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THREE PHENYLPROPANOIDS FROM *JUNIPERUS PHŒNICEA*

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Key Word Index—*Juniperus phœnicea*; Cupressaceae; phenylpropane glucoside derivatives; junipediol A; junipediol A 8-glucoside; junipediol B 8-glucoside; 2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol; 1-β-D-glucosyloxy-2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol; 1-β-D-glucosyloxy-2-(3,4-methylenedioxyphenyl)-propane-1,3-diol.

Abstract—Three new compounds, junipediol A [2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol], junipediol A 8-glucoside [1-β-D-glucosyloxy-2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol] and junipediol B 8-glucoside [1-β-D-glucosyloxy-2-(3,4-methylenedioxyphenyl)-propane-1,3-diol], have been isolated from acetone and methanolic extracts of the aerial parts of *Juniperus phœnicea*. The structural elucidation of these new natural products was achieved mainly by UV, mass and ^1H and ^{13}C NMR spectroscopy. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

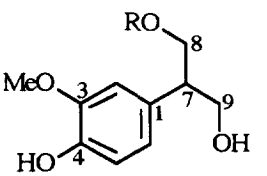
Previous phytochemical studies on *Juniperus phœnicea* showed that this plant accumulates terpenoids, particularly monoterpenes [1], sesquiterpenes [2] and diterpenes [3–5]. Only a few phenolics have been described in this plant. They were biflavones [6, 7] and lignans [5, 8]. We have reported on the presence in this plant of three phenylpropane glycosides, juniperoside, rosarin and skimmin [9], and two furanone glucosides derivatives, psydrin and phœnicein [10]. More recently, we have demonstrated the presence of phœniceroside, a pseudo-dimer of the two previously cited furanones [11].

In this paper, we report on the isolation and structural elucidation of three new phenylpropanoids. These compounds were isolated from acetone and methanolic extracts of *J. phœnicea*.

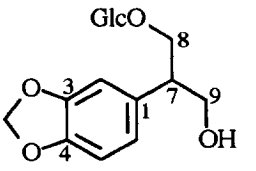
RESULTS AND DISCUSSION

The molecular formulae $C_{10}H_{14}O_4$, $C_{16}H_{24}O_9$ and $C_{16}H_{22}O_9$ for **1**–**3**, respectively, were deduced from DCI and FAB mass spectrometry and ^1H and ^{13}C NMR.

The NMR data for **1** revealed the presence of an aromatic ring and a propane chain. The DCI mass spectrum showed quasimolecular ion peaks at *m/z* 216



1 R = H
2 R = Glc



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$[M + NH_4]^+$ and 198 $[M + NH_4 - H_2O]^+$ in accordance with a phenylpropane aglycone. In the aromatic part of the ^1H NMR spectrum, the signals at δ 6.82 (*br s*, H-2), 6.74 (*d*, $J = 8.1$ Hz; H-5) and 6.68 (*d*, $J = 8.1$ Hz; H-6) defined a 1,3,4-trisubstituted aromatic ring. This was confirmed in the ^{13}C NMR spectrum by three methine peaks at δ 113.1 (C-2), 116.1 (C-5) and 121.7 (C-6) and three quaternary aromatic carbons at δ 133.6 (C-1), 148.9 (C-3) and 146.3 (C-4). The propane chain was defined in the ^1H NMR spectrum by a multiplet signal at δ 2.85 (H-7) and two double doublets (each representing two protons) at δ 3.73 (H-8_A and H-9_A) and 3.82 (H-8_B and H-9_B). This aliphatic part was confirmed in the ^{13}C NMR spectrum by a methine carbon signal at δ 51.6 (C-7) and a methylene peak at δ 65.1 corresponding to two carbons (C-8 and C-9). The overlapped signals H-8 and H-9 in the ^1H NMR spectrum together with those of C-8 and C-9 in the ^{13}C NMR spectrum indicated the identity of the electronic environment for these positions. Moreover, ^3J cross peaks noted during the

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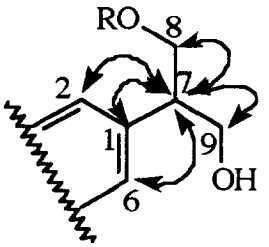

Fig. 1. Selected HMBC correlations observed for compounds **1–3**.

