Na_2CO_3 solution was introduced into a solution of 1 (64 mg, 0.18 mmol) in 5 mL of methanol, and the solution was stirred at room temperature for 16 h. The mixture was diluted with water and extracted with 3 × 10 mL portions of diethyl ether. The combined ether extracts were dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil. HPLC separation (Lichrosorb, 15% EtOAc–CH_2Cl_2) of this oil gave 49 mg (86%) of hydroxycrenulide (2) as a colorless oil: IR (neat) ν_{max} 3550, 2960, 1760, 1660, 1450, 1380, 1105, 1060, 1025, and 785 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz) δ 0.33 (1 H, m), 0.93 (1 H, m), 1.00 (1 H, d, J = 7 Hz), 1.03 (1 H, d, J = 7 Hz), 1.1–1.5 (m), 1.59 (3 H, s), 1.69 (3 H, s), 1.7–2.1 (m), 3.09 (1 H, d, J = 8 Hz), 4.35 (1 H, br t, J = 4 Hz), 4.71 (1 H, dd, J = –17 and 3 Hz), 5.00 (1 H, dd, J = –17 and 2 Hz), 5.07 (1 H, br t, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 8.2 (t), 10.1 (d), 17.4 (q), 17.6 (q), 23.7 (q), 25.6, 25.7, 26.2, 28.4 (t), 32.7 (t), 35.8 (t), 48.4 (t), 49.2 (d), 69.6 (d), 72.6 (t), 123.9 (d), 127.8 (s), 132.1 (s), 169.7 (s), 175.3 (s); MS, m/e 318 (M^+), 300, 275, 149, 123, 121, 119, 109, 95, 86, 71, 69, 57, 41.

Reduction of Acetoxycrenulide (1) to the Triol 4. To a cooled slurry (ca. 10 °C) of $LiAlH_4$ (200 mg) in diethyl ether under N_2 was added a 5-mL ethereal solution of acetoxycrenulide (40 mg) via syringe over a 10-min period. After 2 h the reaction was quenched with careful dropwise addition of H_2O. The mixture was partitioned between 100 mL of Et_2O and 50 mL of H_2O, and the Et_2O layer was dried over $MgSO_4$ and concentrated to yield 4 homogeneous by TLC as a colorless oil: IR (CCl_4) ν_{O-H} 3600–3200 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz) δ 0.50 (1 H, m), 0.64–0.96 (2 H, complex m), 0.99 (6 H, d, J = 7 Hz), 1.56 (3 H, s), 1.66 (3 H, s), 3.02 (1 H, d, J = 10 Hz), 3.66 (2 H, br s, D_2O exch), 3.91 (2 H, dd, J = 12 and 12 Hz, superimposed on a 1 H, broad signal that disappears with D_2O), 4.28 (2 H, m), 4.46 (1 H, d, J = 10 Hz), 5.02 (1 H, t, J = 7.5 Hz); MS, m/e 322 (M^+), 304, 286, 272, 243, 215, 189, 145, 133, 119, 109, 107, 105, 95, 93, 91, 81, 79, 77, 64, 55, 43, 42.

Triacetate 5. A solution of triol 4 in 5 mL of pyridine and 2 mL of acetic anhydride was allowed to stir at room temperature for 65 h. The mixture was then partitioned between Et_2O and H_2O. The Et_2O layers were dried over $MgSO_4$, concentrated, and purified by HPLC on μ-Porasil; ^1H NMR ($CDCl_3$, 220 MHz) δ 0.89 (3 H, m), 0.98 (3 H, d, J = 6 Hz), 1.05 (3 H, d, J = 6 Hz), 1.59 (3 H, s), 1.68 (3 H, s), 1.98 (3 H, s), 2.02 (3 H, s), 2.03 (3 H, s), 3.22 (1 H, d, J = 10 Hz), 4.55 (2 H, s), 4.68 (2 H, s), 5.08 (1 H, t, J = 7.5 Hz), 5.36 (1 H, t, J = 4 Hz); MS, m/e 328 (M^+ – $2CH_3COOH$), 286, 268, 253, 243, 225, 213, 199, 185, 175, 159, 157, 145, 133, 131, 119, 109, 107, 105, 95, 93, 91, 81, 69, 57, 55, 43, 41.

