1,3-Dipolar cycloaddition route to oxygen heterocyclic triones

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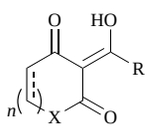
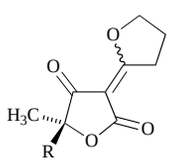
1,3-Dipolar cycloadditon of nitrile oxides, formed *in situ* by dehydration of primary nitro compounds, with pyrrolidine enamines of protected γ-hydroxy-β-keto esters affords isoxazole-4-carboxylates; these are subjected to N–O bond cleavage and lactonisation to afford 3-acyltetronic acids and 3-acyl-4-hydroxy-tetrahydropyran-2-ones.

Introduction

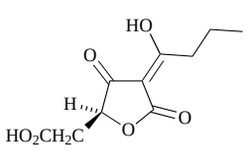
3-Acyltetronic acids (3-acyltetrahydrofuran-2,4-diones) and their six-membered ring analogues, the 3-acyltetrahydropyran-2,4-diones, form a structurally diverse group of biologically active oxacyclic natural products containing the cyclic tricarbonyl moiety **1**.[1] This type of heterocyclic unit is seen also in nitrogen analogues **2**, the 3-acyltetramic acids and 3-acyl-4-hydroxypyridin-2-ones,[2] and is known to exist fully enolised.†,[3] There is considerable interest in these heterocyclic triones, particularly as antibiotics, antiviral and antifungal agents.



1; n = 0,1; X = O
2; n = 0,1; X = NR^1



3; R = H
5; R = CH_2CO_2H



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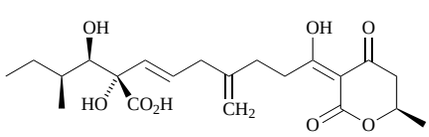

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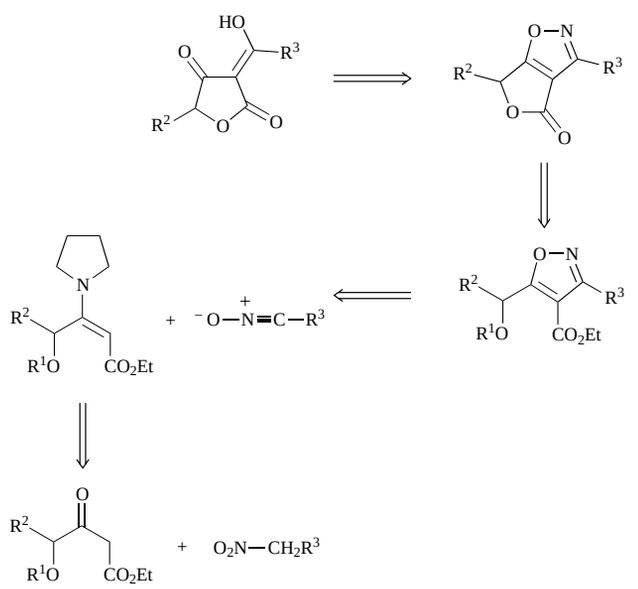
One of the first examples of this natural products class, carolic acid **3** from *Penicillium charlesii*,[4] exhibits an internal ether of the 3-*exo*-enol tautomer.[5] An early synthesis of this and the related carlosic acid **4** was achieved by Bloomer and Kappler.[6] Further simply substituted acyltetronic acids include carlic acid **5** and the recently synthesised agglomerin A.[1] Acyltetronic acid natural products carrying more complex side chains include tetronasin[7] and the closely related tetronomycin,[8] both from *Streptomyces* species, and for which total syntheses have recently been reported.[9] Others include tetronolide, a novel antitumour antibiotic from *Micromonospora chalcea* KY1109,[10] and kijanimicin.[11]

† We illustrate a 3-*exo*-enol tautomer, one of the major tautomers for the oxygen series [refs. 3(*b*),(*c*)]. Distribution between the four possible enol tautomers is different between the oxygen series **1** and nitrogen series **2**.

The 3-acyltetrahydropyran-2,4-dione group is exemplified by alternaric acid **6**,[12] which has phytotoxic and antifungal activities. A recent report describes the stereochemistry determination and a total synthesis.[13]

The range of biological properties displayed by the heterocyclic triones makes them interesting targets for synthesis and biological evaluation. Problems associated with handling these highly polar moieties have prompted us to develop strategies which avoid forming the enolic unit until the final stages of the synthetic sequence.[14]

We propose a new approach, Scheme 1 (illustrated for five-membered targets), combining the known disconnection of 3-acyltetramic acids to β-keto esters[14] with the concept of isoxazoles as masked 1,3-dicarbonyl compounds.[15] The use of isoxazole building blocks allows elaboration *via* non-polar intermediates, and a late unmasking triggered by N–O bond cleavage. A key point in this strategy is the C–C bond formation that attaches the 3-acyl side-chain, which occurs in a 1,3-dipolar cycloaddition and ensures regiospecific *C*-acylation of a 1,3-dicarbonyl compound. The isoxazoles can be accessed by the regiospecific 1,3-dipolar cycloaddition of a nitrile oxide to the pyrrolidine enamine of a β-keto ester, followed by spontaneous elimination of pyrrolidine to leave an isoxazole-4-carboxylate ester.[16] Deprotection of the oxygen substituent allows the required lactonisation before opening of the isoxazole ring by hydrogenation[17] or other N–O bond cleavage method.[18]



