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Combining two-directional synthesis and tandem reactions. Part 21: Exploitation of a dimeric macrocycle for chain terminus differentiation and synthesis of an sp^3-rich library

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Abstract

The application of a tandem condensation/cyclisation/[3+2]-cycloaddition/elimination reaction gives an sp^3-rich tricyclic pyrazoline scaffold with two ethyl esters in a single step from a simple linear starting material. The successive hydrolysis and cyclisation (with Boc anhydride) of these 3-dimensional architectures, generates unprecedented 16-membered macrocyclic bisanhydrides (characterised by XRD). Selective amidations could then be achieved by ring opening with a primary amine followed by HATU-promoted amide coupling to yield an sp^3-rich natural product-like library.

Graphical abstract

Figure options

Keywords

- sp³-rich;
- Natural product-like;
- Scaffold;
- Cycloaddition;
- Two-directional;
- Macrocycle;
- Library;
- Tandem

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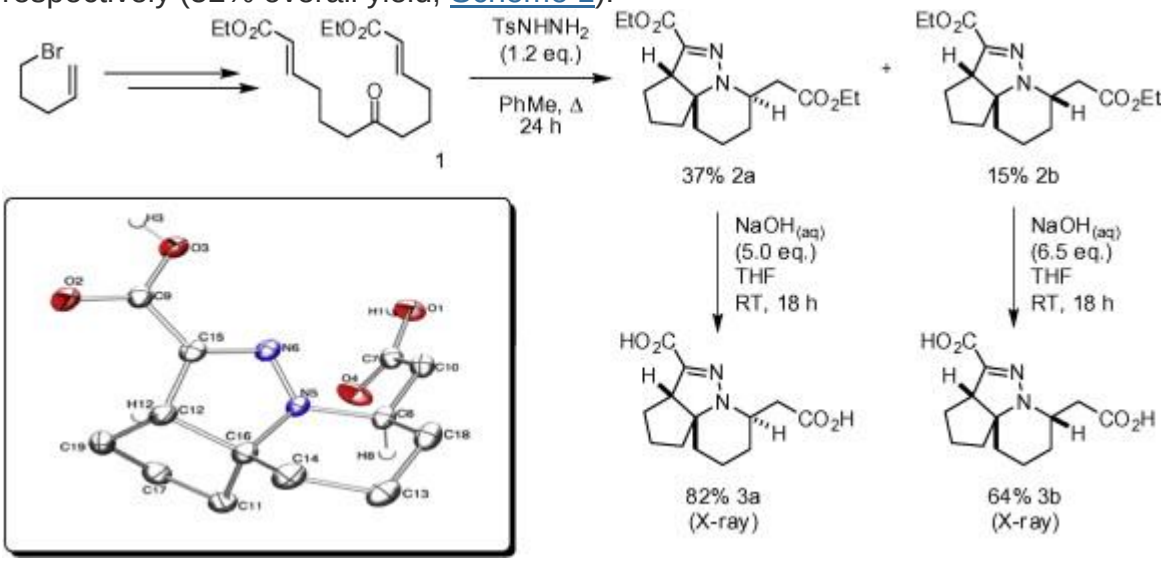
1. Introduction

The development of rapid access strategies towards novel 3-dimensional heterocyclic scaffolds is of high interest to organic and medicinal chemists alike.[1] We have pioneered an approach to complex molecular architectures exploiting two-directional synthesis to make symmetrical polyelectrophilic linear molecules, which undergo tandem reactions when reacted with a range of nucleophiles. These diastereoselective processes yield polycyclic structures with multiple stereocentres in a single reaction pot.[2] We have employed this strategy for the syntheses of several natural products over the past decade, including anatoxin-a, histrionicotoxin, hippodamine, xenovenine and halichlorine.[3] More recently, our attention has been drawn to the synthesis of natural product-like scaffolds for chemical library synthesis.[4] Our previous reports on the use of diester **1** as a substrate for tandem cyclisations described access to a variety of novel scaffolds, including 1,2,3,3a,7,8,9,10-octahydrocyclopenta[4,5]pyrazolo[1,5-*a*]pyridine containing structure **2**.[4] This complex fused heterocyclic core was synthesised via treatment of ketodiester **1** with *para*-toluenesulfonyl hydrazide resulting in a tandem condensation/Michael addition/azamethineimine [3+2] cycloaddition reaction sequence, followed by an elimination step, to deliver the desired scaffold. In order to exploit this useful strategy for the synthesis of derivatives for library synthesis, a method for the selective reaction of the pendant ester functionalities needed to be devised with the ultimate goal of producing a library of diamides. Herein we report our findings on the selective synthesis of this diamide functionalised polycyclic scaffold using a unique dimerisation strategy.

2. Results and discussion

The high yielding synthesis of diester **1** can be easily performed on large scale (>10 g) in three simple steps from 5-bromopent-1-ene (70% overall yield).[3b] As previously reported, the construction of the polycyclic core could be achieved via

reaction of **1** with *para*-toluenesulfonyl hydrazide under reflux to provide compound **2**. In this instance the reaction was carried out for 24 h resulting in a separable mixture of diastereomers **2a** and **2b** in 37% and 15% isolated yields, respectively (52% overall yield; Scheme 1).



Scheme 1.

The synthesis of **3a** and **3b** derived from **1**. Inset—Ortep diagram of **3a**, some hydrogen atoms are omitted for clarity, thermal ellipsoids shown at 50%.

Figure options

It was proposed that the conversion of **1** to **2** initially proceeded via condensation with *para*-toluenesulfonyl hydrazide to produce *N*-sulfonyl hydrazone **A** (Fig. 1). Nucleophilic attack of the imine nitrogen onto one of the α,β-unsaturated esters, followed by proton transfer, then delivered intermediate **B**. The azomethine imine ylide **B** is ideally set up for an intramolecular [3+2]-dipolar cycloaddition with the remaining olefin (Fig. 1). This process sets the remaining stereochemistry of the scaffold core structure to produce intermediate **C** which underwent rapid elimination of *para*-toluenesulfinic acid to produce **2** (Fig. 1). It was presumed that the formation of diastereomer **2b** occurred post cycloaddition through a retro-Michael elimination of the pyrazoline followed by conjugate addition. A similar epimerisation has been noted in a related pyrrolidine system.[5] Another possible reaction pathway is the initial [3+2]-dipolar cycloaddition via an in situ formed diazointermediate (see SI for details).

