Tetrahedron xxx (2014) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Iodocyclisations reactions of Boc- and Cbz-protected *N*-allylguanidines

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ARTICLE INFO

Article history:
Received 14 January 2014
Received in revised form 12 March 2014
Accepted 24 March 2014
Available online xxx

Keywords:
Guanidine
Iodocyclisation
Rearrangement

ABSTRACT

The cyclisation of mono-protected and bis-protected guanidines **8a**–**j** under standard iodocyclisation conditions (I_2/K_2CO_3) gave the guanidine heterocycles **9**–**25** via either a direct cyclisation or by a cyclisation/ring-contraction process, which could be controlled by careful selection of conditions.

1. Introduction

We have previously reported[1–3] on the iodocyclisation[4–11] of allyl substituted guanidines as part of a synthetic approach to a variety of natural products including the hepatotoxin cylindrospermopsin **1**[12,13] the unusual amino acid enduracididine **2**,[14] the cytotoxin nitensidine E **3**,[15] the β-carboline guanidine derivative tiruchanduramine **4**[16] a potent α-glucosidase inhibitor and the cytotoxic guanidine trachycladindole G[17] (Fig. 1).

As part of this work we have studied the cyclisation of a range of mono- and bis-protected allylic and homoallylic substituted guanidines, which have led to the formation of a range of five- and six-membered guanidine heterocycles with a predictable protecting group substitution pattern. We take this opportunity to report our findings in full.

2. Results and discussion

We initially prepared a series of *N*-allyl and *N*-homoallyl guanidines **8a**–**j** via the reaction between the protected pyrazole-carboxamidines[18–20] **6a**–**d** and the amines **7** resulting in the synthesis of the corresponding guanidine in high yields (Scheme 1, Table 1).

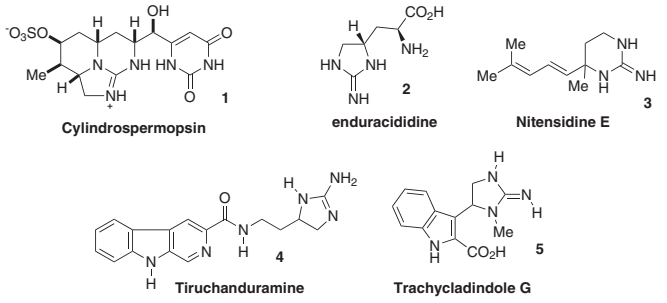

Fig. 1. Target natural products **1**–**5**.

Our initial investigations focused on the formation of five- and six-membered guanidine heterocycles from the bis-protected guanidines and the outcome of this work was much as expected. For example, cyclisation of the guanidine **8a** with iodine in the presence of potassium carbonate gave the corresponding five-membered heterocycle **9a** in 86% yield and similarly the bis-Cbz-protected allyl guanidine **8b** gave **9b** in a 79% yield (Scheme 2).

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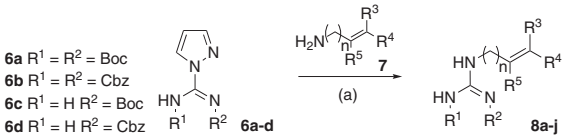
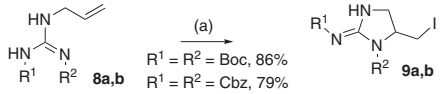
http://dx.doi.org/10.1016/j.tet.2014.03.087



Scheme 1. (a) (Method A) Amine **7**, MeCN/MeOH, 16 h, rt. (Method B) **7**. HCl, NEt_3, $MgSO_4$, CH_3Cl/MeCN, 16 h, rt. (Method C) Amine **7**, reflux, 2.5 h, n=1,2, R^1, R^2, R^3=H, Me.

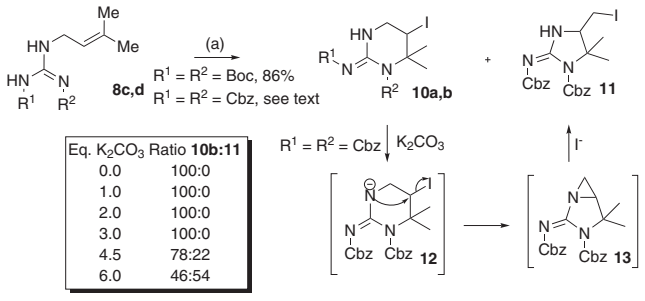
Table 1
Preparation of the *N*-allyl and *N*-homoallyl guanidines **8a**–**j**

8	*n*	R^1	R^2	R^3	R^4	R^5	6	Method	Yield (%)	mp/(°C)
8a	1	Boc	Boc	H	H	H	**6a**	A (MeCN)	78	87–89
8b	1	Cbz	Cbz	H	H	H	**6b**	A (MeCN)	92	46–48
8c	1	Boc	Boc	Me	Me	H	**6a**	B (MeCN)	97	129–132
8d	1	Cbz	Cbz	Me	Me	H	**6b**	B (CH_3Cl)	90	73–76
8e	2	Boc	Boc	H	H	H	**6a**	B (MeCN)	88	82–83
8f	2	Boc	Boc	H	H	Me	**6a**	A (MeOH)	55	70–72
8g	2	Cbz	Cbz	H	H	Me	**6b**	A (MeOH)	86	Wax
8h	1	H	Boc	H	H	H	**6c**	C	80	75–78
8i	1	H	Cbz	H	H	H	**6d**	C	61	119–121
8j	1	H	Cbz	Me	Me	H	**6d**	B (MeCN)	62	81–83



Scheme 2. (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt, 16 h.

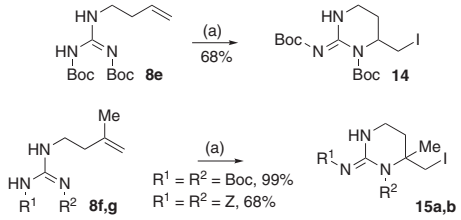
Cyclisation of the dimethylallyl guanidine **8c** was found to be more problematic, the six-membered product **10a** was initially obtained in high yield (ca. 85%) as evidenced by the CH at δ_H 4.27 (1H, dd, *J* 9.1, 5.5 Hz) and δ_C 30.1 ppm, however purification was difficult as the material decomposed on silica gel chromatography. This decomposition was presumably due to the loss of the more sterically hindered Boc-protecting group as similar migration/loss of protecting groups has been observed in the corresponding epoxidation studies.[2] Attempts to recrystallize **10a** were also unsuccessful. Cyclisation of the corresponding Cbz-protected guanidine **8d** was also successful and gave as the major compound a solid product **10b** in 91% yield. This was easily purified by recrystallisation from dichloromethane/petroleum ether and had diagnostic signals at δ_H 4.27 (1H, dd, *J* 8.8 and 5.5 Hz) and δ_C 29.2 ppm corresponding to the CH position. Interestingly, another product compound **11** was also obtained in varying amounts, which gave signals at δ_H 3.17–3.25 (1H, m, CH) and 3.29 (1H, dd, *J* 4.7, 10.1, CH) and δ_C 3.2 ppm indicating that it is a CH_2I containing structure. We repeated the cyclisation with varying amounts of potassium carbonate and found that in the absence of potassium carbonate only the six-membered product **10b** was observed in the crude reaction mixture, however, when more than 4 equiv of base were utilized the side product compound **11** was observed (Scheme 3). It



Scheme 3. (a) CH_3CN, 0–6 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt, 16 h.

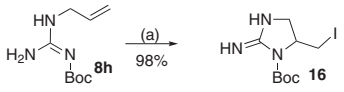
is possible that compound **11** has arisen via a base-mediated ring contraction via the anion **12** and the aziridine **13**. In order to test this hypothesis we took a purified sample of compound **11** and treated it with 5 equiv of finely powdered potassium carbonate in acetonitrile for 16 h at rt. It was found that a mixture of compounds **10b** and **11** was formed, which supports this mechanistic supposition.

We next investigated the cyclisation of the homoallylic guanidine **8e** under these standard conditions to give the six-membered guanidine **14** in 68% yield after chromatography, with the expected signals for the CH_2I group being observed at δ_H 3.09 (1H, dd, *J* 10.6, 9.8 Hz) and δ_H 3.52 (1H, dd, *J* 9.8, 3.8 Hz) and δ_C 6.4 ppm. Similarly the bis-Boc-protected guanidine **8f** was cyclised under the standard conditions to give the six-membered product **15a** in 99% yield, which proved unstable to column chromatography. Diagnostic signals for the CH_2I group were observed at δ_H 3.47 (d, 1H, *J* 10.6 Hz) and 3.74 (d, 1H, *J* 10.6 Hz) and δ_C 12.8 ppm. The bis-Cbz-protected guanidine **8g** was again cyclised under the standard conditions and compound **15b** was obtained in 68% yield by precipitation from dichloromethane/petrol. Similar diagnostic signals for the CH_2I group were observed at δ_H 3.53 (d, 1H, *J* 10.6 Hz) and 3.73 (d, 1H, *J* 10.6 Hz) and δ_C 12.4 ppm (Scheme 4).