Oxidation of Triol 4 to Ketofuran 6. A solution of triol 4 (85 mg) in 1 mL of pyridine was slowly added to a cool (10 °C) solution of CrO_3 (500 mg) in pyridine (5 mL). The resultant brown solution was stirred overnight and subsequently partitioned between H_2O and ether. The ether phase was collected, the water was reextracted with ether, the combined ether extracts were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was reduced in vacuo. HPLC separation (μ-Porasil, 30% Et_2O in petroleum ether) yielded 4-ketocrenulide (43%) and the ketofuran 6 (34%). 4-Ketocrenulide was identified based upon the following spectral characteristics: IR (film) ν_{max} 1765, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz) δ 0.51 (1 H, m), 0.94 (3 H, d, J = 7 Hz), 1.18 (3 H, d, J = 6 Hz), 1.60 (3 H, s), 1.70 (3 H, s), 2.07 (3 H, br m), 2.46 (1 H, d, J = 11 Hz), 2.67 (1 H, d of d, J = 11 and 11 Hz), 4.18 (1 H, d, J = 11 Hz), 4.65 (1 H, d of d, J = –16 and 2.3 Hz), 4.72 (1 H, d of d, J = –16 and 2.3 Hz), 5.05 (1 H, t, J = 7.5 Hz); MS, m/e (relative intensity) 316 (M^+, <1), 301 (<1), 274 (<1), 167 (4), 149 (18), 109 (35), 95 (26), 81 (55), 69 (100), 57 (49), 55 (66), 43 (50). Ketofuran 6 illustrated the following spectral features: IR (film) ν_{max} 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz) δ 0.32 (1 H, m), 0.97 (3 H, d, J = 5 Hz), 1.10 (3 H, d, J = 7.5 Hz), 1.56 (3 H, s), 1.66 (3 H, s), 2.00 (2 H, m), 2.36 (1 H, d, J = 11 Hz), 2.55 (1 H, dd, J = 11 and 11 Hz), 3.74 (1 H, d, J = 11 Hz), 5.05 (1 H, t, J = 7.5 Hz), 7.15 (1 H, s), 7.21 (1 H, s); MS, m/e (relative intensity) 300 (M^+, 10), 285 (2), 258 (4), 245 (4), 229 (4), 215 (3), 201 (4), 189 (7), 175 (7), 161 (16), 147 (19), 133 (26), 119 (33), 109 (48), 107 (24), 105 (45), 100 (45), 95 (37), 91 (48), 81 (44), 69 (100), 57 (41), 55 (70), 43 (48), 41 (70).

Dehydration of Crenulide 4 to the Diene Lactones and 8. A solution of hydroxycrenulide 2 (30 mg, 0.094 mmol) and an excess amount of $POCl_3$ in 4 mL of anhydrous pyridine was stirred under nitrogen atmosphere at 0 °C for 0.5 h. The reaction was quenched by the cautious addition of distilled water, and the aqueous phase was extracted with 3 × 10 mL of diethyl ether. The combined ether extracts were then dried over $MgSO_4$ and reduced in vacuo. Purification by TLC with 5:5:1 hexanes–dichloromethane–ethyl acetate yielded the diene lactone 7 (11 mg, 39%) and diene lactone 8 (8 mg, 28%) as colorless oils. Diene lactone 7: UV (MeOH) λ_{max} 231 nm (ϵ 4600), 274 (ϵ 5400); IR (CCl_4) ν_{max} 2940, 1760, 1640, 1440, 1040, 1020 cm^{-1}; ^1H NMR (CCl_4, 220 MHz) δ 0.55 (1 H, m, C-8α), 0.80 (1 H, m, C-7), 0.95 (1 H, m, C-8β), 1.06 (3 H, d, J = 7 Hz, C-20), 1.07 (3 H, d, J = 7 Hz, C-17), 1.34 (1 H, ddt, J = –14, 7, and 7 Hz, C-11), 1.45 (1 H, ddt, J = –14, 7, and 7 Hz, C-11), 1.47 (1 H, m, C-6), 1.57 (3 H, s, C-16), 1.62 (1 H, m, C-9), 1.67 (3 H, s, C-15), 1.94 (2 H, q, J = 7 Hz, C-12), 2.04 (1 H, ddd, J = –17, 11, and 7 Hz, C-5α), 2.19 (1 H, sextet, J = 7 Hz, C-10), 2.35 (1 H, ddd, J = –17, 4, and 4 Hz, C-5β), 4.56 (1 H, dd, J = 16 and 2 Hz, C-18), 4.72 (1 H, dd, J = 16 and 2 Hz, C-18), 5.00 (1 H, t, J = 7 Hz, C-13), 5.54 (1 H, dd, J = 7 and 4 Hz, C-4); MS, m/e 300 (M^+), 285, 271, 257, 245, 219, 189, 173, 161, 145, 129, 115, 105, 91, 83, 69, 55, 41. Diene lactone 8: UV (MeOH) λ_{max} 321 nm (ϵ 7200); IR (CCl_4) ν_{max} 2940, 1760, 1640, 1440, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.43 (1 H, m), 0.86 (1 H, m), 0.93 (3 H, d, J = 7 Hz), 1.11 (3 H, d, J = 7 Hz), 1.2–1.5 (m), 1.58 (3 H, s), 1.66 (3 H, s), 1.98 (3 H, m), 3.63 (1 H, br m), 4.52 (2 H, d, J = 2.5 Hz), 5.01 (1 H, t,J = 7 Hz), 5.27 (1 H, ddd, J = 12, 5, 2 Hz), 5.48 (1 H, ddd, J = 12, 5, and 2 Hz); MS, m/e 300 (M^+), 285, 271, 257, 245, 217, 215, 201, 189, 173, 157, 145, 129, 115, 105, 91, 77, 69, 55, 41.

