constants and decoupling experiments. The large coupling constant of the anomeric δ 4.45 (1H; d, $J=7.8$ Hz) showed that the glucosidic linkage is β . The coupling constants involving H-6 (10.8, 9.0 Hz) with H-5 and H-7 suggested trans-diaxial dispositions of the protons at C-5 (α), C-6 (β) and C-7 (α), a feature common to guaianolide lactones (Sachdev and Kulshreshtha, 1985). In NOE experiments (NOEDIFF), irradiation of the H-7 (δ 3.10) increased the intensity of the H-8 (δ 5.02) signal and irradiation of H-8 had the same effect on H-7, so that the C-8 radical group must be β -oriented. H-1 (δ 3.05) was assigned an α -orientation on the basis of the NOE irradiation of the H-5 at δ 2.77 which enhanced the H-1 signal. The orientation of H-3 was decided to be α by comparison with the chemical shift and coupling constants of 3β -glucosyl type of guaianolides according to the literature (Warashina, Ishino, Miyase, & Ueno, 1990; Kisiel, & Gromek, 1993; Kisiel, & Barszcz, 1995). Therefore, compound **1** is a derivative of 8-epidesacylcynaropicrin glu-

coside (Kisiel, 1984; Nishimura, Miyase, Ueno, Noro, Kuroyanagi, & Fukushima, 1985). These results were corroborated by XHCORR.

In the different mass spectra of compound **1** (CI-MS, EI-MS, FAB⁺-MS), the molecular ion peak was not detected, but in CI-MS mode (with NH_3), a significant peak at m/z 484 $[\text{M} + \text{NH}_4]^+$ (16%) was identified together with other characteristic peaks at m/z 442 $[\text{M} + \text{NH}_4 - \text{COCH}_3]^+$ (8%), 322 (13%), 308 $[322 - \text{H}_2\text{O}]^+$ (23%), 180 $[\text{glucose}]^+$ (62%), 120 (100%).

The results of all these spectral data led us to assign the structure of **1** as 3- O - β -D-glucopyranosyl-8- O - β -acetyl-1 α H,5 α H,6 β H,7 α H-guai-4(15),10(14),11(13)-triene-6,12-olide, named lapsanoside A.

Compound **2**, obtained as an amorphous powder, exhibited CI-MS spectral parameters nearly identical to those of **1**, except loss of one fragment of (COCH_2) suggested by the absence of the ester side chain previously found in **1**. The ^1H NMR spectrum of compound **2** exhibited the H-8 signal, shifted upfield to 3.89 ($\Delta - 1.13$ ppm) suggesting a hydrogen of a secondary alcohol, and two exomethylene proton signals shifted upfield to 6.13 (1H, $J=3.3$ Hz) ($\Delta + 0.02$ ppm) and 6.10 (1H, $J=3.0$ Hz) ($\Delta + 0.44$ ppm). According to previous reports, this data suggested an α orientation of the hydroxyl function at

