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Flavonol and drimane-type sesquiterpene glycosides of *Warburgia stuhlmannii* leaves

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Abstract

An investigation of methanolic extract of *Warburgia stuhlmannii* leaves has led to the isolation of two new drimane-type sesquiterpene glycosides characterized as mukaadial 6-*O*-β-D-glucopyranoside, mukaadial 6-*O*-α-L-rhamnopyranoside together with two other novel flavonol glycosides identified as 3′,5′-*O*-dimethylmyricetin 3-*O*-β-D-2″,3″-diacetylglucopyranoside and 3′-*O*-methylquercetin 3-*O*-β-D-2″,3″,4″-triacetylglucopyranoside. The known compounds; mukaadial, deacetylugandensolide, quercetin, kaempferol, kaempferol 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-β-D-glucopyranoside, kaempferol 7-*O*-β-D-glucopyranoside, myricetin 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-α-L-rhamnopyranoside, quercetin 3-*O*-sophoroside and isorhamnetin 3-*O*-β-D-glucopyranoside were also isolated from the same extract.

Keywords: *Warburgia stuhlmannii*; Canellaceae; Drimane-type sesquiterpene glycosides; Flavonol glycosides; Leaves

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1. Introduction

Warburgia stuhlmannii (Canellaceae) is well known in herbal medicine as a remedy for microbial infections (Kokwaro, 1976). The plant is typified by sesquiterpenes based on drimane skeleton (Kioy et al., 1990) and some of the secondary metabolites are highly rated biologically as antifeedants (Bosch et al., 1986; Kubo and Nakanishi, 1977, 1979); cytotoxic and molluscicidal (Odyek et al., 1993; Kubo et al., 1983), fungicidal and mitochondrial oxidative phosphorylation (Kubo et al., 1977; Kubo and Taniguchi, 1988; Rajab and Ndegwa, 2000).

Our interest in the drimane related compounds has prompted us to examine the methanolic extract of the plant leaves and this has led to the isolation of two novel drimane glycosides (**1** and **2**) and two new flavonol glycosides (**3** and **4**). Also isolated from the extract were known compounds mukaadial (**5**), deacetylugandensolide (**6**), kaempferol (**7**), quercetin (**8**), kaempferol 3-*O*-α-L-rhamnopyranoside (**9**), kaempferol 7-*O*-β-D-glucopyranoside (**10**), isorhamnetin 3-*O*-β-D-glucopyranoside (**11**), myricetin 3-*O*-α-L-rhamnopyranoside (**12**), quercetin 3-*O*-α-L-rhamnopyranoside (**13**), quercetin 3-*O*-β-D-glucopyranoside (**14**) and quercetin 3-*O*-sophoroside (**15**) (Kioy et al., 1990; Manguro et al., 1996, 1997).

2. Results and discussion

Compound **1**, colourless crystals afforded a molecular ion peak at m/z 413 $[M + H]^+$, calculated for $C_{21}H_{32}O_8$ formula. The IR spectral data showed the presence of a hydroxyl (3500 cm^{-1}), an intramolecular hydrogen bonded hydroxyl (3350 cm^{-1}) and an α,β-unsaturated aldehyde (1650, 1630 cm^{-1}) while its ^1H NMR data were quite similar to those of 9-hydroxy-11,12-dialdehydedrim-7-ene (Kioy et al., 1989, 1990) except for the signals due to a sugar unit. Acid hydrolysis of the compound afforded mukaadial and D-rhamnose as the residues confirmed by co-spotting with authentic samples. The ^{13}C NMR spectrum showed a total of 21 carbon atoms and their multiplicity assignments using DEPT established 10 methines, four methyls, three methylenes and four quartenary carbons. In the ^1H NMR spectrum, an oxymethine signal at δ 4.86 (ddd, $J = 10.5$, 8.7,

