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Tetramic acid and imidazolidinone syntheses via unexpected base induced cyclisations of alanine derived Weinreb amides

Colin L. Gibson *, Alan R. Kennedy, Raghavendar R. Morthala, John A. Parkinson, Colin J. Suckling

Department of Pure and Applied Chemistry, 295 Cathedral Street, University of Strathclyde, Glasgow G1 1XL, UK

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ABSTRACT

Reactions of *N*-protected derivatives of Weinreb amides of alanine with strong base unexpectedly gave tetramic acid derivatives or an imidazolidinone. The tetramic acid derivatives were obtained by unusual cyclisation of *N*-acyl *N*-methoxy derivatives of alanine Weinreb amide upon treatment with potassium hexamethyldisilazide and benzyl bromide. In contrast, treatment of a bromobenzylidine alanine Weinreb amide with potassium hexamethyldisilazide gave rise to cyclisation to form an imidazolidinone.

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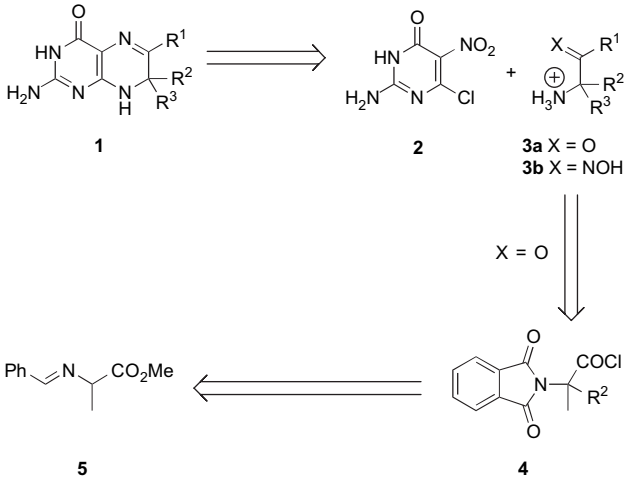
1. Introduction

We have previously reported the preparation of 7,7-dialkylated dihydropteridines **1**. These blocked dihydropteridines were found to be inhibitors of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase, an enzyme in the biosynthetic pathway to dihydrofolate. In our previous synthetic work, the 7,7-dialkylated dihydropteridines **1** were prepared by coupling the nitro chloropyrimidine **2** with α-amino ketones **3a** or oximes **3b** (Scheme 1).[1]



Scheme 1. Retrosynthesis of the blocked dihydropterins **1**.

While the α-amino ketones **3a** or oximes **3b** could be accessed from nitro alcohols or nitroso chloro derivatives, respectively, the method of choice was to use α-amino ketones **3a** prepared from phthalimido acid chlorides **4**. The phthalimido acid chlorides **4**, in turn, were generated by alkylation of benzylidene methyl ester **5**. The interchange of benzylidene nitrogen protection in benzylidene methyl ester **5** into the phthalimido protecting group in phthalimido acids **4** was necessary because of the improved stability of the latter.

As part of a continued programme of development of enzyme inhibitors and activators we recently had a need to prepare a broader spectrum of 7,7-dialkylated dihydropteridines **1** than we had previously generated. The cumbersome functional group interchanges needed to convert benzylidene methyl ester **5** into α-amino ketones **3a** were not conducive to the preparation of small libraries of 7,7-dialkylated dihydropteridines **1**. However, α-amino acids were judged to be advantageous starting points in the preparation of α-amino ketones **3a** since the former provide much of the functionality and carbon backbone for the latter.

It is well established that Weinreb amides provide a facile route to ketones.[2] Consequently, we sought to investigate whether fully *N*-protected α-amino Weinreb amides might serve as more rapid precursors to α-amino ketones **3a**. It was envisaged that this process would involve α-alkylation and suitable functional group interchanges of suitably protected α-amino Weinreb amides.

2. Results and discussion

The starting point, alanine ethyl ester hydrochloride (**6**) was converted into the *N*-acetyl derivative **7** by treatment with acetyl chloride (98%) (Scheme 2). Subsequent treatment of ester **7** with methoxymethylamine hydrochloride and dimethylaluminium chloride smoothly gave the Weinreb amide **8** (92%). Treatment of

* Corresponding author.
E-mail address: c.l.gibson@strath.ac.uk (C.L. Gibson).

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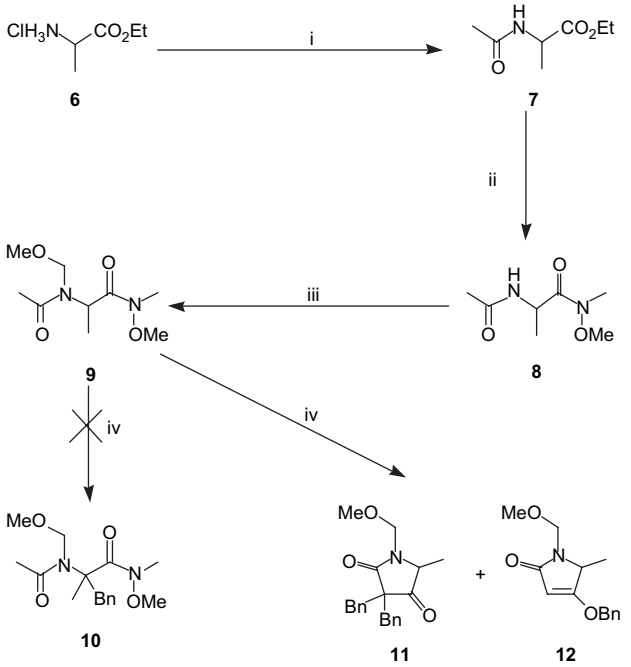
amide **8** with potassium hexamethyldisilazide and MOM chloride provided the desired fully protected α-amino Weinreb amide **9**.



Scheme 2. Reagents and conditions: (i) CH_3COCl, Et_3N, 98%; (ii) NH(OMe)Me·HCl, Me_2AlCl, 92%; (iii) KHMDS, MOMCl, −78 °C to rt, 57%; (iv) KHMDS, $PhCH_2Br$, −78 °C to rt.

