Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 2213–2224

Anomeric spiroannelated 1,4-diazepine 2,5-diones from furano *exo*-glycals: towards a new class of spironucleosides

Claude Taillefumier,* Sabine Thielges and Yves Chapleur

Groupe SUCRES, UMR 7565 CNRS-Université Henri Poincaré-Nancy 1, BP 239, F-54506 Nancy-Vandoeuvre, France

Received 24 October 2003; revised 13 January 2004; accepted 14 January 2004

Abstract—The first synthesis of 1,4-diazepine 2,5-dione peptides containing a β-amino acid in which the β carbon is also the anomeric carbon of a furanoid sugar is described. These new anomeric spirosugars obtained with a stereoselective control in the D-*gulo*, D-*manno*, D-*allo* and D-*ribo* series can be regarded as the first members of a new class of spironucleosides. In the course of our study, two symmetrical tetrameric cyclopeptides comprising two identical sugar β-amino acid and α-amino acid residues were also isolated, these structures could be of interest as new potential host molecules.

1. Introduction

Anomeric spironucleosides are defined as structurally modified nucleosides in which the base unit at the anomeric position is spiro to the sugar moiety. That is when the anomeric carbon belongs to both the sugar and the heterocyclic base. This results in a locked conformation around the *N*-glycosidic bond. This specific conformation in comparison with that of the natural nucleoside, results in modifications of the direction of the hydrogen bonding pattern of the nucleobase and made these compounds good probes to study nucleoside and nucleobase catabolism.

In the last decade, spironucleosides have attracted much attention with the discovery in 1990 of (+)-hydantocidin, the first natural spironucleoside isolated from the culture broth of *Streptomyces hygroscopicus* SANK 63584,[1a] Tu-2474,[1b] and A1491.[1c] However, this class of compounds was known long before the term spironucleoside came into current use.[2] In addition to a unique structure that is a spirohydantoin at the anomeric position of a ribofuranose, (+)-hydantocidin displays both a plant growth regulatory and a strong herbicidal activities against weeds with no toxicity to microorganisms and mammals. This interesting biological profile has prompted many groups to propose total synthesis[3] of this spironucleoside or formal synthesis[4] by preparing the key intermediate that is a fused glycine at the anomeric position of ribofuranose. 1-*epi*hydantocidin[5] as well as all the other stereoisomers[6] some deoxy derivatives[7] and carbocyclic analogues[8] of (+)-hydantocidin were also prepared in order to study the structure–activity-relationship of this class of derivatives. Spirohydantoins of other sugars than ribose were also synthesised in the hope of discovering interesting biological properties.[9] The discovery in 1995 that the glucopyranose analogue[10] **1** is a powerful inhibitor of glycogen phosphorylase has then stimulated the synthesis of hexopyranose analogues[11] of spiro-hydantoins as well as some hexofuranose analogues.[12] Other heterocyclic units than the hydantoin ring have also been incorporated at the anomeric position of sugars to give rise to other classes of spironucleosides.[13] First of all, some thiohydantoin[3d,11b,14] derivatives have been synthesised, mainly in connection with their potent inhibitory activity against glycogen phosphorylase enzymes.[15] A wide range of anomeric spirodiketopiperazines[11a,12a,16] have also been prepared among them the spirodiketopiperazine of glucopyranose **2**[17] is a specific inhibitor of glycogen phosphorylase. The spirodihydrouracile derivative **3**[18] which formally results from the insertion of a methylene group between the anomeric carbon and the nitrogen of the *N*-glycosidic bond of (+)-hydantocidin was designed to study the direction of the hydrogen bonding of the hydantoin part in the natural parent molecule. As representative spironucleoside one can also mention derivatives containing the barbiturate ring system exemplified by the compounds **4**.[19] Intramolecular radical-based cyclisation between the anomeric centre and the nucleobase of modified nucleoside has also been studied and leads to spironucleosides featuring a bicyclic nucleobase spiro to the anomeric centre of the sugar moiety (Fig. 1).[20]

The synthesis and testing of ring-expanded analogues of purine and pyrimidine nucleosides, the so-called 'fat'

Keywords: *exo*-Glycals; Sugar-amino acids; Spironucleosides; Peptidomimetics.
* Corresponding author. Tel.: +33-383-68-47-77; fax: +33-383-68-47-80; e-mail address: claude.taillefumier@sucres.uhp-nancy.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.01.030

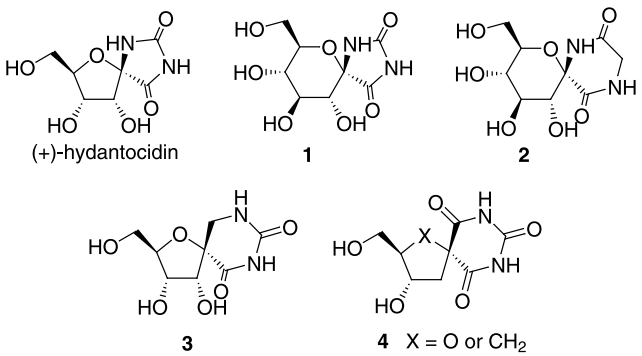


Figure 1. Representative spiroannelated sugar-heterocycles related to spironucleosides.

nucleosides is well documented in the literature. All of these can act as inhibitors of nucleoside and nucleobase catabolic pathways. A wide range of analogues of purine nucleoside containing the 5,7-fused-imidazo[1,3]-diazepine[21] or the 5,7-fused-imidazo[1,4]-diazepine[22] ring systems have been synthesised and possess antiviral and anticancer in vitro activities.[23] Among seven-membered pyrimidine-like nucleosides one can mention 1,3-diazepine-2-one nucleosides[24] and 1,4-diazepine nucleosides.[25] Seven-membered diaza-heterocycle systems not attached by the anomeric carbon of a sugar unit has also been reported in the literature.[26] On the other hand, only few papers report on the preparation of sugar derived annelated (di)azepine derivatives.[27] Herein we wish to report the first synthesis of spiro 1,4-diazepine 2,5-dione heterocycles at the anomeric position of furano sugars. To the best of our knowledge, these new derivatives represented by the generic structure **B** (Fig. 2) are the first anomeric spiroannelated glycodiazepine derivatives.[28]

Our approach toward the spiro diazepinedione-sugar system relies on the coupling of the anomeric amine of the generic structure **A** with α-amino acids to afford dipeptides, followed in turn by ring closure, the crucial stage, to produce the 1,4-diazepin-2,5-dione ring. Indeed the seven-membered ring diazepine dione formation is entropically disfavoured compared to the formation of both the hydantoin cycle or the diketopiperazine cycle which are often spontaneous processes. Therefore, our approach to the design of anomeric spiro diazepinedione–sugar template entails a ready preparation of the anomeric β-amino acids esters **A**. Their synthesis is easily accomplished in a few steps starting from sugar-derived lactone as it was reported in a previous communication.[29] First, sugar lactones are submitted to a Wittig reaction following the procedure

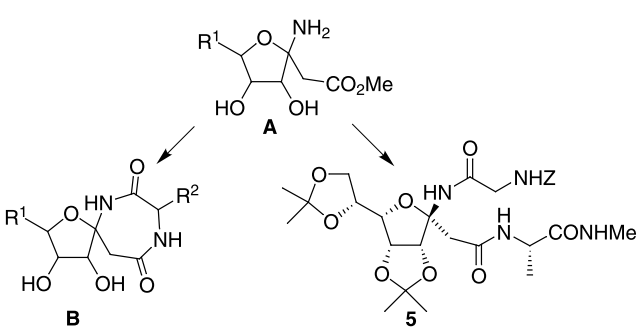


Figure 2.

developed in our group[30] to afford *exo*-glycals[31] functionalised with a carboxylic function. The amino function is then introduced by a 1,4-addition process on the activated anomeric olefins. In our previous communication, we have presented the stereoselective synthesis of compound **5** to outline the synthetic possibilities of structures **A**. Herein we give a full account on the preparation of the glycosyl β-amino esters **A** in the D-*gulo*, D-*manno*, D-*allo* and D-*ribo* series as well as on their elaboration into spirocyclic derivatives **B**.

