TIN (IV) CHLORIDE-PROMOTED REACTIONS OF α-HYDROXY NITRILES WITH β-DICARBONYL COMPOUNDS
SYNTHESIS OF 4-AMINO-2,5-DIHYDRO-2-FURANONES AND THEIR CONVERSION INTO TETRONIC ACID DERIVATIVES

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Abstract- *β-Keto esters and β–diesters react with α-hydroxy nitriles in the presence of stoichiometric amounts of tin(IV) chloride to give 3-acyl-4-amino-2(5H)-furanones (2) and ethyl 4-amino-2,5-dihydro-2-oxofuran-3-carboxylates (3). The acyldihydrofuranones (2) can be converted into acyltetronic acid derivatives (6) while the ethyl furan-3-carboxylates (3) can be converted into tetronic acids (8).*

In the context of our continuous interest in metal-promoted reactions between nitriles and β-dicarbonyls,[1] we have recently described a convenient preparation of substituted 4-aminoquinolines and 4-aminopyridines through metal-promoted reactions of β-keto esters and β-diesters with *o*-aminobenzonitriles and enaminonitriles respectively.[2] The crucial carbon-carbon bond forming reaction between the cyano group and the intercarbonylic methylene of β-dicarbonyls is followed by intramolecular nucleophilic attack of the adjacent amino group to one of the two carbonyls, leading ultimately to the formation of the six-membered heterocyclic ring systems.

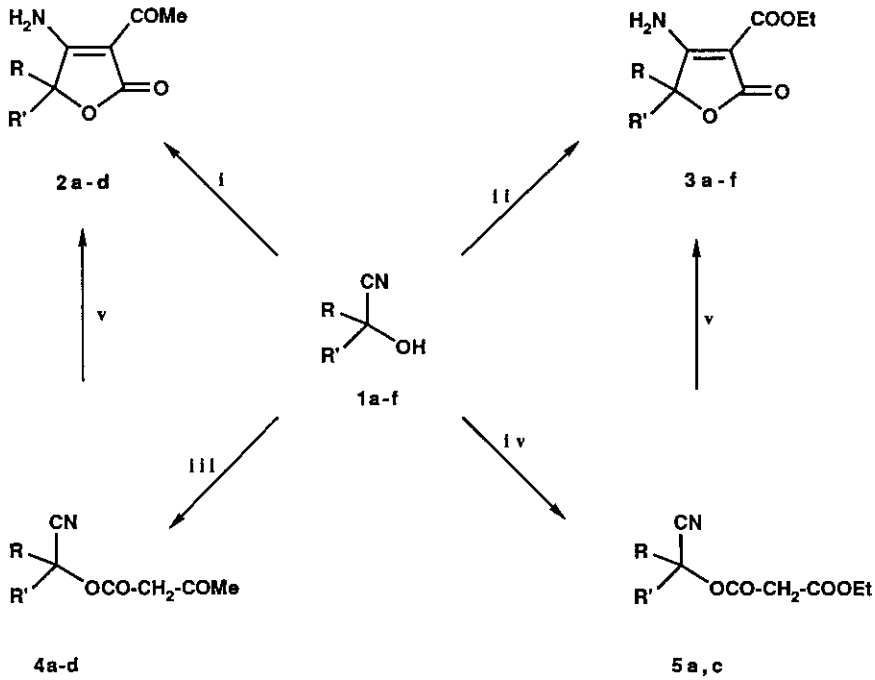
As a logical extension of this chemistry we decided to investigate the metal-promoted reactions of β-dicarbonyls with nitriles bearing other substituents suitable for obtaining heterocycles of medicinal interest.

In this paper we report that the selected α–hydroxy nitriles (**1a-d**) react intermolecularly with methyl or ethyl acetoacetates in the presence of stoichiometric amounts of tin(IV) chloride producing directly the substituted 3-acyl-4-amino-2(5H)-furanones (**2a-d**) in moderate yields (50-60%). Similarly the nitriles (**1a-f**) react with ethyl malonate to give the ethyl 4-amino-2,5-dihydro-2-oxo-3-furancarboxylates (**3a-f,** yields: 60-80%).

Also an alternative two-step sequence was tried, involving first conversion of **1a-d** into the corresponding acetoacetates (**4a-d**) and malonic esters (**5a,c**) through acylation with diketene and ethyl malonyl chloride respectively. These operations proceeded smoothly affording high yields of the substrates required for attempting an intramolecular version of the metal-promoted cyclization.

Disappointingly when these compounds were exposed to the previously experienced reaction conditions in the presence of tin(IV) chloride, formation of aminodihydrofuranones could not be observed.