Attempted alkylation of amide **9** by deprotonation with potassium hexamethyldisilazide and benzyl bromide failed to give any of the anticipated carbon alkylated product **10**. Instead, two compounds **11** and **12** were isolated in equimolar amounts. Spectroscopic analysis in both cases indicated the absence of the expected *N*-acetyl and *N*-methyl groups in the ^{1}H NMR spectra of these two products. In the case of product **11**, the loss of a nitrogen atom was implicated in the mass spectral data (MH^+ 338), which suggested an odd number of nitrogen atoms. This was further evidenced by the observation of a ketone carbonyl (1762 cm^{-1}, 213 ppm) and lactam carbonyl (1696 cm^{-1}, 173 ppm) in the IR and ^{13}C NMR spectra. The presence of a methine (δ^1H/^{13}C: 2.8/55 ppm) coupled to a methyl group (δ^1H/^{13}C: 0.3/13 ppm) taken with the carbonyl group evidence strongly suggested a tetramic acid (2,4-pyrrolidinedione) structure for **11**. The evidence for two *C*-benzyl groups (two sets of AB multiplets at δ^1H=3.25/3.05 and 3.20/3.14 and a 10 proton multiplet at δ^1H=7.23–7.10) and MOM (AB δ^1H=4.62/4.30) functionality from the ^{1}H and ^{13}C NMR spectra led to the proposal of structure **11** for this product. The structure of tetramic acid **11** was established unequivocally by a single crystal X-ray analysis (Fig. 1).

The second product **12** also indicated the loss of a nitrogen atom from the mass spectroscopic analysis (MH^+ 248). In this case, a conjugated lactam was proposed from the IR (1683 (C=O) and 1620 (C=C) cm^{-1}) and ^{13}C NMR spectra (177 ppm (C=O), 172 and 93 ppm (C=C)) together with an olefinic methine (δ^1H=5.1) in the ^{1}H NMR. This evidence together with a methine (δ^1H/^{13}C: 4.17/55 ppm) coupled to a methyl group (δ^1H/^{13}C: 1.39/16 ppm) and *O*-benzyl group (AB multiplet δ^1H=5.01/4.96 or 4.98/4.62) strongly implicated an *O*-benzyl tetramic acid functionality for the structure of **12**. Finally, the presence of the MOM group was evidenced from a methylene (AB multiplet δ 4.98/4.62 or 5.01/4.96) and *O*-methyl (δ^1H/^{13}C: 3.29/55 ppm) resonance in the ^{1}H and ^{13}C NMR spectra. Again, the structure of **12** followed unequivocally from a single crystal X-ray analysis (Fig. 2).

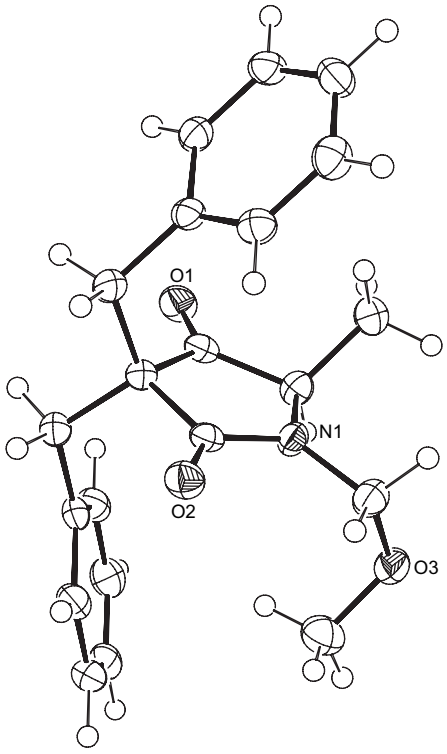


Figure 1. ORTEP representation of tetramic acid **11**.

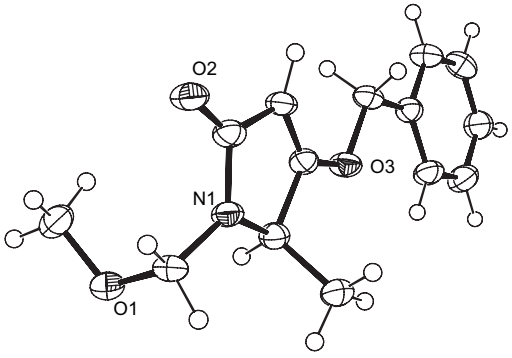
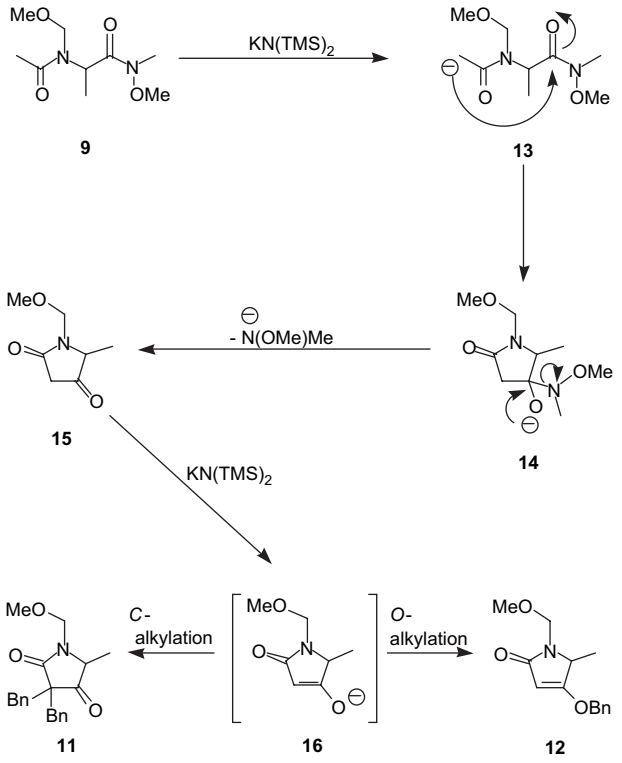


Figure 2. ORTEP representation of tetramic acid **12**.

