Polyhydroxylated Steroidal Glycosides from the Starfish Asterias forbesi

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POLYHYDROXYLATED STEROIDAL GLYCOSIDES FROM THE STARFISH *ASTERIAS FORBESI*

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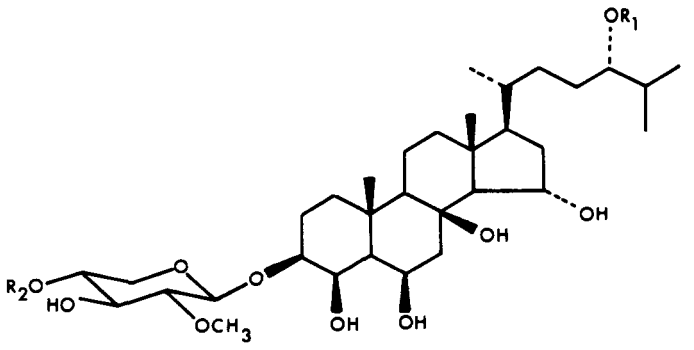
ABSTRACT.—Four new polyhydroxylated steroid glycosides have been isolated from the starfish *Asterias forbesi*, and their structures have been determined by spectroscopic means to be as follows: forbeside I, (24*S*)-3-*O*-(2,4-di-*O*-methyl-β-D-xylopyranosyl)-5α-cholesta-3β,4β,6β,8,15α,24-hexaol [**3**]; forbeside J, (24*S*)-3-*O*-(2,4-di-*O*-methyl-β-D-xylopyranosyl)-24-*O*-α-L-arabinofuranosyl-5α-cholesta-3β,4β,6β,8,15α,24-hexaol [**1**]; forbeside K, (24*Z*)-3-*O*-(2-*O*-methyl-β-D-xylopyranosyl)-27-*O*-α-L-arabinofuranosyl-24-methyl-5α-cholest-24-ene-3β,4β,6β,8,15α,27-hexaol [**4**]; and forbeside L, 3-*O*-(2-*O*-methyl-β-D-xylopyranosyl)-24-ethyl-5α-cholest-4-ene-3β,6β,8,15α,16β,26-hexaol [**5**].

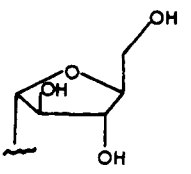
In 1982 Riccio *et al.* (1) first reported the structure of a new type of starfish-derived steroidal glycoside featuring a polyhydroxylated steroidal aglycone. Since then some 60 variations on this theme have been reported in the literature (2). These are generally based on a cholestane or Δ^4 cholestene nucleus with varying degrees of hydroxylation involving some or all of C-4, C-6, C-8, C-15, or C-16 (3), featuring one or two sugar units attached to C-3 and/or to a side chain for which a number of variations exist. This type of compound has been reported from 20 starfish varieties, but only one *Asterias* (4) species has been noted. In our continuing study of the polar constituents of *Asterias forbesi* Desor (Asteriidae, order Forcipulatida) we have encountered four new glycosides possessing polyhydroxylated steroidal aglycones which we designate as forbesides I, J, K, and L. Their structures have been deduced by spectroscopic means.

Forbeside J [**1**] displays a prominent pseudomolecular ion at *m/z* 759 corresponding to $[M(C_{39}H_{68}O_{14}) - H]^-$ in its negative ion fab mass spectrum.

The 500 MHz ^{1}H-nmr spectrum (Table 1) of forbeside J shows two anomeric proton doublets at δ 4.91 ppm (J = 1.7 Hz) and δ 4.45 ppm (J = 7.4 Hz) which together with other data is indicative of the presence of one α-furanosyl unit and one β-pyranosyl unit. Methyl singlets at δ 0.98 ppm and δ 1.44 ppm are assigned to H-18 and H-19, respectively, of the aglycone. A methyl doublet and isopropyl doublets appearing at δ 0.93 ppm are assigned to H-21, H-26, and H-27. Two methoxyl singlets at δ 3.62 ppm and δ 3.46 ppm are also noteworthy.



1 R_1=**a**, R_2=Me
2 R_1=**a**, R_2=H
3 R_1=H, R_2=Me



a

TABLE 1. Nmr Data for Forbesides J [1] and I [3] in CD_3OD.

