Minabeolides: A Group of Withanolides from a Soft Coral, *Minabea* sp.

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Three new C_{28} and five C_{27} steroidal lactones of the withanolide class have been isolated from a soft coral, *Minabea* sp., collected in Truk Lagoon. All the new lactones differ from the conventional withanolides in having a carbonyl group at C-3 rather than at C-1, and five of them also lack the methyl group normally present at C-24. Structures were established from extensive ^1H and ^{13}C NMR data, and proton-carbon NMR correlation data were used to assign chemical shifts to methyl resonances of the lactone ring that had not been differentiated previously or had been misassigned.

Many C_{28} steroidal lactones possessing the ergostane skeleton, i.e., withanolides, have been isolated from various genera of the Solanaceae.[2] The withanolides have been of medicinal interest because several of them have shown tumor-inhibitory activity. In our continuing search for anticancer-active compounds we have isolated a group of C_{27} and C_{28} steroidal lactones of the withanolide class with a Δ^4-3-keto ring A rather than the Δ^2-1-keto ring A that is found in all but a very few[3] plant withanolides. Although a wide variety of novel alkylated and oxygenated sterols and steroids have been isolated from marine sources,[4] this is the first report of steroidal lactones of the withanolide class from marine organisms.

In our earlier work on *Minabea* sp., we isolated a group of diterpene lactones.[5] Further fractionation of the extracts yielded eight steroidal lactones, which we have designated minabeolides-1 to -8.

The formula for minabeolide-1 (1; see Table I) implied 10 degrees of unsaturation. Infrared and ^{13}C NMR absorptions indicated the presence of a cross-conjugated cyclohexadienone (1660 cm^{-1}, 186.4 ppm) and an α,β-unsaturated lactone or ester (1700 cm^{-1}, 167.1 ppm). The cyclohexadienone feature was corroborated by UV data (λ_{max} 240 nm, ϵ, 16 204) and ^1H NMR data (see Table II), which includes three olefinic signals characteristic of a steroidal $\Delta^{1,4}$-dienone.[6a] The proton NMR spectrum of 1 also showed a deshielded methyl singlet at 1.23 ppm, a methyl singlet at 0.77 ppm, and a methyl doublet at 1.01 ppm indicative of the 19-, 18-, and 21-methyl groups, respectively, in a $\Delta^{1,4}$-3-one steroid.[6b] Proton decoupling combined with one-bond and long-range $^1H/^{13}C$ NMR correlation data confirmed partial structure A, which is characteristic of the withanolides and accounts for the lactone feature described above. Complete analysis of the ^{13}C NMR data revealed a close fit between the data for 1 and rings A and B of $\Delta^{1,4}$-androstadiene-3,17-dione and rings C, D, and the entire side chain of the withanolide I.[7-9] Minabeolide-1 was thus assigned structure 1. In the mass spectrum of 1, ions were observed at m/z 125, corresponding to the lactone fragment arising by fission of the C-20,22 bond, and at m/z 297, consistent with the complementary peak for the remainder of the steroid. Since the proton chemical shift and coupling constants for H-22, as well as the ^{13}C chemical shifts for the entire side chain, closely match those of I,[8] we assume that the stereochemistry in the side chain of the two compounds is the same.

Table I

compd	formula	highest mass ions obsd	IR, cm^{-1}	UV[b] λ, nm (ε)
1	$C_{28}H_{38}O_3$	422.2833/ 422.2821[a]	1700, 1660	240 (16 204)
2	$C_{30}H_{40}O_5$	480 420 (M^+ - AcOH)	1740, 1705, 1660	239 (15 551)
3	$C_{28}H_{40}O_3$	424	1700, 1670	
4	$C_{27}H_{38}O_3$	410.2823/ 410.2821[a]	1720, 1660	240 (16 400)
5	$C_{29}H_{40}O_5$	468 408 (M^+ - AcOH)	1735, 1725, 1660	238 (17 691)
6	$C_{27}H_{40}O_3$	412	1725, 1672	239 (10 876)
7	$C_{29}H_{42}O_5$	470 410 (M^+ - AcOH)	1740, 1665	
8	$C_{29}H_{42}O_5$	470.3013/ 470.3032[a]	1735, 1725, 1672	241 (10 715)
9	$C_{30}H_{46}O_6$	470 (M^+ - MeOH)	3450, 1735, 1730, 1660	238 (10 400)

[a] Observed/calculated for specified formula. [b] In 99.9% EtOH.

