

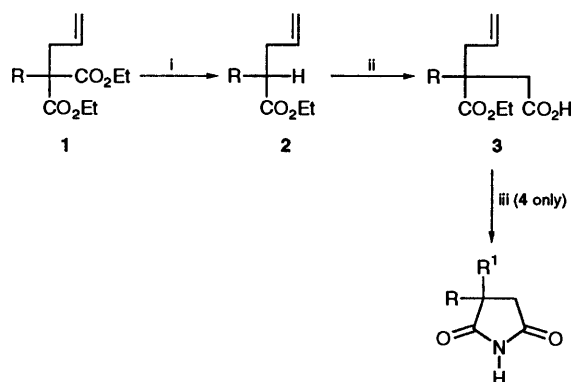
## Synthesis of 3-Octyl-, 3-Cyclohexylmethyl- and 3-Carboxy-3-(prop-2-ynyl)-pyrrolidine-2,5-diones Required as Potential Aromatase Inhibitors

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Routes are described for the synthesis of 3-alkyl-3-(prop-2-ynyl)pyrrolidine-2,5-diones **5** and **6**, which are not available by the literature method for the corresponding prop-2-enyl analogues, and 3-carboxy-3-(prop-2-ynyl)pyrrolidine-2,5-dione **7**.

10 $\beta$ -Prop-2-ynylestr-4-ene-3,17-dione is a mechanism-based inactivator of aromatase due to oxidation of the prop-2-ynyl group to an electrophilic species.<sup>1</sup> We are concerned with the preparation of non-steroidal inactivators such as the title compounds where the propynyl group has been introduced into the skeleton of a known reversible inhibitor<sup>2</sup> of the enzyme, 3-(4-aminophenyl)pyrrolidine-2,5-dione.

Battersby and Westwood<sup>3</sup> have described the synthesis of 3-methyl-3-(prop-2-enyl)pyrrolidine-2,5-dione **4** (Scheme 1).



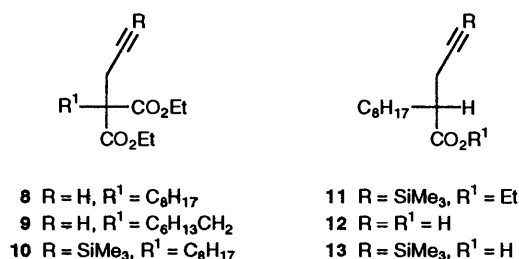
- 4** R = Me, R<sup>1</sup> = CH<sub>2</sub>CH=CH<sub>2</sub>  
**5** R = C<sub>8</sub>H<sub>17</sub>, R<sup>1</sup> = CH<sub>2</sub>C≡CH  
**6** R = C<sub>6</sub>H<sub>13</sub>, R<sup>1</sup> = CH<sub>2</sub>C≡CH  
**7** R = CO<sub>2</sub>H, R<sup>1</sup> = CH<sub>2</sub>C≡CH

**Scheme 1** Reagents: i, LiCl–DMSO–H<sub>2</sub>O, heat, 6 h; ii, LDA–THF, –70 °C, BrCH<sub>2</sub>CO<sub>2</sub>Li, HMPA, H<sup>+</sup>; iii, SOCl<sub>2</sub>, heat, NH<sub>4</sub>OH, KOH, H<sub>2</sub>O–MeOH (1:1); H<sup>+</sup>, Me<sub>3</sub>COCl, heat

We have successfully used this route for the synthesis of other 3-alkyl derivatives<sup>4</sup> and our first plan was to use this procedure for the synthesis of the required diones **5** and **6** starting from the corresponding acetylenic diesters **8** and **9**.

However, on further consideration, we concluded that protection of the ethyne moiety as its C-trimethylsilyl derivative (e.g. **10**) would be necessary particularly in the early stages involving base catalysed reactions.

Our reason for this was that although the acetylenic proton (pK<sub>a</sub> ca. 26–27) is less acidic<sup>4</sup> than the α-carbon of a mono-



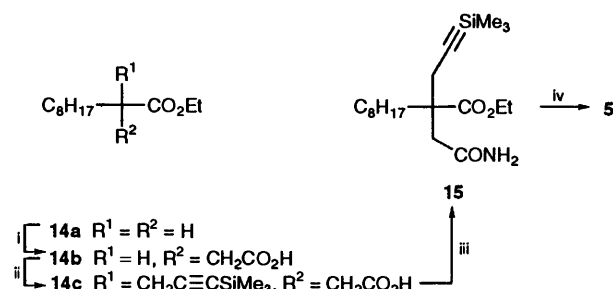
- 8** R = H, R<sup>1</sup> = C<sub>8</sub>H<sub>17</sub>  
**9** R = H, R<sup>1</sup> = C<sub>6</sub>H<sub>13</sub>CH<sub>2</sub>  
**10** R = SiMe<sub>3</sub>, R<sup>1</sup> = C<sub>8</sub>H<sub>17</sub>  
**11** R = SiMe<sub>3</sub>, R<sup>1</sup> = Et  
**12** R = R<sup>1</sup> = H  
**13** R = SiMe<sub>3</sub>, R<sup>1</sup> = H

ester<sup>5</sup> (pK<sub>a</sub> = 24.5 for ethyl acetate) or carboxylic acid salt<sup>5</sup> (pK<sub>a</sub> 24.5 for acetic acid) it is less shielded so that preferential alkylations could well occur on the propynyl terminal carbon, a prediction borne out later.

Trimethyl- or triethyl-silylation of the acetylenic diester **8** gave impure products due to difficulties in separation of the product **10** from unchanged starting material. Attempts to mono-deethoxycarbonylate the crude product with lithium chloride and wet dimethyl sulfoxide (DMSO)<sup>6</sup> to give the crude mono-ester **11**, in the hope that it might be more readily purified, failed and this route had to be abandoned.