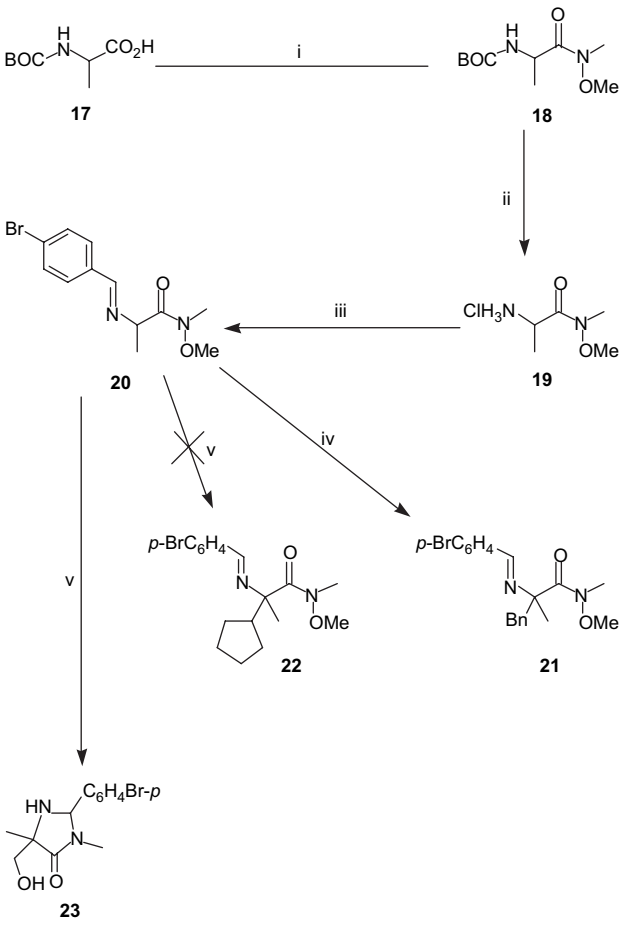
A plausible explanation for the formation of tetramic acids **11** and **12** involves an initial kinetic deprotonation to form the acetyl enolate **13** (Scheme 3). We presume that α-deprotonation is disfavoured on steric grounds. The enolate **13** then undergoes a favoured 5-*exo*-*trig* cyclisation to afford the tetrahedral intermediate **14**. Subsequent elimination of *N*,*O*-dimethylhydroxylamine from **14** provides the tetramic acid **15**. Under the basic conditions, the tetramic acid **15** is deprotonated to afford the enolate **16**. O-Alkylation of enolate **16** with benzyl bromide yields the ether **12**. Alternatively, C-alkylation of enolate **16** followed by deprotonation and a second C-alkylation generates the 3,3-dibenzyl tetramic acid **11**.

The tetramic acid moiety (2,4-pyrrolidinedione) is well represented in nature and such compounds have been found to show a wide range of biological activities including antibiotic, antiviral, mycotoxicity and cytotoxicity.[3] Most of the tetramic acid derivatives contain an acyl group at C-3, which presents an ideal chelation motif for magnesium[4] and calcium.[5] It would appear that this chelation by the C-3-acyl group is necessary for biological activity.

Tetramic acid derivatives with a C-3 acyl group are generally synthesised by the Lacey[6] Dieckmann cyclisation of α-amino acid



Scheme 3. Proposed mechanism for the formation of tetramic acids **11** and **12**.



Scheme 4. Reagents and conditions: (i) MeNH(OMe)·HCl, 2-chloro-4,6-dimethoxy-1,3,5-triazine, *N*-methylmorpholine, THF, 75%; (ii) 4 M HCl, dioxane, 100%; (iii) *p*-BrC_6H_4CHO, Et_3N, CH_2Cl_2, 4 Å molecular sieves, Δ, 90%; (iv) KHMDS, $PhCH_2Br$, −78 °C to rt, 100%; (v) KHMDS, $(CH_2)_4CHBr$, −78 °C to rt, 80%.

esters with β-keto acids or with diketene to afford *N*-acyl derivatives of α-amino acid esters. Base catalysed cyclisation of these *N*-acyl derivatives then provides the C-3 acyl tetramic acids. On the other hand, C-3 unsubstituted tetramic acids are prepared by the method of Jouin et al.[7] involving reaction of an α-amino acid with Meldrum's acid, which affords a β-keto ester. Heating the β-keto ester generates the C-3 unsubstituted tetramic acid. Tetramates may also be prepared by a domino-intramolecular Wittig reaction of α-amino acid esters with the cumulative phosphorus ylide Ph_3PCCO.[8] The results presented above may provide alternative routes to tetramic acids in the form of C-3 unsubstituted derivates (e.g., **12**) or C-3 disubstituted analogues (e.g., **11**).

In view of the interference of the *N*-acyl group in attempted alkylation of amide **9** (Scheme 2) we sought to alter our nitrogen-protecting group strategy. Given the success of the benzylidene nitrogen-protecting group in our previous work,[1] we wished to investigate whether this functionality could be utilised in facile routes to 2,2-disubstituted α-amino ketones (e.g., **3**). Thus, BOC alanine **17** was converted into Weinreb amide **18**[9] (75%) by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and 2-chloro-4,6-dimethoxy[1,3,5]triazine (Scheme 4). Subsequent BOC deprotection afforded the Weinreb amide **19** (100%) that was condensed with 4-bromobenzaldehyde, which gave the bromobenzylidene derivative **20** (90%). The bromobenzylidene Weinreb amide **20** smoothly underwent C-benzylation when treated with potassium hexamethyldisilazide and benzyl bromide and gave the alkylated Weinreb amide **21** (100%). In contrast, attempted alkylation of bromobenzylidene Weinreb amide **20** with the less reactive cyclopentyl bromide gave a single product (80%) that was evidently not the required alkylated product **22**.

The structure of product **23** was established from an analysis of the spectra including 2D NMR data analysis. The microanalysis data suggested an empirical formula of $C_{12}H_{15}BrN_2O_2$ that implied the formation of a constitutional isomer. The absence of the benzylidene functionality was evident from the loss of the IR band at 2254 cm^{-1} observed in the starting material as well as the lack of the imine proton (δ^1H 8.3). In contrast, a 1,4-disubstituted aromatic ring, probably with a bromine substituent, was implicated by the presence of bromine together with signals in the ^{1}H NMR spectra (δ^1H 7.41 and 7.64 doublets, $^3J_{HH}$=8.4 Hz) and ^{13}C NMR (quaternary aryl carbons at δ^{13}C 122 and 138 ppm and aryl methines at δ^{13}C 129 and 131 ppm) from a *para* disubstituted aromatic ring. The lack of the Weinreb amide functionality was implicated by the loss of the *N*-methoxy group (δ^1H 3.67) in the ^{1}H NMR spectrum and loss of the tertiary amide carbonyl in the IR spectrum (1659 cm^{-1}). On the other hand, the presence of a lactam or imidazolidinone was indicated by a strong absorption at 1697 cm^{-1} together with a carbonyl resonance in the ^{13}C NMR data (δ^{13}C 175 ppm). Hydroxy and/or amino groups were implicated by a broad absorption between 3400 and 2580 cm^{-1} and a sharp band at 3270 cm^{-1}. A quaternised α-carbon was observed by ^{13}C *J*-mod NMR and a newly formed hydroxymethyl group on the α-carbon was revealed by 2D [^{1}H, ^{1}H] COSY (Fig. 3b) and 2D [^{1}H, ^{13}C] HSQC and HMBC NMR data (Fig. 3a). The ^{1}H–^{1}H coupling of two diastereotopic protons (δ^1H 3.20 and 3.61) with one proton triplet at δ^1H 5.0, and one proton doublet (δ^1H 2.81) coupling with one proton doublet δ^1H 5.24 could be seen from the 2D COSY data (Fig. 3b). The one proton doublet at δ^1H 2.81 and one proton triplet at δ^1H 5.0 are not in correlation with any carbons (see the 2D [^{1}H, ^{13}C] HSQC NMR data, Fig. 3a, shown in black), which clearly indicates that these two protons are present on different heteroatoms. These findings on careful analysis allowed us to assign the resulting product as structure **23**. This was further confirmed by three-bond correlation 2D [^{1}H, ^{13}C] HMBC