$^1H/^{13}C$ NMR correlation spectroscopy (one bond) confirmed the respective proton and carbon assignments for 1 shown in Tables II and III. Since the carbon resonance at 13.8 ppm can be confidently assigned to C-27 (vs 20.5 ppm for C-28) on the basis of calculated chemical shifts, it follows that H-27 resonates at 1.88 ppm. So far as we are aware this constitutes the first unambiguous specific assignment of H-27 and H-28. The relative order observed here should be applicable to analogous withanolides when the H-27 and H-28 signals are resolved. In earlier reports of similar withanolides these signals have not been distinguished or have been incorrectly assigned.[8]

Long-range $^1H/^{13}C$ NMR correlations also confirmed that C-6 in 1 (and 4) resonates at slightly higher field (32.8 ppm) than does C-7 (33.7 ppm). Accordingly, we have maintained this same relative order in making the chemical shift assignments for all the Δ^4-3-keto steroids in the remainder of Table III, even though the long-range experimental evidence is only available for 1 and 4. This relative order for the C-6 and C-7 ^{13}C NMR chemical shifts is the reverse of assignments made earlier.[7,9]

IR, UV, ^1H NMR and ^{13}C NMR data (see Tables I-III) revealed that minabeolide-2 (2) was identical with 1 except that the 18-methyl group had been converted to an acetoxymethyl. In addition to the appropriate proton and carbon NMR signals for an oxygenated C-18 in 2, the

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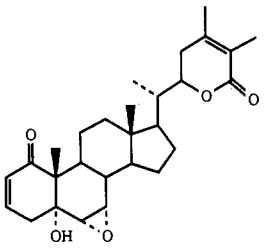
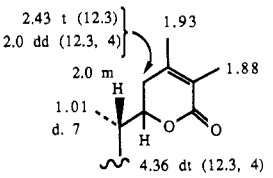
0022-3263/88/1953-3926$01.50/0

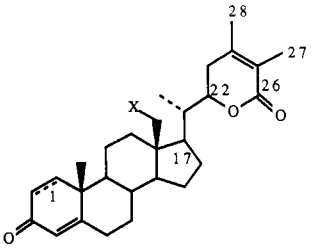
Chart I



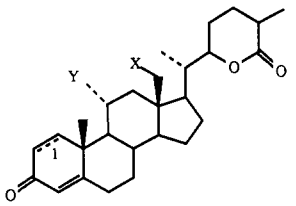
I



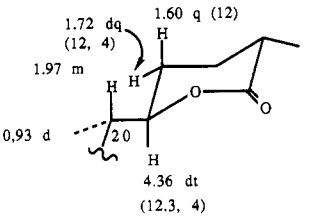
A



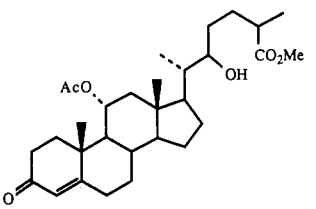
1 X = H, Δ^1
2 X = OAc, Δ^1
3 X = H, 1,2-dihydro



	X	Y
4	H	H, Δ^1
5	OAc	H, Δ^1
6	H	H, 1,2-dihydro
7	OAc	H, 1,2-dihydro
8	H	OAc, 1,2-dihydro



B



9

Table II. ^{1}H NMR Data for 1–9[a]

