Anthoptilides A−E, New Briarane Diterpenes from the Australian Sea Pen *Anthoptilum* cf. *kukenthali*

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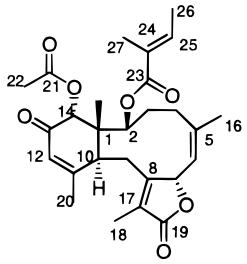
The Australian sea pen *Anthoptilum* cf. *kukenthali* has afforded five new briarane-type diterpenes, anthoptilides A−E. Their structures were determined on the basis of their spectroscopic data. Single-crystal X-ray determination was performed on anthoptilide A. Anthoptilides B and C inhibited the binding of [^{3}H]1,3-dipropyl-8-cyclopentylxanthine ([^{3}H]DPCPX) on adenosine A_1 receptors.

Marine coelenterates of the order Pennatulacea have been proven to be rich sources of diterpenoids belonging to the skeletal class of briaranes, diterpenoid γ-lactones of a highly substituted bicyclo[8.4.0] system.[1−5] Briarane diterpenes isolated from gorgonians, and occasionally their predators, have been reported to have interesting bioactivity ranging from cytotoxic,[6−11] anti-inflamatory,[12−14] antiviral,[6,14] and insecticidal[15] to immunomodulatory[16] activity. In our continuing search for compounds inhibiting the binding of [^{3}H]1,3-dipropyl-8-cyclopentylxanthine ([^{3}H]-DPCPX),[17] a selective A_1 radioligand antagonist, on adenosine A_1 receptors, we examined an extract of the Australian sea pen *Anthoptilum* cf. *kukenthali* Hickson 1916 (phylum Cnidaria, class Octocorallia, order Pennatulacea, family Anthoptilidae). Bioassay-guided purification afforded five new briarane diterpenes, anthoptilide A−E (**1**−**5**), which are reported in this paper. Anthoptilide D contained a benzoate moiety, which is uncommon in the briarane series.[5] The occurrence of a tiglate group has not been reported in briaranes.

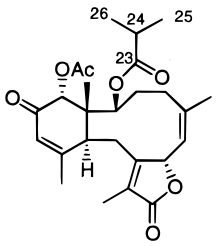
Results and Discussion

Freeze-dried A*nthoptilum* cf. *kukenthali* was extracted exhaustively with CH_2Cl_2. The extract was chromatographed over silica-based diol with hexane, hexanes−EtOAc, EtOAc, and MeOH. The hexanes−EtOAc fraction was rechromatographed on diol normal-phase HPLC to yield anthoptilides A−E (**1**−**5**).

Anthoptilide A (**1**) was isolated as white needles from MeOH. The molecular formula $C_{27}H_{34}O_7$, established by HRESIMS, indicated 11 degrees of unsaturation for **1**. The IR spectrum of **1** showed the presence of a γ-lactone (ν_{max} 1752 cm^{-1}) and ester carbonyl groups (ν_{max} 1698 and 1685 cm^{-1}). The ^{1}H NMR spectrum had resonances due to three oxymethine protons at δ 5.22 (1H, d, J = 9.0 Hz), 5.08 (1H, t, J = 3.6 Hz), and 4.88 (1H, s); four quaternary methyl groups at δ 1.10, 1.90, 1.92, and 2.08; and an acetate methyl at δ 2.00. The ^{13}C NMR spectrum showed four carbonyl resonances at 167.1, 169.0, 173.6, and 193.2 ppm, confirming the presence of a γ-lactone, two ester groups, and a ketone. The HMQC experiment allowed the assignment of all the protons to the corresponding carbon atoms (Table 1). The presence of a tiglate group was indicated by two methyl groups at δ 1.84 (t, J = 1.2 Hz) and 1.82 (dd, J = 6.6, 1.2 Hz), and an olefinic proton at δ 6.83 (ddd, J = 6.6, 6.6, 1.2 Hz), which coupled (HMBC) to C-23 (167.1 ppm), C-24 (128.2 ppm), C-26 (14.6 ppm), and C-27 (12.3 ppm). The resonance of the olefinic proton at δ 6.83 established that this ester group was a tiglate and not the angelate.[18] The main framework of **1** was found to be a briarane-type diterpene and was established by an analysis of 1D and 2D NMR data. The ^{1}H−^{1}H COSY spectrum allowed us to establish the proton sequences from H-2 to H-4 and from H-6 to H-7. The 10-membered ring was established by key HMBC correlations from H-2 to C-1, C-4, C-10; H-7 to C-5, C-6, C-8; and H-9 to C-1, C-7, C-8, C-10. The cyclohexene ring fused to the 10-membered ring at C-1 and C-10 was deduced by HMBC correlations between H-9 and C-1, C-10, C-11; H-14 and C-1, C-10, C-12, C-13, C-15. The α-methyl-