In another approach to the required mono-ester **11**, the diester **8** was hydrolysed and decarboxylated to give the acetylenic acid **12** which was readily silylated as predicted above, to give the protected acid **13**. Repeated attempts to convert the acid **13** into the required ethyl ester **11** with ethanolic triethyl orthoformate in the presence of toluene-*p*-sulfonic acid proved abortive.

The successful route (Scheme 2) was developed from ethyl decanoate **14a** by sequential addition of the carboxymethyl and trimethylsilylpropynyl moieties to the respective anions to give the acid ester **14c**.

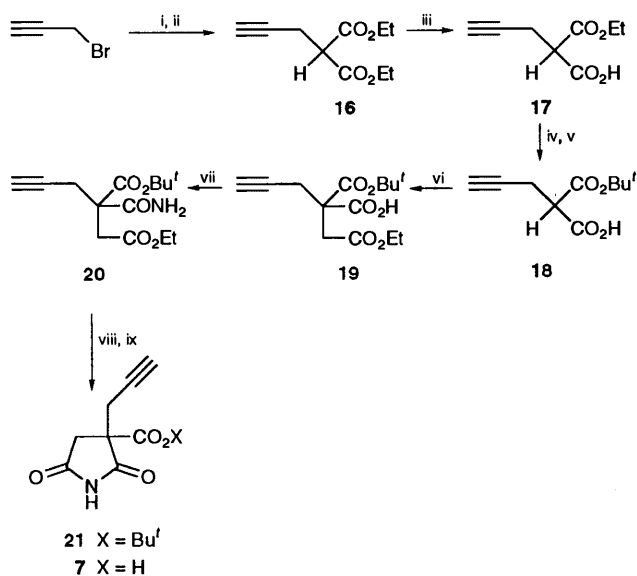


**Scheme 2** Reagents: i, LDA–THF, BrCH<sub>2</sub>CO<sub>2</sub>Li, HMPA, –70 °C, H<sup>+</sup>; ii, 2 LDA, THF, –70 °C, then BrCH<sub>2</sub>C≡CSiMe<sub>3</sub>; H<sub>3</sub>O<sup>+</sup>; iii, Et<sub>3</sub>N, ClCO<sub>2</sub>Et, NH<sub>4</sub>OH; iv, 2 KOH–H<sub>2</sub>OMeOH (1:1)

The order of addition was based on a previous observation that the trimethylsilylpropynyl group is unstable to lithium diisopropylamide (LDA) as evidenced by tar formation in these reactions and the reversed addition gives ethyl 2-(3-trimethylsilylprop-2-ynyl)decanoate which darkens on addition of 1 mol equiv. of LDA.

An attempt to convert the acid ester **14** into its amide **15** by heating with concentrated ammonia was unsuccessful and the route *via* a mixed anhydride was carried out. Treatment of the resulting amide **15** with 2 equiv. of potassium hydroxide in aqueous methanol (1:1) removed the protecting group and unexpectedly yielded the required octyl dione **5**.

The corresponding cyclohexylmethyl 2,5-dione **6** was also prepared by this route, starting from the acetylenic diester **9**.



**Scheme 3** Reagents: i, NaC(CO<sub>2</sub>Et)<sub>3</sub>-DMF-toluene (1:1), 80 °C; ii, NaOEt-THF, 20 °C; iii, KOH-EtOH; iv, DCC, DMAP, Bu<sup>t</sup>OH, CH<sub>2</sub>Cl<sub>2</sub>; v, KOH-H<sub>2</sub>O-MeOH (1:1); vi, 2 LDA, THF, -50 to +4 °C, ClCH<sub>2</sub>CO<sub>2</sub>Et, 18 h, H<sub>3</sub>O<sup>+</sup>; vii, ClCO<sub>2</sub>Et, Et<sub>3</sub>N, NH<sub>3</sub>, 4 °C; viii, KOH-MeOH-H<sub>2</sub>O (1:1), 20 °C, 3 h; ix, CF<sub>3</sub>CO<sub>2</sub>H, PhH, 80 °C, 2 h

An alternative and successful route to the synthesis of the 3-carboxy analogue **7** as set out in Scheme 3, avoided protection of the ethyne grouping and also involved in its final stage, acid-catalysed generation of the free carboxylic acid. In this manner the use of relatively severe alkaline conditions in removal of the protecting groups, which would have undoubtedly led to concomitant ring opening, was avoided.

It became clear from early experiments that the success of this route depended primarily on obtaining the starting acetylenic diester **16** in a high state of purity since the first readily purified crystalline intermediate was the amidic diester **20** some 5 steps later. It has been our experience that the standard alkylation procedures for the preparation of low molecular weight monoalkyl malonates in a high state of purity requires the use of sophisticated fractionating equipment unavailable to us, a situation even more difficult in the case of the diethyl ester of **16** which would have been the ideal starting diester.

We chose, therefore, Rappoport's ingenious procedure<sup>7</sup> whereby the readily purified triethyl alkylmethanetricarboxylates are treated with ethanol-free sodium ethoxide to yield the corresponding monoalkyl malonates. Application of this procedure using prop-2-ynyl bromide furnished the acetylenic diester **16** in a very high overall yield and satisfactory state of purity.

Partial hydrolyses and a re-esterification with *tert*-butyl alcohol converted the acetylenic diester **16** into the *tert*-butyl hydrogen malonate **18** which was transformed into the homologous diester acid **19** via its dianion. Conversion into its crystalline sharp melting amide **20** as before followed by exposure to aqueous methanolic potassium hydroxide yielded the crystalline dioxo ester **21**, which was smoothly dealkylated to the required 2,5-dioxopyrrolidine-3-carboxylic acid **7** by treatment with trifluoroacetic acid in boiling benzene.

