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Synthesis of cyclically constrained sugar derived α/β- and α/γ-peptides†

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Antonio Franconetti, Sorel Jatunov, Pastora Borrachero, Manuel Gómez-Guillén and Francisca Cabrera-Escribano*

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A general approach to enantiopure conformationally constrained sugar derived α/β- and α/γ-peptides has been established. Five-membered ring α/β-peptides were synthesized *via* formyl *C*-glycofuranosides, easy available from hexose-derived azido-2-*equatorial*-OH-glycopyranosides by DAST-promoted ring contraction. By means of a regioselective oxidation with TEMPO at C-6 of hexose-derived 3-azido glycopyranosides as the key step, two- and three-residue α/γ-peptides having a six-membered ring were obtained in good yields and under very simple experimental conditions.

Introduction

The biological function of proteins and RNA, including catalysis and recognition, depends not only on the specificity of macromolecular interactions but also on the folding pattern of these macromolecules that leads to well organized structures.[1] Since many proteins exert their biological activity through relatively small regions of their folded surface, their activity could be reproduced by smaller molecules designed in a way that they not only conserve the function of the protein but also have better pharmacokinetic and pharmacodynamic properties. Unnatural oligomers that can reproduce the three-dimensional shapes and side-chain projection patterns characteristic of natural polypeptides offer a basis for rational development of protein–protein interaction antagonists.[2]

It has been shown, in contrast to α-amino acids which are components of proteins, that short β-, γ-, and δ-amino acid oligomers, especially those that have conformational restrictions, adopt well defined tridimensional structures. The study of non-natural oligomers with discrete folding propensities, so-called foldamers,[3] has demonstrated that a variety of synthetic backbones can show biopolymer-like conformational behavior. To gain a deeper understanding of folding and the functions of the folded molecules, many artificial foldamers have been developed.[4] Early work in this area focused on oligomers comprised of a single type of monomer subunits, but recent efforts have highlighted the potential of mixed or "heterogeneous" backbones to expand the structural and functional repertoire of foldamers.[5] Gellman and co-workers have developed α/β-peptide analogues of HIV gp41 that show potent antiviral activity coupled with improved stability to degradation by proteases. Indeed, they have shown that cyclic replacements can substantially improve the affinity of gp41-mimetic α/β-peptides for a complementary protein surface, which leads to improved efficacy for inhibiting HIV infection relative to α/β-peptides that lack cyclic β-residues.[6] On the other hand, it has been shown that appropriately designed sequences, with a high proportion of the cyclically constrained residues derived from *trans*-2-amino-cyclohexanecarboxylic acid (ACHC), can self-assemble to form lyotropic liquid crystalline (LC) phases in an aqueous solution.[7] Self-assembly of ACHC-rich β-peptides leads to nanofibers that serve as the LC mesogens. A description of factors governing self-assembly of ACHC-rich β-peptides into nanostructures that form LC phases as well as the use of this information to design nanostructures that are functionalized with biological recognition groups have been also provided.[8] Additional examples in the literature have shown nanofibers and lyotropic LCs to be useful for nanocrystal templation,[9] biological sensing,[10] NMR RDC analysis,[11] and as NMR alignment media for small organic molecules in an aqueous solution to provide enantiodiscrimination.[12]

β-Amino acid residues can be endowed with higher intrinsic folding propensities than those of α residues by the use of cyclic constraints to limit backbone torsional mobility, and this capacity for residue-based rigidification has proven to be important for both the structure of β- and α/β-peptide foldamers.[6,13] Analogous benefits should result from the use of constrained γ-amino acid residues, but it is difficult to explore this hypothesis because only a few types of ring-containing γ-amino acids are known.[14] Furthermore, these compounds represent analogues of γ-aminobutyric acid (GABA) which are known to exhibit a wide range of biological properties[15] and

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, C/Profesor García González 1, 41012 Sevilla, Spain. E-mail: fcabrera@us.es; Fax: +34954624960; Tel: +34954556868

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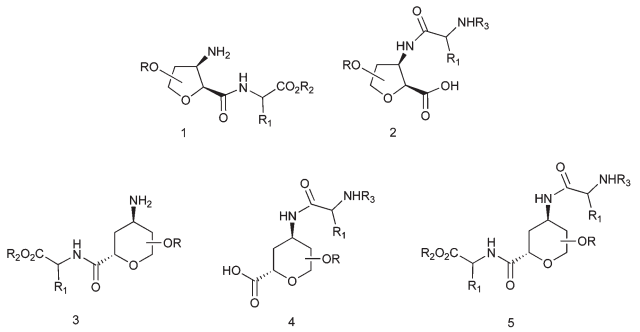


Fig. 1 Structure of the new cyclically constrained α/β- and α/γ-sugar–peptide hybrids.

have found diverse industrial applications.[16] Various GABA derivatives, including γ-amino esters, have been recently prepared[17] *via* an ene–imine reductive coupling reaction catalyzed by a nickel-1,10-phenanthroline complex. γ-Amino acids containing a cyclohexyl constraint on the Cα–Cγ bond and a variable side chain at Cα have been synthesized[18] by a pyrrolidine-catalyzed Michael addition of an aldehyde to 1-nitrocyclohexene as a key step, and it has been demonstrated that this new type of γ-amino acid residue supports helix formation by an α/γ-peptide backbone. In addition, access to cyclic γ-amino acids with up to three stereocenters has been described by enantioselective intramolecular Michael addition of nitronates onto conjugated esters.[19] However, neither the synthesis of enantiomerically pure γ-amino acids nor the synthesis of cyclically constrained variants has been widely reported.[20]

One of the first stages in the generation of non-natural oligo- and polymeric novel structures is the identification of monomer units with predictable stereochemical and conformational preferences. Carbohydrates bearing both an amino and carboxylic acid functionality have been extensively investigated[21] and have found wide applications in the construction of diverse novel structures with unique properties.[20,22] In this context, since carbohydrates are conformationally restricted structures with added hydrogen bond capability and enantiopure diversity we envisaged an easy and advantageous approach to a new kind of cyclic α/β- and α/γ-hybrid peptides (Fig. 1) as potential monomer structure building blocks for foldamers, and self-assembling nanostructured LC phases. In addition, the carbohydrate-based hybrid backbones described herein can be considered as a novel category of sugar amino acids.[21f]

Results and discussion

Here we report a new synthetic approach towards enantiopure *C*-glycofuranoside-based α/β-peptides of structures **1** and **2**, and the preparation of a variety of six membered ring α/γ sugar–peptide hybrids, **3–5**, in a straightforward way from D-glucose.

Conformational stability and specificity are provided by the preorganized β- or γ-amino acid residues, while diversity can

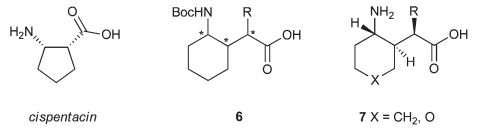


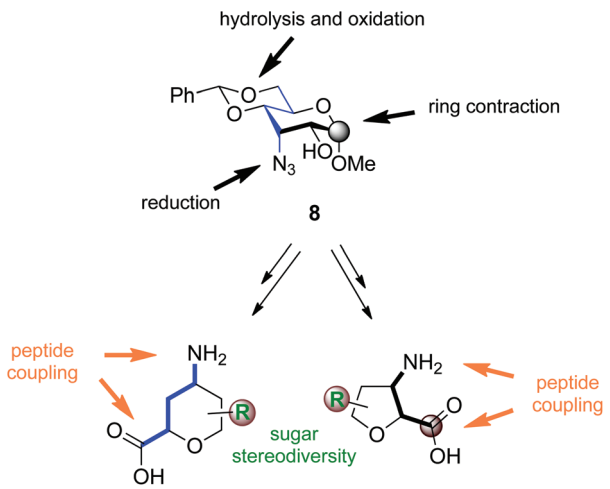
Fig. 2 Cyclically constrained α- and γ-amino acids.

be supplied by readily available α-amino acids. Compounds of types **1** and **2** are structural and configurationally related to the natural antifungal antibiotic cispentacin[23] (Fig. 2), which have been used as a peptidomimetic for proline.

Scheme 1 shows our synthetic carbohydrate-based strategy that holds several interesting features: (a) it is chemically efficient, starting from readily available sugar derivatives (*e.g.*, **8**);[24] (b) amino acids containing both a cyclopentyl or cyclohexyl constraint on the Cα–Cβ bond and Cα–Cβ–Cγ segment, respectively, are affordable; (c) importantly, with this carbohydrate-based procedure, up to four or five contiguous stereocenters can be assembled, which is a remarkable improvement in comparison with related systems **6** and **7**, previously described;[18,19] (d) in addition to the diversity supplied by introducing different available α-amino acids, sugar stereodiversity can be also exploited.

