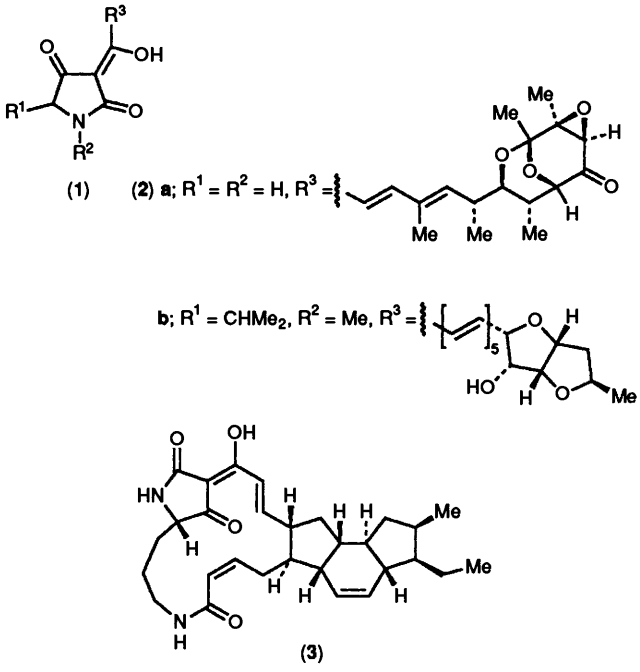
Acylation of Pyrrolidine-2,4-diones: A Synthesis of 3-Acyltetramic Acids. X-Ray Molecular Structure of 3-[1-(Difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione

Raymond C. F. Jones,* Michael J. Begley, Graeme E. Peterson, and Suresh Sumaria
Department of Chemistry, The University, Nottingham, NG7 2RD

Pyrrolidine-2,4-diones, prepared from the corresponding α-amino acid esters by condensation with ethoxycarbonylacetic acid, Dieckmann cyclisation, and hydrolysis–decarboxylation, are acylated at C-3 by the acid chlorides of saturated, unsaturated, and arenecarboxylic acids in the presence of Lewis acids. The most efficient protocol involves boron trifluoride–diethyl ether as Lewis acid, isolation of the neutral boron difluoride complexes of the 3-acyltetramic acids, and their subsequent methanolysis. The quaternary ammonium enolates of 5-substituted pyrrolidine-2,4-diones undergo isomerisation to the exocyclic $\Delta^{5,6}$-isomers during *O*-acylation with acid chlorides.

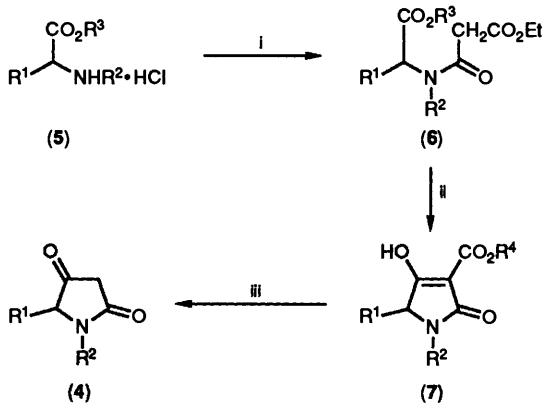
The 3-acyltetramic acids (**1**) form an expanding group of antibiotics and pigments from micro-organisms. They display a range of biological activities; the 3-dienoyl derivative tirandamycin (**2a**), for example, is a potent inhibitor of bacterial DNA-directed RNA polymerase,[1] and the macrocyclic 3-enoyl compound ikarugamycin (**3**) has specific antiprotozoal properties.[2] This has stimulated much recent synthetic activity directed towards the side-chains (R^3) of these metabolites.[3] A further example of the group, the mould pigment erythroskyrine (**2b**), illustrates 3-polyenoyl substitution.[4] The heterocyclic nucleus (**1**) common to the natural products consists of a pyrrolidine-2,4-dione (tetramic acid) (**4**) acylated at C-3 and essentially completely enolised. The 3-acyltetramic acids are represented herein in the 3-*exo*-enol form (**1**) found in the solid state, and as the major tautomer in solution for a number of cases[5] (see later). We have been interested for a number of years in developing flexible syntheses of such systems[6] applicable to targets including those having unsaturated groupings conjugated to the C-3 carbonyl substituent, such as the important 3-dienoyltetramic acids, *e.g.* (**2a**). One of our strategies has centred on the acylation of pyrrolidine-2,4-diones (**4**) or their derivatives,[6c,d,f,g] and we report here details of the Lewis acid-promoted acylation of compounds (**4**) with acid chlorides.[6f,g] The alternative approach of elaboration of a 3-acetyltetramic acid has been investigated by ourselves and others.[6b,7] We also report an unexpected bond migration observed during acylation of the tetra-alkylammonium enolates of diones (**4**) with acid chlorides.[6e]



Results and Discussion

Preparation of the pyrrolidine-2,4-diones used as substrates in our acylation studies proceeded from the appropriate α-amino acid ester hydrochlorides (**5a–f**) as shown in Scheme 1. The ester salts (**5**) were prepared from the corresponding α-amino acids by standard methods, with the exception of (**5d**), which was obtained by extended treatment of *N*-benzyloxycarbonyl-*N*-methyl-L-valine[8] with methanolic hydrogen chloride. Acylation of compounds (**5**) with ethoxycarbonylacetic acid with dicyclohexylcarbodi-imide (DCC) as dehydrating reagent[9] afforded the amides (**6a–f**); use of ethoxycarbonylacetyl chloride also led to acylation,[10] but in lower yields. The amides (**6a–f**) were next cyclised to the 3-alkoxycarbonyltetramic acids (**7a–f**) by means of sodium alkoxide [methoxide for (**6a**) and (**6d**), ethoxide for (**6b**), (**6c**), (**6e**), and (**6f**)] in alcohol or alcohol–benzene mixtures (see Experimental section).[9–11] Transesterification was observed where possible during these cyclisations; amide (**6a**) gave only the 3-*methoxy*carbonyltetramic acid (**7a**) whilst amide (**6d**) gave a mixture of methyl and ethyl esters (**7d**). Attempts to cyclise the amide (**6c**) using sodium 1,1-dimethylpropoxide[12] were not successful and proved sensitive to moisture, resulting only in some partial hydrolysis to an acid-ester (**6g**) that could be re-esterified on treatment with diazomethane to afford the mixed diester (**6h**).

Hydrolysis and decarboxylation to produce the diones (**4a–f**) could be achieved by three procedures, the most efficient technique varying with the substituents on the 3-alkoxycarbonyltetramic acids (**7**). The 5-unsubstituted compounds (**7a**) and (**7b**) could be converted into the diones (**4a**) and (**4b**), respectively, by brief treatment in boiling water,[10] but care



(4) - (7)**a**; $R^1 = R^2 = H$, $R^3 = Et$, $R^4 = Me$
b; $R^1 = H$, $R^2 = Me$, $R^3 = R^4 = Et$
c; $R^1 = Pr^i$, $R^2 = H$, $R^3 = R^4 = Et$
d; $R^1 = Pr^i$, $R^2 = R^3 = Me$, $R^4 = Me/Et$
e; $R^1 = [CH_2]_2CO_2Et$, $R^2 = H$, $R^3 = R^4 = Et$
f; $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Me$, $R^4 = Et$
g; $R^1 = Pr^i$, $R^2 = R^3 = H$
h; $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$

Scheme 1. *Reagents*: i, $EtO_2CCH_2CO_2H$, Et_3N, DCC; ii, (**6a** and **d**): NaOMe; (**6b**, **c**, **e**, and **f**): NaOEt; iii, (**7a**, **d**, and **e**): water, MeCN; (**7b**): water; (**7c** and **f**): TFA–CH_3CO_2H.

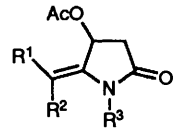
had to be exercised as too long a reaction time resulted in intermolecular aldol condensation between two molecules of dione. Indeed, compound (**4a**) was better prepared by treatment of ester (**7a**) in wet acetonitrile,[9] and this second method was also applied to the preparation of diones (**4d**) and (**4e**), whilst diones (**4c**) and (**4f**) were obtained by treatment of the 3-alkoxycarbonyl derivatives with trifluoroacetic acid (TFA)–glacial acetic acid.[12] Progress in these conversions was monitored by an iron(III) chloride test which gave an intense red colour with compounds (**7**) and a pale brown colour with the diones (**4**); a blue colour was observed when the aldol self-condensation products were present.[10] The tetramic acids (**4**) are represented as pyrrolidine-2,4-diones, although they can be enolised (at C-3) to an extent varying with substitution and solvent, as has been reported by others.[10] For example we observed the tetramic acid (**4c**) to exist in the enol form to the extent of 30% in [$^2H_6$]dimethyl sulphoxide (^{1}H NMR), whereas compounds (**4d**) and (**4e**) (in deuteriochloroform) and (**4f**) (in [$^2H_6$]acetone) showed only the keto form. The dione (**4d**) also displayed in its ^{1}H NMR spectrum a long-range coupling from the methylene protons at C-3 to the proton at C-5, as demonstrated by specific decoupling experiments.

Attempts by others at base-mediated acylation of pyrrolidine-2,4-diones (**4**) have been hampered by the usual problems associated with base-catalysed reactions of 1,3-dicarbonyl compounds. They have generally led either to predominant 4-*O*-acylation, or to low-to-moderate yields of the desired 3-*C*-acylation product, when using various metal enolate derivatives and acid chlorides or fluorides,[13] or triethylamine and an active ester.[14] More recently a procedure for the *in situ* conversion of the 4-*O*-acylated materials into 3-acyltetramic acids has been reported.[15] In an attempt to favour *C*-acylation, we investigated the reaction of tetraalkylammonium enolates of the diones (**4**) with acid chlorides in a non-polar solvent.[6e] Thus dione (**4d**) was treated with aqueous tetraethylammonium hydroxide (1 mol equiv.) and the dried tetraethylammonium enolate salt was acylated with freshly distilled acetyl chloride (3 mol equiv.; dichloromethane; 25 °C; 48 h). The isolated product (55%) was identified as the 4-*O*-acetyl-$\Delta^{5,6}$-isomer (**8a**), *i.e.* *O*-acylation had been accompanied by double-bond migration; the unrearranged enol acetate (**9**) was readily prepared from dione (**4d**), acetyl chloride, and triethylamine (dichloromethane: reflux) for comparison. The ^{1}H and ^{13}C NMR spectra of compound (**8a**) (with appropriate decoupling experiments) clearly revealed the $-CH(OCOCH_3)CH_2-$ and $Me_2C{=}C$ fragments. To examine the generality of this isomerisation the 5-benzyl dione (**4f**) was treated in the same way and afforded two crystalline products that were identified as the (*E*)- and (*Z*)-4-*O*-acetyl-$\Delta^{5,6}$-isomer (**8b**) (59%) and (**8c**) (21%), respectively, by spectroscopic methods including ^{1}H NMR spectra and NOE measurements. For example, irradiation of the methyl signal, δ 1.55 (C_6D_6), led to enhancement of the aromatic proton signals in (*E*)-isomer (**8b**); no corresponding enhancement was observed for (*Z*)-isomer (**8c**). When the minor, (*Z*)-isomer (**8c**) was recrystallised from chloroform–hexane the same 3:1 mixture of isomers (**8b**) and (**8c**) was again formed.