Position	Compound			
	1[a,c]		3[b,c]	
	^{13}C (δ, ppm)	^{1}H (δ, ppm)	^{13}C (δ, ppm)	^{1}H (δ, ppm)
1	41.01	1.03, 1.77	40.95	
2	25.31	1.75, 1.97	25.25	
3	80.53	3.64 m	80.46	3.63 m
4	74.66	4.29 m	74.59	4.27 m
5	50.48	1.24	50.40	
6	76.20	4.29 m	76.13	4.27 m
7	45.24	1.61, 2.45	45.19	
8	76.75		76.76	
9	57.70	0.99	57.63	
10	36.93		36.87	
11	19.38	1.50, 1.82	19.32	
12	42.75	1.25, 1.99	42.57	
13	45.50		45.45	
14	66.55	1.18	66.45	
15	70.16	4.30	70.03	4.27 m
16	41.75	1.76, 1.93	41.63	
17	55.94	1.36	55.84	
18	15.37	0.98 s	15.31	0.96 s
19	18.72	1.44 s	18.66	1.44 s
20	36.39	1.37	36.34	
21	19.07	0.93 d (6.8)	19.03	0.92 d (6.8)
22	32.81	1.02, 1.60	33.31	
23	28.75	1.35, 1.60	31.51	
24	84.75	3.32 m	78.10	3.20 m
25	31.84	1.85	34.59	
26	18.39	0.93 d (6.8)	17.54	0.92 d (6.8)
27	18.43	0.93 d (6.8)	19.53	0.92 d (6.8)
X1′	102.61	4.45 d (7.4)	102.54	4.44 d (7.4)
2′	84.75	2.95 t (8.0)	84.67	2.92 t (8.0)
3′	76.75	3.45 t (8.9)	76.69	3.44 t (8.3)
4′	80.98	3.20 m	80.91	3.20 m
5′	64.25	3.16 dd (11.2, 10.7) 4.02 dd (11.2, 5.0)	64.19	3.17 dd (11.0, 10.5) 4.01 dd (11.0, 5.0)
OMe	59.07	3.46 s	59.03	3.46 s
OMe	61.11	3.62 s	61.07	3.62 s
A1″	109.46	4.91 d (1.7)		
2″	83.96	3.99 m		
3″	78.72	3.86 dd (8.1, 7.3)		
4″	85.04	3.99 m		
5″	62.92	3.65 dd (11.7, 4.6) 3.75 dd (11.4, 3.2)		

[a]Assignments from 500 MHz ^{1}H-^{1}H COSY and HETCOR data.
[b]^{13}C and ^{1}H assignments by comparison with **1**.
[c] Multiplicities were obtained by DEPT spectra.

The ^{13}C-nmr spectrum of forbeside J shows 39 carbon signals (Table 1). Based on a DEPT experiment and comparison with ^{13}C data for granulatoside A [**2**] isolated from the starfish *Choriaster granulatus* (6), 27 of the carbon signals can be easily assigned to the aglycone as shown in Table 1. The remaining 12 carbon signals are in good agreement with those of one α-L-arabinofuranosyl unit (4–7) and one 2,4-di-*O*-methyl-β-D-

xylopyranosyl unit (8–13). The α-L-arabinofuranosyl unit and 2,4-di-*O*-methyl-β-D-xylopyranosyl unit must be connected to C-24 and C-3, respectively, of the aglycone in view of the superimposable ^{13}C chemical shifts for all of the carbon signals with those of granulatoside A aglycone (6).

The nature of the sugars and aglycone were confirmed by 500 MHz ^{1}H-^{1}H COSY and ^{1}H-^{13}C heteronuclear COSY (HETCOR) spectra, which provided unambiguous assignments for all protons of this system for the first time.

Thus forbeside J is formulated as (24*S*)-3-*O*-(2,4-di-*O*-methyl-β-D-xylopyranosyl)-24-*O*-α-L-arabinofuranosyl-5α-cholesta-3β,4β,6β,8,15α,24-hexaol or 4′-methyl-granulatoside A.

Forbeside I [**3**] displays a prominent pseudomolecular ion at *m/z* 627 corresponding to $[M(C_{34}H_{60}O_{10}) - H]^-$ in its negative ion fab mass spectrum. The ^{1}H-nmr spectrum shows one anomeric proton doublet at δ 4.44 ppm ($J = 7.4$ Hz) and two methoxyl singlets at δ 3.62 ppm and δ 3.46 ppm, indicative of the presence of a 2,4-di-*O*-methyl-β-D-xylopyranosyl unit (8–13).