The synthesis of α/β-glycopeptides of general structures **1** and **2** can be achieved *via* formyl *C*-glycofuranosides.[25] The key step in this hydrolysis strategy is clearly a DAST-mediated rearrangement reaction which involves ring contraction of hexose-derived *equatorial*-2-OH-glycopyranosides, leading to formyl *C*-glycofuranosides under remarkably mild conditions. Thus, the precursors **13** and **15** of compounds having general structures **1** and **2** have been successfully obtained from the known methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-allopyranoside (**8**).[24]

Treatment of compound **8** with diethylaminosulfur trifluoride (DAST) in refluxing acetonitrile for 12 min as described previously[26] gave the 2,5-anhydro-1-fluoro-1-*O*-methyl-D-altritol

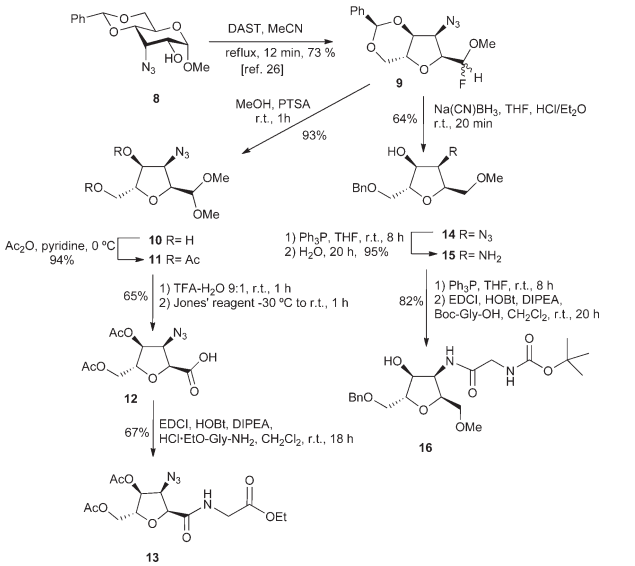


Scheme 1 Main features of the synthetic strategy.

9 (73%) as an epimeric mixture which contains a masked formyl function (Scheme 2).

Compound **9** was transformed, by the action of PTSA and methanol, into the 4,6-*O*-deprotected dimethyl acetal **10** in high yield (93%). When the preceding reaction was performed without purifying the product, and this crude product was subjected to standard acetylation conditions, the 4,6-di-*O*-acetyl derivative **11** (94% after column chromatography) was obtained.[26] Hydrolysis of **11** with 9 : 1 trifluoroacetic acid (TFA)–H_2O, followed by oxidation with aqueous sodium dichromate–sulfuric acid (Jones' reagent), gave the 4,6-di-*O*-acetyl-β-azido acid **12** in 65% yield. Transformation of **12** into **13** was easily achieved for protected glycine (EDCI, HOBt, DIPEA, HCl·EtO-Gly-NH_2, CH_2Cl_2, r.t., 18 h) in good yield (67%). Compound **12** showed in the ^{13}C NMR spectrum three carbonyl carbon signals, among them that of the highest δ value (172.0 ppm) being assigned to the carboxyl carbon. The ^1H NMR spectrum of compound **13** (Table 1) showed a triplet (J 5.0 Hz) at δ 7.07 ppm assigned to the NH proton, and two signals for the two glycine diastereotopic protons at δ 4.11 and 4.07 ppm, as well as the typical quartet/triplet signal tandem for the *O*-ethyl protons of an ester at δ 4.23 and 1.29 ppm; corresponding signals in the ^{13}C NMR spectrum (Table 2) and the high-resolution mass spectrum corroborated the proposed structure.

An alternative, higher yielding experimental protocol, in which the formyl *C*-glycofuranoside synthetic equivalent **9** is subjected to *in situ* hydrolysis, acetylation, and reduction, can be applied to obtain azido acid **12**. Adopting this one-pot procedure (Scheme 3), crude diacetylated aldehyde **17**, obtained *in situ* by hydrolysis (9 : 1 TFA–H_2O, r.t., 1 h) and subsequent acetylation (Ac_2O, pyridine, 0 °C), reacted with sodium



Scheme 2 Synthesis of α/β-glycopeptides.

Table 2 ^{13}C NMR spectroscopic data for characteristic carbons in α/β- and α/γ-hybrid peptides and their most relevant precursors[a]

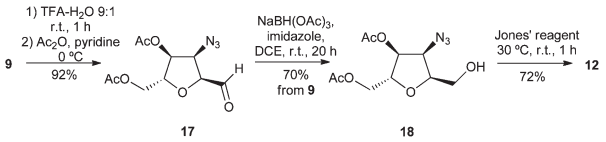
	δ [ppm]					
Cp.	C-1	C-3	C-6	CH_2 Gly residue	CO_2Et	$CO_2{}^tBu$
13	167.3	63.2	63.1	41.0	169.3, 61.8, 14.2	—
14[b]	72.5	66.4	71.3	—	—	—
15	72.7	66.7	71.7	—	—	—
	72.1[c]	65.3[c]	70.4[c]	—	—	—
16	72.9[b]	53.9[b]	72.0[b]	44.9[b]	—	157.0, 79.6, 28.6[b]
	71.9[c]	52.4[c]	70.7[c]	43.4[c]	—	155.8, 78.1, 28.1[c]
22[d]	96.8	65.0	167.8	41.1	169.5, 61.7, 14.2	—
26	97.4	65.1	171.7	40.8	169.1, 60.5, 14.1	—
28	97.2	67.2	170.8	—	—	—
30[b]	97.8	51.3	172.7	44.6	—	157.0 80.5 28.4
31[b]	97.8	49.9	171.5	60.4, 44.5	169.4, 61.7, 14.1	155.9, 80.5, 28.3

[a] At 125.7 MHz in $CDCl_3$, unless otherwise indicated. [b] In acetone-d_6. [c] In DMSO-d_6. [d] At 75.8 MHz.

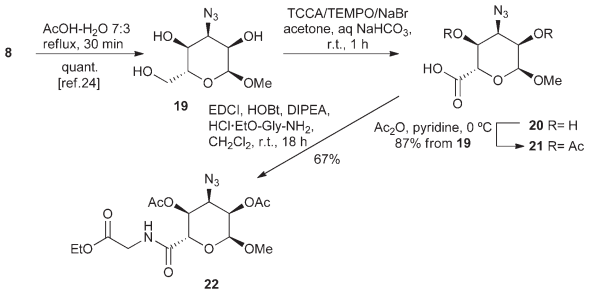
Table 1 ^1H NMR spectroscopic data for characteristic protons in α/β- and α/γ-hybrid peptides and their most relevant precursors[a]

	δ [ppm]					
Cp.	H-1	H-3	N–H	CH_2 Gly residue	CO_2Et	$CO_2{}^tBu$
13	—	4.68dd	7.07t	4.11dd and 4.07dd	4.23q and 1.29t	—
14[b]	3.56dd and 3.43dd[b]	4.14dd[b]	—	—	—	—
15	3.64dd and 3.52dd	4.07dd	—	—	—	—
	3.42m[c]	3.99dd[c]	—	—	—	—
16	3.50dd and 3.40dd	4.58–4.53m	6.43s br	3.77dd and 3.72dd	—	1.43s
	3.35–3.31m[c]	4.33ddd[c]	6.0s br[c]	3.58d[c]	—	1.39s[c]
22[d]	4.92d	4.24dd	6.90t	4.07dd and 3.94dd	4.21q and 1.26t	—
26	5.11–5.10m	4.37dd	7.17t	4.10dd	4.26q and 1.31t	—
28	5.07d	4.41t	—	—	—	—
30[b]	5.07d	4.90m	7.70d and 5.30t	3.96dd and 3.74dd	—	1.43s
31	5.11m	4.94t	7.26–7.22s and 5.49t	4.09dd and 3.79dd	4.22q and 1.28t	1.41s

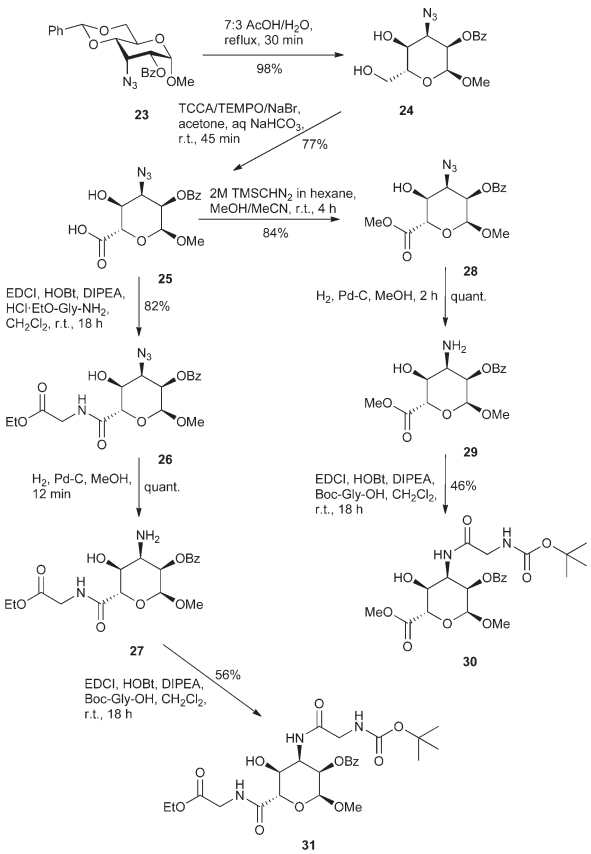
[a] At 500 MHz in $CDCl_3$, unless otherwise indicated. [b] In acetone-d_6. [c] In DMSO-d_6. [d] At 300 MHz.



Scheme 3 Alternative synthesis of the β-azido acid **12**.