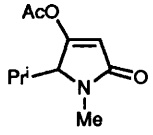
These double-bond shifts may be rationalised as a series of protonation–deprotonation steps catalysed by traces of acid present in the acylation medium, with the $\Delta^{5,6}$ location presumably representing a thermodynamic minimum. No isomerisation of the enol acetate (**9**) was observed on storage in acid-free dichloromethane for several days.

Our attention next focussed on the acylation of pyrrolidine-2,4-diones under acidic conditions. Our first protocol for Lewis acid-mediated acylation of the diones (**4**) involved treatment with an acid chloride and either boron trifluoride–diethyl ether in the absence of solvent,[16] or titanium tetrachloride in nitrobenzene or nitromethane,[17] followed by a basic aqueous work-up to separate the acidic products. In this way the desired 3-*C*-acyltetramic acids (**10a–i**), including 3-enoyl and 3-dienoyl derivatives, were obtained (see Table 1) in reasonable yields from diones (**4c**), (**4d**), and (**4f**). In preliminary experiments, the 5-[2-(ethoxycarbonyl)ethyl]tetramic acid (**4e**) has been shown to undergo acylation with acetyl chloride–boron trifluoride–diethyl ether to afford, after basic aqueous work-up, the 5-(2-carboxyethyl) derivative (**10j**), albeit in low yield. When some of these results were first reported,[6g] they represented the first synthesis of the chromophores of the enoyl- and dienoyl-tetramic acids. We felt, however, that the efficiency of the method could be improved, and investigated further the acylation of the 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**), the nucleus present in erythroskyrine (**2b**).[4] In this series using boron trifluoride–diethyl ether and a basic aqueous work-up, we had isolated little or no acidic material except in the case of acetylation (see Table 1).

The study with dione (**4d**) revealed that a much more efficient procedure for these boron trifluoride-mediated acylations involved isolation of the 3-acyltetramic acids as their neutral boron difluoride complexes (**11**).[6f] Thus, typically, the dione (**4d**) and the acid chloride (3–4 mol equiv.) were heated in boron trifluoride–diethyl ether (usually 50 ml g^{-1}) at 80 °C until the disappearance of the dione as monitored by TLC. In some cases a second portion of acid chloride was added to promote complete reaction. Work-up by addition of water and immediate extraction with organic solvent led to the isolation of neutral material that gave no iron(III) chloride test and could be easily chromatographed to afford the boron difluoride complexes (**11a–f**) (see Table 1, entries 11–16). The side-chains introduced by this method include saturated, enoyl, dienoyl, and aroyl examples. Attempted hydrolysis of the complexes (**11a–f**) using hot aqueous sodium acetate[18] led to extensive degradation, but smooth conversion into the 3-acyltetramic acids (**10b–e**, **k**, and **l**) could be achieved in good yield by simple treatment with methanol, with heating



(8) a; $R^1 = R^2 = R^3 = Me$
b; $R^1 = Ph$, $R^2 = R^3 = H$
c; $R^1 = R^3 = H$, $R^2 = Ph$



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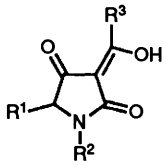
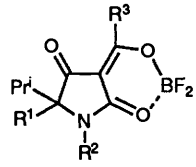


(10) (a); $R^1 = Pr^i$, $R^2 = H$, $R^3 = Me$
(b); $R^1 = Pr^i$, $R^2 = R^3 = Me$
(c); $R^1 = Pr^i$, $R^2 = Me$, $R^3 = [CH_2]_5Me$
(d); $R^1 = Pr^i$, $R^2 = Me$, $R^3 = CH{=}CHMe$
(e); $R^1 = Pr^i$, $R^2 = Me$, $R^3 = CH{=}CMe_2$
(f); $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Me$
(g); $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = [CH_2]_5Me$
(h); $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = CH{=}CHMe$
(i); $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = [CH{=}CH]_2Me$
(j); $R^1 = [CH_2]_2CO_2H$, $R^2 = H$, $R^3 = Me$
(k); $R^1 = Pr^i$, $R^2 = Me$, $R^3 = [CH{=}CH]_2Me$
(l); $R^1 = Pr^i$, $R^2 = Me$, $R^3 = Ph$
(m); $R^1 = Pr^i$, $R^2 = H$, $R^3 = [CH{=}CH]_2Me$



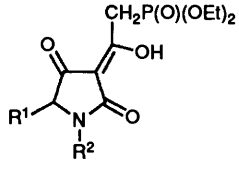
(11) (a); $R^1 = H$, $R^2 = R^3 = Me$
(b); $R^1 = H$, $R^2 = Me$, $R^3 = [CH_2]_5Me$
(c); $R^1 = H$, $R^2 = Me$, $R^3 = CH{=}CHMe$
(d); $R^1 = H$, $R^2 = Me$, $R^3 = CH{=}CMe_2$
(e); $R^1 = H$, $R^2 = Me$, $R^3 = [CH{=}CH]_2Me$
(f); $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
(g); $R^1 = H$, $R^2 = Me$, $R^3 = CH_2D$
(h); $R^1 = R^2 = R^3 = Me$
(i); $R^1 = R^2 = H$, $R^3 = Me$
(j); $R^1 = R^2 = H$, $R^3 = [CH{=}CH]_2Me$

Table 1. Lewis acid-mediated acylation of pyrrolidine-2,4-diones (4).

Entry	Dione (4)	Lewis acid	Boron difluoride complex (11) (Yield/%)	3-Acyltetramic acid (10) (Yield/%)
1	(4c)	BF_3·OEt_2		(10a) (70)
2	(4d)	BF_3·OEt_2		(10b) (45)
3	(4d)	$TiCl_4$		(10c) (31)
4	(4d)	$TiCl_4$		(10d) (60)
5	(4d)	$TiCl_4$		(10e) (21)
6	(4f)	BF_3·OEt_2		(10f) (55)
7	(4f)	BF_3·OEt_2		(10g) (63)
8	(4f)	$TiCl_4$		(10h) (52)
9	(4f)	BF_3·OEt_2		(10i) (33)
10	(4e)	BF_3·OEt_2		(10j) (19)
11	(4d)	BF_3·OEt_2	(11a) (71)	(10b) (93)
12	(4d)	BF_3·OEt_2	(11b) (71)	(10c) (94)
13	(4d)	BF_3·OEt_2	(11c) (78)	(10d) (87)
14	(4d)	BF_3·OEt_2	(11d) (67)	(10e) (92)
15	(4d)	BF_3·OEt_2	(11e) (51)	(10k) (80)
16	(4d)	BF_3·OEt_2	(11f) (50)	(10l) (82)

as required, until consumption of the complex (TLC).[19] This non-basic work-up followed by alcoholysis is the preferred protocol for boron trifluoride–mediated acylations of other 5-substituted pyrrolidine-2,4-diones, including, for example, the 5-benzyl series reported above, where the boron difluoride complexes prove to be partly hydrolysed on aqueous work-up. The overall yields of *C*-acylation recorded here (Table 1) are superior to almost all previously reported examples of direct acylation of pyrrolidine-2,4-diones.[13,14] Application of this acylation protocol to the sensitive 5-unsubstituted diones (**4a**) and (**4b**) was precluded by their ready intermolecular self-condensation;[10] for example, treatment with acetyl chloride–boron trifluoride–diethyl ether led only to the aldol self-condensation products.

In an attempt to use the acylation methodology to insert a functionalised 3-acyl side-chain whose functionality could be utilised in subsequent chain elaboration, we investigated acylation of the diones (**4c**), (**4d**), and (**4f**) with chloroacetyl chloride, but in all cases starting materials were recovered. The application of 3-(phosphonoacetyl)tetramic acids (**12**) to construction of the 3-substituent has been described by several groups;[7] treatment of the dione (**4d**) with diethoxyphosphoryl-acetyl chloride under our preferred conditions led not to the desired 3-*C*-acylation, but instead to formation of the enol ether (**13**) *via* 4-*O*-alkylation. We have also considered the possibility of using the boron difluoride complexes (**11**) as vehicles for side-chain elaboration. Exploratory studies with the 3-acetyl complex (**11a**) showed that treatment with lithium di-isopropylamide (LDA) (1 mol equiv.; −80 °C) followed by quenching with deuterium oxide afforded a monodeuterio product (**11g**). Use of excess of base (2 mol equiv.; −80 °C) and quenching with iodomethane (1 or 2 mol equiv.) gave, as the only isolable product, the 1,5-dimethyl boron difluoride complex (**11h**) in low yield. These reactions may be rationalised as involving a mono- and a di-anion represented as (**14**) and (**15**), respectively. We have to date beeen unsuccessful in efforts to react the monoanion (**14**) with carbon electrophiles; delocalisation of the negative charge onto the electron-deficient boron may be a contributing factor. The relative ease of dianion formation can be attributed in part to the pyrrolic stability of the canonical form (**15**).