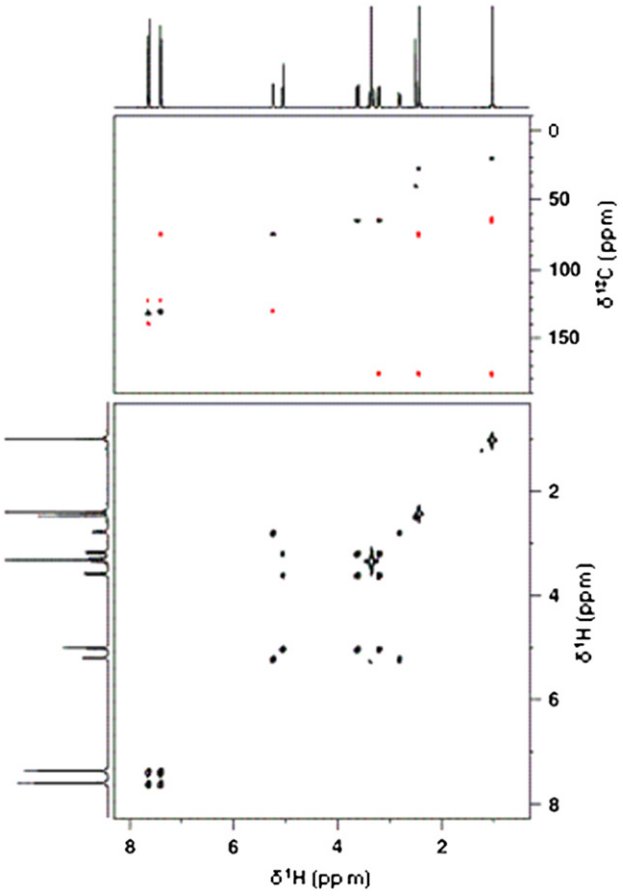


Figure 3. (a) The combined 2 D HSQC (shown in black) and HMBC (shown in red) NMR contour plot of **23** (top spectra); (b) The 2D COSY NMR contour plot of **23** (bottom spectrum).

NMR data (Fig. 3a, shown in red). In this the *C*-methyl (δ^1H 1.03), *N*-methyl (δ^1H 2.44) protons and one methylene proton (δ^1H 3.20) showed three-bond correlation with the carbonyl carbon (δ^{13}C 175.6 ppm). Interestingly, correlation of *C*-methyl protons (δ^1H 1.03) and methylene carbon at δ^{13}C=64.3 ppm, and the correlation of *N*-methyl protons (δ^1H 2.44) with *C*–H carbon at δ^{13}C=74.1 ppm strongly supported the assignment of compound **23** (Fig. 3a, signals are shown in red). The structure of **23** followed unequivocally from a single crystal X-ray analysis (Fig. 4).

A plausible mechanism for the formation of imidazolidinone **23** involves initial α-deprotonation of Weinreb amide **20**, which affords the enolate **24** (Scheme 5). The enolate undergoes cyclisation onto the benzylidine functional group rather than C-alkylation with the hindered cyclopentyl bromide. This cyclisation affords the

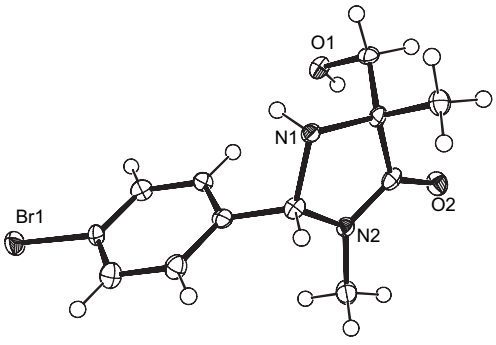
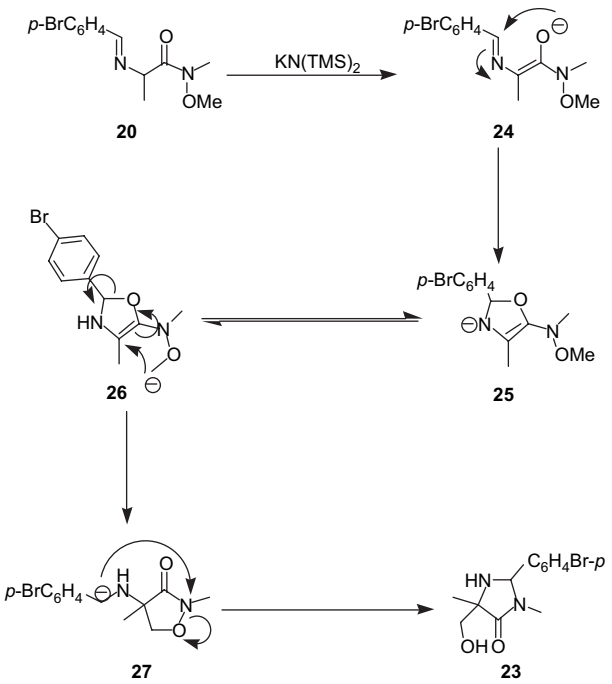


Figure 4. ORTEP representation of imidazolidinone **23**.

dihydrooxazole anion **25**. The anion **25** is presumably still reactive under the strongly basic conditions such that deprotonation of the weakly acidic methoxy group of the amide functionality affords the anion **26**. The anion **26** then undergoes an intramolecular cyclisation and dihydrooxazole ring opening to afford the isoxazolidinone anion **27**. The isoxazolidinone anion **27** then acts as a nucleophile, attacking the nitrogen atom in a favoured 5-*exo*-*tet* fashion with cleavage of the weak nitrogen–oxygen bond and leads to the product **23** upon protonation. This 5-*exo*-*tet* cyclisation is favoured over the alternative 4-*exo*-*trig* cyclisation onto the Weinreb amide carbonyl carbon because the latter is required to proceed via a strained four-membered ring.



Scheme 5. Proposed mechanism for the formation of imidazolidinone **23**.