Scheme 4 Synthesis of the α/γ-amino acid precursor **22** having general structure **3**.



Scheme 5 Synthesis of α/γ-glycopeptides.

triacetoxyborohydride (1.4 mol equiv.) and imidazole (1.4 mol equiv.) in dry 1,2-dichloroethane for 20 h, furnishing primary alcohol **18** (56% after column chromatography). A sample of the crude aldehyde **17** was purified by column chromatography and showed in its ^{1}H NMR spectrum the formyl proton signal as a doublet (J 1.5 Hz) at δ 9.63 ppm, as well as the two acetyl proton singlets at δ 2.17 and 2.11 ppm, and in its ^{13}C NMR spectrum, three carbonyl carbon signals (δ 199.2 ppm for the aldehydic one; 170.6 and 170.3 ppm for the two ester carbonyl carbons). In turn, primary alcohol **18** had an NMR spectra showing a broad OH-proton signal at δ ~1.95 ppm and signals for the two C(1) protons (doublet at δ 3.82 ppm) and for the C(1) nucleus (δ 62.0 ppm). Oxidation of **18** with aqueous dichromate–sulfuric acid (Jones' reagent, −30 °C, r.t., 1 h) gave the 4,6-di-*O*-acetyl-β-azido acid **12** in 72%.

To obtain the methoxymethyl glycofuranosyl glycine derivative **16**, being a precursor of the structure **2**, and the previous vicinal amino alcohol **15**, we started from **9** (Scheme 2). Thus, reduction of **9** dissolved in dry THF, with sodium cyanoborohydride (12.7 mol equiv.) in the presence of 3 Å molecular sieves (r.t., 15 min, and then HCl–Et_2O, 5 min), afforded compound **14** in 64% yield, which was subjected to the Staudinger reaction to give the amine **15** (95%). In turn, the Staudinger reaction of **14**, by using Boc-Gly-OH, gave the dipeptidomimetic **16** in high yield (82%). For this compound ^{1}H NMR coupling constants contrast sharply with those expected for a furanose ring, suggesting a conformational deviation. Thus, the $J_{2,3}$ value of 8 Hz observed matched with a dihedral angle H2–C2–C3–H3 next to 0°, and the $J_{4,5}$ of 3 Hz is remarkably lower than the corresponding usual value (7.5–8.5 Hz) observed for a furanose ring.[25] Preliminary molecular mechanics calculations[26,27] showed a sole low-energy conformer (below 10 kJ mol^{-1}) with a dihedral angle (17–23°) in agreement with the NMR data indicated above. On the other hand, it is noteworthy that introduction of a peptide chain at C-3 provokes a shielding of this nucleus in comparison with its δ value in compounds **14** or **15** (Table 2); in relation to δ values of H-3, a deshielding of 0.4 ppm can be observed from **14** or **15** to **16** (Table 1), both features are consistent with a γ-gauche effect.

The synthesis of α/γ-glycopeptides of types **3–5** was carried out starting from **8** and from its derivative, the known methyl 3-azido-2-*O*-benzoyl-4,6-*O*-benzylidene-3-deoxy-α-D-allopyranoside (**23**),[24] as shown in Schemes 4 and 5, respectively.

Hydrolysis of **8** (Scheme 4) by treatment with AcOH–H_2O (7 : 3, reflux, 30 min) gave quantitatively the triol **19**.[24] Selective oxidation of the primary alcohol at C-6 of **19** was carried out by treatment with the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)–NaBr–trichloro-isocyanuric acid (TCCA) in acetone, and subsequent *in situ* acetylation of the crude diol **20** gave the desired alluronic acid **21** in high yield (87%). Compound **21** showed in its ^{1}H NMR spectrum the singlet at 3.50 ppm for the anomeric methyl group protons as well as the two acetyl proton singlets at δ 2.14 and 2.17 ppm, and in its ^{13}C NMR spectrum three carbonyl carbon signals, among them that of the highest δ value (171.3 ppm) being assigned to the carboxyl carbon. Transformation of **21** into **22** was easily achieved for protected glycine (EDCI, HOBt, DIPEA, HCl·EtO-Gly-NH_2, CH_2Cl_2, r.t., 18 h) in good yield (67%). Compound **22**, which is a precursor of structure **3**, shows in its ^{1}H NMR spectrum (Table 1) a triplet (J 4.5 Hz) at δ 6.90 ppm for the amide proton, two signals at 4.07 and 3.94 ppm (dd each for 1H, J 5.4

and 18.3 Hz) for two methylenic protons of glycine residue, a singlet for the anomeric methyl group at 3.44 ppm, as well as the typical quartet/triplet signal tandem (4.21 and 1.26 ppm) for the *O*-ethyl protons of an ester; corresponding signals in the ^{13}C NMR spectrum (Table 2) and the high-resolution mass spectrum corroborated the α/γ-dipeptidomimetic proposed structure.

Scheme 5 shows the synthesis of the α/γ-glycopeptides **26**, **27**, **30**, and **31**, owning general structures **3–5**. To obtain the key compound, the alluronic acid derivative **25**, methyl α-D-allopyranoside **23** was first hydrolyzed, by the action of AcOH–H_2O (7 : 3, reflux, 30 min, 98%), to the 4,6-*O*-deprotected derivative **24**, the structure of which was deduced from its high-resolution mass spectrum and the absence of any benzylic proton or carbon atom in its ^{1}H and ^{13}C NMR spectra, in particular the easily observable singlet at δ 5.62 ppm for the benzylic proton for compound **23**. Selective oxidation of the primary alcohol at C-6 of **24** was accomplished with TEMPO–NaBr–TCCA in acetone to give the desired carboxylic acid **25** in 77% yield. Compound **25** showed in its ^{13}C NMR spectrum two carbonyl carbon signals, among them that of the highest δ value (171.2 ppm) being assigned to the carboxyl carbon. Transformation of **25** into the azido α/γ-glycopeptide **26** was easily achieved using protected glycine (EDCI, HOBt, DIPEA, HCl·EtO-Gly-NH_2, CH_2Cl_2, r.t., 18 h) in good yield (82%). Catalytic hydrogenation of **26** (H_2, Pd–C, MeOH, 12 min) gave compound **27**, an α/γ-glycopeptide of type **3** in quantitative yield. The ^{1}H NMR spectrum (Table 1) of compound **26** showed a triplet (*J* 5.0 Hz) at δ 7.17 ppm for the amide proton, a signal at 4.10 ppm (dd, *J* 5.5 and 9.5 Hz) for two methylenic protons of the glycine residue, a singlet for the anomeric methyl group at 3.48 ppm, as well as the typical quartet/triplet signal tandem for the *O*-ethyl protons of an ester; corresponding signals in the ^{13}C NMR spectrum (Table 2) and the high-resolution mass spectrum corroborated the proposed structure. Crude 3-amino derivative **27** was chromatographically homogeneous and was used for further transformation without purification by column chromatography.

Alternatively, compound **25** was transformed into the methyl uronate **28**, by treatment with a solution of 2 M $TMSCHN_2$ (trimethylsilyl-diazomethane) in hexane (MeOH–MeCN, r.t., 4 h), in good yield (84%); its spectral data (mainly MS and NMR) corroborated this structure: the novel methyl ester function gave rise to a singlet at δ 3.86 ppm for the three methyl protons, as well as an ester carbonyl signal at 170.8 ppm and an additional methyl carbon signal at 53.0 ppm. Reduction of the azido function in **28** by using H_2, Pd–C (MeOH, 2 h) gave quantitatively the γ-amino ester **29**. Coupling of this compound with protected glycine as an α-amino acid (EDCI, HOBt, DIPEA, Boc-Gly-OH, CH_2Cl_2, r.t., 18 h) furnished the α/γ-sugar peptide hybrid **30** (46%) showing a structure of type **4**. The ^{1}H NMR spectrum (Table 1) of compound **30** showed, as the most relevant signals, a doublet (*J* 6.5 Hz) at 7.70 ppm for the NH amide proton at C-3 and a singlet for the anomeric methyl group at 3.51 ppm, Boc-glycine residue being evidenced by a triplet (*J* 6 Hz) at δ 5.30 ppm for the amide proton, two signals at 3.96 ppm (dd, *J* 5.0 and 15.0 Hz) and 3.74 ppm (dd, *J* 5.0 and 16.0 Hz) for the two methylenic protons, and a singlet at 1.43 ppm for nine protons assigned to the *t*-butyl group; corresponding signals in the ^{13}C NMR spectrum (Table 2) and the high-resolution mass spectrum corroborated the proposed structure.

On the other hand, coupling of compound **27** with protected glycine under the above mentioned conditions easily achieved the α/γ-glycopeptide **31** which has a structure of type **5**. The MS and NMR data of **31** corroborated the assigned structure. Thus, the ^{1}H NMR spectrum (Table 1) of compound **31** showed two amine proton signals, among them that of the highest δ value (broad signal 7.26–7.22 ppm) being assigned to the ethyl glycinate residue, and a triplet (*J* 6.0 Hz) at 5.49 ppm for the C(3) NH proton; the ethoxycarbonyl glycine residue at position 6 gave also a signal (dd, *J* 6.0 and *J* 14.5 Hz) at 4.09 ppm for the two methylenic protons, and the typical quartet/triplet signal tandem (4.22 and 1.28 ppm) for the *O*-ethyl protons of an ester; a singlet for the anomeric methyl group at 3.49 ppm and a singlet at 1.41 ppm for nine protons assigned to the *t*-butyl group were also observed in the spectrum. It is noteworthy that as was observed for compound **30**, two signals at 4.00 and 3.79 ppm appear for each of the diasterotopic methylenic protons of the Boc-glycine residue; corresponding signals in the ^{13}C NMR spectrum (Table 2) and the high-resolution mass spectrum corroborated the proposed structure.