Scheme 4. (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt, 16 h.

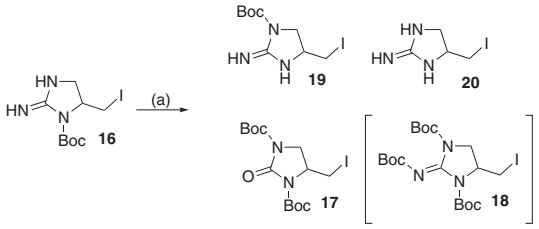
We next investigated the cyclisation of the mono-protected guanidines **8h**–**j**, which proved to be more problematic. Cyclisation reaction of the mono-Boc-allylguanidine **8h** predominantly led to the formation of the product **16** in high yield, however great care was needed as poor stirring led to the formation of rearranged or deprotected products possibly due to the build-up of HI as the reaction proceeds. Cyclisation occurred at the Boc-substituted nitrogen of the guanidine as was apparent from HMBC studies (Scheme 5).



Scheme 5. (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt, 16 h.

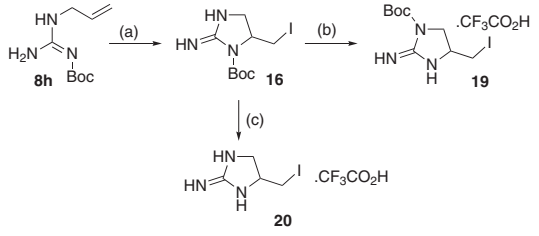
Attempts at purifying compound **16** by column chromatography were problematic as several new products were formed. Previous work[2] on the epoxidation of bis-protected guanidines had demonstrated that cyclic guanidines protected at this position with Boc- and Cbz-protecting groups were prone to migration to hydroxyl groups and it was possible to mediate this by stirring with moist silica gel. An attempt to mimic this with compound **16** was found to give a complex mixture of products and on purification, four compounds were isolated including compound **19** (3% yield), in which the Boc group had migrated, the initially formed compound **16** (4% yield) and a deprotected guanidine **20** (13% yield). Interestingly the urea **17** was also isolated in a low 2% yield, which may have arisen via a sequence of Boc-transfer reactions (possibly via the hydrolysis of a C=*N*-Boc containing intermediate, such as compound **18**, by water[3,21] (Scheme 6)).

Please cite this article in press as: Al Shuhaib, Z.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.03.087



Scheme 6. (a) SiO_2, CH_2Cl_2, stir, 5 d.

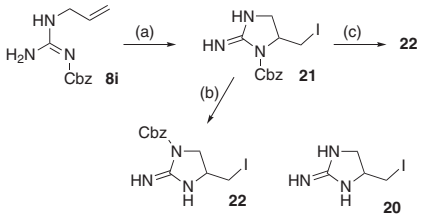
On further analysis it was apparent that on standing, chloroform solutions of the crude product **16** underwent considerable decomposition/rearrangement, with NMR analysis indicating the presence of at least four different compounds. It was thought that trace moisture or acid might be mediating this and we thus took a solution of crude **16** and treated it with an excess of trifluoroacetic acid (TFA) in methanol for 16 h (Scheme 7). On NMR analysis it was



Scheme 7. (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt. (b) TFA, MeOH, 16 h, 51%. (c) TFA/CH_2Cl_2 (1:1), 16 h, 63%.

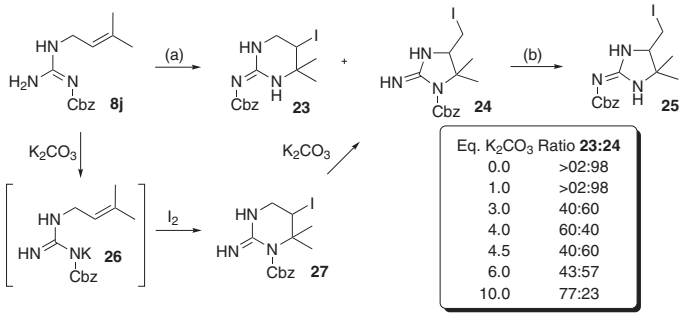
apparent that the initial compound **16** had been converted into a single major compound, which had a ^{1}H NMR spectrum similar to that observed for structure **19**. Final determination of the structure of compound **19** was obtained by HMBC with a correlation between the ring CH_2N signal and the Boc-carbonyl quaternary carbon being observed. Pure compound **19** could be obtained as its trifluoroacetate salt in 51% overall yield by crystallisation from dichloromethane/petroleum ether (5:1). Further to this process treatment of the crude mixture from the iodocyclisation of compound **8h** with a 1:1 mixture of TFA and dichloromethane led to the formation of the fully deprotected guanidine **20** as its TFA salt in 63% overall yield from **8h** (Scheme 7).

We further investigated this process by utilising a Cbz-protected guanidine in the hope that this protecting group might be less likely to undergo rearrangement. Thus cyclisation of mono-Cbz protected allylguanidine **8i** was attempted. Again the expected 5-*exo*-product **21** was observed, which had similar NMR data to compound **16** [δ_H 3.28 (1H, dd, *J* 6.5, 9.8 Hz), 3.38 (1H, dd, *J* 4.7, 9.8 Hz), 3.70 (1H, dd, *J* 5.7, 10.7 Hz), 4.05 (1H, dd, *J* 9.1, 10.5 Hz) 4.16 (1H, dddd, *J* 6.5, 4.7, 5.7, 9.1 Hz), 5.35 (2H, d, *J* 12.3 Hz) and 7.5 (5H, m) and δ_C 9.5, 51.7, 57.3, 68.0, 128.0, 128.5, 134.6, 138.3, 153.5, 154.6]. However this was accompanied by a large number of side-products as was evidenced by a complex NMR spectrum of the crude reaction. Again, attempted purification of this mixture led to further decomposition resulting in the isolation of two compounds, the previously identified de-protected product **20** in 28% yield and the rearranged compound **22** in 8% yield. In order to ascertain if the Cbz-protecting group was migrating in a similar manner to that observed in the Boc-protected series, the reaction was repeated and the resulting crude compound **19** treated with TFA in methanol overnight. This resulted in the formation of a compound **22**, with similar data to **19** at δ_H 3.45 (1H, dd, *J* 11.7, 4.1 Hz, CH), 3.48 (1H, dd, *J* 11.0, 2.2 Hz, CH), 3.63 (1H, dd, *J* 11.0, 5.5 Hz, CH), 3.89 (1H, dd, *J* 10.7, 9.8 Hz, CH), 4.54 (1H, dddd, *J* 11.0, 5.5, 4.1, 2.2 Hz, CH) and δ_C 9.0, 48.3, 58.3, 71.0, 129.9, 129.9, 130.2, 135.7, 152.6, 157.6, but in a much lower yield of 28% (Scheme 8).



Scheme 8. (a) CH_3CN, 4 equiv K_2CO_3, 4 equiv I_2, −15 °C—rt, 16 h. (b) SiO_2, DCM, stir, 5 days (c) TFA, MeOH, 16 h, 28%.

We next investigated the cyclisation of the Cbz-dimethylallyl guanidine **8j**, which was treated under the previously employed conditions and cyclised to give a mixture of two compounds **23** and **24** in a 60:40 ratio. Compound **23** displayed an ABX pattern at δ_H 3.43 (1H, dd, *J* 9.2, 13.6 Hz), 3.55 (1H, dd, *J* 4.6, 13.6 Hz) and 3.97 (1H, dd, *J* 4.6, 9.2 Hz, CH) ppm and a carbon signal at δ_C 27.5 ppm for the CHI group. The other compound **24** displayed a similar ABX pattern at δ_H 3.12 (1H, dd, *J* 8.4, 10.0 Hz), 3.23 (1H, dd, *J* 5.0, 10.0 Hz) and 3.78 (1H, dd, *J* 5.0, 8.4 Hz) ppm whilst giving a signal at δ_C 5.8 ppm for a CH_2 group (Scheme 9). As with previous examples both **23** and **24**



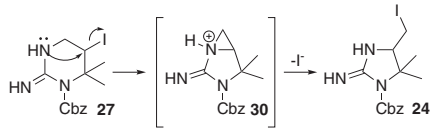
Scheme 9. (a) CH_3CN, K_2CO_3, 0–6 equiv I_2, −15 °C—rt, 16 h, (b) TFA, MeOH, 16 h.

decomposed extensively when in contact with silica gel and they were thus treated with methanolic TFA to give a rearranged mixture containing two products. NMR analysis of the crude mixture indicated that the signals for the major product **23** remained unchanged whilst the minor compound had rearranged to give guanidine **25**, in which the Cbz-group had migrated to the exocyclic nitrogen. This compound displayed an ABX pattern at δ_H 3.36 (1H, dd, *J* 7.6, 11.0 Hz), 3.54 (1H, dd, *J* 4.4, 11.0 Hz) and 3.91 (1H, dd, *J* 4.4, 7.6 Hz) ppm whilst giving a signal at δ_C 2.4 ppm for a CH_2 group.