While the use of *N*-alkyl-*O*-alkylhydroxamates (Weinreb amides) in addition reactions to produce aldehydes and ketones is well precedented, fragmentation of the nitrogen–oxygen bond is a common problem with these carboxylic acid derivatives. Thus, Lubell et al. comment on the formation of *N*-methyl amides by loss of the methoxy group upon treatment of *N*-methyl-*O*-methylhydroxamides with butyllithium or LDA.[10] These workers have observed three modes of nitrogen–oxygen bond cleavage in isoxazolidides upon treatment of these compounds with alkyllithium or Grignard reagents. These include vinyl amide formation through proton abstraction and loss of formamide; *N*-hexylamide production through nucleophilic formamide displacement with butyllithium; and *N*-hydroxypropamide formation from reductive cleavage of the isoxazolidide ring. Furthermore, Mislin et al. have also observed nucleophilic loss of the methoxy group in enolates of *N*-methyl-*O*-methylhydroxamate derivatives of thiazoline-4-carboxylates.[11] These observations of Lubell et al. and Mislin et al. support the proposed mechanistic detail that N–O bond cleavage is, indeed, possible.

In summary, treatment of the *N*-methoxymethyl *N*-acyl Weinreb amide **9** with potassium hexamethyldisilazide and benzyl bromide resulted in unexpected cyclisation to afford the tetramic acid derivatives **11** and **12**. In contrast, the benzylidene Weinreb amide **20** gave rise to cyclisation and N–O bond cleavage upon reaction with potassium hexamethyldisilazide and cyclopentyl bromide to afford the imidazolidinone **23**.

3. Experimental

3.1. General procedures

Anhydrous reactions were carried out under an atmosphere of nitrogen in oven-dried glassware (140 °C). Dichloromethane and THF were dried and deoxygenated using a Pure-Solv 400 purification system by Innovative Technology Inc., USA. Triethylamine was distilled from CaH_2. All other reagents and solvents were used as supplied.

Removal of solvents was carried out by evaporation using a rotary evaporator at reduced pressure (ca. 20 mmHg) unless otherwise stated.

Thin layer chromatography (TLC) was carried out using precoated silica plates (Alugram® Sil G/UV_{254}). Visualisation of TLC plates was achieved by UV (254 nm) and then by 2% aqueous potassium permanganate.

Flash column chromatography was performed according to the procedure of Still et al.[12] using silica gel (230–400 mesh).

Melting points were performed on Reichert 7905 hot stage melting point apparatus and are uncorrected.

Infra red (IR) spectra were recorded on a Nicolet Impact 400 D FTIR spectrometer as KBr discs in the case of solids and NaCl plates for oils. Frequencies are quoted in cm^{-1}.

NMR (^1H, ^{13}C) spectra were recorded on a Bruker Biospin DPX NMR spectrometer operating at 400.13 or 100.13 MHz for ^1H and ^{13}C observation, respectively. Chemical shifts are quoted relative to the residual proton signal of the deuterated solvent in parts per million. Coupling constants (J) are given in hertz. The following abbreviations are used: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; dd=doublet of doublets, br=broad.

Microanalyses were carried out at the University of Strathclyde using Perkin Elmer series II CHN analyser 2400.

Low and high resolution mass spectra were recorded either on a JEOL JMS AX505 mass spectrometer at the University Strathclyde or on a JEOL JMS-7 MS station high resolution magnetic sector at Glasgow University using either fast atom bombardment (FAB), electron impact (EI), electrospray (ESI) or chemical ionisation (CI) methods.

All structures were solved and refined on F^2 to convergence using SHELXS and SHELXL-97.[13] H-atoms were placed in calculated positions and in riding modes. Crystallographic data (excluding structure factors) for the compound reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 678539, 678540 and 678541. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; email: deposit@ccdc.cam.ac.uk).

3.2. Experimental procedures

3.2.1. *Ethyl 2-acetamidopropanoate* **7**

To the stirred solution of alanine ethyl ester hydrochloride **6** (1 g, 6.50 mmol) in dichloromethane (30 mL), at 0 °C, was added triethylamine (1.83 mL, 2 equiv) followed by acetyl chloride (0.46 mL, 1 equiv) in dichloromethane (10 mL) dropwise. The reaction mixture was stirred at room temperature for 2 h, then washed with brine (3×30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound as clear oil (1.01 g, 98%). ν_{max} (liquid film (CH_2Cl_2), cm^{-1}) 3428, 3054, 2986, 1736, 1677, 1510, 1445, 1374, 1210; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, t, J=7.1, –CH_2–CH_3), 1.39 (3H, d, J=7.2, –CH–CH_3), 2.08 (3H, s, CH_3–CO–), 4.20 (2H, q, J=7.1, –CH_2–CH_3), 4.58 (1H, q, J=7.2, –CH–CH_3), 6.07 (1H, br, –NH); ^{13}C (400 MHz, $CDCl_3$) δ_C 14.33 (–CH_2–CH_3), 18.86 (–CH–CH_3), 23.41 (CH_3–CO–), 48.34 (–CH–CH_3), 61.73 (–CH_2–CH_3), 169.70 (CH_3–CO–NH–), 173.45 (–CH–CO–O–); HRMS (FAB): found (MH^+) 160.0975, $C_7H_{13}NO_3$ requires 160.0974.

3.2.2. *2-Acetamido-N-methoxy-N-methylpropanamide* **8**[14]

To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.75 g, 5 equiv) in dichloromethane (30 mL) was added dimethylaluminium chloride (28.3 mL, 5 equiv, 1 M solution in hexane) over the period of 15 min at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min and at room temperature for 45 min. Then, the ethyl 2-acetamidopropanoate **7** (0.9 g, 5.65 mmol) in dichloromethane (20 mL) was added by means of cannula over the period of 20 min. The reaction mixture was stirred for 3.5 h and then quenched with phosphate buffer (pH 8) (85 mL) and the stirring was continued for 15 min. The resulting suspension was diluted with chloroform (30 mL) and filtered through a Celite pad and washed with chloroform (30 mL). The aqueous layer was extracted with chloroform (2×30 mL) and the combined organic layers were washed with brine (3×50 mL), then dried ($MgSO_4$) and concentrated. The resulting crude mixture was purified by column chromatography (10% methanol/ethyl acetate), which afforded the title Weinreb amide **8** as colourless needles (0.9 g, 92%). Mp 79–80 °C; ν_{max} (KBr, cm^{-1}) 3304, 3004, 2986, 1677, 1645, 1556, 1374, 1179, 985; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.31 (3H, d, J=6.8, –CH–CH_3), 1.93 (3H, s, CH_3–CO–), 3.20 (3H, s, –N–CH_3), 3.76 (3H, s, –O–CH_3), 4.95 (1H, q, J=6.8, –CH–CH_3), 6.42 (1H, br, –NH); ^{13}C (400 MHz, $CDCl_3$) δ_C 18.67 (–CH–CH_3), 23.42 (CH_3–CO–NH–), 32.31 (–N–CH_3), 45.66 (–CH–CH_3), 61.80 (–O–CH_3), 169.63 (CH_3–CO–NH–), 173.45 (–CH–CO–N<); $C_7H_{14}N_2O_3$ requires (%): C, 48.26; H, 8.10; N, 16.08, found C, 48.49; H, 8.22; N, 16.14; HRMS (CI): found (MH^+) 175.1085, $C_7H_{14}N_2O_3$ requires 175.1083.

