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ARTICLE TYPE

Preparation of an ABC Tricyclic Model of the Cylindrospermopsin Alkaloids *via* a Biomimetically Inspired Pathway

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Two tricyclic guanidine model compounds **28** and **29** have been prepared in 12 steps from 1,5-pentanediol using a biomimetic synthetic approach. The pivotal reaction in the sequence is a tethered Biginelli condensation between **21**/**22** and β-keto esters **23** and **24**.

Introduction

The cylindrospermopsin alkaloids are a family of polyketide derived marine natural products currently known to be produced by 12 different species of cyanobacteria.[1] Cylindrospermopsin **1** was first isolated from the cyanobacteria *cylindrospermopsis raciborskii* in 1992[1a] and retrospectively identified as the causative agent in an outbreak of hepatoenteritis which affected 148 residents of Great Palm Island Australia.[2] Subsequent to the discovery of cylindrospermopsin, two further metabolites were isolated and characterised, namely the related diastereomer 7-*epi*-cylindrospemropsin[3] **2** and the C-7 deoxygenated biosynthetic intermediate 7-*deoxy*-cylindrospermopsin[4] **3**. Cylindrospermopsin has been shown to display hepatotoxic,[5] cytotoxic,[6] neurotoxic[7] and carcinogenic effects,[8] which are shared with its equally toxic diastereoisomer 7-epicylindrospemropsin[9] **2**, however the deoxygenated analogue 7-deoxycylindrospermopsin **3** has been shown to be devoid of toxicity *in-vivo*[10] (Figure 1). These alkaloids have also been the subject of considerable synthetic interest, resulting in four total syntheses[11] and several general methodological approaches.[12] These approaches generally rely upon the initial construction of either the A or B rings of the toxin, with the tricyclic core being completed by the installation of the C ring at a later stage.

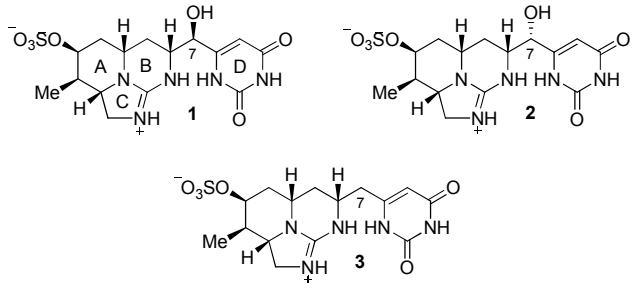

Figure 1 The cylindrospermopsin alkaloids.

Notes and references

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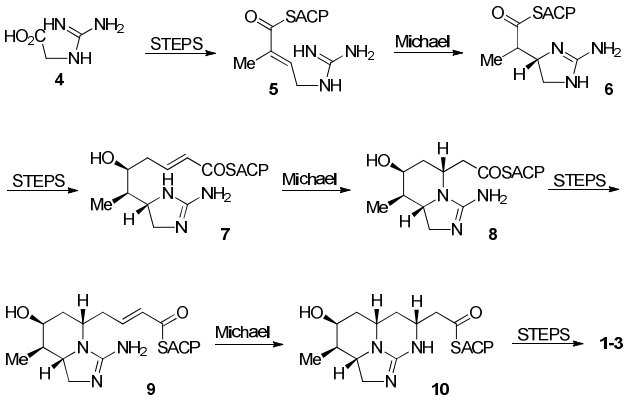
Recent advances have led to the characterisation of the gene cluster responsible for the biosynthesis of cylindrospermopsin in *C. raciborskii* strain AWT205.[13] As previously indicated the starter unit for the polyketide chain is guanidinoacetate **4** which has been shown to be derived from a novel L-arginine:glycine amidinotransferase enzyme.[14] It is believed that the tricyclic guanidinium core of this family of natural products is constructed in a modular fashion from **4**, with sequential polyketide extensions and Michael type ring closures generating in turn the C ring (**5**→**6**), the A ring (**7**→**8**) and the B ring (**9**→**10**) (Scheme 1).



Scheme 1 Proposed biosynthesis of the cylindrospermopsin alkaloids.

Using this biosynthesis as a guide for our synthetic investigations we envisioned a strategy in which

cylindrospermopsin could be separated into two distinct fragments consisting of the uracil D ring and the tricyclic ABC guanidinium core. Initially we concentrated on a preparing a simplified version of the tricyclic guanidinium moiety anticipating that the stereochemistry generated during the formation of the initial C ring juncture would dictate the stereochemistry generated during the closure of the A and B rings. (Figure 2).[12d, 15]

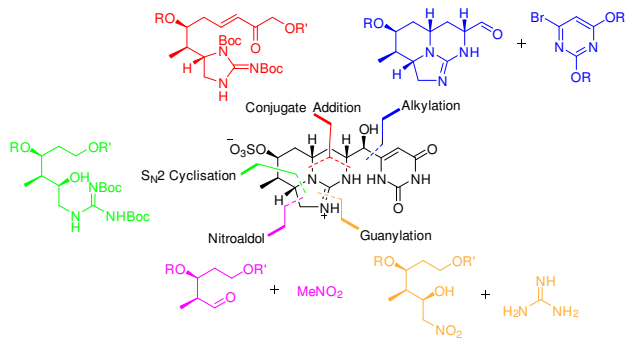


Figure 2 Retrosynthetic analysis of cylindrospermopsin.