Interestingly, it was observed that in the reaction of **8j** in the absence of potassium carbonate the rearranged product **24** was formed almost exclusively and only a trace amount of **23** was observed. As the amount of base was increased a general increase in the amount of **23** formed was observed. This would seem to suggest that under acidic conditions (no carbonate) the cyclisation proceeds via the CbzNH function, leading to intermediate **27** and that **27** undergoes rearrangement under the reaction conditions to give **24**.

In comparing the rearrangement of **10b** and **27** the reason for the different conditions required to effect these two ring contraction reactions might lie in the nature of the guanidine substituents. In compound **12** the delocalization of electron density by the two Cbz-protecting groups reduces the nucleophilicity of the remaining ring nitrogen, but leads to increased NH acidity enabling the reaction to proceed under basic conditions. In the case of compound **26** it is possible that the single Cbz-protecting group does not have such a profound effect and it is postulated that sufficient nucleophilicity is present to enable a similar rearrangement under neutral or mildly acidic conditions (Scheme 10).

In conclusion, we have demonstrated that the cyclisation of mono-protected guanidines is a considerably more complex



Scheme 10. Rearrangement of intermediate **27**.

process than for the bis-protected analogues and the products of these reactions proved to be very sensitive to silica gel chromatography and acid. However, the reactions of simple allyl-substituted guanidines do proceed in high yield and in a predictable manner. Both the bis-Cbz-protected and mono-Cbz-protected guanidines **8d** and **8j** undergo ring contraction rearrangements, which can be controlled to some extent by selecting the conditions and these processes should be of synthetic interest in preparing highly substituted cyclic guanidines.

3. Experimental

3.1. General conditions

Column chromatography was carried out on silica gel (particle size 40–63 μm) and TLCs were conducted on precoated Kieselgel 60 F_{254} (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Ether, THF and dichloromethane were dried on a Pure Solv MD-3 solvent purification system. Dry methanol and DMF was purchased from Aldrich. Chemical shifts are reported in δ values relative to chloroform (7.27/77.0 ppm) as an internal standard. Proton and carbon were recorded in $CDCl_3$ on a Bruker AC400 spectrometer unless otherwise stated. Mass spectra data were obtained at the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea. Infrared spectra were recorded as thin films (oils) on a Bruker Tensor 27 series instrument. Protected pyrazole carboxamidines **6** and amines **7** or their salts were obtained from commercial sources or prepared as described in the Supplementary data.

3.2. Preparation of guanidines 8a–j

3.2.1. Method A. The required amine **7** (1.5–2.0 equiv) and pyrazole-1-carboxamide **6** (1.0 equiv) were dissolved in acetonitrile or methanol (ca. 1 mL per mmol of **6**) and stirred at rt. After the reaction was complete (ca. 16 h, TLC), the mixture was evaporated and purified by column chromatography on silica.

3.2.2. Method B. The required amine hydrochloride salt **7** (1.5–6.0 equiv) and pyrazole-1-carboxamide **6a** (1.0 equiv) were dissolved in acetonitrile or chloroform (ca. 1 mL per mmol) and triethylamine (twofold excess based on **7**) was added drop-wise with stirring, together with anhydrous $MgSO_4$ to dryness. After 16 h the mixture was filtered, evaporated and purified by column chromatography on silica.

3.2.3. Method C. The pyrazole-1-carboxamide **6c** or **6d** was dissolved in allylamine (10 mL, excess) and the solution heated at reflux for 2.5 h. The excess amine was removed under vacuum and the residue purified by recrystallization or column chromatography.

*3.2.4. N-Allyl-N′,N″-bis-Boc-guanidine **8a**.*[19] Method A: allylamine (1.60 g, 28.0 mmol) and **6a** (4.5 g, 14.50 mmol) in acetonitrile gave **8a** (3.40 g, 78%) as a white solid after chromatography (5:95 diethyl ether/PE). Mp 87–89 °C (lit.[19] 83–85 °C); $\boldsymbol{R_f}$ 0.17 (5:95 diethyl ether/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 1.48 (9H, s, ^{t}Bu), 1.49 (9H, s, ^{t}Bu), 4.06 (2H, apparent tt, *J* 5.6, 1.5 Hz, CH_2), 5.15 (1H, dq, *J* 10.4, 1.5 Hz, CH), 5.22 (1H, dq, *J* 17.2, 1.5 Hz, CH), 5.87 (1H, ddt, *J* 17.2, 10.4, 5.6 Hz, CH), 8.39 (1H, br t, *J* 5.6 Hz, NH), 11.51 (1H, br s, NH); $\boldsymbol{\delta_C}$ (100.6 MHz, $CHCl_3$) 28.0, 28.2, 43.2, 79.2, 83.1, 116.7, 133.3, 153.2, 156.0, 163.5; **MS (CI)** *m*/*z* 300 (100% $[M+H^+]$); **HRMS (CI)** found 300.1920. $C_{14}H_{25}N_3O_4$ ($[M+H]^+$) requires 300.1918.

*3.2.5. N-Allyl-N′,N″-bis-Cbz-guanidine **8b**.* Method A: allylamine (0.58 g, 10.2 mmol) and **6b** (1.90 g, 5.02 mmol) in acetonitrile gave **8b** (1.70 g, 92%) as a white solid after chromatography (PE to 10:90 EtOAc/PE). Mp 46–48 °C; $\boldsymbol{R_f}$ 0.45 (25:75 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 3.98–4.02 (2H, m, CH_2), 5.05–5.18 (6H, m, 2× CH_2, 2× CH), 5.76–5.85 (1H, m, CH), 7.15–7.35 (10H, m, 2× Ph), 8.32 (1H, br, NH), 11.67 (1H, br, NH); $\boldsymbol{\delta_C}$ (100.6 MHz, $CHCl_3$) 43.4, 67.2, 68.2, 116.9, 127.9, 128.1, 128.4, 128.5, 128.7, 128.8, 132.9, 134.6, 136.7, 153.8, 155.9, 163.7; $\boldsymbol{\nu_{max}}$ 3339, 3094, 3066, 3034, 2953, 1730, 1637, 1620, 1571; **MS (CI)** *m*/*z* 368.1 (2%, $([M+H]^+)$; **HRMS (CI)** *m*/*z* found 368.1608. $C_{20}H_{22}N_3O_4$ $[M+H]^+$) requires 368.1605.

*3.2.6. N-(3,3-Dimethylallyl)-N′,N″-bis-Boc-guanidine **8c**.* Method B: 1-amino-3-methyl-2-butene hydrochloride salt (0.93 g, 7.68 mmol), **6a** (1.65 g, 5.32 mmol), triethylamine (1.56 g, 1.14 mL, 15.4 mmol) and $MgSO_4$ (ca. 1.00 g) in MeCN (15 mL) gave **8c** (1.68 g, 97%) as a white solid after chromatography (5:95 diethyl ether/PE). Mp 129–132 °C; $\boldsymbol{R_f}$ 0.08 (5:95 diethyl ether/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 1.49, (9H, s, ^{t}Bu), 1.51, (9H, s, ^{t}Bu), 1.67 (3H, s, CH_3), 1.73 (3H, d, *J* 0.8 Hz, CH_3), 3.99 (2H, br t, *J* 6.0 Hz, CH_2), 5.20–5.26 (1H, m, CH), 8.13 (1H, br s, NH), 11.49 (1H, br s, NH); $\boldsymbol{\delta_C}$ (100.6 MHz, $CHCl_3$) 18.0, 25.7, 28.0, 28.3, 39.1, 79.2, 82.9, 119.1, 137.2, 153.2, 156.8, 163.5; $\boldsymbol{\nu_{max}}$ 3344, 1715, 1636; **MS** (ES) 328 (100%, $[M+H^+]$); **HRMS** (ESI) found 328.2235. $C_{16}H_{30}N_3O_4$ ($[M+H^+]$) requires 328.2231.