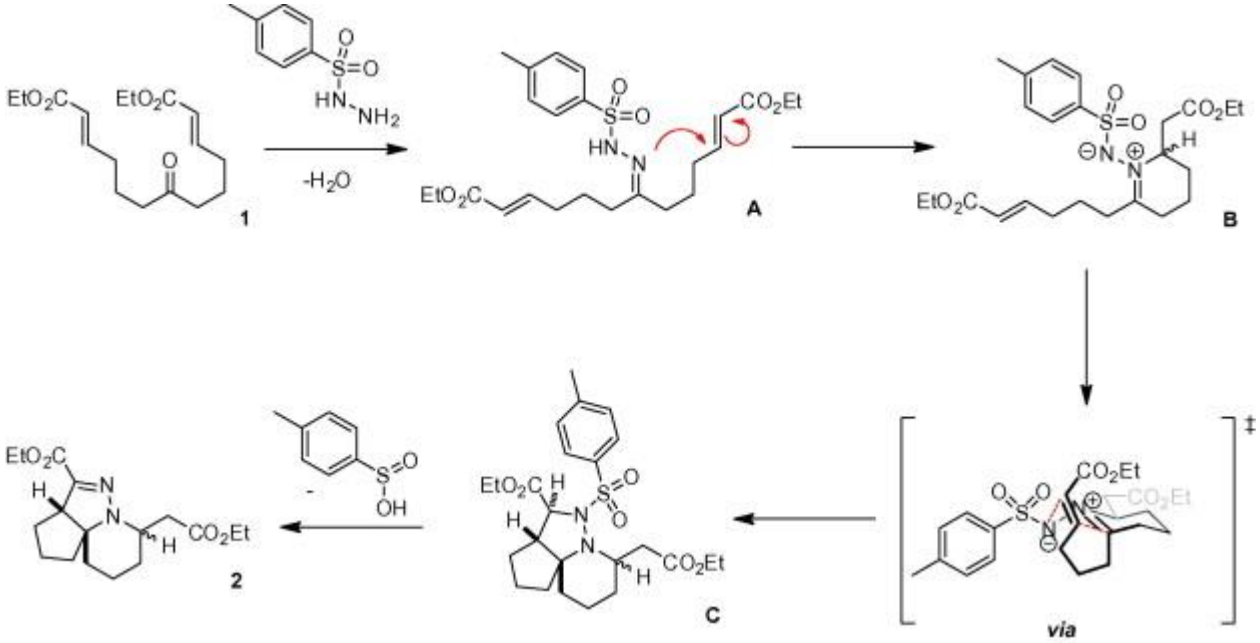


Figure 1.

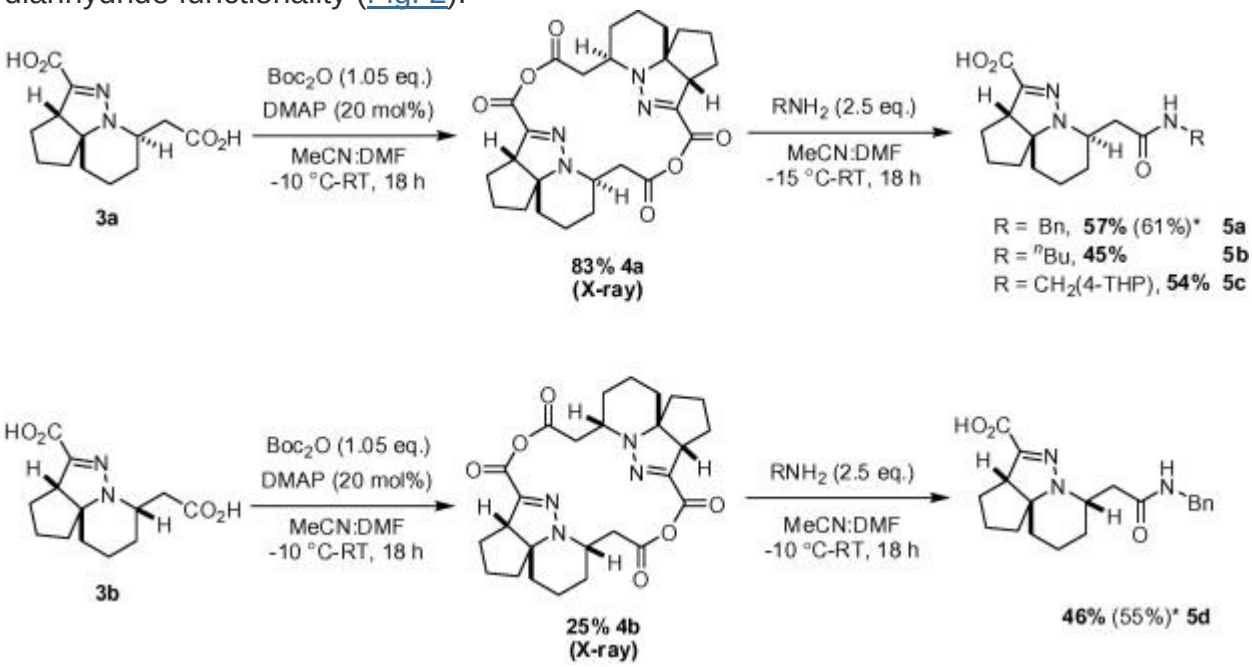
Plausible mechanism for the formation of **2**.

Figure options

With large quantities of the diastereomeric compounds **2a** and **2b** in hand, the selective reaction of a single ester moiety was attempted (reduction, transesterification and transamidation) but met with only limited success. Reduction with multiple hydride reagents ($NaBH_4$, $LiBH_4$, $LiAlH_4$ and DIBAL) under a variety of conditions generally provided only the doubly reduced product or recovered starting material. The same trend was observed when attempting to obtain a monohydrolysed product. Treatment of **2a**with 1 equiv of $NaOH_{(aq)}$ provided a 48% yield of the doubly hydrolysed product and the remainder of the material was untouched. Due to the apparent lack of selectivity, it was deemed that gaining a selective ester functional group interconversion was not possible without substantial further investigation. To circumvent this regioselectivity issue, a new strategy was devised involving full hydrolysis of **2** to the diacid **3**, followed by a selective amidation reaction. Double hydrolysis of **2** was achieved with an excess of hydroxide to provide **3a** and **3b**, in 82% and 64% yields, respectively, after a simple trituration (Scheme 1). The recrystallisation of **3a** and **3b** was performed (MeOH; slow evaporation) to provide crystals of sufficient quality to allow analysis by X-ray crystallography, hence the relative stereochemistry of both **3a** and **3b** was determined unambiguously (Scheme 1, Inset and SI).

Using **3a** as a model substrate, regioselective amidation of one of the carboxylic acid functions was probed. Using a variety of coupling reagents (HATU, CDI, T3P, DCC and DSC), stoichiometries, reaction conditions and hydrolytic workups were assessed but to no avail. The major problems encountered included double amidation, lack of selectivity and purification issues. These observations suggested that the issues stemmed from the high reactivity of activated esters formed in situ. The concurrent production of a non-polar dimeric species derived from the starting diacid **3a** was noted as an interesting observation during some reactions. It was possible to synthesise dimer **4a** by treatment of **3a** by Boc anhydride (1.05 equiv), with a simple trituration providing macrocycle **4a** in 83% yield and high purity

(Scheme 2). This method was also used to produce the diastereomeric macrocycle **4b**, albeit in a modest yield of 25% (Scheme 2). The structure of both **4a** and **4b** were confirmed by NMR and X-ray crystallographic analysis, demonstrating both the relative configuration and the 16-membered macrocyclic dianhydride functionality (Fig. 2).



Scheme 2.