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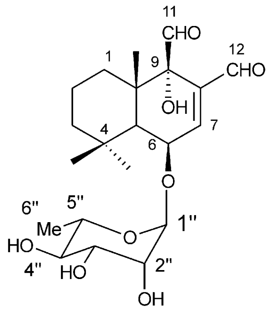

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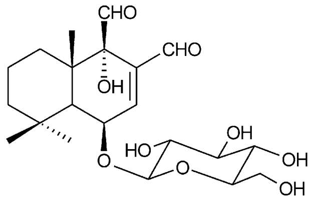

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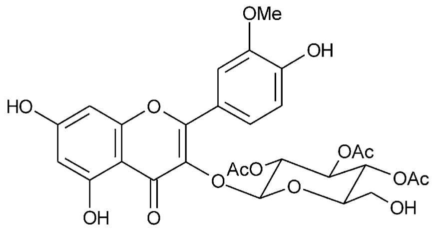

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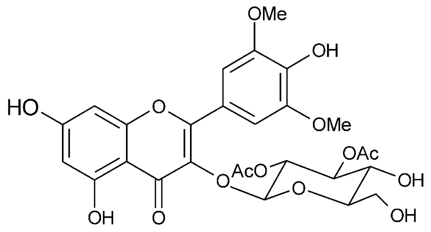

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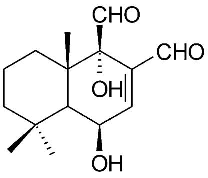

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3.2 Hz) was coupled to two other protons and from decoupling experiments the olefinic proton was shown to be part of the –C=C–CH(*O*-rham)–CH–C(CH_3)$_2$ system analogous to the C-5–C-7 region in mukaadial (**5**) (Kioy et al., 1989). This allowed the sugar moiety to be assigned to C-6 where it is in equatorial configuration, a fact further supported by the deshielding of the C-5 axial proton from δ 2.50 in **5** to δ 2.82 in **1** and the HMBC cross peak (Fig. 1) between the anomeric proton (δ 4.90) and the C-6 (δ 70.60). The structure of the compound was confirmed by NOESY experiments (Fig. 1) whereby the C-4 axial methyl (δ 1.38) was identified by its correlation with the ring junction H-5, which in turn correlated with the axial H-6. The latter was also found to show NOESY cross peak with the anomeric proton (δ 4.90). On this basis compound **1** was established as mukaadial 6-*O*-α-L-rhamnopyranoside.

The other novel drimane sesquiterpene derivative (**2**) showed a molecular ion peak at *m*/*z* 429 [M + H]$^+$ which together with the proton and carbon count from ^{1}H and ^{13}C NMR data established the molecular formula as $C_{21}H_{32}O_9$. The IR absorptions and the ^{1}H NMR spectral data resembled those of compound **1**, thus signifying a glycosidated mukaadial derivative, a fact further supported by acid hydrolysis which released mukaadial and D-glucose identified by direct comparison with authentic samples. The position of glucose attachment to the aglycone was deduced to be at C-6 from the ^{13}C NMR downfield shift at δ 70.40 in comparison with **5** and further confirmed by HMBC and NOESY correlations as in the case of **1**. Therefore, from spectroscopic evidence, compound **2** was concluded as mukaadial 6-*O*-β-D-glucopyranoside.

Along with the drimane sesquiterpene glycosides were two flavonol glycosides (**3** and **4**) also isolated from the same extract.