H	1	2	3	4	5	6	7	8	9
1	7.04 d (10)	7.01 d (10)		7.04 d (10)	6.99 d (10)				
2	6.23 dd (10, 2)	6.24 dd (10, 2)		6.22 dd (10, 1.8)	6.24 dd (10, 1.8)				
4	6.07 br s	6.07 br s	5.72 br s	6.06 br s	6.07 br s	5.72 br s	5.73 br s	5.74 br s	5.79 br s
6	2.46 m	2.44 m		2.48 m 2.35 m					
9								1.42 t (11)	1.42 t (11)
11								5.24 ddd (4.5, 12.3, 11)	5.28 ddd (4.5, 12.2, 11)
12β								2.27 dd (12.3, 4.5)	2.26 dd (12.2, 4.5)
12α								1.25 t (12.3)	1.25 t (12.2)
18	0.77 s	3.91 d (12) 4.35 d (12)	0.74 s	0.76 s	3.89 d (12) 4.30 d (12)	0.73 s	3.87 d (12) 4.30 d (12)	0.81 s	0.86 s
19	1.23 s	1.24 s	1.19 s	1.23 s	1.23 s	1.21 s	1.18 s	1.26 s	1.31 s
20	2.0 m			1.97 m					
21	1.01 d (7)	1.12 d (7)	1.02 d (7)	0.93 d (7)	1.05 d (7)	0.95 d (7)	1.07 d (7)	0.92 d (7)	0.93 d (7)
22	4.36 dt (12.3, 4)	4.38 dt (12,4)	4.37 dt (13, 4)	4.36 dt (12.3, 4)	4.39 dt (12.2, 4)	4.36 dt (12, 4)	4.4 dt (12, 4)	4.33 dt (12, 4)	3.65 br dt (11, 3)
23	2.0 dd (12.3, 4) 2.43 t (12.3)			1.72 dq (12, 4) 1.60 q (12)					
25				2.38 m	2.39 m				2.5 m
27	1.88 br s	1.88 br s	1.90 br s	1.28 d (7)	1.32 d (7)	1.30 d (7)	1.29 d (7)	1.27 d (7)	1.22 d (7)
28	1.93 br s	1.94 br s	1.96 br s						
OAc		2.11 s			2.10 s		2.09 s	2.05 s	2.07 s
OMe									3.72 s

[a] $CDCl_3$, 300 MHz; δ, multiplicity (J in Hz).

Table III. ^{13}C NMR Data for 1–6, 8, and 9[a]