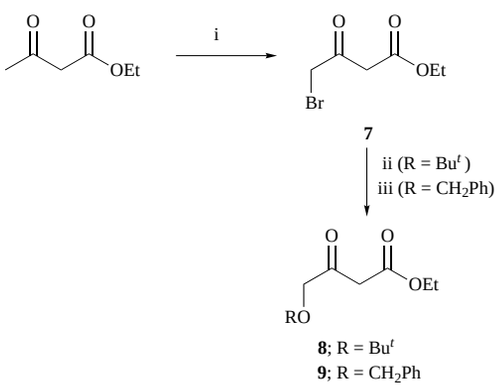
Scheme 1

We report herein details of our results which demonstrate the application of this strategy as a synthetic approach to the oxygen heterocyclic triones **1** (our studies on nitrogen heterocycles **2** will be detailed separately).[19]

Results and discussion

Whilst investigating new methodology to form the 3-acyltetramic acids and the six-membered ring 3-acylpyridones **2**, we turned our attention to the related oxygen-containing heterocycles **1**, the acyltetronic acids and their six-membered ring analogues. We hoped to apply the same type of methodology, namely a 1,3-dipolar cycloaddition strategy to form an isoxazole which acts as a masking structure, in the formation of these oxygen heterocycles.[20] The retrosynthetic strategy for the five-membered series, Scheme 1, suggests a γ-functionalised ethyl acetoacetate as a starting material.

Thus ethyl acetoacetate was brominated at the 4-(γ)-position by treatment with bromine in chloroform to give the bromo ester **7** (86%).[21] The bromine atom was then substituted by treatment of the bromo ester **7** with dry *tert*-butyl alcohol or benzyl alcohol, in the presence of sodium hydride, to form the *tert*-butyl ether **8** (45%) or benzyl ether **9** (48%), respectively, Scheme 2. These yields are moderate but comparable to those reported previously.[22]



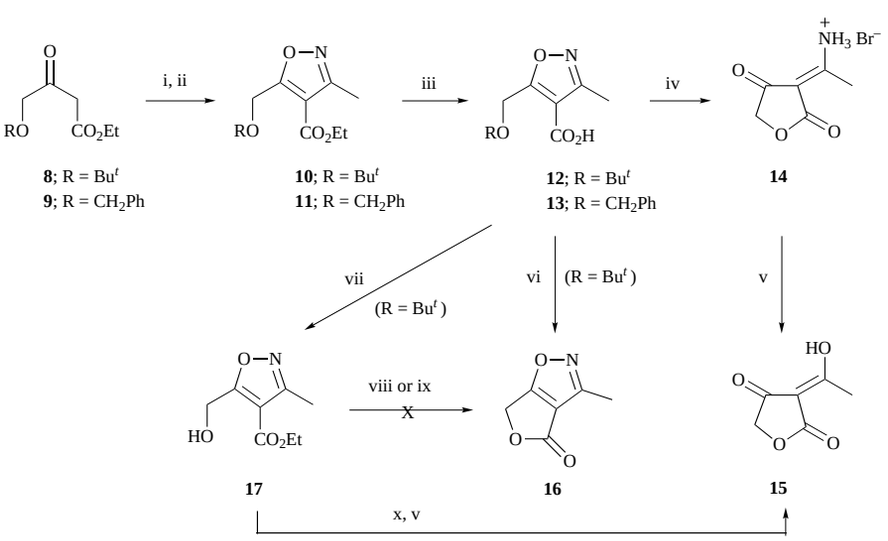
Scheme 2 *Reagents and conditions*: i, Br_2, $CHCl_3$, 0–25 °C; then N_2 stream; ii, NaH, Bu^{t}OH; iii, NaH, $PhCH_2OH$

These two β-keto esters were then converted into their pyrrolidine enamines by reaction with pyrrolidine in toluene under Dean–Stark conditions.[16] Reaction of the enamines, formed from the two β-keto esters **8** and **9**, with acetonitrile oxide generated *in situ* from nitroethane, phosphorus oxychloride and triethylamine, yielded the two isoxazoles, ethyl 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylate **10** (63%) and ethyl 5-benzyloxymethyl-3-methylisoxazole-4-carboxylate **11** (85%), respectively. The assigned regiochemistry is in accord with that previously reported for cycloadditions between nitrile oxides and β-enamino esters,[16] and is substantiated by the subsequent reactions; no product corresponding to the alternative regioisomer was found.