As was shown above for five-membered ring α/β-peptides, the introduction of a peptide chain at C-3 on a hexopyranoside system provokes a shielding of this nucleus and a deshielding of the H-3. Accordingly, taking in comparison δ values of C-3 for compounds **25** and **26** (67.2 and 65.1 ppm, respectively) with that of the same nucleus for compound **31** (49.9 ppm), and the C-3 δ value for compound **28** (67.2 ppm) with that of compound **30** (51.3 ppm), a shielding of more than 15 ppm is observed (Table 2); in turn, the δ value of H-3 moves from 4.35 or 4.37 ppm for **25** and **26**, respectively, to 4.94 ppm for compound **31**, and from 4.41 pm for **28** to 4.90 ppm for compound **30**, with 0.5 ppm being aprox. the observed increase (Table 1).

Conclusions

This work provides a straightforward carbohydrate-based design of novel enantiopure, cyclic α/β- and α/γ-hybrid peptides useful as potential monomer structure building blocks for foldamers, chiral catalysts, and self-assembling nanostructured LC phases. An economical, diversity-oriented strategy to access both five- and six-membered ring heterogeneous backbone subunits has been developed. Five-membered ring α/β-peptides were synthesized *via* formyl *C*-glycofuranosides, easily available from hexose-derived azido-2-*equatorial*-OH-glycopyranosides by DAST-promoted ring contraction. A regioselective oxidation with TEMPO at the primary 6-OH group of hexose-derived azido-glycopyranosides as the key step afforded two- and three-residue α/γ-peptides, having a six-membered

ring, in good yields and under very simple experimental conditions. Our methodology: (1) offers chemical efficiency and operational simplicity, starting from readily inexpensive sugar derivatives; (2) allows complete stereocontrol, and up to four or five contiguous stereocenters can be assembled, that being a remarkable improvement in comparison with related systems previously described; (3) in addition to the diversity supplied by introducing different available α-amino acids, sugar stereodiversity can be also exploited.

Experimental

General methods

All chemicals were purchased and used without further purification. Evaporations were conducted under reduced pressure. TLC was performed on aluminium sheets coated with Kieselgel 60 F254; detection of compounds was accomplished with UV light (254 nm) and by charring with 10% H_2SO_4 or an anisaldehyde reagent. Silica gel 60 (230 mesh) was used for preparative column chromatography. Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. Infrared (IR) spectra were recorded on an FTIR spectrophotometer. ^{1}H (and ^{13}C) NMR spectra were recorded at 300 (75.8 for ^{13}C) and 500 (125.7 for ^{13}C) MHz instruments, using the solvent peak as the internal reference; chemical shifts (δ) are expressed in ppm from TMS; coupling constants (J), in Hz. 2D COSY, and ^{1}H–^{13}C HMQC experiments were used to assist NMR assignments. Mass spectra were recorded by using either CI, EI, or FAB techniques at 70 eV for EI and at 150 eV for CI. FAB mass spectra were recorded by using a thioglycerol matrix. HRMS measurements were made with a resolution of 10 000, by using a magnet sector analyzer.

(1*R* and 1*S*)-2,5-Anhydro-3-azido-4,6-*O*-benzylidene-3-deoxy-1-fluoro-1-*O*-methyl-D-altritol (**9**), as a separable epimeric mixture **9a** and **9b**, were obtained from methyl 3-azido-4,6-*O*-benzylidene-3-dideoxy-α-D-allopyranoside (**8**)[24] in one step by reaction with DAST in acetonitrile following the reported procedure.[25a] Preparation of 2,5-anhydro-3-azido-3-deoxy-aldehydo-D-altrose dimethylacetal (**10**) and subsequent acetylation to give 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-aldehydo-D-altrose dimethylacetal (**11**) were carried out as previously described.[25a]

4,6-Di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altronic acid (12). *Procedure (a)*:[25a] Compound **11** (111 mg, 0.299 mmol) was dissolved in a 9 : 1 TFA–H_2O mixture (3.1 mL) and the solution was allowed to stand at room temperature for 1 h. The reaction was poured into an ice–water mixture (100 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were successively washed with saturated sodium hydrogen carbonate and brine, then dried (Na_2SO_4) and concentrated. The residue (crude **13**) was dissolved in ether (2.3 mL) and cooled to −30 °C. This solution was treated with aqueous sodium dichromate–sulphuric acid (Jones' reagent, 3.6 mL, 2.35 mmol) and was left to reach room temperature. The organic solvent was evaporated under reduced pressure and the residue was filtered through a silica gel path by using ether (100 mL) and then ethyl acetate (150 mL) as eluents, to give pure **12** (44 mg, 65%). *Procedure (b)*: A solution of **18** (50 mg, 0.183 mmol) in ether (2.5 mL) was cooled to −30 °C. This solution was treated with aqueous sodium dichromate–sulphuric acid (Jones' reagent, 3.6 mL, 2.35 mmol) and was left to reach room temperature. The organic solvent was evaporated under reduced pressure and the residue was filtered through a silica gel path by using ether (100 mL) and then ethyl acetate (150 mL) as eluents, to give pure **12** (38 mg, 72%). Compound **12**: R_f 0.37 (1 : 4 acetone–ether); $[\alpha]_D^{25}$ +40.2 (*c* 0.50, CH_2Cl_2); IR ν_{max} 3300 (OH), 2120 (N_3), 1746 (C=O), 1231 and 1119 cm^{-1} (C–O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (dd, 1H, $J_{3,4}$ = 5.0, $J_{4,5}$ = 8.0, H-4), 4.77 (d, 1H, $J_{2,3}$ = 4.5, H-2), 4.69 (dd, 1H, H-3), 4.45 (ddd, 1H, $J_{5,6}$ = 2.8, $J_{5,6'}$ = 4.0, H-5), 4.39 (dd, 1H, $J_{6,6'}$ = 12.5, H-6), 4.15 (dd, 1H, H-6′), and 2.18 and 2.10 (each s, each 3H, 2 CO*Me*); ^{13}C NMR (125.7 MHz) δ 172.0 (*C*OOH), 170.7 and 170.4 (2 *C*OMe), 78.3 and 78.2 (C-2 and C-5), 73.2 (C-4), 62.8 and 62.7 (C-3 and C-6), and 20.9 and 20.4 (2 CO*Me*); CIHRMS: *m*/*z* 288.0836 (calcd for $C_{10}H_{13}N_3O_7 + H^+$: 288.0832).

4,6-Di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-*N*-(ethoxycarbonyl-methyl)-α-D-altruronamide (13). Compound **12** (37 mg, 0.129 mmol) was dissolved, under an argon atmosphere, in CH_2Cl_2 (3 mL); to this solution, ethyl glycinate hydrochloride (26.9 mg, 0.193 mmol) and hydroxy-benzotriazole (HOBt, 17 mg, 0.193 mmol) were added, and the mixture was cooled to 0 °C. After 10 min, DIPEA (33 μL) was added and, 10 min later, *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI, 37 mg, 0.193 mmol) was also added to the mixture, which was left to reach room temperature under stirring. After 20 h, the mixture was diluted with CH_2Cl_2 (20 mL) and successively washed with 1 M HCl (40 mL), a saturated aqueous solution of potassium carbonate (40 mL), water (40 mL), and a saturated aqueous solution of NaCl (40 mL); the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to give the chromatographically homogeneous (R_f 0.53, 10 : 1 CH_2Cl_2 : MeOH) compound **13** (32 mg, 67%) as a syrup; $[\alpha]_D^{24}$ +52 (*c* 0.66, CH_2Cl_2). IR ν_{max} 3298 (NH), 2114 (N_3), 1740 (CO ester), 1674 (CO amide), 1123 (C–O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 7.07 (dd br, 1H, $J_{NH,CH2a}$ = 5.0, N*H*), 5.22 (dd, 1H, $J_{4,5}$ = 8.5, $J_{3,4}$ = 4.5, H-4), 4.68 (dd, 1H, $J_{2,3}$ = 4.5, H-3), 4.62 (d, 1H, H-2), 4.40–4.36 (m, 1H, H-5), 4.36 (dd, 1H, $J_{6,6'}$ = 12.5, $J_{5,6}$ = 2.5, H-6), 4.23 (q, 2H, *J* = 7.0, *Et*), 4.13 (dd, 1H, $J_{5,6'}$ = 4.0, H-6′), 4.11 (dd, 1H, J_{gem} = 18.0, NHCH^a_2), 4.07 (dd, 1H, NHCH^b_2), 2.16, 2.09 (2s, each 3H, CO*Me*), 1.29 (t, 3H, *Et*). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.6, 170.2 (*C*OMe), 169.3 (*C*OOEt), 167.3 (*C*ONH), 80.0 (C-2), 78.0 (C-5), 73.6 (C-4), 63.2 (C-3), 63.1 (C-6), 61.8 (O*C*H_2CH$_3$), 41.0 (NH*C*H_2), 20.9, 20.3 (CO*Me*), 14.2 (OCH$_2$*C*H$_3$). CIHRMS *m*/*z* 373.1349, calcd for $C_{14}H_{20}N_4O_8$ + H: 373.1359.

