Polyhydroxylated Steroids from the South China Sea Gorgonian *Anthogorgia* sp.

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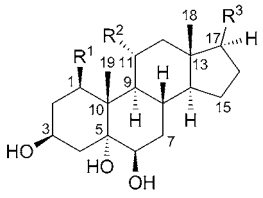
Four new polyhydroxylated steroids, namely anthogorgsteroids A–D (**1**–**4**), were isolated from the South China Sea gorgonian *Anthogorgia* sp. The structures of these compounds were elucidated by detailed spectroscopic analyses and comparison with reported data.

Introduction. – The South China Sea region is a 'biodiversity hotspot', with over 95% of the invertebrates found there being found nowhere else in China. Most of the bio-samples collected for chemical investigation in China originated in this region [1]. Gorgonians of the genus *Anthogorgia* (family Acanthogorgiidae) are prolific in the South China Sea. Literature searching revealed that the chemical constituents of the gorgonians of the genus *Anthogorgia* have not yet been investigated [2]. In the course of our systematic studies on the chemical constituents of the South China Sea corals [3], we made a collection of *Anthogorgia* sp. off Beihai, Guangxi Province, China. Chemical investigation of the Et_2O-soluble fraction from the acetone extract of *Anthogorgia* sp. resulted in the isolation of a ceramide and six steroids [4]. Our continuous investigation of the trace compounds of this animal has now led to the isolation of four new polyhydroxylated steroids, namely anthogorgsteroids A–D (**1**–**4**). All these steroids have the chemical feature of a 3*β*,5*α*,6*β* positioned trihydroxy moiety. We report herein on the isolation and structure elucidation of these compounds.



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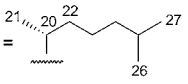

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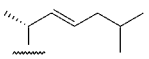

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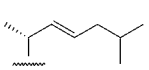

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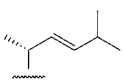

[1)] These two authors contributed equally to this work.

Results and Discussion. – Freshly collected specimen of *Anthogorgia* sp. were immediately frozen and stored at $-20°$ before extraction. The AcOEt-soluble portion of the acetone extract was fractionated by both silica gel and *Sephadex LH-20* column chromatography to afford a steroid mixture. This mixture was separated by reversed-phase HPLC to yield the four pure compounds **1**–**4**.

Anthogorgsteroid A (**1**) was isolated as a white amorphous powder. Its molecular formula $C_{27}H_{48}O_4$ was deduced from the quasi-molecular ion at *m/z* 435.3476 ($[M-H]^+$) in the HR-ESI-MS. The IR spectrum showed the presence of OH groups (3337 cm^{-1}), in agreement with the presence of four O-bearing C-atoms (δ(C) 68.1 (*d*), 69.4 (*d*), 76.5 (*d*), and 77.3 (*s*)) in the ^{13}C-NMR spectrum and three CH–O groups (δ(H) 3.33, 3.73, and 3.86–3.91) in the ^{1}H-NMR spectrum (*Table 1*). The ^{13}C-NMR and DEPT spectra revealed additional 23 sp^3 C-atoms signals (two C, six CH, ten CH_2, and five Me), which were completely assigned to their corresponding H-atom signals by a HMQC experiment (*Table 1*). Analysis of ^{1}H,^{1}H-COSY plot led to the two separated H-atom spin systems CH_2(1) to CH_2(4), and H–C(6) to Me(26) and Me(27)) as shown in the *Figure*. Two significant HMBC cross-peaks from Me(19) to C(1), C(5), C(9), and C(10), and from Me(18) to C(12), C(13), C(14), and C(17) allowed to connect the two H-atom spin systems and to establish the constitution of **1**. The location of OH–C(11) was deduced from the H-atom correlations H–C(9)/H–C(11)/CH_2(12), and further confirmed by the diagnostic long-range correlations from H–C(11) to C(10) and C(13), and from both H–C(9) and CH_2(12) to C(11) (*Fig.*). A comparison of the ^{13}C-NMR data of **1** with those of (3β,5α,6β)-cholestane-3,5,6-triol [4] readily revealed that **1** is its 11-hydroxy analog. A β-configuration of H–C(11) was deduced from its coupling pattern (*dt*, $J = 10.6$, 4.8 Hz) and supported by the observation of distinct NOE cross-peaks between H–C(11) and both Me(18) and Me(19) (*Fig.*). In fact, the 11-epimer of anthogorgsteroid A (**1**), menellsteroid A, was once obtained from the South China See gorgonian *Menella verrucosa*, showing an obviously different coupling pattern (br. *s*) for the α-configuration of H–C(11) [3c]. Anthogorgsteroid A (**1**) was thus determined as (3β,5α,6β,11α)-cholestane-3,5,6,11-tetrol.