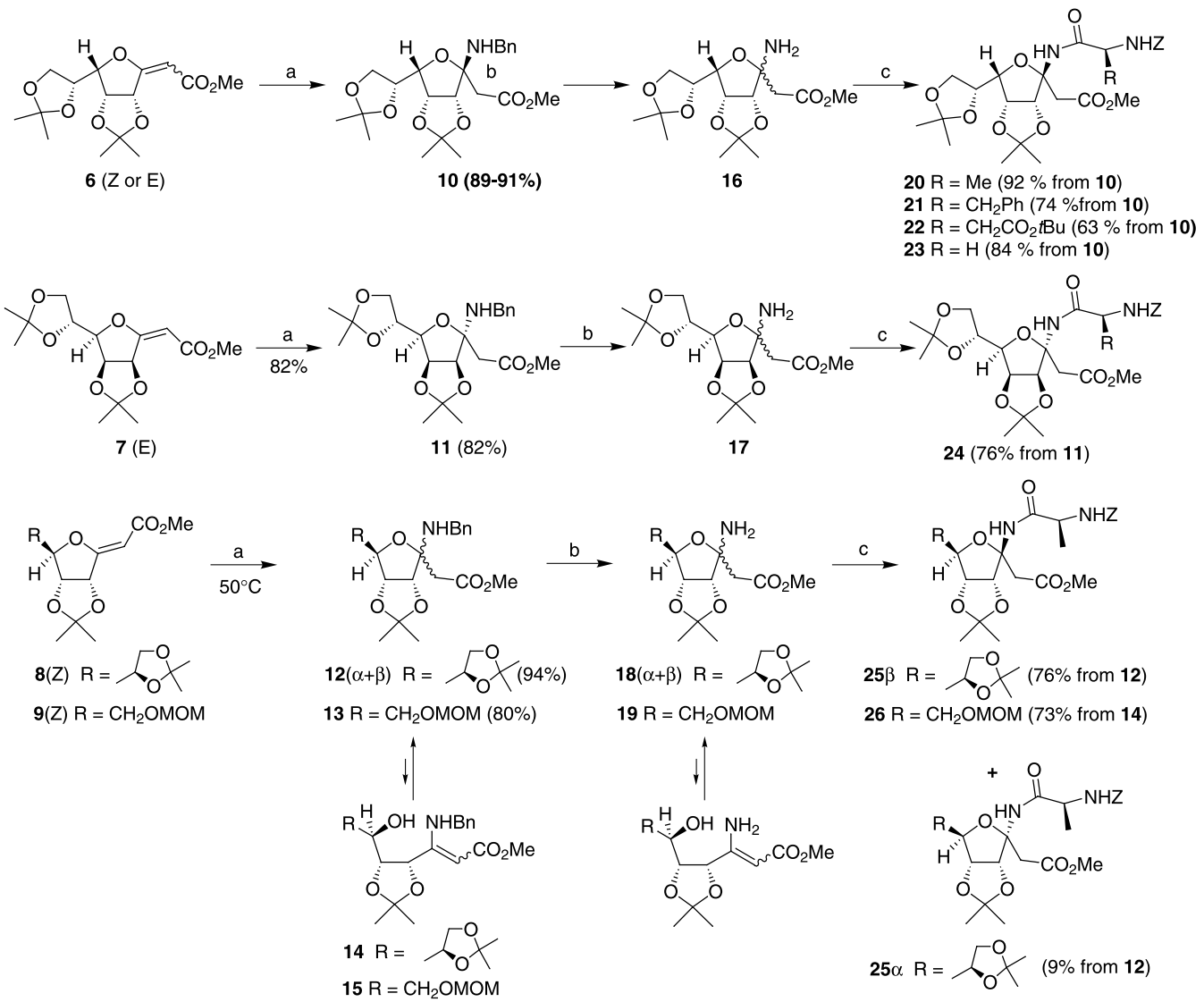
2. Results and discussion

exo-Glycals **6** (D-*gulo*), **7** (D-*manno*) prepared from the corresponding protected sugar lactones by a Wittig reaction, have already been described by us.[30a] The same procedure ($Ph_3P{=}CHCO_2Me$, 2 equiv., toluene, 140 °C, 17 h, stainless sealed vessel) was applied to 2,3-5,6-di-*O*-isopropylidene-D-*allono*-1,4-lactone and to 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-D-*ribono*-1,4-lactone to afford the olefinated sugars **8** (*E*/*Z* 1:2) and **9** (*E*/*Z* 1:2.4) in, respectively, 74 and 79% (based on 19% of recovered starting material) yield. The stereoselective synthesis of β-amino esters by 1,4-addition of a nitrogen nucleophile onto α,β-unsaturated esters is a well known approach that we envisioned to explore with the *exo*-glycals previously prepared. *exo*-Glycals have been recently regarded as Michael acceptors but only with oxygenated nucleophiles.[32] Our first attempt to react sodium azide with the olefin **6** in DMF was unsuccessful. Considering that a benzyl group is easily removed by hydrogenolysis, the aza-Michael addition of benzylamine on **6** was explored. After stirring for two days in neat benzylamine only one stereoisomer **10** was formed in 90% isolated yield as shown by the ^{1}H NMR spectrum of the addition product after silica gel chromatography. Later, in the course of another experiment the ^{1}H NMR of the crude confirmed the presence of only one stereoisomer **10**. The configuration of the anomeric centre was firmly established by X-ray crystallography and NOE measurements. Not surprisingly the benzylamino group is in *trans* relationship to all the substituents of the tetrahydrofuran ring. This stereoselectivity can certainly be explained in term of the approach of the nucleophile by the non-crowded face of the sugar. Heating of the reaction mixture resulted in the isolation of the same isomer **10**, indicating that this less hindered amine is the thermodynamically more stable anomer. The same reaction was conducted on the activated *manno* olefin **7** resulting again in the formation (82%) of only one stereoisomer **11** having the benzylamino group *trans* to all the other substituents. The reaction of benzylamine with **8** having two crowded faces was next examined. In this case a gentle heating at 50 °C of the reaction mixture was necessary to ensure a complete conversion of the starting material affording **12** in 94% yield. ^{1}H NMR of the crude proved quite complex. The doublet of the AB system corresponding to the two H-2 protons (ulosonic numbering) indicated the presence of two stereoisomers **12α** and **12β** along with a third minor compound identified as the enamino ester **14**. It should be noted that such enamino esters have been obtained exclusively or as the major compounds when applying the benzylamine addition procedure to pyrano *exo*-glycals,

these open chain sugars were fully characterised as their acetate.[29] Compounds **12**α and **12β** were inseparable by chromatography indicating a rapid equilibrium probably via the enamino ester **14**. A same behavior was observed upon addition of $BnNH_2$ to the *ribo exo*-glycal **9**, the adduct is obtained as an inseparable mixture of **13** (α/β) and **15**.

The benzyl group of all the *N*-benzyl β-amino esters previously synthesised was removed at normal atmospheric pressure of hydrogen in ethyl acetate using 10% palladium on charcoal as catalyst, to yield the anomeric amines **16**, **17**, **18** and **19** as inseparable mixtures of α and β stereoisomers. One can conclude that the equilibrium between α and β isomers is very fast, this fact is well known with amino glycosides, however studies in Fleet's group have shown that some α-amino esters at the anomeric position of sugars are stable enough to be isolate in pure form using non-protic solvents.[16c]

Coupling of the free amine **16** with a series of *N*-benzyloxycarbonyl α-amino acids (*Z*-GlyOH, *Z*-AlaOH, *Z*-PheOH, *Z*-Asp(O*t*Bu)OH) using PyBOP as coupling reagent was next envisaged. Good to excellent yields (63–92%, two steps) of the corresponding isolated dipeptides **20**–**23** were obtained as shown in Scheme 1. *N*-*tert*-Butyloxycarbonyl amino acids were also tested in the coupling reaction, although the results in term of yield, were similar to that of *Z*-amino acids the latter were preferred because of incompatible condition of deprotection of the BOC group in presence of acetonides. Interestingly, starting from a α/β sugar-amino ester mixture, dipeptides were formed as a unique stereoisomer whatever the nature of the α-amino acid used. For each dipeptide the stereochemistry at the anomeric centre was established by NOE measurements. A NOE was systematically observed between the anomeric NH and H-4 indicating these two protons are on the same face of the molecule. In other words, the anomeric nitrogen is still in an *anti* relationship to the 4,5-fused acetonide (ulosonic numbering). It thus appears that under the coupling conditions, the β-amino ester **16** equilibrate more rapidly than it is acylated and that the less hindered amine β is acylated faster than the α isomer. A similar result

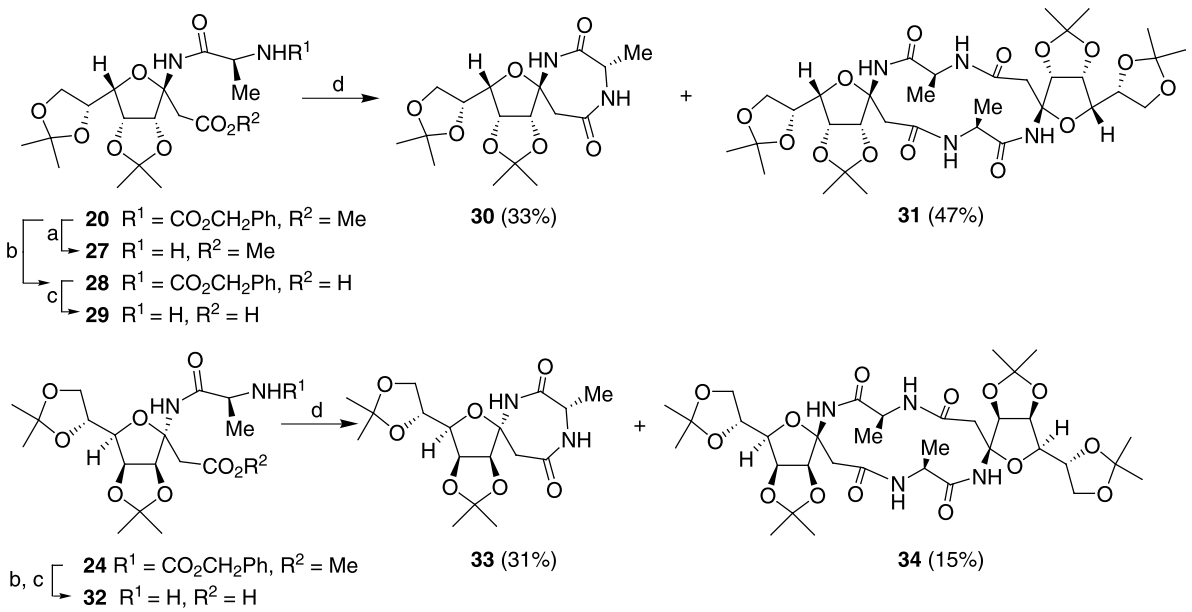


Scheme 1. (a) Neat $BnNH_2$, 48 h; (b) H_2/1 atm, 10% Pd–C, EtOAc; (c) *Z*-X-OH (1.1 equiv.), PyBOP (1.1 equiv.), Et_3N (1.1 equiv.), DMF, room temperature, 14 h.