2,5-Anhydro-3-azido-6-*O*-benzyl-3-deoxy-1-*O*-methyl-D-altritol (14). A solution of **9** (105 mg, 0.340 mmol) in dry THF (4.8 mL) containing 3 Å molecular sieves was treated with $NaCNBH_3$ (273 mg, 4.35 mmol). The mixture was stirred for 15 min, and then Et_2O/HCl (3.5%, 6 mL) was added. After 5 min, the reaction was diluted with H_2O (20 mL) and CH_2Cl_2

(20 mL). After separation, the organic layer was successively washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. Column chromatography (EtOAc–hexane 1 : 3) gave pure **14** (64 mg, 64%). $[\alpha]_D^{24}$ +16.2 (*c* 0.63, CH_2Cl_2). IR ν_{max} 3345 (OH), 2108 (N_3), 1121 and 1006 (C–O–C) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6, δ ppm, *J* Hz) δ 7.36–7.26 (m, 5H, Ph), 4.75 (s br, 1H, OH_{C4}), 4.55 (s, 2H, CH_2Ph), 4.55–4.53 (m, 1H, H-4), 4.17 (ddd, 1H, $J_{1,2} = J_{1',2} = 5.7$, $J_{2,3} = 3.7$, H-2), 4.14 (dd, 1H, $J_{3,4} = 4.2$, H-3), 3.93 (ddd, 1H, $J_{4,5} = 7.5$, $J_{5,6'} = 4.5$, $J_{5,6} = 3.0$, H-5), 3.65 (dd, 1H, $J_{6,6'} = 11.0$, H-6), 3.58 (dd, 1H, H-6′), 3.56 (dd, 1H, $J_{1,1'} = 10.0$, H-1), 3.43 (dd, 1H, H-1′), 3.31 (s, 3H, O*Me*). ^{13}C NMR (125.7 MHz, acetone-d_6) δ 139.8–128.2 (Ph), 82.0 (C-5), 78.4 (C-2), 74.6 (C-4), 73.8 (*C*H_2Ph), 72.5 (C-1), 71.3 (C-6), 66.4 (C-3), 59.1 (O*Me*). CIHRMS *m*/*z* 294.1462, calcd for $C_{14}H_{19}N_3O_4$ + H: 294.1454.

2,5-Anhydro-3-amino-6-*O*-benzyl-3-deoxy-1-*O*-methyl-D-altritol (15). A solution of compound **14** (35.7 mg, 0.122 mmol) in dry THF (1.5 ml) was treated with triphenylphosphine (32 mg, 0.122 mmol). The mixture was allowed to stand at room temperature until monitoring by TLC (3 : 1 EtOAc–hexane) showed that the reaction was complete (8 h). Then 200 μL of water were added and the mixture was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (R_f 0.48, 5 : 1 CH_2Cl_2–MeOH) to give pure **15** (31.0 mg, 95%). $[\alpha]_D^{25}$ +0.5 (*c* 1.2, acetone). IR ν_{max} 3325 (NH, OH), 1113 and 1071 (C–O–C) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6, δ ppm, *J* Hz) δ 7.35–7.33 (m, 5H, Ph), 4.56 (dd, 1H, $J_{3,4} = 6.5$, $J_{4,5} = 1.5$, H-4), 4.56, 4.28 (2d, 1H each, $J_{H,H'} = 12.0$, CH_2Ph), 4.15 (ddd, 1H, $J_{1,2} = J_{1',2} = J_{2,3} = 5.0$, H-2), 4.07 (dd, 1H, H-3), 3.99 (ddd, 1H, $J_{5,6} = J_{5,6'} = 5.0$, H-5), 3.73 (s, 1H, OH), 3.64 (dd, 1H, $J_{1,1'} = 10.8$, H-1), 3.55 (dd, 1H, $J_{6,6'} = 10.8$, H-6), 3.52 (dd, 1H, H-1′), 3.52 (dd, 1H, H-6′), 3.30 (s, 3H, O*Me*). ^1H NMR (500 MHz, DMSO-d_6, δ ppm, J Hz) δ 7.37–7.28 (m, 5H, Ph), 5.33 (s br, 1H, OH_{C4}), 4.51, 4.48 (2d, 1H each, $J_{H,H'} = 12.0$, CH_2Ph), 4.41 (dd, 1H, $J_{3,4} = 6.5$, $J_{4,5} = 1.5$, H-4), 4.04 (ddd, 1H, $J_{1,2} = 7.0$, $J_{1',2} = J_{2,3} = 5.5$, H-2), 3.99 (dd, 1H, H-3), 3.93 (ddd, 1H, $J_{5,6} = J_{5,6'} = 5.5$, H-5), 3.55–3.42 (m, 4H, H-1, H-1′, H-6, H-6′), 3.26 (s, 3H, O*Me*). ^{13}C NMR (125.7 MHz, acetone-d_6) δ 139.7–128.4 (Ph), 84.8 (C-5), 84.5 (C-4), 80.3 (C-2), 73.8 (CH_2Ph), 72.7 (C-1), 71.7 (C-6), 66.7 (C-3), 59.1 (O*Me*). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 132.2–127.9 (Ph), 83.4 (C-5), 83.0 (C-4), 79.1 (C-2), 72.6 (CH_2Ph), 72.1 (C-1), 70.4 (C-6), 65.3 (C-3), 58.7 (O*Me*). CIHRMS *m*/*z* 268.1550, calcd for $C_{14}H_{21}NO_4$ + H: 268.1549.

2,5-Anhydro-3-*N*-*tert*-butoxycarbonylamino-6-*O*-benzyl-3-deoxy-1-*O*-methyl-D-altritol (16). A solution of compound **14** (105 mg, 0.359 mmol) in dry THF (3.5 mL) was treated with triphenylphosphine (103.2 mg, 0.393 mmol). The mixture was allowed to stand at room temperature until monitoring by TLC (3 : 1 EtOAc–hexane) showed that the reaction was completed (8 h). Then 0.5 mL of water were added and the mixture was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure and the residue dried under vacuum. This crude product dissolved in dry CH_2Cl_2 (2.2 mL) was added to a mixture previously prepared as follows: Boc-Gly-OH (90.4 mg, 0.516 mmol) was dissolved, under an argon atmosphere, in dry CH_2Cl_2 (2.2 mL), and HOBt (105 mg, 0.778 mmol) and DIPEA (90 μL, 0.516 mmol) were successively added. The mixture, cooled to 0 °C, was treated with EDCI (150 mg, 0.778 mmol) at the same temperature for 10 min. The reaction mixture containing the crude amine was left to reach room temperature for 20 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and successively washed with 2% HCl (50 mL), a saturated aqueous solution of potassium carbonate (50 mL), water (50 mL), and a saturated aqueous solution of NaCl (50 mL); the organic layer was dried (anhydrous sodium sulfate) and concentrated at reduced pressure. The residue was purified by column chromatography (R_f 0.42, 10 : 1 CH_2Cl_2–acetone) to give pure **16** (125 mg, 82%) as a syrup. $[\alpha]_D^{21}$ +37.2 (*c* 0.77, acetone). IR ν_{max} 3392 (NH, OH), 1719 (CO carbamate), 1605 (CO amide), 1595 (NCO), 1051 (C–O–C) cm^{-1}. ^1H NMR (500 MHz, acetone-d_6, δ ppm, *J* Hz) δ 7.36–7.33 (m, 5H, Ph), 7.09 (d, 1H, $J_{NH,3} = 7.0$, C–CO–N*H*), 6.43 (s br, 1H, O–CO–N*H*), 4.58–4.53 (m, 1H, H-3), 4.57 and 4.58 (each 2d, 1H, $J_{H,H'} = 12.9$, CH_2Ph), 4.45 (d, 1H, $J_{OH,4} = 8.0$, OH_{C4}), 4.31 (ddd, 1H, $J_{2,3} = 8.0$, $J_{1',2} = 4.5$, $J_{1,2} = 3.0$, H-2), 4.17–4.14 (m, 1H, H-4), 4.01 (ddd, 1H, $J_{5,6} = J_{5,6'} = 4.0$, $J_{4,5} = 3.0$, H-5), 3.77 (dd, 1H, $J_{gem} = 16.5$, $J_{NH,CH2a} = 6.0$, NHCH_{a2}), 3.72 (dd, 1H, $J_{NH,CH2b} = 6.0$, NHC$H^b{}_2$), 3.55 (dd, 1H, $J_{6,6'} = 10.5$, H-6), 3.52 (dd, 1H, H-6′), 3.50 (dd, 1H, $J_{1,1'} = 10.5$, H-1), 3.40 (dd, 1H, H-1′), 3.35 (s, 3H, O*Me*), 1.43 (s, 9H, CMe_3). ^1H NMR (500 MHz, DMSO-d_6, δ ppm, *J* Hz) δ 7.37–7.26 (m, 5H, Ph), 7.29–7.26 (m, 1H, C–CO–N*H*), 7.08 (t br, 1H, $J_{NH,CH2Gly} = 6.0$, O–CO–N*H*), 5.36 (d, 1H, $J_{OH,4} = 8.0$, OH_{C4}), 4.51 (s, 2H, CH_2Ph), 4.33 (ddd, 1H, $J_{3,NH} = 8.5$, $J_{2,3} = J_{3,4} = 5.9$, H-3), 4.13 (ddd, 1H, $J_{1,2} = 6.2$, $J_{1',2} = 4.1$, H-2), 4.05 (ddd, 1H, $J_{4,5} = 5.7$, H-4), 3.91 (ddd, 1H, $J_{5,6} = 3.8$, $J_{5,6'} = 5.3$, H-5), 3.58 (d, 2H, NHCH_2), 3.52 (dd, 1H, $J_{6,6'} = 10.6$, H-6), 3.46 (dd, 1H, H-6′), 3.35–3.31 (m, 2H, H-1, H-1′), 3.21 (s, 3H, O*Me*), 1.39 (s, 9H, CMe_3). ^{13}C NMR (125.7 MHz, acetone-d_6) δ 170.5, (N–*C*O–C), 157.0 (N–*C*OO), 139.6–128.2 (Ph), 85.2 (C-5), 79.6 (*C*Me$_3$), 78.9 (C-2), 73.8 (*C*H_2Ph), 73.1 (C-4), 72.9 (C-1), 72.0 (C-6), 59.3 (O*Me*), 53.9 (C-3), 44.9 (*C*H_2NHCO), 28.6 (CMe_3). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 169.6, (N–*C*O–C) 155.8 (N–*C*OO), 138.3–127.3 (Ph), 82.0 (C-5), 78.1 (*C*Me$_3$), 77.7 (C-2), 72.3 (*C*H_2Ph), 71.9 (C-1), 70.9 (C-4), 70.7 (C-6), 58.2 (O*Me*), 52.4 (C-3), 43.4 (*C*H_2NHCO), 28.1 (CMe_3). CIHRMS *m*/*z* 425.2291, calcd for $C_{21}H_{32}N_2O_7$ + H: 425.2288. Anal. calcd for $C_{21}H_{32}N_2O_7$: C, 59.42; H, 7.60; N, 6.60. Found: C, 59.12; H, 7.45; N, 6.72.