Synthesis of **4a–b** and **5a–d** (*—^{1}H NMR yield post reaction work up).

Figure options

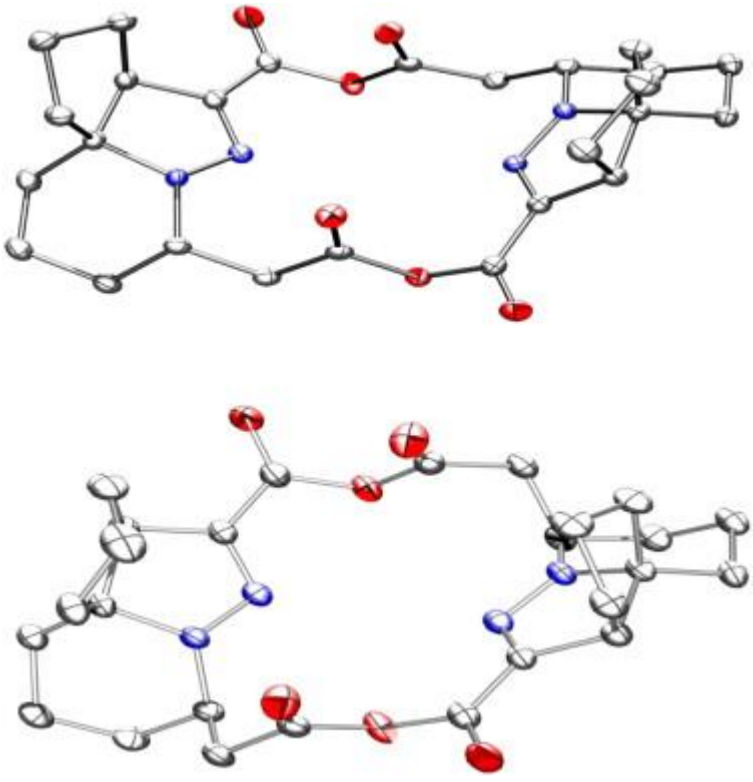


Figure 2.

Ortep diagrams of **4a** (top) and **4b** (bottom), hydrogen atoms and solvent molecules (CH_2Cl_2 for **4a**) are omitted for clarity, thermal ellipsoids shown at 50%.

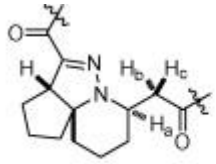
Figure options

With **4a** and **4b** in hand, an attempt to selectively ring open the macrocycle by addition of a primary amine (2.5 equiv) was performed. Pleasingly, initial ring opening followed by the second addition of an amine to generate two molecules of acid-amide product occurred smoothly. Slow addition of the amine to **4** at low temperature was necessary to obtain good selectivities for the aliphatic amidation (Scheme 2). The use of benzylamine, *n*-butylamine and 4-aminomethyl tetrahydropyran all provided the acid-amides **5a**–**d** in moderate yields after trituration from EtOAc/Et_2O. Unfortunately no significant regioselectivity was observed when using the secondary amines piperidine and dimethylamine. In addition, anilines were also found to be poor reactants due to their low nucleophilicity. The reaction selectivity favoured amidation of the aliphatic carbonyl, presumably due the higher electrophillicity at this position, with only minor quantities of the regioisomer, diamide and regenerated diacid observed.

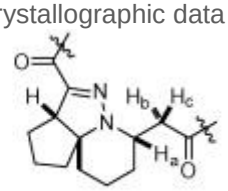
A structural analysis was performed where the $^3J_{HH}$ coupling constants of the methylene-CH_2 were cross-correlated to the torsion angles observed in the solid state structures (Table 1). Firstly it was noted that the piperidinyl nitrogen was near planar in all of the X-ray crystal structures obtained. This demonstrates the level to which the nitrogen lone pair is conjugated through to the α,β-unsaturated ester functionality. A *gauche–trans*conformation is adopted by the carboxymethylene group in all the solid state structures which accounts for the difference in chemical shift in the methylene hydrogens ($\Delta\delta$ = 0.50 ppm). It appears that the proximity of one of the methylene hydrogens to the imine like nitrogen causes a downfield shift in the ^{1}H NMR (H_b and H_c for the major and minor diastereomeric series, respectively, Table 1). Surprisingly large $^3J_{HH}$ coupling constants were observed in both macrocycles, 11.7 Hz and 13.1 Hz for **4a** and **4b**, respectively (Table 1). This can be explained due to the macrocycle effectively locking the conformation of the carboxymethylene group (torsion angles of >170° are noted in the solid state, Table 1).

Table 1.

Selected ^{1}H NMR and X-ray crystallographic data for compounds **2**–**6**



Major Diastereomeric Series



Minor Diastereomeric Series

Figure options

Compound	δ H_a(ppm)	$J_{Ha–Hc}$(Hz)	δ H_b(ppm)	$J_{Ha–Hb}$(Hz)	δ H_c(ppm)	H_a–C–C–$H_c$torsion angle (°)	H_a–C–C–H_b torsion angle (°)
2a	3.80	6.1	3.05	7.9	2.65	—	—
3a	3.86	8.0	3.03	5.9	2.66	172.2	70.8
4a	4.07	11.7	3.22	2.5	2.61	171.0	72.2

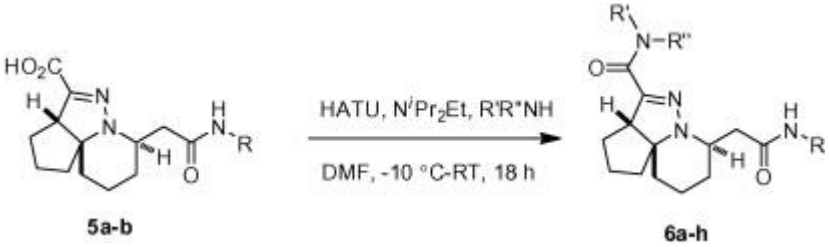
Compound	δ H_a(ppm)	$J_{Ha–Hc}$(Hz)	δ H_b(ppm)	$J_{Ha–Hb}$(Hz)	δ H_c(ppm)	H_a–C–C–$H_c$torsion angle (°)	H_a–C–C–H_b torsion angle (°)
5a–**b** ave.	3.87	9.4	2.93	4.4	2.43	—	—
6a–**h** ave.	3.63	9.6	2.90	4.6	2.39	—	—
2b	4.48	9.0	2.62	6.5	2.78	—	—
3b	4.49	7.4	2.60	8.2	2.78	56.4	174.8
4b	4.76	3.3	2.47	13.1	2.92	55.9 54.8	173.5 172.2
5c	4.29	6.9	2.55	8.0	2.73	—	—

Table options

The second amide bond formation was found to proceed in good to quantitative yields when HATU was used as the coupling agent. Both **5a** and **5b** were coupled to piperidine, *para*-bromobenzylamine, *n*-butylamine and methylamine to provide the diamides **6a**–**h**(Table 2). Figure 3 shows the *C* Log *P* versus MW for a proposed library of 133 members to demonstrate the areas of chemical space accessed by this approach (Fig. 3).[6]

Table 2.