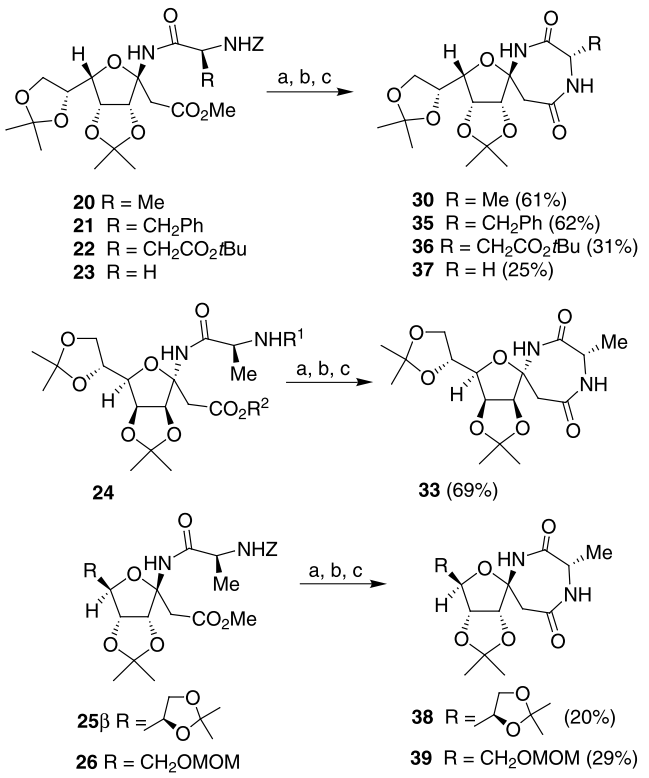
was observed when coupling the amine **17** (*manno* configuration) with *Z*-AlaOH, a single stereoisomer **24** was isolated in 76% yield (two steps). Once more the behaviour of the *allo* derivative was different in the sense that two stereoisomers were formed, **25β** and **25α** in, respectively, 76 and 9% yield. In identical acylating reaction conditions, the *ribo* compound **26** was isolated as a single isomer from **19**. Having in hands a series of fused anomeric dipeptides, we were ready to investigate their ring closure into diazepinediones. We first envisioned the direct reaction of an unmasked amine onto the ester function under basic or heat conditions. Toward this end the benzyloxycarbonyl group of **20** was removed under catalytic hydrogenation conditions to afford the amino ester **27**. Unfortunately, cyclisation of **27** proved unsuccessful when the reaction was either heated or treated with TBAF as a base. Attempt to perform cyclisation under microwave irradiation was also unsuccessful. Our attention therefore turned toward classical peptide chemistry involving the activation of the carboxylic function. From experimental considerations, it seemed to us easier to hydrolyse the ester function prior to remove the benzyloxycarbonyl group and then to cyclise. Employing potassium carbonate (K_2CO_3) in methanol and water at room temperature resulted in smooth formation of the carboxylic acid **28** from **20**, removal of the *Z* group of **28** under catalytic hydrogenation in ethyl acetate/ethanol using 10% palladium on charcoal at normal pressure gave **29** as a very clean compound as shown by ^{1}H NMR of the crude. Among the numerous coupling reagents available for amide bond formation DPPA[33] (diphenylphosphoryl azide) and HATU[34] (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) are often used for small ring formation and as a result were chosen for the lactamisation step. Unexpectedly our first attempt to cyclise compound **29** using DPPA and TEA in DMF at 30 mM concentration gave two products which were separated by column chromatography. HATU/DIPEA-mediated cyclisation in DMF at the same concentration resulted in the same mixture of compounds. The minor compound isolated as a foam in 33% yield (three steps) was clearly identified as the expected spiro-diazepinedione **30**. This compound was fully characterised by NMR, IR and MS spectra. Careful analysis of all the spectroscopic data for the major product (47% yield) established its structure as the hybrid tetrameric cyclopeptide **31**, the latter resulting from the dimerisation of the starting dipeptide. In the mass spectrum (EI+) the highest *m/z* matches the expected molecular ion for the structure **31**. Because of a poor solubility in chloroform, the cyclic dimer was characterized by NMR spectroscopy in DMSO, as expected the ^{1}H NMR spectrum at 298 K indicates a symmetrical conformation. A similar outcome cyclisation was observed with the deprotected *manno* dipeptide **32** prepared from **24**. The expected diazepinedione **33** (31%) was accompanied by the dimeric compound **34** (15%). An attempt to work at a higher concentration in order to move the reaction exclusively or at least in a large proportion to the tetrameric compound was unsuccessful. The synthesis and conformational analysis of cyclic oligomers and homooligomers of sugar amino acids have been investigated recently, this type of structures being of interest as new potential host molecules.[35] However, to the best of our knowledge, compounds **31** and **34** would be the first structures of this type in which the sugar moieties are spiro to the peptide chain (Scheme 2).

Following our aim that is the preparation of spiro-diazepine diones and considering that a higher dilution would avoid the dimerisation of the sugar-dipeptide, cyclisation of **29** at a concentration of 2.5 mM in DMF using diphenyl phosphorazidate activation was next attempted (Scheme 3). In this way, compound **31** was still located on TLC but as a very minor component which was not taken out of the column and the spiro-diazepine diones **30** was isolated in 61% yield.

Following the same route, i.e., saponification of the methyl ester, hydrogenolysis of the *Z* group and DPPA base cyclisation (2.5 mM in DMF) the following dipeptides **21**, **22** and **23** in the D-*gulo* series were transformed respectively



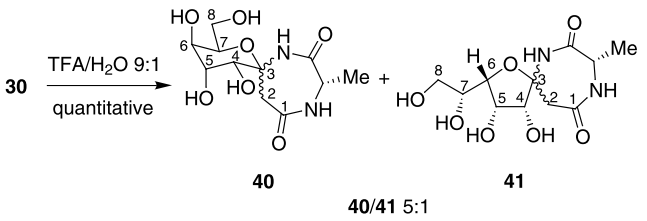
Scheme 2. (a) H_2/1 atm, 10% Pd–C, EtOAc; (b) K_2CO_3 (1.1 equiv.), MeOH/H_2O: 10/1, room temperature, 48 h; (c) H_2/1 atm, 10% Pd–C, EtOH/EtOAc: 1.5/1; (d) DPPA (1.2 equiv.); Et_3N (2 equiv.), DMF (33 ml/mmol), 0 °C to room temperature; 14 h.



Scheme 3. (a) K_2CO_3 (1.1 equiv.), MeOH/H_2O: 10/1, room temperature, 48 h; (c) H_2/1 atm, 10% Pd–C, EtOH/EtOAc: 1.5/1; (d) DPPA (1.2 equiv.); Et_3N (2 equiv.), DMF (400 ml/mmol), 0 °C to room temperature; 14 h.

in **35** (62%), **36** (31%) and **37** (25%). The same route was also applied to the *manno*, *allo* and *ribo* sugar-dipeptides **24**, **25β** and **26**, that were, respectively, transformed into **33** (69%), **38** (20%) and **39** (29%). All these results deserve few comments. It should be noted that the yields are very dependent on the configuration of the sugar as well as the nature of the α-amino acid linked to the anomeric centre. One can compare the yields of cyclisation when the α-amino acid is alanine for the four configurations, D-*gulo*, D-*manno*, D-*allo* and D-*ribo*. Similar yields between 61 and 69% yields are obtained in the D-*gulo* and the D-*manno* series which have both a non-crowded face and as a consequence exactly the same conformation of the tetrahydrofuran sugar ring. The cyclisation of the *allo* and *ribo* compounds **25β** and **26** possessing two crowded faces are by far less efficient, only 20 and 29% yields. Moreover, the crude of these reactions proved to be very difficult to purify. Existence of a long trail on TLC suggested that a polymerisation has occurred prior to the cyclisation. In the D-gulo series, the best yield of cyclisation is obtained with the alanine containing dipeptide, one can say that the presence of a substituent on the α-amino acid seems to promote the ring closure since the lowest yield is obtained with glycine. However the ring closure efficiency decreases dramatically with the Boc-protected aspartic acid containing dipeptide **22** showing that a two bulky group on the lateral chain is unfavourable for the cyclisation.

Removal of the isopropylidene acetal groups of the various sugar-diazepinediones was next envisioned. Deprotection of the acetonides of **30** was obtained quantitatively by treatment with 90% v/v TFA in water. However the ^1H NMR spectrum of the crude showed a splitting of most of the signals indicating the presence of two major compounds. Purification using reversed-phase high performance liquid chromatography led to one compound which was pure enough to be fully analysed by NMR in D_2O. It is noteworthy that in the ^1H NMR the AB system corresponding to the two H-2 protons has almost disappeared indicating a rapid exchange of these protons. That was confirmed in the ^{13}C, the carbon bearing these two exchangeable protons appearing in the base line as a multiplet. A HMBC map was used to determine whether the sugar part of the molecule was in the starting furanose form or in a pyranose form: a cross-peak was found between H-7 (4.11 ppm) and C-3 (98.4) and none between H-6 (3.80) and C-3. This is only possible in a pyranose ring. The second major compound that could not be isolated pure showed a ^1H NMR pattern almost superimposable to the former, consequently we concluded that the two major compounds of the initial mixture are the α and β anomers of the pyranose derivative **40**. A 2D-COSY spectrum of the mixture allowed us to locate four sets of well-separated AB systems corresponding to H-2 protons, two of them belonging to each of the derivatives **40**, the others were tentatively assigned to the furanose derivatives **41**. The isomerisation to gulopyranose isomers observed in this reaction implies a ring opening of the furanose into an imine and/or enamine intermediate, which is then trapped by the C-7 secondary hydroxyl group to give gulopyranose isomers. Using less acidic conditions and heating for the deprotection step (AcOH/H_2O 7:3, 70 °C or MeOH/H_2O 1:1, IR 120 H^+, 65 °C) resulted again in isomerisation to pyranose compounds. These last reactions under typically equilibration conditions should indicate that the pyranodiazepines are thermodynamically more stable than the furano-isomers. In view of the difficulties encountered to obtain pure compounds for the deprotection of **30**, we decided to keep the other sugar-diazepinediones in their protected form (Scheme 4).



Scheme 4. Deprotection of **30**, the ulosonic numbering depicted in this scheme has been used for NMR assignments.

3. Summary

In summary, starting from furano *exo*-glycals, we have developed a straightforward route to novel anomeric spiro sugar-heterocycles related to spironucleosides. These structures that have 1,4-diazepine 2,5-dione seven-membered rings spiro at the anomeric centre of furanoses are reported for the first time. These new compounds bearing a ring-expanded nucleobase can be regarded as the first fat spironucleosides. Removal of the acetonides of **30** under different hydrolysis conditions resulted in the isomerisation to pyranose isomers. This isomerisation process implies a

ring opening and reclosing of an intermediate imine/enamine to the more thermodynamically spiro[5,6] pyranose isomer. In the course of our study two symmetrical tetrameric cyclopeptides **31** and **34** containing two sugar units spiro to the peptide chain were also isolated and characterised. To the best of our knowledge such new spiro templates have no precedent in the literature. We are currently exploring the use of these compounds as biological tools and as peptidomimetic scaffolds.

4. Experimental

4.1. General

General indications. FTIR spectra were recorded on Perkin–Elmer Spectrum 1000 on NaCl windows or KBr pellets. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker AC 250 or on a Bruker DRX 400 spectrometer. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz (Hz). Multiplicities of NMR signals are designed as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines). ^{1}H assignments were confirmed by homonuclear 2D COSY correlated experiments. Attribution of ^{13}C signals are based on the *J*-modulated spin-echo sequence and/or heteronuclear two-dimensional techniques. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were recorded on a Trio 1000 Thermo Quest spectrometer in the electron impact mode or a Platform Micromass spectrometer in the electro spray mode. Specific rotations were determined on a Perkin–Elmer 141 polarimeter (10 cm cell). Elemental analyses were obtained with a Thermofinnigan Flash EA 1112 apparatus. Analytical thin-layer chromatography was performed on Merck 60 F_{254} pre-coated silica gel plates. Compounds were visualized with UV light and (or) 30% methanolic H_2SO_4-heat as developing agent. Preparative chromatography was performed on silica gel 60 (230–40 mesh ASTM). Reverse phase HPLC was performed with a Gilson 321 apparatus equipped with a C18 chromasil column. Detection was carried out using a Polymer Laboratories evaporator light scattering 1000 (PL ELS 1000). Melting points were determined in capillaries on a Tottoli apparatus and are uncorrected.

