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A CONVENIENT SYNTHESIS OF 3-ALKYLTETRONIC ACIDS FROM 3-ACYLTETRONIC ACIDS

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Abstract: Reductive deoxygenation of 3-acyltetronic acids provides 3-alkyltetronic acids in high yields under mild reaction conditions.

Tetronic acids constitute an important class of compounds due to their varied biological activities.[3] In connection with the synthesis of lignan and tetronic acid natural products,[4] and some unusual lipid metabolites from the Gorgonian coral *Plexaura flava*,[5] we were interested in sequential reduction of 3-acyltetronic acids to their completely saturated analogues with control over the reduction sequence. We herein report a chemoselective and high yielding reductive deoxygenation of 3-acyltetronic acids to 3-alkyl tetronic acids.

There are literature reports on the controlled reduction of the basic structural unit embodied in 3-acyltetronic acids with hydrogen and hydride reagents. For example, selective deoxygenation of the ketocarbonyl group in dehydroacetic acid using Pd/C in ethyl acetate at 80 °C has been reported.[6] Similarly the $NaCNBH_3$ - acetic acid reduction of hydroxy coumarins has also been carried out.[7]

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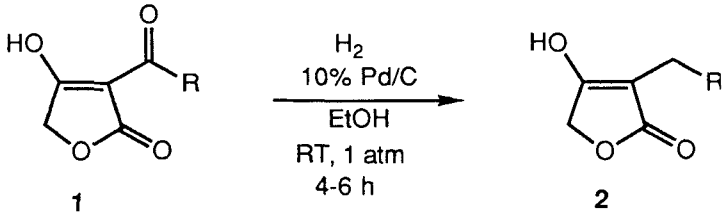
Table 1. Reductive Deoxygenation of 3-acyltetronic acids

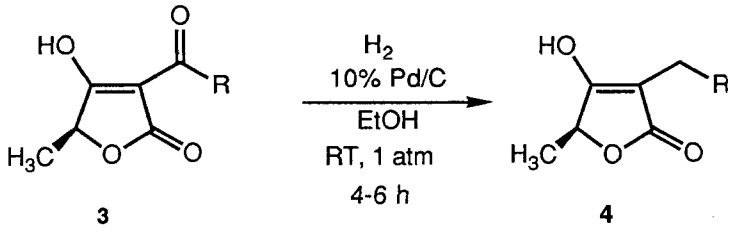


Entry	R	Yield#
a	CH_3*	96*
b	CH_2CH_3*	86
c	$CH_2CH_2CH_3$	84
d	$CH_2(CH_2)_2CH_3$	90
e	$CH_2(CH_2)_3CH_3$*	87*
f	$CH_2C_6H_5$*	93

Key: #Yields are for isolated and purified materials; * Known Compounds: **1a**: Ref. 9; **1b**: Ref. 10; **1e** and **1f**: Ref. 9; **2a**: Ref. 11; **2e**: Ref. 12.

The required 3-acyltetronic and the (S)5-methyl-3-acyltetronic acids were readily prepared in good yields from tetronic acid and (S)5-methyl tetronic acid[8] (of >92% enantiomerical purity) respectively by acylation followed by Fries rearrangement using the reported procedure of Yoshii.[9] Reductive deoxygenation of the 3-acyltetronic acids using 10% Pd/C / H_2 in ethanol at room temperature and 1 atmosphere proceeds in a short time furnishing the 3-alkyl tetronic acids in nearly quantitative yields. The products are isolated easily by filtration of the catalyst and removal of the solvent. The deoxygenation reactions proceed more sluggishly if ethyl acetate is used as the solvent. The results from the reduction of a variety of substrates are tabulated in Tables 1 and 2.

Table 2. Reductive Deoxygenation of (S)5-methyl-3-acyltetronic acids



3 4

Entry	R	Yield*
a	CH_3	95
b	CH_2CH_3	86
c	$CH_2CH_2CH_3$	93
d	$CH(CH_3)_2$	89

Key: * Yields are for isolated and purified materials.

The current procedure coupled with the reported reduction of tetronic acids[13] using H_2/Rh/C under high pressures thus provide ready access to substituted butyrolactones. The utilization of these methodologies for the total synthesis of optically pure blastmycinone[14] and the Gorgonian coral lipid metabolites are currently underway in our laboratories.