Amidation reactions of **5a** and **5b** with various amines



5a-b **6a-h**

Figure options

Entry	R	R′	R″	Yield (%)	Product
1	Bn	Me	H	83	**6a**
2		^{n}Bu	H	Quant.	**6b**
3		(4-BrC_6H_4)CH_2	H	Quant.	**6c**
4		–$CH_2(CH_2)_3CH_2$–		76	**6d**
5	^{n}Bu	Me	H	63	**6e**
6		^{n}Bu	H	88	**6f**
7		(4-BrC_6H_4)CH_2	H	98	**6g**
8		–$CH_2(CH_2)_3CH_2$–		88	**6h**

Table options

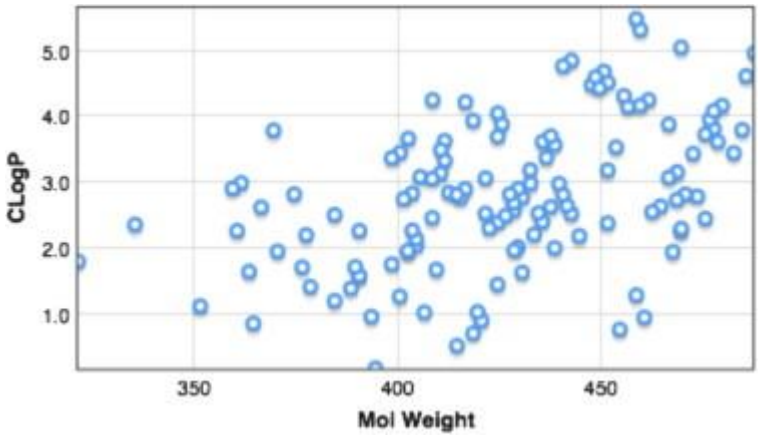


Figure 3.

Chart of *C* Log *P* versus MW for a library of 133 compounds based on scaffold **6**.

Figure options

3. Conclusion

The use of a rapid access route to the interesting 3-dimensional polycyclic 1,2,3,3a,7,8,9,10-octahydrocyclopenta[4,5]pyrazolo[1,5-*a*]pyridine scaffold has been employed to provide material for use in library synthesis. The double hydrolysis of the ethyl esters of **2** followed by a Boc anhydride mediated macrocyclisation was used to prepare bisanhydrides **4a** and **4b**. These novel, highly interesting macrocycles have been fully characterised and the X-ray crystal structures determined. This is the first report of the synthesis and use of such macrocyclic bisanhydrides. The selective amidation to generate compounds **5a** and **5b** was achieved by addition of primary amines into the bisanhydride **4a** at low temperature. This novel route provided access to the regioselective acid-amides **5** in only 3 steps from the cyclised products **2** with no column chromatography necessary. Further derivatisation of acid-amides **5a** and **5b** was achieved using a HATU mediated amide coupling to provide access to the desired diamide derivatives (**6a**–**h**).

4. Experimental

4.1. General experimental details

Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 (Bruker® DPX400, or AV400) or 300 MHz (Bruker® DPX300) NMR spectrometers in $CDCl_3$ or CD_3OD at 300 K (unless stated otherwise). For proton NMR, samples were prepared using ca. 5–10 mg of compound dissolved in 1.0 mL of deuterated solvent and for carbon NMR using ca. 20 mg of compound dissolved in 1.0 mL of deuterated solvent. All spectra were referenced to $CHCl_3$ or CHD_2OD the residual hydrogen solvent peaks for ^1H NMR ($CHCl_3$ δ = 7.26 ppm, CHD_2OD δ = 3.31) and the solvent peak for $^{13}C\{^1H\}$ NMR ($CDCl_3$ δ = 77.0 ppm, CD_3OD δ = 49.0). NMR Chemical shifts (δ) are reported in ppm; coupling constants (J) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, br = broad signal and app = the apparent multiplicity. High resolution mass spectrometry (HRMS) data was obtained using a Bruker® MicroTOF spectrometer measured using electrospray ionization (ESI) in the positive mode. Solvents, unless otherwise stated, were purchased in reagent grade or anhydrous quality and used as received. THF was distilled from Na/benzophenone immediately prior to use. Reagents were either

purchased directly from commercial suppliers or prepared according to literature procedures. All reactions were carried out in round bottomed flasks and sealed with a glass stopper or a rubber septum equipped with an N_2balloon and heated in oil baths with a thermocouple temperature control. Reactions were monitored using aluminium backed silica thin layer chromatography with a fluorescent dye (λ = 254 nm) and visualized under UV illumination or staining with basic $KMnO_4$ or bromocresol green dips. Flash column chromatography was performed manually on silica gel eluting with hexane/ethyl acetate under pressurised air flow.

4.2. General procedure for the cyclisation of **1**

In a 1 L round bottomed flask, diester **1** (6.0 g, 19.4 mmol, 1.0 equiv) was dissolved in toluene (800 mL) and a large stirrer bar was added. To the reaction mixture was added *para*-toluenesulfonyl hydrazide (4.2 g, 22.6 mmol, 1.2 equiv) and the reaction setup was equipped with a Dean–Stark apparatus and condenser. The reaction was heated at reflux for 15 h then allowed to cool to room temperature prior to filtration through a cotton wool plug. The crude reaction mixture was then reduced down in vacuo to yield a thick oil which was subjected to purification via silica gel chromatography (1:9 through to 2:3—EtOAc/Pet Ether 40–60). The product containing fractions were reduced down to yield diastereomers **2a** (2.32 g, 7.2 mmol, 37% yield) and **2b** (953 mg, 3.0 mmol, 15% yield) in an overall yield of 52% (**2a** and **2b** elute in this order and are easily separable).

4.2.1. Compound **2a**

A light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.24 (q, *J* = 7.1, 2H), 4.14 (qd, *J* = 7.1, 1.4, 2H), 3.80 (dddd, *J* = 11.6, 7.9, 6.1, 2.7, 1H), 3.17 (dd, *J* = 9.2, 4.1, 1H), 3.05 (dd, *J* = 16.3, 6.1, 1H), 2.65 (dd, *J* = 16.3, 7.9, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.86–1.34 (m, 10H), 1.31 (t, *J* = 7.1, 3H), 1.25 (t, *J* = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 171.7, 163.8, 138.2, 80.2, 60.4, 60.2, 55.5, 53.2, 38.2, 36.1, 33.4, 32.9, 32.7, 26.5, 21.8, 14.4, 14.1; MS (ESI) *m*/*z* = 667.4 (2 M+H$^+$, 100), 345.2 (M+Na$^+$, 31), 323.2 (M+H$^+$, 61); HRMS = 323.1970 (calcd = 323.1965 $C_{17}H_{27}N_2O_4^+$).