HMBC experiment between the signals at δ 3.73 (H-8_A and H-9_A) and 3.82 (H-8_B and H-9_B) on one hand, and the carbon at δ 65.1 (C-8 and C-9) on the other demonstrated the isopropane chain. The HMBC cross peaks noted for H-7 and/or C-7 and the other surrounding positions (Fig. 1) showed the link between the propane chain and the aromatic ring. The remaining singlet at δ 3.84 (H-10) in the ^{1}H spectrum and δ 56.4 (C-10) in the ^{13}C spectrum indicated the presence of a methoxyl group which was confirmed by an HMBC cross peak between the H-10 protons and the quaternary aromatic carbon at δ 148.9 (C-3). Finally, the chemical shift of the residual quaternary carbon at δ 146.3 (C-4) indicated a hydroxyl group. Moreover, the relative position of the methoxyl group and the hydroxyl one was confirmed by a 1D NOE difference experiment showing a correlation between the H-10 and the H-2 protons. Thus, **1** was identified as 2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol and named junipediol A.

Compounds **2** and **3** are analogous to **1** (quite similar NMR and UV data and gave an identical mustard colour when pulverized with sulphuric vanillin), but their more polar chromatographic behaviours indicated glycosylated compounds. The FAB mass spectra of **2** and **3** showed quasimolecular ion peaks at *m/z* 359 $[M - H]^-$ and 361 $[M + H]^+$ for **2** and *m/z* 357 $[M - H]^-$ and 359 $[M + H]^+$ for **3**. In both cases, the loss of a glucosyl unit was confirmed by the respective ions in the DCI mass spectra at *m/z* 181 $[M - OGlc + H]^+$ for **2** and at *m/z* 179 $[M - OGlc + H]^+$ for **3**. The presence in the DCI mass spectra of both acetylated derivatives (**2a** and **3a**) of ions at *m/z* 331, corresponding to an acetylated glucosyl moiety, was confirmed in their respective ^{1}H and ^{13}C NMR spectra (Tables 1 and 2). Moreover, the ^{1}H and ^{13}C NMR data for both natural products showed the presence of a glucosyl moiety in the β-pyranose form (Tables 1 and 2) [12, 13]. Furthermore, the glucosyl units were also identified after acid hydrolysis of **2** and **3**. The linkage between the sugar residue and the aglycone part was in both cases deduced from an HMBC experiment. ^3J correlations were observed between the anomeric osidic protons δ 4.30 and the aliphatic carbons at δ 72.4 for **2** and δ 72.0 for **3** (C-8). The 500 MHz ^{1}H spectra for **2** and **3** (Table 2) showed, over the corresponding glucosyl signals, a 1,3,4-trisubstituted aromatic ring and an aliphatic isopropane chain as defined for **1** (Table 2). This skeleton was confirmed by the respective ^{13}C NMR spectra (Table 1). The linkages between the propane chains and their respective aromatic rings were established unambiguously by HMBC experiments. The HMBC correlation patterns observed in both cases for **2** and **3** for H-7 (Fig. 1) showed the central position of this atom and demonstrated the link between C-1 and C-7. In the NMR spectra of **3**, the signals at δ 5.87 (H-10) in the ^{1}H spectrum and δ 102.0 (C-10) in the ^{13}C spectrum indicated the presence of a methylenedioxy group. As for **1**, a methoxyl group and a hydroxyl group could be defined in **2**. Moreover, the NMR and mass spectral data for acetylated compounds **2a** and **3a** showed the presence of six acetyl groups for **2a** and only five for **3a**. This was due to the presence of a supplementary acetylatable site located on the position 4 of the aromatic ring in the case of **2** (Tables 1 and 2). Thus, **2** was identified as 1-β-D-glucosyloxy-2-(3-methoxy-4-hydroxyphenyl)-propane-1,3-diol and **3** as 1-β-D-glucosyloxy-2-(3,4-methylenedioxyphenyl)-propane-1,3-diol. The compounds were named junipediol A 8-glucoside and junipediol B 8-glucoside, respectively. Double signals noted for **3** and **3a** indicated the presence of an asymmetric centre. The central carbon of the isopropane chain (C-7) can be considered as a chiral carbon when glucosylation occurs at position 8. In the case of **2**, even though the signals are broad compared to those of **1**, it was impossible to differentiate between the stereomers. This differentiation of the isomers in **3** and **3a** was certainly due to the supplementary methylenedioxy cycle giving a rigidity to the structure.

These three new compounds are very interesting from several points of view. First, the very original skeleton of these phenylpropanoids might be related to that of tropic acid, a part of some tropane alkaloids, atropine and scopolamine. Secondly, another phenylisopropanediol corresponding to the aglycone of **3** has been isolated from the leaves of *J. chinensis* [14]. Even if the skeleton is not exclusively linked to *Juniperus* species because of the tropic acid moiety existing in many tropane alkaloid-producing plants, the degree of oxidation of the propane chain under alcohol functions seems at this date to be characteristic of the *Juniperus* genus.

