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Short Report

New Biflavonoid and Other Constituents from *Luxemburgia nobilis* (EICHL)

Márcia C. C. de Oliveira[a], Mário G. de Carvalho[a]*, Cleber J. da Silva[a] and Alceni A. Werle[b]

[a]*Departamento de Química – ICE, Universidade Federal Rural do Rio de Janeiro, 23851-970, Seropédica - RJ, Brazil*

[b]*Departamento de Química – ICEB, Universidade Federal de Ouro Preto, 35400-000, Ouro Preto - MG, Brazil*

O fracionamento cromatográfico dos extratos orgânicos das folhas e galhos de *Luxemburgia nobilis* (Ochnaceae) forneceu o sitosterol, sitosterol-3-O-βD-glicopiranosil, friedelina, friedelinol, a mistura dos triterpenos lupeol, α-amirina e β-amirina, rutina, epicatequina, uma mistura de duas chalconas, isoliquiritigenina e 3'-hidróxiisoliquiritigenina, duas biflavonas conhecidas, amentoflavona e robustaflavona além de uma biflavona nova, 5,7,4'-triidróxiflavona-(3'-O-4"')-5",7"-diidróxiflavanona. As estruturas foram definidas através dos dados espectrométricos incluindo experimentos bidimensionais de RMN das substâncias naturais e dos derivados metilados e acetilados da biflavona nova.

Chromatographic fractionation of the organic extracts from the leaves and branches of *Luxemburgia nobilis* (Ochnaceae) afforded sitosterol, sitosterol-3-O-βD-glucopyranoside, friedelin, friedelinol, a mixture of triterpenes lupeol, α-amyrin and β-amyrin, rutin, epicatechin, a mixture of two chalcones, 2,4,3',4'-tetrahydroxychalcone and 2,4,4'-trihydroxychalcone, two known biflavones, amentoflavone and robustaflavone along with a new biflavonoid, 5,7,4'-trihydroxyflavone-(3'-O-4'")-5",7"-dihydroxyflavanone. The structures were established from spectral data, including 2D-NMR experiments of the natural substances and of the acetyl and methyl ether derivatives of the new biflavone.

Keywords: *Luxemburgia nobilis,* Ochnaceae, flavonoids, steroids, triterpenes

Introduction

The Ochnaceae family has been characterized as a major source of biflavonoids and up to now it has been best represented by *Ouratea,*[1-5] *Ochna*[6-9] and *Lophira*[10-12] genera. In a previous report, we described the inhibition of murine tumor growth, antiproliferative effects and activation of apoptosis on Erlich tumor cells by flavones isolated from *Ouratea hexasperma*[13] and from *Ouratea semisserrata*.[14] There is only one record of a phytochemical work on a *Luxemburgia* genus where we described the isolation and identification of steroids, fatty acids, betulinic acid, the diterpene epimanoyl oxid, atranorin and two new triglycerides.[15]

In this paper, we report the structure determination of a new biflavonoid, 2",3"-dihydroochnaflavone, two known biflavones, amentoflavone and robustaflavone, the flavonoids rutin, epicatechin, and two chalcones, along with fatty acids, sitosterol, 3-O-β-D-glucopyranosyl-sitosterol and five pentacyclic triterpenes isolated from the branches and leaves of *L. nobilis*.

*e-mail: mgeraldo@ufrrj.br

Results and Discussion

The chromatographic fractionation of the methanol extract from the branches and also of the hexane, ethyl acetate and methanol extracts from the leaves of *L. nobilis* afforded hexadecanoic, eicosanoic and tetraeicosanoic acids, a new biflavonoid, 2",3"-dihydroochnaflavone (**1**); two known biflavones, amentoflavone (**2**) and robustaflavone (**3**); epicatechin (**4**); two chalcones, isoliquiritigenin (**5**) and 3'-hydroxyisoliquiritigenin (**6**); rutin (**7**); sitosterol (**8**); sitosterol 3-O-β-D-glucopyranoside (**9**); friedelin (**10**); friedelinol (**11**) and a mixture of lupeol (**12**), α-amyrin (**13**) and β-amyrin (**14**).

