Efficient Synthesis of Structurally Diverse Diazabicycloalkanes: Scaffolds for Modular Dipeptide Mimetics with Tunable Backbone Conformations

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A stereoselective synthesis of new dipeptide mimetics based on a diazabicycloalkane scaffold is reported. The route starts from enantiomerically pure azabicycloalkenes **1** that are bis(hydroxylated) and coupled *N*-terminally to a second amino acid. The key step of the reaction sequence is an oxidative cleavage of the resulting dipeptides **5** to give highly functionalised diazabicycloalkanes **6**, which can be easily converted into a number of dipeptide mimetics with defined and variable stereochemistry and a number of different amino acid side chains. The backbone dihedral angles within these dipeptide mimetics can be tuned by varying the stereochemistry and the ring sizes of the diazabicycloalkane scaffold. The syntheses of conformationally constrained dipeptide analogues in four to five steps are presented. With the syntheses of dipeptide mimetics **19a**–**c**, suitable linker moieties for conjugation of diazabicycloalkanes to other functional molecules like markers or solid phases are introduced, making these compounds modular dipeptide mimetics that might find applications as modular ligands or as solid-phase-attached scaffolds in combinatorial chemistry.

Introduction

Peptides and proteins play a crucial role in the transmission of information in biological systems. As a consequence, many peptides serve as lead structures for the development of new pharmaceuticals. However, their utility as therapeutics or diagnostics is limited due to their susceptibility to protease degradation, poor bioavailability, and rapid excretion.[1] In addition, many small peptides lack selectivity to a certain receptor due to their high conformational flexibility. A common strategy to overcome these problems is the synthesis of peptide analogues mimicking the bioactive conformation of native peptides at the receptor level.[2] Many different classes of these peptidomimetics have been reported, including amide surrogates[3] such as aminomethylene, oxymethylene, alkene, sulfoxide and others, as well as displacement of a peptide segment with a scaffold.[4] The purpose of these modifications is to (a) increase the binding affinity and specificity of peptidomimetics to a given receptor, (b) increase the longevity of the compound by reducing the likelihood of degradation, and (c) increase the lipophilicity for improved absorption of the compound in biological systems.

Structurally rigid peptidomimetics, in particular, have found numerous applications in medicinal chemistry since they are conformationally preorganised or fixed into a shape that is recognised by a receptor, thus reducing the enthalpy penalty for the receptor-binding event. In addition to advantageous binding properties these compounds often have improved pharmacological profiles. In this context, fused bicyclic systems play an important role in the field of drug discovery. Azabicycloalkanes of type **II** in Figure 1 have been used as tools for rigidifying peptide structures in order to probe conformation-activity relationships.[5] A number of structurally related bicyclic peptide analogues with different ring sizes and heteroatoms have been prepared and incorporated into peptides as turn mimetics.[6−9] Besides this large body of work on turn mimetics there are relatively few known conformationally restricted analogues of extended peptide conformations.[10] The limited interest in these structures is surprising because it is known that a number of biomolecular receptors recognize their peptidic ligands in extended conformations.[11] Among these receptors are proteases,[12] MHC proteins[13] and transferases,[14] all of which are involved in important disease-related biological processes. Rigid mimetics of extended peptide conformations could thus provide valuable ligands for receptors that bind to non-turn peptide conformations such as cancer-specific proteases.

Results and Discussion

We have recently introduced the highly functionalised diazabicycloalkanes **I** as rigid dipeptide analogues.[15] Although a number of efficient syntheses to azabicycloalkanes of type **II** in Figure 1 are known, less attention has been paid to diazabicycloalkane derivatives.[16−18] Demands for

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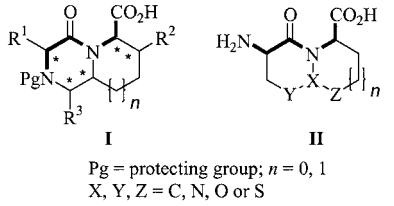
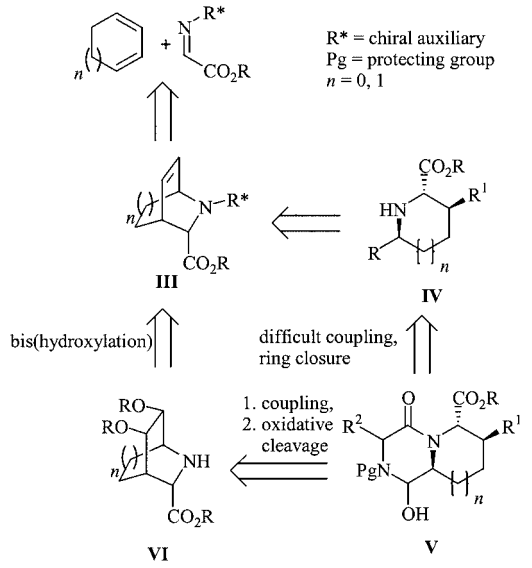


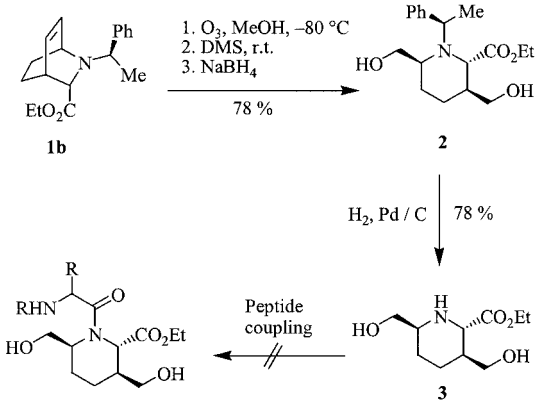
Figure 1. Proposed (**I**) and known (**II**) bicyclic dipeptide mimics

a suitable synthetic route to compounds **I** are high. Such a route has to be (a) short and high yielding, (b) compatible with various side-chain functionalities R^1 and R^2, (c) stereoselective with respect to five stereocentres, and (d) variable in stereochemistry and ring sizes. Furthermore, a suitable synthesis has to provide access to compounds with linker moieties because we are interested in modular ligands that can be attached to markers or a solid phase.[19]

Keeping these requirements in mind we selected structures of type **V** in Scheme 1 as target compounds. An obvious starting point for the retrosynthetic analyses of these bicyclic peptidomimetics **V** (Scheme 1) is the disconnection of the bicyclic ring system along the tertiary amide and the aminal function. A suitably functionalised disubstituted cyclic amino acid **IV** would therefore be a key intermediate. A look at the recent literature reveals that the synthesis of such 3,5-substituted prolines ($n = 0$)[20–22] and especially 3,6-substituted pipecolic acids ($n = 1$)[22,23] is not a trivial task since there are only a few general routes to enantiomerically pure compounds and all of them are multistep procedures. Our first efforts were therefore directed to the development of a short route to suitably functionalised cyclic amino acids of type **IV**. For this purpose we envisioned azabicycloalkenes **III**, which in turn can be synthesised by a known cycloaddition,[24–26] as precursors which, upon oxidative cleavage of the alkene moiety, should give cyclic amino acids **IV**. Coupling of an additional amino acid to its *N*-terminus and intramolecular cyclisation would then give the desired bicyclic structures **V**.



Scheme 1. Retrosynthetic analysis of dipeptide mimics **V**



Scheme 2. Synthesis of substituted pipecolic acid derivatives

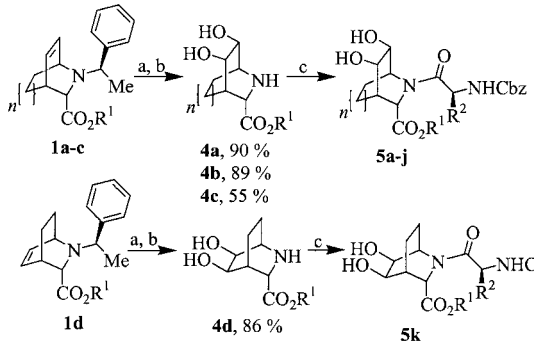
The two-step protocol to enantiomerically pure cyclic amino acids **3** is outlined in Scheme 2. Oxidative cleavage of the azabicyclooctene **1b**[26] with reductive workup gives diol **2** in good yield. Hydrogenolytic removal of the *N*-benzyl group gives the free amino acid **3**, which provides all the necessary functionalities for the synthesis of diazabicycloalkanes **V**. Unfortunately, peptide couplings to the *N*-terminus of the sterically hindered pipecolic acid derivative **3** proved to be extremely difficult. A number of common peptide coupling reagents (among them highly efficient reagents like TFFH and HATU) failed to give the desired dipeptides in reasonable yield.

The synthetic route outlined in Scheme 2 is an efficient procedure for the preparation of enantiomerically pure, substituted proline and pipecolic acid derivatives, and although these cyclic amino acids, like **3**, did not allow the synthesis of the desired diazabicycloalkanes **V** (Scheme 1), they proved to be valuable precursors for a range of different proline and pipecolic acid derivatives that might be useful intermediates for natural product synthesis.[27]

To avoid the difficult peptide coupling to substituted cyclic amino acids of type **IV** (Scheme 1) a second route via bis(hydroxylated) azabicycloalkanes **VI** was tried. Peptide couplings to the structurally similar unnatural amino acid azabicycloheptanecarboxylic acid are known to proceed under standard conditions in good yield.[28] It was therefore assumed that a second amino acid should be easy to couple to **VI** to give the corresponding dipeptide. Oxidative cleavage of the diol function within this dipeptide should then lead to an intermediate bis(aldehyde) in which the α-aminoaldehyde was supposed to cyclise immediately intramolecularly to the target compound **V**.

The first part of this synthesis is outlined in Scheme 3. Enantiomerically pure azabicycloalkenes **1** were synthesised in one step according to a literature protocol from (*R*)-phenylethylamine, cyclopentadiene or cyclohexadiene and

the appropriate glyoxylate by an aza-Diels–Alder reaction on a large scale.[29]



Scheme 3. Conversion of azabicycloalkenes **1a–d** to dipeptides **5a–k**; reagents and conditions: a) cat. $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH/H_2O, 12 h, room temp.; alternatively for **4c**: $KMnO_4$, aq NaOH, *t*BuOH/H_2O, 0 °C, 15 min; b) H_2 (1 atm), 5% Pd/C, EtOH, room temp., 24 h; c) *N*-protected amino acid, DCC, HOBt, DMF, 12 h, 0 °C to room temp.

Bis(hydroxylation) of azabicycloalkenes **1a**, **1b**, and **1d** was performed with $K_2OsO_2(OH)_4/K_2CO_3$ and $K_3Fe(CN)_6$ as cooxidant in good yields. Alternatively, this oxidation may be performed with $KMnO_4$ in aqueous NaOH. Yields for this procedure were slightly lower, as shown for compound **1c** in Scheme 3. However, the use of $KMnO_4$ is more convenient and cheaper for large-scale preparations. Both oxidation methods gave the respective diols as a single diastereoisomer (*dr* > 95:5) as depicted in Scheme 3. Subsequent removal of the phenylethyl group with hydrogen and palladium on activated charcoal gave aminodiols **4a–d** in good yield. The relative stereochemistry of these azabicycloalkanes can be derived from the characteristic ^4J couplings in the bicyclic ring system of **4b** and **4d**, as outlined in Figure 2. Additional 2D-NOESY analysis was in agreement with these structures as indicated in Figure 2 by significant NOESY cross-peaks for all aminodiols **4**. Furthermore, the structure of **4a** was verified by X-ray analysis of its *N*-phenylethyl-substituted precursor (data not shown).[30]

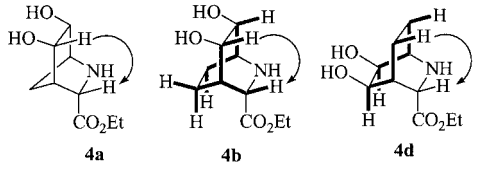


Figure 2. Characteristic ^4J couplings (bold lines) and key NOEs (arrows) for compounds **4a**, **4b**, and **4d**

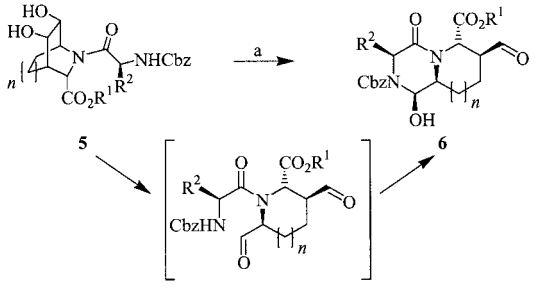
As anticipated, peptide couplings of *N*-protected amino acids to the aminodiols **4a–d** proceed in good yields under standard coupling conditions (DCC/HOBt) and can be performed on a large scale. A range of different dipeptides **5** was thus obtained on a gram scale in only three steps starting from azabicycloalkenes **1**. Table 1 summarises a collection of different functionalised dipeptide derivatives **5** incorporating some common proteinogenic amino acids. It should be noted that the stereochemistry of the azabicycloalkane moiety of these dipeptides can be easily varied by the use of different azabicycloalkenes **1**, as shown by the synthesis of compound **5k**, starting from **1d**, that is outlined in Scheme 3. Different ring sizes (n = 0, 1 in Scheme 3) can also be synthesised starting from azabicycloheptenes, like **1a**, or azabicyclooctenes, like **1b**.

Table 1. Yields for dipeptides **5** synthesised according to Scheme 3

Starting compd.	n	R^1	R^2	Amine **4**	Dipeptide **5**, yield
1a	0	Et	CH_2CO_2Me	**4a**	**5a**, 42%
1a	0	Et	CH_2OH	**4a**	**5b**, 60%
1b	1	Et	H	**4b**	**5c**, 71%
1b	1	Et	$CH(CH_3)_2$	**4b**	**5d**, 82%
1b	1	Et	$(CH_2)_4NHBoc$	**4b**	**5e**, 72%
1b	1	Et	$(CH_2)_2SMe$	**4b**	**5f**, 73%
1b	1	Et	CH_2CO_2Me	**4b**	**5g**, 75%
1c	0	*t*Bu	CH_2CO_2tBu	**4c**	**5h**, 72%
1c	0	*t*Bu	$(CH_2)_2CO_2tBu$	**4c**	**5i**, 70%
1c	0	*t*Bu	$CH_2OTBDMS$	**4c**	**5j**, 53%
1d	1	Et	CH_2CO_2Me	**4d**	**5k**, 33%

As mentioned above, dipeptides **5** should be ideal precursors for oxidative cleavage and subsequent intramolecular cyclisation to bicyclic peptide mimetics of the general structure **V** in Scheme 1. We assumed that treatment of diols **5** with sodium periodate would give an intermediate bis(aldehyde) that would immediately cyclise intramolecularly with a carbamate (Boc or Cbz) NH group of the second amino acid to form the desired bicyclic ring system **V**.

This combination of oxidative cleavage and intramolecular attack of the intermediate bis(aldehyde) by the carbamate NH proceeds with good yields and varying stereoselectivities with respect to the formation of the aminal in **6** (Scheme 4). However, it should be noted, that *N*-acylated aminals like **6** are configurationally not stable under acidic conditions. In consequence, epimerisation of compounds **6** at the aminal position occurred upon storage in $CDCl_3$ and on silica gel leading to a stable 1,3-*cis* configuration of R^2 and the aminal OH group as depicted in Scheme 4 for all aminals **6**, except for compound **6c**, where R^2 is hydrogen (glycine as a second amino acid). Compounds **6** were used in the next steps without further purification.

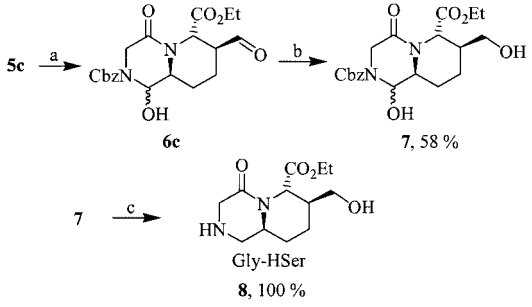


Scheme 4. Synthesis of bicyclic dipeptide mimetics **6**; for the definition of residues see Tables 2 and 3; reagents and conditions: a) $NaIO_4$, acetone/H_2O, 0 °C to room temp., 30–60 min

All NMR spectra of bicyclic aminals **6**, **9**, and **11** show substantial line broadening at room temperature and a double set of signals due to rotational isomerism around the partial C=N double bond of the carbamate protecting group. This double set of signals equilibrated in all cases at temperatures around 340 K in [D_6]DMSO, a coalescence temperature that is expected for these tertiary amides.[31,32] The existence of two energetically similar rotamers for the tertiary amide in **6** hints that the substituents next to the nitrogen atom (R^2 and OH in Scheme 4) must be in an axial arrangement, since steric interactions with the carbamate protecting group are minimised in this position. This bis(axial) arrangement is a consequence of pseudo-allylic 1,3-strain[33] that would be apparent in an equatorial arrangement between R^2 and OH and the carbamate protecting group.

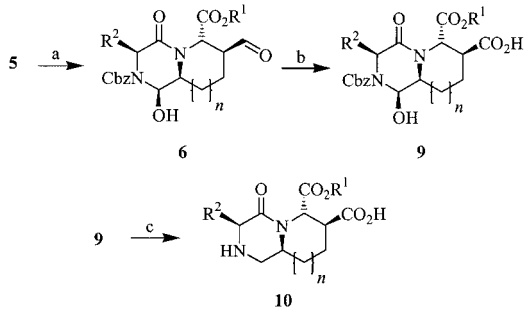
Bicyclic aminals **6** are ideal precursors for a range of different dipeptide mimetics since the aldehyde function attached to the proline or pipecolic acid portion of the bicyclic core can be easily converted into a number of different side-chain functionalities. Since the structure and topology of the second side-chain R^2 are only limited by the choice of α-amino acid coupled to azabicycloalkanes **4**, both amino acid side-chains can be varied and a range of different dipeptide mimetics is accessible. In addition, the aminal function in **6** should offer a suitable site for attachment of linker moieties to the bicyclic core, for example by alkylation of an *N*-acyliminium ion generated in situ.[34]

In a first attempt to check the synthetic potential of dipeptides **5** for the synthesis of diazabicycloalkanes we tried a periodate cleavage of **5c** and a subsequent reduction of the resulting aldehyde side chain in **6c** with sodium borohydride, as outlined in Scheme 5. This reduction to alcohol **7** occurred regioselectively at the free aldehyde position leaving the aminal unaltered. Subsequent hydrogenolytic removal of the Cbz group and in situ reduction of the intermediate imine gave diazabicycloalkane **8**, an H-Gly-HSer-OEt mimetic, in good yield.