## Experimental

<sup>1</sup>H NMR spectra were recorded on a Perkin-Elmer R32 (90 MHz) instrument and <sup>13</sup>C NMR on a JEOL-FX 90Q Fourier Transformer (90 MHz) spectrophotometer using CDCl<sub>3</sub> as solvent and tetramethylsilane (TMS) as internal

standard, unless otherwise stated. *J* values are given in Hz. JMOD was performed using standard JEOL software. Mass spectra were determined using high resolution EI at the SERC Mass Spectrometry Service Centre, University College of Swansea and elemental analysis at the School of Pharmacy, University of London. Melting points were determined on an electrothermal instrument and are uncorrected. Infrared spectra were determined in KBr discs unless otherwise stated using a Perkin-Elmer 681 Infrared Spectrophotometer. Ether refers to diethyl ether and light petroleum to those fractions with b.p. 40–60 °C.

**(RS)-3-Ethoxycarbonyl-3-(3-trimethylsilylprop-2-ynyl)undecanoic Acid 14a.**—**(RS)-3-Ethoxycarbonylundecanoic acid 14b.** To a stirred solution of lithium diisopropylamide (LDA) (74.88 mmol), in tetrahydrofuran (THF) (50 cm<sup>3</sup>) at -75 °C under nitrogen, was added ethyl decanoate **14a** (15.0 g, 74.88 mmol) at a rate such that the reaction temperature remained < -60 °C, and the pale yellow solution was then stirred at -75 °C for 1 h. Separately, bromoacetic acid (11.45 g, 82.37 mmol) in THF (12 cm<sup>3</sup>) was added dropwise under nitrogen to a stirred suspension of finely powdered lithium hydride (1.3 g, 0.1647 mol) in THF (8 cm<sup>3</sup>) at 0 °C. After the evolution of hydrogen had ceased, hexamethylphosphoramide (HMPA) (16.5 cm<sup>3</sup>) was added to the suspension. The resulting solution was then added dropwise to the solution of the ester enolate at a rate such that the reaction temperature remained < -55 °C. The reaction mixture was then gradually warmed to room temperature, stirred overnight and poured onto ice containing an excess of hydrochloric acid (3 mol dm<sup>-3</sup>). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 100 cm<sup>3</sup>). On evaporation of the combined organic portions, the residue obtained was fractionated on a column of dry silica (100 g, 0.04–0.063 mm) using ether. The eluent collected was washed with water (4 × 100 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and evaporated to give a yellow oil (17.4 g). The oil (8.8 g) was then eluted down an Amberlite CG-400 (90 g, basic form) resin with acetone-water mixture (3:1) under mild suction and then light petroleum (5 × 100 cm<sup>3</sup>). The eluent collected was acidified with hydrochloric acid (3 mol dm<sup>-3</sup>) and the organic layer separated, dried (MgSO<sub>4</sub>) and evaporated to give a yellow liquid (2.3 g). Spectroscopic studies on this liquid indicated that it consisted of a mixture of ethyl decanoate and its self-condensed product, ethyl 2-octyl-3-oxododecanoate.

The remaining resin bed was triturated with hydrochloric acid (3 mol dm<sup>-3</sup>; 300 cm<sup>3</sup>) and allowed to stand overnight. After filtration, the resin cake obtained was washed under mild suction with light petroleum (5 × 100 cm<sup>3</sup>). All the filtrates and washes obtained were combined and the organic layer separated, dried (MgSO<sub>4</sub>) and evaporated to give the *acid ester 14b* (6.5 g, 66.4%) as a pale yellow liquid; *R*<sub>f</sub> = 0.79 (ether), 0.49 (light petroleum-ether, 1:1) (Found: C, 65.0; H, 10.3%; (M + H)<sup>+</sup>, 259.1932. C<sub>14</sub>H<sub>26</sub>O<sub>4</sub> requires C, 65.1; H, 10.15%; (M + H)<sup>+</sup>, 259.1909); ν<sub>max</sub>(film)/cm<sup>-1</sup> 3700–2500 (CO<sub>2</sub>H), 1740 (CO<sub>2</sub>Et) and 1710 (CO<sub>2</sub>H); δ<sub>H</sub> 0.47–2.17 [20 H, m, C<sub>8</sub>H<sub>17</sub>CH(CH<sub>2</sub>CO<sub>2</sub>H)CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>], 2.32–3.12 [3 H, m, C<sub>8</sub>H<sub>17</sub>CH(CH<sub>2</sub>CO<sub>2</sub>H)CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>], 4.16 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 11.59 (1 H, s, CO<sub>2</sub>H).

A solution of LDA (82.84 mmol) was generated under nitrogen at -60 °C in THF (85 cm<sup>3</sup>) with the reaction temperature maintained < -40 °C. The acid ester **14b** (10.7 g, 41.42 mmol) in THF (11 cm<sup>3</sup>) was then added dropwise to the base at such a rate that the internal temperature was kept < -60 °C. The yellow mixture was stirred at -70 °C for 1 h after which 3-bromo-1-trimethylsilylprop-1-yne<sup>8</sup> (8.08 g, 42.25 mmol) in THF (8 cm<sup>3</sup>) was added to it. The greenish yellow solution was gradually warmed to room temperature, stirred overnight and poured onto ice containing an excess of