Results and discussion

To test this approach we began with the simple diol, 1,5-pentanediol **11** which was monosilylated in 61% yield by treatment with TBSCl[16] followed by oxidation of the remaining alcohol function under Swern conditions to furnish aldehyde **12** in 89% yield. The β-nitro alcohol **13** was then prepared in 81% yield *via* the nitro-aldol (Henry) reaction between **12** and nitromethane. The nitro functionality of **13** was then reduced with the $NiCl_2/NaBH_4$ system followed by the guanylation of the primary amine formed with **14** which gave the protected guanidine **15** in 78% yield.[17] Subsequently a Mitsunobu type cyclodehydration gave the required C-ring heterocycle **16** in 96% yield.[18] The alkyl chain of **16** was then elaborated by removing the TBS protecting group with TBAF followed by oxidation of alcohol **17** with Dess-Martin periodinane to generate aldehyde **18**. Aldehyde **18** then underwent a Horner-Wadsworth-Emmons reaction with the simple phosphonate **19** to give the model substrate, enone **20** in 86% yield. It was attempted to cyclise enone **20** under a variety of conditions; however the only isolated material was representative of bicyclic guanidine **21** which displays an anti-configuration between the two bridging methine groups as confirmed by X-ray crystallography (Figure 3). Efforts were made to epimerise this material under both basic and acidic conditions *via* retro-Michael addition of the guanidine, however all attempts proved unsuccessful (Scheme 2).[19]

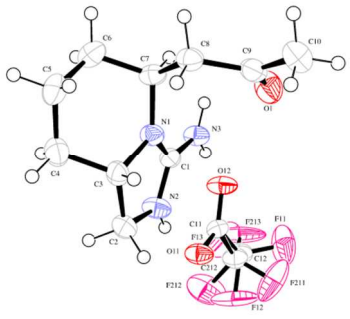
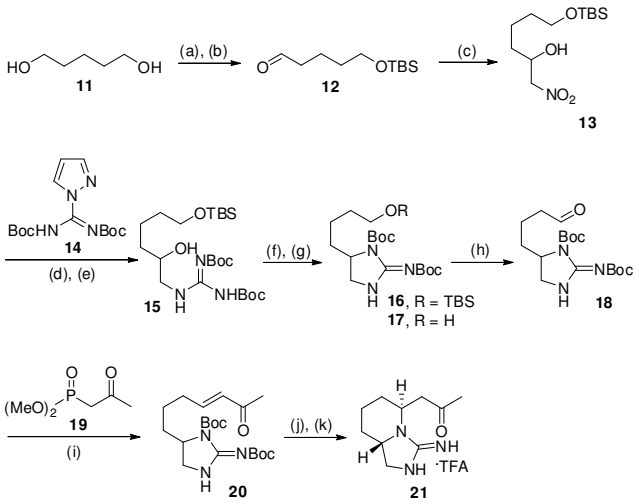


Figure 3 X-ray crystal structure of bicyclic guanidine **21**.



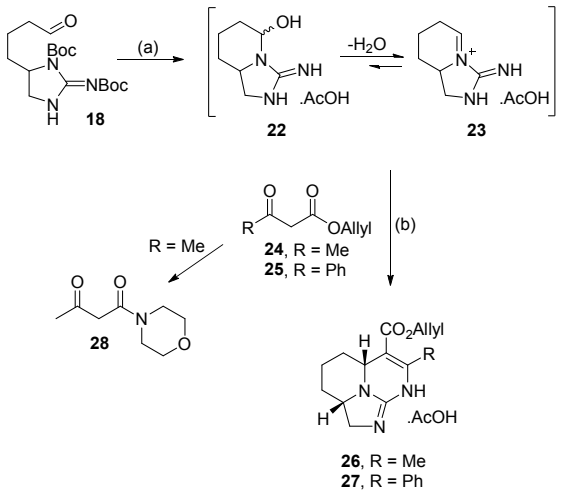
Scheme 2 Reagents and conditions: (a) TBSCl, NaH, THF, 2 h, 61%; (b) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, -78 °C, 3 h, 89%; (c) $MeNO_2$, DIPEA, CH_2Cl_2, 36 h, 81%; (d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, NEt_3, 0 °C, 3 h; (e) **14**, 48 h, 78% (2 steps from **13**); (f) PPh_3, I_2, imidazole, CH_2Cl_2, -20 °C, 1 h, 96%; (g) TBAF, THF, 0°C-rt, 24 h, 99%; (h) Dess-Martin periodinane, pyridine, CH_2Cl_2, 24 h, 96%; (i) LiCl, DIPEA, **19**, CH_3CN, 48 h, 86%; (j) TFA/CH_2Cl_2 (1:1), 2 h; (k) NEt_3, CH_2Cl_2, 48 h, 70% (2 steps from **20**).

Being unable to elaborate enone **20** into a suitable tricycle guanidine, the initial synthetic approach was revised utilising the previously prepared aldehyde **18**. Thus the Boc-protecting groups of **18** were removed to give a mixture of hemiaminal **22** and *N*-acyliminium species **23**. The resulting mixture was then immediately condensed with allyl acetoacetate **24** in the presence of morpholinium acetate under a variety of conditions based on the work of Aaron and Overman.[20] This tethered Biginelli protocol successfully generated tricyclic guanidine **26** the relative stereochemistry of which was determined by 2D NOESY NMR where a strong nOe correlation was observed between the two piperidine methine protons confirming the desired all *syn* relationship (Scheme 3, Table 1).

Initial investigations were conducted using TFA for the deprotection of aldehyde **18** followed by condensation of the resultant material with varying equivalents of **24**, in the presence of morpholinium acetate and Na_2SO_4 at 60 °C (Entries 1-4). An incremental increase in the reaction time from 48 h to 96 h allowed for an appreciable increase in the yield from 4% to 10%, with an excess of β-keto ester **24** generating a further 2% increase in the isolated yield (Entries 1-4). Because of the progressive increase in yield observed with increased reaction time the reaction was allowed to proceed over a 12 day period at a slightly higher temperature of 70 °C (Entry 5). Using such a prolonged reaction time had the greatest observed effect on the isolated yield of guanidine **26** which increased to a more acceptable 21%. Further significant improvements to the yield were also observed when all the anionic species involved in the reaction were of the same nature. Under such condition the TFA used in the initial deprotection step was replaced with AcOH, which gave an increase in the isolated yield of between 36% and 43% (Entry 6). The use of more forcing conditions were also investigated were the reaction was performed at 100 °C in a sealed tube, however,

no improvement in the isolated yield was observed (Entries 7-8). The condensation was also attempted using β-keto ester, **25** which under the best conditions gave the corresponding tricyclic guanidine **27** in an unoptimised 26% yield (Entry 10).The relative stereochemistry of this tricyclic material was assigned by 2D NOESY NMR spectroscopy.