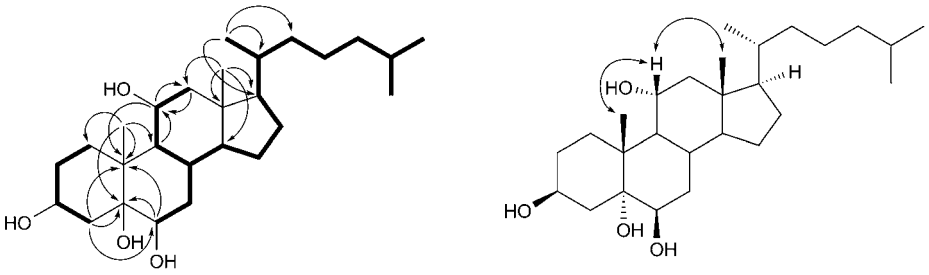

Figure. *^{1}H,^{1}H-COSY* (—), *selected HMBC* (H → C), *and key NOESY* (H ↔ H) *features of* **1**

Anthogorgsteroid B (**2**) was obtained as a white amorphous powder with a molecular formula $C_{27}H_{46}O_4$ as established by HR-ESI-MS, showing two mass units less than **1**. Comparison of the ^{1}H- and ^{13}C-NMR data of **2** with those of **1** (*Table 1*) revealed similarity. The difference was observed in the side chain. Two olefinic H-atom