Lanthanide-Induced ^1H NMR Shift Study of Diene 1. Aliquots of $Eu(fod)_3$ in $CDCl_3$ were added to compound 7 in $CDCl_3$, and sequential 220-MHz ^1H NMR spectra were recorded. Calculations were performed as previously described,[11] and the refined data are presented in Chart I, along with the predicted molecular conformation of diene lactone 7. A best fit situation was found to exist with the europium atom anti to the cyclopropane ring, 2.7 Å from oxygen with a C–O–Eu angle of ca. 105°.

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Registry No. 1, 65043-52-9; 2, 83845-31-2; 4, 65043-57-4; 5, 83845-32-3; 6, 65065-22-7; 7, 83845-33-4; 8, 83845-34-5.

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New Crenulides from the Sea Hare *Aplysia vaccaria*

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The scarcity of natural predators for sea hares has spurred interest in these opisthobranch molluscs as sources of toxins or chemical defense substances.[1] We became interested in *Aplysia vaccaria* because it is reported to eat brown algae, in contrast to *A. californica*, which eats almost exclusively red algae.[2] It is now generally accepted that sea hares concentrate metabolites produced by their dietary algae.[1] In many cases the compounds concentrated

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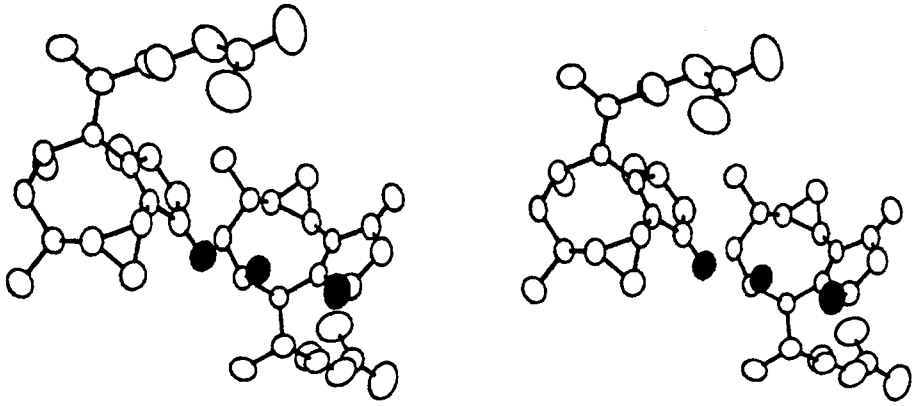
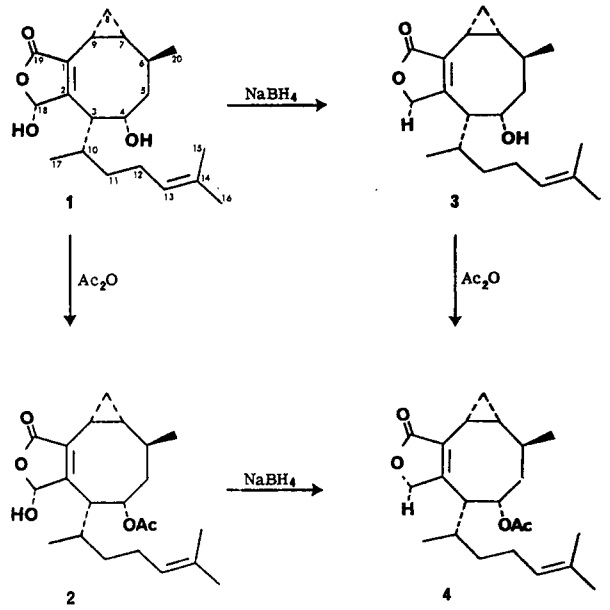


Figure 1. Stereoscopic ORTEP drawing of two molecules of dihydroxycrenulide (1) as they occur in the crystal lattice. Dark atoms are hydrogen bonded. No hydrogens are shown.

by the sea hares have biological activity.