4.2. General method of 1,4-addition of benzylamine to *exo*-glycals 6–9

The *exo*-glycal was dissolved in freshly distilled benzylamine (1 ml/mmol) and the solution was stirred at room temperature until TLC indicated the complete consumption of the starting material (typically between 24 and 48 h). In the case of olefins **8** and **9** a smooth heating at 50 °C was applied to ensure a complete conversion of the starting material. The reaction mixture was then diluted with Et_2O and washed successively with aq. 5 mM H_2SO_4 till slightly acidic pH, saturated aq. $NaHCO_3$ and brine. After drying (Na_2SO_4), filtration and evaporation the crude was chromatographed over silica gel.

4.2.1. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 10. Compound **10** (1.44 g) was synthesised from **6** (1.17 g, 3.72 mmol) in 91% yield, following the general procedure described above and silica gel chromatography with 30% EtOAc in hexane. R_f 0.7 (silica gel, 50% EtOAc in hexane); mp 123 °C; $[\alpha]_D^{26}=-9.6$ (c 0.9 $CHCl_3$); ν_{max} (KBr) 3357 (NH), 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.45 (br s, 6H, 2×CH_3), 2.10–2.23 (m, 1H, NH), 2.94 (d, 1H, J_{gem}=17.5 Hz, H-2), 3.14 (d, 1H, J_{gem}=17.5 Hz, H′-2), 3.65–3.88 (m, 6H, H-8, CO_2CH_3 and CH_2Ph), 4.06 (dd, 1H, $J_{5,6}$=4.4 Hz, $J_{6,7}$=8.0 Hz, H-6), 4.21 (dd, 1H, J_{gem}=8.0 Hz, $J_{7,8'}$=6.5 Hz, H′-8), 4.40 (m, 1H, H-7), 4.45 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.72 (dd, 1H, $J_{5,6}$=4.4 Hz, $J_{4,5}$=5.8 Hz, H-5), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 171.5 (C=O), 140.3 (C_{ipso}), 128.4–126.8 (5C, Ar), 112.7 (acetal), 109.6 (acetal), 95.1 (C-3), 85.9, 81.0, 80.9, 75.5 (4C, C-4, C-5, C-6, C-7), 66.1 (C-8), 51.5 (CO_2CH_3), 45.1 (CH_2Ph), 34.8 (C-2), 26.8, 26.0, 25.3, 24.8 (4×CH_3). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.73; H, 7.37; N, 3.36.

4.2.2. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-α-D-*manno*-3-octulofuranosonic acid, methyl ester, 11. Compound **11** (2.14 g) was synthesised from **6** (1.95 g, 6.20 mmol) in 82% yield, following the general procedure of 1,4-addition described above and silica gel chromatography with 20% EtOAc in hexane. R_f 0.5 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{22}=-4.7$ (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.22 (m, 5H, Ar), 4.73 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.45 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.40 (m, 1H, H-7), 4.22 (dd, 1H, J_{gem}=8.6 Hz, $J_{7,8}$=6.7 Hz, H-8), 4.07 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.6 Hz, H-6), 3.82 (d, 1H, J_{gem}=12.8 Hz, C*H*HPh), 3.75 (dd, 1H, J_{gem}=8.6 Hz, $J_{7,8'}$=6.6 Hz, H′-8), 3;69–3.74 (m, 4H, OCH_3 and C*H*HPh), 3.15 (d, 1H, J_{gem}=17.3 Hz, H-2), 2.95 (d, 1H, J_{gem}=17.3 Hz, H′-2), 1.47 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.5 (C=O), 140.3 (C_{ipso}), 128.7–126.8 (5C, Ar), 112.7 (acetal), 109.6 (acetal), 95.1 (C-3), 85.9 (C-4), 81.0 (C-5 or C-6), 80.9 (C-6 or C-5), 75.5 (C-7), 66.1 (C-8), 51.4 (OCH_3), 44.7 (CH_2Ph), 34.8 (C-2), 26.8, 26.0, 25.3, 24.8 (4× CH_3).

4.2.3. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-D-*allo*-3-octulofuranosonic acid, methyl ester, 12 (equilibrium with 14). Compound **12** (4.09 g) was synthesised from **8** (3.25 g, 10.35 mmol) in 94% yield, following the general procedure of 1,4-addition described above and silica gel chromatography with 20% EtOAc in hexane. R_f 0.7 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{25}=+9.3$ (c 1.1 $CHCl_3$). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.80; H, 7.32; N, 3.39.

4.2.4. 2,3-Dideoxy-7-methoxymethyl-4,5-*O*-isopropylidene-3-benzylamino-D-*ribo*-3-heptulofuranosonic acid, methyl ester, 13 (equilibrium with 15). R_f 0.9–0.7 (silica gel, 50% EtOAc in hexane).

4.3. General method for dipeptide 20–26 preparation

The following procedure was applied to the four *N*-benzyl compounds **10**–**13**. Each of them was dissolved in EtOAc (20 ml/g), 10% Pd/C (10% weight) was added and the

mixture was hydrogenated under atmospheric pressure for a night. The reaction mixture was then filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo to get a crude free amine, which was used, directly in the next step. The above-prepared crude amines **16**–**19** were then reacted as follow. To a solution (0.2 M) of the free amine in dry DMF under argon atmosphere were added successively in one portion the *N*-protected commercially α-amino acid (1.15 equiv.) and the coupling agent PyBOP (1.15 equiv.). After 5 min stirring, Et_3N (1.15 equiv.) was added dropwise. The reaction mixture was stirred overnight after which it was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed successively with water, 5% aq. HCl, water, and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated giving the crude, which was purified by column chromatography.

4.3.1. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 20. Compound **20** (1.185 g) was prepared from **10** (0.983 g, 2.40 mmol) in 92% yield following the above described procedure and purification by silica chromatography (50% EtOAc–hexane).

Glassy solid; R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{22}=-2.5$ (*c* 0.9 $CHCl_3$); ν_{max} (KBr) 3288, 2991, 2935, 1725, 1669, 1524, 1373, 1239, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (br s, 1H, NH), 7.28–7.40 (m, 5H, Ar), 5.28 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=5.6 Hz, NH_{Ala}), 5.21(d, 1H, $J_{4,5}$=5.5 Hz, H-4), 5.14 (m, 2H, CH_2Ph), 4.89 (m, 1H, H-5), 4.21–4.32 (m, 2H, C*H*α and H-7), 4.20 (dd, 1H, J_{gem}=8.3, $J_{7,8}$=6.6 Hz, H-8), 4.16 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.0 Hz, H-6), 3.65–3.76 (m, 4H, H′-8 and OCH_3), 2.99 (m, 2H, 2×H-2), 1.46 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.37–1.41 (m, 6H, CH_{3Ala} and CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.5, 170.7 (2×C=O), 155.7 (C=O carbamate), 136.1 (C_{ipso}), 128.0–128.4 (5C, Ar), 112.8 (acetal), 109.7 (acetal), 92.6 (C-3), 84.8 (C-4), 84.3 (C-6), 81.6 (C-5), 76.2 (C-7), 67.0 (*C*H_2Ph), 65.9 (C-8), 51.9 (CO_2CH_3), 50.9 ($C_{\alpha_{Ala}}$), 38.7 (C-2), 26.6, 25.8, 25.4, 24.4 (4×CH_3), 18.4 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.57): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.11; H, 6.81; N, 5.18.

4.3.2. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[[(phenylmethoxy)carbonyl]amino]acetyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 23. The general procedure for dipeptide preparation was applied to **10** (610 mg, 1.84 mmol) with *Z*-GlyOH α-amino acid. Silica gel chromatography of the crude (60% EtOAc–hexane) led to compound **23** (806 mg) in 84% yield. White foam, R_f 0.6 (silica gel, 70% EtOAc in hexane); $[\alpha]_D^{26}=+9.5$ (*c* 1 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.97 (br s, 2H, 2×H-2), 3.64–3.72 (m, 4H, H-8 and CO_2CH_3), 3.83–3.91 (m, 2H, CH_{2Gly}), 4.14 (dd, 1H, $J_{5,6}$=3.6 Hz, $J_{6,7}$=7.8 Hz, H-6), 4.19 (dd, 1H, *J*=8.2 Hz, *J*=6.7 Hz, H′-8), 4.25 (m, 1H, H-7), 4.89 (m, 1H, H-5), 5.09–5.19 (m, 2H, CH_2Ph), 5.23 (br d, 1H, $J_{4,5}$=5.5 Hz, H-4), 5.36 (m, 1H, NH_{Gly}), 7.29–7.40 (m, 5H, Ar), 7.62 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.3 (C=O), 169.9 (C=O), 156.8 (C=O carbamate), 136.5 (C_{ipso}), 128.5–128.9 (5C, Ar), 113.3 (acetal), 110.1 (acetal), 93.1 (C-3), 85.2 (C-4), 84.8 (C-6), 82.0 (C-5), 76.7 (C-7), 67.6 (*C*H_2Ph), 66.4 (C-8), 52.4 (CO_2CH_3), 45.2 (CH_{2Gly}), 39.0 (C-2), 27.0, 26.2, 25.9, 24.8 (4×CH_3). Anal. calcd for $C_{25}H_{34}N_2O_{10}$ (522.54): C, 57.46; H, 6.56; N, 5.36. Found: C, 57.60; H, 6.51; N, 5.31.

4.3.3. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-aspartyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 22. The general procedure for dipeptide preparation was applied with *Z*-Asp(O*t*Bu)OH. Compound **22** (730 mg) was obtained in 63% yield from **10** (605 mg, 1.90 mmol) after chromatography (silica, 35% EtOAc–hexane).