The next target was the formation of the furan ring in each case. By analogy with our findings in the 3-acylpyrrolidine-2,4-dione series[19a] such cyclisation was not expected to occur spontaneously on removal of the oxygen protecting group, presumably due to steric constraints in the bicyclic system with so many sp^2 centres and the planarity of the target lactone function, therefore further activation of the carboxy-group was required. The ethoxycarbonyl groups of **10** and **11** were hydrolysed by heating at reflux with aqueous sodium hydroxide, yielding the carboxylic acids, 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylic acid **12** (94%) and 5-benzyloxymethyl-3-methylisoxazole-4-carboxylic acid **13** (85%), respectively. Activation of this carboxy-group was achieved by formation of the mixed anhydride with ethyl chloroformate and triethylamine. These intermediates were not isolated but used directly in the next stage of the process. Removal of the side-chain oxygen protecting groups, *tert*-butyl in **12** and benzyl in **13**, was achieved by treatment with two equivalents of HBr in acetic acid which resulted in a spontaneous cyclisation. In contrast to the results found in the nitrogen series[19a] the expected bicycle was not formed but cleavage of the isoxazole ring also occurred to give 3-(1-aminoethylidene)tetrahydrofuran-2,4-dione hydrobromide **14**,‡ in a yield of 35% from the *tert*-butyl ether **12** and a poor 19% from the benzyl ether **13**. This is a novel method for N–O bond reduction as far as we are aware. Samples of the salt **14** from both the *tert*-butyl and benzyl precursors were separately and easily transformed into the 3-acetyltetronic acid **15** by treatment with 2 M sodium hydroxide solution at room temperature. An excellent yield of 84% was obtained when using material originating from the *tert*-butyl ether **12** and 72% when using material from the benzyl ether **13**.

3-Methyl-4,6-dihydrofuro[3,4-*d*]isoxazol-4-one **16**, originally expected from the deprotection step described above, was prepared in a disappointing 6% yield by the treatment of 5-*tert*-butoxymethyl-4-carboxy-3-methylisoxazole **12** with trifluoroacetic anhydride in trifluoroacetic acid, Scheme 3. In addition,

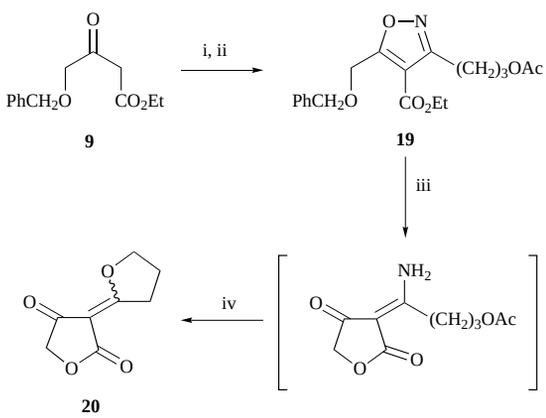
‡ This intermediate is drawn as the enamino ketone tautomer for convenience; we have no further information on the tautomer population.



Scheme 3 *Reagents and conditions*: i, pyrrolidine, toluene, reflux; ii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iii, 2 M NaOH aq., reflux; iv, HBr–AcOH (2 mol equiv.); v, 2 M NaOH aq., 25 °C; vi, trifluoroacetic anhydride, trifluoroacetic acid; vii, trifluoroacetic acid; viii, *p*-TsOH, toluene, reflux; ix, NaOEt, EtOH, reflux; x, H_2, Pd–C, 25 °C

this sample proved difficult to purify. Formation of the furanone ring was also achieved by the treatment of 5-*tert*-butoxymethyl-4-carboxy-3-methylisoxazole **12** with trifluoroacetic acid to form 4-ethoxycarbonyl-5-hydroxymethyl-3-methylisoxazole **17** (46%). Cyclisation of **17** was attempted with toluene-4-sulfonic acid in refluxing toluene but led to the recovery of starting material, the same result being achieved after heating at reflux with sodium ethoxide in ethanol. Formation of the tetronic acid was realised after hydrogenation followed by treatment with aqueous base to form 3-acetyltetronic acid **15**, Scheme 3, in 42% yield.

Having successfully formed 3-acetyltetronic acid **15** *via* this isoxazole strategy we looked to expand the methodology to the incorporation of other side-chains at C-3. To assemble the core structures of carolic **3** and carlic **5** acids[4–6] we required a 4-hydroxy-1-oxobutyl group at C-3. The source of this required functionality was 4-nitrobutyl acetate **18**, prepared in low yield from 4-bromobutyl acetate with sodium nitrite in dimethyl sulfoxide. The enamine generated from the benzyl ether **9** was reacted with 4-nitrobutyl acetate, triethylamine and phosphorus oxychloride to produce the desired 3-(3-acetoxypropyl)-5-benzyloxymethyl-4-ethoxycarbonylisoxazole **19**, although contaminated with 4-nitrobutyl acetate which has the same polarity. Hydrogenation of this crude material used two equivalents of hydrogen and was shown to have both cleaved the isoxazole ring and removed the benzyl group. Base treatment of the crude product led to 3-(tetrahydrofuran-2-ylidene)tetrahydrofuran-2,4-dione **20** (45%) as a mixture of *E*- and *Z*-isomers, Scheme 4.[23]