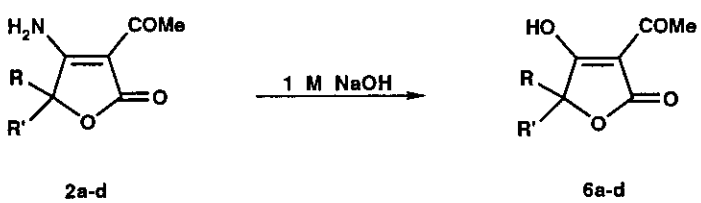
However the desired cyclization could be easily performed, according to the Hiyama's method, by treatment of compounds (**4**) and (**5**) with sodium hydroxide or sodium ethoxide. The expected aminodihydrofuranones (**2a-d**) and (**3a,c**) were obtained in moderate yields.[3]



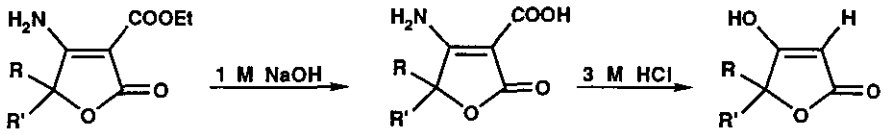
i:$MeCOCH_2COOR,SnCl_4$; ii:$CH_2(COOEt)_2,SnCl_4$; iii:diketene; iv:$EtOOCCH_2COCl$; v:NaOH or EtONa.

For the formulae 1-8:
a:R=R'=Me; b:R=Me,R'=Et; c:$RR'=(CH_2)_5$; d:$RR'=(CH_2)_4$; e:R=Me,R'=H; f:R=Ph,R'=H.

Having access to a convenient source of the acylaminofuranones (**2**) and of aminofurancarboxylates (**3**), we then investigated their conversion into tetronic acid derivatives[4] under different experimental conditions. It is known that 4-aminofuranones can be hydrolyzed to tetronic acid under acidic conditions.[5] In our hand however compound (**2a**) failed to undergo hydrolysis by treatment both with 6 M hydrochloric acid and with sodium nitrite-hydrochloric acid. A smooth transformation to the desired acyltetronic acid derivatives (**6a-d**) was eventually achieved in moderate yields (50-75%) by heating (**2a-d**) for 2-6 h under reflux with 1 M sodium hydroxide.[6]



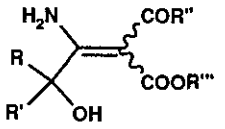
Under the same experimental conditions, the aminofurancarboxylates (**3a-c**) were hydrolyzed in high yields (90-95%) to the corresponding acids (**7a-c**). The treatment of these acids with 3 M HCl under reflux for 1-3 h afforded the tetronic acid derivatives (**8a-c**) in moderate or good yields (65-90%).[7]



3a-c **7a-c** **8a-c**

The obtained results show that tin(IV) chloride can promote the intermolecular reaction of α-hydroxy nitriles with β-keto esters and β-diesters to aminodihydrofuranone derivatives (**2**) and (**3**). This promotion may be related to the ability of tin chloride to coordinate both the β-dicarbonyl compounds and the nitriles[1a,8] thus enhancing their nucleophilic and electrophilic character respectively. On the contrary, tin chloride does not promote the intramolecular cyclization of β-keto esters (**4**) and malonates (**5**) probably owing to difficulties in coordinating both the cyano and the β-dicarbonyl moiety for steric and/or geometric reasons.

According to our previous results the dihydrofuranone derivatives (**2**) and (**3**) are formed through the lactonization of intermediate β-enaminodiones (**9**), this being supported also by the fact that tin chloride does not promote the intramolecular cyclization of compounds (**4**) and (**5**).



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In conclusion tin(IV) chloride promote the synthesis of furanone derivatives (**2**) and (**3**) by the straight reaction of α-hydroxy nitriles with β-keto esters and diesters. The acylfuranones (**2**) and the esters (**3**) can be converted into acyltetronic acid (**6**) and into tetronic acid derivatives (**8**) respectively.

EXPERIMENTAL

Melting points were determined using a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 299B spectrophotometer. The ^{1}H nmr and ^{13}C nmr spectra were recorded on a Bruker AC 200 spectrometer; chemical shift (δ) is given in ppm relative to tetramethylsilane as internal standard. Thin layer chromatography was performed on the pre-coated silica gel 60 F-254 plates manufactured

by Merck, Darmstad, Germany. Column chromatography was carried out using Merck 9385 (230-400 mesh ASTM) silica gel.

2-Hydroxy-2-methylpropanenitrile (**1a**), 2-hydroxypropanenitrile (**1e**) and 2-hydroxy-2-phenylacetonitrile (**1f**) are commercially available. 2-Hydroxy-2-methylbutanenitrile (**1b**), 1-hydroxycyclohexanecarbonitrile (**1c**) and 1-hydroxycyclopentanecarbonitrile (**1d**) were prepared according to the method of Gassman.[9]

a) Reactions of α-hydroxy nitriles (1) with β-keto esters in the presence of $SnCl_4$

3-Acetyl-4-amino-5,5-dimethyl-2(5H)-furanone (2a)

To a solution of methyl acetoacetate (1.08 ml , 10 mmol) in toluene (25 ml) 2-hydroxy-2-methylpropanenitrile (**1a**) (0.91 ml, 10 mmol) and $SnCl_4$ (2.3 ml, 20 mmol) were added. The reaction mixture was heated under reflux in a nitrogen atmosphere for 3 h and then was allowed to cool at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (50 ml) and the solution was stirred vigorously with a saturated aqueous solution of Na_2CO_3 (pH of aqueous layer > 10). The two layers were filtered over Celite and separated. The aqueous layer was extracted again with ethyl acetate (100 ml) and the combined extracts were washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure yielding a crude product, which was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 4:1): colourless crystals, 1.01 g (60%), mp 189-191°C (lit.,[3b] mp 188-89°C); ir (KBr) ν_{max}: 3320, 3290, 1705, 1650, 1540, 1260 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.58 (s, 6H, 2 Me), 2.47 (s, 3H, Me), 7.30 (br, 1H, NH), 9.00 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 24.80 (q, J=127 Hz, 2 Me), 27.52 (q, J=125 Hz, Me), 78.81 (s, C-5), 93.24 (s, C-3), 169.45 (s, C-4), 179.46 (s, C-2), 194.22 (s, COMe).