3.2.3. *2-(N-[Methoxymethyl)acetamido]-N-methoxy-N-methylpropanamide* **9**

2-Acetamido-*N*-methoxy-*N*-methylpropanamide **8** (0.49 g, 2.81 mmol) was dissolved in THF (10 mL) under nitrogen and cooled to −78 °C. KHMDS (5.15 mL, 0.98 equiv, 0.5 M solution in toluene) was then added dropwise and allowed to stir at −78 °C for 30 min. Then, MOMCl (0.67 mL, 3 equiv) was added and the mixture was allowed to warm to room temperature by stirring for 20 h. Saturated aqueous ammonium chloride solution (20 mL) was added and the organic layer was extracted with ethyl acetate (2×20 mL) and washed with brine (3×20 mL), then dried (Na_2SO_4) and concentrated to give crude mixture as a yellow oil. This oil was purified by column chromatography eluting with 2% methanol/ethyl acetate, which gave the title compound **9** as thick colourless oil (0.35 g, 57%). ν_{max} (liquid film, cm^{-1}) 2984, 2904, 1655, 1390, 1237, 1196, 1079, 992; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.36 (3H, d, J=7.3, –CH–CH_3), 2.19 (3H, s, CH_3–CO–), 3.16 (3H, s, –N–CH_3), 3.30 (3H, s, –CH_2–O–CH_3), 3.78 (3H, s, –N–O–CH_3), 4.70 (1H, d, J=10.8, >N–CH_2–O–), 4.74 (1H, d, J=10.8, >N–CH_2–O–), 5.47 (1H, q, J=7.3, –CH–CH_3); ^{13}C (400 MHz, $CDCl_3$) δ_C 15.41 (–CH–CH_3), 21.55 (CH_3–CO–NH–), 32.33 (–N–CH_3), 48.45 (–CH–CH_3), 55.17 (–CH_2–O–CH_3), 61.66 (>N–O–CH_3), 77.41 (>N–CH_2–O–), 172.32 (–CH–CO–N<), 173.35 (CH_3–CO–N<); HRMS (CI): found (MH^+) 219.1348, $C_9H_{18}N_2O_4$ requires 219.1345.

3.2.4. *3,3-Dibenzyl-1-(methoxymethyl)-5-methyl-2,4-pyrrolidinedione* **11** *and 4-(benzyloxy)-1-(methoxymethyl)-5-methyl-1,5-dihydro-2H-pyrrol-2-one* **12**

2-(*N*-(Methoxymethyl)acetamido)-*N*-methoxy-*N*-methylpropanamide **9** (0.3 g, 1.37 mmol) was dissolved in THF (15 mL) and cooled to −78 °C. KHMDS (4.1 mL, 1.5 equiv, 0.5 M in toluene) was then added dropwise and stirred at the same temperature for 30 min. Benzyl bromide (0.5 mL, 3 equiv) was then added dropwise and the cooling bath was removed after 15 min. The resulting reaction mixture was allowed to stir for 16 h. Saturated aqueous ammonium

chloride was added and the organic layer was extracted with ethyl acetate (15 mL) and washed with saturated aqueous sodium bicarbonate (2×20 mL) and brine (2×20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure; the resulting residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexane (9:1) to give two fractions.

The more mobile fraction afforded 3,3-dibenzyl-1-(methoxymethyl)-5-methyl-2,4-pyrrolidinedione **11** (91 mg, 20%) as colourless crystals. Mp 115–116 °C; ν_{max} (KBR, cm^{-1}) 3063, 2951, 2929, 1762, 1696, 1439, 1412, 1249, 1098, 755, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.34 (3H, d, *J*=7.0, –CH–C*H*$_3$), 2.67 (3H, s, –O–C*H*$_3$), 2.88 (1H, q, *J*=7.0, –C*H*–CH$_3$), 3.05 (1H, d, *J*=12.87, –C*H*$_2$–Ph), 3.25 (1H, d, *J*=12.87, –C*H*$_2$–Ph), 3.14 (1H, d, *J*=12.84, –C*H*$_2$–Ph), 3.20 (1H, d, *J*=12.84, –C*H*$_2$–Ph), 4.30 (1H, d, *J*=10.8, >N–C*H*$_2$–O–), 4.62 (1H, d, *J*=10.8, >N–C*H*$_2$–O–), 7.10–7.23 (10H, m, 2×C$_6$*H*$_5$); ^{13}C (400 MHz, $CDCl_3$) δ_C 13.00 (–CH–*C*H$_3$), 41.38, 42.28 (2×CH$_2$Ph), 55.67 (–*C*H–CH$_3$), 60.55 (–O–*C*H$_3$), 61.55 (–CO–*C*–CO), 71.30 (–O–*C*H$_2$–), 127.21–135.63 (2×*C*$_6$H$_5$), 173.52 (–N–*C*O–), 213.71(–C–*C*O–CH); HRMS (FAB): found (MH^+) 338.1758, $C_{21}H_{23}NO_3$ requires 338.1756. Recrystallisation from hexane afforded crystals that were suitable for X-ray crystallography. *Crystal data for* ***11***: $C_{21}H_{23}NO_3$; monoclinic space group $P2_1/c$, a=14.9025(6), b=7.2298(2), c=17.7411(7) Å, β=111.969(2)° V=1772.66(11) Å^3, T=123 K, Z=4, ρ_{calcd}=1.264 Mg m^{-3}, $2\theta_{max}$=54.2°, Mo Kα λ=0.71073 Å. $R1$=0.0509 (for 2282 reflections with $I>2\sigma(I)$), $wR2$=0.1104 and S=1.006 for 228 parameters and 3905 unique reflections. Minimum/maximum residual electron density −0.221/0.192 e Å^{-3}.