Experimental

General procedure for reductive deoxygenation: 1 mmol of 3-acyltetronic acid in 10 mL of ethanol and 1 mol% of the catalyst were stirred in an atmosphere of hydrogen at room temperature and atmospheric pressure. The reductions were monitored by TLC, and workup involved filtration of the catalyst through a pad of celite followed by removal of the solvent under reduced pressure. The products

were further purified by silica gel flash column chromatography, recrystallization and/or sublimation.

4-Hydroxy-3-(1-oxobutyl)-2(5H)-furanone **1c**. The ^{1}H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 77-78°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H, (major)), 4.57 (s, 2H, (minor)), 2.94 (t, J=7.52 Hz, 2H, (minor)), 2.91 (t, J=7.52 Hz, 2H, (major)), 1.76 (m, 2H), 1.04 (t, J=7.52 Hz, 3H, (minor)), 1.03 (t, J=7.52 Hz, 3H, (major)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 197.8, 197.4, 192.0, 191.9, 176.7, 168.1, 100.2, 97.1, 73.5, 68.6, 36.8, 34.5, 19.4, 18.4, 13.6, 13.4; IR ($CHCl_3$) 1770, 1693, 1668, 1601 cm^{-1}; Analysis calc'd for $C_8H_{10}O_4$: C, 56.47; H, 5.92; found: C, 56.62; H, 6.00.

4-Hydroxy-3-(1-oxopentyl)-2(5H)-furanone **1d**. The ^{1}H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 80-81°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 2H, (major)), 4.56 (s, 2H, (major)), 2.95 (t, J=7.52 Hz, 2H, (minor)), 2.93 (t, J=7.52 Hz, 2H, (major)), 1.72 (m, 2H), 1.44 (m, 2H), 0.96 (t, J=7.52 Hz, 3H, (minor)), 0.95 (t, J=7.52 Hz, 3H, (major)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 197.9, 197.6, 192.2, 192.0, 176.7, 168.1, 100.1, 97.0, 73.5, 68.6, 34.7, 32.5, 27.9, 26.9, 22.2, 13.6; IR ($CHCl_3$) 1770, 1693, 1669, 1600 cm^{-1}; Analysis calc'd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.41; H, 6.46.

4-Hydroxy-3-propyl-2(5H)-furanone **2b**. m.p. 97-102°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H), 2.19 (t, J=7.48 Hz, 2H), 1.51 (m, 2H), 0.91 (t, J=7.52 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 179.0, 174.0, 101.5, 67.8, 23.0, 21.0, 13.7; IR ($CHCl_3$) 1748, 1740, 1669 cm^{-1}; Analysis calc'd for $C_7H_{10}O_3$: C, 59.14; H, 7.09; found: C, 59.35; H, 7.06.

3-Butyl-4-hydroxy-2(5H)-furanone **2c**. m.p. 121-123°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H), 2.20 (t, J=7.32 Hz, 2H), 1.46 (m, 2H), 1.32 (m, 2H), 0.89 (t, J=7.33 Hz, 3H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 179.4, 174.7, 101.5, 67.9, 30.0, 22.4, 22.1, 20.7, 13.7, 13.6; IR ($CHCl_3$) 1757, 1734, 1681 cm^{-1}; Analysis calc'd for $C_8H_{12}O_3$: C, 61.52; H, 7.74; found: C, 61.65; H, 7.52.

4-Hydroxy-3-pentyl-2(5H)-furanone **2d**. m.p. 112-113°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H), 2.19 (t, J=7.69 Hz, 2H), 1.46 (m, 2H), 1.28 (m, 4H), 0.86 (t, J=6.96 Hz, 3H); ^{13}C

NMR (400 MHz, $CDCl_3$) δ 179.0, 174.7, 101.5, 67.9, 31.5, 27.5, 22.4, 21.0, 14.0; IR ($CHCl_3$) 1761, 1734, 1664 cm^{-1}; Analysis calc'd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; found: C, 63.66; H, 8.35.