(**1**)



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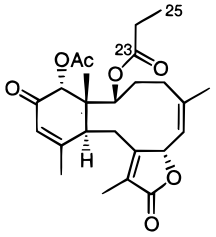

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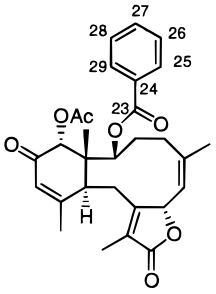

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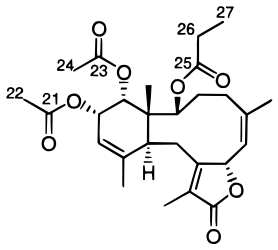

(**5**)

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Table 1. ^{1}H, ^{13}C NMR, HMBC, and ROESY Data of Anthoptilide A (**1**)

position	^{1}H[a]	^{13}C[b]	HMBC[a]	ROESY[a]
1		44.3		
2	5.08 (t, 3.6)	74.5[c]	1, 4, 10, 14, 15, 23	3α, 4α, 16, 22
3*β*	2.27 (m)	33.5[c]		2, 3α, 4α, 4*β*, 7, 9*β*, 15
3α	1.87 (m)			
4*β*	2.65 (d, 13.2)	29.3		4α, 7
4α	2.35 (m)			3*β*, 4*β*
5		144.3		
6	5.22 (d, 9.0)	122.7	4, 16	3α, 3*β*, 9α
7	5.57 (d, 9.0)	80.7	5, 6, 8, 17	3α, 4α, 4*β*, 6, 9α, 9*β*
8		158.1		
9*β*	3.01 (br d, 16.8)	29.3	1, 7, 8, 10, 11, 17	3*β*, 7, 9α, 15
9α	2.62 (dd, 16.8, 8.0)		7, 8, 10, 11, 17	3α, 3*β*, 7, 9*β*, 15
10	3.27 (br)	39.2		12, 20
11		161.2		
12	5.83 (t, 1.2)	123.5	10, 11, 14, 20	10, 20
13		193.2[d]		
14	4.88 (s)	77.3	1, 2, 10, 12, 13, 15, 21	15, 25, 26
15	1.10 (s)	13.7	1, 2, 10, 14	9α, 9*β*, 14
16	2.08 (s)	26.9[c]	5, 6	2, 6
17		125.6		
18	1.92 (s)	9.8	8, 17, 19	9α
19		173.6		
20	1.90 (s)	22.1	10, 11, 12	9α, 12, 14
21		169.0		
22	2.00 (s)	20.8	21	
23		167.1		
24		128.2		
25	6.83 (ddd, 6.6, 6.6, 1.2)	138.3	23, 26, 27	3*β*, 9*β*, 26, 27
26	1.82 (dd, 6.6, 1.2)	14.6	24, 25	25, 27
27	1.84 (t, 1.2)	12.3	23, 24, 25	26, 27

[a] Spectra were recorded in $CDCl_3$ at 25 °C (600 MHz). [b] Spectrum was recorded in $CDCl_3$ at 25 °C (100 MHz). [c] Assignments were based on HMQC and HMBC data recorded in $CDCl_3$ at 25 °C (400 MHz). [d] Broad signal, assignment was based on HMBC data recorded in $CDCl_3$ at 25 °C (400 MHz).