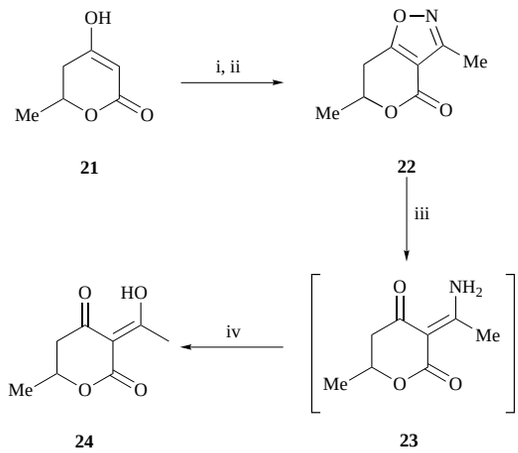
Scheme 4 *Reagents and conditions*: i, pyrrolidine, toluene, reflux; ii, 4-nitrobutyl acetate **18**, Et_3N, $POCl_3$, 0–5 °C; iii, H_2, Pd–C, 25 °C; iv, NaOH aq., 25 °C

In the six-membered ring oxygen series, the 3-acylpyran-2,4-diones, a useful starting point for model reactions is the commercial, racemic 4-hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one **21**. The corresponding enamine was synthesised in the same manner as described for the β-keto esters **8** and **9**, by heating with pyrrolidine under Dean–Stark conditions. This enamine was again reacted, without isolation, with acetonitrile oxide to form the isoxazole **22** (25%). The N–O bond of the isoxazole was cleaved quantitatively by catalytic hydrogenation to yield the intermediate amino ketone **23**‡ which was not characterised but underwent hydrolysis with 2 M sodium hydroxide to produce 3-(1-hydroxyethylidene)-6-methyltetrahydro-2*H*-pyran-2,4-dione **24** (26%), Scheme 5.

We have thus succeeded in validating our new cycloaddition–isoxazole strategy for the synthesis of 3-acyltetronic acids **1** and 3-acyltetrahydropyran-2,4-diones **2**.

Experimental

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-



Scheme 5 *Reagents and conditions*: i, pyrrolidine, toluene, reflux; ii, $EtNO_2$, Et_3N, $POCl_3$, 0–5 °C; iii, H_2, Pd–C; iv, 2 M NaOH aq., 25 °C

Elmer 1720X FT spectrometer. ^{1}H NMR spectra were recorded using the following instruments: at 80 MHz on a Bruker WP80SY, at 250 MHz on a Bruker WM250, at 270 MHz on a JEOL JNM-EX270 or at 400 MHz on a Bruker AM400. *J* Values are given in Hz. ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 instrument at 68 MHz or a Bruker AM400 at 100 MHz and multiplicities were determined using DEPT sequences. Mass spectra were recorded on AEI MS902, VG 7070E or VG Autospec spectrometers using electron impact as the ionisation technique, unless FAB (fast atom bombardment) is indicated. Microanalytical data were obtained using a Perkin-Elmer 240B elemental analyser. All solvents were dried and distilled prior to use.

Ethyl 4-bromo-3-oxobutanoate **7** was prepared as reported[21] in 86% yield. Ethyl 4-*tert*-butoxy-3-oxobutanoate **8** and ethyl 4-benzyloxy-3-oxobutanoate **9** were prepared as reported[22] in 45 and 48% yields, respectively.

Ethyl 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylate 10

Ethyl 4-*tert*-butoxy-3-oxobutanoate **8** (2.02 g, 10.00 mmol) and pyrrolidine (0.90 cm^3, 11.00 mmol) in toluene (30 cm^3) were heated together at reflux under Dean–Stark conditions for 2 h. After this period the solution was cooled and excess solvent evaporated under reduced pressure. To the residue in chloroform (30 cm^3) were added triethylamine (4.18 cm^3, 30.00 mmol) and nitroethane (0.79 cm^3, 11.00 mmol). The mixture was cooled to 0 °C and phosphorus oxychloride (1.03 cm^3, 11.00 mmol) in chloroform (10 cm^3) added dropwise over 45 min. The mixture was then stirred a further 16 h at room temperature before the deep red–brown solution was poured into water (20 cm^3). The separated organic layer was washed successively with hydrochloric acid (6 M, 20 cm^3), aqueous sodium hydroxide (5% w/v, 20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield a brown oil. Purification by flash column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)–ethyl acetate (2 : 1 v/v) yielded the *title compound* as a yellow oil (1.52 g, 63%) (Found: $MH^+ - Bu^t$, 185.0686; C, 59.2; H, 8.0; N, 5.6%. $C_{12}H_{19}NO_4$ requires $MH - Bu^t$, 185.0688; C, 59.5; H, 7.9; N, 5.8%); ν_{max}(film)/cm^{-1} 2977, 2937, 2874, 1720, 1612, 1457, 1366, 1181 and 1106; δ_H(250 MHz; $CDCl_3$) 1.29 [s, 9H, $C(CH_3)_3$], 1.39 (t, 3H, *J* 7, OCH_2CH_3) 2.44 (s, 3H, 3-CH_3), 4.34 (q, 2H, *J* 7, OCH_2CH_3) and 4.81 (s, 2H, OCH_2); δ_C(100 MHz; $CDCl_3$) 11.3, 13.9 and 27.0 (CH_3), 55.3 and 60.4 (CH_2), 74.4, 108.8, 159.2, 161.5 and 174.3 (C); *m/z* 185 ($MH^+ - Bu^t$), 184 ($M^+ - Bu^t$), 140 (100%) and 57 (Bu^t).

