New Steroid Glycosides from the Deep-Water Starfish *Mediaster murrayi*

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Four new 24-*O*-biosides of 5α-cholestane-3*β*,6α,8,15*β*,24-pentaol, designated as mediasterosides M_1 (**1**), M_2 (**2**), M_3 (**3**), and M_4 (**4**), and the previously known 5α-cholestane-3*β*,6*β*,8,15α,16*β*,26-hexaol (**5**) have been isolated from the deep-water starfish *Mediaster murrayi*. Glycosides **1**−**3** contain rare carbohydrate moieties with (1→5) bonds between the monosaccharide units. Compounds **1** and **2** showed the inhibition of cell division of fertilized sea urchin eggs and exhibited moderate hemolytic activities.

Starfish (phylum Echinodermata, class Asteroidea) have proven to be an especially valuable source of structurally diverse steroids.[1,2] In a continuation of our long-term search for new polyhydroxylated steroid metabolites from the starfish inhabiting the northwestern part of the Pacific Ocean,[3,4] we have examined the extracts of the deep-water starfish *Mediaster murrayi* Macan, 1938 (Valvatida, Goniasteridae).

Results and Discussion

The animals were collected using a small trawl from an underwater mountain (depth 400−600 m) in the Philippine Sea. The water-soluble materials from the MeOH extracts of *M. murrayi* were sequentially subjected to column chromatography on Amberlite XAD-2, Sephadex LH-20, Si gel, and Florisil, followed by reversed-phase HPLC on a Silasorb C_{18} column to give **1**, **2**, **3**+**4**, and **5**. The mixture of **3** and **4** was transformed into their corresponding peracetates and separated by HPLC on a Silasorb C_{18} column. Desacetylation of the peracetates gave **3** and **4**, respectively.

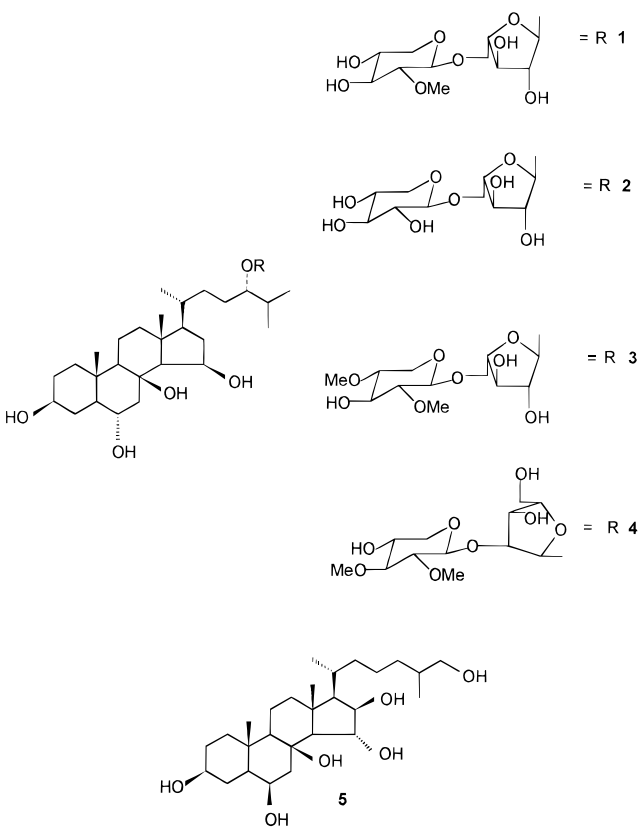

Table 1. Selected NMR Data (C_5D_5N) of the Steroidal Aglycons of Compounds 1−4[a] [*J* (Hz) values are shown in parentheses]

position	δ_C	δ_H	position	δ_C	δ_H
1	39.2		15	70.2	4.75 m
2	32.2		16	42.3	2.61 dt (7.9, 13.8)
3	71.4	3.98 m	17	57.2	
4	33.2	1.82 m 3.09 m	18	16.7	1.61 s
5	54.0	1.52 m	19	14.4	1.37 s
6	66.5	4.37 td (4.0, 10.4)	20	35.6	
7	49.9	3.03 dd (3.6, 12.3)	21	19.0	1.07 d (7.0)
8	76.6		22	32.1	
9	56.8		23	28.4	
10	37.5		24	83.1	3.63 m
11	19.3		25	31.0	1.94 m
12	42.7		26	18.2	0.95 d (7.0)
13	43.8		27	18.4	0.95 d (7.0)
14	61.8	1.12 d (5.8)			