Table 1. ^{1}H- and ^{13}C-*NMR Data* (400 and 100 MHz, resp.; CD_3OD) *of Anthogorgsteroids A* (**1**) *and B* (**2**)[a]). δ in ppm, J in Hz.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
CH_2(1)	1.66–1.71[b]) (H_α), 1.93–1.98[b]) (H_β)	35.2 (*t*)	1.66–1.71[b]) (H_α), 1.93–1.98[b]) (H_β)	35.2 (*t*)
CH_2(2)	1.60–1.65 (*m*, H_α), 1.38–1.43 (*m*, H_β)	32.0 (*t*)	1.60–1.65 (*m*, H_α), 1.38–1.43 (*m*, H_β)	31.9 (*t*)
H–C(3)	3.86–3.91 (*m*)	68.1 (*d*)	3.86–3.91 (*m*)	68.1 (*d*)
CH_2(4)	1.42–1.47 (*m*, H_α), 1.95–2.00 (*m*, H_β)	41.8 (*t*)	1.42–1.47 (*m*, H_α), 1.95–2.00 (*m*, H_β)	41.9 (*t*)
C(5)		77.3 (*s*)		77.3 (*s*)
H–C(6)	3.33 (br. *s*)	76.5 (*d*)	3.33 (br. *s*)	76.5 (*d*)
CH_2(7)	1.63–1.68 (*m*, H_α), 1.37–1.42 (*m*, H_β)	35.1 (*t*)	1.66 (*m*, H_α), 1.40 (*m*, H_β)	35.1 (*t*)
H–C(8)	1.63–1.68 (*m*)	30.3 (*d*)	1.65–1.70 (*m*)	30.3 (*d*)
H–C(9)	1.31–1.36 (*m*)	53.0 (*d*)	1.32–1.37 (*m*)	53.0 (*d*)
C(10)		40.9 (*s*)		40.9 (*s*)
H–C(11)	3.73 (*dt*, J = 10.6, 4.8)	69.4 (*d*)	3.73 (*dt*, J = 10.6, 4.8)	69.3 (*d*)
CH_2(12)	1.09–1.14[b]) (H_α), 2.16 (*dd*, J = 12.0, 4.8, H_β)	52.7 (*t*)	1.11–1.16[b]) (H_α), 2.14 (*dd*, J = 12.0, 4.8, H_β)	52.6 (*t*)
C(13)		44.2 (*s*)		44.0 (*s*)
H–C(14)	1.05–1.10 (*m*)	56.5 (*d*)	1.06–1.11 (*m*)	56.6 (*d*)
CH_2(15)	1.45–1.50 (*m*, H_α), 0.97–1.02 (*m*, H_β)	25.2 (*t*)	1.42–1.47 (*m*, H_α), 0.96–1.01 (*m*, H_β)	25.1 (*t*)
CH_2(16)	1.75–1.80 (*m*, H_α), 1.15–1.20 (*m*, H_β)	29.3 (*t*)	1.59–1.64 (*m*, H_α), 1.15–1.20 (*m*, H_β)	29.8 (*t*)
H–C(17)	1.05–1.10 (*m*)	57.5 (*d*)	1.05–1.10 (*m*)	57.3 (*d*)
Me(18)	0.63 (*s*)	13.4 (*q*)	0.64 (*s*)	13.5 (*q*)
Me(19)	1.17 (*s*)	17.4 (*q*)	1.17 (*s*)	17.4 (*q*)
H–C(20)	1.26–1.31 (*m*)	37.0 (*d*)	1.91–1.96 (*m*)	41.4 (*d*)
Me(21)	0.86 (*d*, J = 6.5)	19.0 (*q*)	0.94 (*d*, J = 6.6)	21.2 (*q*)
CH_2(22) or H–C(22)	0.89–0.94 (*m*, H_a), 1.24–1.29 (*m*, H_b)	37.2 (*t*)	5.11 (*dd*, J = 15.2, 8.2)	139.2 (*d*)
CH_2(23) or H–C(23)	1.25–1.30 (*m*, H_a), 1.06–1.11 (*m*, H_b)	24.8 (*t*)	5.21 (*ddd*, J = 15.2, 7.0, 6.9)	127.5 (*d*)
CH_2(24)	1.02–1.07 (*m*, H_a), 1.02–1.07 (*m*, H_b)	40.6 (*t*)	1.71–1.76 (*m*, H_a), 1.71–1.76 (*m*, H_b)	43.0 (*t*)
H–C(25)	1.40–1.45 (*m*)	29.1 (*d*)	1.46–1.51 (*m*)	29.7 (*d*)
H–C(26)	0.77 (*d*, J = 6.6)	22.8 (*q*)	0.78 (*d*, J = 6.6)	22.6 (*q*)
Me(27)	0.79 (*d*, J = 6.6)	23.1 (*q*)	0.78 (*d*, J = 6.6)	22.6 (*q*)

[a]) Assignments by DEPT, ^{1}H,^{1}H-COSY, HSQC, HMBC, and NOESY. [b]) Overlapped signal.

signals were present as an *AB* system (δ(H) 5.11 (*dd*, J = 15.2, 8.2 Hz) and 5.21 (*ddd*, J = 15.2, 7.0, 6.9 Hz)) in the ^{1}H-NMR spectrum of **2**. This definic bond was assigned to C(22)=C(23) due to the observation of the downfield shift of Me(21) (δ(H) 0.94 in **2** and 0.86 in **1**). This assignment was further supported by the H-atom sequence from Me(21) to Me(26) and Me(27) as shown by the ^{1}H,^{1}H-COSY experiment. The (*E*) configuration of the olefinic bond was established by the large coupling constant (J =

15.2 Hz) between H–C(22) and H–C(23). The assignments of the NMR signals (*Table 1*) of the side chain of **2** were strongly supported by comparison with reported data [3c][3e][5]. These lines of evidence established the structure of **2** as (3*β*,5*α*,6*β*,11*α*,22*E*)-cholest-22-ene-3,5,6,11-tetrol.

Anthogorgsteroid C (**3**), a white amorphous powder, showed the same molecular formula $C_{27}H_{46}O_4$ as **2**, as deduced from its HR-ESI-MS. ^{1}H- and ^{13}C-NMR Data of **3** were also closely correlated to those of compound **2** (*Table 2*), presenting the characteristic signals of an (*E*)-C=C bond (δ(H) 5.13 (*dd*, *J* = 15.2, 8.4 Hz) and 5.18

Table 2. *^{1}H- and ^{13}C-NMR Data* (CD_3OD) *of Anthogorgsteroids C* (**3**) *and D* (**4**)[a]). δ in ppm, *J* in Hz.