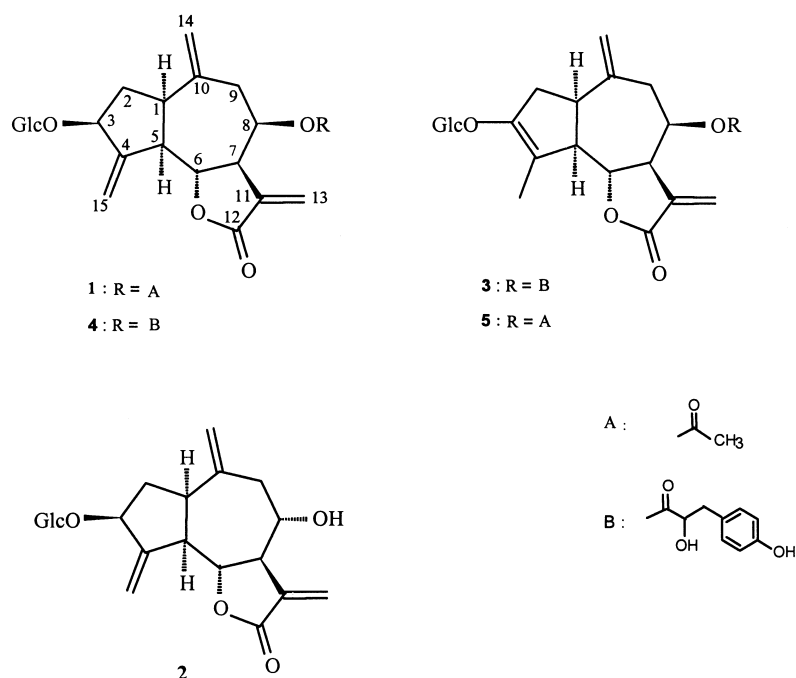


Fig. 1. COSY-DQF correlations of compound **1** and 2-D COSY correlations of compounds **2** and **3**.

C-8 (Miyase, Ueno, Noro, Kuroyanagi, & Fukushima, 1985; Nishimura, Miyase, Ueno, Noro, Kuroyanagi, & Fukushima, 1986).

Spatial correlations and the relative stereochemistry were deduced by spin decoupling experiment and then confirmed by 2-D COSY (Figure 2) and by HOHAHA. The ^{13}C NMR spectrum data Table 3 and DEPT spectral editing confirmed that the compound **2** was crepidate E which has been previously reported (Miyase et al., 1985).

Compound **3** was isolated as an amorphous powder. Its structure was deduced from ^1H NMR (in acetone- d_6 and methanol- d_4) (Table 1), 2-D COSY, ^{13}C NMR Table 3 and CI-MS. The ^1H NMR spectrum of **3** (in methanol- d_4) showed four signals of the *exo*-methylene protons: two doublets at δ 5.97 (2H, d, $J=3.3$ Hz) and 5.36 (2H, d, $J=3.0$ Hz) of exocyclic α -methylene- γ -lactone and two singlets at δ 5.15 (1H, s) and 4.90 (1H, s). The spectrum also exhibited one vinyl methyl signal at δ 1.62 (3H, s). The proton multiplet at δ 4.96 with the strong correlations observed in 2-D-COSY experiment between three proton spin system: δ 4.34 (dd $J=6.8$, 6.6 Hz), δ 3.00 (AB sys.), δ 2.90 (AB sys.) and an AA'BB' system at δ 7.07 and 6.69, indicated the presence of a 8-(4-hydroxyphenyl) lactic ester. This data was corroborated by the mass spectral peaks at m/z 107 $[\text{CH}_2=\text{C}_6\text{H}_4=\text{OH}]^+$ (52%) and 137 $[\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CH}=\text{OH}]^+$. These two peaks have been observed previously in tectoroside (Kisiel, & Kohlmünzer, 1989). 2-D COSY also showed other correlations reported in Fig. 1.

The ^{13}C NMR displayed 12 ethylenic carbons including six aromatic carbons. Knowing that the ^1H NMR spectrum presented only four ethylenic protons, the two olefinic carbon signals at δ 113.8 and 150.7 were assigned to intracyclic carbon. The principal other difference between ^{13}C NMR spectra of **1** and **3** was the presence of the vinylic methyl C-15 (δ 11.1) in **3**.

The coupling constants involving H-6 (9.8, 9.0 Hz) with H-5 and H-7 suggested trans-diaxial dispositions of the protons at C-5 (α), C-6 (β) and C-7 (α). The β linkage of the glucose moiety was deduced from the large coupling constant of the anomeric proton signal. The stereochemistry of the ester side chain at C-8 was concluded to be β from the ^1H NMR spectrum H-13' (δ 5.36) which was shifted upfield by 0.74 ppm compared with that of crepidate E (**2**) and in one earlier report (Miyase et al., 1985).

From these findings, the structure of compound **3** was determined to be 3-*O*- β -glucopyranosyl-8-*O*- β -(4-hydroxyphenyl)-lactyl-1 α H,5 α H,6 β H,7 α H-guai-3(4), 10(14), 11(13)-triene-15-methyl-6,12-olide named lapsanoid B.