The biosynthetic pathway of tropic acid has recently been elucidated [15, 16] and involves a 1,2-migration of the terminal carbonyl of the usual phenylpropanoid structure in order to obtain a ramified chain. The question can now be asked if such a migration is possible in the case of a terminal CH_2OH group, or if reduction occurs consecutively with the migration of a COOH group?

EXPERIMENTAL

Plant material. Juniperus phœnicea L. was collected near Roquemaure in Vaucluse (France). A voucher specimen is deposited at our laboratory (no. 103).

Table 1. ^{13}C NMR data for compounds **1–3** (CD_3OD) and **2a** and **3a** ($CDCl_3$) at 125 MHz

C	1	2	3	2a	3a
Aglycone					
1	133.6	133.6	135.9	137.6	132.7*
2	113.1	113.3	109.7	112.5	108.3
3	148.9	148.9	147.7	151.0	146.6
4	146.3	146.3	149.0	138.9	147.7
5	116.1	116.1	109.0	120.1	108.4
6	121.7	121.8	122.5	122.7	121.3
7	51.6	49.8	49.9	44.3	44.3*
8	65.1	72.4	72.0*	70.4	70.5*
9	65.1	65.0	64.9*	64.5	64.9*
10	56.4	56.5	102.0	55.9	100.9
Glucosyl					
1′		104.8	104.6*	100.7	100.9
2′		75.1	75.1	71.1	71.1*
3′		78.2	78.1	72.7	72.7*
4′		71.7	71.7	68.4	68.4
5′		78.0	78.0	71.9	71.8
6′		62.8	62.8	61.9	61.9*
AcO				20.5–20.8	20.4–20.8
				169.0–170.8	169.2–170.8
				(6 AcO)	(5 AcO)

*Double signals.

General. TLC: precoated silica gel 60F-254 aluminium sheets (Merck); analyti. HPLC: Novapak C18 cartridge (4 μm, 8 × 100 mm) and UV detection; prep. HPLC; Nagel polyamide SC-6; semi-prep. HPLC: Lichroprep DIOL (25–40 μm) and Lichroprep RP18 (15–25 and 25–40 μm). Chromatographic mobilities were recorded in 5 systems: system 1 (silica gel F-254, EtOAc–HCO_2OH–HOAc–H_2O, 20:1:1:2), system 2 [cellulose F-254, *n*-BuOH–HOAc–H_2O, 4:1:5 (upper phase)], system 3 (polyamide, toluene–MeOH, 4:1), system 4 [Waters radial Novapak C18 (4 μm, 8 × 100 mm), H_2O–MeOH (5–50% MeOH in 45 min), 1 ml. min^{-1}]. NMR: 500 MHz for ^1H and 125 MHz for ^{13}C. The solvent signal was used as ref. (δ 3.32 and 49.0 ppm for CD_3OD; δ 7.27 and 77.0 ppm for $CDCl_3$). Complete proton and carbon assignments were based on 1D (^1H standard and ^{13}C *J* mod, 2D ^1H–^1H COSY, ^1H–^{13}C HMQC and ^1H–^{13}C HMBC NMR experi-

Table 2. ^1H NMR data for compounds **1–3** (CD_3OD) and **2a** and **3a** ($CDCl_3$) at 500 MHz