4,6-Di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-*aldehydo*-D-altrose (17) and 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altritol (18).[25a] Diastereomeric mixture **9** (100 mg, 0.324 mmol) was dissolved in a 9 : 1 TFA–H_2O mixture (3 mL) and the solution was allowed to stand at room temperature for 1 h. The reaction was poured into an ice–water mixture (100 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were evaporated under vacuum and the residue, without purification, was dissolved in anhydrous pyridine (1 mL), cooled to 0 °C and treated with acetic anhydride (1 mL). The reaction mixture was stirred at room temperature for 20 h and was poured into an ice–water mixture (100 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were washed

with saturated aqueous sodium hydrogen carbonate, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded crude **17** (81.0 mg, 92%) as a chromatographically homogeneous oil. This product was dissolved in 1,2-dichloroethane (3 mL) and treated with imidazole (28 mg, 0.416 mmol) and sodium triacetoxyborohydride (90.0 mg, 0.426 mmol). The reaction mixture was stirred at room temperature for 24 h and then was diluted with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (1 : 1 ether–hexane) gave pure **18** (62 mg, 70% from **9**).

Compound **17**: R_f 0.37 (1 : 4 EtOAc–hexane); $[\alpha]_D^{25}$ +40.9 (*c* 0.49, CH_2Cl_2); IR ν_{max} 2114 (N_3), 1742 (C═O), 1233 and 1125 (C–O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 9.63 (d, 1H, $J_{CHO,2}$ = 1.5, C*H*O), 4.31 (dd, 1H, $J_{3,4}$ = 5.0, $J_{4,5}$ = 7.0, H-4), 4.69 (dd, 1H, $J_{2,3}$ = 5.0, H-3), 4.46 (dd, 1H, H-2), 4.45 (m, 1H, H-5), 4.39 (dd, 1H, $J_{5,6}$ = 3.2, $J_{6,6'}$ = 12.2, H-6), 4.15 (dd, 1H, $J_{5,6'}$ = 4.2, H-6′), and 2.17 and 2.11 (each s, each 3H, 2 CO*Me*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 199.2 (*C*HO), 170.6 and 170.3 (2 *C*OMe), 82.7 (C-2), 78.8 (C-5), 73.8 (C-4), 63.3 (C-3), 63.1 (C-6), and 20.9 and 20.5 (2 CO*Me*); CIHRMS: *m*/*z* 272.0892, calcd for $C_{10}H_{13}N_3O_6$ + H: 272.0883.

Compound **18**: R_f 0.40 (4 : 1 EtOAc–hexane); $[\alpha]_D^{25}$ +19.4 (*c* 0.72, CH_2Cl_2); IR ν_{max} 3306 (OH), 2108 (N_3), 1227 and 1119 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 5.22 (dd, 1H, $J_{4,5}$ = 7.3, $J_{3,4}$ = 5.2, H-4), 4.41 (dd, 1H, $J_{2,3}$ = 4.8, H-3), 4.32 (dd, 1H, $J_{6,6'}$ = 11.7, $J_{5,6}$ = 3.0, H-6), 4.30–4.21 (m, 2H, H-2 and H-5), 4.11 (dd, 1H, $J_{5,6'}$ = 4.2, H-6′), 3.82 (d, 2H, J_1 and $_{1',2}$ = 6.0, H-1 and H-1′), 2.19 and 2.12 (each s, each 3H, 2 CO*Me*), and 1.95 (br s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.8 and 170.5 (2 *C*OMe), 79.7 and 77.3 (C-5 and C-2), 74.3 (C-4), 63.6 (C-6), 62.5 (C-3), 62.0 (C-1), and 20.9 and 20.5 (2 CO*Me*); CIHRMS: *m*/*z* 274.1026, calcd for $C_{10}H_{15}N_3O_6$ + H: 274.1039.

Methyl 3-azido-2,4-di-*O*-acetyl-3-deoxy-α-D-allopyranosiduronic acid (21). A 15% aqueous solution of sodium hydrogen carbonate (2 mL) was added to a solution of **19** (150 mg. 0.68 mmol) in acetone (5 mL). To this mixture, cooled to 0 °C, the following reagents were successively added: sodium bromide (15.6 mg, 0.15 mmol), TEMPO (2.5 mg, 0.016 mmol), and trichloro-isocyanuric acid (TCCA, 2 portions, each of 158 mg, 0.68 mmol in all, at 10 min intervals). The mixture was left to reach room temperature under stirring. After 1 h, the complete transformation of the starting product was observed (TLC, 5 : 1 CH_2Cl_2–MeOH), and the suspension was then filtered through Celite and the filtrate was treated with saturated aqueous sodium hydrogen carbonate (30 mL) and washed with ethyl acetate (3 × 25 mL). The aqueous layer was acidified with 2 M HCl and evaporated to dryness. The residue, crude product **20**, was treated with acetic anhydride (4 mL) in pyridine (4 mL). After 48 h at 4 °C the mixture was poured onto ice–water (20 mL) to give a syrup that was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 mL), dried (anhydrous sodium sulfate) and the solvent was evaporated to dryness, to give the chromatographically homogeneous (R_f 0.10, 5 : 1 CH_2Cl_2–MeOH) compound **21** as a syrup (138.5 mg, 87%). ^1H NMR (500 MHz, $CDCl_3$ δ ppm, *J* Hz) δ 5.19 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 10.0, H-4), 4.98 (m 2H, $J_{1,2}$ = $J_{2,3}$ = 2.0, H-1, H-2), 4.62 (d, 1H, $J_{5,4}$ = 10.0, H-5), 4.36 (t, 1H, $J_{3,2} \approx J_{3,4}$, H-3), 3.50 (s, 3H, O*Me*), 2.19 and 2.14 (2s, each 3H, CO*Me*). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.3 (*C*OOH), 170.0 and 169.7 (2 *C*OMe), 97.1 (C-1), 68.3 (C-2), 67.9 (C-4), 64.7 (C-3), 59.2 (C-5), 56.9 (O*Me*), 20.8 and 20.6 (2 CO*Me*). CIHRMS *m*/*z* 324.1200, calcd for $C_{14}H_{17}N_3O_6$ + H: 324.1196.