The ^{13}C-nmr spectrum of forbeside I indicates a total of 34 carbon signals (Table 1). Based on a DEPT experiment and comparison with similar compounds (6), 19 carbon signals assignable to the steroid nucleus (from C-1 to C-19) and seven carbon signals assignable to a 2,4-di-*O*-methyl-β-D-xylopyranosyl unit are superimposable with the corresponding signals of forbeside J, while the remaining eight carbon signals are nearly coincident with the ^{13}C chemical shifts for the side chain (from C-20 to C-27) of (24*S*)-5α-cholesta-3β,6α,8,15β,24-pentaol and (24*S*)-5α-cholesta-3β,4β,6α,8,15β,24-hexaol (9), so they must share the same side chain. The ^{1}H-nmr data (Table 1) of forbeside I closely parallel those of forbeside J, except the signal for H-24 which is shifted upfield to δ 3.20 ppm due to the lack of glycosylation at that site.

Thus forbeside I is formulated as (24*S*)-3-*O*-(2,4-di-*O*-methyl-β-D-xylopyranosyl)-5α-cholesta-3β,4β,6β,8,15α,24-hexaol [**3**].

Forbeside K [**4**] displays a base peak at *m/z* 757 corresponding to pseudomolecular ion $[M(C_{39}H_{66}O_{14}) - H]^-$ in its negative ion fab mass spectrum. It also shows two prominent fragments at *m/z* 609 and 611, corresponding to losses of an arabinosyl unit by cleavage of the C-1′–O linkage and a methyl xylosyl unit by cleavage of the C-27–O bond, respectively, from molecular mass of 758.

The ^{1}H-nmr spectrum of forbeside K in CD_3OD (Table 2) shows two methyl singlets at δ 0.96 ppm for H-18, δ 1.44 ppm for H-19, and a methyl doublet at δ 0.96 ppm for H-21. Two anomeric sugar proton doublets at δ 4.46 ppm ($J = 7.5$ Hz) and δ 4.83 ppm ($J = 1.4$ Hz), and a methyl singlet at δ 3.62 ppm are indicative of the presence of an α-L-arabinofuranosyl unit and a 2-*O*-methyl-β-D-xylopyranosyl unit (4–7, 14, 15).

The ^{13}C-nmr spectrum of forbeside K shows a total of 39 carbon signals (Table 2). Based on a DEPT experiment and comparison with forbeside J and related compounds (6), an α-L-arabinofuranosyl unit and a 2-*O*-methyl-β-D-xylopyranosyl unit are immediately identified, since the chemical shifts for both units are virtually coincident with reported data (4–7, 14, 15). Twenty-one carbon signals assignable from C-2 to C-21 of the aglycone are also superimposable with those of forbeside J, so they must share the same steroid ring system. The remaining seven carbon signals are assigned from C-22 to C-28 of the side chain. Two quaternary carbon signals at δ 125.71 ppm and δ 136.33 ppm observed in the ^{13}C-nmr and DEPT spectra are indicative of the presence of a double bond in the side chain. Two methyl carbon signals at δ 19.23 ppm and δ 17.10 ppm must be on a double bond because they give rise to a signal at δ 1.69 ppm in the ^{1}H-nmr spectrum in CD_3OD. These signals appear at δ 1.79 ppm and δ 1.83 ppm in pyridine-d_5. A broad methylene signal at δ 4.09 ppm is present in the ^{1}H-nmr spec-

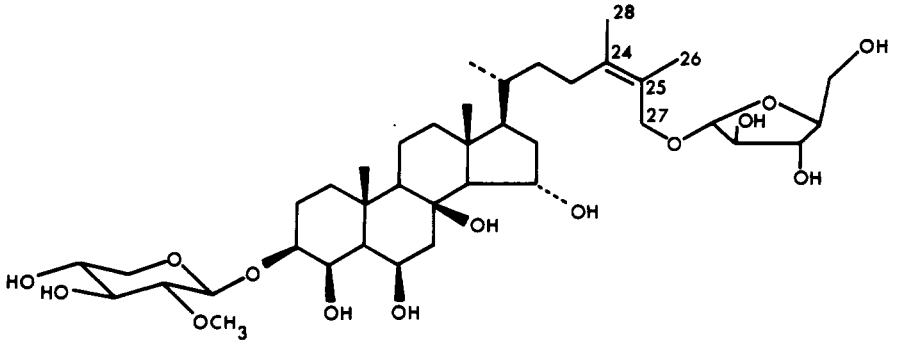
TABLE 2. Nmr Data for Forbeside K [**4**] in CD_3OD.