3-Acetyl-4-amino-5-ethyl-5-methyl-2(5H)-furanone (2b)

To a solution of 2-hydroxy-2-methylbutanenitrile (**1b**) (0.35 g, 3.5 mmol) in ethyl acetate (2 ml) ethyl acetoacetate (0.4 ml, 3.5 mmol) and $SnCl_4$ (0.8 ml, 7.0 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen for 48 h, diluted with ethyl acetate (20 ml) and stirred for 1 h with a saturated aqueous solution of Na_2CO_3 (pH of aqueous layer > 10). The two layers were filtered over Celite and the aqueous layer was extracted with ethyl acetate (100 ml). The combined extracts were washed with water, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give red crystals which were taken up with 1 M HCl. The suspension was stirred at room temperature for 8 h, 1 M NaOH was added (pH > 10) and the resulting mixture was extracted with ethyl acetate (50 ml x 3). The organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 5:1): yellow crystals, mp 187-190°C (EtOH), 0.313 g (50%); ir (KBr) ν_{max}: 3340, 3220, 1715, 1650, 1540, 1200, 1030 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.87 (t, J=7.3 Hz, 3H, Me), 1.56 (s, 3H, Me), 1.89-1.94 (m, 2H, CH_2), 2.46 (s, 3H, Me), 7.82 (br, 1H, NH), 8.93 (br, 1H, NH); ^{13}C nmr ($CDCl_3$) δ: 7.27 (Me), 23.91 (Me), 28.01 (CH_2), 30.80 (Me), 82.59 (C-5), 96.14 (C-3), 171.28 (C-4), 179.45 (C-2), 196.48 (COMe). *Anal.* Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found C, 58.7; H, 7.4; N, 7.5.

3-Acetyl-4-amino-1-oxaspiro[4.5]-3-decen-2-one (2c)

This compound was obtained by reacting 1-hydroxycyclohexanecarbonitrile (**1c**) with methyl acetoacetate according to procedure described for compound (**2b**): yellow crystals, mp 248-250°C (EtOH), yield 51%; ir (KBr) ν_{max}: 3340, 3140 (br), 1740, 1660, 1640, 1520, 1300, 1030 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.20-1.90 (m, 10H, 5 CH_2), 2.27 (s, 3H, Me), 8.89 (br, 1H, NH), 8.94 (br, 1H, NH); ^{13}C nmr (DMSO-d_6)

δ: 21.33 (t, J=125 Hz, 2 CH_2), 23.77 (t, J=119 Hz, CH_2), 27.51 (q, J=126 Hz, Me), 32.95 (t, J=127 Hz, 2 CH_2), 80.24 (s, C-5), 93.28 (s, C-3), 169.54 (s, C-4), 179.22 (s, C-2), 193.90 (s, CO). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.3; H, 7.4; N, 6.5.

3-Acetyl-4-amino-1-oxaspiro[4.4]-3-nonen-2-one (2d)

This compound was obtained by reacting 1-hydroxycyclopentanecarbonitrile (**1d**) with methyl acetoacetate under the same experimental conditions described for **2a**: yellow oil which was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 4:1): colourless crystals, mp 152-154°C (EtOH), yield 55%; ir (KBr) ν_{max}: 3340, 3240-3140, 1740, 1710, 1650, 1540 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.86-2.00 (m, 8H, 4 CH_2), 2.48 (s, 3H, Me), 6.25 (br, 1H, NH), 8.90 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 23.94 (t, J=133 Hz, 2 CH_2), 27.03 (q, J=126 Hz, Me), 37.45 (t, J=131 Hz, 2 CH_2), 88.35 (s, C-5), 94.31 (s, C-3), 168.97 (s, C-4), 177.04 (s, C-2), 193.43 (s, COMe). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.3; H, 6.5; N, 7.0.

b) Reactions of α-hydroxy nitriles (1) and ethyl malonate in the presence of $SnCl_4$

Ethyl 4-amino-5,5-dimethyl-2,5-dihydro-2-oxo-3-furancarboxylate (3a)