The mixture of compounds **4** and **1** (ca. 1:1) was not separated further and the mixture of **5** and **1** (ca. 1:4) also. However, the NMR signals were assigned to the respective compounds by a careful analysis of the integrals, NOESY, HOHAHA, ^{13}C NMR for **4** and the integrals, 2-D COSY, DEPT, ^{13}C XHCORR for **5** (Table 2). The sugar moiety in each glycoside was identified as β -glucopyranoside. The NMR spectral data of **4** were

Table 1
¹H NMR spectral data of compounds 1–3

H	1 (CD ₃ OD)	2 (CD ₃ OD)	3 (CD ₃ OD)	3 (acetone- <i>d</i> ₆)
<i>Aglycone moiety</i>				
1	3.05 br q (9.1)	3.05 br q (8.4)	3.10 m*	overlapped
2	2.29 m	2.32 m	2.40 m	overlapped
2'	1.90 m	1.93 m	2.65–2.75 m*	overlapped
3	4.67 br t (4.8)	4.67 br t (5.8)		
5	2.77 m*	2.65–2.75 m*	2.65–2.75 m*	overlapped
6	4.53 dd (10.8, 9.0)	4.34 dd (10.1, 9.9)	4.20 dd (9.8, 9.0)	4.24 dd (10.3, 9.0)
7	3.10 m	2.65–2.75 m*	3.13 m	3.10 m*
8	5.02 m	3.89 m*	4.96 m*	5.04 dt (5.0, 5.3)
9	2.74 dd (14.8, 4.4)	2.65–2.75 m*	2.65–2.75 m*	overlapped
9'	2.34 dd (13.8, 2.5)	2.20 dd (16.6, 2.9)	2.19 dd (13.9, 4.8)	2.61 dd (13.0, 2.7)
13	6.11 d (3.3)	6.13 d (3.3)	5.97 d (3.3)	5.97 d (3.3)
13'	5.64 d (3.0)	6.10 d (3.0)	5.36 d (3.0)	5.51 d (2.9)
14	5.14 s	5.11 s	5.15 s	5.19 s
14'	4.90 s	4.90 s	4.90 s	4.94 s
15	5.40 s	5.40 br s	1.62 s	1.73 s
15'	5.39 s			
<i>Glucose moiety</i>				
1	4.45 d (7.8)	4.46 d (6.7)	4.57 d (7.4)	4.73 d (7.2)
2	3.15–3.35 m*	3.15–3.35 m*	3.15–3.35 m*	3.20–3.40 m*
3	3.15–3.35 m*	3.15–3.35 m*	3.15–3.35 m*	3.20–3.40 m*
4	3.15–3.35 m*	3.15–3.35 m*	3.15–3.35 m*	3.20–3.40 m*
5	3.15–3.35 m*	3.15–3.35 m*	3.15–3.35 m*	3.20–3.40 m*
6	3.86 d (11.7)	3.87 d (11.8)	3.85 d (12.2)	3.83 d (11.1)
6'	3.67 dd (11.9, 4.9)	3.67 dd (10.5, 5.4)	3.67 dd (11.8, 4.8)	3.69 m
<i>Ester moiety</i>				
OAce	2.15 br s			
β			4.34 dd (6.8, 6.6)	4.36 m
γ			3.00 AB sys	overlapped
γ'			2.90 AB sys	overlapped
2, 6			7.07 d (8.4)	7.15 d (8.4)
3, 5			6.69 d (8.4)	6.79 d (8.4)

Run at 400.0 MHz in methanol-*d*₄ or at 200.0 MHz in acetone-*d*₆.

J values (parentheses) in Hz, δ in ppm.

* Partially overlapped by other signals, therefore, couplings could not be accurately determined.

nearly identical to compounds **1** except that a hydroxyphenyl lactic ester replaced the acetate ester and those of **5** looked very similar to **3** except for acetic residue instead of hydroxyphenyl lactic ester.

These results led us to conclude that compound **4** was tectoroside (Kisiel, & Kohlmünzer, 1989) and compound **5** was 3-*O*-β-D-glucopyranosyl-8-*O*-β-acetyl-1αH,5αH,6βH,7αH-guai-3(4),10(14),11(13)-triene-15-methyl-6,12-olide. To the best of our knowledge, **5** has not been previously detected and thus was named lapsanoside C.