Position	^{13}C (δ, ppm)[a,c]	^{1}H (δ, ppm)[b,c]
1	40.99	
2	25.29	
3	80.53	3.63 m
4	74.63	4.27 m
5	50.31	1.23
6	76.20	4.27 m
7	45.22	1.61 dd (14.1, 3.0)
		2.43 dd (14.1, 3.0)
8	76.82	
9	57.66	
10	36.92	
11	19.36	
12	42.70	
13	45.50	
14	66.47	
15	70.16	4.27 m
16	41.68	
17	55.52	
18	15.35	0.96 s
19	18.71	1.44 s
20	36.25	1.36 m
21	19.10	0.96 d (5.8)
22	31.63	
23	36.25	
24	125.71	
25	136.33	
26	68.46	4.09 s
27	17.10	1.69 s
28	19.23	1.69 s
X1′	102.65	4.46 d (7.5)
2′	84.71	2.90 dd (8.5, 7.8)
3′	77.66	3.35 dd (8.8, 8.1)
4′	71.28	3.45 m
5′	66.87	3.16 dd (11.3, 9.8)
		3.73 dd (10.8, 4.8)
OMe	61.11	3.62 s
A1″	108.04	4.83 d (1.4)
2″	83.73	3.95 m
3″	79.09	3.84 dd (5.8, 3.3)
4″	85.47	3.95 m
5″	63.14	3.63 dd (11.4, 4.6)
		3.74 dd (10.8, 3.3)

[a] ^{13}C assignments by comparison with **3** assisted by DEPT and INEPT experiments.
[b] ^{1}H assignments by comparison with **3** assisted by 2D-COSY data.
[c] Multiplicities were obtained by DEPT spectra.

trum. A selective INEPT experiment (16) reveals that this methylene carbon is connected to C-25 of the double bond. The *Z* configuration for the double bond is determined by the 2D-COSY spectrum, in which the methylene proton signal at δ 4.09 ppm shows a homoallylic cross peak with a methyl singlet at δ 1.69 ppm. Hence the side chain of the aglycone is formulated as shown in structure **4**.

The location of the 2-*O*-methyl-β-D-xylopyranosyl unit at C-3 and the α-L-arabinofuranosyl unit at C-27 of the aglycone are inferred from the coincident ^{13}C-nmr chemical shifts for the steroid ring system with those of similar saponins (6).

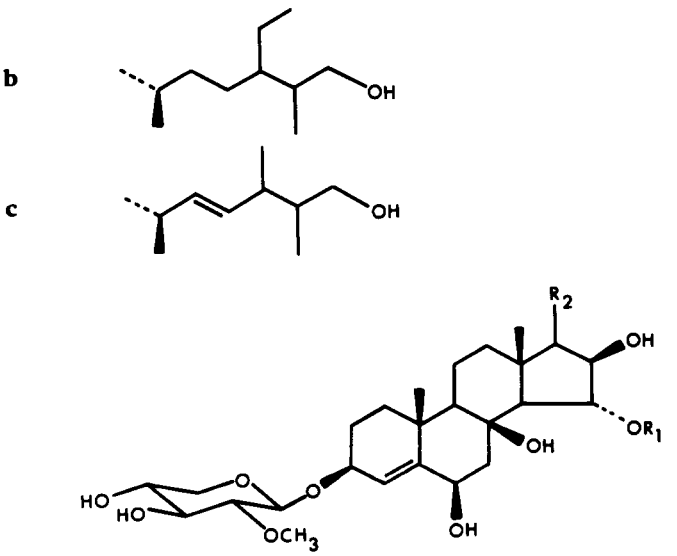


4

Thus, forbeside K is (24Z)-3-*O*-(2-*O*-methyl-β-D-xylopyranosyl)-27-*O*-α-L-arabinofuranosyl-24-methyl-5α-cholest-24-ene-3β,4β,6β,8,15α,27-hexaol [**4**].

Forbeside L [**5**] displays a prominent pseudomolecular ion at *m/z* 639 corresponding to $[M(C_{35}H_{60}O_{10}) - H]^-$ in its negative ion fab mass spectrum. The ^{1}H-nmr spectrum in CD_3OD shows two methyl singlets at δ 1.13 ppm for H-18 and δ 1.37 ppm for H-19; two methyl doublets at δ 0.94 ppm for H-21 and δ 0.86 ppm for H-27; and one methyl triplet at δ 0.89 ppm for H-29. In the downfield region, one anomeric sugar proton doublet at δ 4.42 ppm and a methoxy singlet at δ 3.58 ppm are observed. The 2D-COSY spectrum revealed the presence of the 2-*O*-methyl-β-D-xylopyranosyl unit (4–7, 9, 11).