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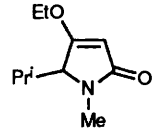

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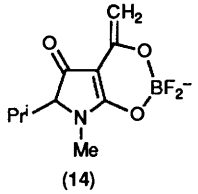

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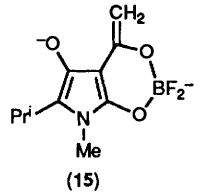

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The boron difluoride complexes (**11**), with the exception of the 3-(hexa-2,4-dienoyl) derivative (**11e**), are crystalline materials that are useful for characterisation of the corresponding 3-acyltetramic acids. The free acids may be converted into the complexes, as illustrated by treatment of compound (**10l**) with boron trifluoride–diethyl ether (1 mol equiv.; CH_2Cl_2; 25 °C) to give complex (**11f**) (73%); likewise reaction of compounds (**10a**) and (**10m**)[6b] [BF_3·OEt_2 (10 mol equiv.);

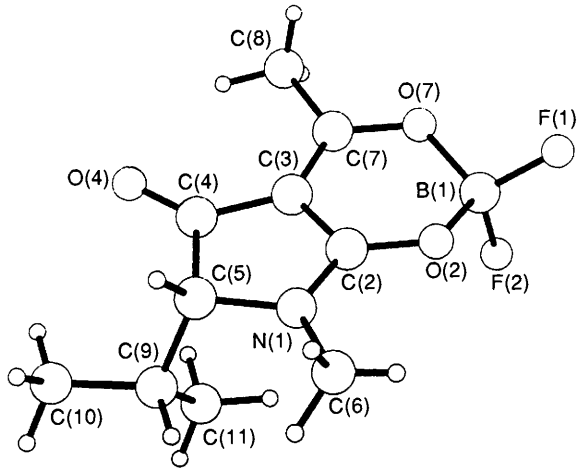


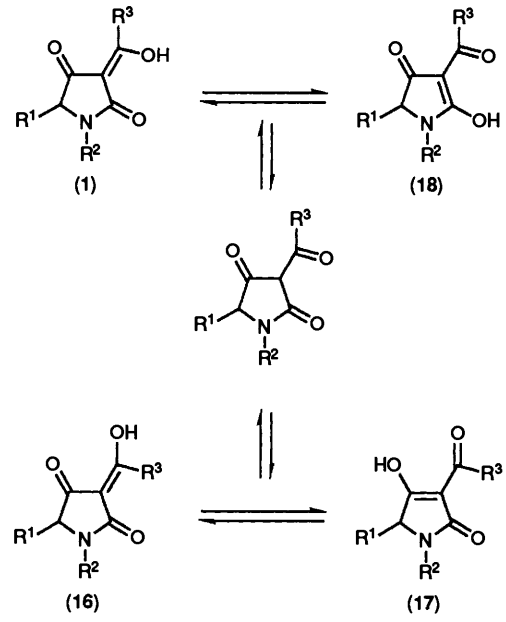
Figure 1. Crystal structure of boron difluoride complex (**11a**) and atomic numbering scheme.

diethyl ether; reflux] gave the complexes (**11i**) (74%) and (**11j**) (56%), respectively. The UV spectra of the complexes (**11**) exhibited absorption maxima very similar to those found in the corresponding 3-acyltetramic acids (**10**). The ^{1}H NMR spectra indicated the formation of complexes of only one of the four possible enol tautomers (Scheme 2) of the 3-acyltetramic acids; their formulation as derivatives (**11**) of the 3-*exo*-enol tautomer of the acids was made initially in accord with the predominance of this tautomer as determined in a number of cases in solution and as found in the solid state,[5] and as supported by calculations (see below). This was confirmed by a single-crystal X-ray structure determination of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11a**), which crystallised from chloroform–hexane as irregular crystals in the triclinic system, space group $P\bar{1}$, a = 7.814(1), b = 7.840(1), c = 10.025(1) Å, α = 93.96(1)°, β = 96.60(1)°, γ = 99.57(1)°. The structure, which was determined from 1 556 observed reflections by direct methods (see Experimental section) and refined to R 4.51%, revealed (Figure 1) that the tetramic acid acts as a bidentate ligand towards the boron, centrally co-ordinated between O(2) and O(7). The six-membered ring containing the boron atom adopts an envelope conformation with the five carbon and oxygen atoms coplanar and the boron atom 0.37 Å out of this plane. The hydrogen bond formed in the absence of the boron difluoride leaves the five carbon and oxygen atoms completely coplanar.[5]

This further example of the dominance of the 3-*exo*-enol tautomer (**1**) prompted us to perform some semi empirical quantum mechanics calculations on the various enol possibilities for 3-acyltetramic acids (Scheme 2). Using the AM1 method,[20] with R^1 = R^2 = H and R^3 = Me, the heat of formation values ΔH_f indicated that tautomer (**1**) was the most stable by 3.75 kJ mol^{-1} from the alternative *exo*-enol (**16**) (assuming comparable entropic contribution in all of the enols), with the other enolic tautomers significantly less stable. This result is in accord with the findings in solution in non-polar solvents that the proportions of the different tautomers are: (**1**), 80 ± 5%; (**16**), 15 ± 3%; (**17**), 5 ± 2%; (**18**), 0%.[5] The 3,4-*endo*-enol (**17**) has been used to represent 3-acyltetramic acids in most of the earlier literature.

Experimental

M.p.s were determined on a Gallenkamp capillary apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer 710B spectrometer, and UV spectra were determined



Scheme 2.

for ethanol solutions on a Pye-Unicam SP800 spectrometer. Molecular masses were determined from mass spectra obtained using an AEI MS 902 or a VG 7070F spectrometer. ^{1}H NMR spectra were obtained using a Perkin-Elmer R24A spectrometer at 60 MHz, an R32 spectrometer at 90 MHz, a JEOL JNM-MH100 instrument at 100 MHz, or a Bruker WM 250 spectrometer at 250 MHz. ^{13}C NMR spectra were obtained using a Bruker WM 250 spectrometer at 62.9 MHz. Medium-pressure column chromatography was carried out using Merck Kieselgel 60 silica gel (Art. 7729) in a 2 in diameter column to a depth of 2 in. TLC was carried out using silica plates—Merck Kieselgel 60 F254. High-pressure liquid chromatography (HPLC) was carried out using a Waters liquid chromatography machine No. 440. Solvent extracts were dried over $MgSO_4$ for 5–10 min. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately prior to use.

N-Methyl-L-valine Methyl Ester Hydrochloride (**5d**).—A solution of *N*-benzyloxycarbonyl-*N*-methyl-L-valine[8] (121.7 g, 0.46 mol) in dry methanol (1.0 l) was saturated with dry hydrogen chloride and the solution was heated under reflux for 4 h. The solvent was removed under reduced pressure and the residue was taken up in water (100 ml). The aqueous solution was washed successively with chloroform (2 × 100 ml) and diethyl ether (100 ml) and evaporated under reduced pressure to yield a solid. Recrystallisation from acetone provided *N*-methyl-L-valine methyl ester hydrochloride (**5d**) (56.79 g, 68%) as white needles, m.p. 139–140 °C (lit.,[21] 140–141 °C); $[\alpha]_D^{28}$ +28.67° (*c* 0.06, EtOH) {lit., [8] $[\alpha]_D^{20}$ +17.5° (*c* 1.0, water)}.

Preparation of the Pyrrolidine-2,4-diones (**4**).—Pyrrolidine-2,4-dione (**4a**) was prepared from glycine ethyl ester hydrochloride *via* *N*-(ethoxycarbonylacetyl)glycine ethyl ester (**6a**) and ethyl 4-hydroxy-2-oxo-2,5-dihydropyrrole-3-carboxylate (**7a**) as reported.[9] The *N*-(ethoxycarbonylacetyl) derivatives (**6b–f**) were also prepared by the method of ref. 9 from the ethyl esters of *N*-methylglycine, valine, and *N*-methylvaline, the diethyl ester of glutamic acid, and the methyl ester of phenylalanine, compounds (**5b–f**) respectively. *N*-methylpyrrolidine-2,4-dione (**4b**) was prepared from amide (**6b**) as reported.[10] The 3-alkoxycarbonyl-4-hydroxy-Δ^3-pyrrolidine-2-ones (**7c–f**) were prepared from amides (**6c–f**), respectively,

with sodium ethoxide (ethanol; reflux) (**7c**, **e**, **f**) or sodium methoxide (methanol; reflux) (**7d**). 5-Isopropylpyrrolidine-2,4-dione (**4c**) was prepared from ester (**7c**) as reported.[12] Diones (**4d** and **e**) were prepared from esters (**7d** and **e**) by the method of ref. 9, (95 and 94%, respectively) and dione (**4f**) from ester (**7f**) by the method of ref. 12 (80%). *5-Isopropyl-1-methylpyrrolidine-2,4-dione* (**4d**) was isolated as a fine powder, m.p. 75–77 °C (Found: M^+, 155.0947. $C_8H_{13}NO_2$ requires M, 155.0948); $[\alpha]_D^{21}$ +4.25° (*c* 0.09, EtOH); ν_{max}(KBr) 3 410, 2 925, 1 920, 1 635, 1 550, and 1 435 cm^{-1}; δ_H($CDCl_3$) 1.0 (6 H, dd, Me_2CH), 2.25 (1 H, m, Me_2CH), 2.95 (2 H, m, CH_2CO), 3.0 (3 H, s, NMe), and 3.75 (1 H, dt, CHN); *m/z* 155 (M^+), 128, 127, 114, 113, 112 (100%), 85, and 57.

Ethyl 3-(3,5-dioxopyrrolidin-2-yl)propionate (**4e**) had m.p. 78–80 °C (Found: C, 54.4; H, 6.8; N, 6.7%; M^+, 199.0851. $C_9H_{13}NO_4$ requires C, 54.27; H, 6.58; N, 7.03%; M, 199.0857); ν_{max}($CHCl_3$) 3 450, 2 985, 1 780, 1 710, and 1 200 cm^{-1}; δ_H($CDCl_3$) 1.25 (3 H, t, $MeCH_2O$), 2.1 (2 H, m, CH_2CH), 2.45 (2 H, m, EtO_2CCH_2), 3.05 (2 H, s, CH_2CO), 4.1 (1 H, m, CHN), 4.2 (2 H, q, OCH_2Me), and 7.9 (1 H, s, NH); *m/z* 199 (M^+), 171, 154, 153 (100%), 125, 111, 84, 70, 56, and 55.

5-Benzylpyrrolidine-2,4-dione (**4f**) had m.p. 136–140 °C; ν_{max}(film) 3 350, 2 895, 1 800br, 1 650, 1 550, 1 390, 1 310, 1 230, and 1 200 cm^{-1}; δ_H[$(CD_3)_2CO$] 2.1 (2 H, m, CH_2CO), 2.75 (1 H, s, NH), 3.1 (2 H, dd, CH_2Ph), 4.4 (1 H, t, $CHCH_2Ph$), and 7.3 (5 H, s, Ph); *m/z* 189 (M^+), 161, 98, 91, and 65.

Attempted Preparation of Ethyl 4-Hydroxy-5-isopropyl-2-oxo-2,5-dihydropyrrole-3-carboxylate (**7c**) *using Sodium 1,1-Dimethylpropoxide*.—A solution of *N*-(ethoxycarbonylacetyl)-L-valine ethyl ester (**6c**) (7.00g, 27 mmol) in dry toluene (50 ml) was added to a solution of sodium 1,1-dimethylpropoxide (2.97 g, 27 mmol) in dry toluene (12.5 ml) and the mixture was stirred for 12 h. The precipitate was collected, taken up in water (100 ml), and the solution was washed with chloroform (2 × 50 ml). The aqueous phase was acidified with dil. hydrochloric acid and extracted with chloroform (3 × 50 ml), and the extracts were dried and evaporated to yield *N*-(ethoxycarbonylacetyl)-L-valine (**6g**) (1.47 g, 24%) as an oil, ν_{max}(liquid film) 3 600–2 400br, 3 300, 1 720, 1 640, 1 540, 1 200, and 1 020 cm^{-1}; δ_H($CDCl_3$) 0.9 (6 H, m, Me_2CH), 1.2 (3 H, t, $MeCH_2$), 2.1 (1 H, m, $CHMe_2$), 3.5 (2 H, s, CH_2), 4.2 (2 H, q, $MeCH_2O$), 4.6 (1 H, m, CHN), 7.9 (1 H, d, NH), and 10.5 (1 H, s, CO_2H).