We describe here the isolation of three new crenulides (1–3) and acetoxycrenulide[3] (4) from the digestive glands



of *A. vaccaria* collected at Dana Point, CA. Homogenation of the digestive glands of the sea hare in 95% ethanol followed by further extraction of the residue with acetone and methylene chloride yielded a black oil after removal of solvents. Chromatography of the extract, first open column on Florisil followed by reverse-phase HPLC and finally by silica gel HPLC yielded a crystalline compound, dihydroxycrenulide (1).

Dihydroxycrenulide displayed a weak molecular ion at m/e 334, which with its off-resonance decoupled ^{13}C NMR spectrum (Table I) indicated the molecular formula $C_{20}H_{30}O_4$. Its infrared spectrum in chloroform showed hydroxyl absorption at 3350 cm^{-1} and a carbonyl stretching band at 1750 cm^{-1}. This, along with UV absorption at 231 nm (ϵ 5400) and a proton NMR signal at δ 5.94, suggested a γ-hydroxy-α,β-unsaturated γ-lactone. Confirmation was provided by the ^1H NMR observation of an aldehyde singlet at δ 8.90 upon treatment of 1 with sodium methoxide-d_3 in methanol-d_4 and the 60-nm red shift of the UV absorbance upon addition of potassium hydroxide in ethanol. Base stabilizes the anion of the ring-opened hydroxy lactone. The 90-MHz proton NMR spectrum in deuterochloroform showed a cyclopropyl multiplet at δ 0.40 (H8a), two overlapping methyl doublets at δ 1.04 and 1.08 (Me 20 and 17), two vinyl methyls (Me 15 and 16), an olefinic triplet at δ 5.08 (H13), and two broad D_2O-exchangeable peaks as well as peaks at δ 3.13 (d, J = 9.5, H3), 4.45 (dd, J = 4.4, 2.5, H4), and 5.94 (d, J = 2.2, H18). The multiplets at δ 5.08, 4.45, and 3.13 could simultaneously be totally decoupled by irradiation of an unresolved five-proton multiplet at δ 1.9 containing resonances from H5a, H5b, H10, H12a, and H12b. There was no coupling between H3 and H4, however. Irradiation of a six-proton multiplet centered at δ 1.3 collapsed the 5.94 doublet and simplified the 0.40 cyclopropyl multiplet. At 500 MHz a single multiplet containing couplings to both protons was evident at δ 1.45 (H9). The proton magnetic resonance spectrum was assigned on the basis of these decouplings and of first-order couplings apparent in the resolution-enhanced 500-MHz spectrum.

Table I. Carbon-13 Chemical Shift Data in ($CDCl_3$) in ppm from Me_4Si

carbon	1	2	3	4
1	133.4 (s)	134.5	128.1	128.7
2	165.0 (s)	162.5	168.5	166.6
3	49.2 (d)	47.6	48.9	47.4
4	70.4 (d)	72.9	70.0	72.2
5	48.3 (t)	44.1	48.6	43.8
6	28.3 (d)	29.0	28.5	29.2
7	10.2 (d)	10.3	10.2	10.2
8	8.4 (t)	8.5	8.2	8.4
9	26.1 (t)	25.5	26.1	25.5
10	32.4 (d)	32.3	32.9	32.8
11	36.5 (t)	36.5	35.8	35.6
12	25.5 (t)	25.7	25.7	25.7
13	123.6 (d)	123.9	123.8	123.5
14	132.3 (s)	132.6	132.3	132.5
15	17.7 (q)	17.7	17.7	17.7
16	25.6 (q)	25.9	25.6	25.9
17	17.2 (q)	16.8	17.4	17.1
18	96.9 (d)	96.7	72.3	71.5
19	171.6 (s)	170.6	174.7	174.2
20	23.7 (q)	23.5	23.7	23.4
21		21.2		21.3
22		168.7		169.8

