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Sugar amino acids at the anomeric position of carbohydrates: synthesis of spirocyclic amino acids of 6-deoxy-L-lyxofuranose

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Abstract—Two anomeric spirodiketopiperazines and one spirohydantoin of 6-deoxy-L-lyxofuranose have been prepared from L-fucono-δ-lactone via ring contraction to the corresponding tetrahydrofuran carboxylate and anomeric functionalization including regioselective bromination and azide displacement.

1. Introduction

Amino acids and carbohydrates are two major components, which generate diversity in Nature. The combination of the structural features of simple amino acids with those of simple carbohydrates gives rise to glycosamino acids (GAAs),[1,2] which can be classified according to the position of the amino acid moiety on the cyclic polyol. Sugar amino acids (SAAs), which result from the direct incorporation of the amino acid moiety into the cyclic carbohydrate scaffold, have emerged as a new class of promising hybrids due to their restricted conformation generating β- and γ-turns as well as helices. As a consequence, SAAs have found many applications as peptide scaffolds in combinatorial chemistry[3] and as peptidomimetics.[4] When oligomerized or incorporated into peptide chains, these SAAs generate carbopeptoids[5] or foldamers[6] with restricted secondary structure displaying novel catalytic and recognition properties. Along with pyranose[7] and oxetanose[8] SAAs, furanose tetrahydrofuran (THF) SAAs[9] are the most thoroughly investigated dipeptide isosteres with significant biological activity.[10]

Among SAAs, a special situation occurs when both the amino and carboxylate groups are born by the same carbon atom of the sugar ring. SAAs with the amino acid moiety at C-2 or C-4 of the sugar template[11,12] have been described and biological activity has been observed when the α-amino acid can incorporate the anomeric centre of the carbohydrate scaffold. When the amine and the acid functionalities are connected together to yield spirohydantoin and spirodiketopiperazines, which on their own have a number of potential chemotherapeutic applications,[13] this can lead to anomeric spirocyclic amino acid carbohydrate hybrids, which have been reported to exhibit chemotherapeutic potency as in spirohydantoin-glucopyranose hybrid **1**. This is a potent inhibitor of glycogen phosphorylase,[14] the enzyme responsible for the regulation of blood sugar level, this result leading to improved syntheses of **1**[15] and design of potent analogues.[16] The natural product hydantocidin **2**, a spirohydantoin structure isolated from *Streptomyces hygroscopicus*[17] incorporates a D-ribofuranosyl unit and displays potent herbicidal and plant growth regulatory activity through inhibition of an adenylosuccinate synthetase.[18] The biological activity of **2** and its unique structure has stimulated considerable efforts towards the efficient synthesis of **2**[19] and its analogues (Fig. 1).[20]

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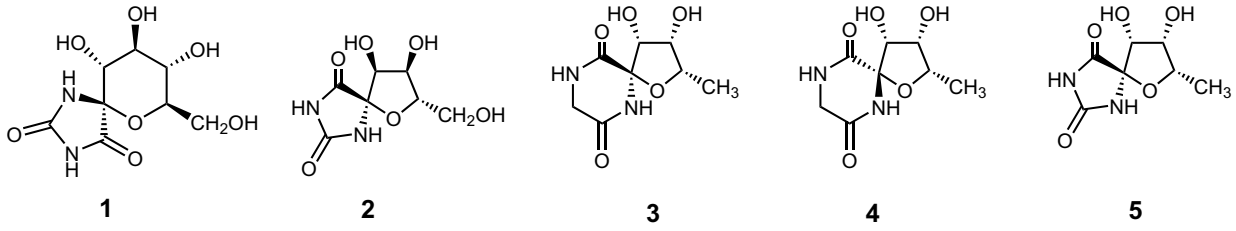


Figure 1. Structure of spirocyclic glucopyranose **1**, hydantocidin **2** and target compounds **3**–**5**.