No other tricyclic products were apparent, however, with the hope of further increasing the reaction yield it was attempted to recycle bicyclic intermediates isolated during purification by re-subjecting them to the reaction conditions. Interestingly even though the reaction conditions employed are equilibrating[21] no further tricyclic material could be generated suggesting that the addition of the β-keto ester to the *N*-acyliminium ion **23** occurs through an irreversible pathway. Another reaction product isolated in low yields was the β-keto ester **28** which is formed from the reaction of **24** with morpholine. No tricyclic material containing morpholine derived esters were observed during any of the reactions run. In an attempt to negate this side reaction which consumes the β-keto ester, *N*-methylmorpholine was used as the base in the reaction (entry 9). However under these conditions no tricyclic material was isolated.



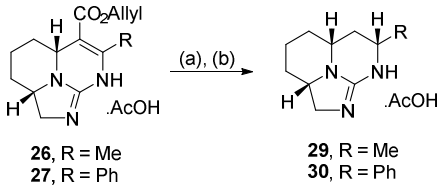
Scheme 3 Reagents and conditions: (a) see table 1.

Table 1 Optimisation of reaction conditions[a]

Entry	R	Deprotection	β-Keto ester (eqv.)	Morpholinium acetate (eqv.)	T	Reaction Time	Yield
1	Me	TFA	3	1.0	60 °C	48 h	4%
2	Me	TFA	2	1.5	60 °C	72 h	8%
3	Me	TFA	1	1.0	60 °C	96 h	10%
4	Me	TFA	3	1.0	60 °C	96 h	12%
5	Me	TFA	5	2.5	70 °C	12 d	21%
6	**Me**	**AcOH**	**5**	**2.5**	**70 °C**	**12 d**	**36-43%**[b]
7[c]	Me	AcOH	5	2.5	100 °C	6 d	26%
8[c]	Me	AcOH	8	4.0	100 °C	12 d	37%
9	Me	AcOH	5	0[d]	70 °C	12 d	0%
10	Ph	AcOH	5	2.5	70 °C	12 d	26%

[a] All reactions were performed on an ~0.5 mmol scale in 2,2,2-trifluoroethanol (1.5 mL) in the presence of sodium sulphate (1 g). [b]Over 12 reactions. [c]Reactions performed in a sealed tube. [d]*N*-methylmorpholine (2.5 eqv.) and AcOH (2.5 eqv.) were added to the reaction as a solution in 2,2,2-trifluoroethanol.

With tricyclic guanidines **26** and **27** in hand deallylation/decarboxylation was undertaken by treatment with $Pd(PPh_3)_4$ followed by treating the resulting material with $NaBH_3CN$ in a 1:1 mixture of AcOH/MeOH to give saturated tricyclic guanidines **29** and **30** in 57% and 53% yield respectively over two steps (Scheme 4).[22] Again 2D NOESY NMR spectroscopy was utilised to confirm that tricyclic guanidines **29** and **30** displayed the correct relatively stereochemistry representative of the ABC core of the cylindrospermopsin alkaloids.



Scheme 4 Reagents and conditions: (a) $Pd(PPh_3)_4$, pyrrolidine, THF/MeOH, 1.5-2 h; (b) $NaBH_3CN$, AcOH/MeOH, 0°C-rt, 16h, 57% (**29**), 53% (**30**) (2 steps).

Conclusions

In conclusion we have demonstrated the use of a nitro-aldol reaction, intramolecular S_N2 cyclisation and tethered Biginelli condensation to produce two model tricyclic guanidinium species which possess the correct relative *syn*-geometry found in the cylindrospermopsin alkaloids. During our initial investigation of the key tethered Biginelli condensation the desired tricyclic dihydropyrimidine could only be generated in an initially low yield of 4%, this could be improved to between 36% and 43% employing optimised reaction conditions. The simple biologically inspired approach that we have demonstrated in combination with a key tethered Biginelli condensation hopefully demonstrates the potential of this methodology for the synthesis of **1**-**3** which we will report in due course.

Acknowledgements

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Experimental Section

General Information

Column chromatography was carried out on silica gel (particle size 40-63 μm) and thin layer chromatography conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All anhydrous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. THF and dichloromethane were dried on a Pure Solv MD-3 solvent purification system. Chemical shifts are reported in δ values relative to chloroform (7.27/77.0 ppm) or methanol (3.31/49.00

ppm) as an internal standard. NMR spectra were recorded on a Bruker Avance 400/500 spectrometer unless otherwise stated. Mass spectra data were obtained at the EPSRC Mass Spectrometry Service Centre at the University of Wales, Swansea.

5-(*tert*-Butyl-dimethyl-silanyloxy)-pentan-1-ol.[16] To a stirred suspension of NaH (3.86 g, 100 mmol) in anhydrous THF (100 mL) was added pentane-1,5-diol (10.52 mL, 100 mmol), after 1 h TBSCl (15.07 g, 100 mol) was added and vigorous stirring continued for a further hour. The reaction mixture was then diluted with diethyl ether (600 mL), washed with potassium carbonate (aq. 10%, 200 mL), brine (200 mL) and the organic extracts dried over magnesium sulfate. After purification by flash column chromatography on silica gel using ethyl acetate/petroleum ether (10:90, 40:60), the title compound was obtained as a clear oil (14.7 g, 67.1 mmol, 67%). R_f = 0.36 (20% ethyl acetate in petrol); v_{max} (chloroform)/cm^{-1} 3417, 2932, 2858, 1471, 1389 and 1361; δ_H (500 MHz; $CDCl_3$) -0.01 (s, 6H), 0.84 (s, 9H), 1.30-1.36 (m, 2H), 1.46-1.54 (m, 4H), 2.74 (br s, 1H) and 3.53-3.57 (m, 4H); δ_C (125 MHz; $CDCl_3$) -5.4, 18.2, 21.9, 25.9, 32.3, 32.4, 62.4 and 63.1.