*3.2.7. N-(3,3-Dimethylallyl)-N′-N″-bis-Cbz-guanidine **8d**.* Method B: a solution of 1-amino-3-methyl-2-butene hydrochloride salt (5.79 g, 47.6 mmol) in chloroform (50 mL) and **6b** (3.0 g, 7.93 mmol) and triethylamine (8.4 mL, 6.06 g, 60 mmol) in acetonitrile (40 mL) dried with $MgSO_4$ (ca. 2.0 g) gave **8d** (2.81 g, 90%) after chromatography (PE to 10:90 EtOAc/PE) as a white solid. Mp 73–76 °C; $\boldsymbol{R_f}$ 0.16 (10:90 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 1.69 (3H, s, CH_3), 1.75 (3H, s, CH_3), 4.00–4.05 (2H, m, CH_2), 5.15 (2H, s, CH_2), 5.18 (2H, s, CH_2), 5.22–5.27 (1H, m, CH), 7.28–7.44 (10H, m, 2× Ph), 8.17 (1H, s, NH), 11.75 (1H, s, NH); $\boldsymbol{\delta_C}$ (100.6 MHz, $CHCl_3$) 18.0, 25.6, 39.3, 67.1, 68.0, 118.8, 127.8, 128.1, 128.3, 128.6, 128.7, 134.6, 136.8, 137.6, 153.8, 155.5, 163.6; $\boldsymbol{\nu_{max}}$ 3342, 3066, 3044, 2933, 1729, 1640; **MS** (CI) 396 (100%, $[M+H^+]$); **HRMS** (ESI) found 396.1920. $C_{22}H_{26}N_3O_4$ ($[M+H^+]$) requires 396.1918.

*3.2.8. N-Homoallyl-N′,N″-bis-(Boc)guanidine **8e**.* Method B: but-3-en-1-amine hydrochloride (3.55 g, 33.2 mmol), **6a** (2.0 g, 6.44 mmol), triethylamine (6.2 mL, 44.3 mmol) and $MgSO_4$ in acetonitrile (50 mL) gave **8e** (1.78 g, 5.68 mmol, 88%) after chromatography (10:90 EtOAc/PE) as a white solid. Mp 82–83 °C; $\boldsymbol{R_f}$ 0.51 (30:70 EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 1.49 (9H, s, ^{t}Bu), 1.51 (9H, s, ^{t}Bu), 2.32 (2H, app qt, *J* 6.8, 1.2 Hz), 3.51 (2H, dt, *J* 6.8, 5.5, CH_2), 5.09–5.17, (2H, m, 2× CH), 5.74–5.84 (1H, m, CH), 8.35 (1H, br s, NH) 11.49 (1H, br s, NH); $\boldsymbol{\delta_C}$ (100.6 MHz, $CHCl_3$) 28.0, 28.3, 33.2, 40.0, 79.2, 83.0, 117.5, 134.8, 153.2, 156.1, 163.6; $\boldsymbol{\nu_{max}}$ 3333, 3293, 3134, 3082, 2980, 2934, 1722, 1640, 1622, 1575; **MS (EI)** 313 (2%, $[M^+]$), 201 (100%); **HRMS (EI) (M^+)** found 313.2002. $C_{15}H_{27}N_3O_4$ ($[M^+]$) requires 313.2002.

*3.2.9. N,N′-bis-Boc-N″-1-(3-methylbut-3-en-1-yl)guanidine **8f**.* Method A: 3-methylbut-3-en-1-amine (24.16 mmol), **6a** (5.00 g, 16.11 mmol) and $MgSO_4$ (ca. 2 g) in methanol (120 mL) gave **8f** (2.89 g, 8.83 mmol, 55% yield) as a white solid after chromatography (10:90 EtOAc/PE). Mp 70–72 °C; $\boldsymbol{R_f}$ 0.20 (10% EtOAc/PE); $\boldsymbol{\delta_H}$ (400 MHz, $CHCl_3$) 1.50 (9H, s, ^{t}Bu), 1.52 (9H, s, ^{t}Bu), 1.76 (3H, s, CH_3),

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2.28 (2H, t, J 6.8 Hz, CH_2), 3.57 (2H, td, *J* 6.8, 3.4 Hz, CH_2), 4.80 (1H, s, CH), 4.86 (1H, s, CH), 8.34 (1H, br t, *J* 3.4 Hz, NH), 11.49 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 22.1, 28.0, 28.3, 36.9, 38.8, 79.2, 82.9, 112.6, 142.0, 153.1, 156.1, 163.6; ν_{max} 3335, 3291, 3148, 3085, 2981, 2936, 1725, 1638, 1617, 1577; **MS (ES)** 328 (100%, ($[M+H]^+$)); **HRMS (ES)** found 328.2234. $C_{16}H_{30}N_3O_4$ ($[M+H]^+$) requires 328.2231.

*3.2.10. N,N′-bis-Cbz-N″-1-(3-methylbut-3-en-1-yl)guanidine **8g**.* Method B: 3-methylbut-3-en-1-amine (23.25 mmol), **6b** (5.80 g, 15.32 mmol) and $MgSO_4$ (ca. 1–2 g) in methanol (120 mL) gave **8g** (5.18 g, 13.10 mmol, 86% yield) as a wax after chromatography (10:90 EtOAc/PE). R_f 0.20 (10:90 EtOAc/PE); δ_H (400 MHz, $CHCl_3$) 1.77 (3H, s, CH_3), 2.31 (2H, t, *J* 6.7 Hz, CH_2), 3.59 (2H, td, *J* 6.7, 5.2 Hz, CH_2), 4.83 (1H, br s, CH), 4.91 (1H, br s, CH), 5.16 (2H, s, CH_2), 5.18 (2H, s, CH_2), 7.27–7.43 (10H, m, 2× Ph), 7.56 (1H, br t, *J* 5.2 Hz, NH), 11.78 (1H, s, NH); δ_C (100.6 MHz, $CHCl_3$) 22.0, 36.7, 39.0, 67.2, 68.1, 112.9, 126.9, 127.9, 128.1, 128.4, 128.5, 128.7, 128.8, 134.7, 136.8, 141.9, 153.8, 155.9, 163.7; ν_{max} (cm^{-1}) 3313, 3282, 3067, 3036, 2940, 2926, 1724, 1622; **MS (ES)** 395 (100%, ($[M+H]^+$)); **HRMS (ES)** found 396.1917. $C_{22}H_{26}N_3O_4$ ($[M+H]^+$) requires 396.1918.

*3.2.11. N-Boc-N′-allylguanidine **8h**.* Method C: allylamine (10 mL) and **6c** (2.0 g, 9.51 mmol) give **8h** (1.51 g, 7.58 mmol, 80%) after recrystallization from dichloromethane/petrol (ca. 1:1) as a white solid. Mp 75–78 °C; δ_H (400 MHz, $CHCl_3$) 1.46 (9H, s, ^{t}Bu), 3.83 (2H, d, *J* 4.9 Hz, CH_2), 5.24 (1H, br d, *J* 10.4 Hz, CH) 5.33 (1H, br d, *J* 17.1 Hz, CH), 5.83 (1H, ddt, *J* 17.1, 10.4, 4.9 Hz, CH), 6.34 (1H, br s, NH), 7.60 (2H, br s, 2× NH); δ_C (100.6 MHz, $CHCl_3$) 28.4, 43.9, 78.1, 117.3, 133.5, 162.1, 163.6; ν_{max} 3468, 3238, 3134, 3010, 1649, 1635, 1591; **HRMS (ES+)** found 200.1391. $C_9H_{18}N_3O_2$ ($[M+H]^+$) requires 200.1394.

*3.2.12. N-Cbz-N′-allylguanidine **8i**.* Method C: allylamine (10 mL) and **6d** (4.00 g, 16.37 mmol) gave **8i** (2.32 g, 9.94 mmol, 61%) as a white solid after chromatography (0:100 to 60:40 EtOAc/PE). Mp 119–121 °C; R_f 0.24 (75:25 EtOAc/PE); δ_H (400 MHz, $CHCl_3$) 3.73 (2H, d, *J* 4.9 Hz, CH_2), 5.07 (2H, s, CH_2), 5.23 (1H, d, *J* 11.3 Hz, CH), 5.25 (1H, d, *J* 16.8 Hz, CH), 5.73 (1H, ddd, *J* 16.8, 11.3, 4.9 Hz, CH), 7.19–7.32 (5H, m, Ph), 7.40 (3H, br s, 3× NH) δ_C (100.6 MHz, $CHCl_3$) 41.9, 66.2, 116.4, 127.8, 128.0, 128.4, 133.6, 137.3, 162.5, 163.6; ν_{max} 3401, 3314, 3254, 3089, 3068, 3032, 2991, 2924, 1629, 1592, 1387; **HRMS (ES+)** found 234.1245. $C_{12}H_{16}N_3O_2$ ($[M+H]^+$) requires 234.1237.