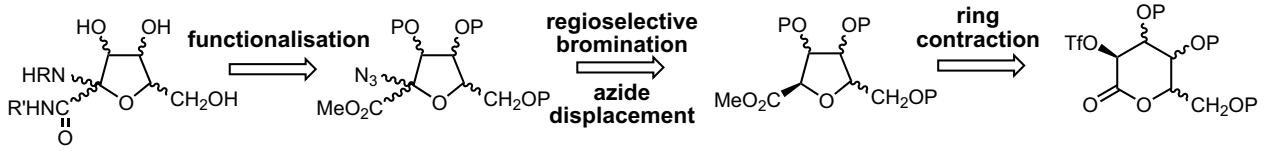
As part of a project devoted to the design of efficient glycogen phosphorylase (GPb) inhibitors as possible therapeutic agents for the treatment of diabetes, we were interested in the synthesis of a range of spirohydantoin and spirodiketopiperazines at the anomeric position of carbohydrates in the furanose form. Herein, we report the synthesis of the spirocyclic amino acids of L-lyxofuranose **3**–**5** (Fig. 1), which can be seen as ring-contracted anomeric SAAs analogues of L-fucopyranose.

2. Results and discussion

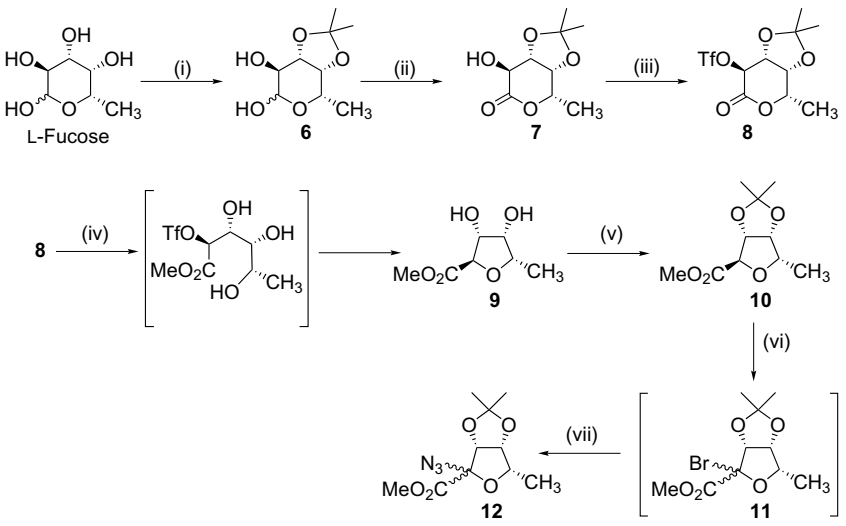
Our strategy is based upon the propensity of the 2-*O*-trifluoromethanesulfonates of carbohydrates γ- and δ-lactones to ring contract in basic[21] or acidic[22] methanol to afford the highly substituted tetrahydrofuran carboxylates. This protocol has been applied to the elaboration of libraries of *C*-glucofuranose based scaffolds.[23] These tetrahydrofuran carboxylates can be regioselectively brominated[24] and subsequently displaced with sodium azide to give access, after further processing, to a range of anomeric THF amino acid monomers derived from a sugar template (Scheme 1).

In our case, L-fucono-δ-lactone is the relevant precursor to access the target compounds **3**–**5**. The anomeric azidoester intermediate was obtained as follows (Scheme 2). Acetonation of the *cis* 3,4 diol of L-fucose with 2,2-dimethoxypropane in the presence of anhydrous copper sulfate in acetone gave the known monoacetonide **6** in 55% yield.[25] The oxidation of compound **6** with bromine–water buffered with barium carbonate, afforded L-fucono-δ-lactone **7** in 73% yield.[26] Triflation of the free secondary alcohol in **7** with trifluoromethanesulfonic anhydride in the presence of pyridine at −30 °C gave the crude triflate **8**, which was reacted with hydrogen chloride in methanol to afford the deprotected methyl ester **9** in an overall yield of 70% from **7**. The formation of methyl ester **9** most likely proceeds with hydrolysis of the acetonide, methanolysis of the lactone and subsequent intramolecular SN_2 ring closure of the resulting open chain hydroxy-triflate with inversion of configuration at C-2. Reprotection of the diol as its acetonide afforded the required methyl ester **10**. The generation of THF α-amino acid derivatives requires functionalization at C-2 of the suitably protected carbohydrate carboxylates, and regioselective bromination of **10** was examined. Treatment of **10** with lithium bis(trimethylsilyl)amide or LDA in THF at −70 °C and subsequent quenching of the transient anion with carbon tetrabromide[27] afforded the epimeric bromoesters **11**, which were treated with sodium azide in dimethylformamide to give a combined yield of 36% of the epimeric azides **12α** and **12β**, respectively, in a 9:1 ratio as determined by NMR. This low yield led us to predict another method to introduce the azido group based on the relative stability of the captodative radical formed by abstraction of hydrogen from C-2.[28] Radical bromination of **10** using *N*-bromosuccinimide in carbon tetrachloride[29] in the presence of benzoyl peroxide as an initiator followed by azide displacement afforded azides **12α** and **12β** in a 55% combined yield. This moderate yield could be tentatively explained by the difficult hydrogen abstraction at C-2 due to the steric hindrance caused by the acetonide and the methyl group. To improve this step and verify our hypothesis, the synthesis of the epimeric methyl ester **15** was achieved (Scheme 3).