To a solution of 2-hydroxy-2-methylpropanenitrile (**1a**) (0.46 ml, 5 mmol) in ethyl acetate (4 ml) ethyl malonate (0.91 ml, 6 mmol) and $SnCl_4$ (1.17 ml, 10 mmol) were added. The reaction mixture was stirred at room temperature under nitrogen for 48 h and the solution was stirred vigorously for 1 h with a saturated aqueous solution of Na_2CO_3 (pH of aqueous layer > 10). The two layers were filtered over Celite and separated. The aqueous layer was extracted again with ethyl acetate (50 ml) and the combined extracts were washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was washed with ethyl ether: colourless crystals of compound (**3a**): 0.31 g. Further amounts of **3a** were obtained washing Celite with hot ethanol and concentrating the solution obtained after filtration: colourless crystals, mp 259-261°C (EtOH), 0.464 g (total yield 78%); ir (KBr) ν_{max}: 3460, 3340, 3300, 1740, 1650, 1570 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.22 (q, J=7.0 Hz, 3H, Me), 1.44 (s, 6H, 2Me), 4.15 (q, J=7.0 Hz, 2H, OCH_2), 8.16 (br, 1H, NH), 8.64 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 14.35 (q, J=125 Hz, 2 Me), 24.85 (q, J=128 Hz, Me), 58.71 (t, J=146 Hz, CH_2), 78.71 (s, C-5), 83.24 (s, C-3), 163.80 (s, COO), 166.89 (s, C-4), 179.72 (s, C-2). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.3; H, 6.6; N, 7.0. Found: C, 54.0; H, 6.7; N, 6.8.

Ethyl 4-amino-2,5-dihydro-5-ethyl-5-methyl-2-oxo-3-furancarboxylate (3b)

This compound was obtained by reacting 2-hydroxy-2-methylbutanenitrile (**1b**) with ethyl malonate according to the procedure described for **3a**: colourless crystals, mp 234-236°C (EtOH), yield 73%; ir (KBr) ν_{max}: 3330, 3220, 1720, 1650, 1580 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 0.68 (t, J=7.3 Hz, 3H, Me), 1.21 (t, J=7.1 Hz, 3H, Me), 1.40 (s, 3H, Me), 1.79 (m, 2H, CH_2), 4.14 (q, J=7.1 Hz, 2H, OCH_2), 8.17 (br, 1H, NH), 8.59 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 6.98 (q, J=123 Hz, Me), 14.43 (q, J=127 Hz, Me), 23.99 (q, J=127 Hz, Me), 29.18 (t, J=129 Hz, CH_2), 59.15 (t, J=147 Hz, OCH_2), 81.75 (s, C-5), 85.16 (s, C-3), 164.80 (s, COO), 168.42 (s, C-4), 179.72 (s, C-2). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.3; H, 7.1; N, 6.6. Found: C, 56.5; H, 6.9; N, 6.7.

Ethyl 4-amino-2-oxo-1-oxaspiro[4.5]-3-decene-3-carboxylate (3c)

This compound was obtained by reacting 1-hydroxycyclohexanecarbonitrile (**1c**) with ethyl malonate as described for compound (**3a**): the oily product obtained was taken up with diethyl ether to give colourless

crystals, mp 264-268°C (EtOH), yield 60%; ir (KBr) ν_{max}: 3360, 3240, 1720, 1650 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.20 (t, J=7.0 Hz, 3H, Me), 1.45-1.69 (m, 8H, 4 CH_2), 1.69-1.88 (m, 2H, CH_2), 4.13 (q, J=7.0 Hz, 2H, CH_2), 8.13 (br, 1H, NH), 8.60 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 14.34 (q, J=125 Hz, Me), 21.33 (t, J=121 Hz, CH_2), 23.75 (t, J=127 Hz, 2 CH_2), 32.98 (t, J=128 Hz, 2 CH_2), 58.72 (t, J=146 Hz, OCH_2), 80.13 (s, C-5), 83.35 (s, C-3), 163.98 (s, COO), 167.13 (s, C-4), 179.45 (s, C-2). *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.4; H, 7.0; N, 5.7.

Ethyl 4-amino-2-oxo-1-oxaspiro[4.4]-3-nonene-3-carboxylate (3d)

This compound was obtained by reacting 1-hydroxycyclopentanecarbonitrile (**1d**) with ethyl malonate according to the procedure described for **3a**: colourless crystals, mp 256-259°C (EtOH), yield 62%; ir (KBr) ν_{max}: 3360, 3240, 1720, 1650, 1570 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.20 (t, J=7.0 Hz, 3H, Me), 1.74-1.82 (m, 8H, 4 CH_2), 4.14 (q, J=7.0 Hz, 2H, OCH_2), 8.15 (br, 1H, NH), 8.66 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 13.95 (q, J=124 Hz, Me), 23.82 (t, J=124 Hz, CH_2), 37.31 (t, J=136 Hz, CH_2), 58.32 (t, J=146 Hz, OCH_2), 84.34 (s, C-3), 88.26 (s, C-5), 163.19 (s, COO), 166.51 (s, C-4), 177.12 (s, C-2). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.7; H, 6.7; N, 6.2. Found: C, 58.5; H, 6.9; N, 6.1.