The cytotoxic activities of Compounds **1**–**3** were evaluated against L-1210 cancer cell lines. At the maximal dose tested (5 μg ml⁻¹) these compounds presented no cytotoxic activity. Our results confirmed the low cyto-

toxicity of the glycosides of sesquiterpene lactones (Seto, Miyase, Umehara, Ueno, Hirano, & Otani, 1988).

Our investigations showed that the latex of *L. communis* contains guaianolide glucosides as most of the Lactuceae. Within the subtribe Crepidinae, the isolation of crepiside E and tectoroside from *L. communis* suggests a close relationship with Crepis (Miyase et al., 1985; Kisiel, & Kohlmünzer, 1989). The structure of lapsanoside A, the major guaianolide in the latex, showed a new example of an esterified 8-epiacycynaropicrin-glucoside. Previously, numerous other ester derivatives of this type of guaianolide glucosides had been reported in several genera of the Asteraceae (Crepis, Ixeris, ...) (Miyase et al., 1985; Warashina, Ishino, Miyase, & Ueno, 1990;

Table 2
¹H NMR spectral data of compounds **4–5**

H	4 (CD ₃ OD)	5 (acetone- <i>d</i> ₆)
<i>Aglycone moiety</i>		
6	4.52 dd (10.8, 9.0)	4.25 m*
8	5.02 m	5.04 m
13	5.93 d (3.4)	6.09 d (3.4)
13'	5.24 d (3.0)	5.75 d (3.0)
14	5.11 d (1.4)	5.19 s
14'	4.83*	4.95 s
15	5.40 s	1.73 s
15'	5.38 s	
<i>Glucose moiety</i>		
1	4.44 d (7.8)	4.73 d (7.7)
2	3.15–3.35 m*	3.20–3.40 m*
3	3.15–3.35 m*	3.20–3.40 m*
4	3.15–3.35 m*	3.20–3.40 m*
5	3.15–3.35 m*	3.20–3.40 m*
6	3.86 d (11.7)	3.86 m*
6'	3.67 dd (11.9, 4.9)	3.67 m*
<i>Ester moiety</i>		
OAc		2.12 s
β	4.34 dd (6.9, 6.5)	
γ	3.01 AB sys	
γ'	2.92 AB sys	
2, 6	7.07 d (8.5)	
3, 5	6.69 d (8.5)	

Run at 400.0 MHz in methanol-*d*₄ or at 200.0 MHz in acetone-*d*₆.

J values (parentheses) in Hz, δ in ppm.

*Partially overlapped by other signals, therefore, couplings could not be accurately determined.

Kisiel, & Barszcz, 1995). Compound **5** is the 8-acetyl ester of crepiside C which was identified in *Ixeris* (Miyase et al., 1985).

3. Experimental

3.1. General procedure

Merck G-60 silica gel was used for CC and Merck Reversed-Phase silica gel for TLC. Semiprep. HPLC was performed on a Gilson apparatus (811B+805+2 pumps 305) (Spherisorb C₁₈ cartridge column (5 μm, 250 × 11.5 mm)) coupled to a UV detector Jasco UV 875. ¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively in methanol-*d*₄ and at 200 MHz in acetone-*d*₆. CI-MS were performed on a Vacum Generator (V.G) TRIO 2 mass spectrometer, 70 eV.

3.2. Plant material

Latex of *L. communis* L. subspecies *communis* was collected in June 1996 from plants just before flowering stage, at Notre Dame d'Oé (Indre et Loire, France), which were dried at 25°C. Voucher specimens are deposited in the Laboratory of Pharmacognosy, University of Tours, France.

3.3. Extraction and isolation of compounds

Dried latex (670 mg) was exhaustively extracted with acetone at room temp. by shaking. After removal of the solvent, the residue (372 mg) was chromatographed on a silica gel column, packed in ether using an ether–acetone gradient solvent system, all fractions having been monitored by TLC. Fractions from ether–acetone (5:5 to 2:8) were evaporated under vacuum and chromatographed on semi-prep. HPLC H₂O–MeOH (50:50) to give **1** (10 mg), **2** (6 mg), **3** (5 mg) and the mixtures of **4**+**1** (12 mg) and **5**+**1** (20 mg).