The more polar fraction afforded 4-(benzyloxy)-1-(methoxymethyl)-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one **12** as colourless crystals (62 mg, 19%). Mp 48–50 °C; ν_{max} (KBR, cm^{-1}) 3098, 2975, 1683, 1620, 1467,1346, 1234, 1082, 830, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.38 (3H, d, *J*=6.7, –CH–C*H*$_3$), 3.29 (3H, s, –O–C*H*$_3$), 4.17 (1H, q, *J*=6.7, –C*H*–CH$_3$), 4.62 (1H, d, *J*=10.9, –O–C*H*$_2$–), 4.98 (1H, d, *J*=10.9, –O–C*H*$_2$–), 4.96 (1H, d, *J*=11.6, –O–C*H*$_2$–), 5.01 (1H, d, *J*=11.6, –O–C*H*$_2$–), 5.10 (1H, s, –C*H*=C–O–), 7.36–7.43 (5H, m, –C$_6$*H*$_5$); ^{13}C (400 MHz, $CDCl_3$) δ_C 16.15 (–CH–*C*H$_3$), 55.51 (–O–*C*H$_3$), 55.89 (–*C*H–CH$_3$), 71.02 (–O–*C*H$_2$), 73.28 (–O–*C*H$_2$), 93.77 (–*C*H=C–O–), 127.94, 128.94 and 134.95 (–CH$_2$–*C*$_6$H$_5$), 172.26 (–CH=*C*–O–), 177.14 (–N–*C*O–CH); HRMS (FAB): found (MH^+) 248.1285, $C_{14}H_{17}NO_3$ requires 248.1287. Recrystallisation from hexane afforded crystals that were suitable for X-ray crystallography. *Crystal data for* ***12***: $C_{14}H_{17}NO_3$; monoclinic space group $P2_1/n$, a=13.0670(10), b=4.6208(3), c=21.371(2) Å, β=95.673(2)°, V=1284.06(18) Å^3, T=123 K, Z=4, ρ_{calcd}=1.279 Mg m^{-3}, $2\theta_{max}$=50.0°, Mo Kα λ=0.71073 Å. Refined as a two component twin (180° rotation about −3 0 1) using the SHELX HKLF 5 methodology. $R1$=0.0712 (for 2305 reflections with $I>2\sigma(I)$), $wR2$=0.1905 and S=1.021 for 166 parameters and 3766 unique reflections. Minimum/maximum residual electron density −0.291/0.327 e Å^{-3}.

3.2.5. *tert*-Butyl 1-(*N*-methoxy-*N*-methylcarbamoyl)ethylcarbamate ***18***[9]

2-[(*tert*-Butoxycarbonyl)amino]propanoic acid **17** (1 g, 5.28 mmol) was dissolved in THF (20 mL) at room temperature under nitrogen. 2-Chloro-4,6-dimethoxy[1,3,5]triazine (1.1 g, 1.2 equiv) and *N*-methylmorpholine (1.75 mL, 3 equiv) were added and the resulting mixture was stirred for 1 h. A white precipitate formed during this time, then *N*,*O*-dimethylhydroxylamine hydrochloride (0.52 g, 1 equiv) was added and the mixture was stirred for 16 h. Water (20 mL) was added and the solution was extracted with ethyl acetate (20 mL). The organic layer was washed with saturated aqueous sodium carbonate solution (2×30 mL), dilute hydrochloric acid (1 M, 2×30 mL) and brine (3×30 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to give a title compound as a white solid (0.92 g, 75%). Mp 154–156 °C; ν_{max} (KBr, cm^{-1}) 3297, 2975, 2937, 1706, 1659, 1542, 1364, 1295, 1179, 1067, 981; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (3H, d, *J*=6.9, –CH–C*H*$_3$), 1.43 (9H, s, –C(C*H*$_3$)$_3$), 3.20 (3H, s, –N–C*H*$_3$), 3.76 (3H, s, –O–C*H*$_3$), 4.68 (1H, m, –C*H*–CH$_3$), 5.26 (1H, br, –N*H*–); ^{13}C (400 MHz, $CDCl_3$) δ_C 18.88 (–CH–*C*H$_3$), 28.59 (–C(*C*H$_3$)$_3$), 32.40 (–N–*C*H$_3$), 46.76 (–*C*H–CH$_3$), 61.80 (–O–*C*H$_3$), 79.73 (–*C*(CH$_3$)$_3$), 155.42 (–O–*C*O–NH–), 173.95 (–CH–*C*O–N<); HRMS (FAB): found (MH^+) 233.1499, $C_{10}H_{20}N_2O_4$ requires 233.1501.

3.2.6. 2-Amino-*N*-methoxy-*N*-methylpropanamide hydrochloride ***19***

To the above *tert*-butyl 1-(*N*-methoxy-*N*-methylcarbamoyl)-ethylcarbamate **18** (0.69 g, 2.96 mmol), was added ice-cold 4 M hydrogen chloride in dioxane (7.4 mL, 10 equiv) and the mixture was stirred for 2 h. The solvent was evaporated under reduced pressure at room temperature to give Weinreb amide hydrochloride as a light yellow foam (0.49 g, 100%). ν_{max} (KBr, cm^{-1}) 3423, 2982, 1666, 1496, 1354, 1230, 1181, 1114, 989; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.36 (3H, d, *J*=6.9, –CH–C*H*$_3$), 3.16 (3H, s, –N–C*H*$_3$), 3.74 (3H, s, –O–C*H*$_3$), 4.15 (1H, q, *J*=6.9, –C*H*–CH$_3$), 8.38 (3H, br, –N*H*$_2$·*H*Cl–); ^{13}C (400 MHz, DMSO-d_6) δ_C 16.76 (–CH–*C*H$_3$), 32.73 (–N–*C*H$_3$), 47.09 (–*C*H–CH$_3$), 62.53 (–O–CH$_3$), 170.35 (–CH–*C*O–N<); HRMS (CI): found (MH^+) 133.0975, $C_5H_{12}N_2O_2$ requires 133.0977.