Ethyl 4-amino-2,5-dihydro-5-methyl-2-oxo-3-furancarboxylate (3e)

This compound was obtained by reacting 2-hydroxypropanenitrile (**1e**) with ethyl malonate according to the procedure described for **3a**: colourless crystals, mp 207-209°C (EtOH), yield 79%; ir (KBr) ν_{max}: 3400, 3300, 3160 (br), 1720, 1670, 1640, 1560, 1240 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.22 (t, J=7.1 Hz, 3H, Me), 1.42 (d, J=6.0 Hz, 3H, Me), 4.16 (q, J=7.1 Hz, 2H, OCH_2), 4.90 (q, J=6.0 Hz, 1H, CH), 8.10 (br, 1H, NH), 8.63 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 14.35 (q, J=126 Hz, Me), 18.79 (q, J=128 Hz, Me), 58.72 (t, J=148 Hz, OCH_2), 71.99 (d, J=156 Hz, C-5), 83.92 (s, C-3), 163.64 (s, COO), 168,01 (s, C-4), 177,19 (s, C-2). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.9; H, 6.0; N, 7.6. Found: C, 51.6; H, 6.2; N, 7.4.

Ethyl 4-amino-2,5-dihydro-2-oxo-5-phenyl-3-furancarboxylate (3f)

This compound was obtained by reacting 2-hydroxy-2-phenylacetonitrile (**1f**) with ethyl malonate as described for compound (**3a**): brown crystals, mp 180-183°C (EtOH), yield 67%; ir (KBr) ν_{max}: 3400, 3230, 1790, 1770, 1690, 1640, 1260 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.25 (t, J=7.1 Hz, 3H, Me), 4.19 (q, J=7.1 Hz, 2H, OCH_2), 5.91 (s, 1H, CH), 7.32-7.44 (m, 5H, Ph), 8.13 (br, 1H, NH), 8.53 (br, 1H, NH); ^{13}C nmr (DMSO-d_6) δ: 14.33 (q, J=126 Hz, Me), 58.94 (t, J=149 Hz, OCH_2), 77.01 (d, J=153 Hz, C-5), 84.43 (s, C-3), 127.40 (d, J=156 Hz, 2 CH, Ar) 128.72 (d, J=161 Hz, 2 CH, Ar), 129.22 (d, J=160 Hz, 1 CH, Ar), 135.76 (s, Ar), 163.52 (s, COO), 168.22 (s, C-4), 175.10 (s, C-2). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.5; H, 5.4; N, 5.4.

c) Synthesis of the acetoacetates (4) and of the malonates (5)

1-Cyano-1-methylethyl acetoacetate (4a)

A mixture of 2-hydroxy-2-methylpropanenitrile (**1a**) (0.5 ml, 5.5 mmol), diketene (0.42 ml, 5.5 mmol) and 4-dimethylaminopyridine (20 mg) was stirred at room temperature for 24 h. The reaction mixture was taken up with ethyl acetate, and the solution was washed with H_2O. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 1:2): yellow oil of **4a**,[3b] 0.72 g (78%); ir (neat) ν_{max}: 2240 (w), 1760, 1720, 1130 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.78 (s, 6H, 2 Me), 2.29 (s, 3H, Me), 3.52 (s, 2H, CH_2); ^{13}C nmr

($CDCl_3$) δ: 26.84 (q, J=131 Hz, 2 Me), 30.44 (q, J=128 Hz, Me), 50.18 (t, J=130 Hz, CH_2), 69.68 (s, C-O), 119.70 (s, CN), 166.30 (s, COO), 201.10 (s, CO).

1-Cyano-1-methylpropyl acetoacetate (4b)

This compound was obtained by reacting 2-hydroxy-2-methylbutanenitrile (**1b**) with diketene as described for **4a**. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 1:3): colourless oil, yield 66.8%; ir (neat) ν_{max}: 2240 (w), 1760, 1720, 1250, 1130 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.10 (t, J=7.4 Hz, 3H, Me), 1.76 (s, 3H, Me), 2.02 (m, 2H, CH_2), 2.27 (s, 3H, Me-CO), 3.52 (s, 2H, CH_2); ^{13}C nmr ($CDCl_3$) δ: 7.85 (q, J=126 Hz, Me), 23.58 (q, J=130 Hz, Me), 29.94 (q, J=127 Hz, Me-CO), 32.56 (t, J=130 Hz, CH_2), 49.62 (t, J=130 Hz, CH_2), 73.11 (s, C-O), 117.98 (s, CN), 165.03 (s, COO), 199.53 (s, CO). *Anal.* Calcd for $C_9H_{13}NO_3$: C, 59.0; H, 7.2; N, 7.7. Found: C, 58.7; H, 7.3; N, 7.5.

1-Cyano-cyclohexyl acetoacetate (4c)

This compound was obtained by reacting 1-hydroxycyclohexanecarbonitrile (**1c**) with diketene under the same experimental conditions described for **4a**: yellow oil, yield 59%; ir (neat) ν_{max}: 1760, 1740, 1660, 1630, 1250, 1140 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.20-1.90 (m, 10H, 5 CH_2), 2.29 (s, 3H, Me), 3.53 (s, 2H, CH_2); ^{13}C nmr ($CDCl_3$) δ: 21.84 (t, J=128 Hz, 2 CH_2), 24.27 (t, J=126 Hz, CH_2), 30.20 (q, J=127 Hz, Me), 34.81 (t, J=131 Hz, 2 CH_2), 49.89 (t, J=130 Hz, CH_2), 73.48 (s, C-O), 118.09 (s, CN), 165.00 (s, COO), 199.87 (s, CO). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.0; H, 7.1; N, 6.5.