Ethyl 5-benzyloxymethyl-3-methylisoxazole-4-carboxylate 11

The procedure described for the preparation of 5-*tert*-

butoxymethyl-4-ethoxycarbonyl-3-methylisoxazole **10** was utilised incorporating the following quantities: ethyl 4-benzyloxy-3-oxobutanoate **9** (13.55 g, 57.00 mmol), pyrrolidine (4.05 g, 57.00 mmol), triethylamine (17.33 g, 171.00 mmol), nitroethane (4.73 g, 62.70 mmol) and phosphorus oxychloride (9.63 g, 62.70 mmol) to yield the *title compound* as a yellow oil (13.32 g, 85%) (Found: MH^+, 276.1256. $C_{15}H_{17}NO_4$ requires *M*H, 276.1235); ν_{max}(film)/cm^{-1} 2982, 1722, 1613, 1454, 1296 and 1106; δ_H(250 MHz; $CDCl_3$) 1.33 (t, 3H, *J* 7, OCH_2CH_3), 2.45 (s, 3H, 3-CH_3), 4.31 (q, 2H, *J* 7, OCH_2CH_3), 4.63 (s, 2H, OCH_2), 4.89 (s, 2H, $PhCH_2$) and 7.35 (s, 5H, Ph); δ_C(100 MHz; $CDCl_3$) 11.4 and 13.9 (CH_3), 60.7, 62.2 and 73.2 (CH_2), 109.8 (C), 127.7, 128.2 and 130.3 (CH), 137.0, 159.6, 161.2 and 173.1 (C); *m*/*z* 276 (MH^+), 170, 105 (100%) and 91 ($PhCH_2^+$).

5-*tert*-Butoxymethyl-3-methylisoxazole-4-carboxylic acid 12

5-*tert*-Butoxymethyl-4-ethoxycarbonyl-3-methylisoxazole **10** (1.30 g, 5.39 mmol) and sodium hydroxide (0.24 g, 5.92 mmol) in water (15 cm^3) were heated together at reflux for 4 h. After this period the mixture was cooled, washed with chloroform (10 cm^3), the aqueous layer acidified to pH 3 with concentrated hydrochloric acid and the resultant precipitate filtered under suction. The white solid was dissolved in chloroform and the solution dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* as a white solid (1.08 g, 94%), mp 110–111 °C (Found: $M^+ - Me$, 198.0760; C, 56.4; H, 7.3; N, 6.6%. $C_{10}H_{15}NO_4$ requires *M* − Me, 198.0766; C, 56.3; H, 7.1; N, 6.6%); ν_{max}($CHCl_3$)/cm^{-1} 2670, 1738 and 1124; δ_H(250 MHz; $CDCl_3$) 1.32 [s, 9H, $C(CH_3)_3$], 2.49 (s, 3H, 3-CH_3) and 4.36 (s, 2H, OCH_2); δ_C(68 MHz; $CDCl_3$) 11.5 and 27.2 (CH_3), 56.1 (CH_2), 75.7, 108.7, 160.3, 166.1 and 175.1 (C); *m*/*z* 198 ($M^+ - Me$), 157 ($MH^+ - Bu^t$), 140, 82 and 57 (Bu^t).

5-Benzyloxymethyl-3-methylisoxazole-4-carboxylic acid 13

The procedure for the preparation of 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylic acid **12** was utilised incorporating the following quantities: ethyl 5-benzyloxymethyl-3-methylisoxazole-4-carboxylate **11** (1.20 g, 4.36 mmol), sodium hydroxide (0.19 g, 4.79 mmol) and water (15 cm^3) to yield the *title compound* as a white solid (0.91 g, 85%), mp 111–112 °C (Found: MH^+, 248.0924; C, 63.0; H, 5.3; N, 5.4%. $C_{13}H_{13}NO_4$ requires *M*H, 248.0923; C, 63.1; H, 5.3; N, 5.7%); ν_{max}($CHCl_3$)/cm^{-1} 1712 and 1117; δ_H(250 MHz; $CDCl_3$) 2.49 (s, 3H, 3-CH_3), 4.07 (s, 2H, OCH_2), 4.91 (s, 2H, $PhCH_2$) and 7.35 (s, 5H, Ph); δ_C(68 MHz; $CDCl_3$) 11.5 (CH_3), 62.5 and 73.5 (CH_2), 109.2 (C), 128.0, 128.7 and 128.4 (CH), 136.8, 160.1, 167.1 and 174.9 (C); *m*/*z* 248 (MH^+), 141 ($MH^+ - PhCH_2O$, 100%) and 91 ($PhCH_2^+$).