R_f 0.6 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{26}=+10.0$ (*c* 1 $CHCl_3$); ν_{max} (neat) 3331, 2984, 2937, 1731, 1681, 1519, 1455, 1371, 1210, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H, NH), 7.29–7.44 (m, 5H, Ar), 5.95 (br d, 1H, $J_{CH_\alpha,NH_{Asp}}$=8.6 Hz, NH_{Asp}), 5.26 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 5.16 (m, 2H, CH_2Ph), 4.88 (m, 1H, H-5), 4.52 (m, 1H, C*H*α), 4.29 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.6 Hz, H-8), 4.08 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.1 Hz, H-6), 3.69 (s, 3H, OCH_3), 3.67 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8'}$=8.0 Hz, H′-8), 3.0 (m, 2H, 2×H-2), 2.93 (dd, 1H, J_{gem}=17.2 Hz, J_{CH_2,CH_α} 5.0 Hz, C*H*HCO_2tBu), 2.61 (dd, 1H, J_{CH_2,CH_α}=5.1 Hz, C*H*HCO_2tBu), 1.28–1.41 (m, 21H, 4×CH_3 and $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz):δ 171.1, 170.8, 170.5 (3×C=O), 155.9 (C=O carbamate), 136.0 (C_{ipso}), 128.1–128.5 (5C, Ar), 112.7 (acetal), 109.7 (acetal), 92.4 (C-3), 84.5 (C-4), 83.8 (C-6), 81.6 (C-5), 76.1 (C-7), 67.2 (*C*H_2Ph), 66.0 (C-8), 51.9 (CO_2CH_3), 51.4 ($C_{\alpha_{Asp}}$), 38.6 (C-2), 37.1 (*C*H_2CO_2tBu), 27.9 (3C, OC(*C*H_3)$_3$), 26.6, 25.8, 25.4, 24.4 (4×CH_3); *m/z* (EI+) 637.1 [$(M+H)^+$, 5%], 621.2 [$(M-CH_3)^+$, 8%], 507.1 (8), 421.1 (13), 367.1 (27), 315.1 (35), 257.0 (45), 230.0 (44), 222.0 (50), 100.9 (50) 90.9 (100). Anal. calcd for $C_{31}H_{44}N_2O_{12}$ (636.69): C, 58.48; H, 6.97; N, 4.40. Found: C, 57.97; H, 6.86; N, 4.31.

4.3.4. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-phenylalanyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 21. The general procedure for dipeptide preparation applied to **10** (613 mg, 1.80 mmol) with the *Z*-PheOH α-amino acid afforded **21** (842 mg) in 74% yield after purification (silica, 30% EtOAc–hexane to 40% EtOAc–hexane).

Glassy solid; R_f 0.6 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{26}=+0.1$ (*c* 0.9 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (br s, 1H, NH), 7.17–7.40 (m, 10H, Ar), 5.30 (m, 1H, NH_{Phe}), 5.16 (d, 1H, $J_{4,5}$=5.6 Hz, H-4), 5.09 (m, 2H, CH_2Ph), 5.85 (m, 1H, H-5), 4.44 (m, 1H, C*H*α), 4.26 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.5 Hz, H-8), 4.10 (dd, 1H, $J_{5,6}$=3.9 Hz, $J_{6,7}$=7.9 Hz, H-6), 3.64–3.72 (m, 4H, H′-8 and OCH_3), 3.08 (m, 2H, CH_2Ph), 2.94 (d, 1H, J_{gem}=16.4 Hz, H-2), 2.78 (d, 1H, J_{gem}=16.4 Hz, H′-2), 1.49 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.0, 170.7 (2×C=O), 155.6 (C=O carbamate), 136.1 (C_{ipso}), 127.0–129.2 (10C, Ar), 112.7 (acetal), 109.6 (acetal), 92.3 (C-3),

84.6 (C-4), 84.1 (C-6), 81.6 (C-5), 76.1 (C-7), 67.0 (CH_2Ph), 65.9 (C-8), 56.3 ($C_{\alpha_{Phe}}$), 51.9 (CO_2CH_3), 38.5 (C-2), 38.1 (CH_2Ph), 26.6, 25.8, 25.4, 24.4 (4×CH_3)); *m/z* (ES+) 635 [(M+Na)$^+$, 50%], 613 [(M+H)$^+$, 90%], 299 (50), 192 (100). Anal. calcd for $C_{32}H_{40}N_2O_{10}$ (612.67): C, 62.73; H, 6.58; N, 4.57. Found: C, 61.77; H, 6.66; N, 5.25.

4.3.5. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*manno*-3-octulofuranosonic acid, methyl ester, 24. The general procedure for dipeptide preparation applied to **11** (990 mg, 2.98 mmol) with the *Z*-AlaOH α-amino acid afforded **24** (1.218 g) as a white foam in 76% yield after purification (silica, 40% EtOAc–hexane).

R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=-24.1$ (*c* 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H, NH), 7.42–7.30 (m, 5H, Ar), 5.34 (d, 1H, *J*=6.1 Hz, NH_{ala}), 5.21 (d, 1H, $J_{4,5}$=5.0 Hz, H-4), 5.14 (d, 1H, J_{gem}=12.1 Hz, C*H*HPh), 5.08 (d, 1H, C*H*HPh), 4.87 (m, 1H, H-5), 4.32–4.10 (m, 4H, H-6, H-7, H-8 and C*H*α), 3.75–3.65 (m, 4H, H′-8 and OCH_3), 3.04 (d, 1H, J_{gem}=16.0 Hz, H-2), 2.98 (d, 1H, H′-2), 1.45 (s, 3H, CH_3), 1.41–1.35 (m, 9H, 2×CH_3 and CH_{3Ala}), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 173.1, 171.1, (2×C=O), 156.3 (NHCO_2CH_2), 136.5 (C_{ipso}), 128.9–128.5 (5C, Ar), 113.2 (acetal), 110.1 (acetal), 93.1 (C-3), 85.1 (C-4), 84.5 (C-6), 81.9 (C-5), 76.6 (C-7), 67.5 (CH_2Ph), 66.4 (C-8), 52.3 (OCH_3), 51.2 ($C_{\alpha_{Ala}}$), 39.0 (C-2), 27.0, 26.2, 25.8, 24.8 (4×CH_3), 18.4 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.24): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.10; H, 6.81; N, 5.13.

4.3.6. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*allo*-3-octulofuranosonic acid, methyl ester, 25β. The general procedure for dipeptide preparation was applied to **12** (1.64 g, 4.95 mmol). Silica chromatography of the crude (20% EtOAc–hexane to 50% EtOAc–hexane) led to compounds **25β** (2.020 g) and **25α** (245 mg) in respectively 76% and 9% yields. (**25β/25α** 8.4:1 ratio). Data for **25β**, foam; R_f 0.5 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=-5.3$ (*c* 1.7 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.29–7.40 (m, 5H, Ar), 7.10 (br s, 1H, NH), 5.31 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=6.5 Hz, NH_{Ala}), 5.12 (s, 2H, CH_2Ph), 4.96 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.88 (dd, 1H, $J_{5,6}$=2.9 Hz, H-5), 4.26 (m, 1H, H-7), 4.21–4.0 (m, 3H, H-6, H-8, C*H*α), 3.80 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8'}$=5.8 Hz, H′-8), 3.67 (s, 3H, OCH_3), 3.23 (d, 1H, J_{gem}=16.0 Hz, H-2), 3.00 (d, 1H, J_{gem}=16.0 Hz, H′-2), 1.51 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (d, 3H, *J*=7.3 Hz, CH_{3Ala}), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.0, 170.9 (2×C=O), 156.1 (C=O carbamate), 136.6 (C_{ipso}), 128.8–128.4 (5C, Ar), 114.0 (acetal), 110.4 (acetal), 94.1 (C-3), 87.3 (C-6), 85.7 (C-4), 82.0 (C-5), 75.6 (C-7), 67.3 (CH_2Ph), 66.8 (C-8), 52.1 (CO_2CH_3), 51.3 ($C_{\alpha_{Ala}}$), 38.0 (C-2), 26.9 (2C, 2×CH_3), 25.5, 25.3 (2×CH_3), 18.9 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.24): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.09; H, 6.80; N, 5.26.

4.3.7. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-α-D-*allo*-3-octulofuranosonic acid, methyl ester, 25α. Gum, R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{22}=+22.3$ (*c* 1.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28–7.40 (m, 5H, Ar), 7.11 (br s, 1H, NH), 5.43 (m, 1H, NH_{Ala}), 5.12 (m, 2H, CH_2Ph), 4.86 (d, 1H, $J_{4,5}$=7.1 Hz, H-4), 4.80 (dd, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.16–4.26 (m, 2H, C*H*α and H-7), 4.07 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8}$=6.8 Hz, H-8), 3.95 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=5.3 Hz, H-6), 3.78 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8'}$=5.7 Hz, H′-8), 3.73 (m, 1H, H-2), 3.66 (s, 3H, OCH_3), 3.01 (d, 1H, J_{gem}=9.9 Hz, H′-2), 1.60 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.38 (d, 3H, *J*=7.0 Hz CH_{3Ala}), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.4, 169.9 (2×C=O), 155.6 (C=O carbamate), 136.2 (C_{ipso}), 128.0–128.4 (5C, Ar), 115.6 (acetal), 109.9 (acetal), 89.0 (C-3), 84.5 (C-4), 82.7 (C-6), 81.3 (C-5), 75.3 (C-7), 66.8 (CH_2Ph), 66.4 (C-8), 51.6 (CO_2CH_3), 51.0 ($C_{\alpha_{Ala}}$), 40.1 (C-2), 26.4, 26.3, 24.8, 24.7 (4×CH_3), 18.9 (CH_{3Ala}); *m/z* (EI+) 537.3 [(M+H)$^+$, 3%], 521.2 [(M−CH_3)$^+$, 6%], 358.1 (6), 315.1 (13), 230.0 (14), 141 (11), 134 (17), 101 (25), 91 (100).