γ-lactone connected to the 10-membered ring at C-7 and C-8 was established by the HMBC correlations from H-7 to C-8 and C-17; and H-18 to C-8, C-17, and C-19. The remaining tertiary methyl groups, *δ* 1.10, 2.08, and 1.90, were attached to the briarane skeleton at C-1, C-5, and C-11 (HMBC), respectively. The positions of the acetate at C-14 and the tiglate at C-2 were supported by HMBC connectivities from H-14 to C-21, and H-2 to C-23, respectively. The relative stereochemistry of **1** was determined by a ROESY experiment. The ROE correlations from H-10 to H-12 and H_3-20 indicated these protons were on the same face of the six-membered ring and were assigned as the α protons, while H-14 showed ROE responses with H-2 and H_3-15, but not with H-10, confirming the *β*-orientation for this proton. A single-crystal X-ray structure analysis confirmed the molecular structure and relative stereochemistry of anthoptilide A as **1** (Figure 1). The absolute chemistry was not determined.

Compound **2** had a molecular formula of $C_{26}H_{34}O_7$ deduced from the pseudomolecular ion *m*/*z* 481.2216 $[M + Na]^+$ in its HRESIMS. Its spectral data (IR, ^{1}H, ^{13}C) indicated that the only difference between **1** and **2** was the ester group at position C-2. ^{1}H NMR, ^{1}H−^{1}H COSY, and HMBC data allowed the elucidation of an isobutyrate with two methyl resonances (*δ* 1.18, d, *J* = 6.0 Hz, H-25; *δ* 1.16, d, *J* = 6.0 Hz, H-26) coupled to a methine group (*δ* 2.56, m, H-24), which showed HMBC correlations to C-23 (176.3 ppm), C-25 (18.6 ppm), and C-26 (18.7 ppm). Key HMBC correlations between H-2 and C-1, C-4, C-15, C-23 confirmed the isobutyrate at C-2. The relative stereochemistry of anthoptilide B was assumed to be the same as that of **1** due to the similarity of proton−proton coupling constants and ^{1}H and ^{13}C chemical shifts. Thus, anthoptilide B was assigned as **2**.

Anthoptilide C (**3**) was isolated as white powder. Its molecular formula of $C_{25}H_{32}O_7$ was deduced from the pseudomolecular ion at *m*/*z* 467.2027 $[M + Na]^+$ in its HRESIMS. ^{1}H and ^{13}C NMR again showed that **3** differed from **1** at position C-2. A propionate was deduced by the HMBC correlations between H-25 (3H, t, *J* = 7.2 Hz, *δ* 1.13) and C-23 (174.0 ppm), C-24 (27.6 ppm), and its position was confirmed by the key HMBC correlations between H-2

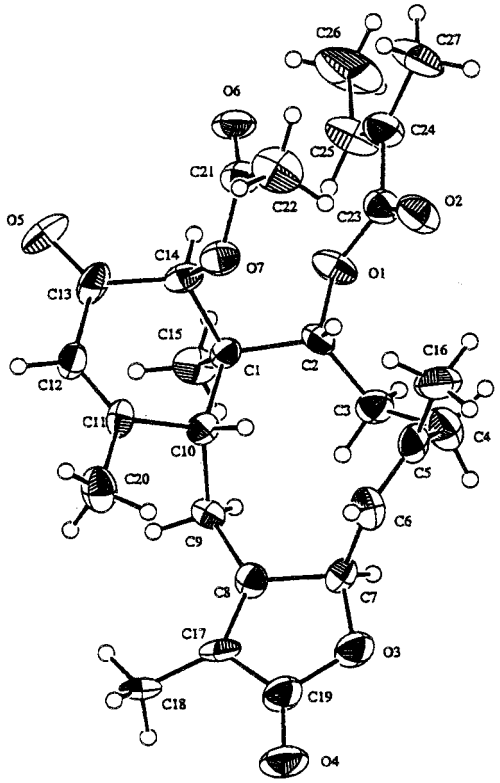

Figure 1. ORTEP representation of **1**.