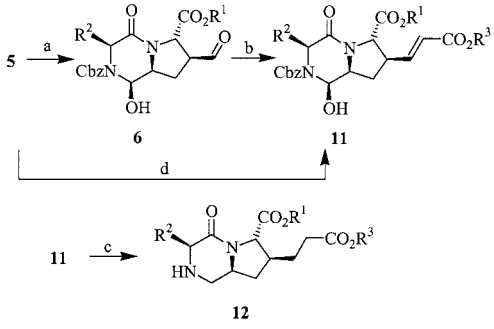


Scheme 5. Reductive conversion of aldehyde **6c** to Gly-HSer mimetic **8**; reagents and conditions: a) $NaIO_4$, acetone/H_2O, 0 °C to room temp., 30−60 min; b) $NaBH_4$, MeOH, 0 °C, 1 h; c) Pd/C, EtOH, room temp., 24 h

Since our interest in diazabicyloalkane dipeptide mimetics was motivated to a large degree by the search for ligands for certain cancer-specific carboxypeptidases,[35] polyanionic structures were of special interest to us.[36,37] In consequence, we were aiming for Asp(Glu)−Asp(Glu) mimetics. Aldehydes **6a**, **6g**, **6h**, and **6j**, derived by periodate cleavage from dipeptides **5a**, **5g**, **5h**, and **5j**, respectively, were therefore oxidised with $NaClO_2$ to give the carboxylic acids **9a**−**d** (Scheme 6). Treatment of these Cbz-protected diazabicycloalkanes with hydrogen and palladium on activated charcoal gave amines **10a**−**d**, which are confor-



Scheme 6. Oxidative side-chain modification of aldehydes **6**; reagents and conditions: a) $NaIO_4$, acetone/H_2O, 0 °C to room temp., 30−60 min; b) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH, H_2O, room temp., 12 h; c) Pd/C, EtOH, room temp., 24 h



Scheme 7. Wittig transformations to side-chain-modified dipeptide mimetics **12**; reagents and conditions: a) $NaIO_4$, acetone/H_2O, 0 °C to room temp., 30−60 min; b) $Ph_3P{=}CHCO_2R^3$, THF, room temp., 12 h; c) Pd/C, EtOH, room temp., 24 h; d) $NaIO_4$, $Ph_3P{=}CHCO_2R^3$, Et_2O, room temp., 24 h

Table 2. Yields for aminals **9** and amines **10** synthesised according to Scheme 6

Starting compd.	*n*	R^1	R^2	Aldehyde **6**	Aminal **9**, yield	Amine **10**, yield
5a	0	Et	CH_2CO_2Me	**6a**	**9a**, 99%	**10a**, 92%
5h	0	*t*Bu	CH_2CO_2tBu	**6h**	**9b**, 25%	**10b**, 64%
5j	0	*t*Bu	$CH_2OTBDMS$	**6j**	**9c**, 62%[a]	**10c**, 58%
5g	1	Et	CH_2CO_2Me	**6g**	**9d**, 21%	**10d**, 82%

[a] Partial loss of the TBDMS protecting group occurred in this reaction (see Exp. Sect.).

Table 3. Yields for the conversion of dipeptides **5** to X_{AA}-HGlu mimetics **12** according to Scheme 7

Starting compd.	R^1	R^2	R^3	Aldehyde **6**[a]	Aminal **11**, yield	Amine **12**, yield
5a	Et	CH_2CO_2Me	Me	–	**11a**, 69%[b]	**12a**, 100%
5h	*t*Bu	CH_2CO_2tBu	*t*Bu	**6h**	**11b**, 55%	**12b**, 77%
5i	*t*Bu	$(CH_2)_2CO_2tBu$	*t*Bu	**6i**	**11c**, 21%	**12c**, 83%
5j	*t*Bu	$CH_2OTBDMS$	*t*Bu	**6j**	**11d**, 43%	**12d**, 92%

[a] Aldehydes **6** were isolated as crude products and used without further purification in the next step. [b] Aminal **11a** was synthesised in a one-pot procedure (method d in Scheme 7).

mationally constrained Asp-Asp, Asp-HGlu, and Ser-Asp mimetics (Table 2).

Variation of the side-chain length in dipeptide mimetics **12** (Scheme 7) to *homo*glutamate analogues was achieved by periodate cleavage of dipeptides **5** and subsequent Wittig reaction of the resulting aldehydes **6h**, **6i**, and **6j** to give the α,β-unsaturated carboxylic acid esters **11b**–**d**, respectively, in good yield almost exclusively as the (*E*) isomer [(*E*)/(*Z*) = 95:5]. Hydrogenation of the Cbz-protected Wittig adducts **11b**–**d** gave diazabicycloalkanes **12b**–**d**, respectively, which are conformationally constrained Asp-HGlu, Glu-HGlu, Ser-HGlu mimetics (Table 3).

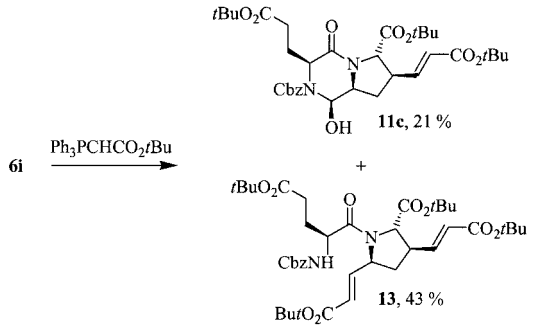
Even more advantageous, the Wittig transformations outlined in Scheme 7 can be performed as a one-pot procedure together with a periodate cleavage directly from diols **5** according to a recently introduced protocol from Taylor,[38] as shown in Scheme 7 for the synthesis of aminal **11a** (method d).

It should be noted that conformationally constrained and enantiomerically pure dipeptide mimetics like **12a** (Scheme 7) can thus be synthesised in only four steps from readily available azabicyloalkenes **1** on a gram scale.

With the exception of **11a** and **12a**, all compounds depicted in Scheme 7 were synthesised using a Cbz/*t*Bu protection strategy. We have used this strategy because of the better crystallisation properties of the intermediates, which is particularly advantageous for large-scale preparations. However, the bulky *t*Bu esters in dipeptides **5h**–**j** lead to significantly lower yields of the desired alkenes **11** during Wittig reactions, as can be seen for the conversion of aldehyde **6i** to olefin **11c** (Scheme 8). The reason for this unexpected finding is the formation of a ring-opened second Wittig adduct **13**. Small portions (13%) of this side product were also detected during conversion of aldehyde **6h** to olefin **12b**.

Acylation of diazabicycloalkanes **12** can be performed under standard conditions with acetic anhydride, benzoyl chloride, or 6-aminocaproic acid without detectable epimerisation as outlined in Scheme 9. *N*-Acetylated diazabicycloalkanes **14** and *N*-benzoylated diazabicycloalkanes **16** were thus obtained in good yields from the free amines **12**. Deprotection of these compounds was done by treatment with a 50% solution of TFA in dichloromethane for 3 h, giving deprotected dipeptide mimetics **15** and **17** quantitatively upon evaporation of the solvent/acid mixture.

Acylation of diazabicycloalkane **12b**–**d** with *N*-Boc-protected 6-aminocaproic acid and subsequent deprotection



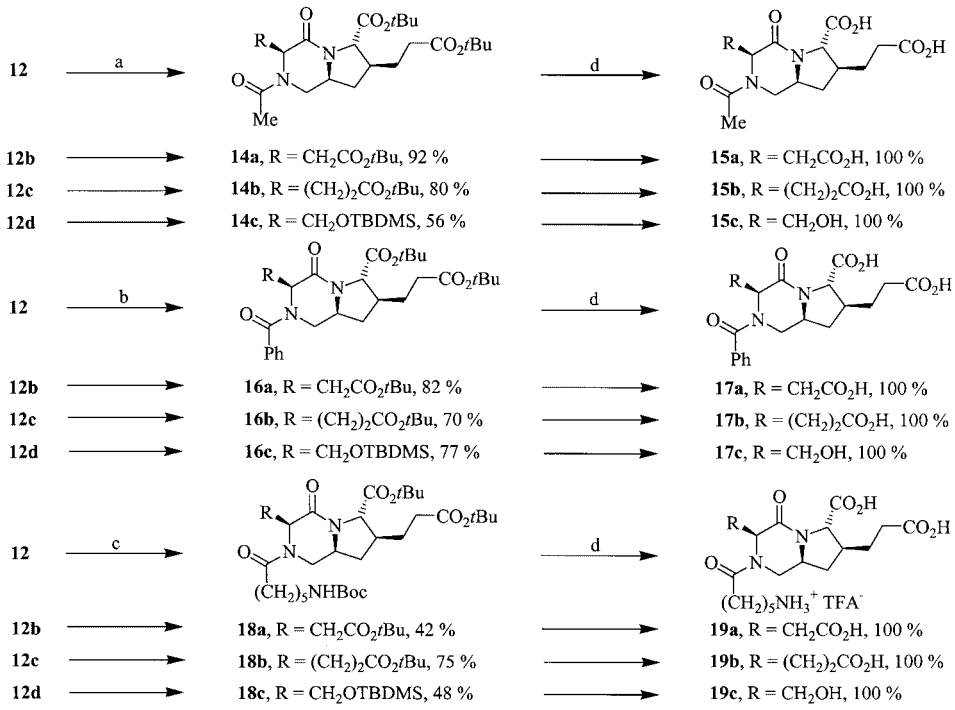
Scheme 8. Side reaction in Wittig conversions of hindered bicyclic aldehyde **6i**

gave dipeptide mimetics **19a**–**c**. These compounds are especially noteworthy because the primary amine provides a suitable anchor for conjugation with marker moieties such as fluorescence dyes[39] or radiopharmaceutical markers.[40] Compounds **19a**–**c** are therefore the first examples of modular dipeptide mimetics on the basis of a diazabicycloalkane scaffold.

Conclusion

In summary, we have reported a short and efficient synthetic sequence for a number of new diazabicycloalkanes which are useful mimetics of various dipeptide conformations. Our synthesis starts with a stereoselective aza-Diels–Alder reaction providing enantiomerically pure azabicycloalkenes **1** on a large scale. Compounds **1** are key intermediates in our synthetic route to diazabicycloalkanes, since they provide the synthetically more challenging part of our target compounds (such as the dipeptide mimetics **15**, **17**, and **19**): a suitably disubstituted cyclic amino acid with defined (and variable) stereochemistry. It is therefore not surprising that azabicycloalkenes **1** can be used to synthesise a number of different functionalised cyclic amino acids[27] which are useful intermediates in natural product synthesis[41–43] and interesting rigid building blocks for peptide synthesis.[44–46]

In this report we have demonstrated azabicycloalkenes **1** to be valuable precursors of diazabicycloalkanes **15**, **17**, and **19**. The major advantages of our route are: a) synthetic efficiency, since diazabicycloalkane target compounds can be synthesised in only five steps starting from an appropriate



Scheme 9. Acylation of diazabicycloalkanes and subsequent deprotection; reagents and conditions: a) Ac_2O, dichloromethane, diisopropylethylamine; b) BzCl, dichloromethane, diisopropylethylamine; c) $BocHN(CH_2)_5CO_2H$, DCC, HOBt, DMF; d) 50% TFA in dichloromethane

glyoxylate, (*R*)-phenylethylamine, and cyclopentadiene or cyclohexadiene; b) practicability for large-scale synthesis; c) a possible fine-tuning of the backbone dihedral angles of the target dipeptide mimetic since stereochemistry and ring sizes in diazabicycloalkanes can be varied by altering reaction conditions and input of the aza-Diels–Alder reaction; d) structural diversity, since both amino acid side-chains of the imitated dipeptide can be varied broadly; and e) establishment of suitable conjugation sites for marker moieties. Diazabicycloalkanes **19a–c**, for example, are therefore dipeptide mimetics with a modular character since they can be conjugated to other functional moieties. Conjugation to markers is one possibility and we are currently probing diazabicycloalkanes like **19a–c** for use as modular ligands for cancer-specific receptors.

Conjugation of diazabicycloalkanes to a solid support is another interesting possibility that would enable one to use the highly functionalised diazabicycloalkane scaffold for combinatorial chemistry. This would, of course, need orthogonal protection groups at all four functionalities in compounds like **6**. We are currently working on the synthesis of these orthogonal protected scaffolds for combinatorial chemistry.

Experimental Section

General Remarks: "Dry" solvents were purified prior to use as follows: methanol was distilled from magnesium, dichloromethane was distilled from $CaCl_2$, THF and Et_2O were distilled from sodium and benzophenone under nitrogen. Thin layer chromatography (TLC) analyses were performed on silica gel 60 F_{254} plates from Merck. Spots were visualised with iodine, ninhydrin (5% in EtOH) or an Mo/Ce staining mixture [50 g of ammonium molybdate(VI) tetrahydrate, 1 g of cerium(IV) sulfate in 100 mL of concentrated H_2SO_4 and 900 mL of water]. For preparative chromatography Merck silica gel 60, 230–400 mesh was used. Melting points were determined in open capillaries in a Dr. Lindström instrument and are uncorrected. Optical rotations $[\alpha]_D$ were determined with a Perkin–Elmer polarimeter (241 MC), at 20 °C, $c = 1$ in methanol unless otherwise indicated. ^1H and ^{13}C NMR spectra were recorded with a Bruker (Karlsruhe) AMX 400 spectrometer (400 MHz/100.6 MHz) or a Bruker (Karlsruhe) DRX 5001 spectrometer (500 MHz/125.8 MHz). Chemical shifts, δ, are presented in parts per million (ppm) and coupling constants, *J*, in Hertz (Hz) from tetramethylsilane (TMS: δ = 0 ppm) as the internal standard for $CDCl_3$ and residual solvent peaks for $[D_4]$MeOH and $[D_6]$DMSO. Mass spectra were obtained with a VG/70–250 F (VG Analytical) instrument in FAB mode in a *p*-nitrobenzyl alcohol matrix or an MAT 95 Trap XL (Thermo Finnigan) instrument in ESI mode (positive mode) using polypropylene glycol or polyethylene glycol as internal standard. Elemental analyses were performed with a C,H,N-Analyser EA 1108 from Carlo Erba. The following starting materials were synthesised according to literature procedures: methyl (triphenylphosphanylidene)acetate,[47] *tert*-butyl (triphenylphosphanylidene)acetate,[48] 6-(*tert*-butoxycarbonylamino)hexanoic acid,[49] ethyl (1*S*,3*S*,4*R*)-2-[(1*R*)-phenylethyl]-2-azabicyclo[2.2.1]-hept-5-ene-3-carboxylate (**1a**),[50] ethyl (1*S*,3*S*,4*R*)-2-[(1*R*)-phenylethyl]-2-azabicyclo[2.2.2]oct-5-en-3-carboxylate (**1b**),[50] ethyl (1*R*,3*S*,4*S*)-2-[(1*R*)-phenylethyl]-2-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**1d**).[26] EA = ethyl acetate; PE = petroleum ether; 50/70 = boiling range 50–70 °C.

***tert*-Butyl (1*S*,3*S*,4*R*)-2-[(1*R*)-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (1c):** Di-*tert*-butylfumarate (35.0 g, 0.153 mol) was dissolved in dry dichloromethane and cooled to −80 °C. Ozone was bubbled through the solution at −80 °C for 7 h until a blue colour persisted. The solution was purged with nitrogen for

2 min and subsequently treated with dimethyl sulfide (57 mL, 0.77 mol) in 50 mL of dichloromethane and stirred at 0 °C for 30 min. Most of the solvent was evaporated at 0−5 °C in vacuo and the remaining residue dissolved in 700 mL of dry dichloromethane. Molecular sieves (4 Å, 100 g) and (*R*)-phenylethylamine (37.1 g, 0.306 mol) were added and the mixture was stirred with a mechanical stirrer under nitrogen at 0 °C for 30 min. The solution was cooled to −80 °C and TFA (34.9 g, 0.306 mol), Et_2O-BF_3 (43.4 g, 0.306 mol) and cyclopentadiene (20.2 g, 0.306 mol) were added at 20 min intervals. The resulting mixture was stirred at −80 °C for 2 h and was allowed to reach room temperature overnight. A saturated aqueous K_2CO_3 solution (400 mL) was added slowly and the mixture was filtered through Celite. The filter cake was rinsed three times with 200 mL of dichloromethane. The filtrate was collected and phases were separated. The aqueous phase was extracted twice with 300 mL of dichloromethane and the combined organic extracts were washed with 200 mL of water, dried with Na_2SO_4, and the solvent was removed in vacuo to give 82.5 g of a yellow oil that slowly crystallised. This crude product was recrystallised from PE (50/70) to give 44.8 g of colourless crystals. The remaining mother liquor was concentrated to dryness and the remaining solid purified by column chromatography (PE/ethyl acetate, 11:1) on silica gel to give an additional 19.4 g (combined 64.2 g, 70% yield) of the title compound and 7.25 g (8% yield) of a second isomer with (1*R*,3*R*,4*S*) stereochemistry. **1c:** R_f = 0.47 [ethyl acetate/PE (50/70), 1:9; iodine]. $[\alpha]_D^{20}$ = −78.4 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 1.36 (d, *J* = 9.1 Hz, 1 H), 1.38 (d, *J* = 6.3 Hz, 3 H), 2.10−2.11 (m, 1 H), 2.11 (d, *J* = 9.1 Hz, 1 H), 2.84−2.85 (m, 1 H), 3.00 (q, *J* = 6.3 Hz, 1 H), 4.26 (d, *J* = 1.0 Hz, 1 H), 6.35 (dd, *J* = 5.7 Hz, 1.3 Hz, 1 H), 6.40 (dd, *J* = 4.7 Hz, 1.5 Hz, 1 H), 7.14−7.17 (m, 1 H), 7.19−7.23 (m, 2 H), 7.28−7.30 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.72, 27.85, 45.30, 49.33, 62.76, 64.05, 65.61, 79.82, 126.95, 128.12, 128.27, 133.12, 136.42, 145.42, 173.44. HRMS (FAB): calcd. for $C_{19}H_{25}NO_2$ [MH^+] 300.1964, found 300.1969. $C_{19}H_{25}NO_2$: calcd. C 76.22, H 8.42, N 4.68; found C 76.16, H 8.45, N 4.64. (1*R*,3*R*,4*S*) Isomer: R_f = 0.74 (ethyl acetate/PE 50/70, 1:9; iodine). $[\alpha]_D^{20}$ = +96.0 (*c* = 0.96, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 7.9 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 1.44 (s, 9 H), 1.85 (d, *J* = 7.9 Hz, 1 H), 2.26−2.27 (m, 1 H), 2.94 (q, *J* = 6.3 Hz, 1 H), 2.96−2.98 (m, 1 H), 3.43−3.45 (m, 1 H), 5.93 (d, *J* = 5.7 Hz, 1 H), 6.33 (d, *J* = 5.7 Hz, 1 H), 7.17−7.19 (m, 1 H), 7.23−7.25 (m, 2 H), 7.29−7.31 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.17, 28.23, 45.77, 49.60, 63.45, 63.54, 64.97, 80.36, 127.09, 127.70, 128.42, 133.76, 136.17, 145.48, 174.29. HRMS (FAB): calcd. for $C_{19}H_{25}NO_2$ [MH^+] 300.1964, found 300.1960. $C_{19}H_{25}NO_2$: calcd. C 76.22, H 8.42, N 4.68; found C 76.20, H 8.37, N 4.67.