Compound **3**, a yellow powder displayed the characteristic aglycone pattern of isorhamnetin (3′-*O*-methylquercetin) namely; a 2H AX, a 3H ABX and a methoxy group in the ^{1}H NMR spectrum (Mizuno et al., 1992a,b). Its ^{13}C NMR spectral data showed upfield and downfield shifts of isorhamnetin signals consistent with 3-*O*-glycosylation (Mizuno et al., 1992a,b; Agrawal, 1989), a fact further supported by UV spectral data as outlined in the experimental section. The sugar unit was identified as D-glucose from acid hydrolysis. The mass spectrum data (see Experimental section) and the H-1″, *J* value (7.7 Hz), together with three signals at δ 2.05, 2.10 and 2.15 indicated that the sugar moiety was a β-D-triacetylglucopyranose. The ^{1}H NMR data indicated C-2″, C-3″ and C-4″ as the acetylation sites as evidenced by downfield shifts of H-4″ (*δ* 5.10), H-2′ (*δ* 5.01) and H-3″ (δ 4.90) signals in comparison with isorhamnetin 3-*O*-β-D-glucopyranoside (**11**). This was further supported by the ^{13}C NMR data which showed upfield shifts for C-1″ (−1.7 ppm) and C-5″ (−2.1 ppm) and the downfield shifts for C-2″ (+ 2.3 ppm), C-3″ (+ 2.5 ppm) and C-4″ (+ 2.1 ppm) relative to **11**. The acetylation sites were conclusively confirmed by HMBC spectrum cross peaks (Fig. 1). Thus, compound **3** was identified as isorhamnetin 3-*O*-β-D-2″,3″,4″-triacetylglucopyranoside.

Compound **4** showed UV data which signified a flavonol glycoside with free hydroxyl groups at C-5, C-7 and C-4′ (Markham, 1982; Markham et al., 1992; Mabry et al., 1970). The chemical shift assignments in the ^{1}H and ^{13}C NMR spectral data supported the identification of the aglycone as syringetin (3′, 5′-*O*-dimethylmyricetin). Acid hydrolysis of the compound yielded glucose as the sugar residue. In the ^{1}H NMR spectrum, two singlets (each 3H) at *δ* 2.01 and 2.10 due to acetoxy groups, and the diagnostic downfield shifts of H-2″ and H-3″ at *δ* 4.95 and 5.20, respectively, suggested a 2″,3″-diacetoxyglucopyranoside. This was corroborated by multiplicity and decoupling experiments: irradiation of the peak at *δ* 5.20 (H-3″) and 4.95 (H-2″) caused simplification of signals at 3.34 (H-4″) and 5.30 (H-1″), respectively. The 2″,3″-diacetylation of glucose was also consistent with ^{13}C NMR data (Table 1) as evidenced by downfield shifts for the peaks of C-2″ (+ 2.5 ppm) and C-3″ (+ 3.0 ppm), and the upfield shifts noted for C-1″ (−2.8 ppm) and C-4″ (−2.3 ppm) in comparison with an authentic sample of 3′,5′-*O*-dimethylmyrecetin 3-*O*-β-D-glucopyranoside (**16**) previously isolated from *Myrsine africana* (Manguro et al., 1995). As was the case with compound **3**, the positions of acetoxy groups in **4** were confirmed further by HMBC experiments. On this basis, compound **4** was structurally elucidated as 3′,5′-*O*-dimethylmyricetin 3-*O*-β-D-2″,3″-diacetylgucopyranoside.