The ^{13}C NMR spectrum of compound **1** shows 28 signals including two signals at δ_{CH} 128.80 and 116.30, each representing two carbon atoms, eight sp^2 CH, two sp^3 carbons (δ_{CH} 78.57 and δ_{CH2} 42.38), fourteen sp^2 quaternary carbons (4xC and 10xC-O) and two carbonyl groups (δ_C 182.22 and 196.48). The ^{1}H NMR spectrum shows two

signals at δ 11.99 and 12.71 indicating the presence of two chelated hydroxyls, which were confirmed by the IR spectrum which exhibits a broad OH absorption band at 3495 cm^{-1} and also a chelated carbonyl absorption at 1646 cm^{-1}. The NMR spectrum shows ten aromatic hydrogen signals including two sets of meta-coupled doublets (^{1}H,^{1}H-COSY) at δ 6.11 and 6.37 (2.0 Hz) and δ 5.81 and 5.82 (2.1 Hz) which belong to the H-6 and H-8 atoms of two flavonoid moieties. These data are in agreement with a flavonoid dimeric structure. The molecular formula $C_{30}H_{20}O_{10}$, which was obtained by HREIMS *m/z* [M^+, 30] 540.10565 (calc. 540.10050 for $C_{30}H_{20}O_{10}$) confirms the latter observation. The presence of a singlet at δ 6.62 (one hydrogen) and three double doublets at δ 5.39 (16.6, and 12.7 Hz), 3.11 (16.6, 12.7 Hz) and 2.66 (16.6, 6.0 Hz) led us to propose a flavone and flavanone unit for the dimer. The data above imply that carbons 6 and 8 of each unit are not involved in the interflavonoid linkage. Ring B of the flavone unit was identified by three hydrogen signals at δ 7.06 (d, 8.7 Hz), 7.62 (d, 2.0 Hz) and 7.80 (dd, 8.7 and 2,0 Hz) corresponding to H-5', H-2'and H-6'of this moiety. Furthermore, the ^{1}H NMR spectrum also shows a set of AA'BB' doublets (*J* 7.8 Hz, 2H each) at δ 7.36 and 6.83 which were assigned to H-2"',6"' and H-3"',5"' of the flavanone moiety, respectively. The cross peaks observed in the ^{13}C,^{1}H-COSY-$^nJ_{CH}$ (n = 2 and 3, HMBC) spectra of **1** show heteronuclear long-range couplings of C-1'with H-5' and of C-1"' with H-3"',5"' which confirm rings B of both flavone and flavanone, respectively. These observations and comparison of the UV absorption maxima (288 and 332 nm) and NMR data with those of the biflavonoid 2,3-dihydroochnaflavone, isolated from *Ochna obtusata*,[6] revealed these to be identical compounds. The differences between the chemical shift of the AA'BB' hydrogen in **1** [δ 7.36 and 6.83 (d, 7.8 Hz, 2H each)] and the values for the same set for the 2,3-dihydroochnaflavone reported in the literature[6] [δ 8.03 and 7.08 (d, 9.0 Hz, 2H)] led to propose the 2",3"-

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra data for biflavonoid **1** (D_3COD) and its trimethyl ether derivative **1a** (D_3CCOCD_3). Chemical shifts are in δ (ppm) and coupling constants (*J*, in parenthesis) in Hz.