To a solution of *N*-(ethoxycarbonylacetyl)-L-valine (**6g**) (1.47 g, 6.36 mmol) in diethyl ether (10 ml) was added an ethereal solution of diazomethane (33.3 mmol) and the mixture was stirred for 1 h. Evaporation of the solvent under reduced pressure yielded a gum, which was chromatographed on a silica gel column under medium pressure with methanol–chloroform (1:99 v/v) as eluant. The solution was dried and evaporated to yield *N*-(ethoxycarbonylacetyl)-L-valine methyl ester (**6h**) (0.8 g, 51%) as an oil, ν_{max}(liquid film) 3 300, 1 730, 1 660, and 1 550 cm^{-1}; δ_H($CDCl_3$) 0.95 (3 H, d, *Me*CH), 1.00 (3 H, d, *Me*CH), 1.3 (3 H, t, CH_2Me), 2.2 (1 H, m Me_2CH), 3.5 (2 H, s, CH_2CO), 3.9 (3 H, s, COMe), 4.3 (2 H, q, OCH_2Me), 4.6 (1 H, m, CHN), and 7.8 (1 H, d, NH).

4-Acetoxy-5-isopropylidene-1-methylpyrrolidine-2-one (**8a**).—To a stirred suspension of 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.5 g, 3.22 mmol) in water (50 ml) was added aqueous tetraethylammonium hydroxide (20% w/v; 2.5 ml). Once the dione had dissolved the water was evaporated off under reduced pressure and the residue was stored *in vacuo* over P_2O_5 overnight. The tetraethylammonium salt was dissolved in dry dichloromethane (25 ml) and stirred at room temperature. Acetyl chloride (0.75 ml, 9.66 mmol) was added and the mixture was stirred at room temperature for 2 days, then washed with water (20 ml), dried, and evaporated to yield the crude product. This material was chromatographed on a silica gel column and eluted with diethyl ether–hexane (3:1 v/v) to afford material that was recrystallised from hexane to yield *4-acetoxy-5-isopropylidene-1-methylpyrrolidine-2-one* (**8a**) (0.35 g, 55%) as white crystals, m.p. 64 °C (Found: C, 60.3; H, 8.0; N, 7.15%; M^+, 197.1058. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.67; N, 7.10%; M, 197.1065); λ_{max}(EtOH) 231 nm (ε 12 660); ν_{max}(Nujol) 1 730, 1 710, 1 670, 1 300, 1 275, 1 240, and 1 140 cm^{-1}; δ_H($CDCl_3$) 1.75 (3 H, s, MeC), 1.95 (3 H, s, MeC), 2.75 (3 H, s, Ac), 2.45 (1 H, d, *J* 18 Hz, CHC*H*H), 2.83 (1 H, dd, *J* 18 and 6.5 Hz, CHCH*H*), 3.30 (3 H, s, NMe), and 5.8 (1 H, d, *J* 6.5 Hz, C*H*CHH); δ_C($CDCl_3$) (with off-resonance multiplicities) 19.1, 20.9, 21.3, 31.1 (all q), 37.8 (t), 68.4 (d), 112.1, 133.3, 170.1, and 173.7 (all s); *m/z* 197 (M^+), 138, 137 (100%), 136, 122, 108, and 94.

(*E*)- and (*Z*)-4-Acetoxy-5-benzylidenepyrrolidine-2-one (**8b**) and (**8c**) were prepared from 5-benzylpyrrolidine-2,4-dione (**4f**) (0.5 g, 26 mmol) as described for compound (**8a**), by reaction with tetraethylammonium hydroxide (20% w/v; 2 ml) and acetyl chloride (0.564 ml, 7.8 mmol). The crude material was chromatographed on a silica gel column and eluted with methanol–chloroform (0.75:99.25 v/v) to yield the pure isomers. Evaporation of the appropriate fractions yielded (E)-*4-acetoxy-5-benzylidenepyrrolidine-2-one* (**8b**) (361 mg, 59%) as white crystals, m.p. 97–98 °C (from chloroform–hexane) (Found: C, 67.5; H, 5.8; N, 6.0%; M^+, 232.0892. $C_{13}H_{13}NO$ requires C, 67.52; H, 5.67; N, 6.06%; M, 231.0889); ν_{max}(Nujol) 3 250, 1 730, 1 710, 1 660, and 1 240 cm^{-1}; δ_H($CDCl_3$) 2.1 (3 H, s, Ac), 2.4* (1 H, dd, *J* 3 and 18 Hz, CHC*H*H), 2.9* (1 H, dd, *J* 8 and 18 Hz, CHCH*H*), 5.85 (1 H, dd, *J* 3 and 8 Hz, C*H*CHH), 5.82 (1 H, s, PhC*H*), 7.32 (5 H, s, CH*Ph*), and 8.70 (1 H, s, NH); *m/z* 231 (M^+), 189, 172, 171 (100%), 170, 144, and 143; and (Z)-4-*acetoxy-5-benzylidenepyrrolidine-2-one* (**8c**) (126 mg, 21%) as white crystals (recrystallisation caused isomerisation to yield a mixture *E*:*Z* 3:11), m.p. 129–131 °C (Found: M^+, 231.0900); ν_{max}(Nujol) 3 195, 1 740, 1 710, 1 678, and 1 250 cm^{-1}; δ_H(C_6D_6) 2.0 (3 H, s, Ac), 2.5* (1 H, dd, *J* 2.4 and 18 Hz, CHC*H*H), 3.05* (1 H, dd, *J* 7.8 and 18 Hz, CHCH*H*), 6.10 (1 H, dd, C*H*CHH), 6.15 (1 H, s, PhC*H*), 7.35 (5 H, m, CH*Ph*), and 8.5 (1 H, s, NH); *m/z* 231 (M^+), 189, 172, 171 (100%), 170, 144, and 143. *Signals collapse to doublets on irradiation of signals at δ 5.85 [*E*-isomer (**8b**)] or δ 6.10 [*Z*-isomer (**8c**)], respectively.

4-Acetoxy-5-isopropyl-1-methyl-1,5-dihydropyrrole-2-one (**9**).—To a stirred solution of 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.1 g, 0.65 mmol) in dry dichloromethane (5 ml) was added triethylamine (143 μl, 1.04 mmol) followed by acetyl chloride (45 μl, 0.65 mmol), and the mixture was heated under reflux for 6 h. The cooled reaction mixture was then washed with water, dried, and evaporated to yield *4-acetoxy-5-isopropyl-1-methyl-1,5-dihydropyrrole-2-one* (**19**) (108.9 mg, 87%) as a red oil (Found: M^+, 197.1055. $C_{10}H_{15}NO_3$ requires M, 197.1058); δ_H($CDCl_3$) 1.0 (6 H, dd, Me_2CH), 2.3 (3 H, s, AcO), 2.38 (1 H, m, Me_2CH), 2.95 (3 H, s, MeN), 4.00 (1 H, d, CHN), and 6.10 (1 H, s, C=CHCO); *m/z* 197 (M^+), 156, 155, 154, 113, 112 (100%), 86, 84, and 70.

3-Acetyl-5-isopropyltetramic Acid (**10a**).—To a stirred solution of 5-isopropylpyrrolidine-2,4-dione (**4c**) (100 mg, 0.7 mmol) in boron trifluoride–diethyl ether (5 ml) was added acetyl chloride (151 μl, 2.1 mmol) and the mixture was heated on an oil-bath (bath temperature 75 °C) for 8 h. After this time further acetyl chloride (50 μl, 0.7 mmol) was added and the mixture was heated for a further 2.5 h at the same

temperature. The cooled reaction mixture was then treated with water (10 ml) and extracted with ethyl acetate (3 × 15 ml). The organic phase was extracted with aqueous sodium hydroxide (5% w/v; 2 × 10 ml) and the combined aqueous layers were washed with chloroform (2 × 10 ml). The aqueous phase was acidified with conc. hydrochloric acid and extracted with chloroform (3 × 10 ml). The chloroform extract was dried, and evaporated under reduced pressure to yield a gum. The product was crystallised from light petroleum (b.p. range 40–60 °C) to yield 3-acetyl-5-isopropyltetramic acid (**10a**) (90.4 mg, 70%) as crystals, m.p. 75–76 °C (lit.,[22] 74–75 °C) (Found: M^+, 183.0900. Calc. for $C_9H_{13}NO_3$: M, 183.0904); λ_{max}(EtOH) 277 nm (16 470); ν_{max}(KBr) 3 250, 3 000, 1 710, 1 660, 1 620, 1 400, and 1 240 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, d, *Me*CH), 1.1 (3 H, d, *Me*CH), 2.1 (1 H, m, MeC*H*), 2.5 (3 H, s, Ac), 3.84 (1 H, s, C*H*NH), 7.80 (1 H, s, NH), and 12.0 (1 H, s, OH); $\delta_C(CDCl_3)$ 15.0, 16.3, 19.1, 19.3, 19.4, 19.5, 20.6, 30.2, 30.3, 64.3, 67.5, 102.3, 105.6, 169.7, 175.7, 184.6, 189.0, 195.4, 200.9, and 229.7; *m/z* 183 (M^+), 168, 141 (100%), 140, 123, 98, 84, and 72.

3-Acetyl-5-isopropyl-1-methyltetramic acid (**10b**) was prepared as described for compound (**10a**) except that acetyl chloride (140μl, 1.86 mmol) was used at 75 °C (oil-bath temperature) for 8.5 h, to yield 3-acetyl-5-isopropyl-1-methyltetramic acid (**10b**) (57.7 mg, 45%) as a red oil, identical with a sample prepared *via* the boron difluoride complex (see below).