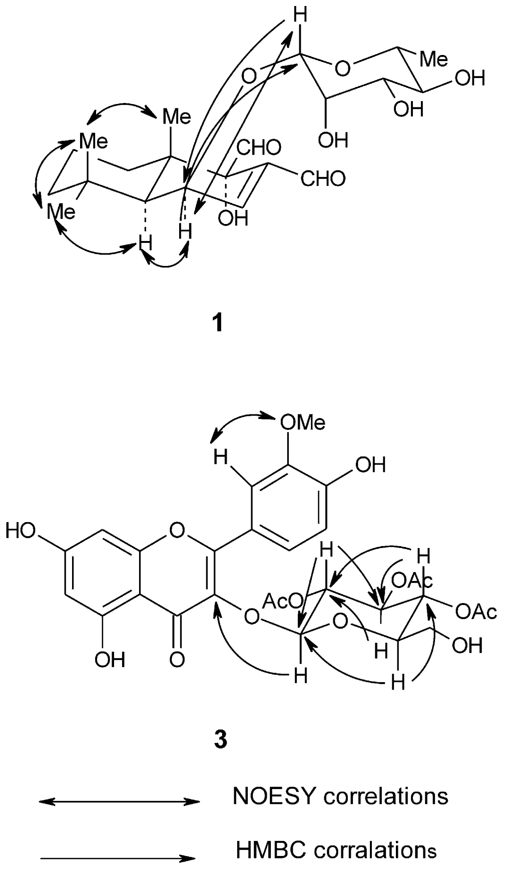

Fig. 1. Cross peaks observed in the HMBC and NOESY spectra of compounds **1** and **3**.

Table 1
^{13}C NMR of flavonol and drimane glycosides

Carbon	1	2	3	4	5
1	43.50	42.70			42.30
2	33.00	33.30	156.50	157.01	33.10
3	17.60	18.00	134.02	134.60	17.35
4	32.70	32.90	179.15	178.63	17.20
5	50.10	49.60	161.01	160.80	48.75
6	70.60	70.40	99.53	99.80	67.95
7	157.40	158.40	164.20	163.70	158.60
8	138.45	139.25	94.64	93.60	138.40
9	78.50	77.80	156.40	156.80	76.80
10	45.15	44.75	104.35	103.95	42.50
11	201.20	201.70			202.60
12	192.70	192.40			192.40
13	17.20	17.90			17.20
14	22.30	23.40			22.40
15	36.12	37.50			36.00
1′	102.50	104.80	121.40	120.00	
2′	70.40	73.40	114.30	107.60	
3′	71.80	74.50	148.10	148.00	
4′	72.20	72.10	146.75	136.30	
5′	71.30	76.20	116.03	148.00	
6′	17.80	61.30	121.81	107.60	
1″			103.00	102.10	
2″			78.20	76.30	
3″			79.63	79.65	
4″			73.60	68.60	
5″			74.40	74.90	
6″			60.77	62.30	
OMe			56.34	56.80	
COO<u>Me</u>			20.50	20.30	
			20.70	21.45	
			21.20		
<u>C</u>OOMe			170.30	170.40	
			170.75	171.30	
			171.03		

3. Experimental

3.1. General experimental procedures

UV and IR spectra were recorded using Beckmann DU-65 spectrophotometer and Perkin-Elmer-FTIR 600 series, respectively. The FAB mass spectra were provided by Polish Academy of Sciences. The NMR data were taken in DMSO-d_6/$CDCl_3$ mixture on a 400 MHz Varian VXR-500 spectrometer. EIMS were measured using 70 eV MAT 8200 A Varian Bremen instrument. Silica gel for both column and tlc plates were impregnated with 2% oxalic acid solution. Semi-preparative high performance liquid chromatography (HPLC) was performed on a Bischoff instrument using a model pump connected to 785 A programmable absorbance detector and a programmable monitor 8252 dual pen recorder.

3.2. Plant material

The leaves of *W. stuhlmannii* were collected from coast province near Kinango in the month of June 1997. Voucher specimens (Olum MU/1997/KEFRI/6) were identified after comparison with authentic samples at the University of Nairobi, Department of Botany Herbarium.