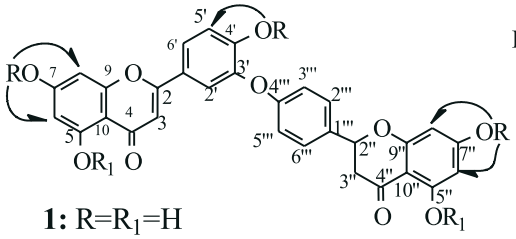
	1		**1a**	
C	δ_C	δ_H	δ_C	δ_H
2	163.94	-	162.54	-
4	182.22	-	182.64	-
5	161.80	-	158.97	-
7	164.66	-	164.71	-
9	157.82	-	158.00	-
10	104.29	-	106.00	-
1'	122.72	-	123.00	-
3'	142.88	-	143.00	-
4'	153.84	-	153.69	-
4"	196.48	-	196.84	-
5"	163.45		163.85	-
7"	167.14	-	168.39	-
9"	163.28	-	166.19	-
10"	102.30	-	101.00	-
1'"	132.77	-	131.51	-
4'"	158.45	-	155.69	-
CH	^{13}C-^{1}H-COSY-$^1J_{CH}$		^{13}C-^{1}H-COSY-$^1J_{CH}$	
3	103.91	6.62 (s)	106.75	6.51(s)
6	99.51	6.11(d, *J* 2.0 Hz)	98.36	6.50(s)
8	94.64	6.37(d, *J* 2.0 Hz)	94.15	6.17(s)
2'	121.22	7.62(d, *J* 7.8 Hz)	120.75	7.64(s)
5'	118.41	7.06(d, *J* 7.0 Hz)	113.85	7.21(d, *J* 8.0 Hz)
6'	125.35	7.71(dd, *J* 7.8 and 2.0 Hz)	125.12	7.80(d, *J* 8.0 Hz)
2"	78.57	5.39(dd, *J* 6.0 and 12.7 Hz)	75.17	5.42(br d, *J* 12.0 Hz)
6"	96.58	5.81(d, *J* 2.0 Hz)	95.03	5.92(s)
8"	95.62	5.82(d, *J* 2.0 Hz)	92.83	5.89(s)
2'"/6'"	128.80	7.36(d, *J* 7.8 Hz)	128.56	7.38(d, *J* 8.0 Hz)
3'"/5'"	116.30	6.83(d, *J* 7.8 Hz)	116.32	6.83(d, *J* 8.0 Hz)
CH_2				
3"	42.38	3.11(dd, *J* 12.7 and 16.6) 2.66 (br d, 16.6 Hz)	43.01	3.04(dd, *J* 12.0 and 16.0 Hz) 2.70(dd, *J* 6.0 and 16.0 Hz)
CH_3				
MeO-7	-		55.38	3.78 (s)
MeO-4'	-		56.11	3.70(s)
MeO-7"	-		55.76	3.77(s)
HO-5	-	12.71(s)	-	12.66(s)
HO-5"	-	11.99(s)	-	11.88(s)

dihydroochnaflavone structure for **1**. The treatment of **1** with diazomethane yielded **1a** with three methoxy groups and two chelated hydroxyls. The results obtained from NOEDIFF-NMR experiments on this derivative, performed with irradiation at the methoxy groups did not reveal any signal enhancements at the doublet at δ 7.62 (d, 2.0 Hz, H-2') and at 7.36 (d, 7.80 Hz, H-3"',5"') but did show nOe at the doublets at δ 7.06 (H-5'), 6.11 (H-6), 6.37 (H-8) 5.81(H-6") and 5.82 (H-8"). These observations further confirm the C-3'-O-C-4'" connection between the flavone and flavanone moieties. The comparison of the ^{13}C NMR spectral data of **1** with those of 2,3-dihydroochnaflavone[6] along with the analysis of the ^{13}C,^{1}H-COSY, $^{n}J_{CH}$ (n = 1, HMQC, Table 1; n = 2 and 3, HMBC) allowed to define the structure of **1** as the new biflavonoid 4',5,7-trihydroxy-flavone-(3'-O-4"')-5",7"-dihydroxyflavanone or 2",3"-dihydroochnaflavone. The ^{1}H and ^{13}C-NMR data of **1b** were used to confirm the proposed structure.

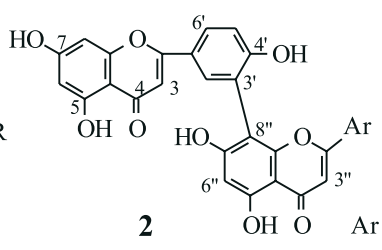
Compounds **2**, **3** and **4** were characterized as amento-flavone, epicatechin and robustaflavone, respectively, with the help of 1D and 2D ^{1}H and ^{13}C NMR analysis of the natural substances and comparison with literature data.[16-20]

The molecular formulas of **5** and **6** were determined to be $C_{15}H_{12}O_4$ and $C_{15}H_{12}O_5$ from the low-resolution mass spectrum, which showed peaks at *m/z* 256 (**5**) and 272 (**6**), in combination with the ^{1}H and ^{13}C-NMR spectra (HBBD and DEPT). The 1D and 2D ^{1}H (^{1}H,^{1}H-COSY and NOESY) and ^{13}C-NMR (HMQC and HMBC) spectra of the mixture of **5** and **6** were analyzed and compared with those of isoliquiritigenin (**5**) reported in the literature[21]. The remaining hydrogen and carbon-13 signals observed in the 1D and 2D NMR spectra along with the peak with *m/z* 172 in the mass spectrum were used to assign the additional structure in the mixture as the chalcone 2,4,3',4'-tetrahydroxychalcone (**6**) registered in the literature.[22]