Ethyl (2*S*,3*S*,6*S*)-3,6-Bis(hydroxymethyl)-1-[(1*R*)-1-phenylethyl]piperidine-2-carboxylate (2): Alkene **1b** (1.68 g) was dissolved in 40 mL of methanol and cooled to −80 °C. Ozone was bubbled through the solution at −80 °C for 20 min until a blue colour persisted. The solution was purged with nitrogen for 2 min and subsequently treated with 9 mL of dimethyl sulfide in 9 mL of dichloromethane and stirred at room temperature for 12 h. The solution was cooled again to 0 °C and $NaBH_4$ (0.89 g, 23.6 mmol) was added. The resulting solution was stirred at 0 °C for 1 h and then treated with 100 mL of water. After stirring for 30 min at room temperature, the solution was extracted three times with 150 mL of ethyl acetate. The combined organic phases were washed with water (50 mL) and brine (50 mL) and dried with Na_2SO_4. After filtration, the solvent was removed in vacuo and 1.86 g of the crude product was obtained as a yellow oil. Purification by column chromatography over silica gel (ethyl acetate/hexane, 1:1) gave 1.48 g (78%) of the title compound as a colourless oil. R_f = 0.33 (ethyl acetate/hexane, 1:1; iodine). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.3 Hz, 3 H), 1.33 (d, *J* = 7.0 Hz, 3 H), 1.50 (m, 1 H), 1.57 (m, 1 H), 1.76 (m, 1 H), 1.82 (m, 1 H), 1.92 (m, 1 H), 3.52 (d, *J* = 2.6 Hz, 1 H), 3.53 (m, 1 H), 3.54 (dd, *J* = 5.3 Hz, 10.7 Hz, 1 H), 3.76 (dd, *J* = 3.8 Hz, 10.7 Hz, 1 H), 3.84 (m, 1 H), 3.88 (dd, *J* = 3.4 Hz, 11.0 Hz, 1 H), 4.17 (m, 2 H), 4.50 (q, *J* = 7.0 Hz, 1 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 7.36 (m, 2 H), 7.41 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.61, 16.17, 22.39, 24.90, 38.73, 55.26, 56.52, 57.13, 60.67, 64.28, 64.47, 127.66, 128.00, 128.92, 144.35 175.89. HRMS (FAB): calcd. for $C_{18}H_{27}NO_4$ [MH^+] 322.2018, found 322.2014. $C_{18}H_{27}NO_4$: calcd. C 67.26, H 8.47, N 4.36; found C 67.31, H 8.49, N 4.35.

Ethyl (2*S*,3*S*,6*S*)-3,6-Bis(hydroxymethyl)piperidine-2-carboxylate (3): Diol **2** (0.29 g) was dissolved in 10 mL of ethanol and 50 mg of Pd/C (5%) was added. The resulting suspension was stirred under hydrogen at room temperature for 24 h. The reaction mixture was filtered through Celite and the Celite washed with 200 mL of dichloromethane. Evaporation of the solvent in vacuo gave 0.16 g (78%) of the title compound as a colourless oil. R_f = 0.39 (diethyl ether/methanol, 95:5; ninhydrin). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22 (m, 2 H), 3.87 (dd, *J* = 8.2 Hz, 10.7 Hz, 1 H), 3.84 (d, *J* = 2.5 Hz, 1 H), 3.70 (dd, *J* = 5.4 Hz, 10.7 Hz, 1 H), 3.64 (br., 3 H), 3.57 (dd, *J* = 3.4 Hz, 11.1 Hz, 1 H), 3.42 (dd, *J* = 7.9 Hz, 11.1 Hz, 1 H), 2.99 (m, 1 H), 2.35 (m, 1 H), 1.62 (m, 2 H), 1.37 (m, 2 H), 1.29 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.63, 23.36, 23.56, 36.40, 53.48, 56.61, 61.50, 64.12, 66.22, 174.24. HRMS (FAB): calcd. for $C_{10}H_{19}NO_4$ [MH^+] 218.1392, found 218.1391. $C_{10}H_{19}NO_4$: calcd. C 55.28, H 8.81, N 6.45; found C 55.30, H 8.79, N 6.44.

General Procedure for the Synthesis of Aminodiols 4 (GP 1): Alkene **1** (31.0 mmol) was dissolved in 90 mL of *t*BuOH and 90 mL of water. $K_3Fe(CN)_6$ (30.4 g, 93 mmol), K_2CO_3 (12.7 g, 93 mmol), and a catalytic amount of $K_2OsO_2(OH)_4$ (100 mg) were added. The resulting yellowish slurry was stirred at room temperature for 12 h. Addition of 100 mL of water, extraction with ethyl acetate, drying of the combined organic phases with Na_2SO_4, and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate, 1:1) to give the diol as a yellow oil. This diol was dissolved in dry EtOH and 500 mg of 5% Pd on activated charcoal was added. The suspension was stirred under hydrogen for 24 h and subsequently filtered through a plug of Celite. The solvent was removed under reduced pressure to give aminodiols **4**.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (4a): The title compound was synthesised according to GP 1 from alkene **1a** (46.9 g, 173 mmol) and obtained as a yellow oil in 31.3 g (90%) yield. R_f = 0.32 (CH_2Cl_2/MeOH, 9:1; ninhydrin). $[\alpha]_D^{20}$ = +11.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.31 (d, *J* = 11.0 Hz, 1 H), 1.80 (d, *J* = 11.0 Hz, 1 H), 2.57 (s, 1 H), 3.27 (s, 1 H), 3.41 (m, 1 H), 3.89 (d, *J* = 6.6 Hz, 1 H), 3.91 (d, *J* = 6.6 Hz, 1 H), 4.01−4.08 (br., 3 H), 4.15−4.22 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.21, 29.16, 47.20, 58.98, 60.20, 62.09, 72.04, 72.33, 172.86. HRMS (FAB): calcd. for $C_9H_{16}NO_4$ [MH^+] 202.1079; found 202.1081. $C_9H_{15}NO_4$: calcd. C 53.72, H 7.51, N 6.96; found C 53.80, H 7.49, N 6.90.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (4b): The title compound was synthesised according to GP 1 from alkene **1b** (28.1 g, 98 mmol) and obtained as a yellow oil in 18.8 g (89%) yield. R_f = 0.20 (CH_2Cl_2/MeOH, 9:1; ninhyd-

rin). ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 1.24−1.27 (m, 1 H), 1.31 (t, *J* = 7.3 Hz, 3 H), 1.51−1.60 (m, 1 H), 1.82−1.89 (m, 1 H), 1.90−196 (m, 1 H), 2.16−2.18 (m, 1 H), 2.94−2.96 (m, 1 H), 3.63−3.66 (m, 1 H), 4.06 (ddd, *J* = 8.5, 3.8, 1.4 Hz, 1 H), 4.10 (ddd, *J* = 8.5, 2.8, 1.4 Hz, 1 H), 4.21−4.33 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.75, 14.94, 20.93, 36.49, 50.47, 57.91, 62.95, 67.80, 68.24, 175.89. HRMS (FAB): calcd. for $C_{10}H_{18}NO_4$ [MH$^+$] 216.1236, found 216.1239. $C_{10}H_{17}NO_4$: calcd. C 55.80, H 7.96, N 6.51; found C 55.64, H 7.99, N 6.52.

***tert*-Butyl (1*S*,3*S*,4*S*,5*S*,6*R*)-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (4c):** Alkene **1c** (12.0 g) was dissolved in a mixture of 180 mL of *t*BuOH and 130 mL of water. The solution was cooled to 0 °C and a solution of $KMnO_4$ (4.6 g, 29.1 mmol) and NaOH (1.0 g) in 160 mL of water was added slowly over 10 min. $NaHSO_3$ (39% in water; 100 mL) was added and the resulting solution was filtered through Celite. The filtrate was concentrated in vacuo to a volume of 350 mL and extracted three times with 100 mL of dichloromethane. The combined organic extracts were dried with Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel [ethyl acetate/PE (50/70), 1:1] to give the diol as a colourless oil in 4.3 g (65%) yield. This diol was dissolved in 200 mL of dry MeOH and treated with 300 mg of 5% palladium on activated charcoal. The suspension was stirred under hydrogen for 24 h and subsequently filtered through a plug of Celite. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel (dichloromethane/MeOH, 98:2) to give the title compound as a colourless oil in 2.95 g (70%) yield. R_f = 0.33 (dichloromethane/MeOH, 9:1). $[\alpha]_D^{20}$ = +12.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (d, *J* = 6.0 Hz, 1 H), 3.87 (d, *J* = 6.0 Hz, 1 H), 3.20−3.49 (br., 2 H), 3.34 (s, 1 H), 3.07 (s, 1 H), 2.55 (s, 1 H), 1.77 (d, *J* = 11.0 Hz, 1 H), 1.48 (s, 9 H), 1.27 (d, *J* = 11.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.84, 82.18, 72.95, 72.81, 60.08, 59.88, 47.58, 29.04, 28.14. HRMS (ESI): calcd. for $C_{11}H_{19}NO_4$ [MH$^+$] 230.1392, found 230.1396.

Ethyl (1*R*,3*S*,4*R*,5*R*,6*S*)-5,6-Dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (4d): The title compound was synthesised according to GP 1 from alkene **1d** (3.40 g, 11.9 mmol) and obtained as a yellow oil in 2.20 g (86%) yield. R_f = 0.27 (CH_2Cl_2/MeOH, 9:1; ninhydrin). $[\alpha]_D^{20}$ = −7.0. ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 1.45−1.55 (m, 1 H), 1.62−1.71 (m, 1 H), 2.00−2.10 (m, 1 H), 2.11−2.19 (m, 1 H), 2.31 (m, 1 H), 3.14 (ddd, *J* = 5.4, 3.6, 2.8 Hz, 1 H), 3.77 (ddd, *J* = 8.4, 3.6, 1.3 Hz, 1 H), 3.95 (ddd, *J* = 8.4, 3.6, 1.8 Hz, 1 H), 4.03 (d, *J* = 2.5 Hz, 1 H), 4.20−4.40 (m, 2 H). ^{13}C NMR (125 MHz, [D$_4$]MeOH): δ = 14.41, 17.36, 17.54, 35.28, 51.15, 57.95, 63.64, 64.25, 65.75, 172.68. HRMS (FAB): calcd. for $C_{10}H_{18}NO_4$ [MH$^+$] 216.1236, found 216.1230. $C_{10}H_{17}NO_4$: calcd. C 55.80, H 7.96, N 6.51; found C 55.86, H 7.90, N 6.55.

General Procedure for the Synthesis of Dipeptides 5 (GP 2): Amine **4** (4.65 mmol) and the appropriate amino acid (9.30 mmol) were dissolved in 20 mL of dry DMF. A solution of HOBt (0.63 g, 4.65 mmol) in 20 mL of dry DMF and a solution of DCC (1.15 g, 5.58 mmol) in 10 mL of dry DMF were added. The resulting suspension was stirred at room temp. under nitrogen for 12 h. DCU was filtered off and DMF was removed in vacuo. The crude product was purified by column chromatography on silica gel to give dipeptides **5** as colourless sticky solids.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-3-methoxycarbonylpropionyl]-5,6-dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (5a): The title compound was synthesised according to GP 2 from amine **4a** (4.0 g, 20 mmol) and Cbz-Asp(OMe)-OH (6.15 g, 21.9 mmol) and was obtained in 3.9 g (8.3 mmol, 42%) yield. R_f = 0.30 (EA/PE, 7:3; Mo/Ce). $[\alpha]_D^{20}$ = −52.2 (*c* = 1.01, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 7.26−7.37 (m, 5 H), 5.00−5.14 (m, 2 H), 4.87 (t, 0.8 H, *J* = 7.3 Hz), 4.48 (t, 0.2 H, *J* = 5.3 Hz), 4.30 (s, 0.2 H), 4.28 (s, 0.8 H), 4.07−4.19 (m, 2 H), 3.99−4.06 (m, 1 H), 3.89 (d, *J* = 5.7 Hz, 0.8 H), 3.82 (s, 1 H), 3.74 (d, *J* = 5.7 Hz, 0.2 H), 3.69 (s, 2.4 H), 3.64 (s, 0.6 H), 2.91 (dd, *J* = 6.7, 16.7 Hz, 0.2 H), 2.81 (dd, *J* = 6.3, 16.1 Hz, 0.8 H), 2.65 (dd, *J* = 7.9, 16.1 Hz, 1 H), 2.60 (s, 0.2 H), 2.49 (s, 0.8 H), 1.92−1.98 (m, 0.8 H), 1.85−1.89 (m, 1 H), 1.68−1.71 (m, 0.2 H), 1.24 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 173.09, 172.10, 171.62, 171.50, 170.91, 158.08, 157.58, 138.10, 138.03, 129.45, 129.00, 128.83, 73.53, 73.50, 73.31, 71.89, 67.86, 67.23, 63.12, 62.98, 62.44, 61.31, 52.51, 52.35, 50.75, 50.20, 48.16, 38.26, 37.27, 29.92, 14.40, 14.29. HRMS (FAB): calcd. for $C_{22}H_{29}N_2O_9$ [MH$^+$] 465.1873, found 465.1878.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-3-hydroxypropionyl]-5,6-dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (5b): The title compound was synthesised according to GP 2 from amine **4a** (4.01 g, 19.3 mmol) and Cbz-Ser-OH (5.3 g, 22 mmol) and was obtained in 5.0 g (60%) yield. R_f = 0.20 (EA/PE, 7:3, Mo/Ce). $[\alpha]_D^{20}$ = −32.7 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 7.25−7.38 (m, 5 H), 5.13 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 4.55 (dd, *J* = 6.9 Hz, 1 H), 4.37 (d, *J* = 7.6 Hz, 1 H), 4.28 (s, 1 H), 4.15 (q, *J* = 7.3 Hz, 2 H), 4.08 (dd, *J* = 5.5, 7.6 Hz, 1 H), 3.89 (t, *J* = 5.5 Hz, 1 H), 3.80 (dd, *J* = 5.7, 11.4 Hz, 1 H), 3.68 (dd, *J* = 6.9, 11.4 Hz, 1 H), 2.50 (s, 1 H), 1.97−2.05 (m, 1 H), 1.62−1.92 (m, 1 H), 1.24 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (125 MHz, [D$_4$]MeOH): δ = 171.70, 171.37, 158.96, 138.52, 129.89, 129.45, 129.28, 127.25, 126.71, 68.00, 63.67, 63.66, 63.20, 61.97, 61.60, 61.47, 55.48, 48.61, 31.74, 14.91. HRMS (FAB): calcd. for $C_{22}H_{31}N_2O_8$ [MH$^+$] 423.1767, found 423.1780.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-(2-Benzyloxycarbonylaminoacetyl)-5,6-dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate (5c): The title compound was synthesised according to GP 2 from amine **4a** (1.00 g, 4.65 mmol) and Cbz-Gly-OH (1.94 g, 9.3 mmol) and was obtained in 1.34 g (71%) yield. R_f = 0.21 (dichloromethane/MeOH, 95:5; Mo/Ce). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.33 (m, 5 H), 5.83 (br., 1 H), 4.33 (s, 1 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 4.13 (dd, *J* = 17.0 Hz, 5.0 Hz, 1 H), 4.06 (dd, *J* = 17.0 Hz, 3.5 Hz, 1 H), 3.98−3.93 (m, 2 H), 3.81 (m, 1 H), 3.73−3.71 (br., 1 H), 3.62−3.60 (br., 1 H), 2.36 (m, 1 H), 2.12−2.10 (m, 1 H), 1.93−1.89 (m, 1 H), 1.77−1.72 (m, 1 H), 1.37−1.33 (m, 1 H), 1.30 (t, *J* = 7.1 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.57, 170.15, 157.12, 136.67, 128.94, 128.58, 128.34, 67.50, 66.59, 65.70, 61.88, 58.09, 50.14, 43.20, 36.02, 18.86, 14.61, 13.24. HRMS (FAB): calcd. for $C_{20}H_{27}N_2O_7$ [MH$^+$] 407.1818, found 407.1840. $C_{20}H_{26}N_2O_7$: calcd. C 59.10, H 6.45, N 6.89; found C 59.00, H 6.51, N 6.90.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-3-methylbutyryl]-5,6-dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (5d): The title compound was synthesised according to GP 2 from amine **4a** (1.00 g, 4.65 mmol) and Cbz-Val-OH (2.33 g, 9.3 mmol) and was obtained in 1.86 g (82%) yield. R_f = 0.24 (dichloromethane/MeOH, 95:5; Mo/Ce). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.29 (m, 5 H), 5.73 (d, *J* = 9.1 Hz, 1 H), 5.10 (d, *J* = 12.3 Hz, 1 H), 5.04 (d, *J* = 12.3 Hz, 1 H), 4.57−4.49 (m, 1 H), 4.34 (m, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 4.05−4.04 (m, 1 H), 3.98−3.95 (m, 1 H), 3.93−3.92 (m, 1 H), 2.35 (m, 1 H), 2.19−2.13 (m, 1 H),