[a] Data extracted from the NMR spectra of **1**. The signals of H_a-4, H-5, H-14, and H-25 were assigned using spin-decoupling experiments for compounds **1**−**4**. The signals of H_3-26 and H_3-27 for **4** differ from compounds **1**−**3** and are 0.99 and 1.02 ppm, respectively.

Mediasterosides M_1 (**1**), M_2 (**2**), M_3 (**3**), and M_4 (**4**) have the same steroid aglycon and showed similar NMR spectra, differing from each other only in the signals of carbohydrate moieties (Tables 1 and 2). The NMR spectra exhibited chemical shifts and corresponding coupling constants closely resembling those of the 3*β*-*O*-glycosylated 6α,8,15*β*-trihydroxylated steroidal nucleus in asterosaponin D_2 from *Distolasterias nippon*.[5] However, there were differences in the ^{13}C NMR resonances of C-2, C-3, and C-4, suggesting that a carbohydrate fragment at C-3 is absent in **1**−**4**. Furthermore, all the signals of steroid nucleus in spectra of **1**−**4** were almost identical to those of ceramasteroside C_5 reported from *Ceramaster patagonicus*.[4] The 3*β*, 6α, 8, 15*β*, and 24 hydroxyl groups in the aglycon of **1**−**4** were confirmed by spin-decoupling experiments. Signals of H-3, H_a-4, H-5, H-6, H-14, H-15, and H-25 were assigned proceeding from characteristic signals of H_e-4, H_e-7, H-16, H_3-26, and H_3-27.

The glycoside **1** exhibited the molecular formula $C_{38}H_{66}O_{13}$ in accordance with elemental analysis, ESIMS, and NMR

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Table 2. Selected NMR Data (C_5D_5N) of the Disaccharide Chains of Compounds **1**−**4**[a] [*J* (Hz) Values Are Shown in Parentheses]

	1		**2**		**3**[b]		**4**[b]	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1′	109.1	5.55 d (1.6)	109.2	5.57 d (1.8)	109.1	5.56 d (2.4)	107.2	5.67 bs
2′	83.9	4.83 dd (2.1, 3.9)	83.9	4.82 m	83.7	4.84 dd (2.7, 4.6)	92.4	4.80 dd (1.2, 2.8)
3′	79.0	4.77 m	79.3	4.88 dd (3.7, 6.4)	79.0	4.75 m	77.6	4.86 m
4′	83.3	4.78 m	83.7	4.81 m	83.0	4.77 m	84.2	4.72 m
5′	69.8	4.47 dd (4.8, 11.0)	69.7	4.52 dd (4.0, 11.4)	69.8	4.46 dd (5.2, 12.2)	62.5	4.42 dd (5.5, 12.5)
5′		4.24 dd (2.4, 11.0)		4.34 dd (3.7, 11.4)		4.25 dd (2.5, 12.2)		4.28 dd (4.6, 12.5)
1″	104.8	4.77 d (8.0)	105.2	4.94 d (8.0)	104.5	4.71 d (7.6)	104.6	4.93 d (7.3)
2″	84.7	3.42 dd (8.0, 9.5)	74.5	4.00 t (8.0)	84.6	3.38 dd (7.3, 8.9)	84.2	3.34 dd (7.3, 8.2)
3″	77.3	4.00 t (9.5)	77.8	4.13 t (8.0)	76.0	3.96 t (8.5)	87.1	3.42 t (8.3)
4″	71.0	4.13 m	70.9	4.18 m	80.5	3.51 m	70.2	4.12 m
5″	67.0	4.24 dd (5.5, 11.0)	66.8	4.30 dd (5.0, 11.5)	63.9	3.31 dd (9.5, 11.2)	66.7	4.18 dd (5.5, 11.0)
5″		3.54 t (11.0)		3.64 dd (9.5, 11.5)		4.17 dd (4.9, 11.2)		3.49 t (10.1)
OMe	60.6	3.87 s			60.5	3.84 s	60.5	3.76 s
OMe					58.6	3.51 s	60.2	3.67 s