3.3. Extraction and isolation

The CH_2Cl_2 defatted powdered dried leaves (approx. 5 kg) was extracted with MeOH (7.5 l×3) at room temperature for two weeks. The extract (approx. 20 l) upon evaporation under reduced pressure afforded a dark green material (205 g). A portion of the extract (190 g) preadsorbed on silica gel was subjected to column chromatography with CH_2Cl_2–MeOH gradient and elution concluded with MeOH, fractions of 100 ml each being collected. A total of 281 fractions were collected and their homogeneity determined by tlc (eluent: CH_2Cl_2–MeOH, 9:1 and 3:2). The corresponding eluates were combined into four pools (I–IV). Pool I (fractions 20–91, 21.5 g) upon further purification by repeated low pressure chromatography using CH_2Cl_2–MeOH (95:5) followed by the same solvent system in the ratio 9:1, collecting 10 ml each afforded **5** (85 mg), **6** (900 mg), **3** (42 mg), **7** (75 mg), **1** (52 mg) and **8** (150 mg). Pool II (fractions 92–164, 15 g) was similarly purified as described for pool I above using CH_2Cl_2–MeOH (9:1) followed by the same solvent system in the ratio 85:15 to give **9** (75 mg), **4** (59 mg), **13** (80 mg), **10** (36 mg) and **2** (75 mg). Pool III (fractions 166–233, 16 g) yielded a gummy material after evaporation in vacuo and was further purified by flash chromatography using CH_2Cl_2–MeOH (4:1) to give **12** (33 mg), **14** (24 mg), **11** (34 mg). Pool IV (fractions 234–281, 26 g) mainly from methanol elution was further rechromatographed with CH_2Cl_2–MeOH mixture of increasing polarity and lastly with MeOH giving 60 fractions of 100 ml each. The eluates 21–47 were found to contain one major compound contaminated with minor impurities, combined and further purified by semi-preparative HPLC on reverse phase (RP-18) using MeOH–H_2O (4:1) to give **15** in 66 mg.

3.4. Mukaadial 6-O-α-L-rhamnopyranoside (**1**)

Colourless crystals, mp > 250 °C. IR ν_{max} (KBr) cm^{-1}: 3500 (OH), 3350 (OH), 1720, 1650, 1630, 1410, 1350, 1200, 1140, 1030, 990, 900, 810, 770. ^{1}H NMR ($CDCl_3$ + one drop DMSO-d_6) δ ppm: 9.60 (*s*, CHO-11), 9.40 (*s*, CHO-12), 7.10 (*d*, *J* = 2.5 Hz, H-7), 4.86 (*ddd*, *J* = 10.5, 8.7, 3.2 Hz, H-6), 4.09 (*s*, OH-9), 2.82 (*d*, *J* = 10 Hz, H-5), 2.50 (*ddd*, *J* = 13.3, 13.1 Hz, H-1_{ax}), 1.85–1.52 (*m*, H-1_{eq}, H-$2_{eq/ax}$), 1.55 (*s*, Me-4_{eq}), 1.38 (*s*, Me-4_{ax}), 1.30 (*s*, Me-10); rhamnose: 4.90 (*d*, *J* = 1.2 Hz, H-1′), 4.10 (*d*, *J* = 3.1 Hz, H-2′), 3.50 (*dd*, *J* = 8.8, 3.2 Hz, H-3′), 3.40 (*dq*, *J* = 11, 6.3 Hz, H-5′), 3.25 (*dd*, *J* = 9.3, 8.2 Hz, H-4′), 1.10 (d, *J* = 6.3 Hz, Me-6′). ^{13}C NMR data: see Table 1. EIMS (70 eV): *m*/*z* (%) 266 (4), 248 $[M-H_2O]^+$ (22), 238 $[M-CHO]^+$ (100), 219 $[M-H_2O-CHO]^+$ (6), 146 (2), 109 (40). FAB-MS: 413 $[M+H]^+$, 267 $[M-146+H]^+$, 249 $[M-H_2O-146+H]^+$, 239 $[M-146-CHO+H]^+$, 147 [rhamnose], 109