The initial reaction of crude triflate **8** with sodium trifluoroacetate in DMF, followed by aqueous work-up with concomitant hydrolysis of the resulting trifluoroacetate ester, gave the inverted 6-deoxy-L-talono-δ-lactone **13** in 62% yield. Triflation of compound **13** with triflic anhydride gave triflate **14** (87% yield), which upon treatment with methanolic hydrogen chloride followed by acetonation afforded the fully protected tetrahydrofuran carboxylate **15** in 97% yield. Radical bromination of **15** afforded a mixture of crude bromides **11α** and **11β**, which were displaced with sodium azide to yield an inseparable mixture of epimeric azidoester **12α** and **12β** in good 74% yield (from **15**) and in a 10:1 ratio, respectively. This is indicative of a stereoselective bromination, an observation most often reported with substrates possessing a 3,4-*O*-isopropylidene-protected



Scheme 1. General strategy for the generation of THF α-amino acid monomers.

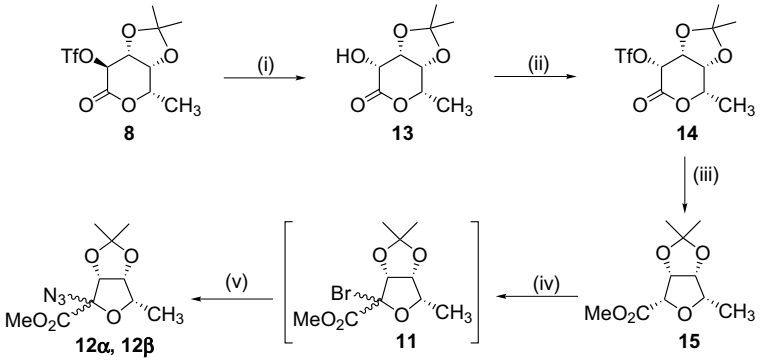


Scheme 2. Synthesis of azidoesters **12α** and **12β** from L-fucose. Reagents and conditions: (i) $CuSO_4$, acetone, 55%; (ii) Br_2, $BaCO_3$, H_2O, 73%; (iii) Tf_2O, pyridine, dichloromethane, −30 °C; (iv) 1% HCl in MeOH; (v) 2,2-dimethoxypropane, acetone, CSA, 70% over two steps; (vi) NBS, CCl_4, $(PhCOO)_2$; (vii) NaN_3, DMF, rt 55% over two steps.