4.3.8. 2,3-Dideoxy-7-(methoxymethyl)-4,5-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-α-D-*ribo*-3-heptulofuranosonic acid, methyl ester, 26. The general procedure for dipeptide preparation was applied to **13** (394 mg, 1.22 mmol) with the *Z*-AlaOH α-amino acid. Silica gel chromatography of the crude (30% EtOAc–hexane to 40% EtOAc–hexane) led to compounds **26** (451 mg) in 73% yield as a clear oil. R_f 0.4 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=+8.7$ (*c* 0.4 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.30 (m, 6H, Ar and NH), 5.40 (m, 1H, NH_{Ala}), 5.12 (m, 2H, CH_2Ph), 5.0 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.77 (brd, 1H, H-5), 4.69 (m, 2H, CH_2OCH$_3$), 4.35 (m, 1H, H-6), 4.17 (m, 1H, C*H*α), 3.72–3.64 (m, 5H, CO_2CH_3 and 2×H-7), 3.40 (s, 3H, OCH_2-OCH_3), 3.32 (brd, 1H, J_{gem}=15.6 Hz, H-2), 2.98 (d, 1H, J_{gem}=15.6 Hz, H′-2), 1.53 (s, 3H, CH_3), 1.40 (d, 3H, *J*=7.0 Hz, CH_{3Ala}), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.9, 170.8 (2×C=O), 156.0 (C=O carbamate), 136.7 (C_{ipso}), 130.1–128.4 (5C, Ar), 114.0 (acetal), 97.1 (CH_2OCH_3), 94.3 (C-3), 86.0 (C-6), 85.6 (C-4), 82.4 (C-5), 68.4 (C-7), 67.3 (CH_2Ph), 56.0 (CH_2OCH_3), 52.1 (CO_2CH_3), 51.3 ($C_{\alpha_{Ala}}$), 38.0 (C-2), 27.0, 25.6 (2×CH_3), 19.0 (CH_{3Ala}); *m/z* (EI+) 511.2 [(M+H)$^+$, 1%], 495.2 [(M−CH_3)$^+$, 2%], 479.1 (2), 377.0 (7), 323.0 (7), 91 (100).

4.4. General procedure for dipeptide cyclisation into diazepinediones

Each of the linear dipeptides **20**–**26** was submitted to the following three steps sequence: saponification of the methyl ester, hydrogenolysis of the benzyloxycarbonyl group and cyclisation into the diazapenidiones **30**, **33** and **35**–**39**. A typical procedure is described from compound **24**. To a solution of **24** (938 mg, 1.75 mmol) in MeOH (20 ml) and water (1.6 ml) was added K_2CO_3 (266 mg, 1.92 mmol, 1.1 equiv.) and the mixture was stirred overnight. TLC (10% MeOH in CH_2Cl_2) indicated the disappearance of the starting material (R_f 0.75) and the appearance of a new spot (R_f 0.1–0.4). The reaction mixture was then carefully acidified to pH≈6 with Amberlite IR-120 (H$^+$) resin (previously washed with water and MeOH). The solution was then filtered and the solvent removed in vacuo. The residue was dried by co-evaporation with MeOH to give the

resulting acid as a solid (945 mg), which was used without further purification. This solid was dissolved in EtOAc (20 ml) and EtOH (10 ml), 10% Pd/C (93 mg) was added and the mixture was hydrogenated under atmospheric pressure for 3 h. The reaction mixture was then filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo to get the corresponding unmasked linear dipeptide (750 mg) which was used directly in the cyclisation step. To a solution of this compound (150 mg), in dry DMF (100 ml) under argon at 0 °C were added successively Et_3N (107 μl, 2 equiv.) and DPPA (99 μl, 1.2 equiv.). The mixture was slowly allowed to warm to room temperature and stirred overnight after which it was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated giving the crude which was purified on silica gel with a preparative HPLC column chromatography (20 mm in diameter, 8 bars) eluting with a gradient (70% EtOAc–hexane to 90% EtOAc–hexane) to afford **33** as a glassy solid (92 mg, 69%, 3steps).

4.4.1. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 30. Compound **30** was synthesised in 61% yield, following the same procedure described above for the preparation of **33** from **24** in identical scale (see general procedure above). Glassy solid; $[\alpha]_D^{22}=-22.9$ (*c* 1 $CHCl_3$); ν_{max} (KBr) 3288, 2985, 2935, 1669, 1530, 1370, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.88 (br s, 1H, NH), 5.80 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=3.6 Hz, NH_{Ala}), 4.86 (dd, 1H, $J_{4,5}$=5.8 Hz, $J_{5,6}$=3.6 Hz, H-5), 4.53 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.32 (m, 1H, H-7), 4.12–4.26 (m, 2H, CH_α and H-8), 4.06 (dd, 1H, $J_{5,6}$=3.6 Hz, $J_{6,7}$=7.3 Hz, H-6), 3.67 (pseudo t, 1H, *J*=8.0 Hz, H′-8), 3.10 (br s, 2H, 2×H-2), 1.51 (s, 3H, CH_3), 1.46 (d, 3H, *J*=6.5 Hz, CH_{3Ala}), 1.43 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.8, 170.6 (2×C=O), 113.8 (acetal), 109.8 (acetal), 91.9 (C-3), 86.6 (C-4), 81.7 (C-6), 80.8 (C-5), 75.6 (C-7), 65.9 (C-8), 50.9 ($C_{\alpha_{Ala}}$), 39.3 (C-2), 26.6, 25.8, 25.5, 24.7 (4×CH_3), 16.3 (CH_{3Ala}).

4.4.2. Compound 31. Compound **31** was synthesised from **29** in 47% yield and was obtained in addition of **30** (33%), following the general procedure described above for the cyclisation of linear dipeptides into diazepinediones. All the reaction conditions were strictly identical to that described except that a higher concentration of the reaction mixture was applied, 30 mM instead of 2.5 mM.

Data for **31**. R_f 0.3 (silica gel, 4% MeOH-EtOAc); $[\alpha]_D^{25}=-66.1$ (*c* 0.2 $CHCl_3$); ^1H NMR (DMSO-d_6, 400 MHz): δ 7.75 (m, 2H, 2×NH), 5.01 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.81 (dd, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.11 (m, 2H, H-7 and C*H*α), 401 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8}$=7.0 Hz, H-8), 3.71 (m, 2H, H-6 and H′-8), 3.20 (d, 1H, J_{gem}=15.0 Hz, H-2), 2.81 (d, 1H, J_{gem}=15.0 Hz, H′-2), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.13 (d, 3H, *J*=7.0 Hz, CH_{3Ala}); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 173.6, 168.1 (2×C=O), 112.2 (acetal), 109.4 (acetal), 93.3 (C-3), 84.6 (C-4), 81.9 (C-6), 81.5 (C-5), 76.1 (C-7), 66.2 (C-8), 49.3 ($C_{\alpha_{Ala}}$), 39.9 (C-2), 27.5, 26.7, 26.2, 25.5 (4×CH_3), 18.5 (CH_{3Ala}); *m/z* (EI^+) 741.8 [$(MH)^+$, 9%], 726.6 [$(MH\text{-}CH_3)^+$, 7%], 582.0 (23), 371.3 (14), 354.2 (35), 283.1 (15), 141.0 (19), 100.9 (100).

4.4.3. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-(1,1-dimethyethyl acetate)-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 36. Compound **36** was synthesised in 31% yield (3 steps) from **22**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation). R_f 0.3 (silica gel, 80% EtOAc in hexane); $[\alpha]_D^{22}=-4.4$ (*c* 0.8 $CHCl_3$); ν_{max} (neat) 3221, 3103, 2980, 2935, 1728, 1675, 1423, 1373; ^1H NMR ($CDCl_3$, 250 MHz): δ 8.17 (br s, 1H, NH), 6.55 (br d, 1H, *J*=5.1 Hz, NH_{Asp}), 4.85 (dd, 1H, $J_{4,5}$=5.8 Hz, $J_{5,6}$=3.7 Hz, H-5), 4.57 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.51 (m, 1H, C*H*α), 4.30 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.0, $J_{7,8}$=6.6 Hz, H-8), 4.99 (dd, 1H, $J_{5,6}$=3.7 Hz, $J_{6,7}$=7.3 Hz, H-6), 3.73 (pseudo t, 1H, *J*=8.0 Hz, H′-8), 3.12 (br s, 2H, 2×H-2), 2.81 (m, 2H, CH_2CO_2tBu), 1.49 (s, 3H, CH_3), 1.46 (s, 9H, $CO_2(CH_3)_3$), 1.42 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.2, 170.1, 169.8 (3×C=O), 113.9 (acetal), 109.8 (acetal), 91.4 (C-3), 86.5 (C-4), 81.8 and 81.6 (C-6 and $OC(CH_3)_3$), 80.6 (C-5), 75.3 (C-7), 65.9 (C-8), 53.0 ($C_{\alpha_{Asp}}$), 40.1 (C-2), 37.0 (CH_2CO_2tBu), 28.0 (3C, $OC(CH_3)_3$), 26.6, 25.9, 25.5, 24.9 (4×CH_3)); *m/z* (ES+) 493 [$(M+Na)^+$, 60%], 471 [$(M+H)^+$, 90%], 415 (100).

4.4.4. [2*S*,3*R*,4*R*,5*R*]-2[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 37. Compound **37** was synthesised in 25% yield (3 steps) from **23**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); R_f 0.5 (silica gel, 50% acetone in Et_2O); $[\alpha]_D^{22}=+8.0$ (*c* 0.8 $CHCl_3$); ν_{max} (neat) 3484, 3288, 3243, 3098, 2985, 2929, 1675, 1376, 1208; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (br s, 1H, NH), 7.56 (pseudo t, 1H, *J*=4.6 Hz, NH_{Gly}), 4.87 (dd, 1H, $J_{4,5}$=5.7 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.53 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.31–4.42 (m, 2H, H-7 and C*H*H_{Gly}), 4.21 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8}$=6.7 Hz, H-8), 3.95 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.1 Hz, H-6), 3.73 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8'}$=7.1 Hz, H′-8), 3.66 (dd, 1H, J_{gem}=15.8 Hz, $J_{CH_2,NH_{Gly}}$=6.5 Hz, C*H*H_{Gly}), 3.23 (d, 1H, J_{gem}=16.3 Hz, H-2), 3.17 (d, 1H, H′-2), 1.50 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.1, 171.5 (2×C=O), 113.9 (acetal), 109.9 (acetal), 91.1 (C-3), 85.7 (C-4), 81.4 (C-6), 80.5 (C-5), 75.3 (C-7), 65.9 (C-8), 46.4 (CH_{2Gly}), 39.6 (C-2), 26.7, 25.9, 25.3, 24.8 (4×CH_3); *m/z* (EI^+) 357 [$(MH)^+$, 5%], 341 [$(M\text{-}CH_3)^+$, 15%], 298 [$(M\text{-}CH_3COCH_3)^+$, 5%], 283 (5), 141 (24), 101 (65), 59 (80), 43 (100).