	3[b])		**4**[c])	
	δ(H)	δ(C)	δ(H)	δ(C)
H–C(1)	3.85 (*dd*, *J* = 11.8, 4.8)	74.3 (*d*)	3.85 (*dd*, *J* = 11.8, 4.8)	74.3 (*d*)
CH_2(2)	1.86–1.91 (*m*, H_α), 1.39–1.44 (*m*, H_β)	42.4 (*t*)	1.86–1.91 (*m*, H_α), 1.39–1.44 (*m*, H_β)	42.5 (*t*)
H–C(3)	3.89–3.94 (*m*)	65.9 (*d*)	3.89–3.94 (*m*)	66.0 (*d*)
CH_2(4)	1.39–1.44 (*m*, H_α), 1.90–1.95 (*m*, H_β)	41.7 (*t*)	1.90–1.95 (*m*, H_β)	41.6 (*t*)
C(5)		77.5 (*s*)		77.5 (*s*)
H–C(6)	3.33 (br. *s*)	77.0 (*d*)	3.33 (br. *s*)	77.1 (*d*)
CH_2(7)	1.59–1.64 (*m*, H_α), 1.38–1.43 (*m*, H_β)	35.2 (*t*)	1.59–1.64 (*m*, H_α), 1.38–1.43 (*m*, H_β)	35.2 (*t*)
H–C(8)	1.60–1.65 (*m*)	32.1 (*d*)	1.60–1.65 (*m*)	32.3 (*d*)
H–C(9)	1.50–1.55 (*m*)	47.4 (*d*)	1.50–1.55 (*m*)	47.4 (*d*)
C(10)		44.9 (*s*)		44.9 (*s*)
CH_2(11)	2.00–2.05 (*m*, H_α), 1.33–1.38 (*m*, H_β)	25.0 (*t*)	2.00–2.05 (*m*, H_α), 1.28–1.33 (*m*, H_β)	25.1 (*t*)
CH_2(12)	1.42–1.47 (*m*, H_α), 1.87–1.92 (*m*, H_β)	41.8 (*t*)	1.41–1.46 (*m*, H_α), 1.86–1.91 (*m*, H_β)	41.9 (*t*)
C(13)		43.3 (*s*)		43.3 (*s*)
H–C(14)	0.96–1.01 (*m*)	57.6 (*d*)	0.96–1.01 (*m*)	57.7 (*d*)
CH_2(15)	1.45–1.50 (*m*, H_α), 0.96–1.01 (*m*, H_β)	25.5 (*t*)	1.45–1.50 (*m*, H_α), 0.96–1.01 (*m*, H_β)	25.4 (*t*)
CH_2(16)	1.48–1.53 (*m*, H_α), 1.10–1.15 (*m*, H_β)	29.8 (*t*)	1.48–1.53 (*m*, H_α), 1.10–1.15 (*m*, H_β)	29.4 (*t*)
H–C(17)	0.98–1.03 (*m*)	57.6 (*d*)	0.99–1.04 (*m*)	57.7 (*d*)
Me(18)	0.63 (*s*)	12.8 (*q*)	0.62 (*s*)	12.7 (*q*)
Me(19)	1.03 (*s*)	10.2 (*q*)	1.03 (*s*)	10.2 (*q*)
H–C(20)	1.93–1.98 (*m*)	41.5 (*d*)	1.92–1.97 (*m*)	41.4 (*d*)
Me(21)	0.90 (*d*, *J* = 6.6)	21.4 (*q*)	0.89 (*d*, *J* = 6.6)	21.3 (*q*)
H–C(22)	5.13 (*dd*, *J* = 15.2, 8.4)	139.5 (*d*)	5.08 (*dd*, *J* = 15.2, 8.2)	135.1 (*d*)
H–C(23)	5.18 (*ddd*, *J* = 15.2, 7.0, 6.9)	127.3 (*d*)	5.17 (*dd*, *J* = 15.2, 6.5)	136.0 (*d*)
CH_2(24)	1.72–1.77 (*m*)	43.1 (*t*)		
H–C(25)	1.45–1.50 (*m*)	29.6 (*d*)	2.05–2.10 (*m*)	32.1 (*d*)
Me(26)	0.77 (*d*, *J* = 7.2)	22.6 (*q*)	0.84 (*d*, *J* = 6.7)	23.2 (*q*)
Me(27)	0.77 (*d*, *J* = 7.2)	22.6 (*q*)	0.84 (*d*, *J* = 6.7)	23.2 (*q*)