hydrochloric acid (3 mol dm<sup>-3</sup>). The organic layer was separated, and the aqueous layer extracted with dichloromethane (4 × 50 cm<sup>3</sup>). The combined organic extracts were evaporated to give a reddish brown oil (15.5 g) which was taken up in light petroleum (300 cm<sup>3</sup>) washed with saturated aqueous sodium hydrogen carbonate (5 × 50 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and evaporated to give an orange-yellow oil (15.3 g). The oil (7.5 g) was then fractionated on a column of wet silica (150 g, 0.04–0.063 mm) using initially light petroleum–ether (20:1) as eluent and then neat ether after the first fraction had been separated. Evaporation of the ethereal eluent gave the *trimethylsilyl acid ester 14c* (6.54 g, 87.4%) as a pale yellow oil, *R<sub>f</sub>* = 0.90 (ether) (Found: C, 65.0; H, 10.0. C<sub>20</sub>H<sub>36</sub>O<sub>4</sub>Si requires C, 65.2; H, 9.85%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3700–2300 (CO<sub>2</sub>H), 2190 (SiC≡C), 1740 (CO<sub>2</sub>Et), 1715 (CO<sub>2</sub>H), 845 and 760 (SiC); *δ*<sub>H</sub>(no TMS) 0.00 [9 H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 0.41–1.96 (20 H, m, CH<sub>2</sub> and CH<sub>3</sub> of octyl, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.67 (4 H, br, s, SiC≡CH<sub>2</sub>, CH<sub>2</sub>CO<sub>2</sub>H), 4.00 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 11.20 (1 H, br, s, CO<sub>2</sub>H); *δ*<sub>C</sub>(JMOD, no TMS) 0.000 [C≡CSi(CH<sub>3</sub>)<sub>3</sub>], 14.014 (CH<sub>3</sub> of octyl and ester), 22.667, 23.885, 24.860, 29.187, 29.796, 31.868, 36.620, 39.301, 46.674, 60.567 and 60.872 (C, aliphatic) 75.801, 77.202 and 78.664 (CDCl<sub>3</sub>), 87.683 (SiC≡C), 103.099 (SiC≡C), 174.269 and 177.255 (C=O of acid and ester).

(RS)-3-Ethoxycarbonyl-3-(3-trimethylsilylprop-2-ynyl)undecanamide **15**.—Ethyl chloroformate (96.5%; 0.66 cm<sup>3</sup>, 6.755 mmol) in dichloromethane (7 cm<sup>3</sup>) was added to a stirred mixture of the trimethylsilyl acid ester **14c** (2.49 g, 6.755 mmol) and triethylamine (0.95 cm<sup>3</sup>, 6.755 mmol) in dichloromethane (7 cm<sup>3</sup>) at 0 °C. After the reaction mixture had been stirred at 0 °C for an additional 1.5 h, concentrated ammonia solution (*d* 0.88; 2.54 cm<sup>3</sup>, 54.04 mmol) was added to it dropwise. The resulting suspension was stirred at room temperature overnight, acidified with hydrochloric acid (3 mol dm<sup>-3</sup>) and the organic layer separated and evaporated. The residue was taken up in light petroleum (100 cm<sup>3</sup>) and washed with aqueous potassium carbonate (1%, 4 × 50 cm<sup>3</sup>) and then with water until neutral. The organic layer was dried (MgSO<sub>4</sub>) and evaporated to give a bright yellow oil (2.64 g) which was then fractionated on a column of wet silica (93 g, 0.04–0.063 mm) using ether as eluent. Evaporation of the eluent of the second fraction collected gave the *amido ester 15* (1.86 g, 74.9%) as a pale yellow oil, *R<sub>f</sub>* = 0.59 (ether) (Found: C, 65.5; H, 10.1; N, 3.8. C<sub>20</sub>H<sub>37</sub>NO<sub>3</sub>Si requires C, 65.35; H, 10.15; N, 3.8%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3440, 3360 and 3200 (NH), 2180 (SiC≡C), 1730 (CO<sub>2</sub>Et), 1670 (CONH<sub>2</sub>), 1610 (CONH<sub>2</sub>), 845 and 760 (SiC); *δ*<sub>H</sub>(no TMS) 0.00 [9 H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 0.50–1.80 (20 H, m, CH<sub>2</sub> and CH<sub>3</sub> of octyl, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.52 and 2.63 (4 H, two s, SiC≡CCH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>), 4.03 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 5.40–6.05 (2 H, br, s, CH<sub>2</sub>CONH<sub>2</sub>).

(RS)-3-Octyl-3-(prop-2-ynyl)pyrrolidine-2,5-dione **5**.—A solution of potassium hydroxide (85%; 0.47 g, 7.120 mmol) in water (10 cm<sup>3</sup>) was added portionwise to a solution of the amido ester **15** (1.05 g, 2.856 mmol) in methanol (10 cm<sup>3</sup>) and the reaction mixture was stirred at room temperature overnight. It was then diluted with water (80 cm<sup>3</sup>) and extracted with chloroform (5 × 25 cm<sup>3</sup>). The combined extracts were evaporated and the residue taken up in light petroleum (75 cm<sup>3</sup>) and the solution washed with saturated aqueous sodium hydrogen carbonate (2 × 25 cm<sup>3</sup>) and water (3 × 25 cm<sup>3</sup>), dried (MgSO<sub>4</sub>) and evaporated to give the *dione 5* (0.65 g, 91.3%) as a pale yellow syrup. This solidified to a colourless wax with time at room temperature in a desiccator, *R<sub>f</sub>* = 0.67 (ether) (Found: C, 71.8; H, 9.1; N, 5.7. C<sub>15</sub>H<sub>23</sub>NO<sub>2</sub> requires C, 72.25; H, 9.30; N, 5.62%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3280 (NH and ≡CH, 2140 (C≡C), 1785 and 1725 (C=O, imide); *δ*<sub>H</sub> 0.37–1.87 (17 H, m, CH<sub>2</sub> and CH<sub>3</sub> of octyl), 2.05 (1 H, t, *J* 2.5, HC≡CCH<sub>2</sub>), 2.25–

3.02 {4 H, [2.36 (dd, *J*<sub>BA</sub> 17 and *J*<sub>XA</sub> 2, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>), 2.56 (d, *J*<sub>BA</sub> 18 CH<sub>A</sub>H<sub>B</sub>CONHCO), 2.65 (dd, *J*<sub>AB</sub> 17 and *J*<sub>XB</sub> 2, H<sub>X</sub>C≡C-CH<sub>A</sub>H<sub>B</sub>), 2.88 (d, *J*<sub>AB</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO)]} and 9.07–9.37 (1 H, br, s, CONHCO).