Controlled evaporation of an ether solution of dihydroxycrenulide produced crystals of orthorhombic space group $P2_12_12_1$ with one molecular per asymmetric unit. Cell constants were a = 7.746 (2) Å, b = 18.302 (8) Å, and c = 13.385 (4) Å (ρ_{obsd} = 1.167, ρ_{calcd} = 1.171 g/mL). Intensity data were collected on a Picker FACS I computer-controlled diffractometer to a Bragg angle of 30° by using Mo Kα radiation, and 2608 (83%) reflections were observed. The structure was solved by direct methods using a magic integer version of MULTAN 78.[4] Preliminary

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refinement was done by block-diagonal least squares; hydrogens were located by difference Fourier maps, and final anisotropic full-matrix refinement gave an R value of 0.056. The crystal shows two hydrogen bonds (Figure 1). The first is an intramolecular association between the lactol hydrogen and the cyclooctanol oxygen. The second hydrogen bond occurs between adjacent molecules in the crystal, from the cyclooctanol hydrogen to the lactone carbonyl oxygen.

The stereochemistry of the crystalline compound explains some ambiguities of its ^1H NMR spectrum. Protons H3 and H4 have a dihedral angle of 80° and do not couple. Protons H18 and H9 are nearly eclipsed and show long range (five bond) homoallylic coupling of 2.2 Hz.

Compounds 2–4 were characterized by their completely analogus spectra and the following interconversions. Treatment of 1 with sodium borohydride reduced the lactol cleanly to hydroxycrenulide (3). The material from the reduction and the isolated compound were identical by ^1H and ^{13}C NMR and by HPLC. The observed optical rotation of the reduction product was 24.3°; the natural isolated material gave 17.6°. Acetylation of hydroxycrenulide from either source gave acetoxycrenulide (4), identical with 4 isolated from the sea hare. The optical rotation of the 4 produced by reduction and acetylation was 20.5°; natural 4 had a rotation of 13.4° (lit.[5] 13°), and 4 produced by acetylation of natural 3 gave a rotation of 14.2°. Proton magnetic resonance spectra at 500 MHz of 4 ($[\alpha]_D$ 20.5°) and 4 ($[\alpha]_D$ 14.2°) were identical. Upon reduction with $NaBH_4$, hydroxyacetoxycrenulide (2) was converted to acetoxycrenulide (4). On the basis of these interconversions, we believe that the structures and relative stereochemistry of 2–4 are defined by the crystal structure of 1.

The crenulides are brown algal metabolites.[6] Thus it appears that *A. vaccaria* concentrates organic compounds from dietary sources as do other *Aplysia* species.[1,2] Since acetoxycrenulide has been shown to be highly toxic to a reef-dwelling fish,[6] it is logical to speculate that this concentration of algal metabolites by *A. vaccaria* is a chemical defense mechanism, giving the animal relief from potential predation by fish.

Experimental Section

All solvents were redistilled prior to use. Commercially available AR chemicals were used without further purification. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer and ultraviolet spectra on a Perkin-Elmer Model 202 spectrophotometer. Optical rotations were taken on a Perkin-Elmer Model 241 polarimeter with a 10-cm cell. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer and ^{13}C NMR spectra on a Bruker WH90 multinuclear spectrometer. The frequency offset in the off-resonance experiments was at δ −4 with a power of 3340 Hz. Low-resolution mass spectra were performed on a Finnigan 1015 S/L spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. High-pressure liquid chromatography was performed on a Waters Assoc. Model 6000A instrument.

Typical Extraction. Freshly collected *A. vaccaria* were sacrificed by injection of a saturated magnesium chloride solution behind the rhinophores. Their digestive glands were removed and homogenized in 95% ethanol in a Waring blender. The suspension was filtered, and the solid residue was rehomogenized in 95% ethanol and refiltered., This second solid residue was then washed with acetone and methylene chloride until filtrates were colorless. The solvents were removed in vacuo, and the resulting oil was partitioned between water and methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to give a black oil, usually about 10 g per animal.

Chromatography. The extract (27 g) was added to a 4.2 × 50 cm column of Florisil prepared in distilled Skellysolve B. Material was eluted from the column with gradient mixtures of hexanes and ethyl acetate. Further purification was accomplished by using methanol–water mixtures on a homemade ODS-treated silica gel HPLC column followed by isopropanol–hexane mixtures on a Whatman Partisil M9 HPLC column.