[a]) Assignments by DEPT, ^{1}H,^{1}H-COSY, HSQC, HMBC, and NOESY. [b]) Measured at 600 (^{1}H) and 150 MHz (^{13}C). [c]) Measured at 400 (^{1}H) and 150 MHz (^{13}C).

(*ddd*, $J = 15.2$, 7.0, 6.9 Hz); δ(C) 139.5 and 127.3), a tertiary O-bearing C-atom (δ(C) 77.5), and three secondary OH groups (δ(H) 3.33, 3.85, and 3.89–3.94; δ(C) 65.9, 74.3, and 77.0). However, the secondary alcohol at C(11) of **2** had to be assigned to C(1) of **3** due to the H-atom sequence from H–C(1) to CH_2(4), and from H–C(9) to CH_2(12), as established by the ^{1}H,^{1}H-COSY experiment. The location of OH–C(1) was confirmed by the distinct HMBC cross-peak Me(19)/C(1). The α configuration of H–C(1) was deduced from its coupling pattern (*dd*, $J = 11.8$, 4.8 Hz) and further confirmed by its NOE with H–C(3). These evidences led anthogorgsteroid C (**3**) to be determined as (1β,3β,5α,6β,22*E*)-cholest-22-ene-1,3,5,6-tetrol.

Anthogorgsteroid D (**4**) was isolated as a white amorphous powder. Its molecular formula was established as $C_{26}H_{44}O_4$ by the HR-EI-MS, and thus possessing 14 mass units less than **3**. The NMR spectra of compound **4** (*Table 2*) were closely related to those of **3**, except for the absence of a CH_2 group (**3**: δ(H) 1.72–1.77 (2 H); δ(C) 43.1). This missing group was readily assigned to CH_2(24) due to the obvious downfield-shifted signals of both Me *d* of the i-Pr group in the ^{1}H-NMR spectrum (δ(H) 0.84 in **4**, 0.77 in **3**). Further evidences came from the spin system Me(21)/H–C(20)/H–C(22)/H–C(23)/H–C(25)/Me(26) and Me(27) established by the ^{1}H,^{1}H-COSY experiment, and the long-range correlation from both Me(26) and Me(27) to C(23) and C(25) as deduced from the HMBC spectrum. Anthogorgsteroid D was then determined as (1β,3β,5α,6β,22*E*)-24-norcholest-22-ene-1,3,5,6-tetrol.

Polyoxygenated steroids with a 3β,5α,6β-positioned trihydroxy moiety are frequently encountered in marine invertebrates, such as in sponges [5c][6], anthozoans [5a][5b][7], and starfishes [8]. Interestingly, the 11-epimers of anthogorgsteroids A and B were once obtained from the South China Sea gorgonian *Menella verrucosa*, as mentioned above [3c]. It was reported that sterols with the 3,5,6-trihydroxy moiety might arise biogenetically from the corresponding sterols with a C(5)=C(6) moiety which are commonly produced by animals [5c]. Further biosynthetic studies are encouraged to verify this hypothesis.