Ethyl [methyl 3-azido-2,4-di-*O*-acetyl-3-deoxy-α-D-allopyranosid]uronyl-glycinate (22). Compound **21** (25 mg, 0.079 mmol) was dissolved, under an argon atmosphere, in CH_2Cl_2 (3 mL); to this solution, ethyl glycinate hydrochloride (26.9 mg, 0.193 mmol) and HOBt (17 mg, 0.193 mmol) were added, and the mixture was cooled to 0 °C. After 10 min, DIPEA (33 μL) was added and, 10 min later, EDCI (37 mg, 0.193 mmol) was also added to the mixture, which was left to reach room temperature under stirring overnight. The mixture was then diluted with CH_2Cl_2 (20 mL) and successively washed with 1 M HCl (40 mL), a saturated aqueous solution of potassium carbonate (40 mL), water (40 mL), and a saturated aqueous solution of NaCl (40 mL); the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to give the chromatographically homogeneous (R_f 0.60, 3 : 1 EtOAc–hexane) compound **22** as a syrup (21.4 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 6.90 (t, 1H, $J_{NH,CH} \approx$ 4.5, NH), 5.12 (dd, 1H, $J_{4,3}$ = 3.6, $J_{4,5}$ = 9.9, H-4), 4.93 (dd 1H, $J_{2,1}$ = 3.9, $J_{2,3}$ = 4.2, H-2), 4.92 (d, 1H, $J_{1,2}$ = 3.9, H-1), 4.24 (dd, 1H, $J_{3,2}$ = $J_{3,4}$ = 3.6, H-3), 4.47 (d, 1H, $J_{5,4}$ = 9.9, H-5), 4.21 (q, 2H, J_{ethyl} = 6.9, CH_2CH$_3$), 4.07 (dd, 1H, $J_{CH,NH}$ = 5.4, J_{gem} = 18.3, NHCH^a_2), 3.94 (dd, 1H, NHCH^b_2), 3.44 (s, 3H, O*Me*), 2.17 and 2.14 (2s, each 3H, CO*Me*), 1.26 (t, 3H, CH$_2$CH_3). ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 169.9, 169.6 (*C*OMe), 169.5 (*C*OOEt), 167.8 (*C*ONH), 96.8 (C-1), 68.6 (C-2), 68.0 (C-4), 65.0 (C-3), 64.9 (C-5), 61.7 (OCH_2CH$_3$), 56.7 (O*Me*), 41.1 (NCH_2CO$_2$Et), 18.7, 17.5 (CO*Me*), 14.2 (OCH$_2$CH_3). CIHRMS: *m*/*z* 403.1467; calculated for $C_{15}H_{22}N_4O_9$ + H: 403.1465.

Methyl 3-azido-2-*O*-benzoyl-3-deoxy-α-D-allopyranoside (24). The acetal **23** (0.519 g, 1.26 mmol) was dissolved in a 7 : 3 mixture of acetic acid–H_2O and heated under reflux for 30 min. Monitoring of the reaction (TLC, 1 : 2 EtOAc–hexane) was maintained until the complete conversion into a new compound. Solvents were co-evaporated with H_2O and eventually with EtOH to leave crystalline compound **24** (0.399 g, 98%); R_f 0.37 (3 : 1 EtOAc–hexane); $[\alpha]_D^{25}$ +26.5 (*c* 1, CH_2Cl_2); IR ν_{max} 3453 (OH), 2110 (N_3), 1720 (C═O), 1267 and 1093 (C–O–C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 8.10, 7.51, 7.44 (m, 5H, Ph), 5.17 (t, 1H, $J_{2,1} \cong J_{2,3}$ = 3.9, H-2), 4.99 (d, 1H, $J_{1,2}$ = 3.9, H-1), 4.39 (t, 1H, $J_{2,3} \cong J_{3,4}$ = 3.3, H-3), 3.89 (dd, 1H, $J_{4,3}$ = 3.3, $J_{2,1} \cong J_{4,5}$ = 8.4, H-4), 3.94–3.79 (m, 3H, H-5, 2H-6), 3.42 (s, 3H, O*Me*). ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 165.7 (O*C*OPh), 134.0, 130.0, 129.0 (Ph), 97.0 (C-1), 70.4 (C-2), 67.7 (C-5 or C-6), 66.4 (C-5 or C-6), 62.2 (C-3), 61.9 (C-4), 56.2 (O*Me*). CIHRMS *m*/*z* 324.1200, calcd for $C_{14}H_{17}N_3O_6$ + H: 324.1196.

Methyl 3-azido-2-*O*-benzoyl-3-deoxy-α-D-allopyranosid-uronic acid (25). A 15% aqueous solution of sodium hydrogen

carbonate (13 mL) was added to a solution of **24** (973 mg. 3.01 mmol) in acetone (30 mL). To this mixture, cooled to 0 °C, the following reagents were successively added: NaBr (62.4 mg, 0.61 mmol), TEMPO (9 mg, 0.058 mmol), and TCCA (2 portions, each of 0.701 g, 6.02 mmol in all, at 10 min intervals). The mixture was left to reach room temperature under stirring. After 45 min, the suspension was filtered through Celite and the filtrate was treated with saturated aqueous sodium carbonate (50 mL) and washed with EtOAc (3 × 25 mL). The aqueous layer was acidified with 2 M HCl and extracted with EtOAc (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to dryness, to give compound **25** as a syrup (0.776 g, 77%); $[\alpha]_D^{25}$ +48.2 (*c* 1, CH_2Cl_2); IR ν_{max} 3197 (OH), 2111 (N_3), 1715 (C═O), 1265 and 1092 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 8.04, 7.53, 7.40 (m, 5H, Ph), 5.12 (d, 1H, $J_{1,2} \cong 0.0$, H-1), 5.04 (dd, 1H, $J_{2,1} \cong J_{2,3} \cong 0.0$, H-2), 4.40 (d 1H, $J_{5,4}$ = 9.5, H-5), 4.35 (br s, 1H, H-3), 4.01 (dd, 1H, $J_{4,3} \cong 0.0$, $J_{4,5}$ = 7.5, H-4), 3.43 (s, 3H, O*Me*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2 (*C*OOH), 165.6 (O*C*OPh), 139.6, 130.2, 128.6, 128.5 (Ph), 97.2 (C-1), 69.4 (C-2), 68.8 (C-4), 67.2 (C-3), 61.1 (C-5), 56.7 (O*Me*). CIHRMS: *m*/*z* 338.0989, calcd for $C_{14}H_{15}N_3O_7$ + H: 338.0988.

Ethyl (methyl 3-azido-2-*O*-benzoyl-3-deoxy-α-D-allopyranosid)uronyl-glycinate (26). Compound **25** (25 mg, 0.074 mmol) was dissolved, under an argon atmosphere, in CH_2Cl_2 (3 mL); to this solution, ethyl glycinate hydrochloride (26.9 mg, 0.193 mmol) and HOBt (17 mg, 0.193 mmol) were added, and the mixture was cooled to 0 °C. After 10 min, DIPEA (33 μL) was added and, 10 min later, EDCI (37 mg, 0.193 mmol) was also added to the mixture, which was left to reach the room temperature under stirring overnight. The mixture was then diluted with CH_2Cl_2 (20 mL) and successively washed with 1 M HCl (40 mL), a saturated aqueous solution of potassium carbonate (40 mL), H_2O (40 mL), and a saturated aqueous solution of NaCl (40 mL); the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to give the chromatographically homogeneous (R_f 0.59, 2 : 1 EtOAc–hexane) compound **26** as a syrup (21.3 mg, 82%). ^1H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 8.11, 7.61, 7.47 (m, 5H, Ph), 7.17 (t, 1H, $J_{NH,CH} \approx 5.0$, NH), 5.11–5.10 (m, 2H, H-2, H-1), 4.43 (d 1H, $J_{4,5}$ = 10.0 H-5), 4.37 (dd, 1H, H-3), 4.26 (q, 2H, J_{ethyl} = 7.0, CH_2CH$_3$), 4.10 (dd, 2H, $J_{CH,NH}$ = 5.5, J_{gem} = 9.5, –NHCH_2CO$_2$Et), 3.98 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 9.5, H-4), 3.48 (s, 3H, O*Me*), 1.31 (t, 3H, CH$_2$CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 171.7 (*C*ONR), 169.1 (*C*O$_2$CH$_2$CH$_3$), 165.6 (O*C*OPh), 133.8, 130.8, 128.8, 128.6, 128.5 (5*C*–Ph), 97.4 (*C*-1), 69.7 (*C*-2), 68.8 (*C*-4), 65.1 (*C*-3), 61.9 (*C*-5), 60.5 (OCH_2CH$_3$), 56.9 (O*Me*), 40.8 (NCH_2CO$_2$Et), 14.1 (OCH$_2$CH_3). CIHRMS: *m*/*z* 423.1441, calcd for $C_{18}H_{22}N_4O_7$ + H: 423.1438.

Ethyl (methyl 3-amino-2-*O*-benzoyl-3-deoxy-α-D-allopyranosid)uronyl-glycinate (27). The Pd/C catalyst (700 mg) was added to a solution of compound **26** (75 mg, 0.213 mmol) in MeOH (10.2 mL), and hydrogen gas (~0.5 L) was bubbled at atmospheric pressure and room temperature through the mixture under shaking. Monitoring of the reaction (TLC) showed that the reaction was completed after 12 min. The excess of hydrogen was displaced by an argon stream, the catalyst was filtered off (Celite on a fritted glass filter) and the filter was washed with cold methanol. Evaporation of the solvent gave 69 mg (quant. yield) of chromatographically homogeneous crude **27** (R_f 0.10, 2 : 1 EtOAc–hexane), pure enough to be used for further transformation.