C	1[b]	2	3	4[c]	5	6	8	9
1	155.8 d	155.4 d	35.7 t	155.8 d	155.4 d	35.7 t	36.6 t	36.6 t
2	127.5 d	127.7 d	34.0 t	127.5 d	127.7 d	34.0 t	34.1 t	34.0 t
3	186.4 s	186.2 s	199.4 s	186.4 s	186.2 s	199.6 s	199.3 s	199.3 s
4	123.9 d	124.0 d	123.9 d	123.9 d	124.0 d	123.8 d	124.7 d	124.7 d
5	169.1 s	168.5 s	170.4 s	169.1 s	168.5 s	171.3 s	170.0 s	169.8 s
6	32.8 t	32.7 t	32.0 t	32.8 t	32.7 t	32.0 t	31.8 t	31.8 t
7	33.7 t	33.6 t	32.8 t	33.7 t	33.6 t	32.8 t	33.4 t	33.4 t
8	35.5 d	35.7 d	35.6 d	35.5 d	35.7 d	35.6 d	35.0 d	35.0 d
9	52.4 d	52.3 d[d]	53.8 d[d]	52.4 d	52.3 d[d]	53.8 d[d]	54.5 d	54.4 d
10	43.6 s	43.4 s	38.6 s	43.5 s	43.4 s	38.6 s	39.7 s	39.8 s
11	22.8 t	22.7 t	21.0 t	22.8 t	22.7 t[e]	21.0 t	70.9 d	70.0 d
12	39.4 t	34.6 t	39.6 t	39.4 t	34.6 t	39.5 t	46.3 t	46.4 t
13	43.1 s	45.9 s	42.8 s	43.1 s	45.9 s	42.8 s	43.1 s	43.1 s
14	55.2 d	54.7 d	55.6 d	55.1 d	54.7 d	55.5 d	55.5 d	55.6 d
15	24.4 t	24.2 t	24.2 t	24.4 t	24.2 t	24.2 t	24.1 t	24.2 t
16	27.3 t	27.0 t	27.3 t	27.2 t	26.9 t	28.6 t	28.5 t	27.3 t
17	52.0 d	52.5 d[d]	52.1 d[d]	52.0 d	52.5 d[d]	52.0 d[d]	51.9 d	53.0 d
18	11.9 q	61.9 t	11.8 q	11.9 q	62.0 t	11.8 q	12.6 q	12.3 q
19	18.7 q	18.7 q	17.4 q	18.7 q	18.7 q	17.3 q	18.3 q	18.3 q
20	38.8 d	39.1 d	38.9 d	39.6 d	39.8 d	39.6 d	39.5 d	39.3 d
21	12.5 q	12.5 q	12.5 q	12.8 q	13.0 q	12.8 q	12.7 q	12.7 q
22	78.2 d	78.0 d	78.3 d	84.1 d	83.8 d	84.2 d	83.8 d	73.1 d
23	29.6 t	29.3 t	29.6 t	22.3 t	22.0 t[e]	22.3 t	22.3 t	27.3 t
24	148.2 s	148.9 s	149.0 s	28.6 t	28.5 t	28.6 t	28.5 t	30.7 t
25	122.0 s	122.1 s	122.0 s	36.4 d	36.5 d	36.5 d	36.1 d	42.1 d
26	167.1 s	167.0 q	167.0 s	174.8 s	174.8 s	174.6 s	174.7 s	177.0 s
27	13.8 q	13.7 q	13.7 q	17.3 q	17.3 q	17.4 q	17.2 q	17.1 q
28	20.5 q	20.5 q	23.7 q					
OAc		171.2 s			171.2 s		170.0 s	169.9 s
		21.1 q			21.2 q		21.9 q	21.9 q
								52.5 q (OMe)

[a] $CDCl_3$, 75 MHz, assignments by comparison to analogous steroids and internal comparisons except where noted. [b] Assignments by one- and two-bond $^1H/^{13}C$ heterocorrelation except for C-7, -8, -9, -11, -14, -15, and -16. [c] Assignments by one- and two-bond $^1H/^{13}C$ heterocorrelations except for C-7, -9, -11, -14, -15, -16, -23, and -24. [d,e] Assignments with identical letters within a column may be interchanged.

signals for C-12 and C-13 are shifted as expected from β and γ effects.[10] In the 70-eV mass spectrum of **2**, the m/z 125 ion, corresponding to a fragment consisting of ring E, is very prominent (80%). In the 12-eV spectrum the base peak, m/z 267, corresponds to loss of AcOH plus loss of the entire side chain.

UV, IR, and especially ^1H and ^{13}C NMR data revealed that minabeolide-3 (**3**) is the 1,2-dihydro analogue of **2**. ^{13}C NMR data for rings A and B match closely those of Δ^4-androstene-3,17-dione[7,9] while the remainder of the signals are nearly identical with those of lactone **1**. In the mass spectrum of **3** the ring E fragment ion (m/z 125) is the base peak.

Minabeolide-4 (**4**) has one less carbon and one fewer degrees of unsaturation than **1**. IR, UV, and NMR data (see Tables I–III) confirm that **4** has the same steroidal skeleton and side-chain C-21 methyl as **1**, thus leaving the remaining two degrees of unsaturation for a saturated δ-lactone ring (IR, 1720 cm^{-1}; ^{13}C, 174.8 ppm). A methyl substituent next to the lactone carbonyl group was indicated by the chemical shifts of this methyl group (1.28 ppm) and the methine proton to which it is coupled (2.38 ppm). The entire side-chain proton and carbon sequence from H-21 to H-27 was discernible from $^1H/^1H$ COSY, $^1H/^{13}C$ COSY, and long-range $^1H/^{13}C$ COSY experiments.