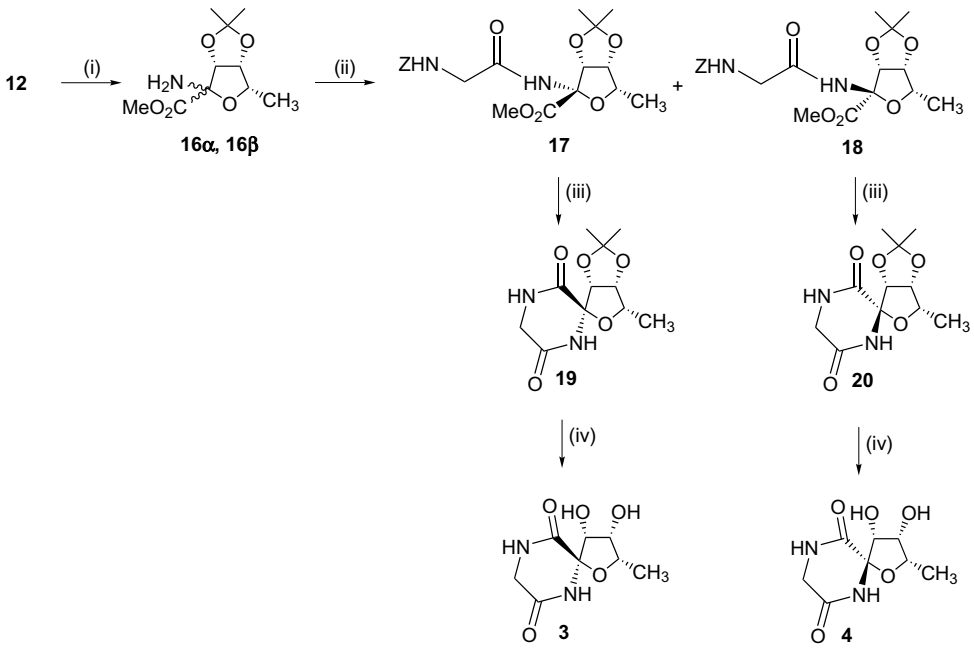
cis-diol function.[30] Azide displacement of the bromide of a highly hindered α-bromotetrahydrofuran ester has been shown to proceed with inversion of configuration.[31]

Completion of the synthesis of the anomeric spirocyclic peptides was achieved as follows (Scheme 4). Hydrogenation of azidoesters **12α** and **12β** in methanol in the presence of Pd/C gave a mixture of epimeric aminoesters **16α** and **16β** (70% yield), which were coupled with *Z*-glycine under standard conditions to afford dipeptide **17** in 17% yield along with 56% of the epimeric dipeptide **18**. Hydrogenolysis of the *Z* protecting group in **17** afforded the corresponding amine, which cyclized upon treatment with *t*-BuOK in THF to afford the spirodiketopiperazine compound **19** in 44% yield over two steps. The same sequence was applied to dipeptide **18** to afford epimeric spirocyclic sugar **20** in 69% yield. The anomeric configurations of **19** and **20** were determined by performing NMR NOE experiments. For spirodiketopiperazine **19**, a weak NOE was observed for NH···H-3. For spirodiketopiperazine **20**, a medium NOE was observed for NH···H-3 and a strong NOE was observed for NH···H-5. This is only consistent with compound **19** having a *trans* H-3/NH relationship and compound **20** having a *cis* H-3/NH and a *cis* H-5/NH relationships. The structure of compound **20** was firmly established by single X-ray crystallographic analysis.[32] Removal of the acetonide group in spirodiketopiperazines **19** and **20** with TFA furnished the spirocyclic sugar amino acids **3** and **4**.

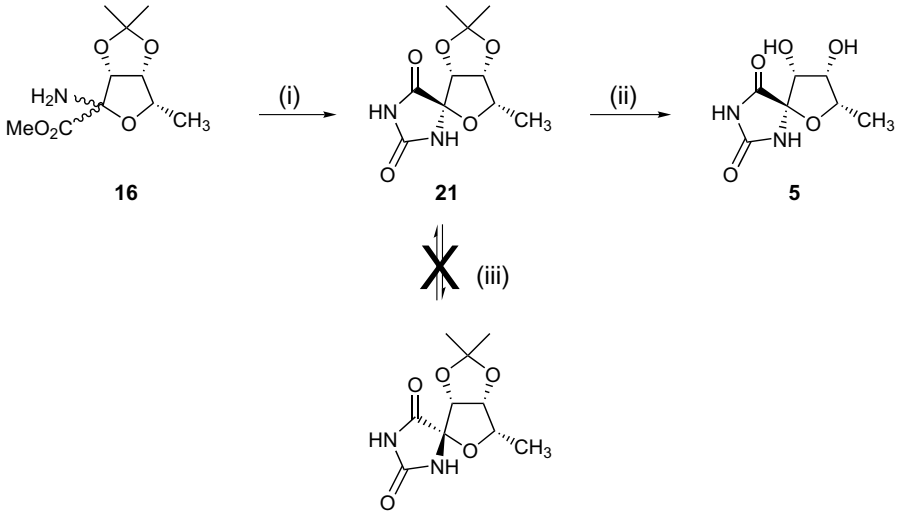
The synthesis of the corresponding anomeric spirohydantoins was then examined (Scheme 5). Using an established methodology for the construction of a spirohydantoin ring,[33] amine **16** was treated with potassium cyanate in acetic acid at 65 °C to afford the intermediate ureas, which spontaneously cyclized in acetic acid to afford the spirocyclic derivative **21** in 74% yield. Final deprotection with aqueous TFA led to the target spirohydantoin **5** in 94% yield. Equilibration of compound **21** to the epimeric spirocyclic compound by treatment with *t*-BuOK in THF proved unsuccessful.