Table 2. ^{1}H NMR Data for Anthoptilides B−E (**2**−**5**)[a]

position	2	3	4	5
2	4.98 (br s)	4.95 (s)	5.27 (br s)	4.78 (br s)
3β	2.53 (m)	2.25 (m)	2.36 (m)	2.16 (m)
3α	1.82 (m)	1.85 (m)	1.96 (m)	1.72 (m)
4β	2.64 (br d)	2.64 (br d)	2.72 (br d)	2.58 (br d)
4α	2.25 (m)	2.30 (m)	2.34 (m)	2.37 (m)
6	5.21 (d, 9.0)	5.20 (d, 9.2)	5.25 (br)	5.17 (br)
7	5.54 (d, 9.0)	5.53 (d, 9.2)	5.60 (d, 9.2)	5.48 (br)
9β	2.98 (d, 16.2)	2.95 (br d, 16.4)	3.06 (d, 16.2)	2.85 (br d, 16.2)
9α	2.61 (dd, 16.2, 8.4)	2.59 (dd, 16.4, 8.4)	2.67 (dd, 16.2, 8.0)	2.53 (dd, 16.2, 8.4)
10	3.20 (br s)	3.17 (br s)	3.36 (br s)	2.76 (br s)
12	5.82 (s)	5.82 (s)	5.84 (t, 1.2)	5.15 (br s)
13				5.47 (br s)
14	4.89 (s)	4.92 (s)	4.95 (s)	5.22 (br s)
15	1.06 (s)	1.04 (s)	1.20 (s)	1.14 (s)
16	2.07 (s)	2.06 (s)	2.14 (br s)	2.07 (s)
18	1.91 (s)	1.89 (s)	1.92 (s)	1.89 (s)
20	1.89 (s)	1.90 (s)	1.93 (s)	1.65 (s)
22	2.00 (s)	2.00 (s)	2.00 (s)	1.98 (s)
24	2.56 (m)	2.33 (m)		1.97 (s)
25	1.18 (d, 6.0)	1.13 (t, 7.2)	7.98 (dd, 7.2, 1.2)	
26	1.16 (d, 6.0)		7.45 (t, 7.2)	2.31 (m)
27			7.58 (dt, 7.2, 1.2)	1.11 (t, 7.2)
28			7.98 (dd, 7.2, 1.2)	
29			7.45 (t, 7.2)	

[a] Spectra were recorded in $CDCl_3$ at 25 °C (400 MHz).

and C-23. Thus, anthoptilide C, with the same relative stereochemisty as **1**, was assigned as **3**.

Anthoptilide D (**4**) was isolated as white powder with the molecular formula of $C_{29}H_{32}O_7$, deduced from HRESIMS, which indicated 14 degrees of unsaturation. ^{1}H and ^{13}C NMR analysis revealed the briarane skeleton as in **1**, **2**, and **3**, accounting for nine degrees of unsaturation. The other five were explained by the presence of a benzoate group. The aromatic proton signals occurred at δ 7.98 (2H, dd, J = 7.2, 1.2 Hz, H-25), 7.45 (2H, t, J = 7.2 Hz, H-26), and 7.58 (2H, dt, J = 7.2, 1.2 Hz, H-27), the ^{13}C signals at 165.8 (C-23), 129.5 (C-24), 129.5 (C-25), 128.6 (C-26), and 133.4 ppm (C-27), with HMBC correlations from H-25 to C-23, C-24, C-27. Positioning the benzoate at C-2 was based on an HMBC connectivity from H-2 (δ 5.27) to the carbonyl carbon (165.8 ppm, C-23). The relative stereochemistry of **4** was similar to **1**. Thus, anthoptilide D was assigned as **4**.

Anthoptilide E (**5**) was isolated as an amorphous solid, and a molecular formula of $C_{27}H_{36}O_8$ was established by HRESIMS. It was observed that the spectral data (^{1}H and ^{13}C NMR) of **5** were similar to **3**, but differed in the absence of a ketone group at 193.3 ppm (C-13 in **3**) and the presence of an oxymethine proton at δ 5.47 (br s), suggesting that the ketone group at C-13 was replaced by an ester group. The ^{13}C NMR spectrum of **5** showed four carbonyl resonances at 170.6 (2C), 173.8 (1C), and 174.4 (1C) ppm, confirming the presence of a γ-lactone and three ester groups. The ^{1}H NMR spectrum revealed the presence of two acetate methyls at δ 1.97 and 1.98 and a propionoxyl group [δ 1.11 (3H, t, J = 7.2 Hz) and 2.31 (2H, m)]. The propionate position at C-2 was confirmed from the HMBC correlations between H-2 (δ 4.78) and C-25 (174.4 ppm). The acetates were positioned at C-13 and C-14, as confirmed by the connectivities (HMBC) between H-13 (δ 5.47) and C-21 (170.6 ppm) and between H-14 (δ 5.22) and C-23 (170.6 ppm). The ROESY experiment showed that **5** had the same relative stereochemistry as **1** at positions C-1, C-2, C-7, and C-10. H-13 had the ROE correlation with H_3-15, describing the β-orientation for this proton. Thus, the structure of anthoptilide E was assigned as **5**.