2.05−1.98 (m, 1 H), 1.95−1.91 (m, 1 H), 1.88−1.85 (m, 1 H), 1.35−1.33 (m, 1 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.75, 170.32, 157.17, 136.57, 128.94, 128.60, 128.31, 67.49, 66.43, 65.83, 61.71, 58.11, 56.35, 51.16, 36.25, 32.08, 19.77, 18.80, 17.69, 14.60, 13.22. HRMS (FAB): calcd. for $C_{23}H_{32}N_2O_7$ [MH^+] 449.2288, found 449.2309. $C_{23}H_{32}N_2O_7$: calcd. C 61.59, H 7.19, N 6.25; found C 61.28, H 7.13, N 6.29.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-6-(*tert*-butoxycarbonylamino)hexanoyl]-5,6-dihydroxy-2-azabicyclo[2.2.2]-octane-3-carboxylate (5e): The title compound was synthesised according to GP 2 from amine **4a** (0.50 g, 2.32 mmol) and ε-Boc-α-Cbz-Lys-OH (1.76 g, 4.64 mmol) and was obtained in 0.97 g (72%) yield. R_f = 0.42 (dichloromethane/MeOH, 9:1; Mo/Ce). ^{1}H NMR (500 MHz, [D_4]MeOH): δ = 7.40−7.35 (m, 5 H), 5.50 (s, 2 H), 4.46−4.45 (m, 1 H), 4.32 (s, 1 H), 4.25−4.15 (m, 2 H), 4.05−4.01 (m, 2 H), 3.98−3.95 (m, 1 H), 3.05−3.01 (m, 2 H), 2.27−2.20 (m, 1 H), 2.18−2.11 (m, 1 H), 1.99−1.95 (m, 1 H), 1.88−1.86 (m, 1 H), 1.81−1.61 (m, 2 H), 1.51−1.49 (m, 1 H), 1.45 (s, 9 H), 1.35−1.27 (m, 2 H). ^{13}C NMR (125 MHz, [D_4]MeOH): δ = 174.15, 172.06, 158.86, 138.58, 129.87, 129.69, 129.41, 129.22, 67.75, 66.85, 62.72, 59.70, 55.21, 52.95, 52.57, 48.79, 37.84, 31.09, 31.03, 29.23, 24.03, 20.02, 14.96, 14.26. HRMS (FAB): calcd. for $C_{29}H_{44}N_3O_9$ [MH^+] 578.3078, found 578.3076. $C_{29}H_{43}N_3O_9$: calcd. C 60.30, H 7.50, N 7.27; found C 60.52, H 7.61, N 7.29.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-4-methylsulfanylbutyryl]-5,6-dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (5f): The title compound was synthesised according to GP 2 from amine **4a** (1.00 g, 4.65 mmol) and Cbz-Met-OH (2.63 g, 9.30 mmol) and was obtained in 1.63 g (73%) yield. R_f = 0.53 (hexane/EtOAc, 1:1; iodine). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39−7.29 (m, 5 H), 5.74 (d, J = 8.5 Hz, 1 H), 5.07 (d, J = 8.5 Hz, 2 H), 4.83 (dd, J = 5.7, 7.6 Hz, 1 H), 4.35 (s, 1 H), 4.22 (m, 2 H), 4.15 (s, 1 H), 3.99−3.91 (m, 2 H), 3.58 (s, 2 H), 2.64−2.55 (m, 2 H), 2.35 (s, 1 H), 2.19−1.80 (m, 8 H) 2.10 (s, 3 H), 1.35−1.24 (m, 4 H), 1.38 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.32, 170.13, 156.74, 136.50, 128.92, 128.61, 128.42, 67.51, 66.54, 65.82, 61.74, 58.01, 50.91, 50.19, 33.21, 30.00, 18.93, 15.78, 14.62, 13.20. HRMS (FAB): calcd. for $C_{23}H_{33}N_2O_7S$ [MH^+] 481.2008, found 481.2003. $C_{23}H_{32}N_2O_7S$: calcd. C 57.48, H 6.71, N 5.83; found C 57.65, H 6.62, N 5.69.

Ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-3-methoxycarbonylpropionyl]-5,6-dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (5g): The title compound was synthesised according to GP 2 from amine **4b** (3.2 g, 15 mmol) and Cbz-Asp(OMe)-OH (5.8 g, 21 mmol) and was obtained in 5.3 g (73%) yield. R_f = 0.29 (EA/PE, 7:3; Mo/Ce). $[\alpha]_D^{20}$ = −21.7 (c = 0.945, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28−7.38 (m, 5 H), 5.96 (d, J = 9.1 Hz, 1 H), 5.05−5.14 (m, 3 H), 4.30 (br., 1 H), 4.10−4.23 (m, 3 H), 3.98−4.04 (m, 1 H), 3.88−3.94 (m, 1 H), 3.66 (s, 3 H), 2.75 (dd, J = 4.7, 15.8 Hz, 1 H), 2.63 (dd, J = 7.8, 16.0 Hz, 1 H), 2.34 (br., 1 H), 2.10−2.19 (m, 1 H), 1.85−1.96 (m, 1 H), 1.76−1.85 (m, 1 H), 1.23−1.31 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.83, 169.82, 169.67, 136.08, 128.71, 128.48, 128.13, 67.51, 66.24, 65.00, 61.45, 57.96, 52.34, 50.78, 48.29, 38.02, 35.77, 18.62, 14.30, 13.01. HRMS (FAB): calcd. for $C_{23}H_{31}N_2O_9$ [MH^+] 479.2030, found 479.2029.

***tert*-Butyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylpropionyl]-5,6-dihydroxy-2-azabicyclo[2.2.1]-heptane-3-carboxylate (5h):** The title compound was synthesised according to GP 2 from amine **4c** (4.42 g, 19.3 mmol) and Cbz-Asp(O*t*Bu)-OH (7.11 g, 22.0 mmol) and was obtained in 7.40 g (72%) yield. R_f = 0.38 (EA/PE, 1:1; Ce/Mo). ^{1}H NMR (500 MHz, [D_4]MeOH, mixture of rotamers): δ = 7.25−7.39 (m, 5 H), 5.02−5.16 (m, 2 H), 4.81−4.85 (m, 1 H), 4.29 (s, 0.3 H), 4.22 (s, 0.7 H), 4.00 (d, J = 5.7 Hz, 1 H), 3.87 (d, J = 5.7 Hz, 1 H), 3.71 (s, 1 H), 2.71 (dd, J = 6.0, 16.1 Hz, 1 H), 2.53 (dd, J = 8.2, 16.1 Hz, 1 H), 2.46 (s, 1 H), 1.95 (d, J = 11.0 Hz, 1 H), 1.87 (d, J = 11.0 Hz, 1 H), 1.45 (s, 9 H), 1.44 (s, 9 H). ^{13}C NMR (125 MHz, [D_4]MeOH): δ = 129.44, 129.00, 128.87, 73.65, 73.55, 67.85, 62.85, 61.99, 51.05, 48.22, 38.85, 29.77, 28.26, 28.21. HRMS (FAB): calcd. for $C_{27}H_{39}N_2O_9$ [MH^+] 535.2656, found 535.2651.

***tert*-Butyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-2-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylbutyryl]-5,6-dihydroxy-2-azabicyclo[2.2.1]-heptane-3-carboxylate (5i):** The title compound was synthesised according to GP 2 from amine **4c** (4.42 g, 19.3 mmol) and Cbz-Glu(O*t*Bu)-OH (7.42 g, 22.0 mmol) and was obtained in 7.41 g (70%) yield. R_f = 0.30 (EA/PE, 1:1; Mo/Ce). $[\alpha]_D^{20}$ = −36.9 (c = 0.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.27−7.37 (m, 5 H), 5.60 (d, J = 8.8 Hz, 0.9 H), 5.57 (d, J = 8.5 Hz, 0.1 H), 5.09 (d, J = 12.3 Hz, 1 H), 5.02 (d, J = 12.3 Hz, 1 H), 4.60 (ddd, J = 4.1, 8.8 Hz, 0.9 H, 4.7), 4.48 (br., 0.1 H), 4.26 (s, 1 H), 3.94 (d, J = 4.8 Hz, 0.9 H), 3.89 (d, J = 4.8 Hz, 1 H), 3.82 (d, J = 4.7 Hz, 0.1 H), 3.77 (s, 1 H), 2.76 (s, 0.1 H), 2.59 (s, 0.9 H), 2.33−2.42 (m, 1.8 H), 2.26−2.32 (m, 0.2 H), 2.00−2.10 (m, 1 H), 1.94 (d, J = 10.7 Hz, 1 H), 1.89 (d, J = 10.8 Hz, 1 H), 1.81 (ddd, J = 6.3, 8.5, 8.8 Hz, 1 H), 1.44 (s, 9 H), 1.43 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer): δ = 172.53, 168.38, 128.66, 128.31, 128.06, 82.00, 81.00, 72.62, 72.46, 67.24, 61.17, 60.41, 51.65, 47.06, 30.79, 29.21, 28.39, 28.24, 28.11. HRMS (FAB): calcd. for $C_{23}H_{31}N_2O_9$ [MH^+] 549.2812, found 549.2818.

***tert*-Butyl (1*S*,3*S*,4*S*,5*S*,6*R*)-2-[(2*S*)-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)propionyl]-5,6-dihydroxy-2-azabicyclo-[2.2.1]heptane-3-carboxylate (5j):** The title compound was synthesised according to GP 2 from amine **4c** (3.60 g, 15.7 mmol) and Cbz-Ser(OTBDMS)-OH (5.15 g, 14.6 mmol) and was obtained in 4.38 g (53%) yield. R_f = 0.58 (EA/PE, 2:1; Mo/Ce). $[\alpha]_D^{20}$ = −35.8 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.27−7.33 (m, 5 H), 5.62 (d, J = 8.8 Hz, 0.7 H), 5.48 (d, J = 7.9 Hz, 0.3 H), 5.01−5.10 (m, 2 H), 4.61 (m, 0.7 H), 4.48 (s, 0.3 H), 4.25 (s, 0.7 H), 4.17−4.21 (m, 0.3 H), 4.14 (s, 0.3 H), 3.94 (d, J = 5.5 Hz, 1 H), 3.89 (d, J = 5.5 Hz, 1 H), 3.80−3.84 (m, 0.8 H), 3.72−3.79 (m, 1.9 H), 3.61 (t, J = 9.3 Hz, 0.3 H), 2.71 (s, 0.3 H), 2.57 (s, 0.7 H), 1.86−1.94 (m, 2 H), 1.43 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 168.93, 168.52, 136.28, 128.67, 128.60, 128.33, 128.14, 128.06, 81.75, 72.65, 72.52, 72.24, 70.85, 67.24, 65.53, 64.23, 61.31, 60.83, 60.63, 59.93, 54.60, 54.04, 48.60, 46.99, 29.28, 28.09, 27.98, 27.28, 26.19, 25.97, 18.41, 5.33, 5.51. HRMS (FAB): calcd. for $C_{23}H_{31}N_2O_9$ [MH^+] 565.2945, found 565.2914.

Ethyl (1*R*,3*S*,4*R*,5*R*,6*S*)-1-[(2*S*)-Benzyloxycarbonylamino-3-methoxycarbonylpropionyl]-5,6-dihydroxy-2-azabicyclo[2.2.2]octane-3-carboxylate (5k): The title compound was synthesised according to GP 2 from amine 4d (0.75 g, 3.72 mmol) and Cbz-Asp(OMe)-OH (1.91 g, 6.79 mmol) and was obtained in 0.59 g (33%) yield. R_f = 0.42 (PE/EA, 7:3; Mo/Ce). ^{1}H NMR (400 MHz, [D_4]MeOH, mixture of rotamers): δ = 7.10−7.50 (m, 5 H), 4.80 (dd, J = 5.4, 8.8 Hz, 1 H), 4.30 (d, J = 3.2 Hz, 1 H), 4.06−4.20 (m, 4 H), 3.87 (dd, J = 3.5, 3.9 Hz, 1 H), 3.67 (s, 3 H), 2.94 (dd, J = 9.1, 16.7 Hz, 1 H), 2.62 (dd, J = 5.7, 16.7 Hz, 1 H), 2.34−2.38 (m, 1 H), 2.05−2.25 (m, 2 H), 1.75−1.85 (m, 2 H), 1.30−1.39 (m, 3 H). ^{13}C NMR (100 MHz, [D_4]MeOH): δ = 171.64, 170.67, 170.59, 156.76, 128.42, 127.93, 127.73, 67.20, 65.18, 63.44, 60.46, 59.75, 52.46,

59.75, 52.46, 50.70, 50.45, 36.02, 35.38, 18.57, 17.10, 14.54. HRMS (FAB): calcd. for $C_{23}H_{30}N_2O_9$ [MH^+] 478.1951, found 478.1959.

Ethyl (6*S*,7*S*,10*S*)-7-Hydroxymethyl-4-oxooctahydropyrido[1,2-*a*]pyrazine-6-carboxylate (8): Diol **5c** (450 mg, 1.11 mmol) was dissolved in 20 mL of acetone/8 mL of water and cooled to −25 °C. $NaIO_4$ (400 mg, 1.87 mmol) was added and the solution was stirred at −25 °C for 30 min. Brine (50 mL) was added and the resulting aqueous solution was extracted with ethyl acetate. The organic phases were dried with Na_2SO_4, filtered, and the solvent was removed in vacuo to give 290 mg (65%) of **6c** as a colourless oil. The product contained some minor impurities but was used without further purification in the next step. Aminal **6c** (290 mg, 0.72 mmol) was dissolved in 25 mL of dry MeOH and $NaBH_4$ (65 mg, 1.43 mmol) was added at 0 °C. The solution was stirred at 0 °C for 1 h. After addition of 25 mL of water, the solution was stirred at room temperature for an additional 15 min. The solution was subsequently saturated with NaCl and extracted with ethyl acetate. Drying of the combined organic phases with Na_2SO_4 and removal of the solvent in vacuo gave the crude product as a 7:3 mixture of diastereoisomers, which was purified by column chromatography on silica gel to give 119 mg (41%) of (1*S*)-**7** and 51 mg (17%) of (1*R*)-**7** as a second fraction as colourless oils. **(1*S*)-7:** R_f = 0.28 (EtOAc/hexane, 9:1; Mo/Ce). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.41−7.34 (m, 5 H), 5.59 (m, 1 H), 5.50 (m, 1 H), 5.19 (s, 2 H), 4.45 (d, *J* = 17.7 Hz, 1 H), 4.30−4.21 (m, 2 H), 4.05 (d, *J* = 17.7 Hz, 1 H), 3.82−3.79 (m, 2 H), 3.55−3.50 (m, 2 H), 2.54−2.53 (m, 1 H), 1.85−1.61 (m, 3 H), 1.50−1.42 (m, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.62, 136.01, 129.01, 128.79, 128.50, 74.75, 68.32, 62.30, 60.80, 55.99, 53.22, 44.62, 36.98, 21.74, 21.43, 14.55. HRMS (FAB): calcd. for $C_{20}H_{26}N_2O_7$ [MH^+] 407.1818, found 407.1799. **(1*R*)-7:** R_f = 0.35 (EtOAc/hexane, 9:1; Mo/Ce). ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.41−7.34 (m, 5 H), 5.59 (s, 1 H), 5.50 (s, 1 H), 5.19 (s, 2 H), 4.45 (d, *J* = 17.7 Hz, 1 H), 4.30−4.21 (m, 2 H), 4.05 (d, *J* = 17.7 Hz, 1 H), 3.82−3.79 (m, 2 H), 3.55−3.50 (m, 2 H), 2.54−2.53 (m, 1 H), 1.85−1.61 (m, 3 H), 1.50−1.42 (m, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.62, 171.04, 166.40, 135.91, 129.04, 128.86, 128.47, 76.72, 68.47, 62.19, 60.80, 58.60, 53.50, 43.68, 37.61, 25.41, 22.58, 14.55. HRMS (FAB): calcd. for $C_{20}H_{26}N_2O_7$ [MH^+] 407.1818, found 407.1814. **8:** The combined diastereoisomers (1*S*)-**7** and (1*R*)-**7** (170 mg, 0.42 mmol) were dissolved in dry EtOH and 100 mg of 5% Pd on activated charcoal was added. The suspension was stirred under hydrogen for 24 h and subsequently filtered through a plug of Celite. The solvent was removed under reduced pressure to give amine **8** as a colourless oil in 107 mg (100%) yield. R_f = 0.54 (dichloromethane/methanol, 8:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 5.45 (s, 1 H), 4.15 (q, *J* = 7.1 Hz, 1 H), 3.62−3.57 (m, 3 H), 3.53−3.48 (m, 2 H), 3.18−3.17 (m, 1 H), 2.69−2.65 (m, 1 H), 2.52−2.50 (m,1 H), 1.68−1.65 (m, 1 H), 1.60−1.52 (m, 1 H), 1.42−1.31 (m, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.24, 171.01, 62.26, 61.93, 53.98, 52.34, 50.55, 49.54, 25.54, 22.11, 14.63. HRMS (FAB): calcd. for $C_{12}H_{21}N_2O_4$ [MH^+] 257.1501, found 257.1532.

General Procedure for the Periodate Cleavage of Dipeptides to Aldehydes 6 (GP 3): Dipeptide **5** (1.0 equiv.) was dissolved in a 2.5:1 mixture of acetone/water (15 mL per 5 mmol) and cooled to 0 °C. $NaIO_4$ (2.0 equiv.) was added and the resulting mixture was stirred at 0 °C for 2 h and then left to reach room temp. After stirring at room temp. for 20 min, brine was added (15 mL per mmol of **5**) and the resulting aqueous solution was extracted with ethyl acetate. The organic phases were dried with Na_2SO_4, filtered, and the solvent was removed in vacuo to give colourless aldehydes **6** that were used without further purification in the next step.