Scheme 3. Synthesis of the azidoesters **12α** and **12β** from triflate **14**. Reagents and conditions: (i) CF_3COONa, DMF, 62% from **7**; (ii) Tf_2O, pyridine, −30 °C, 84%; (iii) 3% HCl in MeOH then 2,2-dimethoxypropane, CSA, acetone, 97%; (iv) NBS, CCl_4, $(PhCOO)_2$; (v) NaN_3, DMF, rt, 74% over two steps.



Scheme 4. Synthesis of the spirodiketopiperazines **3** and **4**. Reagents and conditions: (i) H_2, Pd/C, MeOH, 70%; (ii) *Z*-glycine DCC, 1-hydroxybenzotriazole, dichloromethane, 73%; (iii) H_2, Pd black, MeOH then *t*-BuOK, THF, 44–69%; (iv) 50% aq TFA, 80%.



Scheme 5. Synthesis of the spirohydantoin **5**. Reagents and conditions: (i) KOCN, AcOH, 74%; (ii) 50% aq TFA, 94%; (iii) *t*-BuOK, THF.

3. Conclusion

In summary, this paper reports an efficient synthesis of the anomeric spirodiketopiperazines **3** and **4** and spirohydantoin **5** of 6-deoxy-L-lyxofuranose. The evaluation of these compounds for their herbicidal activity and as glycogen phosphorylase inhibitors is underway.

4. Experimental

Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz) or a Bruker AM 500 (500 MHz) spectrometer. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz), a Bruker AC 200 (50 MHz) or a Bruker AM 500 (125 MHz) spectrometer and multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Infra-red spectra were recorded on a Perkin–Elmer 1750 IR FT spectrophotometer. Mass spectra were recorded on a VG Masslab 20-250, BIO-Q or using desorption chemical ionization (DCI NH_3), chemical ionization (CI NH_3), electrospray or thermospray, or atmospheric pressure chemical ionization ($APCI^+$ or

APCI$^-$) as stated. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalysis service of the Dyson Perrins laboratory. Thin layer chromatography (TLC) was carried out on plastic or aluminium sheets coated with 60 F_{254} silica, and plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; hexane was distilled at 68 °C before use to remove less volatile fractions.