The ^{13}C-nmr spectrum of forbeside L in CD_3OD shows a total of 35 carbon signals (Table 3). On the basis of DEPT experiment, 25 carbon signals assignable to the 2-*O*-methyl-β-D-xylopyranosyl unit and the steroid nucleus (from C-1 to C-19) are almost coincident with those of echinasteroside A [**6**], isolated from *Echinaster sepositus* (14), except for the upfield shift for C-15 (−6.6 ppm) and the downfield shifts for C-14 (+1.9 ppm) and C-16 (+2.8 ppm) due to the lack of sulfate group at C-15 in **5**. The ^{1}H chem-



5 R_1=H, R_2=**b**
6 R_1=SO_3Na, R_2=**c**

TABLE 3. Nmr Data for Forbeside L [5].

Position	CD_3OD		Pyridine-d_5	
	^{13}C (δ, ppm)[a]	^1H (δ, ppm)[b]	^{13}C (δ, ppm)[a]	^1H (δ, ppm)[b]
1	39.71		39.17	
2	27.96		28.09	
3	77.51	4.20 m	76.47	4.49 m
4	126.95	5.64 br s	126.32	5.91 br s
5	148.54		148.49	
6	76.41	4.31 t (2.8)	75.79	4.74 br s
7	44.44	2.58 dd (14.6, 2.6)	44.73	
		1.49 dd (15.0, 3.0)		
8	76.20		75.79	
9	57.86		57.47	
10	37.75		37.47	
11	19.55		19.41	
12	43.02		42.85	
13	45.13		44.86	
14	63.70		64.16	
15	81.02	4.15 dd (11.0, 2.4)	81.02	
16	82.95	3.97 dd (7.5, 2.3)	82.69	
17	60.43		60.43	
18	16.82	1.13 s	17.41	1.65 s
19	22.71	1.37 s	22.90	1.75 s
20	31.06		30.75	
21	18.40	0.94 d (6.6)	18.88	1.14 d (6.6)
22	34.86		34.80	
23	30.80		30.36	
24	43.02		42.81	
25	38.75	1.67 m	39.17	1.95 m
26	66.83	3.52 m	67.32	4.48 m
27	13.69	0.86 d (7.0)	14.24	1.04 d (6.4)
28	23.48		23.19	
29	12.48	0.89 t (7.0)	12.69	0.89 t (7.4)
1′	104.64	4.42 d (7.7)	104.63	4.81 d (7.6)
2′	84.96	2.82 dd (8.8, 7.7)	85.42	3.43 dd (8.2, 7.6)
3′	77.52	3.32 t (8.9)	77.98	4.05 t (8.8)
4′	71.26	3.50 m	71.44	4.21 m
5′	66.64	3.18 d (11.1, 9.8)	66.01	3.63 dd (11.3, 9.5)
		3.81 dd (11.1, 5.2)		4.34 dd (11.3, 5.4)
OMe	61.20	3.58 s	61.00	3.69 s

[a] ^{13}C assignments from comparison with echinasterosides A and B and assisted by DEPT experiment.
[b] ^1H assignments from comparison with desulfated echinasterosides A and B (14) and desulfated attenuatoside S3 (17), and assisted by 2D-COSY.

ical shifts for the steroid nucleus and sugar moiety of forbeside L are in good agreement with those of desulfated echinasteroside A (14). The remaining ten carbon signals are assigned to the side chain for forbeside L. The methylene carbon signal at δ 66.83 ppm indicates that the CH_2OH group must be connected to a methine carbon. The 2D-COSY spectra in CD_3OD and in pyridine-d_5 reveal the presence of a $-CH_2CH_3$ group and a $-CH(CH_3)CH_2OH$ group, so that the side chain of forbeside L is formulated as in the aglycone of attenuatoside S3 (17). Furthermore, the ^1H chemical shifts for the side chain of forbeside L are consistent with those of desulfated attenuatoside S3 (7).

The sugar moiety is located at C-3 in view of the coincident ^{13}C chemical shifts for C-2, C-3, and C-4 with those of echinasteroside A (14). The stereochemistry at C-24 and C-25 remains to be established.