Compound **7** was characterized as rutin by 1D and 2D ^{1}H and ^{13}C NMR spectral analysis of the natural substances and comparison with literature data.[20] The treatment of **7** with diazomethane followed by treatment with Ac_2O and pyridine yielded **7a**, with three methoxyl and seven acethyl groups. The results obtained from NOEDIFF-NMR experiments on this derivative performed with irradiation at the methoxyl groups did not reveal signal enhancements of hydrogens bound to anomeric carbons but showed nOe at the doublets at δ 6.19 (H-6), 6.39 (H-8), 7.52-7.55 (H-2') and 6.84 (H-5'). These observations further confirm the C-



1: R=R_1=H
1a: R= CH_3,R_1=H; n.O.e.
1b: R=R_1=Ac



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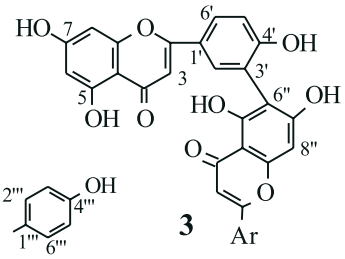

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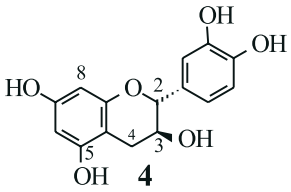

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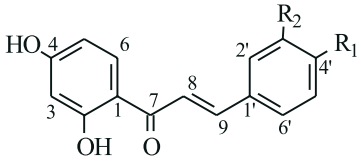
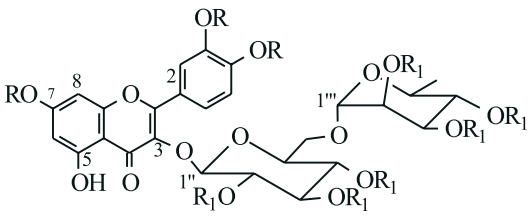
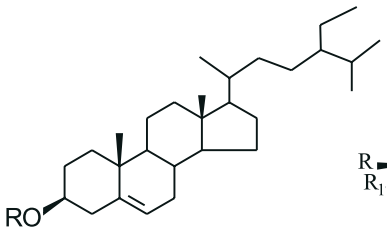


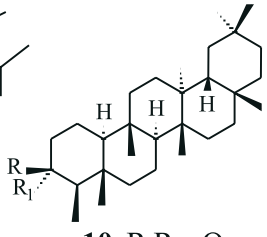
5: R_1=OH,R_2=H
6: R_1=R_2=OH



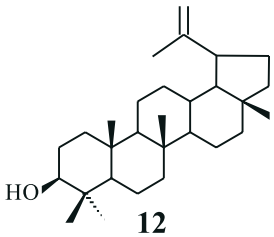
7: R=R_1=H
7a: R= CH_3,R_1=Ac



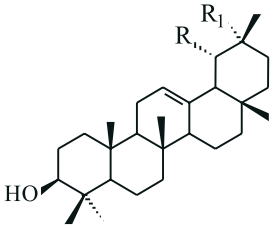
8: R=H
9: R = β,D-glucopiranosyl
9a: R = peracetyl of **9**.



10: R,R_1=O
11: R=OH,R_1=H



12



13: R=H,R_1=CH_3
14: R=CH_3,R_1=H

3-O-glycosyl moiety in the flavone and allowed to identify **7** as rutin.[22,23]

The known natural steroid **8**, its glycoside **9** and the terpenoids **10**-**14** were identified by analysis of their spectral data including the acetyl derivative **9a** and comparison with literature values, mainly ^{13}C NMR chemical shifts described for sitosterol (**8**),[24,25] sitosterol-3O-β-D-glycopiranoside (**9**)[26] and the mixture of lupeol, α-amyrin and β-amyrin (**12**-**14**), friedelin (**10**) and friedelinol (**11**) .[27,28]

Experimental

General procedure

Mp's are uncorrected. NMR spectra in CD_3OD (**1**, **2** ,**3**) or $CDCl_3$ (**1a**) were recorded on Bruker spectrometers (200 and 500 MHz for ^1H and 50.3 and 125 MHz for ^{13}C, respectively) and on a Varian Unity 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer using TMS as internal standard. EIMS: direct inlet at 70 eV on a VG Auto Spec-300 spectrometer; CC: silica gel (Merck and Aldrich 0.05-0.20 mm); TLC: silica gel H or G (Merck and Aldrich) was used to analyse the fractions collected from CC with visualization by UV (254 and 366) and exposure to iodine vapor; UV: recorded in MeOH with a DMS 80 Varian spectrophotometer; IR spectra were recorded on KBr disks on a Perkin-Elmer 1420 spectrophotometer.