Anthoptilide A−E inhibited [^{3}H]CPDPX binding to rat-brain adenosine A_1 receptors with IC_{50} values of 420, 45, 3.1, 500, and 490 μM, respectively.

Experimental Section

General Experimental Procedures. Solvents used were Omnisolv MeOH and EtOAc, while CH_2Cl_2 and hexane were distilled and filtered. The flash column (15 cm × 3.5 cm i.d.) was packed with silica-based diol. A YMC Diol N−P column (5 μm, 15 cm × 4.6 mm i.d.) was used for HPLC. A Waters 600 pump equipped with a 996 PDA detector was used for analytical and semipreparative HPLC separations. NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 and 600 MHz NMR spectrometer with ^{1}H and ^{13}C chemical shifts referenced to the solvent peak δ 7.26 and 77.0 ppm. HRESIMS were measured on a Bruker BioAPEX 47e mass spectrometer. Optical rotations were measured in MeOH using a JASCO P-1020 polarimeter. 2-Chloroadenosine (2-CADO) was purchased from Research Biochemical International; [^{3}H]-1,3-dipropyl-8-cyclopentylxanthine ([^{3}H]DPCPX), from Dupont New Products; and adenosine deaminase type VI, from Sigma Chemical Co.

Animal Material. The animal was collected at the depth of 267 m from CSIRO RV *Southern Surveyor*, on the Northwest side of Port Hedland (18.16.6′ S, 118.11.2′ E), Western Australia. It was identified as *Anthoptilum* cf. *kukenthali* Hickson 1916 (phylum Cnidaria, class Octocorallia, order Pennatulacea, family Anthoptilidae). Voucher specimen QMG306192 has been deposited at the Queensland Museum, South Brisbane, Queensland, Australia.

Extraction and Isolation. Freeze-dried *Anthoptilum* cf. *kukenthali* (2.3 g) was extracted exhaustively with CH_2Cl_2. After evaporation of the solvent, the crude extract (240 mg) was purified through a flash diol column with hexane, hexane−CH_2Cl_2 (1:1), CH_2Cl_2, and MeOH. The active hexane−CH_2Cl_2 (1:1) fraction was then chromatographed further on diol semipreparative HPLC, eluted at 3 mL/min isocratically with hexane−2-propanol (9:1) to give anthoptilides A (13.0 mg, 0.56% dry wt, 18 min), B (13.6 mg, 0.59% dry wt, 16 min), C (10.0 mg, 0.43% dry wt, 19 min), D (8.5 mg, 0.37% dry wt, 21 min), and E (4.0 mg, 0.17% dry wt, 8 min).

Single-Crystal X-ray Crystallography of 1.[19] Suitable colorless, platelike crystals of **1** were obtained by recrystallization from methanol. The crystal (0.50 × 0.05 × 0.15 mm) belongs to the orthorhombic space group $P2_12_12_1$ with a = 9.938(7) Å, b = 28.834(7) Å, c = 8.999(6) Å, V = 2579 Å^3, Z =

Table 3. ^{13}C NMR Data for Anthoptilides B−E (**2**−**5**)[a]

position	2	3	4	5
1	44.0	44.1	44.4	42.6
2	72.4[b]	72.4[b]	74.4[b]	73.6
3	34.0	33.3[b]	33.0[b]	33.7
4	29.3	29.4	29.3	29.5
5	144.3[c]	144.4	144.1	143.8
6	122.6	122.6	122.8	122.8
7	80.6	80.7	80.7	80.8
8	158.0	158.0	158.0	159.1
9	29.3	29.4	29.3	29.6
10	39.2	39.3	39.3	37.8
11	161.1	161.3	161.0	139.3
12	123.4	123.7	123.5	118.3
13	193.3[c]	193.3[c]	193.3[c]	67.8
14	76.6[b]	76.2	77.2	72.1
15	13.1[b]	13.1[b]	14.1[b]	14.8
16	27.8[b]	27.6[b]	27.4[b]	27.7
17	124.7	125.6	125.7	125.1
18	9.8	9.8	9.8	9.7
19	173.5	173.5	173.5	173.8
20	20.7	20.8	22.1	20.9
21	169.0	169.2	169.0	170.6
22	20.8	20.8	20.7	21.2
23	176.3[c]	174.0	165.8	170.6
24	34.2	27.6	129.5	21.1
25	18.6	8.8	129.5	174.4
26	18.7		128.6	27.6
27			133.4	8.8
28			129.5	
29			128.6	