4-Hydroxy-3-(2-phenylethyl)-2(5H)-furanone **2f**. m.p. 196-197°; ^1H NMR (270 MHz, CD_3OD) δ 7.09 (m, 5H), 4.78 (s, 2H), 2.64 (t, J=7.69 Hz, 2H), 2.33 (t, J=7.70 Hz, 2H); ^{13}C NMR (270 MHz, CD_3OD) δ 178.6, 175.6, 142.8, 129.4, 129.3, 127, 100.6, 68.2, 34.6, 24.2; IR ($CHCl_3$) 1748, 1716, 1663 cm^{-1}; Analysis calc'd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; found: C, 70.36; H, 6.14.

3-Acetyl-4-hydroxy-5(S)-methyl-2(5H)-furanone **3a**. The ^1H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 70-71°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.83 (q, J=7.32 Hz, 1H, major), 4.70 (q, J=7.32 Hz, 1H, (minor)), 2.55 (s, 3H), 1.52 (d, J=7.32 Hz, 3H, (major)), 1.50 (d, J=7.32 Hz, 3H, (minor)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 199.1, 198.9, 194.1, 193.3, 187.3, 166.6, 99.1, 96.0, 80.8, 75.2, 21.2, 18.5, 15.7, 15.6; IR ($CHCl_3$) 1765, 1694, 1664, 1610 cm^{-1}; $[\alpha]_D^{20}$ - 44.2° (c=1.06, EtOH); Analysis calc'd for $C_7H_8O_4$: C, 53.85; H, 5.16; found: C, 53.90; H, 5.13.

4-Hydroxy-5(S)-methyl-3-(1-oxopropyl)-2(5H)-furanone **3b**. The ^1H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 53-56°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.83 (q, J=7.33 Hz, 1H, (major)), 4.67 (q, J=7.33 Hz, 1H, (minor)), 2.93 (q, J=7.33 Hz, 2H, (minor)), 2.91 (q, J=7.33 Hz, 2H, (major)), 1.50 (d, J=7.33 Hz, 3H, (major)), 1.47 (d, J=6.60 Hz, 3H, (minor)), 1.22 (t, J=7.33 Hz, 3H, (minor)), 1.20 (t, J=7.33 Hz, 3H, (major)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 199.2, 199.0, 194.9, 192.9, 176.0, 167.5, 99.5, 96.0, 81.6, 75.8, 29.4, 26.2, 16.7, 16.5, 9.4, 8.2; IR ($CHCl_3$) 1764, 1691, 1657, 1604 cm^{-1}; $[\alpha]_D^{20}$ - 35.2° (c=1.04, EtOH); Analysis calc'd for $C_8H_{10}O_4$: C, 56.47; H, 5.92; found: C, 56.51; H, 5.71.

4-Hydroxy-5(S)-methyl-3-(1-oxobutyl)-2(5H)-furanone **3c**. The ^1H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 44-45°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.83 (q, J=7.33 Hz, 1H, (major)), 4.70 (q, J=7.33 Hz, 1H, (minor)), 2.91 (t, J=7.32 Hz, 2H, (major)),

2.90 (t, J=7.32 Hz, 2H, (minor)), 1.75 (m, 2H), 1.53 (d, J=7.60 Hz, 3H, (major)), 1.51 (d, J=7.33 Hz, 3H, (minor)), 1.03 (t, J=7.33 Hz, 3H, (minor)), 1.02 (t, J=7.33 Hz, 3H, (major)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 200.0, 197.7, 194.9, 192.0, 176.0, 167.4, 99.5, 96.5, 81.5, 75.9, 37.0, 35.5, 34.3, 19.3, 18.3, 18.0, 16.6, 13.5; IR ($CHCl_3$) 1763, 1691, 1658, 1603 cm^{-1}; $[\alpha]_D^{20}$ - 36.4° (c=1.02, EtOH); Analysis calc'd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.75; H, 6.37.