3-Heptanoyl-5-isopropyl-1-methyltetramic acid (**10c**).—To a stirred solution of 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (100 mg, 0.62 mmol) in nitromethane (5 ml) was added titanium tetrachloride (0.35 ml) followed by heptanoyl chloride (0.3 ml, 1.86 mmol) and the mixture was heated on an oil-bath (bath temperature 75 °C) for 1 h. The cooled reaction mixture was then treated with water (10 ml) and the mixture was extracted with chloroform (3 × 15 ml). The extracts were dried and evaporated to yield an oil, which was chromatographed on a silica gel column under medium pressure and eluted with methanol–chloroform (2:98 v/v). Evaporation of the appropriate fractions yielded 3-heptanoyl-5-isopropyl-1-methyltetramic acid (**10c**) (53 mg, 31%) as an oil, identical with a sample prepared *via* the boron difluoride complex (see below).

3-(But-2-enoyl)-5-isopropyl-1-methyltetramic acid (**10d**) was prepared as described for compound (**10c**) except that but-2-enoyl chloride (186 μl, 1.86 mmol) was used. The mixture was cooled, diluted with ethyl acetate (20 ml), and treated with brine (20 ml). The mixture was extracted with ethyl acetate (2 × 10 ml) and the combined organic phases were washed with water (2 × 10 ml), dried, and evaporated to yield a gum, which was chromatographed on a silica gel column under medium pressure and eluted with methanol–chloroform (3:97 v/v). The product was taken up in aq. sodium hydroxide (5% w/v; 10 ml) and washed with ethyl acetate (2 × 10 ml). The aqueous phase was acidified with dil. hydrochloric acid and the product was extracted into chloroform (3 × 10 ml). The organic phase was dried and evaporated to yield 3-(but-2-enoyl)-5-isopropyl-1-methyltetramic acid (**10d**) (86 mg, 60%) as a brown oil, identical with a sample prepared *via* the boron difluoride complex (see later).

5-Isopropyl-1-methyl-3-(3-methylbut-2-enoyl)tetramic acid (**10e**) was prepared as described for compound (**10c**) except that 3-methylbut-2-enoyl chloride (215 μl, 1.86 mmol) was used. The mixture was cooled, diluted with ethyl acetate (10 ml), and treated with brine (10 ml). The organic phase was extracted with aq. sodium hydroxide (5% w/v; 2 × 10 ml) and the combined aqueous phases were washed with ethyl acetate (2 × 10 ml). The aqueous phase was acidified with dil. hydrochloric acid and the product was extracted into chloroform (3 × 10 ml). The organic phase was dried and evaporated to yield 5-isopropyl-1-methyl-3-(3-methylbut-2-enoyl)tetramic acid (**10e**) (317 mg, 21%) as an oil, identical with a sample prepared *via* the boron difluoride complex (see later).

3-Acetyl-5-benzyltetramic acid (**10f**) was prepared as described for compound (**10a**), from 5-benzylpyrrolidine-2,4-dione (**4f**) (330 mg, 1.75 mmol) in boron trifluoride–diethyl ether (5 ml) with acetyl chloride (124 μl, 1.59 mmol) at 110 °C (oil-bath temperature) for 8 h. Work-up as before and recrystallisation from methanol yielded 3-acetyl-5-benzyltetramic acid (**10f**) (220 mg, 55%) as yellow plates, m.p. 148–153 °C (lit.,[22] 151–151.5 °C); ν_{max}(KBr) 3 150, 1 710, 1 640, and 1 610 cm^{-1}; $\delta_H(CDCl_3)$ 2.5 (3 H, s, Ac), 2.7 (1 H, dd, C*H*HPh), 3.3 (1 H, dd, CH*H*Ph), 4.1 (1 H, dd, C*H*NH), 7.1 (1 H, br s, NH), 7.3 (5 H, m, Ph), and 12.2 (1 H, br s, OH).

5-Benzyl-3-heptanoyltetramic acid (**10g**) was prepared as for compound (**10a**), from 5-benzylpyrrolidine-2,4-dione (**4f**) (100 mg, 0.53 mmol) in boron trifluoride–diethyl ether (5 ml) with heptanoyl chloride (0.245 ml, 1.59 mmol) at 110 °C (oil-bath temperature) for 2.5 h. Work-up as before and crystallisation from methanol afforded *3-heptanoyl-5-benzyltetramic acid* (**10g**) (260 mg, 63%) as plates, m.p. 114–115 °C (Found: C, 71.5; H, 7.55; N, 4.6. $C_{28}H_{23}NO_3$ requires C, 71.76; H, 7.64; N, 4.65%); ν_{max}(KBr) 3 200, 1 710, 1 640, and 1 610 cm^{-1}; λ_{max}(EtOH) 244 (8 500) and 279 nm (14 500) [in 0.01M-ethanolic KOH: 240 (14 500) and 279 nm (18 150); in 0.01M-ethanolic H_2SO_4: 280 nm (13 300)]; $\delta_H(CDCl_3)$ 0.9 (3 H, m, *Me*CH_2), 1.4–1.7 [8 H, m, $CH_2[CH_2]_4Me$], 2.8 (3 H, m, $COCH_2$ and C*H*HPh), 3.2 (1 H, dd, CH*H*Ph), 4.0 (1 H, dd, C*H*NH), 6.6 (1 H, br s, NH), 7.3 (5 H, m, Ph), and 11.9 (1 H, br s, OH); *m/z* 301 (M^+).

5-Benzyl-3-(but-2-enoyl)tetramic Acid (**10h**).—To a stirred suspension of 5-benzylpyrrolidine-2,4-dione (**4f**) (100 mg, 0.53 mmol) in dry nitrobenzene (5 ml) were added but-2-enoyl chloride (55 μl, 0.53 mmol) and titanium tetrachloride (0.3 ml), and the mixture was heated at 50–55 °C (oil-bath temperature) for 1 h, at which time further but-2-enoyl chloride (55 μl) was added. After a further 1 h at 50–55 °C the mixture was cooled and poured onto ice containing conc. hydrochloric acid. The mixture was extracted with chloroform and the chloroform solution was extracted with aq. sodium hydroxide (5% w/v). The basic extracts were acidified (conc. hydrochloric acid) and extracted with chloroform, and the extract was washed with water, dried, and evaporated under reduced pressure to leave a solid residue. Crystallisation from ethanol yielded *5-benzyl-3-(but-2-enoyl)tetramic acid* (**10h**) (70 mg, 52%) as yellow needles, m.p. 220–224 °C (Found: C, 69.7; H, 6.1; N, 5.4. $C_{15}H_{15}HO_3$ requires C, 70.03; H, 5.83; N, 5.44%); ν_{max}(KBr) 3 200, 1 700, 1 660, 1 640, and 1 590 cm^{-1}; λ_{max}(EtOH) 234 (11 300) and 316 nm (17 200) [in 0.01M-ethanolic KOH: 241 (16 700) and 313 nm (17 200); in 0.01M-methanolic H_2SO_4: 226 (10 700) and 318 nm (18 650)]; $\delta_H(CDCl_3)$ 2.0 (3 H, d, Me), 2.6 (1 H, dd, C*H*HPh), 3.2 (1 H, dd, CH*H*Ph), 3.9 (1 H, dd, C*H*NH), 6.4 (1 H, br s, NH), 7.2 (7 H, m, CH=CH and Ph), and 11.9 (1 H, br s, OH); *m/z* 257 (M^+).

5-Benzyl-3-(hexa-2,4-dienoyl)tetramic acid (**10i**) was prepared as for compound (**10a**), from 5-benzylpyrrolidine-2,4-dione (**4f**) (100 mg, 0.53 mmol) in boron trifluoride–diethyl ether (5 ml) with hexa-2,4-dienoyl chloride (194 μl, 1.59 mmol) at 100 °C (oil-bath temperature) for 2.5 h. Work-up as before and crystallisation from ethanol gave *5-benzyl-3-(hexa-2,4-dienoyl)tetramic acid* (**10i**) (50 mg, 33%) as yellow plates, m.p. 190–197 °C (Found: C, 71.9; H, 5.8; N, 5.2. $C_{17}H_{17}NO_3$ requires C, 72.06; H, 6.04; N, 4.94%); ν_{max}(KBr) 3 150, 1 690, 1 650, 1 620, and 1 560 cm^{-1}; λ_{max}(EtOH) 238 (8 500) and 355

nm (30 100) [in 0.1M-ethanolic KOH: 258 (17 200), 283 (18 550), and 333 nm (20 300); in 0.01M-ethanolic H_2SO_4: 354 (30 500) and 386sh nm (26 500)]; $\delta_H(CDCl_3)$ 2.0 (3 H, d, Me), 2.7 (1 H, dd, C*H*HPh), 3.3 (1 H, dd, CH*H*Ph), 4.1 (1 H, dd, C*H*NH), 6.3 (1 H, br s, NH), 6.4 (2 H, m, MeC*H*=C*H*), and 7.3 (8 H, m, COCH=CH, OH, and Ph); *m/z* 283 (M^+).

3-Acetyl-5-(2-carboxyethyl)tetramic acid (**10j**) was prepared as described for compound (**10a**), from *ethyl* 3-(3,5-*dioxopyrrolidin*-2-*yl*)*propionate* (**4e**) (160 mg, 0.8 mmol) in boron trifluoride–diethyl ether (7 ml) with acetyl chloride (166 μl, 2.4 mmol) at 80 °C (oil-bath temperature) for 1 h. After this time further acetyl chloride (0.166 ml, 2.4 mmol) was added and the mixture was heated overnight on the oil-bath (bath temperature 90 °C). The cooled reaction mixture was then treated with water (15 ml) and extracted with ethyl acetate (3 × 20 ml). The organic extract was dried and evaporated, the residue was taken up in methanol (20 ml), and the solution was refluxed for 1 h. The methanol was evaporated off and the residue was taken up in aq. sodium hydroxide (5% w/v; 20 ml) and washed with ethyl acetate (3 × 20 ml). The aqueous phase was acidified with conc. hydrochloric acid and extracted with chloroform (3 × 20 ml). The extract was dried, and evaporated under reduced pressure to yield 3-*acetyl*-5-(2-*carboxyethyl*)*tetramic acid* (**10j**) (0.032 g, 19%) as a crystalline solid, m.p. 129–133 °C (Found: MH^+, 214.0723. $C_9H_{11}NO_5$ requires *MH*, 214.0730); $\nu_{max}(CHCl_3)$ 3 600–2 955br, 3 050, 2 450, 1 720, 1 680, 1 640, and 1 540 cm^{-1}; $\delta_H(CD_3OD)$ 2.0 (4 H, m, CH_2CH_2), 2.45 (3 H, s, Ac), 4.0 (1 H, t, C*H*CH_2), and 4.90 (3 H, s, NH and 2 × OH); *m/z* 214 (MH^+), 198, 197, 196, 195, 168, 126, 124, 112, 85, and 84 (100%).