(RS)-3-Cyclohexylmethyl-3-(prop-2-ynyl)pyrrolidine-2,5-dione **6**.—This dione was obtained similarly (Scheme 2) *via* the intermediates described below as colourless crystals, m.p. 97.4–98.5 °C; *R<sub>f</sub>* = 0.71 (ether), 0.62 (light petroleum–ether, 1:3) (Found: C, 71.85; H, 8.2; N, 6.1. C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub> requires C, 72.1; H, 8.2; N, 6.0%); *v*<sub>max</sub>(KBr)/cm<sup>-1</sup> 3300 (≡CH, 3200), 3180 (NH) and 1775 and 1715 (C=O, imide); *δ*<sub>H</sub> 0.43–1.84 (13 H, m, CH<sub>2</sub> and CH of cyclohexylmethyl), 2.05 (1 H, t, *J* 2.5, HC≡CCH<sub>2</sub>), 2.23–2.63 {2 H, [2.37 (dd, *J*<sub>BA</sub> 17 and *J*<sub>XA</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>), 2.62 (dd, *J*<sub>AB</sub> 17 and *J*<sub>XB</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>)]}·2.63–3.03 {2 H [2.64 (d, *J*<sub>BA</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO), 2.89 (d, *J*<sub>AB</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO)]} and 9.15 (1 H, br s, CONHCO).

(RS)-1-Ethyl Hydrogen 2-Cyclohexylsuccinate.—A pale yellow oil, *R<sub>f</sub>* = 0.62 (light petroleum–ether, 1:3), 0.50 (light petroleum–ether, 1:1) (Found: C, 63.9; H, 9.15. C<sub>13</sub>H<sub>22</sub>O<sub>4</sub> requires C, 64.45; H, 9.15%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3700–2350 (CO<sub>2</sub>H), 1730 (CO<sub>2</sub>Et) and 1710 (CO<sub>2</sub>H); *δ*<sub>H</sub> 0.56–2.13 (16 H, m, CH<sub>2</sub> and CH of cyclohexylmethyl, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.30–3.10 [3 H, m, CH(CH<sub>2</sub>CO<sub>2</sub>H)CO<sub>2</sub>Et], 4.12 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 11.28 (1 H, s, CO<sub>2</sub>H); *δ*<sub>C</sub>(JMOD) 0.000 (TMS), 14.197, 21.753, 26.323, 26.686, 33.208, 33.452, 35.524, 36.499, 38.814 and 39.789 (C, aliphatic), 60.567 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 75.922, 77.324 and 78.786 (CDCl<sub>3</sub>), 175.122 and 177.742 (CO<sub>2</sub>H and CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

(RS)-1-Ethyl 2-Cyclohexylmethyl-2-(3-trimethylsilylprop-2-ynyl)succinate.—A bright yellow syrup, *R<sub>f</sub>* = 0.79 (ether) (Found: C, 64.7; H, 9.2. C<sub>19</sub>H<sub>32</sub>O<sub>4</sub>Si requires C, 64.7; H, 9.15%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3700–2400 (CO<sub>2</sub>H), 2190 (SiC≡CH), 1730 (CO<sub>2</sub>Et), 1710 (CO<sub>2</sub>H) and 845 and 765 (SiC); *δ*<sub>H</sub>(no TMS) 0.00 [9 H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 0.60–2.02 (16 H, m, CH<sub>2</sub> and CH of cyclohexylmethyl, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.68 (4 H, s, SiC≡CH<sub>2</sub>, CH<sub>2</sub>CO<sub>2</sub>H), 3.99 (2 H, q, *J* 7 CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 10.69 (1 H, s, CO<sub>2</sub>H).

(RS)-3-Cyclohexylmethyl-3-ethoxycarbonyl-6-trimethylsilylhex-5-ynamide.—Colourless crystals, m.p. 96.5–96.9 °C, *R<sub>f</sub>* = 0.48 (light petroleum–acetone, 3:1) (Found: C, 65.5; H, 9.6; N, 4.0. C<sub>19</sub>H<sub>33</sub>NO<sub>3</sub>Si requires C, 64.9; H, 9.5; N, 4.0%); *v*<sub>max</sub>(KBr)/cm<sup>-1</sup> 3420, 3360, 3200, 3010 (NH), 2180 (SiC≡CH), 1715 (CO<sub>2</sub>Et), 1680 (CO<sub>2</sub>NH<sub>2</sub>), 1625 (CO<sub>2</sub>NH<sub>2</sub>), 845 and 765 (SiC); *δ*<sub>H</sub>(no TMS) 0.00 [9 H, s, Si(CH<sub>3</sub>)<sub>3</sub>], 0.62–2.02 (16 H, m, CH<sub>2</sub> and CH of cyclohexylmethyl, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.51 (2 H, s, SiC≡CCH<sub>2</sub>), 2.66 (2 H, s, CH<sub>2</sub>CONH<sub>2</sub>), 4.01 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 5.73 and 6.17 (2 H, two br s, CONH<sub>2</sub>).

Diethyl Prop-2-ynylmalonate **16**.—Triethyl but-3-yne-1,1,1-tricarboxylate.—3-Bromopropyne (80% wt. solution in toluene; 28.5 cm<sup>3</sup>, 0.1904 mol) was added to a solution of triethyl sodiomethanetricarboxylate (24.20 g, 95.21 mmol) in toluene–dimethylformamide (1:1, 240 cm<sup>3</sup>) and the mixture was stirred and heated at 80 °C for 1.5 h. The resultant, cooled yellow suspension was filtered and the residue washed with toluene (5 × 20 cm<sup>3</sup>). The combined filtrates were washed with water (5 × 50 cm<sup>3</sup>), evaporated and dried (azeotropically with propan-2-ol) to give a brown liquid (26.60 g) which on distillation gave the *tricarboxylate* (24.57 g, 95.5%) as a pale yellow liquid, b.p. 96–98 °C/0.20 mmHg (Found: C, 57.7; H, 6.8. C<sub>13</sub>H<sub>18</sub>O<sub>6</sub> requires C, 57.75; H, 6.7%); *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3290 (≡CH), 2130 (C≡C) and 1745 (CO<sub>2</sub>Et); *δ*<sub>H</sub> 1.30 (9 H, t, *J* 7 CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.08 (1 H, t, *J* 2, HC≡CH<sub>2</sub>), 3.01 (2 H, d, *J* 2, HC≡CH<sub>2</sub>) and 4.28 (6 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