Thus, forbeside L has the structure 3-*O*-(2-*O*-methyl-β-D-xylopyranosyl)-24-ethyl-5α-cholest-4-ene-3β,6β,8,15α,16β,26-hexaol [**5**].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Nmr spectra were recorded on Varian 200 and Bruker AM-500 NMR spectrometers using TMS as internal reference. $^1H/^1H$ correlation (COSY) spectra were acquired as 512 F1D's of 2K data points and 3.3 KHz spectral window, using a 90° pulse of 22 μsec and a recycle time of 3.3 sec. Spectra were processed using sine-bell squared functions shifted π/4 in F1 and were zero-filled in F1 for a final digital resolution of 3.2 Hz per point. $^1H/^{13}C$ correlation (HETCOR) spectra were acquired as 256 F1D's of 4K data points with a 3-sec recycle time and 14 KHz and 2.8 KHz spectral windows in F2 (^{13}C) and F1 (^1H), respectively. The data matrix was zero-filled in F1, processed using sine-bell squared functions shifted π/2 in F2 and π/4 in F1, and plotted as power spectra. Fab mass spectra were recorded on a Kratos MS50 instrument using Xenon as ionizing gas. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Preparative tlc was performed with precoated Si gel F254 (1 mm) and KC18F reversed-phase (0.25 mm) plates.

ISOLATION OF FORBESIDES I, J, K, AND L.—The starfish *A. forbesi* (20 kg wet wt) was extracted with MeOH as previously described (18). The MeOH eluate from the Amberlite XAD-2 column was concentrated to small volume (250 ml) and treated with cold Me_2CO (2500 ml). The Me_2CO-soluble portion was filtered and evaporated yielding an extract (2.3 g) which was dissolved in $CHCl_3$-MeOH (9:1) and filtered; the filtrate was chromatographed on a Si gel (200 g, 230–400 mesh) column and eluted with the same solvent system, yielding nine fractions.

Fraction 3 (60 mg) was rechromatographed on a Si gel (30 g, 230–400 mesh) column and eluted with $CHCl_3$-MeOH (19:1), yielding forbeside I (16 mg).

Fraction 6 was recrystallized with Me_2CO-MeOH (9:1) yielding forbeside J (25 mg).

Fraction 7 (86 mg) was rechromatographed on a Si gel (40 g, 230–400 mesh) column and eluted with $CHCl_3$-MeOH (9:1), yielding a mixture of forbesides K and L (ca. 25 mg). The pure forbesides K (10 mg) and L (7 mg) were obtained by careful chromatography over a Lichroprep RP-18 column (10 g, 25–40 μm) using MeOH-H_2O (9:1) as solvent.

Forbeside I [**3**].—Colorless powder: mp 214° (dec); $[\alpha]_D$ −8.0° ($c = 0.6$, H_2O); ^1H and ^{13}C nmr see Table 1; negative ion fabms (magic bullet) *m/z* $[M]^-$ 628 (3%), $[M-H]^-$ 627 (5%), $[M-OH]^-$ 611 (2%), 467 (2%).

Forbeside J [**1**].—Colorless powder: mp 250° (dec); $[\alpha]_D$ −17.4° ($c = 1.0$, H_2O); ^1H and ^{13}C nmr see Table 1; negative ion fabms (magic bullet) *m/z* $[M]^-$ 760 (4%), $[M-H]^-$ 759 (8%), $[M-OH]^-$ 743 (1%), $[M-Ara, C_5H_9O_4]^-$ 627 (1%).

Forbeside K [**4**].—Colorless powder: mp 221° (dec); $[\alpha]_D$ −9.2° ($c = 0.6$, H_2O); ^1H and ^{13}C nmr see Table 2; negative ion fabms (magic bullet) *m/z* $[M-H]^-$ 757 (100%), $[M-Ara, C_5H_9O_5]^-$ 609 (11%), $[609-OH]^-$ 592 (12%), $[M-Mexyl, C_6H_{11}O_4]$ 611 (8%).

Forbeside L [**5**].—Colorless powder: mp 210° (dec); $[\alpha]_D$ −7.8° ($c = 0.4$, H_2O), ^1H and ^{13}C nmr see Table 3; negative ion fabms (magic bullet) *m/z* $[M-H]^-$ 639 (8%), $[M-Mexyl, C_6H_{11}O_5]^-$ 477 (3%).

ACKNOWLEDGMENTS

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