3.5. Mukaadial 6-O-β-D-glucopyranoside (**2**)

Colourless crystals, mp 180–183 °C (sublimes). IR ν_{max} (KBr) cm^{-1}: 3550 (O–H), 1725 (CHO), 1674 (α,β-unsaturated CHO), 1650, 1640, 1470, 1405, 1380, 1250, 1215, 1180, 1050, 960. ^{1}H NMR ($CDCl_3$ + one drop DMSO-d_6) δ ppm: 9.50 (*s*, CHO-11), 9.30 (*s*, CHO-12), 7.01 (*d*, *J* = 2.4 Hz, H-7), 5.01 (*ddd*, *J* = 10.5, 9.0, 3.0 Hz, H-6), 4.10 (*s*, OH-9), 2.80 (*d*, *J* = 10 Hz, H-5), 2.30 (*ddd*, *J* = 13.2, 13.2, 3.5 Hz, H-$1_{eq/ax}$), 1.60 (*s*, Me-4_{eq}), 1.80–1.50 (*m*, H-$3_{eq/ax}$), 1.40 (*s*, Me-4_{ax}), 1.25 (*s*, Me-10); glucose: 5.10 (*d*, *J* = 7.8 Hz, H-1′), 3.80 (*dd*, *J* = 12.0, 2.4 Hz, H-$6'_B$), 3.65 (*dd*, *J* = 12.0, 5.4 Hz, H-$6'_A$), 3.54 (*dd*, *J* = 9.0, 6.8 Hz, H-2′), 3.46 (m, H-4′), 3.36 (*t*, *J* = 9 Hz, H-3′), 3.20 (*ddd*, *J* = 9.6, 5.2, 2.8 Hz, H-5′). ^{13}C NMR data: see Table 1. EIMS (70 eV): *m*/*z* (%) 267 $[M+1]^+$ (3), 266 (5), 237 (100), 109 (30), 69 (70), 43 (85). FAB-MS 429 $[M+H]^+$, 267 $[M-162+H]^+$, 249 $[M-162-H_2O+H]^+$, 238 $[M-162-H_2O-CHO+H]^+$, 163 $[glucose]^+$, 109, 69, 43.

3.6. Isorhamnetin 3-O-β-D-2″,3″,4″-triacetylglucopyranoside (**3**)

A yellow amorphous powder. UV α_{max} (MeOH) nm: 258, 356; (+$AlCl_3$): 266, 302, 401; (+$AlCl_3$/HCl): 262, 302, 402; (+NaOMe): 270, 326, 418; (+NaOAc): 272, 321, 408; (+ NaOAc/H_3BO_3): 255, 268, 358. ^1H NMR ($CDCl_3$ + one drop DMSO-d_6) δ ppm. 12.30 (*s*, OH-5, D_2O exchang.), 10.20 (*br s*, OH-7, D_2O exchang.), 8.50 (*br s*, OH- 4′, D_2O exchang.), 7.80 (*d*, *J* = 2.0 Hz, H-2′), 7.40 (*dd*, *J* = 8.1, 2.1 Hz, H-6′), 6.90 (*d*, *J* = 8.1 Hz, H-5′), 6.40 (*d*, *J* = 2.1 Hz, H-8), 6.25 (*d*, *J* = 2.1 Hz, H-6), 3.80 (*s*, OMe); Sugar: 5.30 (*d*, *J* = 7.7 Hz, H-1″), 5.10 (*dd*, *J* = 5.5, 3.5 Hz, H-4″), 5.01 (*d*, *J* = 8 Hz, H-2″), 4.90 (*dd*, *J* = 8, 5.5 Hz, H-3″), 3.90 (*d*, *J* = 6.7 Hz, H-6″$_B$), 3.75 (*d*, *J* = 6.6 Hz, H-6″$_A$), 3.40 (*m*, H-5″), 2.15 (*s*, OAc-4″), 2.10 (*s*, OAc-3″), 2.05 (*s*, OAc-2″). ^{13} C NMR data: see Table 1. EIMS (70 eV): *m*/*z* (%) 316 (100), 153 (13), 151 (6), 43 (20). FAB-MS 605 $[M+H]^+$, 317 $[M-288+H]^+$, 289, 246, 163, 152.