*Triethyl but-3-yne-1,1,1-tricarboxylate* (24.40 g, 90.28 mmol) in THF (30 cm<sup>3</sup>) was added portionwise to a suspension of sodium ethoxide powder (7.6 g, 0.1128 mol) in THF (260 cm<sup>3</sup>). After being stirred at room temp. for 1 h, the reaction mixture was acidified with hydrochloric acid (1 mol dm<sup>-3</sup>) and the aqueous layer separated and extracted with dichloromethane (4 × 50 cm<sup>3</sup>). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to give a brown liquid (18.71 g) which on distillation gave the title compound **16** (16.20 g, 90.5%) as a pale yellow liquid, b.p. 71–72 °C/0.15 mmHg [Found: C, 60.45; H, 7.0%; (M + NH<sub>4</sub>)<sup>+</sup>, 216.1236. C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> requires C, 60.6; H, 7.1%; (M + NH<sub>4</sub>)<sup>+</sup>, 216.1236];  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3290 (C≡CH), 2130 (C≡C), 1750 (CO<sub>2</sub>Et) and 1740 (CO<sub>2</sub>Et);  $\delta_{\text{H}}$  1.28 (6 H, t, *J* 7, 2 × CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.06 (1 H, t, *J* 2, HC≡CCH<sub>2</sub>), 2.79 (2 H, dd, *J*<sub>YH</sub> 7 and *J*<sub>XH</sub> 3, H<sub>X</sub>C≡CCH<sub>2</sub>CH<sub>Y</sub>), 3.58 (1 H, t, *J* 8, CH<sub>2</sub>CHCO<sub>2</sub>Et) and 4.24 (4 H, q, *J* 7, 2 × CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>);  $\delta_{\text{C}}(\text{JMOD})$ , 14.075 (2 × CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 18.462 (C≡CCH<sub>2</sub>), 51.305 (CHCO<sub>2</sub>Et), 61.664 (2 × CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 70.560 and 80.127 (HC≡C) and 167.810 (2 × CO<sub>2</sub>Et).

(RS)-*Ethyl Hydrogen 2-Propynylmalonate* **17**.—Potassium hydroxide (85%; 6.60 g, 0.10 mol) in absolute ethanol (150 cm<sup>3</sup>) was added to the above ester **16** (19.83 g, 0.10 mol) in ethanol (30 cm<sup>3</sup>) and the mixture stirred at room temp. for 2 h. The mixture was stored overnight after which the resulting potassium salt was collected, washed with light petroleum (5 × 25 cm<sup>3</sup>) and dried *in vacuo* overnight at 60 °C to give a creamy white solid (17.34 g). The salt was then dissolved in water (100 cm<sup>3</sup>) and the solution acidified with hydrochloric acid (3 mol dm<sup>-3</sup>) and extracted with dichloromethane (5 × 50 cm<sup>3</sup>). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give the acid **17** (12.69 g, 74.6%) as a pale yellow liquid (Found: C, 56.05; H, 5.85. C<sub>8</sub>H<sub>10</sub>O<sub>4</sub> requires C, 56.45; H, 5.9%);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3700–2400 (CO<sub>2</sub>H), 3300 (≡CH), 2130 (C≡C) and 1735 (C=O);  $\delta_{\text{H}}$  1.30 (3 H, t, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.12 (1 H, t, *J* 2, HC≡CH<sub>2</sub>), 2.81 (2 H, dd, *J*<sub>YH</sub> 7 and *J*<sub>XH</sub> 2.5, H<sub>X</sub>C≡CCH<sub>2</sub>CH<sub>Y</sub>), 3.68 (1 H, t, *J* 7, CH<sub>2</sub>CHCO<sub>2</sub>Et), 4.27 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 10.98 (1 H, s, CO<sub>2</sub>H).

(RS)-*tert-Butyl 2-Ethoxycarbonylpent-4-ynoate*.—1,3-Dicyclohexylcarbodiimide in dichloromethane (67.4 cm<sup>3</sup>, 65.10 mmol) was added to 2-ethoxycarbonylpent-4-ynoic acid **17** (10.07 g, 59.18 mmol), 2-methylpropan-2-ol (16.8 cm<sup>3</sup>, 0.1775 mol) and 4-dimethylaminopyridine (0.72 g, 5.918 mmol) in dichloromethane (120 cm<sup>3</sup>) at 0 °C. The white suspension formed was stirred at room temp. overnight, collected and washed with dichloromethane (4 × 50 cm<sup>3</sup>). The combined filtrates and washes were evaporated and the residue taken up in light petroleum (200 cm<sup>3</sup>) and the solution washed with dilute hydrochloric acid (4 × 50 cm<sup>3</sup>) followed by aqueous potassium carbonate (1%; 4 × 50 cm<sup>3</sup>). The organic layer was dried (MgSO<sub>4</sub>) and evaporated to give a pale yellow liquid (13.00 g) which on distillation in the presence of anhydrous potassium carbonate (~0.2 g) gave the ester (9.89 g, 73.9%) as a colourless liquid b.p. 82–83 °C/0.50 mmHg [Found: (M + NH<sub>4</sub>)<sup>+</sup>, 244.1548. C<sub>12</sub>H<sub>22</sub>NO<sub>4</sub> requires (M + NH<sub>4</sub>)<sup>+</sup>, 244.1549];  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3300 (C≡CH), 2140 (C≡C and N=C=N), 1745 (C=O) and 1730 (C=O);  $\delta_{\text{H}}$  1.29 (3 H, t, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.49 [9 H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 2.04 (1 H, t, *J* 2, HC≡CCH<sub>2</sub>), 2.73 (2 H, dd, *J*<sub>YH</sub> 8 and *J*<sub>XH</sub> 3, H<sub>X</sub>C≡CCH<sub>2</sub>CH<sub>Y</sub>), 3.48 (1 H, t, *J* 7.5, HC≡CCH<sub>2</sub>CH) and 4.23 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). The crude ester was used for the following reaction without further purification.