*3.2.13. N-Cbz-N′-(dimethylallyl)guanidine **8j**.* Method B: 1-amino-3-methyl-2-butene hydrochloride salt (1.5 g, 12.33 mmol), **6d** (1.00 g, 4.094 mmol), triethylamine (2.5 g, 3.5 mL, 22.7 mmol) and $MgSO_4$ (ca. 1.0 g) in acetonitrile (10 mL) at rt for 16 h followed by reflux for 8 h gave **8j** (0.667 g, 2.55 mmol, 62%) as an off-white solid after chromatography (0:100 to 80:40 EtOAc/PE). Mp 81–83 °C; R_f 0.21 (70:30 EtOAc/PE); δ_H (400 MHz, $CHCl_3$) 1.52 (3H, s, CH_3), 1.61 (3H, s, CH_3), 3.56 (2H, d, *J* 6.3 Hz, CH_2), 4.97 (2H, s, CH_2), 5.00–5.06 (1H, m, CH), 6.60 (2H, br s, NH_2) 7.16–7.28 (5H, m, Ph), 9.0 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 17.7, 25.5, 39.2, 66.0, 120.0, 127.5, 127.7, 128.2, 136.4, 137.4, 162.2, 163.6; ν_{max} 3306, 3018, 1627, 1589; **HRMS (ES+)** found 262.1551. $C_{14}H_{20}N_3O_2$ ($[M+H^+]$) requires 262.1550.

3.3. Iodocyclisation reactions

3.3.1. General method. Iodine (3–4 equiv) is added to a cooled (−15 °C), stirred mixture of the guanidines **8a**–**j** (1 equiv) and finely powdered anhydrous potassium carbonate (0–6 equiv) in dry MeCN (ca. 20 mL per mmol **8a**–**j**). The resulting mixture was stirred to rt over 16 h, then sodium thiosulfate solution (aq, satd) was added until decolourisation occurred. The resulting mixture was then extracted with dichloromethane (3×20 mL) and the combined organic phases dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography on silica gel (EtOAc/PE) or recrystallization gave the desired products.

*3.3.2. tert-Butyl-1-(Boc)-5-(iodomethyl)imidazolidin-2-ylidenecarbamate **9a**.* Using the general method, iodine (0.95 g, 3.74 mmol), **8a** (0.28 g, 0.935 mmol) and potassium carbonate (0.52 g, 0.77 mmol) gave **9a** (0.34 g, 0.80 mmol, 86%) after recrystallization (50:50 Et_2O/PE). Mp 60–62 °C; R_f 0.22 (10:90 Et_2O/PE); δ_H (400 MHz, $CHCl_3$) 1.46 (9H, s, ^{t}Bu), 1.52 (9H, s, ^{t}Bu), 3.25 (1H, dd, *J* 9.3, 8.9 Hz, CH), 3.35 (1H, br d, *J* 9.3 Hz, CH), 3.58 (1H, dd, *J* 2.4, 13.5 Hz, CH), 3.85–3.95 (1H, m, CH), 4.15–4.25 (1H, br m, CH), 9.30 (1H, br s, NH) δ_C (100.6 MHz, $CHCl_3$) 8.0, 27.9, 28.0, 56.7, 81.0, 83.9, 150.7 (2× C not detected); ν_{max} 3316, 2976, 2933, 1760, 1708, 1530; **MS (CI)** 426 (30%, $[M+H]^+$); **HRMS (CI)** found 426.0886. $C_{14}H_{25}IN_3O_4$ ($[M+H]^+$) requires 426.0884.

*3.3.3. Benzyl-1-((benzyloxy)-carbonyl)-5-(iodomethyl)-imidazolidin-2-ylidene carbamate **9b**.* Using the general method, iodine (1.38 g, 5.44 mmol), **8b** (0.5 g, 1.36 mmol) and potassium carbonate (0.75 g, 5.44 mmol) gave **9b** (0.53 g, 1.07 mmol, 79%) after chromatography (EtOAc/PE 20/80–50/50) as a pale yellow solid. Mp 103–105 °C; R_f 0.23 (50:50 EtOAc/PE); δ_H (400 MHz, $CHCl_3$) 3.31 (1H, dd, *J* 9.0, 9.8 Hz, CH), 3.43 (1H, dd, *J* 9.8, 2.2 Hz, CH), 3.60 (1H, dd, *J* 11.6, 3.2 Hz, CH), 3.86 (1H, dd, J 11.6, 9.1 Hz, CH), 4.39–4.46 (1H, m, CH), 5.17 (2H, s, CH_2), 5.28 (1H, d, *J* 12.3 Hz, CH), 5.34 (1H, d, *J* 12.3 Hz, CH), 7.29–7.47 (10H, m, 2× Ph), 8.5 (1H, br s, NH) δ_C (100.6 MHz, $CHCl_3$) 7.1, 46.2, 57.5, 68.7, 128.1 (CH), 128.0, 128.1, 128.2, 128.4, 128.6, 128.7, 134.8, 136.2, 151.1, 161.0, 167.7; ν_{max} 3350, 3050, 3025, 1761, 1713, 1652, 1605; **MS (EI)** 493 (8%), 218 (100%); **HRMS (EI)** found 493.0498. $C_{20}H_{20}IN_3O_4$ ($[M^+]$) requires 493.0499.

*3.3.4. 2-tert-Butoxycarbonylimino-5-iodo-6,6-dimethyl-tetrahydropyrimidine-1-carbozylic acid tert-butylester **10a**.* Using the general method, iodine (1.16 g, 4.57 mmol), **8c** (0.50 g, 1.53 mmol) and potassium carbonate (0.86 g, 6.22 mmol) gave **10a** (588 mg, 1.30 mmol, 85%) as an unstable oil. δ_H (400 MHz, $CHCl_3$) 1.41 (9H, s, ^{t}Bu), 1.50 (3H, s, Me), 1.51 (9H, s, ^{t}Bu), 1.52 (3H, s, Me), 3.72 (1H, dd, *J* 13.4, 9.2 Hz, CH), 3.83 (1H, dd, *J* 13.4, 5.4 Hz, CH), 4.23 (1H, dd, *J* 9.2, 5.4 Hz, CH), 9.40 (1H, bd s, NH); δ_C (100.6 MHz, $CHCl_3$) 24.1, 26.6, 27.4, 28.2, 30.1, 46.8, 57.1, 77.7, 84.0, 152.0, 156.2, 163.5 ν_{max} 3268, 1750, 1603; **HRMS (CI)** compound underwent decomposition.

*3.3.5. Benzyl-2-(benzyloxycarbonyl)-5-iodo-6,6-dimethyl-tetrahydropyrimidine-1(2H)-carboxylate **10b**.* Using the general method, iodine (0.52 g, 2.04 mmol, 4.0 equiv), **8d** (0.202 g, 0.51 mmol) and potassium carbonate (0.07 g, 0.51 mmol, 1.0 equiv) gave **10b** (0.242 g, 91%) on recrystallization from dichloromethane/PE (1:4). Mp 123–125 °C δ_H (400 MHz, $CHCl_3$) 1.51 (3H, CH_3), 1.53 (3H, CH_3), 3.78 (1H, dd, *J* 13.6, 8.8 Hz, CH), 3.90 (1H, dd, *J* 13.6, 5.5 Hz CH) 4.26 (1H, dd, *J* 8.8, 5.5 Hz CH) 5.09 (2H, AB pattern, *J* 12.6, CH_2), 5.30 (2H, AB pattern, *J* 12.0, CH_2), 7.25–7.48 (10H, m, 2× Ph), 9.71 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 24.6, 26.4, 29.2, 46.9, 57.8, 66.9, 70.0, 127.6, 127.9, 128.3, 128.5, 128.6, 134.5, 137.2, 153.6, 156.6, 163.6; ν_{max} 3253, 3066, 3017, 2952 (C–H), 1752, 1631, 1605; **MS (CI)** 522 (100%, $[M+H^+]$); **HRMS (CI)** found 522.0886. $C_{22}H_{25}IN_3O_4$ $[M+H^+]$ requires 522.0884.