4.1. 3,4-*O*-Isopropylidene-L-fucose 6

L-Fucose (19.54 g, 119 mmol) and anhydrous copper sulfate (39 g, 244.4 mmol, 2 equiv) were suspended in HPLC grade acetone (300 ml) under N_2. The suspension was stirred for 16 h under N_2 by which time, TLC (ethyl acetate) showed some diacetonide (R_f 0.9), some monoacetonide (R_f 0.5 and R_f 0.4) and some starting material (R_f 0.0). The suspension was filtered through a sinta funnel topped with a 2 mm filter sheet, which was eluted with acetone (200 ml). The filter cake was dried on the vacuum line for 5 h, suspended again in acetone and stirred for 16 h under N_2. This procedure was repeated twice. The filtrates were combined, concentrated in vacuo to afford a white solid, which was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 2:1 then ethyl acetate) afforded 3,4-*O*-isopropylidene-L-fucose **6** (13.35 g, 55% yield) as a white solid: mp 105–108 °C (ethyl acetate); $[\alpha]_D^{22} = -84.5$ (*c* 2.2, H_2O, 1 h); [lit. mp 110–111 °C (ethyl acetate); $[\alpha]_D^{21} = -90 \rightarrow -68$ (*c* 0.2, H_2O, equil. over 24 h)]; ν_{max} (KBr)/cm^{-1}: 3403 (br, OH); δ_H (500 MHz, CD_3OD): 1.25 (3H, d, $J_{5,6}$ 6.7 Hz, $CH_3\alpha$), 1.33, 1.47 (6H, 2 × s, $(CH_3)_2C\alpha$), 1.33 (3H, d, $J_{5,6}$ 6.7 Hz, $CH_3\beta$), 1.34, 1.49 (6H, 2 × s, $(CH_3)_2C\beta$), 3.35 (1H, app t, *J* 7.6 Hz, H-2β), 3.61 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 7.1 Hz, H-2α), 3.94 (1H, dq, $J_{4,5}$ 2.2 Hz, $J_{5,6}$ 6.7 Hz, H-5β), 3.97 (1H, dd, $J_{3,4}$ 5.4 Hz, $J_{2,3}$ 7.4 Hz, H-3β), 4.04 (1H, dd, $J_{4,5}$ 2.2 Hz, $J_{3,4}$ 5.4 Hz, H-4β), 4.08 (1H, dd, $J_{4,5}$ 2.4 Hz, $J_{3,4}$ 5.8 Hz, H-4α), 4.18 (1H, dd, $J_{3,4}$ 5.8 Hz, $J_{2,3}$ 7.1 Hz, H-3α), 4.35 (1H, dq, $J_{4,5}$ 2.4 Hz, $J_{5,6}$ 6.7 Hz, H-5α), 4.39 (1H, d, $J_{1,2}$ 8.2 Hz, H-1β), 5.01 (1H, d, $J_{1,2}$ 3.6 Hz, H-1α); δ_C (125 MHz, CD_3OD): 16.7 (q, $CH_3\alpha$), 16.9 (q, $CH_3\beta$), 26.3 (q, $(CH_3)_2C\alpha$), 26.6 (q, $(CH_3)_2C\beta$), 28.3 (q, $(CH_3)_2C\alpha$), 28.5 (q, $(CH_3)_2C\beta$), 64.3, 69.9, 71.2, 75.5, 77.2, 77.5, 77.8, 80.9 (8 × d, C-2α, C-3α, C-4α, C-5α, C-2β, C-3β, C-4β, C-5β), 93.4 (d, C-1α), 97.5 (d, C-1β), 109.8 (s, $C(CH_3)_2\alpha$), 110.5 (s, $C(CH_3)_2\beta$); *m*/*z* (CI, NH_3): 222 ($M+NH_4^+$, 18%), 204 ($M+NH_4^+-H_2O$, 100%), 187 ($M+H^+-H_2O$, 37%); (Found: C, 52.73; H, 8.15; $C_9H_{16}O_5$ requires C, 52.93; H, 7.90).

4.2. 3,4-*O*-Isopropylidene-L-fucono-1,5-lactone 7

Barium carbonate (20.3 g, 102.9 mmol, 3 equiv) was added to a solution of 3,4-*O*-isopropylidene-L-fucose **6** (7.0 g, 34.3 mmol) in distilled water (100 ml) under vigorous stirring. The resulting suspension was cooled to 0 °C and bromine (6.2 ml, 120.1 mmol, 3.5 equiv) was added by portions over 5 min. The solution was stirred at 0 °C for 20 min and then stirred at room temperature for 3 h by which time TLC (ethyl acetate) showed a major product (R_f 0.8), a minor product (R_f 0.6) and a trace of the starting material (R_f 0.5 and R_f 0.4). The excess of barium carbonate was filtered off through a Celite plug, which was eluted with water (150 ml). To bubble off the excess of bromine, nitrogen was passed through the orange solution until all the colour had disappeared. The aqueous solution was extracted with ethyl acetate (3 × 200 ml). The organic extracts were combined, dried over magnesium sulfate and the solvent removed under reduced pressure. The resulting white solid was purified by flash chromatography (ethyl acetate/hexane 1:2 then 1:1) to afford 3,4-*O*-isopropylidene-L-fucono-1,5-lactone **7** (5.055 g, 73% yield) as a white crystalline solid: mp 92–94 °C (ethyl acetate/hexane); $[\alpha]_D^{24} = -148.2$ (*c* 1.09, $CHCl_3$) [lit. mp 98–99 °C (ethyl acetate); $[\alpha]_D^{21} = -137$ (*c* 0.1, $CHCl_3$)]; ν_{max} (film)/cm^{-1}: 3356 (br, OH), 1729 (C=O); δ_H (500 MHz, $CDCl_3$): 1.36, 1.42 (6H, s, $(CH_3)_2C$), 1.45 (3H, d, $J_{5,6}$ 6.7 Hz, CH_3), 4.37 (1H, dd, $J_{4,5}$ 1.9 Hz, $J_{3,4}$ 7.5 Hz, H-4), 4.38 (1H, d, $J_{2,3}$ 2.7 Hz, H-2), 4.56 (1H, dd, $J_{2,3}$ 2.7 Hz, $J_{3,4}$ 7.5 Hz, H-3), 5.02 (1H, dq, $J_{5,6}$ 6.7, 1.9 Hz, H-5); δ_C (125 MHz, $CDCl_3$): 16.0 (q, Me), 24.1 (q, Me_2C), 26.0 (q, Me_2C), 69.2, 73.1, 73.9, 75.5 (4 × d, C-2, C-3, C-4, C-5), 110.1 (s, CMe_2), 170.9 (s, C-1); *m*/*z* (CI; NH_3): 220 ($M+NH_4^+$, 100%), 203 ($M+H^+$, 18%), (Found: C, 53.55; H, 7.13; $C_9H_{14}O_5$ requires C, 53.44; H, 6.98).