Acylation of Pyrrolidine-2,4-diones (**4**) *to give Boron Difluoride Complexes* (**11**).—3-[1-(*Difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11a**). To a stirred solution of 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (2.2 g, 14.2 mmol) in boron trifluoride–diethyl ether (65 ml) was added acetyl chloride (2.93 ml, 42.6 mmol), and the mixture was heated on an oil-bath (bath temperature 80 °C) for 4 h. After this time further acetyl chloride (1.95 ml, 21.3 mmol) was added and the mixture was heated for a further 4 h at the same temperature. The cooled reaction mixture was then treated with saturated aq. ammonium chloride (150 ml). The mixture was immediately extracted with ethyl acetate (3 × 75 ml), and the extracts were dried and evaporated to yield a red oil, which was chromatographed on a silica gel column, under medium pressure, and eluted with methanol–chloroform (1:99 v/v). The product was recrystallised from chloroform–hexane to yield 3-[1-(*difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11a**) (2.5 g, 71%) as white triclinic needles, m.p. 101–102 °C (Found: C, 49.2; H, 5.9; N, 5.8%; M^+, 245.1063. $C_{10}H_{14}BF_2NO_3$ requires C, 49.02; H, 5.76; N, 5.72%; *M*, 245.1092); λ_{max}(EtOH) 235 nm (5 900) and 281 (13 560); ν_{max}(Nujol) 2 950, 1 725, 1 650, 1 595, 1 530, 1 180, and 1 020 cm^{-1}; $\delta_H(CDCl_3)$ 0.95 (3 H, d, *Me*CH), 1.175 (3 H, d, *Me*CH), 2.35 (1 H, m, C*H*CHN), 2.53 (3 H, s, MeCO), 3.22 (3 H, s, NH), and 3.85 (1 H, d, CHN); *m/z* 245 (M^+), 203 (100%), 202, 183, 160, 159, and 137.

3-[1-(Difluoroboryloxy)heptylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11b**) was prepared by the method used for complex (**11a**), from 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.1 g, 0.645 mmol) in boron trifluoride–diethyl ether (5 ml) with heptanoyl chloride (0.3 mmol) at 90 °C (oil-bath temperature) for 6.5 h. Further heptanoyl chloride (0.1 ml, 0.645 mmol) was then added and the mixture was heated for a further 2.5 h. The cooled reaction mixture was then treated with water (10 ml), extracted with ethyl acetate (3 × 15 ml), and the extracts were dried and evaporated to yield a gum, which was chromatographed on a silica gel column under medium pressure and eluted with cyclohexane–ethyl acetate (1:4 v/v). The product was taken up in chloroform (50 ml) and the solution was washed with saturated aq. sodium hydrogen carbonate (1 × 10 ml), dried, and evaporated. The product was recrystallised from chloroform–hexane to yield 3-[1-(*difluoroboryloxy*)*heptylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11b**) (144 mg, 71%) as white crystals, m.p. 74–75 °C (Found: C, 57.4; H, 8.0; N, 4.3%; M^+, 315.1788. $C_{15}H_{24}BF_2NO_3$ requires C, 57.17; H, 7.68; N, 4.44%; *M*, 315.1761); λ_{max} 236 (5 775) and 282 nm (15 440); ν_{max}(Nujol) 1 720, 1 660, 1 580, and 1 540 cm^{-1}; $\delta_H(CDCl_3)$ 1.0 (6 H, dd, (Me_2CH), 1.5 (11 H, m, $[CH_2]_4$Me), 2.35 (1 H, m, C*H*Me_2), 2.8 (2 H, t, C$H_2[CH_2]_4$), 3.15 (3 H, s, NMe), and 3.75 (1 H, d, NCH); *m/z* 315 (M^+), 296, 273, 272, 258, 245 (100%), 203, and 160.

3-[1-(Difluoroboryloxy)but-2-enylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11c**) was prepared by the method used for complex (**11a**), from 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.1 g, 0.645 mmol) in boron trifluoride–diethyl ether (5 ml) with but-2-enoyl chloride (186 μl, 1.93 mmol) at 80 °C (oil-bath temperature) for 5.5 h. The cooled reaction mixture was then treated with water (10 ml), extracted with chloroform (3 × 15 ml), and the extracts were dried and evaporated to yield a gum, which was chromatographed on a silica gel column under medium pressure and eluted with chloroform. The product was recrystallised from chloroform–hexane to yield 3-[1-(*difluoroboryloxy*)*but*-2-*enylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11c**) (0.136 g, 78%) as white crystals, m.p. 123–124 °C (Found: C, 52.7; H, 6.0; N, 5.0%; M^+, 271.1170. $C_{12}H_{16}BF_2NO_3$ requires C, 53.17; H, 5.95; N, 5.17%; *M*, 271.1151); λ_{max} 230 (11 795) and 322.5 nm (17 075); ν_{max}(Nujol) 1 730, 1 650, 1 560, 1 525, and 1 185 cm^{-1}; $\delta_H(CDCl_3)$ 0.95 (3 H, d, *Me*CH), 1.15 (3 H, d, *Me*CH), 2.05 (3 H, d, *Me*CH=), 2.35 (1 H, m, C*H*Me_2), 3.15 (3 H, s, NMe), 3.75 (1 H, d, CHN), 7.02 (1 H, d, COC*H*=CHMe), and 7.4 (1 H, dq, MeC*H*=CH); *m/z* 271 (M^+), 252, 229, 228, 209, 187, 158, 134, and 69 (100%).

3-(1-Difluoroboryloxy-3-methylbut-2-enylidene)-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11d**) was prepared by the method used for complex (**11a**), from 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.1 g, 0.645 mmol) in boron trifluoride–diethyl ether (5 ml) with 3-methylbut-2-enoyl chloride (215 μl, 1.93 mmol) at 80 °C (oil-bath temperature) for 7 h. The cooled reaction mixture was worked up as for complex (**11c**) to yield a gum, which was chromatographed on a silica gel column under medium pressure and eluted with ethyl acetate–cyclohexane (1:3 v/v). The product was collected and chromatographed on a second silica gel column under medium pressure, eluted with chloroform, and then recrystallised from chloroform–hexane to yield 3-(1-*difluoroboroyloxy*-3-*methylbut*-2-*enylidene*)-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11d**) (123 mg, 67%) as white crystals, m.p. 137–138 °C (Found: C, 55.0; H, 6.4; N, 4.8%; M^+, 285.1346. $C_{13}H_{18}BF_2NO_3$ requires C, 54.77; H, 6.36; N, 4.91%; *M*, 285.1345); λ_{max}(336) (18 660) and 247 nm (8 570); $\nu_{max}(CHCl_3)$ 3 050, 2 995, 1 700, 1 640, 1 530, 1 375, 1 035, and 907 cm^{-1}; $\delta_H(CDCl_3)$ 0.95 (3 H, d, *Me*CH), 1.15 (3 H, d, *Me*CH), 2.1 (3 H, s, CH=C*Me*), 2.35 (3 H, s, CH=C*Me*), 2.30 (1 H, m, C*H*Me_2), 3.12 (3 H, s, NMe), 3.70 (1 H, d, CHN), and 6.9 (1 H, s, C*H*=CMe_2); *m/z* 285 (M^+), 243, 242, 187, 83 (100%), 55, 43, and 42.

3-[1-(Difluoroboryloxy)hexa-2,4-dienylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11e**) was prepared by the method used for complex (**11a**), from 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (1 g, 6.45 mmol) in boron trifluoride–diethyl ether (30 ml) with hexa-2,4-dienoyl chloride (3.2 ml, 25.8 mmol) at 80 °C (oil-bath temperature) for 45 min. The cooled reaction mixture was worked up and chromatographed

twice on silica, as for complex (**11d**). Evaporation of the appropriate fractions yielded 3-[1-(*difluoroboryloxy*)*hexa*-2,4-*dienylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11e**) (0.98 g, 51%) as a gum (Found: M^+, 297.1371. $C_{14}H_{18}BF_2NO_3$ requires M, 297.1396); λ_{max}(357) (25 850) and 242 nm (7 850); ν_{max}(liquid film) 2 995, 1 710, 1 640, 1 610, 1 540, 1 510, and 1 030 cm^{-1}; $\delta_H(CDCl_3)$ 0.95 (3 H, d, *Me*CH), 1.15 (3 H, d, *Me*CH), 1.95 (3 H, d, CH=CH*Me*), 2.35 (1 H, m, Me_2CH), 3.15 (3 H, s, NMe), 3.75 (1 H, d, CHN), 6.3–6.5 (2 H, m, C*H*=C*H*Me), 6.9 (1 H, d, COC*H*=CH), and 7.7 (1 H, dm, COCH=C*H*); *m*/*z* 297 (M^+), 296, 255, 254, 230, 187, 95 (100%), 67, and 42.

3-[α-(Difluoroboryloxy)benzylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11f**) was prepared by the method used for complex (**11a**), from 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (0.50 g, 3.22 mmol) in boron trifluoride–diethyl ether (15 ml) with benzoyl chloride (1.5 ml, 12.88 mmol) at 85 °C (oil-bath temperature) for 5 h. Further benzoyl chloride (1.5 ml, 12.88 mmol) was then added and the mixture was heated for a further 16 h, and was then worked up and chromatographed twice on silica, as for complex (**11d**); the first column was eluted with chloroform and the second with ethyl acetate–cyclohexane (4:1 v/v). The product was recrystallised from chloroform–hexane to yield 3-[α-(*difluoroboryloxy*)*benzylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11f**) (0.483 g, 50%) as white crystals, m.p. 148–149 °C (Found: C, 58.8; H, 5.4; N, 4.5%; M^+, 307.1182. $C_{15}H_{16}BF_2NO_3$ requires C, 58.67; H, 5.25; N, 4.56%; M, 307.1191); λ_{max} 240 (12 790) and 324 nm (23 195); $\nu_{max}(CHCl_3)$ 2 995, 1 720, 1 700, 1 640, 1 520, 1 495, and 1 040 cm^{-1}; $\delta_H(CDCl_3)$ 1.0 (6 H, dd, Me_2CH), 2.4 (1 H, m, C*H*Me_2), 3.3 (3 H, s, NMe), 3.68 (1 H, d, NCH), 7.6 (3 H, m, Ph), and 8.4 (2 H, m, Ph); *m*/*z* 307 (M^+), 364, 345, and 205 (100%).