(RS)-2-(*tert-Butoxycarbonyl*)pent-4-ynoic acid **18**.—A solution of potassium hydroxide (85%; 4.53 g, 68.67 mmol) in water (45 cm<sup>3</sup>) was added to a solution of the crude ester (12.43 g,

54.93 mmol) in methanol (45 cm<sup>3</sup>). After the mixture had been stirred at room temp. overnight it was diluted with water (90 cm<sup>3</sup>) and the resulting mixture was washed with dichloromethane (5 × 25 cm<sup>3</sup>). The aqueous layer was acidified with hydrochloric acid (3 mol dm<sup>-3</sup>) and extracted with dichloromethane (5 × 25 cm<sup>3</sup>). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give the acid ester **18** (10.24 g, 94.0%) as a colourless oil [Found: (M + NH<sub>4</sub>)<sup>+</sup>, 216.1236. C<sub>10</sub>H<sub>18</sub>O<sub>4</sub>N requires (M + NH<sub>4</sub>)<sup>+</sup>, 216.1236];  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3700–2500 (CO<sub>2</sub>H), 3310 (≡CH), 2130 (C≡C) and 1735 (C=O);  $\delta_{\text{H}}$  1.50 [9 H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 2.05 (1 H, t, *J* 3, CH<sub>2</sub>C≡CH), 2.77 (2 H, dd, *J*<sub>YH</sub> and *J*<sub>XH</sub> 2, H<sub>X</sub>C≡CCH<sub>2</sub>CH<sub>Y</sub>), 3.55 (1 H, t, *J* 7, HC≡CCH<sub>2</sub>CH) and 10.89 (1 H, s, CO<sub>2</sub>H). The crude acid ester was used for the next reaction without further purification.

(RS)-1-*tert-Butyl 4-Ethyl 2-Carboxy-2-propynylsuccinate* **19**.—To a stirred solution of the crude acid ester **18** (9.68 g, 48.86 mmol) and diisopropylamine (13.7 cm<sup>3</sup>, 97.72 mmol) in THF (100 cm<sup>3</sup>) at –60 °C under nitrogen was added butyllithium (1.6 mol dm<sup>-3</sup> solution in hexanes; 61.1 cm<sup>3</sup>, 97.72 mmol) at a rate such that the reaction temperature did not exceed –50 °C. The resulting pale yellow solution was warmed to 4 °C and maintained at this temperature for an additional 15 min before ethyl chloroacetate (97%, 5.38 cm<sup>3</sup>, 48.86 mmol) in THF (5 cm<sup>3</sup>) was added to it dropwise. The mixture was then stirred overnight at room temperature, acidified with hydrochloric acid (1 mol dm<sup>-3</sup>) and extracted with dichloromethane (4 × 25 cm<sup>3</sup>). The combined extracts were evaporated and the residue was treated with aqueous potassium carbonate (2%; 350 cm<sup>3</sup>), washed with dichloromethane (5 × 50 cm<sup>3</sup>), acidified with hydrochloric acid (3 mol dm<sup>-3</sup>) and extracted with dichloromethane (5 × 50 cm<sup>3</sup>). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give the diester **19** (12.58 g, 90.6%) as a thick yellow oil [Found: C, 59.1; H, 7.15; (M + H)<sup>+</sup>, 285.1338. C<sub>14</sub>H<sub>20</sub>O<sub>6</sub> requires C, 59.1; H, 7.1%; (M + H)<sup>+</sup>, 285.1338];  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3700–2400 (CO<sub>2</sub>H), 3290 (≡CH), 2130 (C≡C) and 1735 (C=O);  $\delta_{\text{H}}$  1.24 (3 H, t, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.48 [9 H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 2.08 (1 H, t, *J* 2, HC≡CCH<sub>2</sub>), 2.95 (2 H, d, *J* 2, HC≡CCH<sub>2</sub>), 3.12 (2 H, s, CH<sub>2</sub>CO<sub>2</sub>Et), 4.12 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 10.17 (1 H, s, CO<sub>2</sub>H).

1-*tert-Butyl 4-Ethyl 2-Carbamoyl-2-propynylsuccinate* **20**.—Ethyl chloroformate (2.97 cm<sup>3</sup>, 29.91 mmol) in dichloromethane (10 cm<sup>3</sup>) was added to a stirred solution of triethylamine (4.35 cm<sup>3</sup>, 31.34 mmol) and the acid diester **19** (8.10 g, 28.49 mmol) in dichloromethane (100 cm<sup>3</sup>) at 4 °C. After the mixture had been stirred for 30 min, gaseous ammonia (calcium chloride dried) was bubbled slowly into it for 1.5 h. The resulting white suspension was stirred overnight at room temp. collected and washed with dichloromethane (4 × 25 cm<sup>3</sup>). The combined organic layers were evaporated and the residue taken up in ether (100 cm<sup>3</sup>) and washed successively with dilute sulfuric acid (5 × 25 cm<sup>3</sup>), aqueous potassium carbonate (2%, 5 × 25 cm<sup>3</sup>) and water (2 × 25 cm<sup>3</sup>). The ethereal layer was dried (MgSO<sub>4</sub>) and evaporated to give a pale yellow oil which was dissolved in hot light petroleum–ether (2:1). On cooling, the amido diester **20** (4.23 g, 52.4%) separated as colourless crystals, m.p. 102.1–104.4 °C [Found: C, 59.15; H, 7.65; N, 4.85%; (M + H)<sup>+</sup>, 284.1498. C<sub>14</sub>H<sub>21</sub>O<sub>5</sub>N requires C, 59.35; H, 7.45; N, 4.95%; (M + H)<sup>+</sup>, 284.1498];  $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$  3420 and 3330 (NH), 3280 (≡CH), 1735 (C=O, esters), 1680 (CONH<sub>2</sub>) and 1620 (CONH<sub>2</sub>);  $\delta_{\text{H}}$  1.25 (3 H, t, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.46 (9 H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 2.11 (1 H, t, *J* 2, HC≡CCH<sub>2</sub>), 2.55–2.95 {2 H [2.71 (dd, *J*<sub>BA</sub> 16 and *J*<sub>XA</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>), 2.93 (dd, *J*<sub>AB</sub> 16 and *J*<sub>XB</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>)]}, 3.00–3.30 {2 H, [2.96 (d, *J*<sub>BA</sub> 16, CH<sub>A</sub>H<sub>B</sub>CO<sub>2</sub>Et), 3.17 (d, *J*<sub>AB</sub> 16, CH<sub>A</sub>H<sub>B</sub>CO<sub>2</sub>Et)]}, 4.10 (2 H, q, *J* 7, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>) and 5.75–6.40 and 7.05–7.65 (2 H, 2 × br s, CONH<sub>2</sub>).