5-(*tert*-Butyl-dimethyl-silanyloxy)-pentanal (12).[23] To a cooled (-78 °C) and stirred solution of oxalyl chloride (3.98 mL, 46.4 mmol) in anhydrous CH_2Cl_2 (120 mL) was added anhydrous DMSO (5.96 mL, 84.0 mmol). After 20 min a solution of alcohol **11** (6.34 g, 29.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was added to the reaction mixture. After a further 20 min NEt_3 (24.2 mL, 173.9 mmol) was also added. After 3 h TLC analysis indicated the complete consumption of **11** and the reaction was diluted with brine (100 mL) and warmed to rt. After separation the organic layer was washed with brine (2 x 100 mL), HCl (0.25 M, 3 x 100 mL) and water (3 x 100 mL). After drying and evaporation the resulting yellow oil was dissolved in petroleum ether (50 mL) and passed through a plug of silica (ca. 1 cm) eluting with further petroleum ether (200 mL). After evaporation **12** was obtained as a pale yellow oil (5.57 g, 25.7 mmol, 89%) which was used without further purification. R_f = 0.62 (20% ethyl acetate in petrol); v_{max} (chloroform)/cm^{-1} 2954, 2930, 2857, 1728, 1472, 1388 and 1361; δ_H (500 MHz; $CDCl_3$) 0.01 (s, 6H), 0.85 (s, 9H), 1.49-1.54 (m, 2H), 1.64-1.70 (m, 2H), 2.42 (td, J = 7.4, 1.7 Hz, 2H), 3.59 (t, J = 6.2 Hz, 2H) and 9.73 (t, J = 1.7 Hz, 1H); δ_C (125 MHz; $CDCl_3$) -5.4, 18.2, 18.6, 25.9, 32.0, 43.5, 62.5 and 202.4.

6-(*tert*-Butyl-dimethyl-silanyloxy)-1-nitro-pentan-2-ol (13). To a stirred solution of aldehyde **12** (4.93 g, 22.7 mmol) in CH_2Cl_2 (80 mL) at rt was added nitromethane (73.7 mL, 1.36 mol) and the mixture cooled (0 °C) and DIPEA (9.90 mL, 56.9 mmol) added. Reaction progress was monitored via TLC and after 5 days the reaction was quenched with an ammonium chloride solution (sat, 200 mL), separated and the aqueous layer extracted with chloroform (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate and purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (10:90, 30:70). Fractions eluting in 10:90 ethyl acetate/petroleum ether gave **13** as a pale yellow oil (5.11 g, 18.4 mmol, 81%). R_f = 0.29 (20% ethyl acetate in petrol); v_{max} (chloroform)/cm^{-1} 3418, 2953, 2931, 2858, 1556, 1471, 1463, 1421, 1385 and 1361; δ_H (500 MHz; $CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.43-1.59 (m, 6H), 2.87 (br s, 1H), 3.62 (t, J = 5.9 Hz, 2H), 4.30-4.34 (m, 1H), 4.37 (dd, J = 12.6, 8.5 Hz, 1H) and 4.42 (dd, J = 12.6, 3.1 Hz, 1H); δ_C (125 MHz; $CDCl_3$) -5.4, 18.3, 21.6, 25.9, 32.1, 33.4, 62.8, 68.6 and 80.6; LRMS, CI, *m/z* 295 ([M+NH_3]$^+$, 3%), 278 ([M+H]$^+$, 9%), 235 (5), 234 (30), 219 (7), 218 (20), 217 (100), 176 (5), 159 (8), 132 (6), 102 (3), 91 (6) and 85 (6); HRMS, ESI, *m/z* $C_{12}H_{28}NO_4Si$, requires 287.1782, found 287.1784 [M+H]$^+$.

***N*,*N*'-*bis*-(*tert*-Butyloxycarbonyl)-*N*''-(6-(*tert*-butyldimethylsilyloxy)-2-hydroxyhexyl)-guanidine (15).** To a vigorously stirred, cooled (0 °C) solution of nickel (II) chloride hexahydrate (8.67 g, 36.5 mmol) in methanol (50 mL) was added $NaBH_4$ (4.10 g, 109.4 mmol) and stirring continued for 30 min. To the resultant black suspension was added nitro-alcohol **13** (3.38 g, 12.2 mmol) in methanol (20 mL), followed by the portion-wise addition of further $NaBH_4$ (9.23 g, 246.8 mmol). The reaction mixture was stirred for a further 2 h at rt and then filtered through a pad of Celite® (ca. 5 cm) and washed with methanol (3 x 50 mL). NEt_3 (149 mL, 1.07 mol) was added and after stirring for 45 min, the guanylating agent **14** (4.14 g, 13.4 mmol) dissolved in methanol (15 mL) was also added. After 48 h the reaction was diluted with water (400 mL) and extracted with ethyl acetate (3 x 250mL). The combined organic extracts were dried over magnesium sulfate, evaporated and the resultant reaction material purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (5:95, 25:75). Fractions eluting in 10:90 ethyl acetate/petroleum ether gave **15** as a clear oil (4.66 g, 9.5 mmol, 78%). R_f = 0.34 (40% ether in petrol); v_{max} (chloroform)/cm^{-1} 3330, 3291, 3156, 2982, 2933, 2859, 1724, 1618, 1601, 1577, 1472, 1460, 1411, 1394, 1368 and 1335; δ_H (500 MHz; $CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.34-1.62 (m, 6H), 1.47 (s, 9H, Boc), 1.49 (s, 9H, Boc), 3.33-3.39 (m, 1H), 3.54 (ddd, J = 14.2, 6.3, 2.2 Hz, 1H), 3.61 (t, J = 6.3 Hz, 2H), 3.71-3.80 (br m, 1H), 4.58 (br s, 1H), 8.64-8.69 (br m, 1H) and 11.47 (s, 1H); δ_C (125 MHz; $CDCl_3$) -5.3, 18.4, 21.8, 26.0, 28.0, 28.2, 32.7, 34.9, 47.6, 63.1, 71.8, 79.5, 83.4, 153.1, 157.4 and 162.9; LRMS, CI, *m/z* 491 ([M+H]$^+$, 40%), 434 (4), 390 (3), 373 (4), 370 (1), 320 (2), 275 (3), 274 (9), 273 (14), 248 (6), 232 (11), 231 (44), 217 (100), 204 (11), 175 (4), 174 (5), 160 (15) 159 (21), 145 (20), 132 (16), 104 (18), 92 (18), 60 (30), 58 (49) and 45 (71); HRMS, ESI, *m/z* $C_{23}H_{48}N_3O_6Si$, requires 490.3307, found 490.3312 [M+H]$^+$.