[a] Spectra were recorded in $CDCl_3$ at 25 °C (100 MHz). [b] Assignments were based on HMQC and HMBC data recorded in $CDCl_3$ at 25 °C (400 MHz). [c] Assignments were based on HMBC data recorded in $CDCl_3$ at 25 °C (400 MHz).

4, $D_{calc} = 1.212$ g cm^{-3}. Intensity data were measured on a Rigaku AFC7R diffractometer with graphite monochromated Mo *K*α radiation with $\lambda = 0.710\,69$ Å to $2\theta_{max} = 50°$ yielding 2636 unique reflections, 870 with $I > 2\sigma(I)$ being considered observed. The structure was solved by direct methods and refined by a full-matrix least-squares procedure (program TeXsan, 1992).[20] The non-hydrogen atoms were refined anisotropically; $(x, y, z, U_{iso})_H$ were included and constrained at estimated values. Weights derivative of $w = 1/[\sigma^2(F)]$ were employed. The refinement converged to a final $R = 0.059$, $R_w = 0.051$ for 308 variable parameters.

Receptor Binding Assays. Binding of **1**−**5** to A_1 receptors from rat-brain membranes were performed as described previously.[21] Data were analyzed using a nonlinear, least-squares regression program (Prism 2.0) to determine IC_{50} values.

Anthoptilide A (1): white solid; $[\alpha]^{25}_D$ +92.6° (*c* 0.63 in MeOH); UV (MeOH) λ_{max} (ϵ) 216 (20 200), 241 nm (11 020); IR (film) 1751, 1690, 1685, 1257, 1220 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; (+)-HRESIMS *m*/*z* 493.2218 (calcd for M + Na, $C_{27}H_{34}O_7Na$ 493.2197).

Anthoptilide B (2): white solid, $[\alpha]^{25}_D$ +59.1° (*c* 0.52 in MeOH); UV (MeOH) λ_{max} (ϵ) 216 (18 930), 241 nm (15 370); IR (film) 1752 (br), 1692, 1223 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 3; (+)-HRESIMS *m*/*z* 481.2216 (calcd for M + Na, $C_{26}H_{34}O_7Na$ 481.2197).

Anthoptilide C (3): white solid, $[\alpha]^{25}_D$ +17.6° (*c* 0.19 in MeOH); UV (MeOH) λ_{max} (ϵ) 213 (16 100), 241 nm (13 820); IR (film) 1749, 1717, 1698, 1684, 1653, 1558, 1541, 1507, 1222 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C MMR data, see Table 3; (+)-HRESIMS *m*/*z* 467.2027 (calcd for M + Na, $C_{25}H_{32}O_7Na$ 467.2040).

Anthoptilide D (4): white powder, $[\alpha]^{25}_D$ +104.2° (*c* 0.49 in MeOH); UV (MeOH) λ_{max} (ϵ) 228 nm (7750); IR (film) 1750 (br), 1717, 1698, 1685, 1269 (br), 1221 (br) cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 3; (+)-HRESIMS *m*/*z* 515.2052 (calcd for M + Na, $C_{29}H_{32}O_7Na$ 515.2040).

Anthoptilide E (5): amorphous solid, $[\alpha]^{25}_D$ +2.2° (*c* 0.28 in MeOH); UV (MeOH) λ_{max} (ϵ) 202 (13 420), 218 nm (10 160); IR (film) 1746 (br), 1666, 1246 cm^{-1}; ^1H NMR data, see Table 2, ^{13}C NMR data, see Table 3; (+)-HRESIMS *m*/*z* 511.2294 (calcd for M + Na, $C_{27}H_{36}O_8Na$ 511.2302).

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