Methyl (methyl 3-azido-2-*O*-benzoyl-3-deoxy-α-D-allopyranosid)uronate (28). An argon stream was bubbled through a solution of the alluronic acid derivative **25** (248.3 mg, 0.74 mmol) in 1 : 1 MeOH–MeCN, and a 2 M solution of $TMSCHN_2$ (1.41 mL, 8.83 mmol) in hexane was added. Monitoring of the reaction (TLC, 9 : 1 CH_2Cl_2–MeOH) indicated its completion after 4 h. The solvents were evaporated to give compound **28** (217.1 mg, 84%); R_f 0.8 (the same elution system); IR ν_{max} 3381 (OH), 2111 (N_3), 1724 (C═O), 1267 and 1173 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 8.11, 7.61, 7.48 (m, 5H, Ph), 5.19 (t, 1H, $J_{2,1} \cong J_{2,3}$ = 4.0, H-2), 5.07 (d, 1H, $J_{1,2}$ = 4.0, H-1), 4.43 (br d 1H, H-5), 4.41 (t, 1H, $J_{2,3} \cong J_{3,4}$ = 3.3, H-3), 4.04 (dd, 1H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 9.5, H-4), 3.86 (s, 3H, COOCH_3), 3.49 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8 (*C*O$_2$CH$_3$), 165.7 (O*C*OPh), 133.9, 130.3, 128.8, 128.7 (Ph), 97.2 (*C*-1), 69.5 (*C*-2), 68.4 (*C*-4), 67.2 (*C*-3), 61.2 (*C*-5), 56.8 (OCH_3), 53.0 (CO$_2$CH_3). CIHRMS *m*/*z* 352.1141, calcd for $C_{15}H_{17}N_3O_7$ + H: 352.1145.

Methyl (methyl 3-amino-2-*O*-benzoyl-3-deoxy-α-D-allopyranosid)uronate (29). The Pd/C catalyst (900 mg) was added to a solution of the azide **28** (148.7 mg, 0.42 mmol) in MeOH (20 mL). This mixture was shaken at room temperature and a hydrogen stream was bubbled through it at atmospheric pressure. The pressure was maintained until monitoring of the reaction (TLC, 9 : 1 CH_2Cl_2–MeOH) showed its completion after 2 h. The excess of hydrogen was displaced by an argon stream, the catalyst was filtered off (Celite on a fritted glass filter) and the filter was washed with a few portions of cold MeOH. The filtrate and washings were concentrated to dryness to leave 186 mg (>99%) of chromatographically homogeneous crude **29** (R_f 0.70 the same elution system), pure enough to be used for further transformation.

Methyl [methyl 2-*O*-benzoyl-3-(*N*-*tert*-butoxycarbonyl-glycyl-amido)-3-deoxy-α-D-allopyranosid]uronate (30). Boc-Gly-OH (136 mg, 0.93 mmol) was dissolved, under an argon atmosphere, in dry CH_2Cl_2 (10 mL), and HOBt (167 mg, 1.24 mmol) and DIPEA (161 μL, 0.93 mmol) were successively added. The mixture, cooled to 0 °C, was treated with EDCI (237.7 mg, 1.24 mmol) at the same temperature for 10 min, after that a solution of the crude compound **29** (217.1 mg, 0.62 mmol) in dry CH_2Cl_2 (10 mL) was added, and the reaction mixture was left to reach the room temperature overnight. The mixture was then diluted with CH_2Cl_2 (30 mL) and successively washed with 2% HCl (50 mL), a saturated aqueous solution of potassium carbonate (50 mL), water (50 mL), and a saturated aqueous solution of NaCl (50 mL); the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. Purification of the residue by column chromatography (1 : 1 to 3 : 1 EtOAc–hexane) gave pure **30** (206 mg, 46%); R_f 0.38 (1 : 1 EtOAc–hexane); $[\alpha]_D^{21}$ +20.2 (*c* 1, CH_2Cl_2); IR ν_{max} 3380 (NH, OH), 1719 (CO ester, carbamate), 1671 (CO amide), 1601 (NCO), 1068

(C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, δ ppm, J Hz) δ 7.96, 7.51, 7.39 (m, 5H, Ph), 7.70 [br d, 1H, $J_{3,NH}$ = 6.5, N*H*COCH$_2$NHCO$_2$C(CH$_3$)$_3$], 5.30 [t, 1H, $J_{H,CH2}$ = 6.0, COCH$_2$N*H*-CO$_2$C(CH$_3$)$_3$], 5.19 (t, 1H, $J_{2,3}$ = $J_{2,1}$ = 3.8, H-2), 5.07 (d, 1H, $J_{1,2}$ = 3.4, H-1), 4.90 (m, 1H, $J_{3,2}$ = $J_{3,4}$ = 3.5, H-3), 4.24 (d, $J_{3,4}$ = 10.0, H-5), 4.11 (dd, 1H, $J_{4,3}$ = 3,7, $J_{4,5}$ = 9.8, H-4), 3.96 (dd, 1H, J_{gem} = 15.0, –C*H*$_{2a}$NHCO$_2$Bu^t), 3.83 (s, 3H, COOC*H*$_3$), 3.74 (dd, 1H, J_{CH2NH} = 5.0 J_{gem} = 16.0, –C*H*$_{2b}$NHCO$_2$Bu^t), 3.50 (s, 3H, OC*H*$_3$), 1.43 [s, 9H, C(C*H*$_3$)$_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7 (*C*-6), 169.9 (O*C*OPh), 165.3 (NH*C*OCH$_2$), 157.0 (N–*C*OOBu^t), 133.7, 130.2, 129.1, 128.7, 128.0 (Ph), 97.8 (*C*-1), 80.5 (*C*Me$_3$), 69.5 (*C*-4), 68.4 (*C*-5), 66.9 (*C*-2), 56.4 (OCH$_3$), 52.9 CO$_2$*C*H$_3$), 51.3 (*C*-3), 44.6 (*C*H$_2$NH), 28.4 [C(*C*H$_3$)$_3$]. CIHRMS: m/z 483.1958, calcd for $C_{22}H_{30}N_2O_{10}$ + H: 483.1979.

Ethyl [methyl 2-*O*-benzoyl-3-(*N*-*tert*-butoxycarbonyl-glycyl-amido)-3-deoxy-α-D-allopyranosid]uronyl-glycinate (31). Boc-Gly-OH (90.4 mg, 0.516 mmol) was dissolved, under an argon atmosphere, in dry CH_2Cl_2 (2.2 mL), and HOBt (105 mg, 0.778 mmol) and DIPEA (90 μL, 0.516 mmol) were successively added. The mixture, cooled to 0 °C, was treated with EDCI (150 mg, 0.778 mmol) at the same temperature for 10 min, after that a solution of the crude compound **27** (69 mg, 0.213 mmol) in dry CH_2Cl_2 (2.2 mL) was added, and the reaction mixture was left to reach room temperature overnight. The mixture was then diluted with CH_2Cl_2 (30 mL) and successively washed with 2% HCl (50 mL), a saturated aqueous solution of potassium carbonate (50 mL), H_2O (50 mL), and a saturated aqueous solution of NaCl (50 mL); the organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to give, after column chromatography (2 : 1 EtOAc–hexane), compound **31** (66 mg, 56%) as a syrup; R_f 0.11 (same elution system); $[\alpha]_D^{25}$ +13.4 (*c* 1, CH_2Cl_2); IR ν_{max} 3377 (NH, OH), 1718 (CO carbamate), 1671 (CO amide), 1601 (NCO), 1069 (C–O–C) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm, J Hz) δ 8.00, 7.55, 7.43 (m, 5H, Ph), 7.26–7.22 (br s, 1H, N*H*CH$_2$CO$_2$Et), 5.49 (t, 1H, $J_{H,CH2}$ = 6.0, CON*H*CH$_2$NH), 5.11 (br m, 2H, H-2, H-1), 4.94 (br t, 1H, $J_{3,4}$ = 4.0, H-3), 4.22 (q, 2H, J_{ethyl} = 7,0, C*H*$_2$CH$_3$), 4.20 (d, 1H, $J_{5,4}$ = 7.5, H-5), 4.09 (dd, 2H, $J_{H,NH}$ = 6.0, J_{gem} = 14.5, –NHC*H*$_{2a}$CO$_2$Et, –C*H*$_{2a}$NHCO$_2$Bu^t), 3.97 (dd, 1H, $J_{4,3}$ = 4.0, $J_{4,5}$ = 10.0, H-4), 3.79 (dd, 2H, J_{CH2NH} = 5.5 J_{gem} = 17, –NHC*H*$_{2b}$CO$_2$Et, –C*H*$_{2b}$NHCO$_2$Bu^t), 3.49 (s, 3H, OC*H*$_3$), 1.41 [s, 9H, C(C*H*$_3$)$_3$], 1.28 (t, 3H, J_{ethyl} = 7.5, CH$_2$C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5 (*C*-6), 170.7 (NH*C*OCH$_2$NHCO$_2$Bu^t), 169.4 (*C*O$_2$Et), 165.4 (O*C*OPh), 155.9 (N–*C*O$_2$Bu^t), 133.6, 130.1, 129.0, 128.5, (Ph), 97.8 (*C*-1), 80.5 (*C*Me$_3$), 69.0 (*C*-4), 66.7 (*C*-2), 61.7 (*C*H$_2$CH$_3$), 60.4 (O$_2$C–*C*H$_2$NH), 56.4 (OCH$_3$), 49.9 (*C*-3), 44.5 (*C*H$_2$NH), 40.9 (*C*-5), 28.3 [C(*C*H$_3$)$_3$], 14.1 (CH$_2$*C*H$_3$). CIHRMS: m/z 554.2355, calcd for $C_{25}H_{35}N_3O_{11}$ + H: 554.2350.

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