4.2.2. Compound **2b**

Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.48 (m, 1H), 4.27 (qd, *J* = 7.1, 1.1, 2H), 4.13 (q, *J* = 7.1, 2H), 3.23 (dd, *J* = 9.0, 4.8, 1H), 2.78 (dd, *J* = 15.0, 6.5, 1H), 2.62 (dd, *J* = 15.0, 9.0, 1H), 2.12 (m, 1H), 1.97 (m, 1H), 1.88–1.49 (m, 10H), 1.33 (t, *J* = 7.1, 3H), 1.24 (t, *J* = 7.1, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 171.0, 163.4, 138.3, 78.2, 60.6, 60.5, 57.1, 55.1, 40.0, 39.0, 34.4, 32.8, 28.7, 26.3, 16.9, 14.5, 14.2; MS (ESI) *m*/*z* = 667.4 (2 M+H$^+$, 100), 345.2 (M+Na$^+$, 46), 323.2 (M+H$^+$, 26); HRMS = 323.1964 (calcd = 323.1965 $C_{17}H_{27}N_2O_4^+$).

4.3. Procedure for the hydrolysis of **2a**

In a 50 mL round bottomed flask, compound **2a** (1.0 g, 3.1 mmol, 1.0 equiv) was dissolved in THF (23 mL) and a large stirrer bar was added. To the reaction mixture was added aqueous NaOH solution (1.0 M, 15.5 mL, 15.5 mmol, 5.0 equiv) and the reaction setup was stirred vigorously at room temperature for 24 h. To the reaction mixture was then added aqueous HCl (0.5 M, 40 mL) and the mixture extracted with EtOAc (3 × 80 mL). The organic extracts were then dried ($MgSO_4$), filtered, and reduced in vacuo to yield a crude semisolid which was triturated (EtOAc/Pet Ether 40–60—1:1, 10 mL) with sonication. The suspended solid was then filtered and washed (Pet Ether 40–60, 2 mL) to yield the product **3a** (675 mg, 2.53 mmol, 82% yield).

4.3.1. Compound **3a**

Colourless crystalline solid; mp = 161–163 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ = 3.83 (dddd, *J* = 11.7, 7.7, 6.5, 2.8, 1H), 3.14 (dd, *J* = 9.3, 3.8, 1H), 2.98 (dd, *J* = 16.3, 7.7,

1H), 2.59 (dd, *J* = 16.3, 6.5, 1H), 2.29 (m, 1H), 1.94 (m, 1H), 1.85–1.50 (m, 9H), 1.31 (m, 1H); ^{13}C NMR (CD_3OD, 101 MHz) δ = 175.2, 167.1, 139.3, 82.4, 56.5, 54.8, 39.0, 37.0, 34.4, 34.2, 34.1, 27.6, 22.9; MS (ESI) *m*/*z* = 289.1 ($M+Na^+$, 100), 267.1 ($M+H^+$, 19); HRMS = 289.1158 (calcd = 289.1159 $C_{13}H_{18}N_2NaO_4^+$). Crystals of sufficient quality to obtain an X-ray crystal structure (CCDC 1039024) were obtained by slow evaporation of **3a** from a solution of methanol.

4.4. Procedure for the hydrolysis of **2b**

In a 100 mL round bottomed flask, compound **2b** (953 mg, 3.0 mmol, 1.0 equiv) was dissolved in THF (50 mL) and a large stirrer bar was added. To the reaction mixture was added aqueous NaOH solution (1.0 M, 20.0 mL, 20.0 mmol, 6.8 equiv) and the reaction setup was stirred vigorously at room temperature for 24 h. To the reaction mixture was then added aqueous HCl (0.5 M, 40 mL) and the mixture extracted with EtOAc (3 × 80 mL). The organic extracts were then dried ($MgSO_4$), filtered, and reduced down in vacuo to yield a crude semisolid which was triturated (EtOAc/Pet Ether 40–60—1:1, 10 mL) with sonication. The suspended solid was then filtered and washed (Pet Ether 40–60, 2 mL) to yield the product **3b** (504 mg, 1.89 mmol, 64% yield).

4.4.1. Compound **3b**

Off white solid (CCDC 1039026); mp = 154–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.49 (m, 1H), 3.23 (dd, *J* = 9.0, 4.7, 1H), 2.78 (dd, *J* = 15.0, 8.2, 1H), 2.60 (dd, *J* = 15.0, 7.4, 1H), 2.16 (m, 1H), 2.03–1.51 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 176.5, 166.8, 137.4, 79.4, 56.3, 55.4, 40.1, 38.7, 34.7, 32.6, 29.2, 26.3, 16.9; MS (ESI) *m*/*z* = 555.2 (2 $M+Na^+$, 100), 289.1 ($M+Na^+$, 51), 267.1 ($M+H^+$, 29); HRMS = 289.1158 (calcd = 289.1154 $C_{13}H_{18}N_2NaO_4^+$).

4.5. Procedure for the macrocyclisation of **3a**

In a 50 mL round bottomed flask, compound **3a** (1.25 g, 4.69 mmol, 1.0 equiv) was dissolved in MeCN/DMF (10:1, 44 mL) along with DMAP (120 mg, 20 mol %) and a stirrer bar was added. To the stirred reaction mixture at −5 °C was added a solution of di-*tert*-butyl dicarbonate (1.08 g, 4.9 mmol, 1.05 equiv dissolved in 20 mL of MeCN) dropwise over 10 min and the reaction mixture was allowed to warm up to room temperature over 18 h with stirring. The reaction mixture was then worked up with aqueous HCl (0.05 M, 120 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were then dried ($MgSO_4$), filtered, and reduced down in vacuo to yield a crude solid which was triturated (EtOAc/Pet Ether 40–60—3:1, 5 mL) with sonication. The suspended solid was then filtered and washed (EtOAc, 2 mL) to yield the product **4a** (963 mg, 1.94 mmol, 83% yield).

4.5.1. Compound **4a**

Colourless crystalline solid; mp = 192–194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.07 (app tt, *J* = 11.7, 2.5, 1H), 3.30 (app t, *J* = 6.1, 1H), 3.22 (dd, *J* = 17.5, 11.7, 1H), 2.61 (dd, *J* = 17.5, 2.5, 1H), 2.32 (m, 1H), 1.99–1.89 (m, 2H), 1.87–1.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 167.2, 159.7, 133.8, 81.1, 53.6, 52.9, 37.0, 36.9, 35.4, 33.5, 33.4, 25.8, 21.7; MS (ESI) *m*/*z* = 519.2 ($M+Na^+$, 100), 497.2 ($M+H^+$, 17), 289 ($C_{13}H_{18}N_2O_4+Na^+$, 32), 193.1 ($C_{11}H_{16}N_2O+H^+$, 43); HRMS = 519.2240 (calcd = 519.2214 $C_{26}H_{32}N_4NaO_6^+$). Crystals of sufficient quality to obtain an X-ray crystal structure (CCDC 1039023) were obtained by slow evaporation of **4a** from a solution of CH_2Cl_2/EtOAc—2:1.