The stereochemistry depicted in partial structure B is assigned to the lactone ring of **4** on the basis of coupling data. Irradiation of the H-20 signal (confirmed by the COSY spectrum to be centered at 1.97 ppm) removed only a 4-Hz coupling from the H-22 signal (4.36 ppm). Therefore H-22 must be axially oriented to account for the 12-Hz coupling to one of the C-23 protons. The methyl group (C-27) was assigned the equatorial orientation because in the difference decoupled spectrum obtained by irradiation of this methyl signal, the residual H-25 signal posseses multiplicities (J = 4, 12 Hz) consistent with an axial proton in a six-membered ring.

Minabeolide-5 (**5**) contains an acetoxy group not present in (**4**), but otherwise contains the same functionality (see Tables I–III). The structure of **5** was assigned by correlation of its ^1H and ^{13}C NMR data with that of **2** (ring A–D) and **4** (side chain and lactone).

Minabeolide-6 (**6**) was recognized as the 1,2-dihydro analogue of **4** from its formula and comparison of the IR, ^1H NMR, and ^{13}C NMR data for the two compounds. ^1H and ^{13}C NMR data for the steroid nucleus of **6** coincide with those of **3**, while ^1H and ^{13}C NMR data for the side chain of **6** match those of **4**.

The formulas and spectral data of **7** and **8**, minabeolides-7 and -8, indicated that they were acetoxy derivatives of **6**. Proton NMR data for **7** revealed that the usual 18-methyl signal was missing and that an isolated $-CH_2O-$ group was present (doublets at 3.87 and 4.30 ppm (J = 12)). This corresponds to the ^1H NMR data observed for H-18 in **2**, and hence structure **7** is proposed. Insufficient material was available to obtain ^{13}C NMR data for **7**.

From proton and carbon NMR data it could be concluded that **8** is identical with **6** with respect to ring A, the side chain, and the quaternary methyl groups. The acetoxy group could be decisively assigned to the 11α position by consideration of the multiplicity of the acetoxy deshielded methine proton (ddd, J = 12.3, 11.0, 4.3 Hz) at 5.24 ppm and the fact that this proton experienced a nuclear Overhauser enhancement upon irradiation of each of the quaternary methyl signals.

The lactone rings of **5**–**8** are assigned the same stereochemistry as was determined for **4** because the ^1H NMR chemical shifts for H-22 and H-27 in all of these compounds are nearly the same and the J values for H-22 are

(10) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: London, 1976; Chapter 2.

consistent throughout this series of compounds. Also, the ^{13}C NMR signals for C-22, and -25, and -27 are the same for **5**, **6**, and **8** (data not available for **7**).

The formula of **9** differed from that of **7** and **8** by addition of the elements of methanol. In contrast to all the other minabeolides, **9** contained hydroxyl absorption in the IR, and its proton NMR spectrum contained a methoxy signal at 3.72 ppm. The proton NMR spectrum also showed signals appropriate for H-4 of a Δ^4-3-keto steroid, an acetoxy-deshielded H-11β, and two quaternary and two secondary methyl groups at nearly the same positions as were found for **8**. Notably missing from the proton NMR spectrum of **9** was the dt at 4.33 ppm characteristic of the lactone methine proton in **4**–**8**. Instead, a broad dt at 3.65 ppm was observed, consistent with deshielding expected of an OH rather than a lactone oxygen. Difference decoupling confirmed that this proton and the C-21 methyl protons are coupled to the same methine proton at ~1.75 ppm. Hence there is oxygenation at C-22 as in the lactones. The downfield doublet methyl signal at 1.22 ppm is coupled to a methine proton at ~2.5 ppm, the same position that H-26 is found in lactone **4**. These data and the correspondence of the ^{13}C NMR data of **9** and **8** support the hydroxy ester structure shown for the former (**9**), which is thus methyl 11α-acetoxy-22-hydroxy-3-oxocholest-4-en-26-oate. The structure of ester **9** was confirmed by conversion of **9** into **8** by warming of the former in $CHCl_3$ with *p*-toluenesulfonic acid. Since the soft coral was initially extracted with methanol, it is possible that **9** is an artifact.