3.2.7. 2-{[(*E*)-(4-Bromophenyl)methylidene]amino}-*N*-methoxy-*N*-methylpropanamide ***20***

To the solution of 2-amino-*N*-methoxy-*N*-methylpropanamide hydrochloride **19** (0.43 g, 2.58 mmol) in dry dichloromethane (10 mL) with 4 Å molecular sieves, triethylamine (0.36 mL, 1 equiv) was added, after stirring for 5 min, 4-bromobenzaldehyde (0.43 g, 0.9 equiv) was added and the reaction mixture was heated to reflux. After 16 h, the reaction mixture was filtered and washed with water (3×15 mL) and dried ($MgSO_4$), then concentrated under reduced pressure gave the title compound as a light brown thick oil (0.69 g, 90%). ν_{max} (liquid film (CH_2Cl_2), cm^{-1}) 3155, 2982, 1659, 1590, 1470, 1383, 1096, 650; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40 (3H, d, *J*=6.9, –CH–C*H*$_3$), 3.21 (3H, s, –N–C*H*$_3$), 3.67 (3H, s, –O–C*H*$_3$), 4.70 (1H, q, *J*=6.9, –C*H*–CH$_3$), 7.56–7.53 (2H, d, *J*=8.7, C$_6$*H*$_4$), 7.66–7.64 (2H, d, *J*=8.7, C$_6$*H*$_4$), 8.30 (1H, s, –C*H*=N–); ^{13}C (400 MHz, $CDCl_3$) δ_C 18.8 (–CH–*C*H$_3$), 32.80 (–N–*C*H$_3$), 61.83 (–*C*H–CH$_3$), 63.60 (–O–*C*H$_3$), 125.61, 129.98, 132.68 and 135.34 (*C*$_6$H$_4$), 161.08 (C$_6$H$_4$–*C*=N–); HRMS (FAB): found (MH^+) 299.0396, $C_{12}H_{15}^{79}BrN_2O_2$ requires 299.0395.

3.2.8. 2-{[(*E*)-(4-Bromophenyl)methylidene]amino}-*N*-methoxy-*N*,2-dimethyl-3-phenylpropanamide ***21***

The above 2-{[(*E*)-(4-bromophenyl)methylidene]amino}-*N*-methoxy-*N*-methylpropanamide **20** (0.44 g, 1.47 mmol) was dissolved in THF (10 mL) under nitrogen and this solution was cooled to −78 °C. KHMDS (2.94 mL, 1 equiv, 0.5 M solution in toluene) was then added dropwise and allowed to stir at the same temperature for 30 min. Then, benzyl bromide (0.17 mL, 1 equiv) was added and the mixture was allowed to warm to room temperature by stirring for 20 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×30 mL), the combined extracts were washed with brine (3×30 mL) and dried over Na_2SO_4, then concentrated under reduced pressure to give light yellow semi-solid, which on storing at 4–8 °C for 16 h afforded a yellow solid (0.57 g, 100%). Mp 104–106 °C; ν_{max} (KBr, cm^{-1}) 3082, 2944, 2896, 1650, 1632, 1585, 1482, 1466, 1452, 1373, 1066, 827, 702; ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (3H, s, >C–C*H*$_3$), 3.30 (3H, s, –N–C*H*$_3$), 3.35 (1H, d, *J*=13.2, >C–C*H*$_2$–C$_6$H$_5$), 3.47 (1H, d, *J*=13.2, >C–C*H*$_2$–C$_6$H$_5$), 3.53 (3H, s, –O–C*H*$_3$), 7.15–7.37 (5H, m, CH$_2$–C$_6$*H*$_5$), 7.64–7.66 (2H, d, *J*=8.5, Br–C$_6$*H*$_4$), 7.71–7.69 (2H, d, *J*=8.5, Br–C$_6$*H*$_4$), 7.90 (1H, s, –C*H*=N–); ^{13}C (400 MHz, $CDCl_3$) δ_C 21.31 (>C–CH$_3$), 34.16 (–N–*C*H$_3$), 44.57 (>C–CH$_2$–C$_6$H$_5$), 61.32 (>*C*–CH$_2$–C$_6$H$_5$), 69.78 (–O–CH$_3$),

125.34, 126.63, 127.88, 129.68, 131.62, 132.19, 135.53 and 137.00 (C_6H_5 and C_6H_4), 157.03 (–*C*H=N–), 174.60 (>C–*C*O–N<); HRMS (EI): found (MH^+) 388.0789, $C_{19}H_{21}^{79}BrN_2O_2$ requires 388.0786.

3.2.9. 2-(4-Bromophenyl)-5-(hydroxymethyl)-3,5-dimethyl-4-imidazolidinone **23**

Using the procedure described above for 2-{[(*E*)-(4-bromophenyl)methylidene]amino}-*N*-methoxy-*N*,2-dimethyl-3-phenylpropanamide **21** with 2-{[(*E*)-(4-bromophenyl)methylidene]amino}-*N*-methoxy-*N*-methylpropanamide **20** (3.80 g, 12.9 mmol) and cyclopentyl bromide (1.38 mL, 1 equiv) afforded a crude yellow solid. This solid upon recrystallisation from THF afforded the title compound as a white solid (3.06 g, 80%). Mp 188–189 °C; ν_{max} (KBr, cm^{-1}) 3400–2580 (br), 3423, 3271, 3080, 2969, 1697, 1488, 1402, 1304, 1069, 1063, 1013, 820; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.03 (3H, s, >C–CH_3), 2.44 (3H, s, –N–CH_3), 2.81 (1H, d, *J*=8.6, –CH–N*H*–), 3.18–3.22 (1H, dd, *J*=5.6 and 10.9, >C–CH_2–OH), 3.60–3.64 (1H, dd, *J*=5.6 and 10.9, >C–CH_2–OH), 5.03 (1H, t, *J*=5.6, –CH_2–O*H*), 5.25 (1H, d, *J*=8.6, –C*H*–NH–), 7.41 (2H, d, *J*=8.4, Br–C_6H_4–), 7.64 (2H, d, *J*=8.4, Br–C_6H_4–); ^{13}C (400 MHz, DMSO-d_6) δ_C 19.90 (>C–*C*H$_3$), 26.99 (–N–*C*H$_3$), 63.59 (>*C*(CH$_3$)–CH$_2$–), 64.28 (>C–*C*H$_2$–OH), 74.10 (–*C*H–NH–), 122.19, 129.76, 131.70 and 138.92 (Br–*C*$_6$H$_4$–), 175.59 (–*C*O–); $C_{12}H_{15}BrN_2O_2$ requires (%): C, 48.18; H, 5.05; N, 9.36; Br, 26.71, found C, 48.17; H, 4.82; N, 9.26; Br, 27.11. Recrystallisation from THF afforded crystals that were suitable for X-ray crystallography. *Crystal data for* ***23***: $C_{12}H_{15}BrN_2O_2$; monoclinic space group $P2_1/n$, a=12.2321(9), b=5.2691(3), c=19.7231(14) Å, β=90.138(3)°, V=1271.19(15) Å^3, T=120 K, Z=4, ρ_{calcd}=1.563 Mg m^{-3}, $2\theta_{max}$=52.0°, Mo Kα λ=0.71073 Å. $R1$=0.0605 (for 1758 reflections with $I>2\sigma(I)$), $wR2$=0.1193 and S=1.178 for 156 parameters and 2435 unique reflections. Minimum/maximum residual electron density −0.588/0.561 e Å^{-3}.

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