4.6. Procedure for the macrocyclisation of **3b**

In a 25 mL round bottomed flask, compound **3b** (375 mg, 1.41 mmol, 1.0 equiv) was dissolved in MeCN/DMF (10:1, 13.2 mL) along with DMAP (36 mg, 20 mol %) and a stirrer bar was added. To the stirred reaction mixture at −15 °C was added a solution

of di-*tert*-butyl dicarbonate (324 mg, 1.48 mmol, 1.05 equiv dissolved in 6.0 mL of MeCN) dropwise over 10 min and the reaction mixture was allowed to warm up to room temperature over 18 h with stirring. The progress of the reaction was monitored by TLC (basic $KMnO_4$ stain) which showed that the reaction was not as clean as observed in the synthesis of **4a**, hence the reaction was allowed to equilibrate for a further 72 h. After this time a further quantity of di-*tert*-butyl dicarbonate (97 mg, 0.44 mmol, 0.30 equiv dissolved in 2.0 mL of MeCN) was added dropwise over 10 min at −15 °C and the reaction mixture was then allowed to warm up to room temperature over the subsequent 18 h. At this point little difference to the initial analysis was observed so the reaction mixture was then worked up with aqueous HCl (0.05 M, 100 mL) and extracted with CH_2Cl_2 (3 × 80 mL) and EtOAc (2 × 50 mL). The organic extracts were combined then dried ($MgSO_4$), filtered, and reduced down in vacuo to yield a crude solid which purified via silica gel chromatography (1:9 through to 2:3—EtOAc/Pet Ether 40–60). The product containing fractions were reduced down to yield compound **4b** (88 mg, 0.18 mmol, 25% yield).

4.6.1. Compound **4b**

White crystalline solid; mp = 193–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.76 (ddd, *J* = 13.1, 5.8, 3.3, 1H), 3.29 (dd, *J* = 8.7, 5.0, 1H), 2.92 (app t, *J* = 13.1, 1H), 2.47 (dd, *J* = 12.9, 3.3, 1H), 2.37 (app dt, *J* = 12.5, 6.2, 1H), 2.07–1.91 (m, 2H), 1.84–1.48 (m, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 166.7, 159.2, 135.0, 79.8, 57.1, 55.7, 40.2, 39.6, 36.2, 32.5, 31.2, 26.0, 17.3; MS (ESI) *m*/*z* = 519.2 ($M+Na^+$, 100), 497.2 ($M+H^+$, 18), 289 ($C_{13}H_{18}N_2O_4+Na^+$, 4), 193.1 ($C_{11}H_{16}N_2O+H^+$, 11); HRMS = 519.2233 (calcd = 519.2214 $C_{26}H_{32}N_4NaO_6^+$). Crystals of sufficient quality to obtain an X-ray crystal structure (CCDC 1039025) were obtained by slow evaporation of **4b** from a solution of CH_2Cl_2:EtOAc—2:1.

4.7. General procedure for the macrocyclic ring opening of **4a** and **4b** with an amine

A round bottomed flask, containing a 20 mM solution of macrocycle **4a** or **4b** (1.0 equiv) in MeCN/DMF—1:1 and a stirrer bar was cooled to around -18 °C using a salt/ice bath. To the stirred reaction mixture a 0.2 M solution of the primary amine (2.5 equiv) in MeCN/DMF 1:1 was added dropwise over 10 min and the reaction mixture was allowed to warm up to room temperature over 18 h with stirring. The reaction mixture was then worked up with aqueous HCl (0.05 M) and extracted thrice with EtOAc. The organic extracts were then dried ($MgSO_4$), filtered, and reduced down in vacuo to yield a crude gummy product which was thoroughly dried under high vacuum (ca. 1 mbar). The purified products could then be obtained by trituration of the crude product with various solvents and solvent mixtures (e.g., Et_2O, EtOAc/Pet Ether 40–60—1:1, EtOAc/Et_2O—1:1) where the suspended solid was then filtered and washed (Et_2O) to yield the desired product **5**.

4.7.1. Compound **5a**

The general protocol was performed on 0.40 mmol of **4a** which (after trituration with EtOAc/Et_2O—1:1) provided compound **5a** (163 mg, 0.46 mmol, 57% yield) as a white solid; mp = 96–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.29–7.18 (m, 5H), 6.65 (br dd, *J* = 6.7, 5.0, 1H), 4.55 (dd, *J* = 14.8, 6.7, 1H), 4.25 (dd, *J* = 14.8, 5.0, 1H), 3.87 (dddd, *J* = 12.1, 9.5, 4.3, 2.7, 1H), 3.16 (dd, *J* = 9.4, 3.9, 1H), 2.95 (dd, *J* = 14.0, 9.5, 1H), 2.45 (dd, *J* = 14.0, 4.3, 1H), 2.19 (ddd, *J* = 12.8, 6.1, 3.2, 1H), 1.90 (m, 1H), 1.82–1.61 (m, 6H), 1.60–1.45 (m, 2H), 1.42–1.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.1, 166.5, 138.2, 137.2, 128.5, 127.6, 127.3, 81.5, 54.7, 54.5, 43.5, 40.4, 36.1, 33.7, 33.6, 33.0, 26.6, 21.9; MS (ESI) *m*/*z* = 378.2 ($M+Na^+$, 89), 356.2 ($M+H^+$, 100); HRMS = 356.1979 (calcd = 519.1969 $C_{20}H_{26}N_3O_3^+$).

4.7.2. Compound **5b**

The general protocol was performed on 0.40 mmol of **4a** which (after trituration with Et_2O) provided compound **5b** (116 mg, 0.36 mmol, 45% yield) as a white solid; mp = 182–185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.32 (br m, 1H), 3.86 (dddd, *J* = 12.0, 9.2, 4.5, 2.9, 1H), 3.32 (m, 1H), 3.19 (dd, *J* = 9.3, 3.9, 1H), 3.10 (m, 1H), 2.90 (dd, *J* = 13.9, 9.2, 1H), 2.41 (dd, *J* = 13.9, 4.5, 1H), 2.24 (m, 1H), 1.94 (m, 1H), 1.84–1.21 (m, 14H), 0.87 (t, *J* = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.0, 166.8, 137.1, 81.5, 54.7, 54.7, 40.5, 39.2, 36.2, 33.8, 33.6, 33.1, 31.5, 26.7, 21.9, 19.9, 13.7; MS (ESI) *m*/*z* = 344.2 ($M+Na^+$, 68), 322.2 ($M+H^+$, 100); HRMS = 322.2123 (calcd = 522.2125 $C_{17}H_{28}N_3O_3^+$).

4.7.3. Compound **5c**

The general protocol was performed on 96 µmol of **4a** which (after trituration with Et_2O) provided compound **5c** (37 mg, 107 µmol, 54% yield) as a white solid; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 6.50 (br m, 1H), 3.97–3.82 (m, 3H), 3.39–3.24 (m, 3H), 3.19 (dd, *J* = 9.3, 3.6, 1H), 2.98–2.85 (m, 2H), 2.43 (dd, *J* = 13.8, 4.1, 1H), 2.24 (m, 1H), 1. 49 (m, 1H), 1.84–1.17 (m, 15H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ = 171.1, 166.9, 137.0, 81.5, 67.6, 54.7, 45.2, 40.6, 36.2, 35.3, 33.8, 33.7, 33.1, 30.5, 26.7, 21.9 (16 out of a possibly 17 resonances observed); MS (ESI) *m*/*z* = 386.2 ($M+Na^+$, 100), 364.2 ($M+H^+$, 84); HRMS = 364.2225 (calcd = 364.2231 $C_{19}H_{30}N_3O_4^+$).