3.7. 3′,5′-O-Dimethylmyricetin 3-O-β-D-2″,3″-diacetyl-gucopyranoside (4)

Yellow amorphous powder, mp > 250 °C. UV λ_{max} (MeOH) nm: 254, 267, 258; (+$AlCl_3$): 272, 310, 401; (+$AlCl_3$/HCl): 270, 310, 402; (+NaOMe): 270, 330, 422; (+NaOAc): 267, 320, 425; (+NaOAc/H_3BO_3): 268, 362. ^1H NMR ($CDCl_3$ + one drop DMSO-d_6) δ ppm: 12.40 (s, OH-5, D_2O exchang.), 10.30 (*br s*, OH-7, D_2O exchang.), 8.20 (*br s*, OH-4′, D_2O exchang.), 7.40 (*s*, H-2′ and H-6′), 6.40 (*d*, *J* = 2.2 Hz, H-8), 6.23 (*d*, *J* = 2.2 Hz, H-6), 3.75 (*s*, 6H, 2×OMe), sugar: 5.30 (*d*, *J* = 7.8 Hz, H-1″), 5.20 (*dd*, *J* = 8.3, 2.4 Hz, H-3″), 4.95 (*m*, H-2″), 3.80 (*d*, *J* = 8.2, 3.4 Hz, H-6″$_B$), 3.60 (*d*, *J* = 8.2, 3.3 Hz, H-6″$_A$), 3.50 (*ddd*, *J* = 5.3, 3.2 Hz, H-5″), 3.34 (*m*, H-4″), 2.10 (*s*, OAc-3″), 2.01 (*s*, OAc-2″). ^{13}C NMR data: see Table 1. EIMS (70 eV): *m*/*z* (%) 346 (100), 181 (5), 180 (3), 151 (20), 43 (85). FAB-MS 593 $[M+H]^+$, 347 $[M-246+H]^+$, 181, 151.

3.8. Mukaadial (5)

Needle like crystals from *n*-hexane–CH_2Cl_2 mixture, mp 245–246 °C; $[\alpha]_D^{25}$ −25° (MeOH, *c* 1.0). IR ν_{max} (KBr) cm^{-1}: 3450 (OH), 1725, 1660, 1630, 1450, 1400, 1370, 1050 . ^1H NMR ($CDCl_3$) δ ppm: 9.70 (s, CHO-11), 9.50 (*s*, CHO-12), 7.10 (*d*, *J* = 2.4 Hz, H-7), 4.66 (*ddd*, *J* = 11.2, 8.7, 2.4 Hz, H-6$_{ax}$), 4.94 (*d*, *J* = 1.8 Hz, OH-6), 4.04 (*s*, OH-9), 2.50 (*d*, *J* = 11.0 Hz, H-5$_{ax}$), 2.10 (*ddd*, *J* = 13.1, 13.0, 3.1 Hz, H-1$_{eq}$), 1.53–1.20 (*m*, H-1$_{eq}$, H-2$_{eq/ax}$, H-3$_{eq/ax}$), 1.18 (s, Me-4$_{ax}$), 1.14 (s, Me-4$_{eq}$). EIMS (70 eV): *m*/*z* (%): 266 $[M]^+$(4), 248 $[M–H_2O]^+$ (8), 230 $[M–2H_2O]^+$ (25), 237 $[M–CHO]^+$ (100), 109 (13), 95 (43), 83 (55), 55 (75), 43 (85).

3.9. Acid hydrolysis

Compounds (**1**–**4**), each 15 mg in a mixture of 8% HCl (2 ml) and MeOH (20 ml) were separately heated under reflux for 2 h. The reaction mixtures were reduced under pressure to dryness, dissolved in H_2O (3 ml) and neutralized with NaOH. The neutralized products were then subjected to tlc (eluent: EtOAc–MeOH–H_2O–HOAc, 6:2:1:1). The chromatograms were sprayed with aniline hydrogen phthalate followed by heating at 100 °C. The sugars were identified after comparison with authentic samples.

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