***tert*-Butyl-2-((*tert*-butoxycarbonyl)imino)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)imidazolidine-1-carboxylate (16).** A stirred solution of alcohol **15** (7.79 g, 15.9 mmol) in CH_2Cl_2 (150 mL) was cooled (-20 °C) and PPh_3 (9.59 g, 36.6 mmol), imidazole (4.22 g, 62.0 mmol, 3.9 eqv) and I_2 (7.48 g, 31.8 mmol, 2 eqv) were added. Reaction progress was monitored by TLC and after stirring for 2 h 30 min the reaction mixture was diluted with chloroform (150 mL), washed with an ammonium chloride solution (sat, 150 mL) and then brine (150 mL). After drying over magnesium sulfate and evaporation, the reaction material was purified by flash column chromatography on silica

gel using ethyl acetate/petroleum ether (10:90, 40:60). Fractions eluting in 30:70 ethyl acetate/petroleum ether gave **16** as a pale yellow oil (7.31 g, 15.5 mmol, 98%). R_f = 0.18 (40% ethyl acetate in petrol); ν_{max} (chloroform)/cm^{-1} 3313, 2954, 2930, 2858, 1760, 1703, 1651, 1604, 1532, 1473, 1460, 1438 and 1368; δ_H (500 MHz; $CDCl_3$) 0.02 (s, 6H), 0.87 (s, 9H), 1.28-1.39 (m, 2H), 1.44-1.67 (m, 4H), 1.47 (s, 9H), 1.50 (s, 9H), 3.35-3.50 (br m, 1H), 3.58 (t, J = 6.5 Hz, 2H), 3.73-3.86 (br m, 1H) and 4.03-4.15 (br m, 1H); δ_C (125 MHz; $CDCl_3$) -5.3, 18.3, 20.7, 25.9, 28.1, 28.1, 32.6, 33.6, 56.4, 56.4, 62.7 and 82.8, four quaternary carbon signals were not detected; LRMS, CI, *m/z* 473 ([M+H]$^+$, 100%), 430 (2), 416 (20), 372 (76), 357 (35), 330 (2), 316 (16), 302 (12), 272 (18), 257 (31), 243 (7), 214 (8), 184 (15), 159 (6), 148 (13), 132 (29), 116 (11), 84 (57), 69 (37), 58 (96) and 45 (44); HRMS, ESI, *m/z* $C_{23}H_{46}N_3O_5Si$, requires 472.3201, found 472.3201 [M+H]$^+$.

2-*tert*-Butoxycarbonylimido-4-(4-hydroxy-butyl)-imidazolidine-1-carboxylic acid *tert*-butyl ester (17). To a stirred solution of guanidine heterocycle **16** (72.4 mg, 0.154 mmol) in THF (2 mL) at 0 °C was added a solution of TBAF in THF (1 M, 0.16 mL, 0.16 mmol). Reaction progress was monitored by TLC and after 24 h the reaction was quenched with an ammonium chloride solution (sat, 2 mL) and extracted with chloroform (3 x 5 mL). The combined organic extracts were then washed with brine (5 mL) and dried over magnesium sulfate. After evaporation, purification was achieved by flash column chromatography on silica gel using ethyl acetate/petroleum ether (80:20 to 100:0) and ethyl acetate/methanol (90:10). Fractions eluting in ethyl acetate gave **17** as a clear oil (54.4 mg, 0.152 mmol, 99%). R_f = 0.03 (100% ethyl acetate); ν_{max} (chloroform)/cm^{-1} 3318, 2981, 2932, 2865, 1745, 1701, 1649, 1602, 1532, 1476, 1457 and 1370; δ_H (500 MHz; $CDCl_3$) 1.20-1.27 (m, 2H), 1.36 (s, 9H), 1.40 (s, 9H), 1.42-1.58 (m, 4H), 3.24-3.43 (br m, 1H), 3.50 (t, J = 6.3 Hz, 2H), 3.62-3.77 (br m, 1H) and 3.93-4.08 (br m, 1H); δ_C (125 MHz; $CDCl_3$) 20.2, 27.8, 27.8, 32.0, 33.2, 56.0, 56.0, 61.8, 80.2 and 82.6, three quaternary carbon signals were not detected; LRMS, CI, *m/z* 358 ([M+H]$^+$, 55%), 319 (5), 302 (36), 279 (7), 258 (29), 243 (18), 211 (5), 202 (30), 186 (13), 156 (8), 133 (40), 116 (29), 98 (20), 79 (48), 69 (53), 58 (100) and 45 (54); HRMS, ESI, *m/z* $C_{17}H_{31}N_3O_5$, requires 358.2336, found 358.2335 [M+H]$^+$.