Plant material

Luxemburgia nobilis (Ochnaceae) was collected in Morro de São Sebastião, Ouro Preto, Minas Gerais, Brazil and authenticated by botanist Jorge L. Silva. A voucher specimen (Nº 6737) is deposited at the Herbário José Badini of the Instituto de Ciências Exatas e Biológicas of the Universidade Federal de Ouro Preto, Minas Gerais state, Brazil.

Extraction and isolation

Dried and powdered leaves and branches were successively extracted by maceration using organic solvents at room temperature. The solvents were removed under vacuum to yield residues from **H**exane (**LNLH**, 2.0 g), ethyl **A**cetate (**LNLA**, 17.7 g) and **M**ethanol (**LNLM**, 20 g) from the **L**eaves and **H**exane (**LNBH**, 3.85 g) and **M**ethanol (**LNBM**, 20.0 g) from the **B**ranches of *L. nobilis*. The **LNLH** residue was fractionated on a silica gel column (**A**) using hexane, CH_2Cl_2 and methanol increasing the polarity to 100% methanol. The **A**-1/4, **A**-6/9 and **A**-31/35 fractions were crystallized and yielded hexadecanoic acid (mp 68 °C, 200.0 mg, acetone), a mixture of tetraeicosanoic and eicosanoic acids (130.0 mg, acetone) and sitosterol (**8**, 97.0 mg, hexane). The **LNLA** residue was chromatographed on a silica gel column (**B**) using CH_2Cl_2/MeOH increasing the polarity to 100% MeOH. The **B**-1/48 fractions were fractionated on a flash column of silica gel using $CHCl_3$ and yielded friedelin (**10**, mp 300 ºC, 107.0 mg). Fractions **B**-49/54 and **B**-55/64 were filtered on silica gel and sephadex columns using $CHCl_3$/MeOH (9:1) and afforded biflavone **2** (88.80 mg) and biflavone **1** (130.0 mg), respectively. The **LNLM** residue was fractionated on a silica gel column (**C**) using ethyl acetate increasing the polarity to 100% methanol. Fractions **C**-10/15 were filtered on a Sephadex column and purified by preparative TLC using $CHCl_3$/MeOH and yielded triterpenes friedelinol (**11**, mp 301 ºC, 45 mg) and friedelin (**10**, 53 mg); fractions **C**-26/30 were dissolved in methanol and after addition of $CHCl_3$ afforded a precipitate corresponding to the biflavone **3** (gum, 50.0 mg). Fractions **C**-32-39 yielded **1** (mp 220 ºC, 295.0 mg) after precipitation from acetone. The work up of residue **LNBH** has been previously described.[15] Finally, **LNBM** residue was subjected to column chromatography (**D**) on silica gel using ethyl acetate/methanol increasing the polarity to 100% methanol. Fraction **D**-2 was purified with a silica gel column and preparative TLC using $CHCl_3$/MeOH (9:1) to yield a mixture of triterpenes lupeol (**12**), β-amyrin (**13**) and α-amyrin (**14**) (80.0 mg) besides epicatechin (**4**, oil, 30.0 mg). Fractions **D**-8/12 were filtered on a silica gel column using CH_2Cl_2/MeOH (7:3) affording epicatechin (**4**, 200 mg). Fractions **D**-18/20 yielded a residue identified as 3O-βD-glucopyranosylsitosterol (**9**, mp 300 ºC, 35.0 mg). Filtration on sephadex column of fractions D-33/35 yielded two fractions which were recrystallized from EtOAc:MeOH (9:1) and further purified by preparative TLC affording the same glycoside **9** (85.00 mg) and a mixture of chalcones **5** and **6**. Compound **7** (1.00 g), known as rutin, was obtained from filtration of **D**-36/63 with sephadex using MeOH as solvent.