[a] ^{1}H NMR assignments aided by spin-decoupling experiments for compounds **1**−**4**. [b] ^{13}C NMR data extracted from the spectra of the mixture of compounds **3** and **4**.

spectral data. The ESIMS of **1** showed a molecular anion peak at *m*/*z* 729 $[M - H]^-$ and a fragment ion peak at *m*/*z* 565, corresponding to the loss of an *O*-methylpentose unit (164 mass units). The glycoside **1** gave 2-*O*-methyl-D-xylose and L-arabinose as a result of acid hydrolysis. The ^{13}C and ^{1}H NMR signals, as well as the corresponding coupling constants of the terminal monosaccharide in the spectra of the **1**, coincided with analogous data of the terminal 2-*O*-methyl-*β*-xylopyranose unit from the spectra of crossasteroside P_1.[6] The signals of the steroidal side chain and the arabinosyl residue coincided with those reported for crossasteroside P_4 from the same starfish (*Crossaster papposus*),[7] which has a 2,4-di-*O*-Me-*β*-D-Xyl$_p$-(1→5)-α-L-Ara$_f$ disaccharide unit attached to C-24. These data suggested that the carbohydrate moiety in **1** comprises a 2-*O*-Me-*β*-D-Xyl$_p$-(1→5)-α-L-Ara$_f$ unit. All sugar signals in the ^{1}H NMR spectrum of **1** were assigned using spin-decoupling techniques (Table 2). The presence of the (1→5) interglycosidic linkage and the attachment of the carbohydrate fragments to C-24 were confirmed by the following additional data. The triplet signal of C-5′ in the arabinosyl residue of **1** was shifted from *δ* 62.5 to 69.8, in comparison with unsubstituted arabinose, as a result of the attachment of the 2-*O*-methylxylose unit at this position. The irradiation of H-1′ (*δ* 5.55) gave an enhancement of H-24 (*δ* 3.63) and H-2′ (*δ* 4.83) under NOE conditions. On the basis of all the abovementioned data, the structure of mediasteroside M_1 (**1**) was established as 24-*O*-[2-*O*-methyl-*β*-D-xylopyranosyl-(1→5)-α-L-arabinofuranosyl]-5α-cholestane-3*β*,6α,8,15*β*,24-pentaol.

The ESIMS of **2** showed a molecular anion peak at *m*/*z* 715 $[M - H]^-$ and fragment ions at *m*/*z* 583 and 451, due to the sequential loss of the first pentose unit (132 mass units) and the second pentose unit (132 mass units). Acid hydrolysis of **2** gave L-arabinose and D-xylose. NMR data of the end *β*-D-xylopyranose in the carbohydrate moiety of **2** were identical with those of solasteroside S_1 from *Solaster dawsoni*,[8] while other signals of the side chain and arabinosyl residue were in good agreement with those of **1**. NOE enhancement of H-1″ at *δ* 4.94 after irradiation of the signal of H-5′ at *δ* 4.52 confirmed the attachment of xylose to C-5′ of arabinose. The enhancements of H-24 at *δ* 3.63 and H-2′ at *δ* 4.82 after irradiation of the signal of H-1′ at *δ* 5.57 established the position of the carbohydrate moiety at C-24 in **2**. Therefore, the structure of mediasteroside M_2 (**2**) could be defined as 24-*O*-[*β*-D-xylopyranosyl-(1→5)-α-L-arabinofuranosyl]-5α-cholestane-3*β*,6α,8,15*β*,24-pentaol.