1,9-Dihydroxycrenulide (1). The material eluted with 60% ethyl acetate in hexanes was rechromatographed by using 25% H_2O in methanol on a C18-treated Lichrosorb SI-100 column and further purified on Partisil M9 with 8% isopropanol in hexanes. This oil was crystallized from ether to give 1 (100 mg): mp 114–115 °C; $[\alpha]_D$ 25.9° (*c* 1.19, $CHCl_3$); MS, *m/e* 334 (M^+), 316, 301, 298, 283, 274, 255, 205, 161, 109, 105, 91, 79, 77, 69, 67, 55, 43, *41* (base peak); IR ($CHCl_3$) cm^{-1} 3350, 2950, 1750, 1666, 1455, 1375, 1340, 1290, 1220, 1180, 1160, 1105, 1055, 1030, 975, 955, 895, 855; ^1H NMR (500 MHz, $CDCl_3$) δ 0.40 (br q, *J* = 5.5, H8a), 0.98 (ddt, *J* = 5.5, 10.0, 8.8, H7), 1.04 (d, *J* = 6.8, Me 20), 1.06 (dt, *J* = 5.5, 8.8, H8b), 1.08 (d, *J* = 6.9, Me 17), 1.14 (ddt, *J* = 5.5, 13.5, 8.8, H11a), 1.3 (m, H11b, H6), 1.45 (tdd, *J* = 8.8, 5.5, 2.2, H9), 1.60 (s, Me 16), 1.70 (s, Me 15), 1.80 (dd, *J* = 15.1, 4.4, H5a), 1.93 (ddd, *J* = 15.1, 10.0, 2.5, H5b), 1.96 (m, H12a, H12b), 2.09 (dtq, *J* = 9.5, 7.0, 6.9, H10), 3.13 (d, *J* = 9.5, H3), 4.45 (dd, *J* = 4.4, 2.5, H4), 5.08 (tsep, *J* = 7.2, 1.0, H13), 5.94 (d, *J* = 2.2, H18); UV (EtOH) 231 (ϵ 5400), 208 (5680); UV ($EtOH/OH^-$) 268 (ϵ 5400).

1-Hydroxy-9-acetoxycrenulide (2). The Florisil fraction obtained with 50% ethyl acetate in hexanes was rechromatographed on ODS-treated Lichrosorb with 25% H_2O in methanol and then on Partisil M9 with 3% isopropanol in hexanes to afford pure 2 (45 mg): $[\alpha]_D$ 26.53° (*c* 1.93, $CHCl_3$); MS (no M^+), *m/e* 334, 316, 298, 274, 256, 255, 229, 227, 205, 161, 159, 133, 131, 109, 105, 91, 69, 55, *43*, 41; IR ($CHCl_3$) cm^{-1} 3500, 2980, 2920, 1760, 1665, 1450, 1370, 1250, 1220 (br), 1140, 1100, 1050, 1030, 1020, 980, 910; ^1H NMR (90 MHz, $CDCl_3$) δ 0.3 (m, 1 H), 1.03 (d, *J* = 7, 3 H), 1.10 (d, *J* = 7, 3 H), 1.4 (m, 6 H), 1.57 (s, 3 H), 1.63 (s, 3 H), 1.9 (m, 4 H), 2.06 (s, 3 H), 3.18 (d, *J* = 8, 1 H), 5.07 (t, *J* = 7, 1 H), 5.51 (dd, *J* = 3.5, 3.5, 1 H), 5.94 (d, *J* = 2.5, 1 H); UV (EtOH) 225 (ϵ 6445), 208 (6607); UV ($EtOH/OH^-$) 265 (ϵ 6500).

9-Hydroxycrenulide (3). The material eluting from silica gel with 50% ethyl acetate in hexanes was rechromatographed by using 25% H_2O in methanol on a C18-treated Lichrosorb column and then 6% isopropanol in hexanes on Partisil M9 to give oily 3 (20 mg): $[\alpha]_D$ 17.60° (*c* 1.64, $CHCl_3$); MS, *m/e* 318 (weak), 275, 274, 258, 257, 219, 205, 109, 105, 91, 81, 79, 77, 69, 67, 55, 43, *41*; IR (CCl_4) cm^{-1} 3470, 2950, 2900, 1735, 1667, 1455, 1380, 1110, 1060, 1035, 910; ^1H NMR (90 MHz, $CDCl_3$) δ 0.33 (m, 1 H) 1.02 (d, *J* = 7, 3 H), 1.05 (d, *J* = 7, 3 H), 1.3 (m, 6 H), 1.62 (s, 3 H), 1.71 (s, 3 H), 1.9 (m, 5 H), 3.09 (d, *J* = 8, 1 H), 4.34 (m, 1 H), 4.67 (dd, *J* = 17, 3.5, 1 H), 5.01 (dd, *J* = 17, 3, 1 H), 5.08 (t, *J* = 7, 1 H); UV (EtOH) 231 (ϵ 5786), 209 (4308).