H	1	2	3	2a	3a
Aglycone					
2	6.82 *br s*	6.88 *d* (1.1)	6.85 *s*	6.81 *d* (1.9)	6.72 *d* (1.8)*
5	6.74 *d* (8.1)	6.72 *d* (8.1)	6.72 *d* (8)	6.95 *d* (8.1)	6.75 *d* (8)*
6	6.68 *d* (8.1)	6.70 *dd* (8.1, 1.1)	6.75 *d* (8)	6.78 *dd* (8.1, 1.9)	6.66 *dd* (8, 1.8)*
7	2.85 *m*	2.99 *m*	3.18 *m*	3.23 *m*	3.16 *m**
8	3.73 *dd* (10.8, 6.5)	3.80 *dd* (9.9, 7.4)	3.80 *m**	3.67 *dd* (9.8, 7.4)	3.64 *m**
	3.82 *dd* (10.8, 6.9)	4.10 *dd* (9.9, 5.6)	4.05 *dd* (9.9, 5.7)	4.11 *dd* (9.8, 4.8)	4.10 *m*
9	3.73 *dd* (10.8, 6.5)	3.76 *dd* (11, 6.1)	3.75 *m*	4.32 *dd* (11.1, 5.9)	*ca* 4.23 *m* (2H)*
	3.82 *dd* (10.8, 6.9)	3.88 *dd* (11, 6.5)	3.85 *m*	4.36 *dd* (11.1, 7)	
10	3.84 *s*	3.84 *s*	5.87 *s*	3.83 *s*	5.95 *s*
Glucosyl					
1′		4.30 *d* (7.8)	4.30 *d* (7.8)*	4.49 *d* (8)	4.47 *d* (8)*
2′		3.18 *dd* (9.1, 7.8)	3.19 *m*	5.00 *dd* (9.7, 8)	5.00 *dd* (9.7, 8)*
3′		*ca* 3.35 *m*	3.34 *m*	5.18 *t* (9.7)	5.18 *t* (9.7)*
4′		3.27 *m*	3.28 *m*	5.08 *t* (9.7)	5.08 *t* (9.7)*
5′		3.26 *m*	3.26 *m*	3.69 *m*	3.68 *m*
6′		3.65 *dd* (11.8, 5.2)	3.66 *m*	4.14 *dd* (12.3, 2.4)	4.13 *m*
		3.85 *dd* (11.8, 1.6)	3.86 *m*	4.25 *dd* (12.3, 4.7)	4.27 *m*
AcO				1.97–2.08 *s* (5 × 3H)	1.93–2.09 *s* (5 × 3H)*
				2.30 *s* (3H)	

*Double signals.

ments. FAB- and DCI-MS were recorded with a Nermag Sidar V 3.1, spectrometer. Acid hydrolysis was in 2 N HCl under reflux. Glucose was identified by TLC on silica gel (EtOAc–H_2O–MeOH–HOAc 13:3:3:4) with detection with *p*-anisidine phthalate reagent [17].

Acetylation of compounds **2** *and* **3**. The compound (2mg) was dissolved in pyridine–Ac_2O (0.5 ml:2 ml) and the mixt. left for 48 hr in the dark. It was then poured on to iced water, and the aq. mixt. extracted (×3) with 10 ml. The combined C_6H_6 phases were washed (×3) with 10 ml portions of H_2O and then dried over Nu_2CO_3. Compounds **2a** and **3a** were purified by HPLC (250–4 Merk Lichrosorb silica gel 60 7 μm column eluted with hexane–*iso*-PrOH 9:1) leading to 3 mg of each derivative.

Extraction and isolation. Air-dried leaves of *J. phœnicea* (637 g) were successively extracted at room temp. with petrol (53.5 g), $CHCl_3$ (45 g), EtOAc (11 g), Me_2CO (52 g) and MeOH (130 g). The Me_2CO extract was solubilized in 300 ml H_2O and then extracted (×3) with 100 ml portions of EtOAc and *n*-BuOH. After concn, the BuOH and EtOAc residues weighed 30 g and 10 g, respectively. The aq. residual phase (12 g) was added to 90 g polyamide MN SC-6 in a batchwise manner, and then eluted (×5) with 400 ml portions of MeOH. After the analysis of the 5 frs by TLC (silica gel; EtOAc–H_2O–HOAc-HCO_2H, 20:2:1:1) and HPLC (Nova-pak C18 4 μm, 8 × 100 mm; MeOH–H_2O, 5–80% MeOH in 50 min), the residues of the 3 first extracts were combined (11 g) and submitted to prep. HPLC (Merck 200 × 40 mm Prep Septech column using Lichroprep 100 RP18 15–25 μm as stationary phase with an aq. MeOH stepped gradient). Ten frs were obtained: A, B and C (5% MeOH), D and E (10% MeOH), F and G (20% MeOH), H and I (40% MeOH) and J (100% MeOH). The chromatography was monitored by UV detection at 254 nm. Fr. F (530 mg) was kept for further investigations and submitted to a prep. MPLC fractionation (460 × 15 mm column using Macherey-Nagel MNSC-6 polyamide 7 μm as stationary phase with a MeOH stepped gradient into toluene). The fr. eluted with 20% MeOH contained **3** as the major compound. Final purification was carried out by MPLC (Merck Lichroprep DIOL column, 15–25 μm, 15 × 460 mm, hexane–MeOH–*iso*-PrOH, 18:5:2) affording 14 mg pure **3**.