***tert*-Butyl 2-(*tert*-butoxycarbonylimino)-5-(4-oxobutyl)imidazolidine-1-carboxylate (18).** To a solution of alcohol **17** (260 mg, 0.73 mmol) in CH_2Cl_2 (2 mL) at rt was added pyridine (0.18 mL, 2.19 mmol) and Dess-Martin periodinane (310 mg, 0.73 mmol) and the mixture stirred for 24 h. The reaction was then filtered through a tight plug of cotton wool, diluted with chloroform (20 mL) and washed with $NaHCO_3$ (sat, 3 x 10 mL). Residual pyridine was removed by azeotropic evaporation with toluene (3 x 10 mL) to give **18** as a clear oil (249 mg, 0.70 mmol, 96%) which was used immediately without further purification. R_f = 0.30 (1% methanol in ethyl acetate); ν_{max} (chloroform)/cm^{-1} 3336, 2987, 2942, 2882, 1758, 1710, 1656, 1609, 1536, 1482, 1443, 1374 and 1320; δ_H (500 MHz; $CDCl_3$) 1.42 (s, 9H), 1.47 (s, 9H), 1.51-1.63 (m, 4H), 2.44 (td, J = 6.7, 1.0 Hz, 2H), 3.44 (dd, J = 12.6, 3.2 Hz, 1H), 3.80 (dd, J = 12.6, 9.3 Hz, 1H), 4.05-4.09 (m, 1H) and 9.71 (s, 1H); δ_C (125 MHz; $CDCl_3$) 16.6, 27.9, 28.0, 33.0, 43.2, 55.9, 55.9, 80.6, 83.1 and 201.2, three quaternary carbon signals were not detected; LRMS, ESI, *m/z* 414 (15), 388 ([M+MeOH+H]$^+$, 100%), 356 ([M+H]$^+$, 15%), 332 (6), 316 (12), 300 (10), 260 (14), 214 (12), 182 (10) and 164 (4); HRMS, ESI, *m/z* $C_{17}H_{30}N_3O_5$, requires 356.2180, found 356.2186 [M+H]$^+$.

***tert*-Butyl-2-(*tert*-butoxycarbonylimino)-5-((*E*)-6-oxohept-4-enyl)imidazolidine-1-carboxylate (20).** To a stirred suspension of lithium chloride (28.2 mg, 0.65 mmol) in anhydrous acetonitrile (3 mL) was added phosphonate **19** (75 µL, 0.54 mmol). After 10 min, DIPEA (0.11 mL, 0.65 mmol) was then added and the mixture stirred for a further 10 min. At this point aldehyde **18** (192 mg, 0.54 mmol) dissolved in acetonitrile (2 mL) was added and the mixture stirred for 48 h. The reaction was diluted with water (15 mL) and extracted with diethyl ether (3 x 15 mL) and the combined organic extracts washed with brine (10 mL) and dried over magnesium sulfate. After evaporation, enone **20** (183 mg, 0.46 mmol, 86%) was obtained as a pale yellow oil and used without further purification. R_f = 0.22 (100% ethyl acetate); ν_{max} (chloroform)/cm^{-1} 3320, 2980, 2933, 2860, 1764, 1707, 1678, 1650, 1605, 1532, 1374 and 1327; δ_H (500 MHz; $CDCl_3$) 1.34-1.45 (m, 2H), 1.47 (s, 9H), 1.51 (s, 9H), 1.59-1.71 (m, 4H), 2.23 (s, 3H), 3.40-3.54 (br m, 1H), 3.72-3.88 (m, 1H), 4.09-4.20 (br m, 1H), 6.07 (d, J = 15.8 Hz, 1H) and 6.74 (dt, J = 15.8, 7.0 Hz, 1H); δ_C (125 MHz; $CDCl_3$) 22.7, 27.0, 28.1, 28.1, 32.1, 33.3, 56.1, 56.1, 80.8, 83.1, 131.7, 146.9 and 198.3, three quaternary carbon signals were not detected; LRMS, ESI, *m/z* 791 ([2M+H]$^+$, 79%), 762 (7), 708 (3), 692 (6), 593 (7), 448 (12), 430 (17), 412 (49), 396 ([M+H]$^+$, 100%), 374 (2), 356 (13), 340 (27), 296 (10), 279 (19), 256 (6), 240 (23), 212 (3) and 196 (17); HRMS, ESI, *m/z* $C_{20}H_{34}N_3O_5$, requires 396.2493, found 396.2497 [M+H]$^+$.

(5*S*,8a*S*)-5-(2-Oxopropyl)hexahydroimidazo[1,5-*a*]pyridin-3(2*H*)-iminium trifluoroacetate (21). To a stirred solution of enone **20** (162 mg, 0.41 mmol) in CH_2Cl_2 (1.5 mL) was added trifluoroacetic acid (1.5 mL) and the mixture stirred at rt for 24 h. After evaporation under reduced pressure, residual trifluoroacetic acid was removed by azeotropic evaporation with chloroform (3 x 15 mL) and the residue dried under high vacuum for 4 h. The resultant guanidinium salt was dissolved in CH_2Cl_2 (4 mL) and triethylamine (70 µL, 0.45 mmol) was added and the mixture stirred at rt for 48 h. After evaporation, purification by flash column chromatography on silica gel using methanol/chloroform (0:100 to 14:86 in 1% increments) gave **198** (89 mg, 0.28 mmol, 70%) as a viscous oil. An analytical sample was obtained by slow crystallisation from ethyl acetate. *Rf* = 0.08 (10% methanol in chloroform); m.p. 149-153 °C (dec.); ν_{max} (chloroform)/cm^{-1} 3400, 2953, 2875, 1714, 1682, 1579, 1530, 1482, 1430, 1367 and 1320; δ_H (500 MHz; $CDCl_3$) 1.43 (qd, J = 13.6, 3.2 Hz, 1H), 1.50-1.59 (m, 1H), 1.63 (d, J = 13.6 Hz, 1H), 1.71-1.75 (m, 1H) 1.80 (dt, J = 13.6, 3.2 Hz, 1H), 1.92 (dd, J = 12.8, 3.0 Hz, 1H), 2.20 (s, 3H), 2.54 (dd, J = 18.3, 3.2 Hz, 1H), 3.05 (dd, J = 18.3, 9.3 Hz, 1H), 3.23 (dd, J = 9.5, 7.3 Hz, 1H), 3.77 (t, J = 9.5 Hz, 1H), 3.86 (app td, J = 11.5, 3.6 Hz, 1H), 4.36-4.43 (m, 1H) and 9.75 (s, 1H, NH); δ_C (125 MHz; $CDCl_3$) 18.2, 28.9, 30.1, 31.0, 44.3, 45.4,