General Procedure for the Oxidation of Aldehydes to Carboxylic Acids 9 (GP 4): An aqueous solution (5 mL of water per mmol of **6**) of $NaClO_2$ (1.3 equiv.) and NaH_2PO_4 (1.2 equiv.) was added to a solution of aldehyde **6** (1 equiv.) and 2-methylbut-2-ene (2 equiv.) in *t*BuOH (60 mL per mmol of **6**). The mixture was stirred at room temp. for 12 h before the solvent was removed in vacuo. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, gradient) on silica gel to give products **9** as colourless sticky solids.

General Procedure for the Hydrogenation to Amines 10 and 12 (GP 5): Aminals **9** or **11** were dissolved in dry EtOH and a catalytic amount of 5% Pd on activated charcoal (50 mg/mmol aminal) was added. The suspension was stirred under hydrogen for 24 h and subsequently filtered through a plug of Celite. The solvent was removed under reduced pressure to give products **10** or **12**.

Ethyl (3*S*,6*S*,7*S*,9*S*)-7-Carboxy-3-methoxycarbonylmethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (10a): Dipeptide **5a** (2.00 g, 4.34 mmol) was treated with $NaIO_4$ as described in GP 3 to give of the crude aldehyde **6a** (1.95 g, 4.22 mmol), which was used without further purification in the next step. This aldehyde was oxidised according to GP 4 to give 1.91 g of the carboxylic acid **9a** (92%). R_f = 0.62 (dichloromethane/MeOH, 8:2; Mo/Ce). $[\alpha]_D^{20}$ = +40.2 (*c* = 0.955, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 7.35 (m, 5 H), 5.95 (br., 1 H), 5.92 (s, 0.5 H), 5.79 (s, 0.5 H), 5.17 (m, 2 H), 4.89 (d, *J* = 6.8 Hz, 1 H), 4.82 (br. m, 0.5 H), 4.73 (br. m, 0.5 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.97 (br. m, 1 H), 3.64 (s, 1.5 H), 3.56 (s, 1.5 H), 3.10 (br. m, 2 H), 2.93 (br. m, 1 H), 2.40 (m, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, [D_4]MeOH, mixture of rotamers): δ = 173.43, 173.06, 172.83, 168.18, 155.25, 154.98, 137.44, 129.58, 129.32, 129.21, 129.11, 74.28, 73.80, 68.95, 68.87, 63.89, 63.83, 63.74, 62.78, 53.65, 53.37, 52.38, 52.30, 41.13, 40.02, 33.41, 14.39. HRMS (FAB): calcd. for $C_{22}H_{26}N_2O_{10}$ [*M* + Na]$^+$ 501.1485, found 501.1501. **10a:** Aminal **9a** (0.35 g. 0.73 mmol) was hydrogenated according to GP 5 to give 0.22 g (92%) of the title compound **10a**. R_f = 0.19 (dichloromethane/MeOH, 8:2; ninhydrin). $[\alpha]_D^{20}$ = −33.9 (*c* = 0.34, MeOH). ^1H NMR (500 MHz, [D_4]MeOH): δ = 4.81 (d, *J* = 7.9 Hz, 1 H), 4.24−4.18 (m, 2 H), 3.99 (dd, *J* = 8.5 Hz, 1 H), 3.97−3.90 (m, 1 H), 3.71 (s, 3 H), 3.27−3.22 (m, 1 H), 3.14−3.07 (m, 1 H), 2.88−2.76 (m, 3 H), 2.48−2.42 (ddd, *J* = 5.4, 6.9, 12.3 Hz, 1 H), 1.80 (dd, 1 H, *J* = 12.0 Hz), 1.27 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, [D_4]MeOH): δ = 175.59, 173.46, 172.28, 170.15, 62.98, 62.74, 60.58, 54.29, 52.42, 47.91, 44.79, 37.49, 35.89, 14.41. HRMS (FAB): calcd. for $C_{14}H_{20}N_2O_7$ [MH^+] 329.1349, found 329.1366.

***tert*-Butyl (3*S*,6*S*,7*S*,9*S*)-3-*tert*-Butoxycarbonylmethyl-7-carboxy-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (10b):** Dipeptide **5h** (1.71 g, 3.20 mmol) was treated with $NaIO_4$ as described in GP 3 to give 1.80 g of the crude aldehyde **6h**, which was used without further purification in the next step. This aldehyde was oxidised according to GP 4 to give 0.44 g of the carboxylic acid **9b** (25%). R_f = 0.45 (dichloromethane/MeOH, 9:1; Mo/Ce). $[\alpha]_D^{20}$ = +50.3 (*c* = 1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers): δ = 7.31−7.40 (m, 5 H), 5.88 (s, 0.5 H), 5.73 (s, 0.5 H), 5.12−5.26 (m, 2 H), 4.79 (d, *J* = 6.6 Hz, 1 H), 4.66 (br., 0.4 H), 4.60 (br., 0.6 H), 3.90−4.01 (m, 1 H), 3.19 (t, *J* = 17.7 Hz, 0.6 H), 3.05−3.14 (m, 2 H), 2.86 (d, *J* = 19.2 Hz, 0.4 H), 2.43−2.54 (m, 1 H), 2.32−2.43 (m, 1 H), 1.45 (s, 9 H), 1.42 (s, 5.4 H), 1.41 (s, 3.6 H). ^{13}C NMR (100 MHz, [D_4]MeOH, mixture of conformers): δ = 172.18, 171.56, 170.73, 169.73, 83.37, 83.27, 82.42, 82.09, 63.99, 63.69, 60.17, 60.11, 55.58, 54.04, 49.94, 44.86, 38.57, 38.39, 36.09, 35.99, 28.37, 28.20. HRMS (ESI): calcd. for $C_{27}H_{36}N_2NaO_{10}$ [*M* + Na]$^+$ 571.2267, found 571.2301. **10b:** Aminal **9b** (0.32 g,

0.58 mmol) was hydrogenated according to GP 5 to give 0.15 g (64%) of the title compound **10b**. R_f = 0.36 (dichloromethane/MeOH, 9:1; ninhydrin). $[\alpha]_D^{20}$ = −37.9 (*c* = 0.605, MeOH). ^{1}H NMR (500 MHz, [D$_4$]MeOH, mixture of conformers): δ = 4.62−4.75 (m, 1 H), 4.03−4.17 (m, 0.2 H), 3.95−3.99 (m, 0.8 H), 3.86−3.96 (m, 0.8 H), 3.59−3.79 (m, 0.2 H), 3.36−3.50 (m, 0.2 H), 3.21−3.32 (m, 0.8 H), 2.94−3.07 (m, 1 H), 2.77−2.89 (m, 1 H), 2.54−2.77 (m, 2 H), 2.34−2.45 (m, 1 H), 1.62−1.83 (m, 1 H), 1.47 (s, 14.4 H), 1.46 (s, 3.6 H). ^{13}C NMR (100 MHz, [D$_4$]MeOH, mixture of conformers): δ = 172.18, 171.56, 170.73, 169.73, 83.37, 83.27, 82.42, 82.09, 63.99, 63.69, 60.17, 60.11, 55.58, 54.04, 49.94, 44.86, 38.57, 38.39, 36.09, 35.99, 28.37, 28.20. HRMS (ESI): calcd. for $C_{19}H_{30}N_2NaO_7$ [M + Na]$^+$ 421.1951, found 421.1948.

Ethyl (3*S*,6*S*,7*S*,10*S*)-7-Carboxy-3-methoxycarbonylmethyl-4-oxo-octahydropyrido[1,2-*a*]pyrazine-6-carboxylate (10d): Dipeptide **5g** (5.0 g, 10.5 mmol) was treated with $NaIO_4$ as described in GP 3 to give 4.71 g (94%) of the crude aldehyde **6g**, which was used without further purification in the next step. This aldehyde was oxidised according to GP 4 to give 1.04 g of the carboxylic acid **9d** (21%). R_f = 0.38 (dichloromethane/MeOH, 9:1; Mo/Ce). $[\alpha]_D^{20}$ = +37.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 7.30−7.39 (m, 5 H), 5.80 (br. s, 1 H), 5.69 (br., 0.5 H), 5.53 (br., 0.5 H), 5.10−5.23 (m, 2 H), 4.90 (t, *J* = 5.4 Hz, 0.5 H), 4.80 (t, *J* = 4.7 Hz, 0.5 H), 4.15−4.22 (m, 2 H), 3.74 (br., 0.5 H), 3.72 (br., 0.5 H), 3.66 (s, 1.5 H), 3.55 (s, 1.5 H), 3.35 (br., 1 H), 3.10−3.24 (m, 1 H), 2.94−3.08 (m, 1 H), 2.28 (d, *J* = 12.9 Hz, 1 H), 1.93 (dd, *J* = 16.2, 13.2 Hz, 1 H), 1.58−1.67 (m, 1 H), 1.52 (ddt, *J* = 3.1, 3.8, 12.9 Hz, 1 H), 1.22−1.37 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 175.29, 128.74, 128.54, 128.35, 128.24, 74.88, 74.39, 68.64, 68.47, 62.22, 56.25, 56.15, 53.46, 52.67, 52.61, 52.50, 52.36, 40.21, 39.13, 37.12, 23.20, 21.08, 20.95, 14.27. HRMS (FAB): calcd. for $C_{23}H_{28}N_2NaO_{10}$ [M + Na]$^+$ 515.1642, found 515.1657. (**10d**): Aminal **9d** (0.39 mmol, 0.19 g) was hydrogenated according to GP 5 to give 0.11 g (82%) of the title compound **10d**. R_f = 0.13 (dichloromethane/MeOH, 9:1; Mo/Ce). $[\alpha]_D^{20}$ = −15.8 (*c* = 0.525, MeOH). ^{1}H NMR (500 MHz, [D$_4$]MeOH): δ = 5.81 (s., 1 H), 4.43−4.48 (m, 1 H), 3.91−3.98 (m, 1 H), 3.77 (s, 3 H), 3.58−3.71 (m, 1 H), 3.41 (dd, *J* = 6.9, 12.9 Hz, 1 H), 3.35 (br., 1 H), 3.21 (dd, *J* = 7.6, 18.0 Hz, 1 H), 3.08 (dd, *J* = 2.8, 18.0 Hz, 1 H), 2.28−2.34 (m, 1 H), 1.64−1.80 (m, 3 H), 1.31 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, [D$_4$]MeOH): δ = 174.46, 171.93, 170.69, 166.03, 63.45, 54.98, 54.32, 53.14, 51.20, 44.41, 41.37, 34.56, 26.78, 22.86, 14.45. HRMS (ESI): calcd. for $C_{15}H_{22}N_2NaO_7$ [M + Na$^+$] 365.1325, found 365.1345.

***tert*-Butyl (3*S*,6*S*,7*S*,9*S*)-(*tert*-Butyldimethylsilanyloxymethyl)-7-carboxy-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (10c):** Dipeptide **5j** (2.01 g, 3.56 mmol) was treated with $NaIO_4$ as described in GP 3 to give 2.0 g of the crude aldehyde **6j**, which was used without further purification in the next step. This aldehyde was oxidised according to GP 4 and purified by column chromatography with EtOAc/PE as eluent to give 0.4 g (19%) of the carboxylic acid **9c** and 0.8 g (43%) of the corresponding deprotected alcohol. R_f(**9c**) = 0.38 (dichloromethane/MeOH, 9:1; Mo/Ce). $[\alpha]_D^{20}$ = +14.4 (*c* = 1.95, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 7.31−7.39 (m, 5 H), 5.85 (dd, *J* = 2.5, 9.5 Hz, 0.5 H), 5.72 (dd, *J* = 2.5, 9.8 Hz, 0.5 H), 5.37 (d, *J* = 9.3 Hz, 0.5 H), 5.16−5.26 (m, 2.5 H), 4.70−4.74 (m, 1.5 H), 4.66−4.68 (m, 0.5 H), 4.26−4.32 (m, 1 H), 3.84−3.94 (m, 1.5 H), 3.69 (dd, *J* = 1.6, 10.1 Hz, 0.5 H), 3.00−3.08 (m, 1 H), 2.30−2.41 (m, 2 H), 1.46 (s, 9 H), 0.87 (s, 4.5 H), 0.85 (s, 4.5 H), 0.09 (s, 1.5 H), 0.08 (s, 1.5 H), 0.07 (s, 1.5 H), 0.06 (s, 1.5 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 175.14, 169.70, 163.43, 163.25, 158.03, 135.90, 128.80, 128.73, 128.63, 128.48, 128.32, 128.20, 82.64, 71.66, 71.29, 68.35, 68.15, 63.35, 62.40, 62.29, 62.24, 61.95, 61.87, 58.21, 58.11, 45.63, 33.87, 28.02, 25.80, 18.33, −5.55, −5.66. HRMS (ESI): calcd. for $C_{28}H_{42}N_2NaO_9Si$ [M + Na]$^+$ 601.2557, found 601.2359. **10c:** Aminal **9c** (150 mg, 0.43 mmol) was hydrogenated according to GP 5 and purified by column chromatography with dichloromethane/methanol as the eluent to give 63 mg (58%) of the title compound **10c**. R_f = 0.37 (dichloromethane/methanol, 9:1; Mo/Ce). $[\alpha]_D^{20}$ = −16.9 (*c* = 1.685, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.39 (br., 2 H), 4.71 (d, *J* = 7.6 Hz, 1 H), 3.92−3.96 (m, 3 H), 3.67 (dd, 1 H, *J* = 5.4 Hz), 3.29 (dd, *J* = 3.5, 12.0 Hz, 1 H), 2.98−3.05 (m, 1 H), 2.90−2.96 (m, 1 H), 2.32−2.38 (m, 1 H), 1.77 (dd, *J* = 11.4, 22.7 Hz, 1 H), 1.45 (s, 9 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.05, 169.89, 165.99, 82.40, 63.03, 61.98, 58.33, 57.62, 46.48, 44.41, 34.58, 28.05, 25.99, 18.32, −5.30, −5.33. HRMS (ESI): calcd. for $C_{20}H_{36}N_2NaO_6Si$ [M + Na]$^+$ 451.2240, found 451.2236.

General Procedure for the Olefination of Aldehydes 6 to Alkenes 11 (GP 6): The appropriate phosphorane (2 equiv.) was added to a solution of aldehyde **6** (1 equiv.) in dry THF (30 mL per mmol aldehyde) and the resulting mixture was stirred at room temp. for 12 h. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography (EtOAc/PE, gradient) to give alkenes **11** as white solids.

Ethyl (3*S*,6*S*,7*S*,9*S*)-7-(2-Methoxycarbonylethyl)-3-(methoxycarbonylmethyl)-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (12a): $NaIO_4$ (1.1 g, 5.1 mmol) was dissolved in 7.85 mL of water. This aqueous 0.65 M solution was added dropwise to a vigorously stirred suspension of 12 g of silica in 40 mL of Et_2O. A solution of **5a** (2.0 g, 4.3 mmol) and methyl (triphenylphosphanylidene)acetate (2.6 g, 7.8 mmol) in 20 mL of Et_2O was added to this mixture. The reaction mixture was stirred at room temp. for 12 h and a further portion of methyl (triphenylphosphanylidene)acetate (2.6 g, 7.8 mmol) was added. The mixture was stirred at room temp. for a further 12 h, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, gradient) to obtain **11a** in 1.4 g (2.7 mmol, 69%) yield. R_f = 0.73 (EtOAc/PE, 7:3; Mo/Ce). $[\alpha]_D^{20}$ = +37.8 (*c* = 1.21, $CHCl_3$). ^{1}H NMR [500 MHz, $CDCl_3$, mixture of rotamers and (*E*)/(*Z*) isomers]: δ = 7.31−7.40 (m, 5 H), 6.93 (dd, *J* = 7.9, 15.8 Hz, 0.8 H), 6.19 (t, *J* = 10.4 Hz, 0.2 H), 5.96 (d, *J* = 15.8 Hz, 1 H), 5.89−5.94 (m, 0.4 H), 5.73−5.79 (m, 0.6 H), 5.58−5.64 (br., 0.5 H), 5.10−5.27 (m, 2 H), 5.00−5.08 (br., 0.5 H), 4.68−4.74 (m, 0.4 H), 4.61−4.67 (m, 0.6 H), 4.24 (d, *J* = 9.1 Hz, 1 H), 4.18−4.24 (m, 1 H), 4.13−4.18 (q, *J* = 7.9 Hz, 1 H), 3.97−4.07 (m, 1 H), 3.75 (s, 1.8 H), 3.69 (s, 1.2 H), 3.68 (s, 1.8 H) 3.62 (s, 1.2 H), 3.07−3.30 (m, 2 H), 2.94−3.03 (m, 1 H), 2.31 (dt, *J* = 5.7, 6.6 Hz, 0.2 H), 2.15−2.26 (m, 1.6 H), 2.02−2.09 (m, 0.2 H), 1.25 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR [100 MHz, [D$_4$]MeOH, mixture of rotamers and (*E*)/(*Z*) isomers]: δ = 166.23, 164.85, 144.99, 128.79, 128.63, 128.33, 123.50, 122.43, 73.70, 73.31, 68.51, 68.36, 64.45, 63.55, 62.16, 62.00, 61.88, 61.66, 52.68, 52.17, 51.88, 51.48, 44.22, 35.09, 35.57, 34.11, 14.33. HRMS (FAB): calcd. for $C_{25}H_{31}N_2O_{10}$ [MH$^+$] 519.1979, found 519.2003. **12a:** Aminal **11a** (1.27 g, 2.45 mmol) was hydrogenated according to GP 5 to give 0.91 g (100%) of the title compound **12a**. R_f = 0.50 (dichloromethane/MeOH, 95:5; Mo/Ce). $[\alpha]_D^{20}$ = −81.5 (*c* = 0.455, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.6 Hz, 2 H), 4.06 (d, *J* = 7.9 Hz, 1 H), 3.90 (dd, *J* = 3.5, 10.1 Hz, 1 H), 3.74−3.81 (m, 1 H), 3.63 (s, 3 H), 3.61 (s, 3 H), 3.13 (dd, *J* = 13.2, 4.1 Hz, 1 H),

2.83 (dd, J = 16.3, 3.7 Hz, 1 H), 2.60 (dd, J = 16.3, 9.7 Hz, 1 H), 2.57 (dd, J = 13.2, 9.5 Hz, 1 H), 2.36 (t, J = 7.6 Hz, 2 H), 2.31 (br. s, 1 H), 2.10−2.20 (m, 2 H), 2.00 (ddd, J = 13.9, 6.3, 7.3 Hz, 1 H), 1.73 (ddd, J = 13.9, 6.0, 7.9 Hz, 1 H), 1.22 (t, J = 7.3 Hz, 3 H), 1.25 (dd, J = 11.4, 10.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.13, 172.32, 171.55.168.55, 63.76, 61.37, 60.18, 53.44, 51.79, 51.68, 44.76, 41.50, 37.16, 37.94, 32.14, 28.87, 14.13. HRMS (FAB): calcd. for $C_{17}H_{27}N_2O_7$ [MH^+] 371.1818, found 371.1834.