Experimental Section

^1H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75.4 MHz on a Varian XL-300 spectrometer; chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. IR spectra were measured on a Perkin-Elmer Model 298 spectrometer. Low-resolution mass spectra were recorded on a Hewlett-Packard 5985B mass spectrometer. High-resolution mass spectra were recorded on a VG ZAB-E mass spectrometer. An Altex 5 μm × 9.6 mm × 29.9 cm semipreprative Adsorbosphere reverse-phase C_{18} column was used for separation and purification.

Extraction and Isolation Procedures. Freshly thawed specimens, collected and shipped frozen from Truk Lagoon, Sept, 1984, were allowed to soak in MeOH (2 L) for 10 h and in $CHCl_3$–MeOH (1:1) (3 × 2 L); dry weight after extraction, 250 g. The solutions were evaporated nearly to dryness, and the combined concentrates were diluted with water (0.4 L) and extracted with $CHCl_3$ (3 × 2 L). The $CHCl_3$ solubles (9.92 g) were chromatographed on silica gel using acetone–hexane (5:95 → 1:1) and collecting 25 fractions (500 mL of each). Fractions 11, 12, and 13 were subjected separately to reverse-phase HPLC (C_{18}) using MeOH–H_2O (7:3) to yield nine pure compounds. ^1H and ^{13}C NMR data for minabeolides-1 to -8 and ester **9** are in Tables II and III.

Minabeolide-1: 22 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 422 (M^+, 66), 301 (94), 297 (7), 173 (20), 147 (46), 145 (33), 125 (85), 121 (100).

Minabeolide-2: 1.4 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 480 (M^+, 4), 420 (M^+ – AcOH, 19), 299 (16), 295 (5), 267 (35), 145 (54), 125 (80), 121 (100).

Minabeolide-3: 1 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 424 (M^+, 7), 300 (7), 224 (18), 229 (17), 181 (15), 174 (16), 147 (14), 125 (100).

Minabeolide-4: 25 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 410 (M^+, 6), 267 (13), 173 (16), 145 (34), 122 (100), 113 (26).

Minabeolide-5: 1.5 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 468 (M^+, 2), 408 (M^+ – AcOH, 16), 287 (17), 253 (16), 173 (21), 147 (42), 121 (100), 113 (20).

Minabeolide-6: 3.8 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 412 (M^+, 52), 394 (20), 299 (4), 244 (70), 229 (54), 227 (32), 174 (52), 147 (76), 131 (50), 122 (75), 121 (83), 113 (91), 91 (100).

Minabeolide-7: ~0.4 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 470 (M^+, 4), 410 (M^+ – AcOH, 25), 392 (10), 268 (68), 173 (24), 159 (25), 145 (50), 113 (100).

Minabeolide-8: 11 mg; colorless oil; low-resolution mass spectrum (70 eV), *m/z* (relative intensity) 411 (M^+ – AcO, 17), 410 (M^+ – AcOH, 53), 225 (27), 173 (35), 161 (36), 145 (71), 122 (100), 121 (92), 113 (52).

Ester 9: 6 mg; colorless oil; low-resolution mass spectrum (12 eV), *m/z* (relative intensity) 470 (M^+ – MeOH, 6), 411 (29), 410 (100), 395 (48), 267 (44), 145 (63), 122 (40), 113 (21).

Conversion of Ester 9 to Minabeolide-8. To a solution of **9** in $CHCl_3$ (2.5 mL) was added *p*-toluenesulfonic acid (3.0 mg), and the resulting mixture was heated at 40 °C for 2 h. The solvent was evaporated and the oily brown residue was passed through a short Sep-Pak (Waters Associates) silica gel column using hexane–acetone (8:2) to give a pure compound identical with minabeolide-8 by ^1H NMR analysis.

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