9-Acetoxycrenulide (4). The fraction eluted with 25% ethyl acetate in hexanes was rechromatographed by using 15% H_2O in methanol on a C18-treated Lichrosorb column followed by 3% isopropanol in hexanes on Partisil M9 to give oily 4 (40 mg): $[\alpha]_D$ 13.4° (*c* 1.30, $CHCl_3$); MS, *m/e* 360 (weak), 318, 300, 275, 257, 219, 201, 189, 145, 109, 105, 95, 93, *91*, 82, 81, 79, 77, 69, 67, 55, 53, 43, 41; IR (CCl_4) cm^{-1} 2910, 2850, 1765, 1735, 1666, 1450, 1365, 1300, 1240, 1225, 1160, 1095, 1045, 1035, 1030; ^1H NMR (500 MHz, $CDCl_3$) δ 0.36 (q, *J* = 5, H8a), 0.96 (m, H7a), 0.98 (d, *J* = 6.83, Me20), 1.01 (d, *J* = 6.76, Me17), 1.03 (dt, *J* = 5.5, 8.8, H8b), 1.12 (dtd, *J* = 5.5, 8.8, 13.5, H11a), 1.28 (m, H11b, H6), 1.49 (tdd, *J* = 8.8, 5.5, 2.5, H9), 1.58 (s, Me 16), 1.69 (s, Me 15), 1.78 (dd, *J* = 15.1, 3.1, H5a), 1.81 (dd, *J* = 15.1, 3.1, H5b), 1.93 (m, H12a, H12b), 2.03 (s, Ac), 2.06 (dtq, *J* = 8, 7, 6.8, H10), 3.21 (d, *J* = 8.0,

(4) (a) P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, MULTAN 78, NRCC version of Aug 1978. "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data". (b) Difference Fourier maps were calculated on a time-shared HP-3000 computer in the University of California, Riverside Instrument Network by using Zalkin's FORDAP, block-diagonal least-squares refinement used Spark and Gantzel's BDLSQ. (c) Scattering powers for valence C and neutral O and H were taken from "International Tables for X-ray Crystallography", 1962, Vol. III, pp 202–206. No anomalous dispersion or absorption corrections were made.

(5) W. Fenical in "Marine Natural Products", P. J. Scheuer, Ed. Academic Press, New York, 1978, Vol. II, p 207.

(6) H. H. Sun, F. J. McEnroe, and W. Fenical, *J. Org. Chem.*, preceding paper in this issue.

H3), 4.72 (dd, J = 18, 2.5, H18a), 4.82 (dd, J = 18, 2.5, H18b), 5.04 (tsep, J = 7.2, 1.0, H13), 5.45 (br s, H4); UV (EtOH) 227 (ε 6195), 208 (5162).

Reduction of 1 to 3. A solution of 14.3 mg of **1** in 1 mL of absolute ethanol was treated with 5 mg of $NaBH_4$. The mixture was stirred at room temperature for 80 min and then quenched with several drops of 5% HCl. After addition of 3 mL of water, the product was extracted four times with 3-mL portions of diethyl ether and then dried over anhydrous K_2CO_3. Filtration and evaporation of solvent left 12.7 mg of nearly pure **3**, which after HPLC had $[\alpha]_D$ 24.3° (c 1.07, $CHCl_3$).

Reduction of 2 to 4. This was analogous to preparation of **3** from **1** above. From 25 mg **2**, 22 mg of crude **4** was obtained. After purification by HPLC, its spectral properties matched those of natural **4**.

Acetylation of 3 to 4. To a solution of 13.0 mg of **3** in 1 mL of dry pyridine, 50 μL of freshly distilled acetic anhydride was added, and the reaction was allowed to proceed at room temperature for 17 h. Methylene chloride (10 mL) was added, and the solution was washed with 10% HCl (2×), saturated $CuSO_4$ (2×), and H_2O (1×) to remove the pyridine. After drying with anhydrous $MgSO_4$ and removal of solvent, 12 mg of **4** remained, about 95% pure by ^1H NMR. This material was purified by HPLC on Partisil M9 and Lichrosorb-ODS. From natural **3**, $[\alpha]_D$ 14.2° (c 1.21, $CHCl_3$); from synthetic **3**, $[\alpha]_D$ 20.5° (c 0.57, $CHCl_3$).