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Experimental Part

General. Column chromatography (CC): silica gel (SiO_2; 200–300, and 400–500 mesh; *Yantai Jiangyou Silica Gel Co., Ltd.*, P. R. China). Anal. TLC: precoated SiO_2 plates (*HSGF-254*; *Yantai Jiangyou Silica Gel Co., Ltd.*, P. R. China); detection under UV light or by heating after spraying with anisaldehyde H_2SO_4 reagent. Semi-prep. reversed-phase HPLC: *Agilent-1100* system equipped with a refractive-index detector; *YMC-Pack-ODS-A* column (particle size 5 μm, 250 × 10 mm); t_R in min. Optical rotations: *Autopol-IV* polarimeter; at the Na_D line (590 nm); in $CHCl_3$. IR Spectra: *Nexus-470* FT-IR spectrophotometer (*Nicolet*, USA); in thin polymer films; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-400* and *-Avance-600* spectrometers at 300 K; δ in ppm rel. to the residual C*H*$_3$OH signal (δ(H) 3.21) and CD_3OD (δ(C) 49.0) as internal standard, *J* in Hz; assignments supported by ^{1}H,^{1}H-COSY, HSQC, HMBC, and NOESY experiments. HR-ESI-MS: *Q-TOF-Micro* mass spectrometer, resolution 5000 (*Waters*, USA); in *m*/*z*; an i-PrOH soln. of NaI (2 mg/ml) was used as reference compound.

Animal Material. The gorgonian *Anthogorgia* sp. was collected from the South China Sea in July 2008 and identified by Dr. *Xiu-Bao Li*, the South China Sea Institute of Oceanology, Academia Sinica. A voucher specimen (ZS-1) was deposited with the Second Military Medical University.

Extraction and Isolation. The frozen animals (2.2 kg, wet weight) were cut into small pieces and subsequently extracted with acetone (3×5 l) at r.t. The crude extract of *Anthogorgia* sp. was partitioned between Et_2O and H_2O. The Et_2O extract was concentrated to give a dark green residue (28.0 g). The crude extract was fractionated by CC (SiO_2, $0 \rightarrow 100\%$ acetone/light petroleum ether) followed by CC (*Sephadex LH-20*) and repeated normal-phase CC (SiO_2) to afford the steroid mixture. This mixture was subjected to semi-prep. reversed-phase HPLC (*ODS-HG-5* (5 μm, 250×10 mm), MeOH/H_2O 3:1, 1.0 ml/min^{-1}): pure **1** (1.2 mg; t_R 118.0), **2** (2.7 mg; t_R 89.0), **3** (1.7 mg; t_R 148.0), and **4** (2.1 mg; t_R 97).

Anthogorgsteroid A (=*(3β,5α,6β,11α)-Cholestane-3,5,6,11-tetrol*; **1**): White amorphous powder. M.p. 122–124°. $[\alpha]_D^{20} = -5.3$ ($c = 0.50$, $CHCl_3$). IR (film): 3397, 2929, 2867, 1626, 1463, 1377, 1034. ^{1}H- and ^{13}C-NMR: *Table 1*. HR-ESI-MS: 435.3476 ($[M-H]^-$, $C_{27}H_{47}O^-$; calc. 435.3474).

Anthogorgsteroid B (=*(3β,5α,6β,11α,22*E*)-Cholest-22-ene-3,5,6,11-tetrol*; **2**): White amorphous powder. M.p. 144–146°. $[\alpha]_D^{20} = -27.5$ ($c = 0.45$, $CHCl_3$). IR (film): 3398, 2951, 2929, 2868, 1604, 1462, 1376, 1035, 962. ^{1}H- and ^{13}C-NMR: *Table 1*. HR-ESI-MS: 457.3295 ($[M+Na]^+$, $C_{27}H_{46}NaO_4^+$; calc. 457.3294).

Anthogorgsteroid C (=*(1β,3β,5α,6β,22*E*)-Cholest-22-ene-1,3,5,6-tetrol*; **3**): White amorphous powder. M.p. 260–262°. $[\alpha]_D^{20} = -21.5$ ($c = 0.50$, $CHCl_3$). IR (film): 3337, 2951, 2927, 2867, 1662, 1459, 1377, 1042, 964. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-ESI-MS: 457.3291 ($[M+Na]^+$, $C_{27}H_{46}NaO_4^+$; calc. 457.3294).

Anthogorgsteroid D (=*(1β,3β,5α,6β,22*E*)-24-Norcholest-22-ene-1,3,5,6-tetraol*; **4**): White amorphous powder. M.p. 266–268°. $[\alpha]_D^{20} = -10.8$ ($c = 0.50$, $CHCl_3$). IR (film): 3359, 2922, 2852, 1659, 1464, 1375, 1039, 963. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-ESI-MS: 443.3134 ($[M+Na]^+$, $C_{26}H_{44}NaO_4^+$; calc. 443.3137).

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