4.4.5. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-benzyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 35. $[\alpha]_D^{22}=-76.2$ (*c* 1 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (br s, 1H, NH), 7.25–7.38 (m, 5H, Ar), 6.05 (br s, 1H, NH_{Phe}), 4.87 (dd, 1H, $J_{4,5}$=5.6 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.57 (d, 1H, $J_{4,5}$=5.6 Hz, H-4), 4.35 (m, 1H, H-7), 4.30 (m, 1H, C*H*α), 4.21 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.6 Hz, H-8), 4.09 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=7.8 Hz, H-6), 3.72 (*pseudo* t, 1H, *J*=8.0 Hz,

H′-8), 3.38 (dd, 1H, J_{gem}=14.3 Hz, $J_{CH_2,}CH_\alpha$=4.5 Hz, C*H*HPh), 2.99–3.16 (m, 3H, 2×H-2 and C*H*HPh), 1.50 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.7, 170.0 (2×C=O), 136.1 (C_{ipso}), 127.3–130.2 (5C Ar), 113.9 (acetal), 109.8 (acetal), 91.1 (C-3), 86.5 (C-4), 81.8 (C-6), 80.7 (C-5), 75.4 (C-7), 65.9 (C-8), 57.5 ($C_{\alpha_{Phe}}$), 40.2 (C-2), 37.0 (*C*H_2Ph), 26.6, 25.8, 25.4, 24.7 (4×CH_3); *m/z* (EI$^+$) 447.3 [(MH)$^+$, 3%], 446.2 [M$^+$, 7%], 431.2 [(M−CH_3)$^+$, 7%], 355.2 (4), 297.1 (5), 239.0 (9), 166.7 (8), 141.0 (19), 119.9 (62), 100.9 (100).

4.4.6. [2*R*,3*S*,4*S*,5*S*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 33. The synthesis of **33** from **24** is described in the general procedure of cyclisation. Glassy solid; R_f 0.3 (silica gel, EtOAc); $[\alpha]_D^{22}$=−16.0 (*c* 0.8 $CHCl_3$); ν_{max} (KBr) 3435, 2987, 1685, 1457, 1382, 1211; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (br s, 1H, NH), 7.62 (d, 1H, $J_{CH_\alpha,}NH_{Ala}$=5.0 Hz, NH_{Ala}), 4.87 (dd, 1H, $J_{4,5}$=5.7 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.60 (m, 1H, CH_α), 4.52 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.35 (m, 1H, H-7), 4.20 (dd, 1H, J_{gem}=8.5 Hz, $J_{7,8}$=6.6 Hz, H-8), 3.91 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.2 Hz, H-6), 3.73 (dd, 1H, J_{gem}=8.5 Hz, $J_{7,8'}$=6.8 Hz, H′-8), 3.28 (d, 1H, J_{gem}=16.6 Hz, H-2), 3.19 (d, 1H, J_{gem}=16.6 Hz, H′-2), 1.48 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (d, 3H, *J*=6.7 Hz, CH_{3Ala}), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 175.0, 172.2 (2×C=O), 114.0 (acetal), 110.3 (acetal), 91.3 (C-3), 86.0 (C-4), 81.4 (C-6), 81.0 (C-5), 75.7 (C-7), 66.4 (C-8), 49.3 ($C_{\alpha_{Ala}}$), 40.5 (C-2), 27.2, 26.3, 25.7, 25.3 (4×CH_3), 14.5 (CH_{3Ala}); *m/z* (EI$^+$) 371.1 [(MH)$^+$, 6%], 370.1 [M$^+$, 5%], 356.1 [(MH−CH_3)$^+$, 2%], 355.1 [(M−CH_3)$^+$, 10%], 312.1 [(M−CH_3COCH_3)$^+$, 5%), 183.0 (11), 140.9 (22), 100.9 (100).

4.4.7. Compound 34. Compound **34** was synthesised from **32** in 15% yield and was obtained in addition of **33** (31%), following the general procedure described for the cyclisation of linear dipeptides into diazepinediones. All the reaction conditions were strictly identical to that described above except that a higher concentration of the reaction mixture was applied, 30 mM instead of 2.5 mM.

Data for **34**. R_f 0.1 (silica gel, EtOAc); $[\alpha]_D^{25}$=−25.0 (*c* 1.6 $CHCl_3$); ν_{max} (neat) 3535, 3305, 2987, 2936, 1662, 1533, 1455, 1373; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H, NH), 7.13 (br d, 1H, *J*=6.8 Hz, NH_{Ala}), 5.12 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 5.08 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=3.9 Hz, H-5), 4.48 (m, 1H, C*H*α), 4.36 (dd, 1H, $J_{5,6}$=3.9 Hz, $J_{6,7}$=7.9 Hz, H-6), 4.29–4.15 (m, 2H, H-7 and H-8), 3.69 (m, 1H, H′-8), 3.19 (d, 1H, J_{gem}=13.6 Hz, H-2), 2.78 (d, 1H, J_{gem}=13.6 Hz, H′-2), 1.52 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.23 (d, 3H, *J*=6.9 Hz, CH_{3Ala}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 173.3, 169.9 (2×C=O), 113.8 (acetal), 110.3 (acetal), 94.1 (C-3), 85.6 (C-6), 85.3 (C-4), 83.5 (C-5), 76.9 (C-7), 66.8 (C-8), 48.5 ($C_{\alpha_{Ala}}$), 43.5 (C-2), 27.0, 26.3, 25.8, 24.9 (4×CH_3), 15.0 (CH_{3Ala}); *m/z* (EI$^+$) 741.8 [(MH)$^+$, 26%], 741.0 [M$^+$, 9%], 725.6 [(M−CH_3)$^+$, 27%], 581.1 (14), 527.1 (10), 371.1 (12), 354.1 (42), 283.0 (22), 140 (20), 100.9 (100).

4.4.8. [2*R*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 38. Compound **38** was synthesised in 20% yield (3 steps) from **25β**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); Glassy solid; R_f 0.3 (silica gel, EtOAc); $[\alpha]_D^{26}$=−67.3 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (br s, 1H, NH), 5.89 (br s, 1H, NH_{Ala}), 4.87 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=1.2 Hz, H-5), 4.54 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.37 (m, 1H, H-7), 4.28 (m, 1H, H-6), 4.13–4.22 (m, 2H, CH_α and H-8), 3.75 (dd, 1H, J_{gem}=8.8 Hz, $J_{7,8'}$=6.6 Hz, H′-8), 3.21 (d, 1H, J_{gem}=14.3 Hz, H-2), 2.96 (br d, 1H, J_{gem}=14.5 Hz, H′-2), 1.56 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.46 (d, 3H, *J*=6.7 Hz, CH_{3Ala}), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.7, 169.5 (2×C=O), 113.9 (acetal), 110.6 (acetal), 93.8 (C-3), 88.5 (C-4), 85.1 (C-6), 80.5 (C-5), 75.9 (C-7), 65.6 (C-8), 50.1 ($C_{\alpha_{Ala}}$), 40.1 (C-2), 26.09, 26.05, 24.7, 24.3 (4×CH_3), 15.5 (CH_{3Ala}); *m/z* (EI+) 371.2 [(M+H)$^+$, 14%], 370.2 [M$^+$, 4%], 355.2 [(M-CH_3)$^+$, 41%], 269.1 (64), 141.0 (53), 101.0 (100).

4.4.9. [2*R*,3*R*,4*R*,5*R*,8*S*]-2[(Methoxymethoxy)methyl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-decane 7,10-dione, 39. Compound **39** was synthesised in 29% yield (3 steps) from **26**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); R_f 0.4 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$=−40.0 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (br s, 1H, NH), 6.29 (br s, 1H, NH_{Ala}), 4.90 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=1.4 Hz, H-5), 4.73 (m, 2H, OC*H*$_2$OCH$_3$), 4.55 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.46 (m, 1H, H-6), 4.16 (m, 1H, CH_α), 3.76 (dd, 1H, J_{gem}=10.9 Hz, $J_{6,7}$=1.9 Hz, H-7), 3.64 (dd, 1H, J_{gem}=10.9 Hz, $J_{6,7'}$=2.1 Hz, H′-7), 3.41 (s, 3H, OCH_2OCH_3), 3.21 (d, 1H, J_{gem}=14.0 Hz, H-2), 2.93 (br d, 1H, J_{gem}=14.0 Hz, H′-2), 1.56 (s, 3H, CH_3), 1.43 (d, 3H, *J*=6.8 Hz, CH_{3Ala}), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.4, 169.8 (2×C=O), 111.4 (acetal), 97.2 (O*C*H$_2$OCH$_3$), 94.3 (C-3), 89.1 (C-4), 84.3 (C-6), 82.6 (C-5), 69.0 (C-7), 56.4 (OCH$_2$O*C*H$_3$), 50.4 ($C_{\alpha_{Ala}}$), 40,7 (C-2), 26.5, 25.1 (2×CH_3), 15.8 (CH_{3Ala}); *m/z* (EI+) 345.1 [(M+H)$^+$, 2%], 329.0 [(M−CH_3)$^+$, 2%], 313.0 (3), 269 (3), 257.0 (3), 241 (3), 215 (6), 157 (25), 67.9 (100).

4.4.10. Deprotection of 30. Compound **30** (45 mg, 0.12 mmol) was treated with a 90 vol% TFA/H_2O solution cooled at 0 °C, for 4 h. The mixture was concentrated in vacuo and coevaporated with toluene (3×) and MeOH (3×) to give quantitatively a mixture of the two pyranoid anomers **40** and the two furanoid anomers **41** in a 5:1 ratio. Purification using reversed-phase high performance liquid chromatography by gradient elution (2% CH_3CN/H_2O to 8% CH_3CN/H_2O) allowed us to isolate pure, one isomer of the pyranose derivatives **40**.

Data for the pure **40** derivative: ^{1}H NMR (D_2O, 400 MHz): δ 4.21 (m, 1H, CH_α), 4.11(m, 1H, H-7), 3.93 (pseudo t, 1H, *J*=3.7 Hz, H-5), 3.80 (br d, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$<1.0 Hz, H-6), 3.71 (d, 1H, $J_{4,5}$=3.4 Hz, H-4), 3.63 (m, 2H, 2×H-8), 2.50–2.75 (m, 2×H-2 partially exchanged), 1.29 (d, 3H, *J*=7.3 Hz, CH_{3Ala}); ^{13}C NMR (D_20, 100.6 MHz): δ 178.4,

171.9 (2×C=O), 98.4 (C-3), 71.7 (C-5), 69.8 (C-6), 68.2 (C-7), 66.3 (C-4), 61.4 (C-8), 49.8 ($C_{\alpha_{Ala}}$), 43,0 (m, C-2), 16.9 (CH_{3Ala}); *m/z* (EI+) 290.0 [M^+, 3%].