(RS)-3-(tert-Butoxycarbonyl)-3-(prop-2-ynyl)pyrrolidine-2,5-dione **21**.—Potassium hydroxide (85%; 0.69 g, 10.50 mmol) in water (15 cm<sup>3</sup>) was added to a solution of the amido diester **20** (2.38 g, 8.400 mmol) in methanol (15 cm<sup>3</sup>). After being stirred at room temp. for 3 h, the solution was acidified with dilute hydrochloric acid (1 mol dm<sup>-3</sup>) and the product extracted with dichloromethane (5 × 25 cm<sup>3</sup>). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated to give a colourless crystalline solid (1.74 g), m.p. 110.8–111.4 °C. Upon cooling a solution in hot light petroleum–ether (2:1) the dione **21** (1.68 g, 84.3%) separated as a colourless crystalline solid, m.p. 111.1–112.0 °C, *R<sub>f</sub>* = 0.73 (acetone–ether, 1:1) (Found: C, 60.4; H, 6.5; N, 5.85. C<sub>12</sub>H<sub>15</sub>NO<sub>4</sub> requires C, 60.75; H, 6.35; N, 5.90%); *v*<sub>max</sub>(KBr)/cm<sup>-1</sup> 3280 (≡CH), 3240 (NH), 1780 (C=O, imide), 1735 (CO<sub>2</sub>Bu') and 1720 (C=O, imide); *δ*<sub>H</sub> 1.47 [9 H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>], 2.09 (1 H, t, *J* 3, HC≡CCH<sub>2</sub>), 2.65–3.00 {2 H, [2.77 (dd, *J*<sub>BA</sub> 16 and *J*<sub>XA</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>), 3.01 (dd, *J*<sub>AB</sub> 16 and *J*<sub>XB</sub> 3, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>)]}, 3.01–3.28 {2 H, [2.94 (d, *J*<sub>BA</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO), 3.19 (d, *J*<sub>AB</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO)]} and 9.02–9.57 (1 H, br s, CONHCO).

(RS)-3-Carboxy-3-(prop-2-ynyl)pyrrolidine-2,5-dione **7**.—Tri-fluoroacetic acid (1.99 cm<sup>3</sup>, 25.29 mmol) was added to a solution of the dione **21** (1.00 g, 4.215 mmol) in benzene (20 cm<sup>3</sup>) and the mixture was heated and stirred at 80 °C for 2 h. The crude reaction mixture was evaporated and the residue (0.70 g) dissolved in ethyl acetate (50 cm<sup>3</sup>). This solution was washed with water (3 × 25 cm<sup>3</sup>) and extracted with saturated aqueous sodium hydrogen carbonate (50 cm<sup>3</sup>). The aqueous layer was separated, acidified with dilute hydrochloric acid (1 mol dm<sup>-3</sup>) and extracted with ethyl acetate (2 × 25 cm<sup>3</sup>). The combined extracts were dried (MgSO<sub>4</sub>) and evaporated to give the acid dione **7** (0.50 g, 65.5%) as a viscous pale yellow

syrup [Found: C, 52.7; H, 4.1; N, 7.55%; (M + NH<sub>4</sub>)<sup>+</sup>, 199.0720. C<sub>8</sub>H<sub>7</sub>NO<sub>4</sub> requires C, 53.04; H, 3.89; N, 7.73%; (M + NH<sub>4</sub>)<sup>+</sup>, 199.0720]. *v*<sub>max</sub>(film)/cm<sup>-1</sup> 3700–2500 (CO<sub>2</sub>H), 3300 (≡CH), 1785 (C=O, imide) and 1730 (C=O); *δ*<sub>H</sub> ([<sup>2</sup>H<sub>6</sub>]acetone) 2.53 (1 H, t, *J* 3, HC≡CCH<sub>2</sub>), 2.73–3.03 {2 H, [2.83 (dd, *J*<sub>BA</sub> 17 and *J*<sub>XA</sub> 2, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>), 3.13 (dd, *J*<sub>AB</sub> 17 and *J*<sub>XB</sub> 2, H<sub>X</sub>C≡CCH<sub>A</sub>H<sub>B</sub>)]}, 3.03–3.43 {2 H, [2.94 (d, *J*<sub>BA</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO), 3.24 (d, *J*<sub>AB</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO)]} and 10.27–10.78 (1 H, br s, CONHCO) and 11.30 (1 H, br s, CO<sub>2</sub>H); *δ*<sub>H</sub>(D<sub>2</sub>O, 3-(trimethylsilyl)propane-1-sulfonic acid, sodium salt hydrate) 2.48 (1 H, t, *J* 2, HC≡CCH<sub>2</sub>), 2.92 (2 H, d, *J* 2, HC≡CCH<sub>2</sub>), 3.01 (1 H, d, *J*<sub>BA</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO), 3.36 (1 H, d, *J*<sub>AB</sub> 18, CH<sub>A</sub>H<sub>B</sub>CONHCO).

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