4.3. 2-Trifluoromethanesulfonyl-3,4-*O*-isopropylidene-L-fucono-1,5-lactone 8 and methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate 10

3,4-*O*-Isopropylidene-L-fucono-1,5-lactone **7** (3.31 g, 16.38 mmol) was dissolved in dry dichloromethane (100 ml) under N_2 and the solution cooled to −30 °C. Dry pyridine (4 ml, 49.14 mmol, 3 equiv) was added followed by the dropwise addition of triflic anhydride (41 ml, 24.57 mmol, 1.5 equiv) over 5 min. The solution was stirred at −20 °C under N_2. After 20 min, TLC (ethyl acetate/hexane 1:2) showed some starting material as still remaining. Some more triflic anhydride (1 ml, 0.4 equiv) was added to complete the reaction. The reaction was quenched by the addition of five drops of water. The solution was filtered through a Celite plug topped with magnesium sulfate and eluted with dichloromethane. The organic extracts were combined and dried (magnesium sulfate). The solvent was removed in vacuo and coevaporated with toluene to afford the crude 2-trifluoromethanesulfonyl-3,4-*O*-isopropylidene-L-fucono-1,5-lactone **8** as an oil: $[\alpha]_D^{21} = -64.3$ (*c* 1.11, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1766 (C=O); δ_H (200 MHz, $CDCl_3$): 1.38, 1.44 (3H, s, $(CH_3)_2C$), 1.52 (3H, d, $J_{5,6}$ 6.6 Hz, CH_3), 4.46 (1H, dd, $J_{4,5}$ 1.6 Hz, $J_{3,4}$ 7.2 Hz, H-4), 4.72 (1H, dd, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.2 Hz, H-3), 4.81 (1H, dq, $J_{5,6}$ 6.6, 1.6 Hz, H-5), 5.14 (1H, d, $J = 2.7$ Hz, H-2); δ_C (50 MHz, $CDCl_3$): 16.1 (q, CH_3), 23.9 (q, $(CH_3)_2C$), 25.7 (q, $(CH_3)_2C$), 73.4, 73.7, 74.3, 77.1 (4 × d, C-2, C-3, C-4, C-5), 111.6 (s, $(CH_3)_2C$), 162.1 (s, C-1); *m*/*z* (CI; NH_3): 352 ($M+NH_4^+$, 100%).

Crude triflate **8** was dissolved in 1% HCl in methanol (20 ml) under N_2 and the solution stirred at room temper-