***tert*-Butyl (3*S*,6*S*,7*S*,9*S*)-7-(2-*tert*-Butoxycarbonylethyl)-3-*tert*-butoxycarbonylmethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (12b):** Dipeptide **5h** (1.56 g, 2.92 mmol) was treated with $NaIO_4$ as described in GP 3 to give 1.50 g of the crude aldehyde **6h**, which was used without further purification in the next step. This aldehyde was treated with *tert*-butyl (triphenylphosphanylidene)acetate according to GP 6 to give 1.02 g of the olefin **11b** (55%). R_f = 0.33 (EtOAc/PE, 1:2; Mo/Ce). $[\alpha]_D^{20}$ = +24.6 (c = 0.365, MeOH). ^{1}H NMR (500 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 7.29−7.44 (m, 5 H), 6.83 (dd, J = 7.9, 15.5 Hz, 1 H), 5.91 (d, J = 15.3 Hz, 1 H), 5.90 (br., 0.5 H), 5.87 (br., 0.5 H), 5.25 (d, J = 12.6 Hz, 1 H), 5.18 (d, J = 12.6 Hz, 1 H), 4.96−5.01 (m, 0.5 H), 4.90−4.96 (m, 0.5 H), 4.07 (d, J = 9.2 Hz, 1 H), 3.99 (dd, J = 5.0, 5.4 Hz, 0.5 H), 3.97 (dd, J = 5.0, 5.4 Hz, 0.5 H), 2.91−3.00 (m, 1 H), 2.70−2.83 (m, 1 H), 2.61−2.69 (m, 0.5 H), 2.53−2.59 (d, J = 15.5 Hz, 0.5 H), 2.14−2.22 (m, 1 H), 1.92−2.01 (m, 1 H), 1.49 (s, 9 H), 1.46 (s, 4.5 H), 1.45 (s, 9 H), 1.41 (s, 4.5 H). ^{13}C NMR (100 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 171.06, 168.49, 166.71, 146.33, 137.44, 129.55, 129.22, 128.96, 126.33, 83.45, 81.83, 74.19, 73.65, 68.74, 65.39, 63.70, 53.59, 52.19, 45.50, 42.57, 41.35, 35.27, 28.36, 28.32, 28.26. HRMS (FAB): calcd. for $C_{39}H_{57}N_2O_{11}$ [MH^+] 631.3231, found 631.3246. **12b:** Aminal **11b** (0.58 g, 0.92 mmol) was hydrogenated according to GP 5 to give 0.34 g (77%) of the title compound **12b**. R_f = 0.22 (dichloromethane/MeOH, 91:1; ninhydrin). $[\alpha]_D^{20}$ = −53.6 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.57 (br., 1 H), 4.03 (d, J = 7.1 Hz, 1 H), 3.99 (d, J = 7.6 Hz, 1 H), 3.95 (m, 1 H), 3.37 (d, J = 11.0 Hz, 1 H), 2.96 (d, J = 16.5 Hz, 1 H), 2.82 (d, J = 11.0 Hz, 1 H), 2.74 (dd, J = 8.8, 16.5 Hz, 1 H), 2.30 (t, J = 7.6 Hz, 2 H), 2.13−2.26 (m, 2 H), 1.98 (dt, J = 6.7, 14.3 Hz, 1 H), 1.71 (ddd, J = 6.7, 7.4, 14.3 Hz, 1 H), 1.46 (s, 9 H), 1.43 (s, 9 H), 1.42 (s, 9 H), 1.23−1.28 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.14, 170.77, 170.42, 82.13, 81.54, 80.67, 65.82, 58.26, 52.86, 44.83, 41.60, 37.33, 36.97, 33.76, 29.14, 28.26, 28.22, 28.09. HRMS (FAB): calcd. for $C_{25}H_{43}N_2O_7$ [MH^+] 483.3070, found 483.3074.

***tert*-Butyl (3*S*,6*S*,7*S*,9*S*)-3,7-Bis(2-*tert*-butoxycarbonylethyl)-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (12c):** Dipeptide **5i** (2.00 g, 3.65 mmol) was treated with $NaIO_4$ as described in GP 3 to give 2.40 g of the crude aldehyde **6i**, which was used without further purification in the next step. This aldehyde was treated with *tert*-butyl (triphenylphosphanylidene)acetate according to GP 6 to give 0.61 g of the olefin **11c** (21%). R_f = 0.45 (EtOAc/PE, 1:2; Mo/Ce). $[\alpha]_D^{20}$ = +26.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 7.31−7.42 (m, 5 H), 6.82 (dd, J = 8.2, 15.5 Hz, 1 H), 5.88−5.97 (m, 2 H), 5.15−5.25 (m, 2 H), 4.51−4.58 (m, 0.5 H), 4.43−4.50 (m, 0.5 H), 4.07 (d, J = 9.5 Hz, 1 H), 3.92−3.97 (m, 1 H), 2.90−3.00 (m, 1 H), 2.46−2.54 (m, 1 H), 2.24−2.39 (m, 2 H), 2.14−2.23 (m, 1 H), 2.01−2.12 (m, 1 H), 1.94−2.00 (m, 1 H), 1.49 (s, 9 H), 1.48 (s, 9 H), 1.46 (s, 4.5 H), 1.44 (s, 4.5 H). ^{13}C NMR (100 MHz, [D$_4$]MeOH, mixture of rotamers): δ = 168.83, 146.14, 129.63, 129.37, 126.40, 124.12, 83.55, 81.92, 81.46, 74.35, 74.04, 68.91, 65.46, 63.73, 63.49, 55.89, 55.79 45.55, 34.82, 32.08, 29.39, 28.38, 28.35, 28.26. HRMS (FAB): calcd. for $C_{34}H_{49}N_2O_{10}$ [MH^+] 645.3387, found 645.3440. **12c:** Aminal **11c** (0.71 g, 1.10 mmol) was hydrogenated according to GP 5 to give 0.45 g (83%) of the title compound **12c**. R_f = 0.23 (dichloromethane/MeOH, 98:2; Mo/Ce). $[\alpha]_D^{20}$ = −40.2 (c = 0.99, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.97 (d, J = 7.6 Hz, 1 H), 3.74 (ddt, J = 4.1, 6.3, 10.7 Hz), 3.33 (dd, J = 4.4, 10.4 Hz, 1 H), 3.05 (dd, J = 4.1, 13.6 Hz, 1 H), 2.56 (dd, J = 10.1, 13.6 Hz, 1 H), 2.36 (d, J = 6.9 Hz, 1 H), 2.34 (d, J = 6.9 Hz, 1 H), 2.28 (t, J = 7.7 Hz, 2 H), 2.07−2.15 (m, 3 H), 1.95−1.99 (m, 1 H), 1.80−1.87 (m, 1 H), 1.69 (m, 1 H), 1.45 (s, 9 H), 1.41 (s, 9 H), 1.40 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.14, 171.26, 169.74, 164.70, 81.99, 80.65, 80.25, 64.54, 60.45, 56.27, 44.29, 41.68, 37.30, 33.82, 33.46, 29.51, 28.26, 28.14, 28.13, 27.60. HRMS (ESI): calcd. for $C_{26}H_{44}N_2NaO_7$ [$M + Na$]$^+$ 519.3046, found 519.3073.

***tert*-Butyl (3*S*,6*S*,7*S*,9*S*)-7-(2-*tert*-Butoxycarbonylethyl)-3-(*tert*-butyldimethylsilanyloxymethyl)-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (12d):** Dipeptide **5j** (2.01 g, 3.56 mmol) was treated with $NaIO_4$ as described in GP 3 to give 2.01 g of the crude aldehyde **6j**, which was used without further purification in the next step. This aldehyde was treated with *tert*-butyl (triphenylphosphanylidene)acetate according to GP 6 to give 1.00 g of the olefin **11d** (43%). R_f = 0.21 (EtOAc/PE, 1:4; Mo/Ce). $[\alpha]_D^{20}$ = +31.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 7.37−7.32 (m, 5 H), 6.80 (dd, J = 2.8, 15.5 Hz, 0.5 H), 6.77 (dd, J = 2.8, 15.5 Hz, 0.5 H), 5.86 (d, J = 15.5 Hz, 1 H), 5.85 (m, 0.4 H), 5.72 (dd, J = 2.5, 8.2 Hz, 0.6 H), 5.29 (d, J = 8.2 Hz, 0.6 H), 5.24 (d, J = 12.0 Hz, 0.6 H), 5.18 (d, J = 12.0 Hz, 1.4 H), 5.11 (d, J = 8.2 Hz, 0.4 H), 4.70 (s, 0.6 H), 4.65 (s, 0.4 H), 4.31−4.27 (m, 1 H), 4.10 (d, J = 4.7 Hz, 0.5 H), 4.08 (d, J = 4.7 Hz, 0.5 H), 3.91 (m, 1 H), 3.86 (dd, J = 1.9, 9.8 Hz, 0.6 H), 3.69 (dd, J = 1.9, 9.8 Hz, 0.4 H), 2.88 (m, 1 H), 2.19−2.10 (m, 1 H), 2.08−2.00 (m, 1 H), 1.49 (s, 9 H), 1.46 (s, 9 H), 0.87 (s, 5.4 H), 0.86 (s, 3.6 H), 0.10 (s, 5.4 H), 0.09 (s, 3.6 H), 0.07 (s, 5.4 H), 0.60 (s, 3.6 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 165.55, 163.74, 144.73, 129.11, 129.04, 128.93, 128.78, 128.62, 128.50, 125.58, 82.77, 81.18, 72.00, 71.65, 68.61, 68.42, 64.15, 64.10, 63.40, 62.65, 62.44, 58.46, 58.34, 44.31, 34.50, 28.51, 28.42, 26.08, 5.20, 5.23, 5.32. HRMS (FAB): calcd. for $C_{34}H_{53}N_2O_9Si$ [MH^+] 661.3520, found 661.3545. **12d:** Aminal **11d** (0.95 g, 1.44 mmol) was hydrogenated according to GP 5 to give 0.74 g (100%) of the title compound **12d**. R_f = 0.11 (EtOAc/PE, 1:1; ninhydrin). $[\alpha]_D^{20}$ = −54.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of conformers): δ = 4.16 (d, 0.3 H J = 3.8, 10.1 Hz), 4.06 (m, 0.3 H), 4.04 (d, J = 7.6 Hz, 0.3 H), 3.98 (d, J = 7.6 Hz, 0.7 H), 3.81−3.94 (m, 2 H), 3.77 (dd, J = 2.5, 10.1 Hz, 0.3 H), 3.58 (dd, J = 7.6, 3.8 Hz, 0.7 H), 3.55 (t, J = 2.5 Hz, 0.3 H), 3.17−3.25 (m, 0.6 H), 3.14 (dd, J = 3.8, 12.0 Hz, 0.7 H), 2.85 (dd, J = 10.1, 12.0 Hz, 0.7 H), 2.29−2.35 (m, 2 H), 2.06−2.23 (m, 2 H), 1.94−2.03 (m, 1 H), 1.71 (ddd, J = 7.9, 14.5, 21.8 Hz, 1 H), 1.48 (s, 9 H), 1.44 (s, 9 H), 1.06−1.20 (m, 1 H), 0.88 (s, 6.3 H), 0.86 (s, 2.7 H), 0.06 (s, 2.1 H), 0.05 (s, 2.1), 0.03 (s, 0.9 H), 0.01 (0.9 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of conformers): δ = 65.80, 64.46, 64.25, 64.10, 59.73, 58.50, 49.45, 45.34, 41.65, 37.28, 37.03, 33.94, 33.88, 29.49, 28.24, 28.23, 26.06, 26.03. HRMS (ESI): calcd. for $C_{26}H_{48}N_2NaO_6Si$ [$M + Na$]$^+$ 535.3179, found 535.3180.

One-Pot Oxidation/Wittig Reaction and Subsequent Reduction to Dipeptide Mimetic 12a: $NaIO_4$ (1.1 g, 5.1 mmol) was dissolved in 7.85 mL of water. This aqueous 0.65 M solution was added dropwise to a vigorously stirred suspension of 12 g of silica in 40 mL of Et_2O. A solution of **5a** (1.8 g, 3.9 mmol) and methyl (triphenylphosphanylidene)acetate (2.6 g, 7.8 mmol) in 20 mL of Et_2O was added to this mixture. The reaction mixture was stirred at room

temp. for 12 h and another portion of methyl (triphenylphosphanylidene)acetate (2.6 g, 7.8 mmol) was added. The mixture was stirred at room temp. for a further 12 h, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, gradient) to obtain **11a** in 1.4 g (2.7 mmol, 69%) yield. Subsequent hydrogenation according to GP 5 led to title compound **12a** in 100% yield.

General Procedure for the Synthesis of Diazabicycloalkanes 15 (GP 7): A solution of 0.21 mmol of the appropriate amine in dry dichloromethane was cooled to 0 °C under nitrogen and DIPEA (23.4 μL, 0.24 mmol) and acetic acid anhydride (22.2 μL, 0.24 mmol) were added. The reaction mixture was stirred for 3 h at this temperature before it was acidified by adding 5 mL of saturated NH_4Cl solution. The resulting mixture was extracted with dichloromethane and the organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography to give pure **14**. Compound **14** was dissolved in 50% TFA in dichloromethane and stirred at room temp. for 3 h before the TFA and dichloromethane were removed at reduced pressure to give target structure **15**.

(3*S*,6*S*,7*S*,9*S*)-2-Acetyl-7-(2-carboxyethyl)-3-carboxymethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (15a): Amine **12b** (100 mg, 0.21 mmol) was converted according to GP 7 and purified by column chromatography with CH_2Cl_2/MeOH as the eluent to give **14a** as a colourless oil in 97 mg (92%) yield. R_f = 0.33 (CH_2Cl_2/MeOH, 98:2; Mo/Ce). $[\alpha]_D^{20}$ = +22.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 4.93 (t, *J* = 4.4 Hz, 0.5 H), 4.90 (dd, *J* = 4.1, 13.3 Hz, 0.5 H), 4.74 (dd, *J* = 5.0, 7.2 Hz, 0.5 H), 4.07 (d, *J* = 7.8 Hz, 0.5 H), 4.02 (d, *J* = 7.9 Hz, 0.5 H), 3.91 (dd, *J* = 3.5, 12.9 Hz, 0.5 H), 3.86 (dddd, *J* = 3.8, 4.1, 4.6, 10.5 Hz, 0.5 H), 3.78 (ddt, *J* = 4.1, 10.7, 10.9 Hz, 0.5 H), 3.58 (dd, *J* = 10.4, 12.9 Hz, 0.5 H), 3.10 (dd, *J* = 4.8, 16.7 Hz, 0.5 H), 2.88 (dd, *J* = 4.4, 16.7 Hz, 0.5 H), 2.85 (dd, *J* = 4.7, 15.8 Hz, 0.5 H), 2.77 (dd, *J* = 7.6, 15.8 Hz, 0.5 H), 2.63 (dd, *J* = 10.7, 13.2 Hz, 0.5 H), 2.33 (t, *J* = 7.6 Hz, 1 H), 2.32 (t, *J* = 7.6 Hz, 1 H), 2.17−2.26 (m, 2 H), 2.20 (s, 1.5 H), 2.13 (s, 1.5 H), 2.05 (ddd, *J* = 6.3, 7.4, 14.2 Hz, 1 H), 1.75 (ddd, *J* = 7.0, 7.3, 14.2 Hz, 1 H), 1.48 (s, 4.5 H), 1.47 (s, 4.5 H), 1.44 (s, 4.5 H), 1.43 (s, 4.5 H), 1.42 (s, 4.5 H), 1.39 (s, 4.5 H), 1.29−1.37 (m, 0.5 H), 1.17−1.27 (m, 0.5 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 168.83, 82.31, 82.12, 81.87, 80.92, 80.74, 80.72, 64.74, 64.62, 58.27, 58.01, 55.45, 51.99, 47.91, 41.75, 41.66, 41.38, 39.24, 36.80, 36.55, 36.29, 33.82, 33.76, 29.24, 28.96, 28.24, 28.22, 28.15, 28.12, 22.09, 21.39. HRMS (FAB): calcd. for $C_{32}H_{46}N_2O_8$ [MH^+] 525.3176; found 525.3265. **15a:** The title compound was synthesised according to GP 7 from **14a** (83.0 mg, 0.16 mmol) as a colourless solid in 56 mg (100%) yield. $[\alpha]_D^{20}$ = +11.2 (*c* = 0.37, H_2O). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers): δ = 4.86 (t, *J* = 5.7 Hz, 0.6 H), 4.69 (t, *J* = 6.1 Hz, 0.3 H), 4.62 (dd, *J* = 3.5, 12.9 Hz, 0.3 H), 4.17−4.23 (m, 0.1 H), 4.08 (dd, *J* = 3.2, 13.6 Hz, 0.7 H), 3.98−4.06 (m, 0.1 H), 3.85 (d, *J* = 8.5 Hz, 1 H), 3.77−3.84 (m, 0.6 H), 3.54−3.61 (m, 0.3 H), 3.24 (dd, *J* = 10.7, 13.5 Hz, 0.7 H), 2.89−3.02 (m, 0.5 H), 2.75−2.78 (m, 0.5 H), 2.66−2.74 (m, 0.3 H), 2.64 (dd, *J* = 3.5, 15.4 Hz, 1 H), 2.26−2.33 (m, 2 H), 2.11−2.20 (m, 2 H), 2.10 (s, 1 H), 2.07 (s, 2 H), 1.90−2.00 (m, 1 H), 1.54−1.66 (m, 1 H), 1.33−1.41 (m, 0.3 H), 1.18−1.29 (m, 0.7 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers): δ = 174.05, 174.00, 172.59, 171.93, 171.79, 171.30, 168.59, 165.74, 165.38, 65.06, 63.76, 63.66, 58.35, 57.79, 54.79, 54.35, 51.07, 50.69, 46.30, 41.14, 40.39, 37.74, 36.10, 35.54, 35.30, 35.16, 31.84, 28.08, 21.60, 21.08. HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_8$ [M + Na]$^+$ 379.1117, found 379.1138.