The ESIMS of **3** gave a molecular anion peak at *m*/*z* 743 $[M - H]^-$ and a fragment ion at *m*/*z* 767, corresponding to the loss of a di-*O*-methylpentose unit (178 mass units). Analysis of the ^{1}H NMR spectra of **3** indicated the presence of a 2,4-di-*O*-Me-*β*-D-Xyl$_p$-(1→5)-α-L-Ara$_f$ carbohydrate moiety, found earlier in crossasteroside P_4 from *C. papposus*[7] (Table 2). Accordingly, the identity of the corresponding signals with those described earlier[7] as well as spin-decoupling and NOE experiments performed in the same manner as for **1** and **2** showed that **3** is 24-*O*-[*β*-D-2,4-di-*O*-methylxylopyranosyl-(1→5)-α-L-arabinofuranosyl]-5α-cholestane-3*β*,6α,8,15*β*,24-pentaol.

The ESIMS of **4** gave a molecular anion peak at *m*/*z* 743 $[M - H]^-$. The signals of H-1′ through H-5′ in the ^{1}H NMR spectrum of **4** were similar to those of the α-arabinofuranose unit, glycosylated at C-2′, in culcitoside C_1 from C*ulcita novaeguinea*[9] (Table 2). The signals of the terminal monosaccharide in the ^{1}H NMR spectrum of **4** measured in CD_3OD (see Experimental Section) coincided with those of 2,3-di-*O*-methylxylopyranose of henricioside H_2 from *Henricia derjugini*.[10] This suggested that **4** has a 2,3-di-*O*-methyl-*β*-xylopyranosyl-(1→2)-α-arabinofuranosyl disaccharide unit. NOE on H-1′ of arabinose in **4** at *δ* 5.67 resulted in the irradiation of the signal of H-24 at *δ* 3.63. The ^{13}C NMR spectrum was obtained only for the mixture of **3** and **4** (Table 2). This spectrum contained the signals of the carbohydrate chain of **3,** which were practically identical with those of crossasteroside P_4.[7] The signals of the carbohydrate chain of **4** were obtained by subtraction of the spectrum of **3** from the spectrum of **3**+**4**. These signals confirmed the presence of the (1→2) bond between the monosaccharide units. The signal of C-2′ (92.4 ppm) was shifted to lower field and the signals of C-1′ (107.2 ppm) and C-3′ (77.6 ppm) were shifted to higher field, when compared with the spectra of **1**−**3**, due to 2-*O*-glycosylation of the arabinosyl residue. On the basis of this evidence the structure of **4** was established as 24-*O*-[2,3-di-*O*-methyl-*β*-xylopyranosyl-(1→2)-α-arabinofuranosyl]-5α-cholestane-3*β*,6α,8,15*β*,24-pentaol.

(24*S*)-Configurations in **1**−**4** were suggested on the basis of the ^{13}C NMR chemical shifts of the side-chain carbons, which were identical with those of 24-*O*-glycosylated steroid polyols for which 24*S* stereochemistry was determined.[11]

Glycosides **1**−**3** contain rare carbohydrate moieties with a (1→5) bond between the monosaccharide units. Earlier, this type of asterosaponin carbohydrate chain was known only for crossasteroside P_4 from *C. papposus*.[7]

Steroid **5** was identified as the known cholestane-3*β*,6*β*,8,15α,16*β*,26-hexaol[12] by direct comparison (^{1}H NMR, TLC, $[\alpha]_D$) with an authentic sample, previously isolated by our group from *C. papposus*.[13]

Mediasterosides M_1 (**1**) and M_2 (**2**) showed 100% inhibition of cell division of the fertilized eggs of the sea urchin *Strongylocentrotus intermedius* at doses of 2.5×10^{-5} M and 1×10^{-4} M, respectively. When tested for hemolytic activity, **1** and **2** were active with ED_{50} values 6.6×10^{-5} M and 3.5×10^{-5} M, using 1% suspensions of mouse erythrocytes.