1-Cyano-cyclopentyl acetoacetate (4d)

This compound was obtained by reacting 1-hydroxycyclopentanecarbonitrile (**1d**) with diketene as described for **4a**: yellow oil, yield 73%; ir (KBr) ν_{max}: 2240 (w), 1760, 1720, 1240, 1140 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.83 (m, 4H, 2 CH_2), 2.27 (s, 3H, Me), 2.27-2.32 (m, 4H, 2 CH_2), 3.53 (s, 2H, CH_2); ^{13}C nmr ($CDCl_3$) δ: 23,27 (t, J=129 Hz, 2 CH_2), 30.27 (q, J=127 Hz, Me), 38.84 (t, J=133 Hz, 2 CH_2), 49.74 (t, J=130 Hz, CH_2), 77.27 (s, C-O), 119.01 (s, CN), 165.62 (s, COO), 199.97 (s, CO). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.8; H, 6.6; N, 7.2.

1-Cyano-1-methylethyl ethyl malonate (5a)

To a solution of 2-hydroxy-2-methylpropanenitrile (**1a**) (2.75 ml, 30 mmol) in anhydrous THF (20 ml) 50% sodium hydride (0.840 g, 35 mmol) and ethyl malonyl chloride (4.6 ml, 35 mmol) were added. The resulting suspension was stirred at room temperature for 2 h. The reaction mixture was treated with H_2O (100 ml) and with 1 M HCl (pH *ca.* 1) and extracted with ethyl acetate (50 ml x 3). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give an oil, which was purified by flash chromatography on silica gel (eluent: ethyl acetate-light petroleum 1:3): colourless oil, 3.13 g, (49%); ir (neat) ν_{max}: 1770, 1740, 1370, 1330, 1130 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.28 (t, J=7.1 Hz, 3H, Me), 1.78 (s, 6H, 2 Me), 3.41 (s, 2H, CH_2), 4.21 (q, J=7.1 Hz, 2H, OCH_2); ^{13}C nmr ($CDCl_3$) δ: 14.07 (q, J=126 Hz, Me), 26.70 (q, J=130 Hz, 2 Me), 41.63 (t, J=131 Hz, CH_2), 61.87 (t, J=147 Hz, OCH_2), 69.43 (s, C-O), 118.85 (s, CN), 164.56 (s, COO), 165.82 (s, COO). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.3; H, 6.6; N, 7.0. Found: C, 54.4; H, 6.4; N, 7.1.

1-Cyano-cyclohexyl ethyl malonate (5c)

This compound was obtained by reacting 1-hydroxycyclohexanecarbonitrile (**1c**) with ethyl malonyl chloride according to the procedure described for **5a** but heating at 60°C for 6 h: colourless oil, yield 67%; ir (neat) ν_{max}: 1760, 1740, 1130 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.29 (t, J=7.1 Hz, 3H, Me), 1.57-1.98 (m, 8H, 4 CH_2), 2.22-2.27 (m, 2H, CH_2), 3.42 (s, 2H, CH_2), 4.22 (q, J=7.1 Hz, 2H, OCH_2). *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.0; H, 7.0; N, 5.6.

d) Cyclization of the acetoacetates (4)

a) *In the presence of $SnCl_4$:* A solution of **4a** (0.19 g, 1.1 mmol) in methylene chloride (2 ml) was heated under reflux for 5 h in the presence of $SnCl_4$ (0.18 ml, 1.6 mmol) to give a complex reaction mixture in which compound (**2a**) was not detected.

b) *In the presence of sodium hydroxide:* A solution of **4a** (0.595 g, 3.53 mmol) in 1 M NaOH (5.3 ml, 5.3 mmol) was stirred at room temperature for 1 h and acidified with 1 M HCl (pH *ca.* 1). The separated colourless crystals were filtered off and dried (P_2O_5): 0.266 g corresponding to **2a**. The aqueous solution was extracted with ethyl acetate (20 ml x 3) and the extracts were dried (Na_2SO_4) and concentrated to give further 0.210 g of compound (**2a**) (total yield 88%).

Under the same experimental conditions the acetoacetate (**4b**) gave **2b** in 79% yield, **4c** afforded **2c** in 84% yield and **4d** gave the compound (**2d**) in 74% yield.

c) *In the presence of sodium ethoxide:* The acetoacetate (**4a**) (0.570 g, 3.4 mmol) was added to a 1M solution of sodium ethoxide in ethanol (4.07 ml, 4.07 mmol) and the reaction mixture was stirred at room temperature for 2 h, treated with 1 M HCl to *ca.* pH 1 and evaporated under reduced pressure to a solid residue which was extracted with hot ethanol (15 ml x 3). The extracts were concentrated to give yellow crystals of **4a**: 0.505 g (88%).