4-Hydroxy-5(S)-methyl-3-(2-methyl-1-oxopropyl)-2(5H)-furanone **3d**. The ^1H and ^{13}C nmr spectra indicate the presence of two tautomeric forms.: m.p. 62-63°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.82 (q, J=7.33 Hz, 1H, (major)), 4.67 (q, J=7.33 Hz, 1H, (minor)), 3.69 (sep, J=6.60 Hz, 1H, (minor)), 3.57 (sep, J=6.59 Hz, 1H, (major)), 1.51 (d, J=7.33 Hz, 3H, (major)), 1.47 (d, J=6.59 Hz, 3H, (minor)), 1.22 (d, J=6.59 Hz, 3H, (minor)), 1.20 (d, J=6.59 Hz, 3H, (major)); ^{13}C NMR (270 MHz, $CDCl_3$) δ 202.4, 200.3, 196.6, 194.6, 176.5, 167.3, 98.5, 95.1, 81.6, 75.8, 33.6, 31.2, 18.5, 18.4, 18.2, 18.0, 16.7, 16.6; IR ($CHCl_3$) 1760, 1690, 1651, 1599 cm^{-1}; $[\alpha]_D^{20}$ - 32.0° (c=1.00, EtOH); Analysis calc'd for $C_9H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.81; H, 6.45.

3-Ethyl-4-hydroxy-5(S)-methyl-2(5H)-furanone **4a**. m.p. 99-101°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.86 (q, J=6.59 Hz, 1H), 2.21 (q, J=7.33 Hz, 2H), 1.51 (d, J=6.60 Hz, 3H), 1.06 (t, J=7.33 Hz, 3H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 178.1, 177.6, 100.5, 75.5, 17.8, 14.4, 12.6; IR ($CHCl_3$) 1756, 1723, 1656 cm^{-1}; $[\alpha]_D^{20}$ 14.9° (c=1.00, EtOH); Analysis calc'd for $C_7H_{10}O_3$: C, 59.14; H, 7.09; found: C, 58.96; H, 7.22.

4-Hydroxy-5(S)-methyl-3-propyl-2(5H)-furanone **4b**. m.p. 59-61°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.86 (q, J=6.59 Hz, 1H), 2.21 (t, J=7.33 Hz, 2H), 1.52 (d, J=6.59 Hz,3H), 1,50 (m, 2H), 0.92 (t, J=7.33 Hz, 3H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 178.1, 177.6, 100.5, 75.0, 22.8, 21.2, 17.8, 13.6; IR ($CHCl_3$) 1740, 1734, 1653 cm^{-1}; $[\alpha]_D^{20}$ 16.5° (c=1.00, EtOH); Analysis calc'd for $C_8H_{12}O_3$: C, 61.52; H, 7.74; found: C, 61.74; H, 7.49.

3-Butyl-4-hydroxy-5(S)-methyl-2(5H)-furanone **4c**. m.p. 57-58°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.80 (q, J=6.59 Hz, 1H), 2.18 (t, J=7.33 Hz, 2H), 1.65 (bs, 1H), 1.49 (d, J=6.59 Hz,

3H), 1.49 (m, 3H), 1.35 (m, 2H), 0.92 (t, J=7.33 Hz, 3H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 177.3, 177.0, 101.0, 75.1, 30.1, 22.4, 20.8, 17.8, 17.5; IR ($CHCl_3$) 1755, 1723, 1663 cm^{-1}; $[\alpha]_D^{20}$ 16.8° (c=0.75, EtOH); Analysis calc'd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; found: C, 63.40; H, 8.03.

4-Hydroxy-5(S)-methyl-3-(2-methylpropyl)-2(5H)-furanone **4d**. m.p. 91-93°; ^1H NMR (270 MHz, $CDCl_3$) δ 4.84 (q, J=6.59 Hz, 1H), 2.08 (d, J=6.60 Hz, 2H), 1.88 (m, 1H), 1.51 (d, J=6.69 Hz, 3H), 0.91 (d, J=6.60 Hz, 3H), 0.90 (d, J=6.60 Hz, 3H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 179.0, 178.2, 99.6, 75.5, 29.8, 27.4, 22.2, 22.1, 18.0; IR ($CHCl_3$) 1745, 1705, 1677 cm^{-1}; $[\alpha]_D^{20}$ 17.1° (c=0.6, EtOH); Analysis calc'd for $C_9H_{14}O_3$: C, 63.51; H, 8.29; found: C, 63.56; H, 8.20.

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