Experimental Section

General Experimental Procedures. The optical rotations were determined on a Perkin−Elmer 141 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer at 250 and 62.9 MHz with tetramethylsilane as an internal standard. MS were obtained by consecutive MS−MS experiments on a LCQ ion-trap mass spectrometer (Finnigan MAT, San Jose, CA) equipped with a standard ESI (electrospray ionization) source. HPLC separations were conducted on a column with Silasorb C_{18} (13 μ, 250 × 9.4 mm) using a DuPont 8800 chromatograph equipped with differential refractometer. GLC analysis was carried out using a Tsvet-110 apparatus, with a glass column (0.3 × 150 cm) containing 1.5% QF-1 as the stationary liquid phase and Chromatone N−HMDS as the stationary solid phase. The following experimental conditions were used: carrier gas, Ar at 60 mL/min; column temperature from 150 to 225 °C/min. Column low-pressure liquid chromatography separations were performed using Si gel L (40/100 μm, Chemapol, Prague, Czech Republic), Florisil (100−200 mesh, Koch-Light Laboratories Ltd., U.K.), Amberlite XAD-2 (20−80 mesh), and Sephadex LH-20 (Sigma Chemical Co). Glass plates (4.5 × 6.0 cm) with Si gel L (5/40 μm, Chemapol) were used for thin-layer chromatography.

Animal Material. Specimens of *M. murrayi* were collected by dredging from a depth of 400−600 m in the Philippines Sea (research vessel *Akademik Oparin*; 13th scientific cruise) in April 1991. Species identification was carried out by Dr. A. V. Smirnov (Zoological Institute of the Russian Academy of Science, Saint Petersburg, Russia). Voucher specimens (no. 01345) are kept in the zoological collection of the Zoological Institute.

Extraction and Isolation. The lyophilized animals (4.5 kg) were extracted twice with MeOH. The combined extracts were evaporated, and the residue was dissolved in distilled H_2O. The H_2O-soluble fraction was passed through an Amberlite XAD-2 column (1 kg) and eluted with distilled H_2O until a negative chloride reaction was obtained, followed by MeOH. The MeOH eluate was evaporated to give a brownish material (19.0 g) that was chromatographed on a Sephadex LH-20 column (4 × 100 cm) with MeOH−H_2O (2:1). Fractions were analyzed by TLC on Si gel in $CHCl_3$−MeOH−H_2O (30:15:2) and detected by spraying with H_2SO_4. Two subfractions containing mixtures of polyhydroxylated steroids were purified on a Si gel column (4 × 18 cm) using $CHCl_3$−MeOH (4:0.5 → 2:1) and analyzed by TLC on Si gel in toluene−EtOH (9:5). This afforded four main fractions, containing **1** (R_f 0.38), **2** (R_f 0.33), a mixture of **3** and **4** (R_f 0.47), and **5** (R_f 0.55). Each fraction was chromatographed on a Florisil column (2 × 15 cm) using $CHCl_3$−MeOH (20:1 → 20:5), but this gave only one pure compound **2** (31 mg). HPLC of the remaining fractions on a Silasorb C_{18} (13 μ, 250 × 9.4 mm, 3 mL/min) column with MeOH−H_2O (4:1) yielded pure **1** (83 mg), **5** (5 mg), and a mixture of **3** and **4** 2:1 (23 mg).

A mixture of **3** and **4** (23 mg) was treated with 5 mL of Ac_2O−pyridine (1:1) at room temperature for 12 h. The reaction solution was evaporated under reduced pressure and then chromatographed by HPLC on a Silasorb C_{18} (13 μ, 250 × 9.4 mm, 3 mL/min) column with EtOH−H_2O (7:1) to give the peracetates of **3** (5.0 mg) and **4** (3.0 mg). The peracetate of **3** was treated with dry 3% MeONa−MeOH (2 mL) at room temperature for 12 h. The reaction mixture was neutralized by adding aqueous 0.5 N HCl and then evaporated. The residue was purified by reversed-phase column chromatography on a powdered Teflon (Polychrom-1, Biolar, Latvia) column with EtOH−H_2O gradient (0:1 → 1:1) to give pure **3** (3 mg). The peracetate of **4** was treated in the same manner as described above to give pure compound **4** (2 mg).

Compound 1: amorphous powder; $[\alpha]_D$ −36.0° (*c* 0.3, MeOH); ^{1}H and ^{13}C NMR (aglycon), see Table 1; ^{1}H and ^{13}C NMR (sugars), see Table 2; ESIMS (negative ion mode) *m/z* 729 $[M - H]^-$, 565 $[(M - H) - C_6H_{12}O_5]^-$; *anal.* C 62.44%, H 9.06%, calcd for $C_{38}H_{66}O_{13}$, C 62.47%, H 9.04%.