3-(1-Aminoethylidene)tetrahydrofuran-2,4-dione hydrobromide 14

To 5-*tert*-Butoxymethyl-3-methylisoxazole-4-carboxylic acid **12** (0.43 g, 2.00 mmol) in anhydrous THF (30 cm^3) at 0 °C was added triethylamine (0.28 cm^3, 2.00 mmol) and the mixture stirred for 10 min. Ethyl chloroformate (0.19 cm^3, 2.00 mmol) was then added and the resultant suspension stirred for 15 h at room temperature before filtration and evaporation of the solvent to yield the mixed anhydride. To the crude mixed anhydride was added hydrogen bromide in acetic acid (32% w/v, 1.06 cm^3, 4.2 mmol) and the solution stirred for 16 h at room temperature. Addition of dry diethyl ether resulted in precipitation of the product which was isolated by filtration under suction and dried to yield the *title compound* as a pale cream solid (156.40 mg, 35%), mp 200–204 °C (Found: $M^+ - HBr$, 141.0424. $C_6H_8NO_3Br$ requires *M* − HBr, 141.0426); ν_{max}(KBr)/cm^{-1} 1738, 1662 and 1625; δ_H(250 MHz; CD_3OD) 2.55 (s, 3H, CH_3) and 4.50 (s, 2H, OCH_2); δ_C(100 MHz; CD_3OD) 18.7 (CH_3), 70.7 (CH_2), 90.2, 171.2, 173.2 and 195.6 (C); *m*/*z* 141 ($M^+ - HBr$, 100%), 83 and 79.

The hydrobromide salt **14** was also prepared from 5-benzyloxymethyl-4-carboxy-3-methylisoxazole **13** using the above method, in 19% yield.

3-(1-Hydroxyethylidene)tetrahydrofuran-2,4-dione-(3-acetyltetronic acid) 15

3-(1-Aminoethylidene)tetrahydrofuran-2,4-dione hydrobromide **14** (100.00 mg, 0.45 mmol) in aqueous sodium hydroxide (2 M, 5 cm^3) was stirred at room temperature for 3 h. Careful acidification to pH 1 with concentrated hydrochloric acid, extraction with chloroform (3 × 20 cm^3), drying ($MgSO_4$) and evaporation of the organic extracts yielded the title compound as an off-white solid (53.70 mg, 84%), mp 80–82 °C (lit.,[24] 81–83 °C) (Found: M^+, 142.0263; $C_6H_6O_4$ requires *M*, 142.0266); ν_{max}($CHCl_3$)/cm^{-1} 1770, 1698, 1673 and 1610; δ_H(400 MHz; $CDCl_3$) 2.55 (s, 3H, CH_3, tautomer 1), 2.57 (s, 3H, CH_3, tautomer 2), 4.57 (s, 2H, CH_2, tautomer 1) and 4.57 (s, 2H, CH_2, tautomer 2); δ_C(68 MHz; $CDCl_3$) 19.6 (CH_3, tautomer 2), 22.0 (CH_3, tautomer 1), 68.8 (CH_2, tautomer 1), 73.6 (CH_2, tautomer 2), 97.7 (C, tautomer 2), 100.6 (C, tautomer 1), 168.2 (C, tautomer 1), 176.5 (C, tautomer 2), 188.1 (C, tautomer 2) 192.0 (C, tautomer 2), 193.9 (C, tautomer 1) and 197.8 (C, tautomer 1); *m*/*z* 142 (M^+, 93%), 127 and 84 (100).

3-Methyl-4,6-dihydrofuro[3,4-*d*]isoxazol-4-one 16

5-*tert*-Butoxymethyl-3-methylisoxazole-4-carboxylic acid **12** (0.21 g, 1.00 mmol) and trifluoroacetic anhydride (0.13 g, 0.60 mmol) were stirred together in trifluoroacetic acid (2 cm^3) for 2 h at room temperature. Diethyl ether (5 cm^3) was then added and the separated ether layer washed with saturated aqueous sodium hydrogen carbonate (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* as an off-white solid (8.30 mg, 6%), mp 198–200 °C (Found: M^+, 139.0269. $C_6H_5NO_3$ requires *M*, 139.0269); δ_H(250 MHz; $CDCl_3$) 2.30 (s, 3H, CH_3) and 4.82 (s, 2H, OCH_2); δ_C(68 MHz; CD_3OD) 11.5 (CH_3), 63.7 (CH_2), 110.2, 161.5, 164.8 and 177.3 (C); *m*/*z* 139 (M^+) and 81 (100%).

Ethyl 5-hydroxymethyl-3-methylisoxazole-4-carboxylate 17

Ethyl 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylate **10** (4.00 g, 17.00 mmol) in trifluoroacetic acid (40 cm^3) was stirred at room temperature for 1 h. After stirring diethyl ether was added (400 cm^3) and the organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with light petroleum (bp 40–60 °C)–ethyl acetate (1 : 1 v/v) yielded the *title compound* as a clear oil (1.40 g, 46%) (Found: M^+, 185.0659. $C_8H_{11}NO_4$ requires *M*, 185.0688); ν_{max}(film)/cm^{-1} 3417, 2984, 2939, 1723, 1609, 1108 and 782; δ_H(250 MHz; $CDCl_3$) 1.40 (t, 3H, *J* 7, OCH_2CH_3), 2.45 (s, 3H, 3-CH_3), 4.37 (q, 2H, *J* 7, OCH_2CH_3) and 4.88 (s, 2H, CH_2OH); δ_C(68 MHz; $CDCl_3$) 12.0 and 14.4 (CH_3), 61.8 and 59.9 (CH_2), 109.9, 160.0, 163.3 and 177.2 (C); *m*/*z* 185 (M^+) and 138 (100%).