*3.3.6. Benzyl-2-(((benzyloxy)carbonyl)imino)-4-(iodomethyl)-5,5-dimethylimidazolidine-1-carboxylate **11**.* Evaporation of the combined mother liquors from several preparations of **10b** followed by chromatography in diethyl ether/PE (50:50) gave **11** as a waxy solid. R_f 0.21 (25:75 EtOAc/PE); δ_H (100.6 MHz, $CHCl_3$) 1.44 (3H, CH_3), 1.57 (3H, CH_3), 3.17–3.25 (1H, m, CH), 3.29 (1H, dd, *J* 10.1, 4.7 Hz, CH) 3.82–3.85 (1H, m, CH), 5.18 (2H, AB pattern, *J* 12.4 Hz, CH_2), 5.29 (2H, s, CH_2) 7.30–7.50 (10H, m, 2× Ph), 9.19 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 3.2, 19.3, 26.1, 46.7, 64.0, 67.3, 68.5, 127.9, 128.1,

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128.2, 128.3, 128.4, 128.5, 134.8, 136.4, 151.5, 153.6, 156.5; ν_{max} 3331, 3034, 3006, 2960, 2932, 1758, 1726, 1652, 1613; **MS (CI)** 522 (85%, [M+H$^+$]), 544 (85%, [M+Na$^+$]), 1065 (65%, [2M+Na$^+$]); **HRMS (CI)** found 522.0874. $C_{22}H_{25}IN_3O_4$ [M+H$^+$] requires 522.0884.

*3.3.7. Benzyl-3-((benzyloxy)carbonyl)-tetrahydro-4-(iodomethyl) pyrimidin-2-(1H)-ylidene carbamate **14**.* Using the general method, iodine (1.19 g, 4.69 mmol), **8e** (0.37 g, 1.18 mmol) and potassium carbonate (0.65 g, 4.70 mmol) gave **14** (0.35 g, 68%) after chromatography (EtOAc/PE 15/85–30/70) as a white solid. Mp 107–108 °C; R_f 0.34 (30:70 EtOAc/PE); δ_H (400 MHz, $CHCl_3$) 1.47 (9H, s, ^{t}Bu) 1.52 (9H, s, ^{t}Bu), 2.07–2.15 (1H, m, CH), 2.23–2.32 (1H, m, CH), 3.09 (1H, dd, *J* 10.6, 9.8 Hz, CH), 3.35 (2H, t, *J* 6.2 Hz, CH_2), 3.52 (1H, dd, *J* 9.8, 3.8 Hz, CH), 4.36–4.43 (1H, m, CH), 9.0 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 6.1, 27.6, 28.0, 28.2, 36.7, 54.1, 79.4, 83.5, 151.9, 157.9, 162.2; ν_{max} 3153, 2920, 2725, 1735, 1714, 1650; **MS (EI)** 439 (3%, [M$^+$]); **HRMS (EI)** found 439.0967. $C_{15}H_{26}IN_3O_4$ [M$^+$] requires 439.0968.

*3.3.8. tert-Butyl 2-(tert-butoxycarbonylimino)-6-(iodomethyl)-6-methyl tetrahydropyrimidine-1(2H)-carboxylate **15a**.* Using the general method, iodine (1.55 g, 6.11 mmol), **8f** (0.50 g, 1.53 mmol) and potassium carbonate (1.26 g, 9.12 mmol) gave **15a** (0.69 g, 99%) as a yellow gum, which was unstable to chromatography. δ_H (400 MHz, $CHCl_3$) 1.44 (9H, s, ^{t}Bu), 1.53 (9H, s, CH_3), 1.56 (3H, s, CH_3), 1.90 (1H, ddd, *J* 13.6, 98, 6.1 Hz, CH), 2.33 (1H, dt, *J* 13.6, 5.9 Hz, CH), 3.25–3.37 (2H, m, CH_2), 3.47 (1H, d, *J* 10.6 Hz, CH), 3.74 (1H, d, *J* 10.6 Hz, CH), 9.54 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 12.8, 24.0, 27.6, 28.3, 33.2, 35.7, 55.7, 77.9, 84.1, 152.6, 157.2, 163.6; ν_{max} 3263, 2977, 2932, 1738, 1614; **MS (ESI)** 454 (100%, [M+H$^+$]); **HRMS (ES)** found 454.1195. $C_{16}H_{29}IN_3O_4$ ([M+H$^+$]) requires 454.1197.

*3.3.9. Benzyl 2-(((benzyloxy)carbonyl)imino)-6-(iodomethyl)-6-methyltetrahydropyrimidine-1(2H)-carboxylate **15b**.* Using the general method, iodine (1.27 g, 5.04 mmol), **8g** (0.50 g, 1.264 mmol) and potassium carbonate (1.05 g, 7.58 mmol) gave crude **15b** (0.69 g), which was dissolved in dichloromethane (ca. 5 mL) and diluted with petrol to the cloud point. After cooling (−20 °C) overnight a small amount of dark oil precipitated. The supernatant liquid was decanted, warmed to rt and diluted with further PE (50 mL). After cooling (−20 °C) overnight, the supernatant was removed again and the precipitated gum was washed with a small portion of PE, which was again decanted to give on drying under vacuum the product **15b** (0.45 g, 0.86 mmol, 68% yield) as a yellow gum. δ_H (400 MHz, $CHCl_3$) 1.52 (3H, s, CH_3), 1.90 (1H, ddd, *J* 13.8, 9.0, 6.0 Hz, CH), 2.37 (1H, dt, *J* 13.8, 4.9 Hz, CH), 3.27–3.40 (2H, m, CH_2), 3.53 (1H, d, *J* 10.6 Hz, CH), 3.73 (1H, d, *J* 10.6 Hz, CH), 5.07 (1H, d, *J* 12.5 Hz, CH), 5.13 (1H, d, *J* 12.5 Hz, CH), 5.23 (1H, d, *J* 12.1 Hz, CH), 5.32 (1H, d, *J* 12.1 Hz, CH), 7.28–7.48 (10H, m, 2× Ph), 9.81 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 12.4, 24.0, 33.1, 35.7, 56.5, 66.9, 70.0, 127.7, 127.9, 128.3, 128.5, 128.7, 134.6, 137.2, 154.1, 157.6, 163.7; ν_{max} (cm^{-1}) 3263, 3173, 3063, 3032, 2943, 2886, 1743, 1700, 1610; **MS (ES)** 521 (100%, ([M+H]$^+$)); **HRMS (ES)** found 522.0878. $C_{22}H_{25}IN_3O_4$ ([M+H]$^+$) requires 522.0884.

*3.3.10. tert-Butyl 2-imino-5-(iodomethyl)imidazolidine-1-carboxylate **16**.* Using the general method, iodine (2.55 g, 10.1 mmol), **8h** (0.50 g, 2.51 mmol) and potassium carbonate (1.40 g, 10.1 mmol) gave crude **16** (0.80 g, 98%) as an oil. δ_H (400 MHz, CD_3OD) 1.60 (9H, s, ^{t}Bu), 3.45 (1H, dd, *J* 11.5, 4.2 Hz, CH), 3.52 (1H, dd, *J* 10.7, 2.1 Hz, CH), 3.72 (1H, dd, *J* 10.7, 5.8 Hz, CH), 3.89 (1H, dd, *J* 11.5, 9.7 Hz, CH), 4.47 (1H, dddd, *J* 9.7, 5.8, 4.2, 2.1 Hz, CH) δ_H (DMSO) 1.50 (9H, s, ^{t}Bu), 3.17 (1H, dd, *J* 11.7, 4.2, CH) 3.46 (1H, dd, *J* 10.5, 1.9 Hz, CH), 3.57 (1H, dd, *J* 10.5, 5.6 Hz, CH), 3.71 (1H, dd, *J* 11.7, 9.6 Hz, CH), 3.88 (1H, dd, *J* 11.5, 9.7 Hz, CH), 4.47 (1H, dddd, *J* 9.6, 5.6, 4.2, 1.9 Hz, CH); δ_H (400.MHz, $CHCl_3$) 1.58 (9H, s, ^{t}Bu), 3.38 (1H, dd, *J* 10.4, 2.0 Hz, CH), 3.47–3.55 (2H, m, 2× CH), 3.96 (1H, dd, *J* 10.4, 9.6 Hz, CH), 4.34–4.44 (1H, m, CH), 8.03 (2H, br s 2× NH); δ_C (100.6 MHz, CD_3OD) 10.5, 28.3, 54.7, 58.5 79.5, 152.0, 157.1; δ_C (100.6 MHz, $(CD_3)_2SO$) 11.7, 27.5, 48.4, 56.3, 84.9, 150.0, 154.6; δ_C (100.6 MHz, $CHCl_3$) 7.7, 28.0, 49.9, 57.2, 86.6, 2× C not detected.