4',5,7-trihydroxyflavone-(3'-O-4'')-5'',7''-dihydroxy-flavanone (1): mp 220 ºC (EtOAc). UV: λ_{max}^{MeOH}/nm (log ε): 288 (3,29), 332 (3,42) nm. $[\alpha]_D$: +7.0 (Me_2CO, c 0.6), IR ν_{max} /cm^{-1}: 3433, 3096, 1773, 1693, 1646, 1617, 1507, 1473, 1428, 1371, 1337, 1266, 1193, 1130, 1077, 1030, 902, 841(KBr). ^1H NMR (500 MHz, methanol-d_4) and ^{13}C NMR (125 MHz, methanol-d_4), Table-1; EI-MS (70 ev), *m/z* (%) [$M^{+\cdot}$, 540 (13)], 389 (6), 314 (5), 286 (5), 272 (11), 212 (7), 179 (5), 166 (11), 152 (29), 137 (16), 126 (100), 110 (26), 97 (20), 81 (23), 69 (47), 57 (34); HREIMS *m/z* [$M^{+\cdot}$] 540.10565 (calcd 540.10050 for $C_{30}H_{20}O_{10}$).

*4',7-dimethoxy-5-hydroxyflavone-(3'-O-4"')-7"-methoxy-5"-hydroxyflavanone (**1a**), trimethyl ether of* **1**: Prepared by treating a methanol solution of **1** (20 mg) with ethereal diazomethane. After evaporation of the solvent, the residue was dissolved in acetone and purified by CC on silica gel. A fraction eluted with acetone yielded **1a** (20 mg): mp 186 °C (AcOEt). UV: λ_{max}^{MeOH}/ nm (log ε): 210 (3.60), 270 (3.20), 380 (3.2), 330 (3.06). IR ν_{max} /cm^{-1}: 3443, 3076, 2935, 2840, 1643, 1612, 15606, 1440, 1378, 1266, 1115, 1160 893 (KBr); ^{1}H (400 MHz, D_3CCOCD_3); ^{13}C (50.3 MHz, $CDCl_3$) NMR, Table-1. ^{1}H-NMR-NOEDIFF in $CDCl_3$.

*Peracetyl derivative of **1** (**1b**):* The peracetate of **1** (**1b**), was prepared with Ac_2O, pyridine and DMAP at room temperature for 24 h and was isolated as colorless needles from acetone: mp 230 °C; IR ν_{max} /cm^{-1} 1772, 1694, 1646 (KBr); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7,64 (dd, 1H, *J* 8.5, 2.0 Hz, H-6'), 7.45 (d, 1H, *J* 2.0 Hz, H-2'), 7.44 (d, 2H, *J* 8.8 Hz, H-2''', 6'''), 7.30 (d, 1H, *J* 8.5, H-5'), 7.27 (d, 1H, *J* 2.2 Hz, H-8), 7.05 (d, 2H, *J* 8.8 Hz, H-3''', 5'''), 6.82 (d, 1H, *J* 2.2 Hz, H-6), 6.78 (d, 1H, *J* 2.2 Hz, H-8"), 6.52 (d, 1H, *J* 2.2 Hz, H-6"), 6.51 (s, 1H, H-3), 5.48 (dd, *J* 13.08, 2.8 Hz, H-2"), 3.05 (dd, 1H, *J* 16.7, 13.08, H-3" ax), 2.78 (dd, 1H, *J* 16.7, 2.8, H-3" eq), 2.20, 2.32, 2.38, 2.39 and 2.40 (s, 3H each, OAc-5,7,4',5",7"); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.90 (C-2), 108.87 (C-3), 176.17 (C-4), 155.87 (C-5), 113.85 (C-6), 160.97 (C-7), 109.11 (C-8), 153.96 (C-9), 111.50 (C-10), 133.56 (C-1'), 118.17 (C-2'), 148.80 (C-3'), 144.56 (C-4'), 124.66 (C-5'), 122.29 (C-6'), 78.97 (C-2"), 44.96 (C-3"), 188.99 (C-4"), 156.84 (C-5"), 110.55 (C-6"), 163.11 (C-7"), 109.05 (C-8"), 150.11 (C-9"), 114.50 (C-10"), 130.07 (C-1"'), 128.06 (C-2'", 6"'), 118.54 (C-3"', 5"'), 151.16 (C-4"'), 168-169,5 (O-$\underline{C}OCH_3$), 20,7-21,8 (O-CO$\underline{C}H_3$).

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