Conversion of Boron Difluoride Complexes (**11**) *into* 3-*Acyltetramic Acids* (**10**).—3-*Acetyl*-5-*isopropyl*-1-*methyltetramic acid* (**10b**). A stirred solution of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11a**) (55.7 mg, 0.28 mmol) in methanol (10 ml) was heated under reflux for 2 h. The cooled reaction mixture was diluted with ethyl acetate (10 ml) and the methanol was evaporated off under reduced pressure. The residue was washed with water (10 ml), dried, and evaporated to yield 3-*acetyl*-5-*isopropyl*-1-*methyltetramic acid* (**10b**) (41.7 mg, 93%) as a red oil (Found: M^+, 197.1062. $C_{10}H_{15}NO_3$ requires M, 197.1052); ν_{max}(film) 3 500, 2 995, 2 885, 1 700, 1 660, 1 620, 1 490, 1 460, 1 380, 1 320, 1 260, and 1 230 cm^{-1}; λ_{max} 279 nm (12 600); $\delta_H(CDCl_3)$ 1.0 (6 H, dd, Me_2CH), 2.25 (1 H, m, C*H*Me_2), 2.45 (3 H, d, Ac), 2.95 (3 H, d, NMe), 3.6 (1 H, dd, CHN), and 12.8 (1 H, s, OH); $\delta_C(CDCl_3)$ 16.5, 17.2, 17.3, 17.6, 19.4, 20.1, 27.32, 28.9, 29.1, 68.5, 71.5, 102.5, 105.9, 167.1, 173.4, 183, 187.2, 194.3, and 200.3; *m*/*z* 197 (M^+), 155, 154 (100%), and 112.

3-Heptanoyl-5-isopropyl-1-methyltetramic acid (**10c**) was prepared as described for compound (**10b**), from 3-[1-(difluoroboryloxy)heptylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11b**) (54 mg, 0.2 mmol) in methanol (10 ml) at reflux for 40 min to yield 3-*heptanoyl*-5-*isopropyl*-1-*methyltetramic acid* (**10e**) (43 mg, 94%) as an oil (Found: M^+, 267.1823. $C_{15}H_{25}NO_3$ requires M, 267.1814); $\nu_{max}(CHCl_3)$ 2 995, 2 885, 1 705, 1 640, 1 615, and 1 460 cm^{-1}; λ_{max} 220 (6 570) and 282 nm (11 860); $\delta_H(CDCl_3)$ 0.9 (3 H, d, *Me*CH), 1.0 (3 H, d, *Me*CH), 1.3–1.8 (11 H, m, $[CH_2]_4Me$), 2.45 (1 H, m, C*H*Me_2), 2.8 (2 H, t, $COCH_2$), 2.95 (3 H, d, NMe), 3.6 (1 H, dd, CHN), and 11.3 (1 H, s, OH); *m*/*z* 267 (M^+), 266, 224 (100%), 210, 197, 182, 155, 154, 140, 112, 85, 69, and 55.

3-(But-2-enoyl)-5-isopropyl-1-methyltetramic acid (**10d**) was prepared as described for compound (**10b**), from 3-[1-(difluoroboryloxy)but-2-enylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11c**) (8.5 mg, 0.03 mmol) in methanol (2.5 ml) at reflux for 1 h to yield 3-(*but*-2-*enoyl*)-5-*isopropyl*-1-*methyltetramic acid* (**10d**) (6 mg, 87%) as a brown oil (Found: M^+, 223.1217. $C_{12}H_{17}NO_3$ requires M, 223.1227); $\nu_{max}(CHCl_3)$ 3 600, 2 995, 1 700, 1 645, 1 585, 1 480, 1 475, and 1 400 cm^{-1}; λ_{max} 230 (10 700) and 322 nm (15 860); $\delta_H(CDCl_3)$ 1.0 (6 H, dd, Me_2CH), 2.05 (3 H, d, *Me*CH=CH), 2.4 (1 H, m, C*H*Me_2), 3.0 (3 H, s, NMe), 3.6 (1 H, dd, CHN), 7.2 (1 H, d, C*H*=CHMe), 7.3 (1 H, m, CH=C*H*Me), and 12.9 (1 H, br s, OH); *m*/*z* 223 (M^+), 181, 180 (100%), 139, 138, 86, and 69.

5-*Isopropyl*-1-*methyl*-3-(3-*methylbut*-2-*enoyl*)*tetramic acid* (**10e**) was prepared as described for compound (**10b**), from 3-(1-difluoroboryloxy-3-methylbut-2-enylidene)-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11d**) (93.6 mg, 0.39 mmol) in methanol (10 ml) at reflux for 3 h to afford 5-*isopropyl*-1-*methyl*-3-(3-*methylbut*-2-*enoyl*)*tetramic acid* (**10e**) (71.1 mg, 92%) as a brown oil (Found: M^+, 237.1369. $C_{13}H_{19}NO_3$ requires M, 237.1375); $\nu_{max}(CHCl_3)$ 2 990, 1 695, 1 630, 1 575, 1 480, 1 475, 1 440, 1 400, and 1 380 cm^{-1}; λ_{max} 238 (7 290) and 330 nm (12 910); $\delta_H(CDCl_3)$ 0.9 (3 H, d, *Me*CH), 1.0 (3 H, d, *Me*CH), 2.05 (3 H, s, CH=C*Me*), 2.2 (1 H, m, C*H*Me_2), 2.3 (3 H, s, CH=C*Me*), 3.0 (3 H, d, MeN), 3.6 (1 H, dd, CHN), 7.0 (1 H, d, C*H*CHMe_2), and 12.5 (1 H, br s, OH); *m*/*z* 237 (M^+), 194, 182, 166, 139, 138 (100%), 83, and 73.

3-(Hexa-2,4-dienoyl)-5-isopropyl-1-methyltetramic acid (**10k**) was prepared as described for compound (**10b**), from 3-[1-(difluoroboryloxy)hexa-2,4-dienylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11e**) (83.8 mg, 0.33 mmol) in methanol (10 ml) at reflux for 1 h. The cooled reaction mixture was diluted with ethyl acetate (10 ml) and the methanol was evaporated off under reduced pressure. The residue was extracted with aq. sodium hydroxide (5% w/v; 2 × 10 ml) and the aq. phase was washed with chloroform (2 × 10 ml), acidified with dil. hydrochloric acid, and extracted with chloroform. The extract was washed with water (10 ml), dried, and evaporated to yield 3-(*hexa*-2,4-*dienoyl*)-5-*isopropyl*-1-*methyltetramic acid* (**10k**) (55.3 mg, 80%) as a yellow crystalline solid below room temperature, m.p. 5–10 °C (Found: M^+, 249.1366. $C_{14}H_{19}NO_3$ requires M, 249.1367); $\nu_{max}(CHCl_3)$ 3 400, 2 995, 1 700, 1 625, 1 575, 1 445, 1 000, and 600 cm^{-1}; λ_{max} 241 (7 500) and 355 nm (25 500); $\delta_H(CDCl_3)$ 0.95 (3 H, dd, *Me*CH), 1.15 (3 H, dd, *Me*CH), 1.9 (3 H, d, CH=CH*Me*), 2.35 (1 H, m, C*H*Me_2), 2.95 (3 H, d, NMe), 3.60 (1 H, dd, CHN), 6.25 (1 H, d, CHCHC*H*CHMe), 6.30 (1 H, d, C*H*Me), 7.05 (1 H, d, COCH), 7.30 (1 H, m, COCHC*H*), and 12.0 (1 H, s, OH); *m*/*z* 249 (M^+), 234, 208, 207, 206, 182, 162, 139, 138 (100%), 112, 95, 94, 86, 57, and 41.

3-Benzoyl-5-isopropyl-1-methyltetramic acid (**10l**) was prepared as described for compound (**10b**), from 3-[α-(difluoroboryloxy)benzylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11f**) (50 mg, 0.19 mmol) in methanol (10 ml) at reflux for 2 h to afford 3-*benzoyl*-5-*isopropyl*-1-*methyltetramic acid* (**10l**) (34.2 mg; 82%) as an oil (Found: M^+, 259.1202. $C_{15}H_{17}NO_3$ requires M, 259.1196); ν_{max}(film) 3 600, 3 100, 3 000, 1 730, 1 650, 1 620, 1 500, and 1 420 cm^{-1}; λ_{max} 217 (14 400) and 296 nm (16 350); $\delta_H(CDCl_3)$ 1.0 (6 H, dd, Me_2CH), 2.35 (1 H, m, C*H*Me_2), 3.0 (3 H, s, MeN), 3.6 (1 H, dd, CHN), 7.6–8.25 (5 H, m, Ph), and 12.0 (1 H, s, OH); *m*/*z* 259 (M^+), 217, 216 (100%), 139, 138, 122, 105, and 77.

Attempted Acylation of 5-*Isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**4d**) *with Diethoxyphosphorylacetyl Chloride: Preparation of* 4-*Ethoxy*-5-*isopropyl*-1-*methyl*-1,5-*dihydropyrrol*-2-*one* (**13**).—A solution of 5-isopropyl-1-methylpyrrolidine-2,4-dione (**4d**) (100 mg, 0.65 mmol) in boron trifluoride–diethyl ether (5 ml) was added to diethoxyphosphorylacetyl chloride (0.4 g, 3 mol equiv.; prepared from diethoxyphosphorylacetic acid[23] and thionyl chloride) and the mixture was stirred in an oil-bath

(bath temperature 100 °C) for 5 days. The cooled reaction mixture was then treated with water (10 ml). The mixture was extracted with chloroform (3 × 15 ml) and the extracts were dried and evaporated to yield an oil, which was chromatographed on a silica gel column under medium pressure and eluted with cyclohexane–ethyl acetate (3:1 v/v). The product was immediately chromatographed on a second silica gel column and eluted with methanol–chloroform (5:95 v/v). Evaporation of the appropriate fractions yielded 4-*ethoxy*-5-*isopropyl*-1-*methyl*-1,5-*dihydropyrrol*-2-*one* (**13**) (57 mg, 48%) as an oil (Found: M^+, 183.1260. $C_{10}H_{17}NO_2$ requires M, 183.1262); ν_{max}($CHCl_3$) 3 300, 1 660, 1 620, 1 415, 1 390, 1 360, 1 335, and 1 025 cm^{-1}; δ_H($CDCl_3$) 1.0 (6 H, dd, Me_2CH), 1.38 (3 H, t, OCH_2Me), 2.15 (1 H, m, $CHMe_2$), 2.87 (3 H, s, NMe), 3.70 (1 H, d, CHN), 3.95 (2 H, q, OCH_2Me), and 5.00 (1 H, s, OCCHCO); *m/z* 183 (M^+), 141, 140 (100%), 112, and 83. Some starting dione (**4d**) (29 mg, 29%) was also recovered.