(3*S*,6*S*,7*S*,9*S*)-2-Acetyl-3,7-bis(2-carboxyethyl)-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (15b): Amine **12c** (65 mg, 0.13 mmol) was converted according to GP 7 and purified by column chromatography with ethyl acetate/PE as the eluent to give **14b** as a colourless oil in 58 mg (80%) yield. R_f = 0.49 (ethyl acetate/PE, 4:1; Mo/Ce). $[\alpha]_D^{20}$ = +17.6 (*c* = 1.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 5.06 (dd, *J* = 4.5, 9.1 Hz, 0.4 H), 4.88 (dd, *J* = 3.2, 13.2 Hz, 0.6 H), 4.35 (t, *J* = 7.1 Hz, 0.6 H), 4.00 (d, *J* = 7.6 Hz, 0.4 H), 3.98 (d, *J* = 7.9 Hz, 0.6 H) 3.94 (dd, *J* = 3.2, 13.9 Hz, 0.4 H), 3.82 (dt, *J* = 4.1, 11.0 Hz, 0.4 H), 3.76 (dt, *J* = 4.1, 13.1 Hz, 0.6 H), 3.11 (dd, *J* = 10.7, 13.9 Hz, 0.4 H), 2.52 (dd, *J* = 10.7, 13.6 Hz, 0.6 H), 2.41 (dd, *J* = 7.3 Hz, 1.2 H), 2.23−2.36 (m, 3.6 H), 2.17−2.23 (m, 2 H), 2.13 (s, 1.8 H), 2.11 (s, 1.2 H), 1.92−2.09 (m, 2.2 H), 1.68−1.78 (m, 1 H), 1.47 (s, 5.4 H), 1.46 (s, 3.6 H), 1.43 (s, 3.6 H), 1.43 (s, 5.4 H), 1.41 (s, 5.4 H), 1.40 (s, 3.6 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.65, 172.11, 171.89, 170.59, 170.47, 169.55, 168.74, 166.96, 166.17, 82.29, 82.25, 81.01, 80.75, 80.74, 80.34, 64.50, 64.48, 58.30, 57.81, 57.69, 53.97, 46.48, 41.71, 41.59, 41.02, 36.61, 36.49, 33.73, 32.50, 31.97, 29.36, 29.29, 28.22, 28.19, 28.18, 28.09, 27.92, 27.92, 26.69, 21.70, 21.39. HRMS (ESI): calcd. for $C_{28}H_{46}N_2NaO_8$ [M + Na]$^+$ 561.3152, found 561.3136. **15b:** The title compound was synthesised according to GP 7 from **14b** (48.4 mg, 0.09 mmol) and obtained as a colourless solid in 33 mg (100%) yield. $[\alpha]_D^{20}$ = +22.5 (*c* = 0.307, H_2O). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers): δ = 5.01 (dd, *J* = 4.1, 10.1 Hz, 0.8 H), 4.73 (dd, *J* = 3.2, 13.5 Hz, 0.2 H), 4.60 (dd, *J* = 5.7, 9.9 Hz, 0.2 H), 4.25 (dd, *J* = 3.2, 14.2 Hz, 0.8 H), 4.15 (d, *J* = 8.5 Hz, 1 H), 3.97 (dt, *J* = 4.1, 11.0 Hz, 0.8 H), 3.82 (dt, *J* = 4.1, 11.0 Hz, 0.2 H), 3.24 (dd, *J* = 10.7, 14.2 Hz, 0.8 H), 2.83 (dd, *J* = 11.0, 13.6 Hz, 0.2 H), 2.49−2.60 (m, 2.4 H), 2.46 (dd, *J* = 6.6, 13.2 Hz, 1.6 H), 2.32−2.43 (m, 2 H), 2.23−2.32 (m, 1 H), 2.20 (s, 2.4 H), 2.19 (s, 0.6 H), 2.09−2.17 (m, 1 H), 2.01−2.09 (m, 1 H), 1.76−1.85 (m, 1 H), 1.43 (dd, *J* = 11.3, 12.7 Hz, 0.8 H), 1.42 (dd, *J* = 7.6, 18.9 Hz, 0.2 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers): δ = 178.20, 177.55, 175.25, 173.24, 169.24, 64.25, 58.94, 58.34, 58.07, 53.93, 45.74, 41.68, 40.69, 35.47, 35.28, 32.18, 30.49, 30.44, 28.05, 26.97, 26.00, 20.93, 20.85. HRMS (ESI): calcd. for $C_{16}H_{23}N_2O_8$ [MH^+] 371.1454, found 371.1458.

(3*S*,6*S*,7*S*,9*S*)-2-Acetyl-7-(2-carboxyethyl)-3-hydroxymethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (15c): Amine **12d** (127 mg, 0.25 mmol) was converted according to GP 7 and purified by column chromatography with ethyl acetate/PE as the eluent to give **14c** as a colourless oil in 78 mg (56%) yield. R_f = 0.40 (ethyl acetate/hexane, 1:4; Mo/Ce). $[\alpha]_D^{20}$ = +6.8 (*c* = 0.785, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 4.97 (dd, *J* = 3.5, 13.2 Hz, 0.6 H), 4.88 (br., 0.4 H), 4.42 (dd, *J* = 2.8, 6.0 Hz, 0.6 H), 4.31 (dd, *J* = 1.9, 20.1 Hz, 0.4 H), 4.04−4.08 (m, 1 H), 3.97−4.01 (m, 1.4 H), 3.92−3.97 (m, 0.6 H), 3.85 (dt, *J* = 3.8, 11.0 Hz, 0.4 H), 3.76 (dt, *J* = 4.1, 11.0 Hz, 0.6 H), 3.61 (dd, *J* = 11.0, 12.9 Hz, 0.4 H), 2.77 (dd, *J* = 11.0, 12.9 Hz, 0.6 H), 2.29−2.34 (m, 2 H), 2.17−2.25 (m, 2 H), 2.15 (s, 1.2 H), 2.14 (s, 1.8 H), 1.94−2.05 (m, 1 H), 1.71 (dt, *J* = 6.9, 13.9 Hz, 1 H), 1.48 (s, 5.4 H), 1.47 (s, 3.6 H), 1.44 (s, 3.6 H), 1.43 (s, 5.4 H), 0.85 (s, 5.4 H), 0.84 (s, 3.6 H), 0.03 (s, 1.5 H), 0.02 (s, 1.5 H), 0.00 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.17, 172.13, 170.69, 169.78, 168.49, 165.44, 164.33, 82.33, 82.20, 80.74, 64.72, 64.57, 64.49, 64.45, 60.42, 58.15, 57.99, 56.62, 49.12, 41.86, 41.72, 41.61, 36.73, 36.71, 33.79, 33.75, 29.56, 29.38, 28.23, 28.12, 25.98, 25.92, 21.86, 21.64, 18.28, 18.22, −5.39, −5.46. HRMS (ESI): calcd. for $C_{28}H_{50}N_2NaO_7Si$ [M + Na]$^+$ 577.3285, found 577.3297. **15c:** The title compound was synthesised according to GP 7 in the presence of 5% H_2O from **14c** (57 mg, 0.1 mmol) and

obtained as a colourless solid in 33 mg (100%) yield. $[\alpha]_D^{20} = +18$ ($c = 0.1$, DMSO). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers and conformers): δ = 4.89 (t, $J = 3.5$ Hz, 0.2 H), 4.84 (dd, $J = 4.7$, 13.6 Hz, 0.2 H), 4.72 (dd, $J = 4.7$, 12.3 Hz, 0.4 H), 4.66 (dd, $J = 3.8$, 6.3 Hz, 0.2 H), 4.54−4.61 (m, 0.7 H), 4.36 (dd, $J = 3.8$, 14.2 Hz, 0.2 H), 4.16−4.27 (m, 1.6 H), 3.95−4.15 (m, 1.2 H), 3.80−3.94 (m, 1 H), 3.41 (dd, $J = 10.7$, 13.9 Hz, 0.4 H), 3.37 (dd, $J = 11.3$, 12.6 Hz, 0.2 H), 3.29 (dd, $J = 11.0$, 12.6 Hz, 0.4 H), 2.93 (dd, $J = 11.0$, 13.6 Hz, 0.2 H), 2.46−2.61 (m, 3 H), 2.33−2.46 (m, 1 H), 2.24 (s, 1 H), 2.20 (s, 0.6 H), 2.15 (s, 1 H), 2.10−2.18 (m, 1 H), 2.10 (s, 0.5 H), 1.83 (ddd, $J = 8.5$, 15.4, 23.9 Hz, 1 H), 1.50−1.59 (m, 0.5 H), 1.38−1.47 (m, 0.5 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers and conformers): δ = 178.21, 174.51, 167.62, 162.67, 64.61, 64.26, 62.78, 62.26, 62.16, 60.62, 58.76, 58.37, 56.90, 55.43, 53.94, 48.42, 42.07, 41.07, 41.60, 41.53, 39.98, 35.44, 35.30, 32.05, 32.12, 27.94, 27.86, 27.74, 21.16, 20.97, 20.35. HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_7$ $[M + Na]^+$ 351.1168, found 351.1183.

General Procedure for the Synthesis of Diazabicycloalkanes 17 (GP 8): A solution of 0.21 mmol of the appropriate amine in dry dichloromethane was cooled to 0 °C under nitrogen and DIPEA (23.4 μL, 0.24 mmol) and benzoyl chloride (28.5 μL, 0.24 mmol) were added. The reaction mixture was stirred for 3 h at this temperature before it was acidified by adding 5 mL of saturated NH_4Cl solution. The resulting mixture was extracted with dichloromethane and the organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude product which was purified by column chromatography to give pure **14**. Compound **14** was dissolved in 50% TFA in dichloromethane and stirred at room temp. for 3 h before the TFA and dichloromethane were removed at reduced pressure to give target structure **17**.

(3*S*,6*S*,7*S*,9*S*)-2-Benzoyl-7-(2-carboxyethyl)-3-carboxymethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (17a): Amine **12b** (100 mg, 0.21 mmol) was converted according to GP 8 and purified by column chromatography with CH_2Cl_2/MeOH as the eluent to give **16a** as a colourless oil in 115 mg (82%) yield. R_f = 0.41 (CH_2Cl_2/MeOH, 98:2; Mo/Ce). $[\alpha]_D^{20} = +48.5$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.47 (m, 5 H), 5.15 (t, $J = 4.1$ Hz, 1 H), 4.08 (d, $J = 8.5$ Hz, 1 H), 3.92 (dd, $J = 2.8$, 12.6 Hz, 1 H), 3.75−3.84 (m, 1 H), 3.54 (t, $J = 12.0$ Hz, 1 H), 3.21 (dd, $J = 4.1$, 16.7 Hz, 1 H), 3.05 (dd, $J = 4.1$, 16.7 Hz, 1 H), 2.29 (t, $J = 7.3$ Hz, 2 H), 2.14−2.24 (m, 1 H), 2.08 (ddd, $J = 5.6$, 6.0, 11.6 Hz, 1 H), 2.03 (ddd, $J = 6.6$, 7.3, 13.9 Hz, 1 H), 1.72 (ddd, $J = 7.3$, 7.9, 13.9 Hz, 1 H), 1.48 (s, 9 H), 1.43 (s, 9 H), 1.42 (s, 9 H), 1.23 (dd, $J = 11.0$, 11.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.15, 130.30, 128.83, 127.24, 82.19, 81.06, 80.71, 64.81, 58.29, 52.04, 49.53, 41.62, 36.52, 36.27, 33.77, 28.93, 28.22, 28.13. HRMS (FAB): calcd. for $C_{32}H_{46}N_2O_8$ $[MH^+]$ 587.3332; found 587.3324. **17a:** The title compound was synthesised according to GP 8 from **16a** (95.0 mg, 0.16 mmol) and obtained as a colourless solid in 67 mg (100%) yield. $[\alpha]_D^{20} = +47.8$ ($c = 0.625$, H_2O). ^{1}H NMR (400 MHz, [D_4]MeOH, mixture of rotamers): δ = 7.42−7.52 (m, 5 H), 5.23 (t, $J = 4.3$ Hz, 0.1 H), 5.16 (t, $J = 4.3$ Hz, 0.9 H), 4.12 (d, $J = 8.7$ Hz, 1 H), 3.97 (dd, $J = 3.3$, 13.2 Hz, 1 H), 3.85−3.94 (m, 1 H), 3.55 (dd, $J = 10.7$, 12.5 Hz, 1 H), 3.15 (dd, $J = 5.1$, 16.5 Hz, 1 H), 3.03 (dd, $J = 4.3$, 16.5 Hz, 1 H), 2.36−3.48 (m, 2 H), 2.25−2.36 (m, 1 H), 2.07−2.21 (m, 2 H), 1.68−1.80 (m, 1 H), 1.22−1.33 (m, 1 H). ^{13}C NMR (100 MHz, [D_4]MeOH): δ = 174.63, 174.38, 173.85, 172.69, 168.06, 136.47, 131.52, 129.92, 128.02, 65.43, 65.36, 59.71, 53.15, 49.85, 42.94, 36.78, 36.25, 32.89, 32.79, 29.64, 29.53. HRMS (FAB): calcd. for $C_{20}H_{23}N_2O_8$ $[MH^+]$: 419.1454; found 419.1454.

(3*S*,6*S*,7*S*,9*S*)-2-Benzoyl-3,7-bis(2-carboxyethyl)-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (17b): Amine **12c** (100 mg, 0.20 mmol) was converted according to GP 8 and purified by column chromatography with ethyl acetate/PE as the eluent to give **16b** as a colourless oil containing minor impurities in 84 mg (70%) yield. R_f = 0.56 (ethyl acetate/hexane, 1:1; Mo/Ce). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 7.34−7.45 (m, 5 H), 5.22 (dd, $J = 5.1$, 8.2 Hz, 0.7 H), 4.94−4.96 (m, 0.3 H), 4.29 (br., 0.3 H), 4.01 (d, $J = 7.9$ Hz, 1 H), 3.98−4.03 (m, 0.3 H), 3.95 (dd, $J = 3.2$, 13.2 Hz, 0.7 H), 3.77 (dt, $J = 4.1$, 14.8 Hz, 0.7 H), 3.07 (dd, $J = 11.0$, 13.2 Hz, 0.7 H), 2.82 (t, $J = 12.0$ Hz, 0.3 H), 2.53−2.62 (m, 0.7 H), 2.31−2.47 (m, 2.3 H), 2.28 (t, $J = 7.3$ Hz, 2 H), 2.10−2.18 (m, 1 H), 2.01−2.10 (m, 2 H), 1.93−2.01 (m, 1 H), 1.64−1.75 (m, 1 H), 1.48 (s, 9 H), 1.41 (br., 18 H), 1.04−1.14 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 173.27, 172.60, 172.08, 170.24, 166.65, 135.42, 130.14, 128.99, 128.85, 126.87, 82.29, 80.73, 80.52, 64.53, 64.36, 58.70, 58.45, 58.02, 53.90, 47.47, 41.75, 41.54, 36.66, 36.45, 33.70, 32.53, 33.26, 29.52, 29.28, 28.22, 28.20, 28.09, 27.17. HRMS (ESI): calcd. for $C_{33}H_{48}N_2NaO_8$ $[M + Na]^+$ 623.3328, found 623.3333. **17a:** The title compound was synthesised according to GP 8 from **16b** (77.3 mg, 0.16 mmol) and obtained as a colourless solid containing minor impurities in 56 mg (100%) yield. ^{1}H NMR (500 MHz, D_2O, mixture of rotmers): δ = 7.46−7.60 (m, 5 H), 5.21 (dd, $J = 4.1$, 10.1 Hz, 0.9 H), 4.90 (dd, $J = 3.5$, 13.2 Hz, 0.1 H), 4.55 (dd, $J = 5.4$, 18.5 Hz, 0.1 H, 6-H), 4.17 (d, $J = 9.9$ Hz, 1 H), 4.06 (dd, $J = 3.5$, 14.2 Hz, 0.9 H), 3.88−3.95 (m, 1 H), 3.29 (dd, $J = 10.8$, 14.2 Hz, 0.9 H), 3.11 (dd, $J = 11.0$, 13.2 Hz, 0.1 H), 2.59−2.67 (m, 2 H), 2.32−2.58 (m, 4 H), 2.18−2.27 (m, 1 H), 2.07−2.17 (m, 2 H), 1.74−1.82 (m, 1 H), 1.33 (dd, $J = 11.7$, 23.3 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O): δ = 178.16, 177.16, 175.24, 173.32, 168.80, 131.03, 129.47, 129.47, 126.65, 64.29, 59.00, 54.28, 46.80, 41.60, 35.19, 32.11, 30.61, 27.97, 26.16. HRMS (ESI): calcd. for $C_{21}H_{24}N_2NaO_8$ $[M + Na]^+$ 455.1430, found 455.1426.