Under the same experimental conditions the acetoacetate (**4c**) gave **2c** in 75% yield.

e) Cyclization of the malonates (5)

a) *In the presence of $SnCl_4$:* A solution of **5a** (0.53 g, 2.6 mmol) in methylene chloride (2 ml) was heated under reflux for 5 h in the presence of $SnCl_4$ (0.37 ml, 3.18 mmol) to give a complex reaction mixture in which compound (**3a**) was not detected.

b) *In the presence of sodium hydroxide*: compound (**5a**) (0.54 g, 2.7 mmol) treated with 1 M NaOH (4.1 ml, 4.1 mmol) under the same experimental conditions described for **4a** gave **3a** in 43% yield. Similarly **5c** gave **3c** in 11% yield.

c) *In the presence of sodium ethoxide*: treatment of compound (**5a**) (0.48 g, 2.4 mmol) with 1M solution of sodium ethoxide in ethanol (3.6 ml, 3.6 mmol) under the same experimental conditions described for **4a** gave compound (**3a**) in 34% yield. Similarly compound (**5c**) gave **3c** in 57% yield.

f) Conversion of 4-amino-2-furanones (2) and (3) into tetronic acid derivatives (6) and (8)

3-Acetyl-4-hydroxy-5,5-dimethyl-2(5H)-furanone (6a)

A solution of amino furanone (**2a**) (0.3 g, 1.77 mmol) in 1 M NaOH (4 ml) was heated under reflux for 2 h. The yellow solution was extracted with ethyl acetate (10 ml x 3), acidified with 1 M HCl to pH *ca.*1, saturated with NaCl and extracted again with ethyl acetate (10 ml x 3). The latter organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give yellow crystals, which were taken up with ethyl ether (4 ml). The resulting suspension was filtered and the solution was concentrated to give yellow crystals of **6a**, mp 60-63°C (lit.,[6a] mp 64-65°C), 0.160 g (53%); ir (Nujol) ν_{max}: 1760, 1665, 1620, 1470, 1170, 1020 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.35 (s, 6H, 2 Me), 2.43 (s, 3H, Me), 8.90 (br, 1H, OH); ^{13}C nmr (DMSO-d_6) δ: 23.62 (q, J=128 Hz, 2 Me), 27.40 (q, J=126 Hz, Me), 82.49 (s, C-5), 97.00 (s, C-3), 169.04 (s, C-2), 190.06 (s, CO), 196.27 (s, C-4).

3-Acetyl-5-ethyl-4-hydroxy-5-methyl-2(5H)-furanone (6b)

This compound was obtained by heating **2b** under reflux in 1 M NaOH for 5 h: oil, yield 52%; ir (neat) ν_{max}: 1760, 1690, 1610, 1460, 1250, 1120 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 0.75 (t, J=7.2 Hz, 3H, Me), 1.33 (s, 3H, Me), 1.71 (m, 2H, CH_2), 2.44 (s, 3H, Me), 10.00 (br, 1H, OH); ^{13}C nmr (DMSO-d_6) δ: 7.33 (q, J=125 Hz, Me), 22.16 (q, J=128 Hz, Me), 23.49 (q, J=126 Hz, Me), 29.38 (t, J=128 Hz, CH_2), 85.14 (s, C-5), 98.44 (s, C-3), 169.33 (s, C-2), 189.94 (s, CO), 195.90 (s, C-4). *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.7; H, 6.6. Found: C, 59.0; H, 6.7.

3-Acetyl-4-hydroxy-1-oxaspiro[4.5]-3-decen-2-one (6c)

This compound was obtained by heating **2c** under reflux in 1 M NaOH for 6 h: yellow crystals, mp 122-124°C (lit.,[6a] mp 125-126°C), yield 50%; ir (Nujol): 3600-2700 (br), 1670, 1620, 1320 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.75 (m, 10H, 5 CH_2), 2.55 (s, 3H, Me), 9.97 (br, 1H, OH).

3-Acetyl-4-hydroxy-1-oxaspiro[4.4]-3-nonen-2-one (6d)

This compound was obtained by heating **2d** under reflux in 1 M NaOH for 4 h: yellow crystals, mp 71-73°C (EtOH), yield 74%; ir (Nujol) ν_{max}: 1690, 1610, 1160 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.00 (m, 8H, 4 CH_2), 2.56 (s, 3H, Me), 10.70 (br, 1H, OH); ^{13}C nmr ($CDCl_3$): two species are present: a) the major one (*ca.* 70%) δ: 22.20 (q, J=129 Hz, Me), 25.18 (t, J=133 Hz, 2 CH_2), 36.78 (t, J=133 Hz, 2 CH_2), 92.80 (s, C-5), 100.26 (s, C-3), 167.35 (s, C-2), 193.80 (s, CO), 201.60 (s, C-4); b) the minor one (*ca.* 30%) δ: 19.28 (q, J=129 Hz, Me), 24.75 (t, J=130 Hz, 2 CH_2), 39.59 (t, J=134 Hz, 2 CH_2), 97.59 (s, C-5), 98.76 (s, C-3), 175.03 (s, C-2), 187.66 (s, CO), 197.33 (C-4). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2. Found C, 61.0; H, 6.3.