Compound 2: amorphous powder; $[\alpha]_D$ −15.8° (*c* 1.2, MeOH); ^{1}H and ^{13}C NMR data (aglycon), see Table 1; ^{1}H and ^{13}C NMR data (sugars), see Table 2; ESIMS (negative ion mode) *m/z* 715 $[M - H]^-$, 583 $[(M - H) - C_5H_8O_4]^-$.

Compound 3: amorphous powder; $[\alpha]_D$ −22.5° (*c* 0.4, MeOH); ^{1}H and ^{13}C NMR data (aglycon), see Table 1; ^{1}H and ^{13}C NMR data (sugars), see Tables 2; ESIMS (negative ion mode) *m/z* 743 $[M - H]^-$, 565 $[(M - H) - C_7H_{14}O_5]^-$.

Compound 4: amorphous powder; $[\alpha]_D$ −10.4° (*c* 0.2, MeOH); ^{1}H and ^{13}C NMR data (aglycon), see Table 1; ^{1}H and ^{13}C NMR data (sugars), see Table 2; selected ^{1}H NMR (CD_3-OD) signals for the 2,3-di-*O*-methyl-β-xylopyranosyl unit in **4** were: δ 4.42 (1H, d, J = 7.6 Hz, H-1″), 2.90 (1H, dd, J = 7.6, 8.8 Hz, H-2″), 3.03 (1H, t, J = 8.8 Hz, H-3″), 3.49 (1H, m, H-4″), 3.78 (1H, dd, J = 6.0, 11.0 Hz, H_e-5″), 3.13 (1H, t, J = 10.8 Hz, H_a-5″), 3.55 (3H, s, OMe), 3.59 (3H, s, OMe); ESIMS (negative ion mode) *m/z* 743 $[M - H]^-$.

Compound 5: amorphous powder; $[\alpha]_D$ +26.9° (*c* 0.4, MeOH); ^{1}H NMR data were identical with those reported by Kicha et al.[13]

Acid Hydrolysis of 1 and 2, and Sugar Analysis. A solution of glycoside **1** (5.5 mg) in aqueous 2N HCl (3 mL) was heated at 100 °C for 4 h. The genins were removed by extraction with $CHCl_3$. The aqueous layer was neutralized by the addition of Dowex (HCO_3-) resin, and the resin was filtered off. The filtrate was analyzed by TLC on Si gel in BuOH−EtOH−H_2O (4:1:2), and the 2-*O*-methylxylose and arabinose units were identified. The 2-*O*-methylxylose moiety was assigned to the D-configuration and arabinose moiety was assigned to the L-configuration by the optical rotation observed for the monosaccharide mixture $[\alpha]_D$ +70.0° (*c* 0.2, H_2O), calcd $[\alpha]_D$ +70.5°. To this monosaccharide mixture was added 1 mL of pyridine and 2 mg of $NH_2OH \cdot HCl$. The mixture was heated at 100 °C for 1 h, then 1 mL of Ac_2O was added and heating continued at 100 °C for another 1 h. Solvents were removed under reduced pressure and the resulting aldononitrile peracetates were analyzed by GLC using standard aldononitrile peracetates as reference samples. The 2-*O*-Me-Xyl and Ara units were identified in the ratio (1:1).

A solution of the glycoside **2** (5.0 mg) in aqueous 2 N HCl (3 mL) was heated at 100 °C for 4 h. The aqueous layer was treated in the same manner as described for **1** and was analyzed by TLC and GLC. The xylose and arabinose units were identified in the ratio (1:1). The xylose was assigned to the D-configuration and arabinose was assigned to the L-configuration by the observed optical rotation of the monosaccharide mixture $[\alpha]_D$ +56.5° (*c* 0.2, H_2O), calcd $[\alpha]_D$ +61.9°.

Bioassay. Hemolytic activity was determined according to the method previously reported.[14] Compounds were tested for the inhibition of cell division of the fertilized eggs of the sea urchin *S. intermedius* by the method.[15]

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