47.6, 53.7, 157.9 and 206.7; LRMS, Positive ESI, *m/z* 391 ([2M+H]$^+$, 22%), 196 ([M+H]$^+$, 100%), 138 (5) and 130 (8); LRMS, Negative ESI *m/z* 227 ([2M-H]$^-$, 44%), and 113 ([M-H]$^-$, 100%); HRMS, ESI, *m/z* $C_{10}H_{18}N_3O$, requires 196.1444, found 196.1441 [M+H]$^+$.

General procedure for tethered Biginelli condensations: A solution of aldehyde **18** (~0.5 mmol) in glacial acetic acid (3 mL) was stirred at rt for 24 h. After evaporation under reduced pressure, residual acetic acid was removed by co-evaporation with chloroform (3 x 15 mL) and the residue dried under high vacuum for 4 h. The resultant salts where then dissolved in trifluoroethanol (1.5 mL) and morpholine acetate (2.5 eqv.), anhydrous sodium sulfate (1 g) and the relevant β-keto ester (5 eqv.) added and the mixture stirred at 70 °C for 12 days. After cooling to rt and evaporation, purification was achieved by flash column chromatography on silica gel using methanol/chloroform (stepwise gradient of 0.5% increments 0:100 to 4:96) containing 1% acetic acid.

(5a*R*,8a*S*)-5-((Allyloxy)carbonyl)-4-methyl-3,5a,6,7,8,8a-hexahydro-1*H*-2,2a^1,3-triazaacenaphthylen-2-ium acetate (26). Following the general procedure outlined above tricyclic guanidine **26** was obtained as a tan oil in yields of 36-43%. Upon standing or in a methanol solution the acetate counterion was slowly converted to the corresponding carbonate by atmospheric CO_2. R_f = 0.26 (10% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3400, 2949, 2932, 2905, 2862, 1696, 1679, 1637, 1605, 1449, 1407, 1391 and 1337; δ_H (500 MHz; $CDCl_3$) 1.32-1.40 (m, 1H), 1.51-1.66 (m, 2H), 1.70 (dd, *J* = 12.9, 3.2 Hz, 1H) 1.87 (dt, *J* = 13.3, 2.9 Hz, 1H), 1.96 (dd, *J* = 13.1, 3.0 Hz, 1H) 2.00 (s, 3H), 2.36 (s, 3H), 3.39 (dd, *J* = 10.4, 1.9 Hz, 1H), 3.75 (t, *J* = 9.5 Hz, 1H), 3.89-3.93 (m, 1H), 4.41 (dd, *J* = 2.8, 11.4 Hz, 1H), 4.63-4.64 (m, 2H), 5.23-5.32 (m, 2H) and 5.89-5.97 (m, 1H); δ_C (125 MHz; $CDCl_3$) 18.6, 21.3, 24.0, 29.5, 31.3, 48.0, 52.6, 57.9, 65.0, 101.5, 118.2, 132.2, 146.7, 154.6, 165.1 and 179.5; LRMS, Positive ESI, *m/z* 523 ([2M+H]$^+$, 5%), 402 (4), 314 (15), 304 (6), 262 ([M+H]$^+$, 100) and 222 (2); LRMS, Negative ESI *m/z* 165 (6) 113 (20) 77 (100), 75 (62), 60 ([CO_3]$^{2-}$, 37%) and 59 ([M-H]$^-$, 68%); HRMS, ESI, *m/z* $C_{14}H_{20}N_3O_2$, requires 262.1550, found 262.1548 [M+H]$^+$.

(5a*R*,8a*S*)-5-((Allyloxy)carbonyl)-4-phenyl-3,5a,6,7,8,8a-hexahydro-1*H*-2,2a^1,3-triazaacenaphthylen-2-ium acetate (27). Was prepared following the general procedure outlined above giving tricyclic guanidine **27** as a tan oil in 26% yield after chromatography. R_f = 0.24 (10% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3338, 2926, 2859, 1693, 1668, 1648, 1606, 1493, 1448 and 1375; δ_H (500 MHz; $CDCl_3$) 1.50-1.71 (m, 4H) 1.81-1.88 (m, 1H), 1.98-2.05 (m, 1H), 3.15-3.23 (m, 1H), 3.62 (t, *J* = 7.2 Hz, 1H), 3.85-3.93 (m, 1H), 4.37 (d, *J* = 5.4 Hz, 2H), 4.53 (dd, *J* = 11.1, 2.7 Hz, 1H), 4.93-5.03 (m, 2H), 5.50-5.57 (m, 1H) and 7.30-7.36 (m, 5H); δ_C (125 MHz; $CDCl_3$) 21.3, 29.6 31.3, 48.2, 53.4, 58.0, 65.3, 103.5, 118.3, 128.1, 128.4, 130.2, 131.2, 133.2, 144.5, 153.5 and 164.8; LRMS, Positive ESI, *m/z* 422 ([M+2AcOH]$^+$, 5%), 390 (6), 382 ([M+AcOH]$^+$, 9%), 342 (13), 324 ([M+H]$^+$, 100%), 316 (69), 290 (12) and 276 (8); LRMS, Negative ESI *m/z* 121 (4) 113 (3) 77 (18), 59 ([M-H]$^-$, 100%), 46 (3) and 45 (12); HRMS, ESI, *m/z* $C_{19}H_{22}N_3O_2$, requires 324.1707, found 324.1705 [M+H]$^+$.