Monodeuteriation of 3-[1-(*Difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11a**).—To a stirred solution of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11a**) (0.1 g, 0.408 mol) in dry THF (5 ml) at −78 °C under nitrogen was added LDA (2.35 ml of a 0.19M solution in THF–hexanes, 0.45 mmol) and the mixture was stirred for 0.5 h. To the mixture was added deuterium oxide (4.5 ml) and the solution was allowed to warm up to room temperature. The aqueous solution was then extracted with chloroform (3 × 20 ml) and the extract was dried and evaporated to yield the *monodeuterio product* (**11g**) (49.5 mg, 50%) as white crystals, m.p. 102 °C (Found: M^+, 246.1086. $C_{10}H_{13}BDF_2NO_3$ requires M, 246.1097); ν_{max}(Nujol) 2 950, 1 725, 1 640, 1 590, 1 540, and 1 180 cm^{-1}; δ_H($CDCl_3$) 1.10 (6 H, dd, Me_2CH), 2.4 (1 H, m, $CHMe_2$), 2.5 (2 H, m, CH_2D), 3.2 (3 H, s, NMe), and 3.8 (1 H, d, NCH); *m/z* 246 (M^+), 226, 204 (100%), and 183.

3-[1-(*Difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1,5-*dimethylpyrrolidine*-2,4-*dione* (**11h**).—To a stirred solution of 3-[1-(difluoroboryloxy)ethylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11a**) (0.2 g, 0.816 mmol) in dry THF (10 ml) at − 78 °C under nitrogen was added LDA (5.33 ml of a 0.34M solution in THF–hexanes, 1.79 mmol) and the mixture was stirred for 0.5 h. To the mixture was added iodomethane (0.5 ml, 10 mol equiv.) and the solution was stirred for a further 5 h at −78 °C. After this time the reaction mixture was allowed to warm up slowly and was stirred overnight at room temperature. The reaction mixture was then treated with saturated aq. ammonium chloride (20 ml) and extracted with ethyl acetate (3 × 20 ml). The extract was dried and evaporated to yield a red oil, which was chromatographed on a silica gel column under medium pressure and eluted with chloroform. The product was recrystallised from chloroform–hexane to yield 3-[1-(*difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1,5-*dimethylpyrrolidine*-2,4-*dione* (**11h**) (50 mg, 25%) as white crystals, m.p. 110–112 °C (Found: M^+, 259.1190. $C_{11}H_{16}BF_2NO_3$ requires M, 259.1191); ν_{max}(Nujol) 3 050, 2 885, 1 700, 1 660, and 1 490 cm^{-1}; δ_H($CDCl_3$) 1.0 (6 H, dd, Me_2CH), 1.4 (3 H, s, MeC), 2.1 (1 H, m, $CHMe_2$), 2.54 (3 H, s, MeCO), and 3.1 (3 H, s, NMe); δ_C($CDCl_3$) (with off-resonance multiplicities) 16.1, 16.8, 18.9, 20.9, and 25.8 (all q), 33.5 (d), 76.5, 99.6, 170.5, 185.2, and 193.3 (all s); *m/z* 259 (M^+), 240, 218, 217, 216 (100%), 215, 197, 174, 173, 154, and 56.

3-[α-(*Difluoroboryloxy*)*benzylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11f**) *from the Tetramic Acid* (**10l**).—To a solution of 3-benzoyl-5-isopropyl-1-methyltetramic acid (**10l**) (90 mg, 0.35 mmol) in dichloromethane (5 ml) was added boron trifluoride–diethyl ether (5 ml) and the mixture was stirred at 25 °C for 5 h, then was treated with water (10 ml) and extracted with chloroform (3 × 20 ml). The combined extracts were dried and evaporated to yield a gum, which was chromatographed on a silica gel column under medium pressure and eluted with cyclohexane–ethyl acetate (3:2 v/v) to afford, after recrystallisation from chloroform–hexane, 3-[α-(difluoroboryloxy)benzylidene]-5-isopropyl-1-methylpyrrolidine-2,4-dione (**11f**) (78 mg, 73%) as white crystals, m.p. 148–149 °C, identical with a sample prepared by boron trifluoride-mediated acylation (see earlier).

3-[1-(*Difluoroboryloxy*)*ethylidene*]-5-*isopropylpyrrolidine*-2,4-*dione* (**11i**).—To a stirred solution of 3-acetyl-5-isopropyltetramic acid (**10a**) (200 mg, 1.1 mmol) in dry diethyl ether (20 ml) was added dropwise boron trifluoride–diethyl ether (2.7 ml, 11 mmol) and the solution was heated under reflux for 5 h and then left at 25 °C for 15 h. The mixture was washed with water (20 ml), dried, and evaporated under reduced pressure, and the residue was chromatographed on a silica gel column under medium pressure and eluted with ethyl acetate–cyclohexane (2:3 v/v) to afford 3-[1-(*difluoroboryloxy*)*ethylidene*]-5-*isopropylpyrrolidine*-2,4-*dione* (**11i**) (188 mg, 74%) as a white solid, m.p. 143–145 °C (Found: M^+, 231.0856. $C_9H_{12}BF_2NO_3$ requires M, 231.0868); ν_{max} 3 410, 2 970, 1 720, 1 645, 1 590, 1 565, 1 410, 1 180, 1 030, and 930 cm^{-1}; δ_H[$(CD_3)_2SO$–$CDCl_3$] 0.8 and 1.02 (6 H, 2 d, *J* 7 Hz, $CHMe_2$), 2.2 (1 H, m, $CHMe_2$), 2.50 (3 H, s, MeCO), 3.5 (1 H, br s, NH), and 4.12 (1 H, d, *J* 4 Hz, CHN); δ_C($CDCl_3$) 16.0, 18.9, and 21.1 (3 × CH_3), 29.9 and 67.7 (2 × CH), 110.0, 149.5, 191.2, and 225.2 (4 × quat. C); *m/z* 231 (M^+, 5%), 230, 212, 211, 189 (100), 188, 169, and 120.

3-[1-(Difluoroboryloxy)hexa-2,4-dienylidene]-5-isopropylpyrrolidine-2,4-dione (**11j**) was prepared as described for compound (**11i**), from 3-(hexa-2,4-dienoyl)-5-isopropyltetramic acid[6b] (**10m**) (200 mg, 0.85 mmol) and boron trifluoride–diethyl ether (2.1 ml, 8.5 mmol) in diethyl ether (20 ml) at reflux for 17 h. Evaporation of the cooled solution under reduced pressure afforded a residue, which was chromatographed on silica gel under medium pressure and eluted with ethyl acetate–cyclohexane (3:7 v/v), to give 3-[1-(difluoroboryloxy)hexa-2,4-dienylidene]-5-isopropylpyrrolidine-2,4-dione (**11j**) as a yellow solid (135 mg, 56%) that was only partially characterised; δ_H($CDCl_3$) 0.93 and 1.15 (6 H, 2 d, $CHMe_2$), 1.99 (3 H, br d, *Me*CH=), 2.35 (1 H, m, $CHMe_2$), 4.09 (1 H, d, CHN), 6.48 and 6.57 (2 H, 2 m, MeC*H*=C*H*), 7.09 [1 H, d, *J* 15 Hz, C(OB)C*H*=CH], 7.82 [1 H, dm, *J* 15 Hz, C(OB)CH=C*H*], and 8.37 (1 H, br s, NH).

Crystallographic Analysis of 3-[1-(*Difluoroboryloxy*)*ethylidene*]-5-*isopropyl*-1-*methylpyrrolidine*-2,4-*dione* (**11a**).—Crystals of (**11a**) were obtained as detailed above.

Crystal data. $C_{10}H_{14}BF_2NO_3$, M = 245.04. Triclinic, a = 7.814(1), b = 7.840(1), c = 10.025(1) Å, α = 93.96(1), β = 96.60(1), γ = 99.57(1)°, V = 599.19 $Å^3$, Z = 2, D_c = 1.41 g cm^{-3}, $F(000)$ = 256, space group $P\bar{1}$, Cu-K_α radiation, λ = 1.541 78 Å, μ(Cu-K_α) = 10.3 cm^{-1}.

A crystal of approximate dimensions 0.5 × 0.15 × 0.05 mm was mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections with θ ~ 30° were used to determine accurate lattice parameters by least squares. Intensity data were collected for 1° ≤ θ ≤ 76°, using an ω/2θ scan. Standard reflections monitored throughout data collection showed no deterioration in intensity. A total of 2 506 independent reflections was measured of which 1 556 were considered observed with $I > 3\sigma(I)$ and used in the subsequent refinement. The data were corrected for Lorentz and polarisation factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system

Table 2. Fractional atomic co-ordinates with standard deviations in parentheses.

Atom	*x*	*y*	*z*
N(1)	0.680 7(2)	0.488 6(2)	0.263 5(2)
C(2)	0.526 3(3)	0.454 8(3)	0.305 2(2)
C(3)	0.468 3(3)	0.273 4(3)	0.310 8(2)
C(4)	0.610 2(3)	0.187 1(3)	0.274 9(2)
C(5)	0.749 7(3)	0.327 5(3)	0.233 3(2)
C(6)	0.781 2(4)	0.661 6(3)	0.259 2(4)
C(7)	0.315 2(3)	0.219 8(3)	0.361 3(2)
C(8)	0.251 8(6)	0.037 0(5)	0.386 8(5)
C(9)	0.775 1(3)	0.302 2(3)	0.084 0(3)
C(10)	0.879 1(6)	0.156 3(5)	0.060 3(4)
C(11)	0.600 5(4)	0.270 0(4)	−0.008 1(3)
O(2)	0.440 6(2)	0.573 3(2)	0.342 0(2)
O(4)	0.621 7(3)	0.034 6(2)	0.275 4(2)
O(7)	0.216 3(2)	0.332 2(2)	0.391 4(2)
B(1)	0.250 4(3)	0.513 7(4)	0.353 6(3)
F(1)	0.203 7(2)	0.620 5(2)	0.450 8(2)
F(2)	0.157 4(2)	0.520 7(2)	0.230 1(2)

of programs.[24] The structure was solved by direct methods using the MULTAN program.[25] 200 Reflections with *E*-values >1.7 were used. Many runs of the program were required before a set of phases generated from a manually chosen starting set of origin determining and permuted reflections gave an *E*-map which revealed the approximate positions of all 17 non-hydrogen atoms. Least-squares refinement, including anisotropic thermal parameters for non-hydrogen atoms and isotropic refinement of hydrogen atoms located in a difference Fourier synthesis, terminated at *R* 0.0451 (R_w 0.0540) after 20 cycles of refinement, with a maximum δ/σ of 0.1. In the later cycles a weighting scheme based on a Chebyshev polynomial was used. The correctness of the structure was demonstrated in a final difference map which showed no features in excess of 0.2 eÅ^{-3}.

The refined fractional atomic co-ordinates are shown in Table 2 together with their standard deviations.*

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* *Supplementary Data* (see section 5.6.3 of Instructions for Authors, in the January issue). Bond lengths and bond angles, together with their standard deviations, and anisotropic thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre.

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