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Registry No. 1, 85443-36-3; 2, 85443-37-4; 3, 83845-31-2; 4, 65043-52-9.

Supplementary Material Available: Tables listing final atomic coordinates and thermal parameters (Table A) and bond distances and angles (Table B) for 1 (6 pages). Ordering information is given on any current masthead page.

An Efficient Method for Synthesis of Symmetrical Diketones via Reaction of α-Amino-α-arylacetonitriles (Masked Acyl Anion Equivalents) with Alkyl Dibromides

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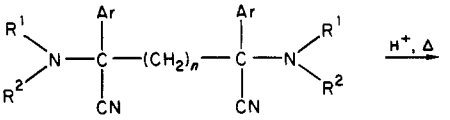
Anions derived from α-amino-α-arylacetonitriles are related as masked acyl anion equivalents. The utility of their anions in the formation of carbon–carbon bonds has been reported.[1] The utilization of such masked acyl anions is, however, not universal. The choice of substituents α to the nitrile group appears to be critical. We report here a new synthetic method for symmetrical diketones by reaction of the masked acyl anions formed from α-(dimethylamino)-α-arylacetonitrile (**1**) and derivatives with alkyl dibromides followed by hydrolysis. Many synthetic routes to 1,4-diketones have been reported.[2] However, this method is found to be useful for preparation of not only 1,4-diketones but also other symmetrical diketones having longer polymethylene chains.

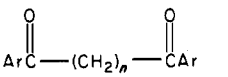
Various α-amino-α-phenylacetonitriles (**1a–e**) were prepared for investigation of the influence of the amino groups on the preferential formation of 2,5-diamino-2,5-diphenyladiponitriles (**2**) as the precursors of the corresponding diketones. The reactions of **1a–e** with 1,2-dibromoethane were carried out in a mixture of tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) containing lithium diisopropylamide (LDA). When the amino group was dimethylamine (**1a**), the yield of **2** was superior to that obtained in the case of diethyl-

Scheme I

1a, $R^1 = R^2$ = Me; Ar = Ph; 83%
b, $R^1 = R^2$ = Et; Ar = Ph; 81%
c, $R^1, R^2 = -(CH_2)_4-$; Ar = Ph; 81%
d, $R^1, R^2 = -(CH_2)_2O(CH_2)_2-$; Ar = Ph; 87%
e, R^1 = Me; R^2 = Ar = Ph; 67%
10a, $R^1 = R^2$ = Me; Ar = *p*-MeOPh; 75%
11a, $R^1 = R^2$ = Me; Ar = *p*-ClPh; 88%
12a, $R^1 = R^2$ = Me; Ar =  ; 74%



2a, $R^1 = R^2$ = Me; Ar = Ph; n = 2; 64%
b, $R^1 = R^2$ = Et; Ar = Ph; n = 2; 22%
c, $R^1, R^2 = -(CH_2)_4-$; Ar = Ph; n = 2; 48%
3a, $R^1 = R^2$ = Me; Ar = Ph; n = 3; 80%
4a, $R^1 = R^2$ = Me; Ar = Ph; n = 6; 88%
5a, $R^1 = R^2$ = Me; Ar = Ph; n = 10; >90%[a]
13a, $R^1 = R^2$ = Me; Ar = *p*-MeOPh; n = 2; 37%
14a, $R^1 = R^2$ = Me; Ar = *p*-ClPh; n = 2; 59%
15a, $R^1 = R^2$ = Me; Ar =  ; n = 2; 24%
16a, $R^1 = R^2$ = Me; Ar =  ; n = 3; 78%



6, Ar = Ph; n = 2; 92% from **2a**, 88% from **2c**
7, Ar = Ph; n = 3; 84%
8, Ar = Ph; n = 6; 98%
9, Ar = Ph; n = 10; 84%[b]
17, Ar = *p*-MeOPh; n = 2; 76%
18, Ar = *p*-ClPh; n = 2; 78%
19, Ar =  ; n = 2; 93%
20, Ar =  ; n = 3; 86%

[a] Not isolated. [b] Overall yield from **1a**.

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