4.7.4. Compound **5d**

The general protocol was performed on 0.10 mmol of **4b** which (after trituration with EtOAc/Et_2O—3:1) provided compound **5d** (33 mg, 0.09 mmol, 46% yield) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36–7.22 (m, 5H), 6.10 (br m, 1H), 4.48 (dd, *J* = 14.6, 5.9, 1H), 4.38 (dd, *J* = 14.6, 5.5, 1H), 4.29 (m, 1H), 3.23 (dd, *J* = 8.8, 4.5, 1H), 2.73 (dd, *J* = 15.0, 8.0, 1H), 2.55 (dd, *J* = 15.0, 6.9, 1H), 2.03–1.52 (m, 11H), 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.2, 165.5, 138.5, 138.0, 128.7, 127.9, 127.5, 79.2, 56.3, 55.6, 43.7, 40.8, 40.4, 34.2, 32.6, 28.7, 26.1, 16.8; MS (ESI) *m*/*z* = 378.2 ($M+Na^+$, 100), 356.2 ($M+H^+$, 22); HRMS = 356.1971 (calcd = 519.1969 $C_{20}H_{26}N_3O_3^+$).

4.8. General procedure for the coupling of **5a** and **5b** with an amine

To a round bottomed flask equipped with a stirrer bar, containing a 100 mM solution of carboxylic acid **5a** or **5b** (1.0 equiv) in DMF, the amine (2.0 equiv) and DIPEA (2.0 equiv: note if a hydrochloride salt of the amine was used a larger excess of DIPEA was as used as appropriate) was added. The reaction vessel was cooled to around −18 °C using a salt/ice bath and a solution of HATU (ca. 0.5 M) was added, the reaction mixture was allowed to warm up to room temperature over 18 h with stirring. The reaction mixture was then worked up with the addition of aqueous 1 M HCl (30 mL) and extracted with EtOAc (100 mL). The organic extract was washed sequentially aqueous 1 M HCl (30 mL), saturated $NaHCO_{3(aq)}$ (30 mL) and 20% brine (2 × 30 mL). The organic solution was then dried ($MgSO_4$), filtered, and reduced down in vacuo and dried under high vacuum (ca. 1 mbar) to yield the desired product **6**.

4.8.1. Compound **6a**

The general protocol was performed on 0.11 mmol of **5a** which provided compound **6a**(34 mg, 93 mmol, 83% yield) as a clear gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.33–7.17 (m, 5H), 6.33 (br m, 1H), 6.23 (br m, 1H), 4.50 (dd, *J* = 14.6, 6.0, 1H), 4.33 (dd, *J* = 14.6, 5.1, 1H), 3.65 (dddd, *J* = 11.8, 9.9, 4.4, 2.8, 1H), 3.18 (dd, *J* = 9.7, 4.5, 1H), 2.94 (dd, *J* = 15.0, 9.9, 1H), 2.81 (d, *J* = 5.5, 3H), 2.45 (dd, *J* = 15.0, 4.4, 1H), 2.06 (ddd, *J* = 12.2, 6.3, 2.9, 1H), 1.90 (m, 1H), 1.74–1.20 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.1, 163.4, 145.9, 138.1, 128.7, 127.7, 127.5, 80.6, 55.7, 53.7, 49.3, 43.6, 40.4, 35.9, 32.1, 32.0, 27.2, 25.8, 21.6; MS

(ESI) *m*/*z* = 391.2 ($M+Na^+$, 89), 369.2 ($M+H^+$, 100); HRMS = 369.2299 (calcd = 369.2285 $C_{21}H_{28}N_4O_2^+$).

4.8.2. Compound **6b**

The general protocol was performed on 0.11 mmol of **5a** which provided compound **6b**(46 mg, 0.11 mmol, quantitative yield) as a clear gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.33–7.18 (m, 5H), 6.37 (br m, 1H), 6.26 (br m, 1H), 4.49 (dd, *J* = 14.7, 6.0, 1H), 4.35 (dd, *J* = 14.7, 5.2, 1H), 3.64 (dddd, *J* = 11.8, 9.8, 4.4, 2.8, 1H), 3.25 (m, 2H), 3.16 (dd, *J* = 9.8, 4.6, 1H), 2.97 (dd, *J* = 15.1, 9.8, 1H), 2.43 (dd, *J* = 15.1, 4.4, 1H), 2.05 (ddd, *J* = 12.0, 5.8, 3.4, 1H), 1.90 (m, 1H), 1.76–1.22 (m, 14H), 0.91 (t, *J* = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.1, 162.7, 146.1, 138.1, 128.7, 127.6, 127.5, 80.7, 55.7, 53.7, 43.6, 40.4, 38.9, 35.8, 32.1, 32.0, 32.0, 31.9, 27.2, 21.6, 20.2, 13.8; MS (ESI) *m*/*z* = 433.3 ($M+Na^+$, 99), 411.3 ($M+H^+$, 100); HRMS = 411.2773 (calcd = 411.2755 $C_{24}H_{34}N_4O_2^+$).

4.8.3. Compound **6c**

The general protocol was performed on 0.11 mmol of **5a** which provided compound **6c**(59 mg, 0.11 mmol, quantitative yield) as a white solid; mp = 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.42 (d, *J* = 8.4, 2H), 7.28–7.23 (m, 3H), 7.20–7.15 (m, 2H), 7.12 (d, *J* = 8.4, 2H), 6.57 (br m, 1H), 6.19 (br m, 1H), 4.48 (dd, *J* = 15.0, 6.0, 1H), 4.45 (dd, *J* = 15.0, 6.3, 1H), 4.32 (dd, *J* = 15.0, 2.8, 1H), 4.30 (dd, *J* = 15.0, 1.9, 1H), 3.68 (dddd, *J* = 12.0, 9.5, 4.7, 2.8, 1H), 3.19 (dd, *J* = 9.7, 4.5, 1H), 2.89 (dd, *J* = 15.0, 9.5, 1H), 2.43 (dd, *J* = 15.0, 4.7, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.76–1.22 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 170.8, 162.9, 144.9, 138.1, 137.8, 131.7, 129.6, 128.7, 127.6, 127.5, 121.2, 80.8, 55.6, 53.7, 43.5, 42.5, 40.4, 35.9, 32.3, 32.2 (2×C), 27.2, 21.6; MS (ESI) *m*/*z* = 547.2 ($MBr^{81}+Na^+$, 84), 545.2 ($MBr^{79}+Na^+$, 85), 525.2 ($MBr^{81}+H^+$, 98), 523.2 ($MBr^{79}+H^+$, 100); HRMS = 523.1737 (calcd = 523.1703 $C_{27}H_{31}N_4O_2Br^{79+}$).