References and notes

1. (a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Nonma, T.; Tohjigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293. (b) Ciba-Geigi AG. DE Pat. 4,129,616 A1, 1990. (c) Mitsubishi Kasei Corp. Jpn. Pat. 04/222,589 A, 1990.
2. (a) Zavgorodny, S. G. *Tetrahedron Lett.* **1981**, *22*, 3003–3006. (b) Ferris, J. P.; Devadas, B. *Tetrahedron Lett.* **1986**, *27*, 323–326. (c) Ferris, J. P.; Devadas, B. *J. Org. Chem.* **1987**, *52*, 2355–2361. (d) Yokoyama, M.; Yamada, N. *Tetrahedron Lett.* **1989**, *30*, 3675–3676. (e) Fernandez-Bolanos, J.; Blasco Lopez, A.; Fuentes Mota, J. *Carbohydr. Res.* **1990**, *199*, 239–242.
3. (a) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S. *Tetrahedron* **1991**, *47*, 2111–2120. (b) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133–2144. (c) Chemla, P. *Tetrahedron Lett.* **1993**, *34*, 7391–7394. (d) Shiozaki, M. *Carbohydr. Res.* **2002**, *337*, 2077–2088.
4. (a) Dondoni, A.; Scherrmann, M. C.; Marra, A.; Delépine, J. L. *J. Org. Chem.* **1994**, *59*, 7517–7520. (b) Lakhrissi, M.; Chapleur, Y. *Tetrahedron Lett.* **1998**, *39*, 4659–4662.
5. Fairbanks, A. J.; Ford, P. S.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 3327–3330.
6. (a) Mio, S.; Ueda, M.; Hamura, M.; Kitagawa, J.; Sugai, S. *Tetrahedron* **1991**, *47*, 2145–2154. (b) Mio, S.; Shiraishai, M.; Sugai, S. *Tetrahedron* **1991**, *47*, 2121–2132.
7. (a) Renard, A.; Kotera, M.; Lhomme, J. *Tetrahedron Lett.* **1998**, *39*, 3129–3132. (b) Renard, A.; Kotera, M.; Brochier, M.-C.; Lhomme, J. *Eur. J. Org. Chem.* **2000**, 1831–1840.
8. Sano, H.; Sugai, S. *Tetrahedron* **1995**, *51*, 4635–4646.
9. Burton, J. W.; Son, J. C.; Fairbanks, A. J.; Choi, S. S.; Taylor, H.; Watkin, D. J.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 6119–6122.
10. Bichard, C. J. F.; Mitchell, E. P.; Wormald, M. R.; Watson, K. A.; Johnson, L. N.; Zographos, S. E.; Koutra, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2145–2148.
11. (a) Estevez, J. C.; Smith, M. D.; Wormald, M. R.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 391–394. (b) Osz, E.; Sos, E.; Somsak, L.; Szilagyi, L.; Dinya, Z. *Tetrahedron* **1997**, *53*, 5813–5824.
12. (a) Estevez, J. C.; Smith, M. D.; Lane, A. L.; Crook, S.; Watkins, D. J.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 387–390. (b) Agasimundin, Y. S.; Mumper, M. W.; Hosmane, R. S. *Bioorg. Med. Chem.* **1998**, *6*, 911–923.
13. (a) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2000**, *11*, 435–452. (b) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267–1277.
14. Gasch, C.; Salameh, B. A. B.; Pradera, M. A.; Fuentes, J. *Tetrahedron Lett.* **2001**, *42*, 8615–8617.
15. Oikonomakos, N. G.; Skamnaki, V. T.; Ösb, E.; Szilagyi, L.; Somsak, L.; Docsa, T.; Toth, B.; Gergely, P. *Bioorg. Med. Chem.* **2002**, *10*, 261–268.
16. (a) Estevez, J. C.; Ardron, H.; Wormald, M. R.; Brown, D.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *35*, 8889–8890. (b) Estevez, J. C.; Long, D. D.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 8287–8290. (c) Estevez, J. C.; Burton, J. W.; Estevez, R. J.; Ardron, H.; Wormald, M. R.; Dwek, R. A.; Brown, D.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2137–2154. (d) Paquette, L. A.; Brand, S.; Behrens, C. *J. Org. Chem.* **1999**, *64*, 2010–2025. (e) Long, D. D.; Tennant-Eyles, R. J.; Estevez, J. C.; Wormald, M. R.; Dwek, R. A.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 807–813.
17. Krülle, T. M.; Watson, K. A.; Gregoriou, M.; Johnson, L. N.; Crook, S.; Watkin, D. J.; Griffiths, R. C.; Nash, R. J.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 8291–8294.
18. Sano, H.; Mio, S.; Kitagawa, J.; Sugai, S. *Tetrahedron: Asymmetry* **1994**, *5*, 2233–2240.
19. Renard, A.; Lhomme, J.; Kotera, M. *J. Org. Chem.* **2002**, *67*, 1302–1307.
20. (a) Kittaka, A.; Tanaka, H.; Odanaka, Y.; Ohnuki, K.; Yamaguchi, K.; Miyasaka, T. *J. g. Chem.* **1994**, *59*, 3636–3641. (b) Kittaka, A.; Tanaka, H.; Yamada, N.; Miyasaka, T. *Tetrahedron Lett.* **1996**, *37*, 2801–2804. (c) Gimisis, T.; Chatgilialoglu, C. *J. Org. Chem.* **1996**, *61*, 1908–1909. (d) Kittaka, A.; Tanaka, H.; Kato, H.; Nonaka, Y.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1997**, *38*, 6421–6424. (e) Gimisis, T.; Castellari, C.; Chatgilialoglu, C. *Chem. Commun.* **1997**, 2089–2090. (f) Kittaka, A.; Kato, H.; Tanaka, H.; Nonaka, Y.; Amano, M.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron* **1999**, *55*, 5319–5344. (g) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.* **1999**, *5*, 2866–2876.
21. (a) Wang, L.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2893–2896. (b) Zhang, N.; Chen, H.-M.; Sood, R.; Kalicharran, K.; Fattom, A. I.; Naso, R. B.; Barnard, D. L.; Sidwell, R. W.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3391–3394.
22. Hosmane, R. S.; Bhan, A.; Karpel, R. L.; Siriwardane, U.; Hosmane, N. S. *J. Org. Chem.* **1990**, *55*, 5882–5890.
23. Bretner, M.; Beckett, D.; Sood, R. K.; Baldisseri, D. M.; Hosmane, R. S. *Bioorg. Med. Chem.* **1999**, *7*, 2931–2936.
24. (a) Marquez, V. E.; Liu, P. S.; Kelley, J. A.; Driscoll, J. S. *J. Med. Chem.* **1980**, *23*, 715–717. (b) Kim, C. H.; Marquez, V. E. *J. Org. Chem.* **1987**, *52*, 1979–1983.
25. Zia-Ul-Haq, M.; Hameed, S.; Duddeck, H.; Ahmed, R. *Turk. J. Chem.* **2002**, *26*, 807–813.
26. (a) Bouhlal, D.; Godé, P.; Goethals, G.; Massoui, M.; Villa, P.; Martin, P. *Carbohydr. Res.* **2000**, *329*, 207–214. (b) Bouhlal, D.; Martin, P.; Massoui, M.; Nowogrocki, G.; Pilard, S.; Villa, P.; Goethals, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1573–1577.
27. (a) Abrous, L.; Hynes, J.; Friedrich, S. R.; Smith, A. B.; Hirschmann, R. *Org. Lett.* **2001**, *3*, 1089–1092. (b) Thiering, S.; Sowa, C. E.; Thiem, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 801–806. (c) Thiering, S.; Sund, C.; Thiem, J.; Giesler, A.; Kopf, J. *Carbohydr. Res.* **2001**, *336*, 271–282.
28. For the synthesis of a sugar derived anomeric spiroannelated azepindiones see: Sowa, C. E.; Stark, M.; Heidelberg, T.; Thiem, J. *Synlett* **1996**, *3*, 227–228.
29. Taillefumier, C.; Lakhrissi, Y.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1707–1711.
30. (a) Lakhrissi, M.; Chapleur, Y. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 750–752. (b) Lakhrissi, M.; Taillefumier, C.;

Chaouch, A.; Didierjean, C.; Aubry, A.; Chapleur, Y. *Tetrahedron Lett.* **1998**, *39*, 6457–6460.
31. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
32. Chang, C. F.; Yang, W. B.; Chang, C. C.; Lin, C. H. *Tetrahedron Lett.* **2002**, *43*, 6515–6519.
33. For an example of DPPA-mediated lactamisation, see: Ma, D.; Tang, W.; Kozikowski, A. P.; Lewin, N. E.; Blumberg, P. M. *J. Org. Chem.* **1999**, *64*, 6366–6373.
34. For an example of HATU-mediated lactamisation, see: Weitz, I. S.; Pellegrini, M.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **1997**, *62*, 2527–2534.
35. (a) von Roedern, E. G.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 670–671. (b) von Roedern, E. G.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156–10167. (c) van Well, R. M.; Overkleeft, H. S.; Overhand, M.; Vang Carstenen, E.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 9331–9335. (d) Lohof, E.; Planker, E.; Mang, C.; Burkhart, F.; Dechantsreiter, M. A.; Haubner, R.; Wester, H. J.; Schwaiger, M.; Holzemann, G.; Goodman, S. L.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2761–2764. (e) Locardi, E.; Stockle, M.; Gruner, S.; Kessler, H. *J. Am. Chem. Soc.* **2001**, *123*, 8189–8196. (f) Gruner, S. A. W.; Kéri, G.; Schwab, R.; Venetianer, A.; Kessler, H. *Org. Lett.* **2001**, *3*, 3723–3725. (g) Stöckle, M.; Voll, G.; Günther, R.; Lohof, E.; Locardi, E.; Gruner, S.; Kessler, H. *Org. Lett.* **2002**, *4*, 2501–2504. (h) Gruner, S. A. W.; Truffault, V.; Voll, G.; Locardi, E.; Stöckle, M.; Kessler, H. *Chem. Eur. J.* **2002**, *8*, 4365–4376. (i) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M.; KiranKumar, S.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257–6263.