(3*S*,6*S*,7*S*,9*S*)-2-Benzoyl-7-(2-carboxyethyl)-3-hydroxymethyl-4-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic Acid (17c): Amine **12d** (489 mg, 0.95 mmol) was converted according to GP 8 and purified by column chromatography with ethyl acetate/PE as the eluent to give **16c** as a colourless oil in 450 mg (77%) yield. R_f = 0.50 (ethyl acetate/hexane, 1:1; Mo/Ce). $[\alpha]_D^{20} = +87.7$ ($c = 0.93$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; mixture of rotamers): δ = 7.47−7.37 (m, 5 H), 5.05 (s, 0.7 H), 4.99 (dd, $J = 3.7$, 12.8 Hz, 0.3 H), 4.41 (dd, $J = 1.9$, 10.1 Hz, 0.7 H), 4.34 (br. s, 0.3 H), 4.13 (dd, $J = 2.5$, 10.1 Hz, 0.7 H), 4.12−4.09 (m, 0.3 H), 4.08 (d, $J = 7.7$ Hz, 0.7 H), 4.02 (d, $J = 7.7$ Hz, 0.3 H), 3.96 (dd, $J = 3.7$, 12.8 Hz, 0.7 H), 3.95−3.92 (m, 0.3 H), 3.87−3.80 (m, 0.7 H), 3.76 (dd, $J = 2.4$, 10.4 Hz, 0.3 H), 3.56 (dd, $J = 11.0$, 12.9 Hz, 0.7 H), 3.28 (t, $J = 11.7$ Hz, 0.3 H), 2.34 (t, $J = 7.6$ Hz, 0.6 H), 2.29 (t, $J = 7.3$ Hz, 1.4 H), 2.26−2.16 (m, 1 H), 2.12−2.05 (m, 0.7 H), 2.04−1.93 (m, 1 H), 1.75−1.62 (m, 1 H), 1.50 (s, 6.3 H), 1.48 (s, 2.7 H), 1.45 (s, 2.7 H), 1.43 (s, 6.3 H), 1.30−1.19 (m, 1 H), 1.06 (t, $J = 11.4$ Hz, 1 H), 0.87 (s, 9 H), 0.07 (s, 0.9 H), 0.06 (s, 2.1 H), 0.05 (s, 2.1 H), 0.01 (s, 0.9 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.14, 170.76, 165.25, 162.07, 135.82, 130.03, 128.86, 127.08, 126.90, 82.27, 80.72, 64.69, 64.50, 58.30, 56.93, 50.20, 43.48, 41.78, 41.59, 36.69, 33.77, 29.62, 29.53, 28.23, 28.14, 26.01, 18.25, −5.35, −5.40. HRMS (ESI): calcd. for $C_{33}H_{52}N_2NaO_7Si$ $[M + Na]^+$ 639.3441, found 639.3454. **17c:** The title compound was synthesised according to GP 8 from **16c** (67 mg, 0.1 mmol) in the presence of 5% H_2O and obtained as a colourless solid in 42 mg (100%) yield. $[\alpha]_D^{20} = -5.8$ ($c = 0.5$, H_2O). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers and conformers): δ = 7.97−8.00 (m, 0.5 H), 7.71−7.75 (m, 0.5 H), 7.47−7.60 (m, 4 H), 5.10 (dd, $J = 5.0$, 12.9 Hz, 0.4 H),

5.06 (t, J = 3.2 Hz, 0.4 H), 4.94 (dd, J = 3.5, 13.2 Hz, 0.2 H), 4.81−4.83 (m, 0.4 H), 4.69 (dd, J = 2.2, 4.7 Hz, 0.4 H), 4.44−4.48 (m, 0.2 H), 4.17−4.27 (m, 2 H), 4.14 (dd, J = 3.4, 13.5 Hz, 0.4 H), 4.09 (dd, J = 3.2, 12.0 Hz, 0.4 H), 3.92−3.99 (m, 1 H), 3.78 (dd, J = 3.5, 12.3 Hz, 0.2 H), 3.42 (dd, J = 10.7, 13.6 Hz, 0.4 H), 3.36 (dd, J = 11.5, 12.6 Hz, 0.4 H), 3.19 (dd, J = 10.7, 13.2 Hz, 0.2 H), 2.33−2.57 (m, 4 H), 2.13−2.20 (m, 0.5 H), 2.00−2.13 (m, 1 H), 1.68−1.81 (m, 1 H), 1.44 (dd, J = 10.7, 21.7 Hz, 0.5 H), 1.35 (dd, J = 11.6, 23.3 Hz, 0.5 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers and conformers): δ = 167.32, 162.61, 134.43, 134.82, 131.06, 129.83, 129.37, 129.31, 128.61, 126.84, 64.51, 64.32, 64.30, 63.46, 63.34, 58.84, 57.25, 55.37, 54.35, 49.61, 44.49, 41.58, 41.30, 36.27, 35.26, 32.09, 31.97, 28.10, 27.85. HRMS (ESI): calcd. for $C_{19}H_{22}N_2NaO_7$ [M + Na]$^+$ 413.1325 found 413.1325.

General Procedure for the Synthesis of Diazabicycloalkanes 19 (GP 9): A solution of 0.21 mmol of the appropriate amine **12** in 2.5 mL of dry DMF was cooled to 0 °C under nitrogen and a solution of HOBt (28.4 mg, 0.21 mmol) and 6-(*tert*-butoxycarbonylamino)hexanoic acid (57.8 mg, 0.25 mol) in 2.5 mL of dry DMF was added. A solution of DCC (51.4 mg, 0.25 mmol) in 2.5 mL of dry DMF was added to this mixture. The reaction mixture was stirred at 0 °C for 3 h and then left to reach room temp. After 15 h, the solvent was removed under reduced pressure. The resulting solid was dissolved in 10 mL of ethyl acetate and this solution was washed with saturated solutions of $KHSO_4$, $NaHCO_3$, and NaCl. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography to give pure **18**. Compound **18** was dissolved in 50% TFA in dichloromethane and stirred at room temp. for 3 h before the TFA and dichloromethane were removed at reduced pressure to give target structure **19**.

{6-[(3*S*,6*S*,7*S*,9*S*)-6-Carboxy-7-(2-carboxyethyl)-3-carboxymethyl-4-oxohexahydropyrrolo[1,2-*a*]pyrazin-2-yl]-6-oxohexyl}ammonium Trifluoroacetate (19a): Amine **12b** (100 mg, 0.21 mmol) was converted according to GP 9 and purified by column chromatography with ethyl acetate/PE as the eluent to give **18a** as a colourless oil in 69 mg (47%) yield. R_f = 0.47 (ethyl acetate/hexane, 1:1; Mo/Ce). $[\alpha]_D^{20}$ = +30.8 (c = 1.21, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): 4.94 (t, J = 4.7 Hz, 0.5 H), 4.89 (dd, J = 3.5, 13.2 Hz, 0.5 H), 4.77 (dd, J = 5.1, 6.9 Hz, 0.5 H), 4.77 (br., 0.5 H), 4.60 (br., 0.5 H), 4.06 (d, J = 8.2 Hz, 0.5 H), 4.01 (d, J = 7.9 Hz, 0.5 H), 3.96 (dd, J = 3.2, 13.3 Hz, 0.5 H), 3.83 (dt, J = 3.8, 14.8 Hz, 0.5 H), 3.75 (dt, J = 3.9, 15.1 Hz, 0.5 H), 3.51 (dd, J = 9.0, 13.3 Hz, 0.5 H), 3.04−3.14 (m, 2.5 H), 2.86 (dd, J = 4.4, 11.7 Hz, 0.5 H), 2.83 (dd, J = 4.7, 16.4 Hz, 0.5 H), 2.73 (dd, J = 6.6, 15.4 Hz, 0.5 H), 2.61 (dd, J = 10.7, 13.2 Hz, 0.5 H), 2.38−2.51 (m, 1 H), 2.28−2.37 (m, 3 H), 2.13−2.26 (m, 2 H), 1.98−2.09 (m, 1 H), 1.69−1.78 (m, 1 H), 1.58−1.69 (m, 2 H), 1.46 (s, 9 H), 1.43 (s, 4.5 H), 1.42 (s, 9 H), 1.41 (s, 4.5 H), 1.38 (s, 9 H), 1.30−1.38 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.50, 172.17, 172.12, 171.14, 170.80, 170.65, 170.35, 169.47, 166.32, 165.65, 82.29, 82.12, 81.81, 80.88, 80.70, 64.72, 64.50, 58.36, 58.06, 54.65, 52.04, 46.97, 41.73, 41.64, 41.48, 40.47, 40.40, 39.29, 36.79, 36.53, 36.28, 33.79, 33.73, 32.69, 29.97, 29.26, 28.94, 28.55, 28.21, 28.20, 28.14, 28.09, 26.53, 25.73, 25.06, 24.67. HRMS (ESI): calcd. for $C_{36}H_{61}N_3NaO_{10}$ [M + Na]$^+$ 718.4254, found 718.4269. **19a:** The title compound was synthesised according to GP 9 from **18a** (52 mg, 0.07 mmol) as a colourless solid in 39 mg (100%) yield. $[\alpha]_D^{20}$ = +20.2 (c = 0.4675, H_2O). ^{1}H NMR (500 MHz, [D$_6$]DMSO, mixture of rotamers): δ = 12.25 (br., 3 H), 7.66 (br., 3 H), 4.89 (dd, J = 5.7 Hz, 0.7 H), 4.71 (dd, J = 6.0 Hz, 0.3 H), 4.63 (dd, J = 3.4, 12.9 Hz, 0.3 H), 4.14 (dd, J = 3.4, 13.2 Hz, 0.7 H), 3.86 (d, J = 8.5 Hz, 1 H), 3.72−3.78 (m, 0.7 H), 3.50−3.59 (m, 0.3 H), 3.22 (dd, J = 10.7, 13.6 Hz, 0.7 H), 2.70−2.82 (m, 3 H), 2.59−2.68 (m, 1.3 H), 2.50−2.55 (m, 0.6 H), 2.35−2.42 (m, 1.4 H), 2.27−2.34 (m, 2 H), 2.10−2.23 (m, 2 H), 1.91−2.01 (m, 1 H), 1.57−1.65 (m, 1 H), 1.47−1.57 (m, 4 H), 1.20−1.35 (m, 3 H). ^{13}C NMR (100 MHz, DMSO [D$_6$]): δ = 174.04, 172.60, 171.79, 170.67, 165.74, 63.63, 58.44, 51.19, 45.37, 41.17, 38.74, 36.10, 35.18, 32.18, 31.81, 28.04, 26.86, 25.42, 25.96. HRMS (ESI): calcd. for $C_{19}H_{30}N_3O_8$ [MH$^+$] 428.2033, found 428.2014.

{6-[(3*S*,6*S*,7*S*,9*S*)-6-Carboxy-3,7-bis(2-carboxyethyl)-4-oxohexahydropyrrolo[1,2-*a*]pyrazin-2-yl]-6-oxohexyl}ammonium Trifluoroacetate (19b): Amine **12c** (64.6 mg 0.13 mmol) was converted according to GP 9 and purified by column chromatography with ethyl acetate/PE as the eluent to give **18b** as a colourless oil in 69 mg (75%) yield. R_f = 0.26 (ethyl acetate/hexane, 1:1; cerium sulfate). $[\alpha]_D^{20}$ = +15.2 (c = 0.94, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers): δ = 5.07 (dd, J = 4.4, 9.1 Hz, 0.5 H), 4.88 (t, J = 13.3 Hz, 0.5 H), 4.68 (br., 0.5 H), 4.60 (br., 0.5 H), 4.39 (t, J = 6.9 Hz, 0.5 H), 3.97−4.02 (m, 1.5 H), 3.78−3.84 (m, 0.5 H), 3.71−3.77 (m, 0.5 H), 3.03−3.15 (m, 2.5 H), 2.54 (dd, J = 10.7, 13.2 Hz, 0.5 H), 2.35−2.46 (m, 2 H), 2.14−2.34 (m, 6 H), 1.90−2.09 (m, 3 H), 1.70−1.78 (m, 1 H), 1.62−1.69 (m, 2 H), 1.28−1.53 (m, 40 H), 1.15−1.24 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.67, 172.13, 171.95, 170.66, 167.10, 166.24, 82.27, 81.00, 80.76, 80.74, 64.51, 64.41, 58.44, 57.91, 56.89, 53.97, 45.58, 41.73, 41.64, 41.15, 40.47, 36.64, 36.53, 33.75, 33.36, 32.58, 32.00, 30.01, 29.43, 29.33, 28.58, 28.24, 28.21, 28.12, 27.97, 26.89, 26.63, 25.05, 24.63. HRMS (FAB): calcd. for $C_{37}H_{63}N_3NaO_{10}$ [M + Na]$^+$ 732.4411, found 732.4437. **19b:** The title compound was synthesised according to GP 9 from **18b** (50 mg, 0.07 mmol) as a colourless solid in 39 mg (100%) yield. $[\alpha]_D^{20}$ = +28.3 (c = 0.555, H_2O). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers): δ = 5.06 (dd, 0.7 H, J = 10.1, 4.1 Hz), 4.73−4.77 (m, 0.3 H), 4.65 (dd, 0.3 H, J = 5.4, 9.1 Hz), 4.30 (dd, 0.7 H, J = 3.2, 14.5 Hz), 4.16 (d, J = 8.8 Hz, 1 H), 3.91−3.98 (m, 0.7 H), 3.76−3.84 (m, 0.3 H), 3.24 (dd, 0.7 H, J = 11.1, 14.5 Hz), 2.98−3.04 (m, 2 H), 2.86 (dd, 0.3 H, J = 10.7, 13.6 Hz), 2.20−2.64 (m, 9 H), 2.02−2.18 (m, 2 H), 1.77−1.87 (m, 1 H), 1.68−1.74 (m, 2 H), 1.61−1.68 (m, 2 H), 1.39−1.47 (m, 3 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers): δ = 178.22, 169.34, 64.24, 59.13, 58.54 (C-5), 57.31 (C-8), 53.97 (C-8), 45.02 (C-6), 41.69 (C-3), 41.00 (C-6), 39.67 (C-22), 35.50 (C-4), 35.30 (C-4), 32.85 (C-11), 32.18 (C-15), 30.47 (C-18), 28.05 (C-14), 26.87 (C-21), 25.97 (C-10), 25.65 (C-20), 24.38 (C-19). HRMS (ESI): calcd. for $C_{20}H_{32}N_3O_8$ [MH$^+$] 442.2189, found 442.2204.

6-[(3*S*,6*S*,7*S*,9*S*)-6-Carboxy-7-(2-carboxyethyl)-3-hydroxymethyl-4-oxohexahydropyrrolo[1,2-*a*]pyrazin-2-yl]-6-oxohexylammonium Trifluoroacetate (19c): Amine **12d** (107 mg, 0.21 mmol) was converted according to GP 9 and purified by column chromatography with ethyl acetate/PE as the eluent to give **18c** as a colourless oil in 72 mg (48%) yield. R_f = 0.29 (ethyl acetate/hexane, 1:1; cerium sulfate). $[\alpha]_D^{20}$ = +21.8 (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ = 4.97 (dd, J = 3.8, 12.7 Hz, 0.5 H), 4.90 (br., 0.5 H), 4.46 (dd, J = 2.8, 5.9 Hz, 0.5 H), 4.31 (dd, J = 2.0, 10.2 Hz, 0.5 H), 3.90−4.12 (m, 3 H), 3.79−3.88 (m, 0.5 H), 3.70−3.78 (m, 0.5 H), 3.58 (dd, J = 10.9, 13.2 Hz, 0.5 H), 3.05−3.16 (m, 2 H), 2.80 (dd, J = 10.5, 13.0 Hz, 0.5 H), 2.29−2.40 (m, 4 H), 2.15−2.26 (m, 2 H), 1.97−2.06 (m, 1 H), 1.62−1.75 (m, 3 H), 1.46−1.56 (m, 2 H), 1.48 (s, 4.5 H), 1.48 (s, 1.5 H), 1.44 (s, 4.5 H), 1.44 (s, 9 H), 1.44 (s, 4.5 H), 1.30−1.40 (m, 2 H), 1.10−1.22 (m, 1 H), 0.85 (s, 4.5 H), 0.64 (s, 4.5 H), 0.03 (s, 1.5 H), 0.02 (s, 1.5

H), 0.00 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 172.13, 170.71, 170.47, 165.56, 164.38, 82.30, 82.20, 80.72, 64.71, 64.64, 64.48, 64.42, 59.57, 58.24, 58.04, 56.66, 48.22, 42.01, 41.68, 41.59, 40.50, 36.72, 36.68, 33.73, 33.52, 33.06, 30.05, 29.98, 29.53, 29.39, 28.54, 28.21, 28.08, 26.66, 26.60, 25.96, 25.89, 25.72, 25.04, −5.57. HRMS (ESI): calcd. for $C_{37}H_{67}N_3NaO_9Si$ [M + Na]$^+$ 748.4544, found 748.4504. **19c:** The title compound was synthesised according to GP 9 from **18c** (36 mg, 0.05 mmol) as a colourless solid in 25 mg (100%) yield. $[\alpha]_D^{20}$ = +4.8 (*c* = 1.26, H_2O). ^{1}H NMR (500 MHz, D_2O, mixture of rotamers/conformers): δ = 4.91 (dd, *J* = 3.0 Hz, 0.3 H), 4.86 (dd, *J* = 3.5, 13.6 Hz, 0.2 H), 4.76−4.81 (m, 0.5 H), 4.70 (dd, *J* = 3.5, 6.3 Hz, 0.2 H), 4.53−4.58 (m, 0.7 H), 4.40 (dd, *J* = 3.5, 13.9 Hz, 0.3 H), 4.31−4.36 (m, 0.3 H), 4.16−4.25 (m, 1.3 H), 4.13 (dd, *J* = 3.5, 13.0 Hz, 0.3 H), 3.87−4.07 (m, 1.7 H), 3.76−3.87 (m, 0.3 H), 3.40 (dd, *J* = 10.7, 13.9 Hz, 0.3 H), 3.28 (dd, *J* = 12.0, 13.9 Hz, 0.5 H), 2.97−3.03 (m, 2 H), 2.93 (dd, *J* = 12.9 Hz, 11.4 Hz, 0.2 H), 2.45−2.63 (m, 4.3 H), 2.32−2.45 (m, 1 H), 2.13 (dt, *J* = 6.5, 13.2 Hz, 1 H), 1.76−2.06 (m, 2 H), 1.60−1.75 (m, 4 H), 1.29−1.54 (m, 3 H). ^{13}C NMR (100 MHz, D_2O, mixture of rotamers/conformers): δ = 162.71, 64.66, 64.24, 63.05, 62.31, 62.25, 59.91, 58.95, 58.53, 56.93, 55.43, 53.97, 47.76, 44.57, 42.09, 41.63, 41.41, 39.64, 36.17, 35.46, 35.32, 33.48, 33.04, 32.51, 32.12, 32.05, 27.96, 27.87, 26.85, 26.79, 25.58, 25.40, 24.48, 24.40, 23.96. HRMS (ESI): calcd. for $C_{18}H_{30}N_3O_7$ [MH$^+$] 400.2084, found 400.2100.

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