3-(1-Hydroxyethylidene)tetrahydrofuran-2,4-dione (3-acetyltetronic acid) 15

Ethyl 5-hydroxymethyl-3-methylisoxazole-4-carboxylate **17** (2.44 g, 13.18 mmol) and palladium on charcoal (10%, 0.24 g, 2.66 mmol) were stirred together under hydrogen (1 atm) until hydrogen absorption ceased (591.00 cm^3, 26.37 mmol). After this period the mixture was filtered through Kieselgühr and the filtrate evaporated under reduced pressure to yield a white solid. To this material was added aqueous sodium hydroxide (2 M, 150 cm^3) and the mixture stirred at room temperature for 3 h before acidification to pH 1 with concentrated hydrochloric acid. The product was extracted with chloroform, the organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield the title compound as a white solid (0.78 g, 42%), identical to that described above.

4-Nitrobutyl acetate 18

4-Bromobutyl acetate (10.00 g, 51.55 mmol) was poured into a stirred solution of dimethyl sulfoxide (60 cm^3) and sodium nitrite (6.18 g, 89.50 mmol) immersed in a water bath held at room temperature. Stirring was continued for 4 h after which the mixture was poured into ice–water (120 cm^3) and pentane (200 cm^3). After separation, the aqueous layer was further extracted with pentane (4 × 20 cm^3), the combined organic extracts were washed with water (4 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by column chromatography on silica, eluting with light petroleum (bp 40–60 °C)–ethyl acetate (9:1 v/v) yielded the *title compound* as a clear oil (0.83 g, 10%) (Found: M^+ − HOAc, 101.0428. $C_6H_{11}NO_3$ requires *M* − HOAc, 101.0477); ν_{max}(film)/cm^{-1} 3582, 2962, 1737, 1552, 1368 and 1240; δ_H(250 MHz; $CDCl_3$) 1.76 (m, 2H, $O_2NCH_2CH_2$), 2.07 (s, 3H, OCH_3), 2.09 (m, 2H, CH_2CH_2OAc), 4.12 (t, 2H, CH_2OAc) and 4.44 (t, 2H, CH_2NO_2); δ_C(68 MHz; $CDCl_3$) 20.7 (CH_3), 23.9, 25.3, 63.0 and 74.8 (CH_2), 170.7 (C); *m*/*z* 101 (M^+ − HOAc) and 43 (100%).

3-(Tetrahydrofuran-2-ylidene)tetrahydrofuran-2,4-dione 20

The procedure described for the preparation of ethyl 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylate **10** was utilised incorporating the following quantities: ethyl 4-benzyloxy-3-oxobutanoate **9** (0.93 g, 3.95 mmol), pyrrolidine (0.28 g, 3.95 mmol), triethylamine (1.20 g, 11.85 mmol), 4-nitrobutyl acetate **18** (0.70 g, 4.35 mmol) and phosphorus oxychloride (0.67 g, 4.35 mmol) to yield ethyl 5-benzyloxymethyl-3-(3-acetoxypropyl)isoxazole-4-carboxylate **19** (a) and 4-nitrobutyl acetate **18** (b) as a yellow oil which could not be separated, even after repeated column chromatography; δ_H(250 MHz; $CDCl_3$) 1.33 (t, 3H, *J* 7, OCH_2CH_3, a), 1.75 (m, 2H, $CH_2CH_2NO_2$, b), 2.05 (m, 2H, CH_2CH_2OAc, a,b), 2.05 (s, 3H, OAc, a,b), 2.97 (t, 2H, *J* 7.5, $CH_2CH_2CH_2OAc$, a), 4.11 (t, 2H, *J* 6.3, CH_2OAc, b), 4.15 (t, 2H, *J* 6.4, CH_2OAc, a), 4.31 (q, 2H, *J* 7, OCH_2CH_3, a), 4.42 (t, 2H, *J* 7, CH_2NO_2, b), 4.65 (s, 2H, OCH_2, a), 4.89 (s, 2H, $PhCH_2$, a) and 7.35 (s, 5H, Ph, a); δ_C(68 MHz; $CDCl_3$) 14.1 (CH_3, a), 20.8 (CH_3, b), 20.8 (CH_2, a), 22.7 (CH_2, a), 24.1 (CH_2, b), 25.4 (CH_2, b), 26.5 (CH_2, a), 60.9 (CH_2, b), 62.4 (CH_2, a), 63.1 (CH_2, b), 63.6 (CH_2, a), 73.4 (CH_2, a), 75.0 (CH_2, b), 109.5 (C, a), 128.4 (CH, a), 137.1 (C, a), 161.4 (C, a), 162.4 (C, a), 170.9 (C, a), 171.0 (C, a) and 173.6 (C, a). This mixture was used directly in the next step.