3.4. Lapsanoside A (**1**)

Large needles (from MeOH–H₂O). CI-MS *m/z* (rel. int. %) 484 [M+NH₄]⁺ (16), 442 [M+NH₄–COCH₃]⁺ (8), 391 (7), 322 (13), 308 [322–H₂O]⁺ (23), 279 (46), 227 [C₁₅H₁₅O₂]⁺ (80), 217 (37), 180 [glucose]⁺ (62), 120 (100). ¹H and ¹³C NMR: Tabs. 1 and 3.

3.5. Crepiside E (**2**)

Amorphous powder. CI-MS *m/z* (rel. int. %) 442 [M+NH₄]⁺ (9), 391 (5), 322 (3), 308 [322–H₂O]⁺ (6), 279 (15), 217 (46), 214 (67), 180 [glucose]⁺ (71), 134 (71), 69 (100). ¹H and ¹³C NMR: Table 1 and Table 3.

3.6. Lapsanoside B (**3**)

3.6.1. Amorphous powder

CI-MS *m/z* (rel. int. %) 419 (0.2), 391 (1), 363 (0.5), 322 (0.3), 296 (2), 279 (20), 217 (100), 180 [glucose]⁺ (21), 137 [HO–C₆H₄–CH₂–CH=OH]⁺ (5), 107 [CH₂=C₆H₄–OH]⁺ (52), 69 (61). ¹H and ¹³C NMR: Tabs. 1 and 3.

3.7. Cytotoxicity

The cytotoxic activity of each sesquiterpene lactone glucoside was evaluated against Lymphoid Leukemia L1210 by the method describe in (Kline, & Platonova, 1980), and measured with Coulter Counter ZM apparatus (Coultronic).

Table 3
¹³C NMR spectral data of compounds 1–5.

C	1 (CD ₃ OD)	2 (CD ₃ OD)	3 (CD ₃ OD)	4 (CD ₃ OD)	5 (acetone- <i>d</i> ₆)
1	46.5	46.5	46.2 ^a	46.6 ^a	45.5
2	35.9	37.8	34.7	36.1 ^b	34.7
3	79.7	79.9 ^a	150.7	79.2 ^c	151.0
4	148.8	149.1	113.8	148.7	115.1
5	52.8	52.9	54.5	53.2	54.6
6	78.3	79.1 ^a	81.9	78.5 ^c	81.5
7	46.7	50.5	46.8 ^a	46.7 ^a	49.5
8	74.2	72.0	73.1	74.2 ^d	74.4 ^a
9	37.4	40.9	39.6 ^b	37.7 ^b	38.8
10	143.3	143.8	143.3	143.0	143.2
11	139.0	140.2	137.8	138.5	138.1
12	167.3	n.d.	170.5	170.0	167.1
13	120.9	121.4	122.2	121.4	121.5
14	117.2	116.3	117.2	117.5	117.2
15	115.3	114.8	11.1	115.3	11.7
<i>Glucose moiety</i>					
1	100.6	101.0	100.6	100.6	101.3
2	74.4	74.2	75.3	75.0 ^d	74.5 ^a
3	76.9	76.9	77.0 ^c	76.9	77.3 ^b
4	70.8	70.8	70.5	70.8	71.2
5	77.2	77.2	77.1 ^c	77.2	77.7 ^b
6	61.8	61.8	61.6	61.8	62.5
<i>Ester side chain moiety</i>					
1	171.0				169.7
2	19.9				20.9
1			127.7	127.9	
2, 6			130.5	130.6	
3, 5			115.1	115.3	
4			156.4	156.5	
α			173.2	173.4	
β			73.9	73.1 ^d	
γ			39.9 ^b	39.6	

Run at 100.0 MHz in methanol-*d*₄ and at 50.3 MHz in acetone-*d*₆.

^{a–d} Assignments may be interchanged in each column.

n.d. means not detected.

Acknowledgements

The authors wish to thank Dr. B. Brasme (Centre de Recherche de Santé des Armées, La Tronche, France) and A. Croisy (INSERM, U 350, Orsay, France) who provided technical assistance.

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