*3.3.11. Rearrangement of **16** on silica gel.* Crude **16** (0.74 g) was dissolved in dichloromethane (5 mL) and silica gel (5 g) was added and the resultant slurry (ensuring sufficient dichloromethane was added to maintain a slurry) stirred for 5 days. The slurry was then washed onto a sintered filter using dichloromethane, which was washed with excess dichloromethane to give after evaporation a crude extract (0.15 g). The silica pad was further washed with excess methanol to give after evaporation a further crude extract (0.43 g). Column chromatography of the dichloromethane extract (EtOAc/petrol, 0:100 to 20:80 in 10% steps) gave the urea **17** (15.0 mg, 1.5%) as a solid. Chromatography of the methanolic extract (0:100 to 30:70 MeOH/$CHCl_3$) gave **19** (19.0 mg, 3%) and **20** (95.0 mg, 13%) as solids.

*3.3.11.1. 4-Iodomethyl-2-oxo-imidazolidine-1,3-dicarboxylic acid di-tert-butyl ester **17**.* Mp 123–125 °C; R_f 0.21 (5:95 EtOAc/PE petrol); δ_H (400 MHz, $CHCl_3$) 1.49 (9H, s, ^{t}Bu), 1.50 (9H, s, ^{t}Bu), 3.31 (1H, dd, *J* 10.1, 8.5 Hz, CH), 3.45 (1H, dd, *J* 10.1, 2.5 Hz, CH), 3.56 (1H, dd, *J* 11.0, 3.2 Hz, CH), 3.76 (1H, dd, *J* 11.0, 9.2 Hz, CH), 4.16–4.22 (1H, m, CH); δ_C (100.6 MHz, $CHCl_3$) 7.7, 28.0, 29.7, 45.9, 51.2, 83.7, 84.1 (3× C not observed); ν_{max} 1789, 1738; **HRMS (ES+)** found 427.0726. $C_{14}H_{23}IN_2O_5$ [(M+H)$^+$] requires 427.0724.

*3.3.11.2. tert-Butyl 2-imino-4-(iodomethyl)imidazolidine-1-carboxylate **19**.* R_f 0.29 (10:90 MeOH/$CHCl_3$); δ_H (400 MHz, CD_3OD) 1.57 (9H, s, ^{t}Bu), 3.41 (2H, d, *J* 4.1 Hz, CH_2), 3.70 (1H, dd, *J* 10.5, 4.6 Hz, CH), 4.03–4.08 (1H, m, CH), 4.09 (1H, dd, *J* 10.5, 9.6 Hz, CH) δ_C (100.6 MHz, CD_3OD) 11.4, 28.8, 57.8, 55.5, 83.6, 154.6, 165.4.

*3.3.11.3. 4-Iodomethyl-imidazolidin-2-ylideneamine-H_2CO_3 **20**.* R_f 0.29 (20:80 MeOH/$CHCl_3$); δ_H (400 MHz, CD_3OD) 3.39–3.49 (3H, m, CH, CH_2), 3.87 (1H, app t, *J* 10.0 Hz, CH), 4.13–4.18 (1H, m, CH); δ_C (100.6 MHz, CD_3OD) 11.2, 50.7, 57.0, 151.2, 161.2; ν_{max} 3419, 1731, 1687; **HRMS (ES+)** found 225.9836. $C_4H_8IN_3$ [(M+H)$^+$] requires 225.9836.

*3.3.12. Rearrangement of **16** using trifluoroacetic acid: tert-butyl 2-imino-4-(iodomethyl)imidazolidine-1-carboxylate trifluoroacetate salt **19**.* Crude **16** (0.498 g, from **8h** (0.30 g, 1.51 mmol)) was dissolved in methanol (5 mL) and trifluoroacetic acid (0.38 mL, 4.9 mmol) was added and the reaction stirred for 16 h. On evaporation a solid (0.65 g) was obtained, which was dissolved in minimum volume of DCM (ca. 5–10 mL), which was diluted with a small volume of PE (1–2 mL) and placed in a freezer overnight to give **19** (0.34 g, 51%) as a pale yellow solid. Mp 90–92 °C; R_f 0.29 (10:90 MeOH/$CHCl_3$); δ_H (400 MHz, CD_3OD) 1.60 (9H, s, ^{t}Bu), 3.42 (1H, dd, *J* 10.6, 4.5 Hz, CH), 3.54 (1H, dd, *J* 11.0, 2.0 Hz, CH), 3.74 (1H, dd, *J* 11.0, 5.5 Hz, CH), 3.90 (1H, dd, *J* 10.6, 9.9 Hz, CH), 4.51 (1H, *J* 9.9, 5.5, 4.5, 2.0 Hz, CH) δ_H (400 MHz, $CHCl_3$) 1.56 (9H, s, ^{t}Bu), 3.36 (1H, dd, *J* 10.8, 2.2 Hz, CH), 3.46 (1H, dd, *J* 10.8, 4.3 Hz, CH), 3.52 (1H, dd, *J* 10.8, 6.6 Hz, CH), 3.87 (1H, dd, *J* 10.8, 9.4 Hz, CH), 4.39 (1H, dddd, *J* 9.4, 6.6, 4.3, 2.2 Hz, CH) 7.75 (1H, br s, NH), 11.07 (1H, br s, NH), 11.88 (1H, br s, NH); δ_H (400 MHz, DMSO) 1.52 (9H, s, ^{t}Bu), 3.24 (1H, dd, *J* 10.5, 4.2 Hz, CH), 3.52 (1H, dd, *J* 10.6, 2.0 Hz, CH), 3.64 (1H, dd, *J* 10.6, 5.2 Hz, CH), 3.77 (1H, dd, *J* 10.5, 9.9 Hz, CH), 4.42 (1H, dddd, *J* 9.9, 5.2, 4.2, 2.0 Hz, CH) 7.75 (1H, br s, NH), 11.07 (1H, br s, NH), 11.88 (1H, br s, NH); δ_C (100.6 MHz, $CHCl_3$) 7.0, 27.8, 46.9, 56.8, 87.4, 116.5 (q, $^1J_{C-F}$ 292.0 Hz), 149.9, 156.9, 163.2 (q, $^2J_{C-C-F}$ 35.0 Hz); ν_{max} 3306, 1752, 1679; **MS (ES+)** 326 (45%, [M+H]$^+$), 270 (100%);

HRMS (ES+) found 326.0363. $C_9H_{17}IN_3O_2$ [$(M+H)^+$] requires 326.0360.

*3.3.13. 4-(Iodomethyl)imidazolidin-2-imine 2,2,2-trifluoroacetate **20**.* Using the general method, iodine (1.05 g, 4.13 mmol), **8h** (0.203 g, 1.02 mmol) and potassium carbonate (1.15 g, 8.33 mmol) gave crude **16** (0.297 g, 90%) as an oil. This was dissolved in CH_2Cl_2 (3 mL), cooled (0 °C) and trifluoroacetic acid (3 mL) added and the mixture stirred for 1 h. Evaporation and chromatography (0–20% MeOH in $CHCl_3$ containing 0.1% TFA) gave **20**.HCO_2CF_3 (0.219 g, 0.65 mmol, 63%) as a clear gum. δ_H (400 MHz, CD_3OD) 3.35–3.44 (3H, m, 3× CH), 3.83 (1H, t, *J* 9.9 Hz, CH), 4.07–4.14 (1H, m, CH); δ_C (100.6 MHz, CD_3OD) 10.1, 50.2, 56.6, 118.0 (q, J_{C-F} 291.0 Hz) 160.9, 162.8 (q, $^2J_{C-C-F}$ 36.0 Hz); ν_{max} 3425, 1730, 1685; **HRMS (ES+)** found 225.9838. $C_4H_8IN_3$ [$(M+H)^+$] requires 225.9836.