4-Amino-2,5-dihydro-5,5-dimethyl-2-oxo-3-furancarboxylic acid (7a)

A suspension of compound (**3a**) (0.39 g, 2 mmol) in 1 M NaOH (4 ml) was stirred at room temperature for 72 h. The suspension was extracted with ethyl acetate (10 ml x 3) and the aqueous layer was acidified with 1 M HCl to give a colourless precipitate of **7a** which was filtered off. The aqueous solution was extracted with ethyl acetate (10 ml x 3) and the organic layer was dried (Na_2SO_4) and concentrated to give additional crop of **7a**: colurless crystals, mp 199-202°C (EtOH), 0.33 g (total yield 97%); ir (KBr) ν_{max}: 3420, 3160 (br), 1720, 1650, 1560, 1060 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.44 (s, 6H, 2 Me), 8.16 (br, 1H, NH), 8.71 (br, 1H, NH), 11.00 (br, 1H, COOH); ^{13}C nmr (DMSO-d_6) δ: 24.87 (q, J=131 Hz, 2 Me), 79.47 (s, C-5), 83.38 (s, C-3), 165.20 (s, COO), 168.66 (s, C-4), 179.97 (s, C-2). *Anal.* Calcd for $C_7H_9NO_4$: C, 49.1; H, 5.3; N, 8.2. Found: C, 49.3; H, 5.1; N, 8.3.

4-Amino-2,5-dihydro-5-ethyl-5-methyl-2-oxo-3-furancarboxylic acid (7b)

This compound was obtained from **3b** according to the procedure described for **7a**: colourless crystals, mp 183-186°C (EtOH), yield 92%; ir (KBr) ν_{max}: 3420, 3160, 1625, 1560, 1070 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 0.68 (t, J=7.3 Hz, 3H, Me), 1.41 (s, 3H, Me), 1.70-1.90 (m, 2H, CH_2), 8.18 (br, 1H, NH), 8.67 (br, 1H, NH), 11.90 (br, 1H, COOH). *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.9; H, 6.0; N, 7.6. Found: C, 52.1; H, 5.8; N, 7.4.

4-Amino-2-oxo-1-oxaspiro[4.5]-3-decene-3-carboxylic acid (7c)

This compound was obtained from **3c** according to the procedure described for **7a**: colourless crystals, mp 194-198°C (EtOH), yield 93.8%; ir (KBr) ν_{max}: 3420, 3180, 1720, 1650 (br), 1560 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.30-1.90 (m, 10H, 2 CH_2), 8.16 (br, 1H, NH), 8.67 (br, 1H, NH), 11.83 (br, 1H, COOH). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.2; N, 6.6. Found: C, 56.6; H, 6.4; N, 6.5.

5,5-Dimethyl-4-hydroxy-2(5H)-furanone (8a)

A suspension of **7a** (0.143 g, 0.78 mmol) in 3 M HCl (2 ml) was heated under reflux for 1 h and the resulting solution was extracted with ethyl acetate (10 ml x 3). The organic layer was dried (Na_2SO_4) and concentrated to give colourless crystals, mp 138-142°C (lit.,[6a] mp 142-143°C), 0.070 g, (65%); ir (KBr) ν_{max}: 3200-2300, 1720 (br), 1560 (br), 1290 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.36 (s, 6H, 2 Me), 4.79 (s, 1H), 12.80 (br, 1H, OH); ^{13}C nmr (DMSO-d_6) δ: 24.03 (q, J=128 Hz, 2 Me), 81.42 (s, C-5), 85.94 (d, J=177 Hz, C-3), 172.06 (s, C-2), 185.39 (s, C-4).

5-Ethyl-4-hydroxy-5-methyl-2(5H)-furanone (8b)

This compound was obtained from **7b** according to the procedure described for **8a**: yellow oil, yield 90%; ir (neat) ν_{max}: 3200-2400, 1700 (br), 1620 (br), 1250 (br) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 0.71 (t, J=7.3 Hz, 3H, Me), 1.33 (s, 3H, Me), 1.33 (m, 2H, CH_2), 4.84 (s, 1H, CH), 12.90 (br, 1H, OH); ^{13}C nmr (DMSO-d_6) δ: 12.40 (q, J=126 Hz, Me), 28.08 (q, J=129 Hz, Me), 34.07 (t, J=129 Hz, CH_2), 88.96 (s, C-5), 92.64 (d, J=178 Hz, C-3), 173.57 (s, C-2), 188.98 (s, C-4). *Anal.* Calcd for $C_7H_{10}O_3$: C, 59.1; H, 7.1. Found C, 58.9; H, 7.3.

4-Hydroxy-1-oxaspiro[4.5]-3-decen-2-one (8c)

This compound was obtained from **7c** according to the procedure described for **8a**: yellow crystals, mp 194-196 °C (lit.,[6a] mp 198-199°C), yield 87.4%; ir (KBr) ν_{max}: 3100-2300, 1690, 1570 (br), 1310 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.10-1.75 (m, 10H, $5CH_2$), 4.81 (s, 1H, CH), 12.63 (br, 1H, OH); ^{13}C nmr (DMSO-d_6) δ: 21.49 (t, J=126 Hz, 2 CH_2), 23.95 (t, J=124 Hz, CH_2), 32.39 (t, J=127 Hz, 2 CH_2), 82.57 (s, C-5), 86.26 (d, J=177 Hz, C-3), 172.08 (s, C-2), 185.28 (s, C-4).

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