The MeOH extract was submitted to liquid–liquid fractionation as for the Me_2CO one, leading to 50 g of BuOH extract and 10 g of EtOAc extract. The aq. residual phase (70 g) was then fractionated by CC (900 × 90 mm column using Macherey-Nagel polyamide MN SC-6 as stationary phase with an aq. MeOH stepped gradient). Six frs. were obtained: A (100% H_2O), B (10% MeOH), C (20% MeOH), D (40% MeOH), E (60% MeOH) and F (100% MeOH). The chromatography was screened by TLC (silica gel; EtOAc–H_2O–HOAc–HCO_2H, 20:2:1:1). Fr. A (50 g) was kept for further investigation; it was submitted to prep. HPLC fractionation (Merck 200 × 40 mm Prep Septech column using Lichroprep 100 RP18 15–25 μm as stationary phase with an aq. MeOH stepped gradient). Six frs were obtained: A1 and A2 (0% MeOH), A3 (10% MeOH), A4 (20% MeOH), A5 (50% MeOH) and A6 (80% MeOH). The chromatography was monitored by UV detection at 254 nm. Fr. A3 (1.5 g) was fractionated on a 570 × 25 mm column using Sephadex LH-20 eluted with MeOH. The resulting most important fr. (900 mg) was fractionated by MPLC (Merck Lichroprep DIOL column, 15–25 μm, 15 × 460 mm, hexane–MeOH–*iso*–PrOH, 18:5:2–27:20:3). Compound **1** was present in the fr. eluted with hexane–MeOH–*iso*–PrOH (18:5:2) and purified by MPLC (230 × 15 mm on Merck Lichroprep 100 RP18, 25–40 μm), 100% H_2O affording 6 mg pure **1**. Compound **2** was present in the fr. eluted with hexane–MeOH–*iso*-PrOH (27:20:3) and was purified by two fractionations by MPLC (230 × 15 mm on Merck Lichroprep 100 RP18 25–40 μm), 100% H_2O affording 23 mg pure **2**.

2-(3-*Methoxy*-4-*hydroxyphenyl*)-*propane*-1,3-*diol* (**1**). UV λ_{max}^{MeOH} nm: 227, 277; DCI MS (NH_3 + isobutane): *m/z* 216 $[M + NH_4]^+$ (100), 198 $[M + NH_4 - H_2O]^+$ (11). Chromatographic behaviour: R_f 0.64 (system 1); R_f 0.66 (system 2); R_f 0.37 (system 3); R_t 10 min (system 4).

1-β-D-*Glucosyloxy*-2-(3-*methoxy*-4-*hydroxyphenyl*-*propane*-1,3-*diol* (**2**). UV λ_{max}^{MeOH} nm: 227, 277; DCI + MS (NH_3 + isobutane): *m/z* 378 $[M + NH_4]^+$ (100), 361 $[M + H]^+$ (12), 360 $[M + NH_4 - H_2O]^+$ (7), 181 $[M - OGlc + H]^+$ (15). FAB MS (glycerol + NaCl): *m/z* 383 $[M + Na]^+$ (100), 361 $[M + H]^+$ (6); FAB MS (glycerol + NaCl): *m/z* 395 $[M + Cl]^-$ (24), 359 $[M - H]^-$ (100). Chromatographic behaviour: R_f 0.36 (system 1); R_f 0.16 (system 2); R_f 0.23 (system 3); R_t 7 min (system 4).

1-β-D-*Glucosyloxy*-2-(3,4-*methylenedioxyphenyl*)-*propane*-1,3-*diol* (**3**). UV λ_{max}^{MeOH} nm: 232, 284. DCI MS (NH_3 + isobutane): *m/z* 376 $[M + NH_4]^+$ (27), 359 $[M + H]^+$ (7), 179 $[M - OGlc + H]^+$ (100), 148 $[M - OGlc - CH_2OH + H]^+$ (26). FAB MS (glycerol + NaCl): *m/z* 381 $[M + Na]^+$ (62), 359 $[M + H]^+$ (31); FAB MS (glycerol + NaCl): *m/z* 393 $[M + Cl]^-$ (77), 357 $[M - H]^-$ (61). Chromatographic behaviour: R_f 0.43 (system 1); R_f 0.38 (system 2); R_f 0.32 (system 3); R_t 22 min (system 4).

Compound **2a**. UV λ_{max}^{MeOH} nm: 271; DCI MS (NH_3 + isobutane): *m/z* 630 $[M + NH_4]^+$ (100), 612 $[M + NH_4 - H_2O]^+$ (4), 570 $[M - OAc]^+$ (6), 331 [tetracetylglucose]$^+$ (42).

Compound **3a**. UV λ_{max}^{MeOH} nm: 235, 287; DCI MS (NH_3 + isobutane): *m/z* 586 $[M + NH_4]^+$ (100), 568 $[M + NH_4 - H_2O]^+$ (9), 331 [tetracetylglucose]$^+$ (31).

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