1-Morpholinobutane-1,3-dione (28). Following the general procedure outlined above amide **28** was isolated as a pale yellow oil (13% (based on **23**)). R_f = 0.39 (10% methanol in chloroform); δ_H (500 MHz; $CDCl_3$) 2.24 (s, 3H), 3.38 (t, *J* = 4.8 Hz, 2H), 3.53 (s, 2H) 3.58-3.60 (m, 2H) and 3.62-3.65 (m, 4H); δ_C (125 MHz; $CDCl_3$) 30.2, 42.1, 46.7, 49.7, 66.5, 66.6, 165.0 and 202.0; LRMS, Positive EI, *m/z* 172 ([M+H]$^+$, 34%), 171 (M$^+$, 54%), 128 (77), 87 (30), 86 (96), 85 (30), 57 (68), 56 (52) and 43 (100).

General Procedure for deallylation/decarboxylation of dihydropyrimidines: To a stirred solution of tricyclic guanidine (~0.1 mmol) in a mixture of anhydrous methanol (1 mL) and anhydrous THF (1 mL) was added tetrakis(triphenylphosphine)-palladium(0) (0.02 eqv) and pyrrolidine (1.2 eqv). The reaction was stirred at rt and progress monitored by TLC. After 1.5-2 h the solvent was removed under reduced pressure and the residue dissolved in methanol (1 mL) and acetic acid (1 mL) and cooled (0 °C), whereupon $NaBH_3CN$ (5 eqv) was added and the mixture stirred to rt over 16 h. After evaporation, the reaction material was purified by flash column chromatography on silica gel using methanol/chloroform (stepwise gradient of 1% increments 0:100 to 10:90) containing 1% acetic acid.

(4*S*,5a*R*,8a*S*)-4-Methyl-3,4,5,5a,6,7,8,8a-octahydro-1*H*-2,2a^1,3-triazaacenaphthylen-2-ium acetate (29). Following the general procedure outlined above guanidine **29** was obtained as a pale yellow oil in a 57% yield after chromatography. Upon standing or in methanol solution the acetate counterion is slowly converted to the carbonate by atmospheric CO_2. R_f = 0.15 (10% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3145, 2924, 2853, 1666, 1445, 1338 and 1332; δ_H (500 MHz; $CDCl_3$) 1.11-1.19 (m, 1H), 1.27-1.49 (m, 4H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.90-2.05 (m, 2H), 1.98 (s, 3H), 2.11 (app dt, *J* = 13.4, 3.6 Hz, 1H), 3.18-3.27 (m, 2H), 3.50-3.58 (m, 1H), 3.62-3.69 (m, 1H) and 3.77-3.84 (m, 1H); δ_C (125 MHz; $CDCl_3$) 20.6, 22.2, 24.5, 29.7, 31.1, 37.1, 45.5, 48.5, 50.1, 56.8 and 155.4; LRMS, Positive ESI, *m/z* 395 (5), 239 (2) and 180 ([M+H]$^+$, 100%); LRMS, Negative ESI *m/z* 113 (7), 77 (100), 75 (7), 60 ([CO_3]$^{2-}$, 30%), 59 ([M-H]$^-$, 12%), 45 (14), 35 (6) and 33 (3); HRMS, ESI, *m/z* $C_{10}H_{18}N_3$, requires 180.1495, found 180.1492 [M+H]$^+$.

(4*R*,5a*R*,8a*S*)-4-Phenyl-3,4,5,5a,6,7,8,8a-octahydro-1*H*-2,2a^1,3-triazaacenaphthylen-2-iumacetate (30). Following the general procedure outlined above guanidine **30** was obtained as a pale yellow oil in 53% yield after chromatography. Upon standing or in methanol solution the acetate counter-ion is slowly converted to the carbonate by atmospheric CO_2. R_f = 0.08 (10% methanol in chloroform); ν_{max} (chloroform)/cm^{-1} 3156, 2942, 2928, 2863, 1671, 1607, 1556, 1455 and 1379; δ_H (500 MHz; CD_3OD) 1.22-1.29 (m, 1H), 1.35-1.45 (m, 1H), 1.50-1.59 (m, 1H), 1.80 (app dt, *J* = 13.5, 11.5, 11.0 Hz, 1H), 1.96-2.02 (m, 2H), 2.09-2.14 (m, 1H), 2.36 (app dt, *J* = 13.5, 3.3, 3.3 Hz, 1H), 3.25-3.29 (m, 1H), 3.52 (app tt, *J* = 11.3, 11.0, 4.0, 3.3 Hz, 1H), 3.82-3.89 (m, 2H), 4.62 (dd, *J* = 11.5, 3.3 Hz, 1H) and 7.31-7.45

(m, 5H); δ_C (125 MHz; $CDCl_3$) 22.2, 23.0, 29.5, 30.9, 38.7, 48.6, 50.4, 54.0, 57.1, 126.1, 128.5, 129.1, 139.1, 155.9 and 174.0; LRMS, Positive ESI, *m/z* 483 ($[2M+H]^+$, 6%), 284 (4) and 242 ($[M+H]^+$, 100%); LRMS, Negative ESI *m/z* 120 (10), 92 (12), 76 (42), 75 (100), 59 ($[M-H]^-$, 18%), 45 (16) and 32 (5); HRMS, ESI, *m/z* $C_{15}H_{20}N_3$, requires 242.1648, found 242.1652 $[M+H]^+$.

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