4.8.4. Compound **6d**

The general protocol was performed on 0.05 mmol of **5a** which provided compound **6d**(16.1 mg, 0.038 mmol, 76% yield) as a clear gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.32–7.18 (m, 5H), 6.43 (br m, 1H), 4.48 (dd, *J* = 14.7, 5.9, 1H), 4.31 (dd, *J* = 14.7, 5.2, 1H), 3.69–3.52 (m, 5H), 3.22 (dd, *J* = 9.6, 5.0, 1H), 2.97 (dd, *J* = 14.8, 10.3, 1H), 2.40 (dd, *J* = 14.8, 4.0, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.76–1.22 (m, 16H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.3, 162.7, 146.9, 138.1, 128.7, 127.7, 127.5, 79.0, 58.6, 53.7, 43.6, 40.7, 35.7, 31.9, 31.8, 31.6, 29.7, 27.1, 24.7, 21.5 (20 out of a possibly 21 resonances observed); MS (ESI) *m*/*z* = 445.3 ($M+Na^+$, 95), 423.3 ($M+H^+$, 100); HRMS = 423.2774 (calcd = 423.2755 $C_{25}H_{35}N_4O_2^+$).

4.8.5. Compound **6e**

The general protocol was performed on 75 µmol of **5b** which provided compound **6e**(15.7 mg, 47 µmol, 63% yield) as a clear gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.41 (br m, 1H), 6.04 (br m, 1H), 3.61 (dddd, *J* = 12.0, 9.5, 4.8, 2.8, 1H), 3.35–3.10 (m, 2H), 3.20 (dd, *J* = 9.4, 4.4, 1H), 2.88 (d, *J* = 5.1, 3H), 2.87 (dd, *J* = 14.9, 9.5, 1H), 2.36 (dd, *J* = 14.9, 4.8, 1H), 2.13 (m, 1H), 1.97 (m, 1H), 1.79–1.49 (m, 8H), 1.45–1.39 (m, 2H), 1.33–1.21 (m, 4H), 0.88 (t, *J* = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 171.1, 163.5, 145.6, 80.7, 55.6, 53.8, 40.6, 39.1, 35.9, 32.2, 32.1, 31.6, 27.3, 25.8, 21.6, 20.0, 13.7; MS (ESI) *m*/*z* = 357.2 ($M+Na^+$, 99), 335.2 ($M+H^+$, 100); HRMS = 335.2447 (calcd = 335.2442 $C_{18}H_{31}N_4O_2^+$).

4.8.6. Compound **6f**

The general protocol was performed on 75 µmol of **5b** which provided compound **6f**(25 mg, 67 µmol, 89% yield) as a clear gum; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 6.35 (br m, 1H), 6.00 (br m, 1H), 3.61 (dddd, *J* = 12.0, 9.2, 4.8, 2.7,

1H), 3.36–3.15 (m, 4H), 3.16 (dd, *J* = 9.8, 4.6, 5H), 2.90 (dd, *J* = 15.0, 9.2, 1H), 2.37 (dd, *J* = 15.0, 4.8, 1H), 2.13 (m, 1H), 1.98 (m, 1H), 1.83–1.47 (m, 8H), 1.47–1.20 (m, 6H), 0.94 (t, *J* = 7.3, 3H), 0.89 (t, *J* = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) *δ* = 171.2, 162.8, 145.6, 80.6, 55.6, 53.8, 40.5, 39.0, 38.8, 35.9, 32.2 (2×C), 32.1, 32.0, 31.6, 27.2, 21.6, 20.1, 20.0, 13.8, 13.7; MS (ESI) *m*/*z* = 399.3 ($M+Na^+$, 89), 377.3 ($M+H^+$, 100); HRMS = 377.2925 (calcd = 377.2911 $C_{21}H_{37}N_4O_2^+$).

4.8.7. Compound **6g**

The general protocol was performed on 75 µmol of **5b** which provided compound **6g**(36 mg, 74 µmol, 98% yield) as a white solid; mp = 61–63 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* = 7.45 (d, *J* = 8.4, 2H), 7.20 (d, *J* = 8.4, 2H), 6.68 (br m, 1H), 5.86 (br m, 1H), 4.48 (dd, *J* = 15.0, 6.4, 1H), 4.41 (dd, *J* = 15.0, 6.0, 1H), 3.65 (dddd, *J* = 11.6, 8.6, 5.4, 2.7, 1H), 3.33–3.08 (m, 3H), 2.83 (dd, *J* = 14.8, 8.6, 1H), 2.33 (dd, *J* = 14.8, 5.4, 1H), 2.15 (m, 1H), 1.99 (m, 1H), 1.86–1.50 (m, 8H), 1.48–1.34 (m, 2H), 1.32–1.17 (m, 4H), 0.86 (t, *J* = 7.3, 3H) (Note: signals at 4.48 and 4.41 are heavily roofed); ^{13}C NMR ($CDCl_3$, 101 MHz) *δ* = 170.9, 163.0, 144.5, 137.8, 131.7, 129.6, 121.3, 80.8, 55.5, 53.8, 42.5, 40.6, 39.1, 35.9, 32.3 (2×C), 31.6, 27.2, 21.7, 20.0, 13.7 (Note; 21 out of a possible 22 resonances observed); MS (ESI) *m*/*z* = 513.2 ($MBr^{81}+Na^+$, 45), 511.2 ($MBr^{79}+Na^+$, 44), 491.2 ($MBr^{81}+H^+$, 98), 489.2 ($MBr^{79}+H^+$, 100); HRMS = 489.1897 (calcd = 489.1860 $C_{24}H_{34}N_4O_2Br^{79+}$).

4.8.8. Compound **6h**

The general protocol was performed on 75 µmol of **5b** which provided compound **6h**(25.6 mg, 66 µmol, 88% yield) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* = 6.09 (br m, 1H), 3.90–3.50 (br m, 4H), 3.60 (dddd, *J* = 11.6, 9.8, 4.2, 2.7, 1H), 3.30–3.16 (m, 3H), 2.85 (dd, *J* = 14.8, 9.8, 1H), 2.33 (dd, *J* = 14.8, 4.2, 1H), 2.12 (m, 1H), 1.98 (m, 1H), 1.81–1.48 (m, 14H), 1.46–1.36 (m, 2H), 1.35–1.21 (m, 4H), 0.89 (t, *J* = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) *δ* = 171.3, 162.8, 146.5, 78.9, 58.5, 53.7, 40.7, 39.0, 35.7, 32.1, 31.9, 31.6, 29.6, 27.2, 24.7, 21.5, 20.0, 13.7 (18 out of a possibly 20 resonances observed); MS (ESI) *m*/*z* = 411.3 ($M+Na^+$, 100), 389.3 ($M+H^+$, 97); HRMS = 389.2926 (calcd = 389.2911 $C_{22}H_{37}N_4O_2^+$).

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Supplementary data

Supplementary data 1.
Spectral data.

Help with PDF files

Options

Open Data

Supplementary data 2.

Help with ZIP files

Options

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