The procedure outlined for the synthesis of 3-acetyltetronic acid **15** from **17** was used incorporating the following quantities: 3-(3-acetoxypropyl)-5-benzyloxymethyl-4-ethoxycarbonylisoxazole **19** (0.14 g, mixture as described above, approx. 0.40 mmol), palladium on charcoal (10%, 0.02 g), hydrogen (17.92 cm^3, 0.80 mmol) and aqueous sodium hydroxide (2 M, 10 cm^3) to yield the *title compound* (30 mg, 45%) as a 5:4 mixture of *Z* and *E* isomers (Found: M^+, 168.0430. $C_8H_8O_4$ requires *M*, 168.0423); δ_H(250 MHz; $CDCl_3$)§ 2.22 (m, 2H, OCH_2CH_2, *E*,*Z*), 3.37 (t, 2H, $OCH_2CH_2CH_2$, *E*,*Z*), 4.43 [s, 2H, $OCH_2C(O)$, *Z*], 4.45 [s, 2H, $OCH_2C(O)$, *E*], 4.72 (t, 2H, OCH_2CH_2, *Z*) and 4.74 (t, 2H, OCH_2CH_2, *E*); δ_C(68 MHz; $CDCl_3$)¶ 21.7 (CH_2, *E*,*Z*), 33.3 (CH_2, *E*), 33.7 (CH_2, *Z*), 72.0 (CH_2, *E*), 72.5 (CH_2, *Z*), 77.6 (CH_2, *Z*), 78.2 (CH_2, *E*), 96.1 (C, *Z*), 97.0 (C, *E*), 168.1 (C, *Z*), 172.3 (C, *E*), 186.6 (C, *E*), 187.4 (C, *Z*), 196.3 (C, *E*) and 200.2 (C, *Z*).

3,6-Dimethyl-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazol-4-one 22

The procedure outlined for the synthesis of ethyl 5-*tert*-butoxymethyl-3-methylisoxazole-4-carboxylate **10** was utilised incorporating the following quantities: 4-hydroxy-6-methyl-5,6-dihydro-2*H*-pyran-2-one **21** (1.00 g, 7.80 mmol), pyrrolidine (0.72 cm^3, 8.58 mmol), triethylamine (3.26 cm^3, 23.40 mmol), nitroethane (0.62 cm^3, 8.58 mmol) and phosphorus oxychloride (0.80 cm^3, 8.58 mmol) to yield the *title compound* as a yellow solid (0.32 g, 25%), mp 72–73 °C (Found: M^+, 167.0594; C, 57.4; H, 5.5; N, 8.3%. $C_8H_9NO_3$ requires *M*, 167.0582; C, 57.47; H, 5.43, N, 8.38%); ν_{max}($CHCl_3$)/cm^{-1} 1729, 1632, 1368, 1322, 1241, 1189 and 1028; δ_H(250 MHz; $CDCl_3$) 1.60 (d, 3H, *J* 6, 6-CH_3), 2.46 (s, 3H, 3-CH_3), 2.99 (dd, 1H, $CHCHH$), 3.25 (dd, 1H, $CHCHH$) and 4.82 (m, 1H, $CHCH_2$); δ_C(68 MHz; $CDCl_3$) 10.06 and 20.42 (CH_3), 29.83 and 75.06 (CH_2), 106.59, 158.06, 160.83 and 176.03 (C); *m*/*z* 167 (M^+), 123 (100%), 81 and 67.

3-(1-Hydroxyethylidene)-6-methyltetrahydro-2*H*-pyran-2,4-dione 24

3,6-Dimethyl-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazol-4-one **22** (0.16 g, 0.96 mmol) in ethanol (5 cm^3) was stirred with palladium on charcoal (10% w/w, 1.6 mg) under hydrogen (1 atm), until hydrogen absorption ceased after 24 h. The suspension was filtered through Kieselgühr and the filtrate evaporated under reduced pressure to yield a white solid (0.15 g, 97%). To this solid was added aqueous sodium hydroxide (2 M, 15 cm^3) and the solution stirred for 2.5 h at room temperature before acidification to pH 1 with concentrated hydrochloric acid. The resultant precipitate was filtered under suction and the filtrate extracted with chloroform (3 × 50 cm^3). The extracts and filtered solid were combined, and the solution was dried ($MgSO_4$) and evaporated under reduced pressure to yield a pale yellow solid. Recrystallisation from diethyl ether gave the *title compound* as an off-white solid (42.5 mg, 26%), mp 98–99 °C (Found: M^+, 170.0578; C, 56.6; H, 5.9%. $C_8H_{10}O_4$ requires *M*, 170.0579; C, 56.47; H, 5.92); ν_{max}($CHCl_3$)/cm^{-1} 1713 and 1568; δ_H(250 MHz; $CDCl_3$) 1.47 (d, 3H, 6-CH_3), 1.65 (1H, br s, OH), 2.62 (s, 3H, 3-CH_3), 2.65 (m, 2H, $CHCH_2$) and 4.52 (m, 1H, $CHCH_2$); δ_C(68 MHz; $CDCl_3$) 20.6 and 26.5 (CH_3), 39.4 (CH_2), 70.3 (CH), 103.2 164.3, 195.0 and 201.08 (C); *m*/*z* 170 (M^+), 129 (100%) and 69.

§ Signals of *E* and *Z* isomers assigned from ^1H–^{13}C COSY spectrum.
¶ Signal of *E* and *Z* isomers assigned by analogy.[23]

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