*3.3.14. Benzyl-2-imino-4-(iodomethyl)imidazolidine-1-carboxylate **22**.* Using the general method, iodine (2.44 g, 9.61 mmol), **8i** (0.50 g, 2.14 mmol) and potassium carbonate (1.33 g, 9.62 mmol) gave crude benzyl 2-imino-4-(iodomethyl)imidazolidine-1-carboxylate **21** (0.722 g) as a solid. Partial data: δ_H (400 MHz, $CDCl_3$) 3.28 (1H, dd, *J* 9.8, 6.5 Hz, CH), 3.38 (1H, dd, *J* 9.8, 4.7 Hz, CH), 3.70 (1H, dd, *J* 10.7, 5.7 Hz, CH), 4.05 (1H, dd, *J* 10.7, 9.1 Hz, CH) 4.20 (1H, dddd, *J* 9.1, 6.5, 5.7, 4.7 Hz, CH), 5.35 (2H, AB pattern, *J* 12.3 Hz, CH_2), 7.37–7.49 (5H, m, Ph) δ_C (100.6 MHz, $CHCl_3$) 9.5, 51.7, 57.3, 68.0, 128.0, 128.5, 134.6, 138.3, 153.5, 154.6. *Rearrangement of **21** using silica gel*: Crude **21** (0.722 g, 2.14 mmol) was dissolved in dichloromethane (5 mL) and silica gel (5 g) was added and the resultant slurry (sufficient dichloromethane was added to maintain a slurry) was stirred for 5 days. The slurry was then washed onto a sintered filter and washed with excess dichloromethane to give after evaporation a crude extract (0.366 g). The silica pad was further washed with excess methanol to give after evaporation a second crude extract (0.262 g). The dichloromethane was subject to chromatography (EtOAc/PE, 0:100 to 70:30 in 10% steps) to give **22** (61 mg, 8%) as a solid, R_f 0.10 (50:50 EtOAc/PE). Chromatography of the methanolic extract (0:100 to 30:70 MeOH/$CHCl_3$) gave the previously isolated **20** (0.135 g, 28%) as a solid. *Rearrangement of **21** using trifluoroacetic acid*: Crude **21** (0.529 g, from **8i** (0.30 g, 1.286 mmol)) was dissolved in methanol (5 mL) and trifluoroacetic acid (0.32 mL, 4.2 mmol) was added and the reaction was stirred for 16 h. On evaporation a solid (0.69 g) was obtained, which was dissolved in dichloromethane (ca. 5 mL) and diluted with ether (ca. 1–2 mL) and placed in a freezer. An off white solid (81 mg) initially precipitated, which was removed by decanting the mother liquor and proved to be very hygroscopic and gave a complex NMR spectrum. Further dilution of the decanted mother liquor with hexane (ca. 1–2 mL) and standing overnight in the freezer gave a pale yellow precipitate of **22** (0.222 g, 48%), which was of ca. 90% purity. A higher purity sample (0.129 g, 28%) was obtained on repeating this procedure. Mp 114–116 °C; R_f 0.16 (10% MeOH/$CHCl_3$); δ_H (400 MHz, $CHCl_3$) 3.32 (1H, br d, *J* 10.4 Hz, CH), 3.41–3.45 (1H, m, CH), 3.54 (1H, dd, *J* 10.8, 4.1 Hz, CH), 3.88 (1H, dd, *J* 10.8, 9.8 Hz, CH), 4.43–4.47 (1H, m, CH), 5.31 (1H, d, *J* 11.7 Hz, CH), 5.40 (1H, d, *J* 11.7 Hz, CH), 7.38–7.45 (5H, m, Ph), 7.71 (1H, br s, NH), 11.55 (1H, br s, NH), 12.48 (1H, br s, NH); δ_H (400 MHz, CD_3OD) 3.45 (1H, dd, *J* 11.7, 4.1 Hz, CH), 3.48 (1H, dd, *J* 11.0, 2.2 Hz, CH), 3.63 (1H, dd, *J* 11.0, 5.5 Hz, CH), 3.89 (1H, dd, *J* 10.7, 9.8 Hz, CH), 4.54 (1H, dddd, *J* 11.0, 5.5, 4.1, 2.2 Hz, CH), 5.34 (1H, d, *J* 12.0 Hz, CH), 5.45 (1H, d, *J* 12.0 Hz, CH), 7.37–7.47 (5H, m, Ph); δ_C (100.6 MHz, CD_3OD) 9.0, 48.3, 58.3, 71.0, 129.9, 129.9, 130.2, 135.7, 152.6, 157.6; ν_{max} (Nujol) 3324, 1714, 1623, 1583; **HRMS (ES+)** found 360.0209. $C_{12}H_{15}IN_3O_2$ [$(M+H)^+$] requires 360.0204.

*3.3.15. Benzyl (5-iodo-4,4-dimethyltetrahydropyrimidin-2(1H)-ylidene)carbamate **23** and benzyl 2-imino-4-(iodomethyl)-5,5-dimethylimidazolidine-1-carboxylate **24**.* Using the general method, iodine (1.31 g, 5.17 mmol, 4.5 equiv), potassium carbonate (0.48 g, 3.44 mmol, 3 equiv) and **8j** (0.30 g, 1.148 mmol) gave a solid (0.417 g), which was composed of **23** and **24** in a 40:60 ratio. This mixture was dissolved in methanol (ca. 5 mL), cooled (−20 °C) and on standing overnight **23** (0.115 g, 0.297 mmol, 26%) was obtained as off white solid. The remaining mother liquor on evaporation gave **24** (0.302 g, 68%, ca. 90% pure) as an oil. Compound **23** mp 160–162 °C; R_f 0.29 (5:95 MeOH/$CHCl_3$); δ_H (400 MHz, $CHCl_3$) 1.35 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.43 (1H, dd, *J* 9.2, 13.6 Hz, CH), 3.55 (1H, dd, *J* 4.6, 13.6 Hz, CH), 3.97 (1H, dd, *J* 4.6, 9.2 Hz, CH), 5.02 (2H, s, CH_2), 7.30–7.36 (5H, m, Ph), 8.70 (1H, br s, NH), 9.70 (1H, br s, NH); δ_H (400 MHz, CD_3OD) 1.46 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.73 (1H, dd, *J* 7.0, 14.2 Hz, CH), 3.94 (1H, dd, *J* 4.4, 14.2 Hz, CH), 4.45 (1H, dd, *J* 4.4, 7.0 Hz), 5.09 (2H, s, CH_2), 7.28–7.40 (5H, m, Ph); δ_C (100.6 MHz, $CHCl_3$) 27.5, 29.2, 29.3, 46.3, 52.5, 66.3, 128.0, 128.3, 128.6, 137.0, 157.6, 163.1; δ_C (100.6 MHz, CD_3OD) 28.8, 30.4, 31.3, 48.9, 54.9, 68.3, 129.6, 129.7, 130.2, 139.6, 159.2, 165.0; ν_{max} 3340, 1706, 1634, 1553; **HRMS (ES+)** found 388.0522. $C_{14}H_{19}IN_3O_2$ [$(M+H)^+$] requires 388.0517. Compound **24** (partial data) δ_H (400 MHz, $CHCl_3$) 1.35 (3H, s, CH_3), 1.51 (3H, s, CH_3), 3.17 (1H, dd, *J* 8.3, 10.0 Hz, CH), 3.22 (1H, dd, *J* 5.0, 10.0 Hz, CH), 3.78 (1H, dd, *J* 8.3, 5.0 Hz, CH), 5.24 (2H, s, CH_2), 7.31–7.45 (5H, m, Ph); δ_C (100.6 MHz, $CHCl_3$) 5.7, 19.1, 27.5, 46.1, 67.8, 71.9, 128.1, 128.4, 128.5, 134.5, 152.9, 162.9.

*3.3.16. Rearrangement of **22** using trifluoroacetic acid: preparation of benzyl (5-(iodomethyl)-4,4-dimethylimidazolidin-2-ylidene)carbamate **25**.* A mixture of **23** and **24** (33:67, 0.421 g, from **8j** (1.027 mmol)) was dissolved in methanol (5 mL) and trifluoroacetic acid (0.13 mL, 194 mg, 1.7 mmol) was added and the mixture stirred for 16 h. On evaporation a solid (0.607 g) was obtained, which was dissolved in dichloromethane (3 mL), diluted with ether (ca. 10 mL) and cooled (−20 °C) overnight to give **25** (66.0 mg, 17%) as a pale yellow solid. The remaining supernatant liquid was evaporated (0.484 g) and on chromatography (0:100 to 80:20 EtOAc/PE in 10% steps) gave the previously isolated **23** (58.2 mg, 15%), as a white solid. Mp 86–88 °C; R_f 0.17 (10:90 MeOH/$CHCl_3$); δ_H (400 MHz, CD_3OD) 1.56 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.36 (1H, dd, *J* 11.0, 7.6 Hz, CH), 3.54 (1H, dd, *J* 11.0, 4.4 Hz, CH), 3.91 (1H, dd, *J* 7.6, 4.4 Hz, CH), 5.42 (2H, s, CH_2), 7.40–7.51 (5H, m, Ph) δ_C (100.6 MHz, CD_3OD) 2.4, 19.8, 27.4, 65.4, 69.1, 71.0, 139.9, 130.1, 130.2, 135.6, 153.2, 157.4; ν_{max} 3335, 1716, 1611, 1515; **HRMS (ES+)** found 388.0510. $C_{14}H_{19}IN_3O_2$ [$(M+H)^+$] requires 388.0516.

Acknowledgements

Thanks are given to the EPSRC (D.M.E., EP/J01821X/1), the European Social Fund (D.H.D., P.H., I.J.), Menai Organics (D.H.D.), Phytoquest Limited (I.J.) and to the Leonardo Da Vinci programme (K.K. and H.F.) for funding and to the EPSRC Mass Spectrometry Centre at Swansea for invaluable assistance.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.087.

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Please cite this article in press as: Al Shuhaib, Z.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.03.087