ature. After 16 h, TLC (ethyl acetate/hexane 1:1) showed no starting material and two new products (R_f 0.8 and R_f 0.4). The reaction mixture was diluted with ethyl acetate (20 ml) and neutralized with an excess of sodium bicarbonate. The solution was filtered through a Celite pad eluted with ethyl acetate and then concentrated in vacuo. The resulting oil was dissolved in an acetone/2,2-dimethoxypropane solution (9:1, 150 ml) and camphorsulfonic acid (33 mg) was added. The solution was stirred under N_2 for 6 h by which time TLC (ethyl acetate/hexane 1:1) showed one main product (R_f 0.8). The solution was neutralized with an excess of sodium bicarbonate. The solution was filtered through a Celite pad eluted with ethyl acetate and then concentrated in vacuo. The residue was partitioned between $CHCl_3$ (100 ml) and water (100 ml). The aqueous layer was extracted with $CHCl_3$ (2 × 100 ml). The organic extracts were combined, dried (magnesium sulfate) and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate/hexane 1:4 then 1:3 then 1:2) afforded methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **10** (2.741 g, 75% yield) as a colourless oil: $[\alpha]_D^{22} = -33.8$ (*c* 1.95, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1754 (C=O); δ_H (500 MHz, $CDCl_3$): 1.35, 1.51 (6H, 2 × s, $(CH_3)_2C$), 1.36 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3), 3.76 (3H, s, CH_3O_2C), 4.14 (1H, dq, $J_{5,6}$ 6.3 Hz, $J_{5,4}$ 3.6 Hz, H-5), 4.54 (1H, s, H-2), 4.58 (1H, dd, $J_{4,5}$ 3.6 Hz, $J_{4,3}$ 6.0 Hz, H-4), 4.97 (1H, d, $J_{3,4}$ 6.0 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 13.7 (q, CH_3), 25.1 (q, $(CH_3)_2C$), 26.2 (q, $(CH_3)_2C$), 52.2 (q, CH_3O_2C), 78.4, 81.9, 82.5, 84.6 (4 × d, C-2, C-3, C-4, C-5), 112.9 (s, $(CH_3)_2C$), 171.1 (s, C-1); *m*/*z* (CI; NH_3): 234 ($M+NH_4^+$, 100%), 217 ($M+H^+$, 35%); (Found: C, 55.79; H, 7.17; $C_{10}H_{16}O_5$ requires C, 55.53; H, 7.46).

4.4. Methyl 2,5-anhydro-2-bromo-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 11, methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-talonate 12α and methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 12β

4.4.1. Method 1. Methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **10** (115 mg, 0.53 mmol) was dissolved in anhydrous THF under N_2. The solution was cooled to −70 °C and $LiN(TMS)_2$ (1.33 ml, 1.33 mmol, 1 M solution in THF) was added over 3 min and the reaction mixture then stirred for 5 min. The reaction was then quenched with CBr_4 and stirred for 40 min. The reaction mixture was then diluted with CH_2Cl_2 (20 ml), and washed with water (20 ml). The organic layer was dried over $MgSO_4$, and the solvent evaporated. The crude bromoester **11** was dissolved in dry DMF (2 ml) under N_2 and sodium azide (38 mg, 0.58 mmol) was added. The solution was stirred for 16 h under N_2. The solvent was removed under reduced pressure and coevaporated with toluene (3 × 20 ml). The residue was preadsorbed on silica and purified by flash chromatography (ethyl acetate/hexane 1:5) to afford a mixture of azidoesters **12** (49 mg, 0.191 mmol) in 36% yield from **11**.

4.4.2. Method 2. Methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **10** (119 mg, 0.551 mmol) was dissolved in carbon tetrachloride (4 ml) under N_2. *N*-Bromosuccinimide (127 mg, 0.716 mmol, 1.3 equiv) and benzoyl peroxide (5 mg) were added under N_2. The solution was degassed three times and air replaced with N_2. The suspension was plunged into an oil bath at 80 °C and stirred for 25 min when TLC (ethyl acetate/hexane 1:2) showed a new product (R_f 0.7) and a trace of starting material (R_f 0.25). The flask was plunged in an ice bath. The solution was filtered and the sinta funnel eluted with carbon tetrachloride. The solvent was removed under reduced pressure to give the crude bromoester **11**, which was dissolved in dry DMF (3 ml) under N_2, and sodium azide (107 mg, 1.64 mmol) was added. The solution was stirred for 12 h under N_2. The solvent was removed under reduced pressure and coevaporated with toluene (3 × 20 ml). The residue was preadsorbed on silica and purified by flash chromatography (ethyl acetate/hexane 1:5) to afford a mixture of azidoesters **12α** and **12β** (77 mg, 0.303 mmol) in 55% yield and in a 9:1 ratio from **10**.

4.4.3. Method 3. Methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **15** (1 g, 4.63 mmol) was dissolved in carbon tetrachloride under N_2. *N*-Bromosuccinimide (1.071 g, 6.02 mmol, 1.3 equiv) and benzoyl peroxide (10 mg) were added under N_2. The solution was degassed three times and air replaced with N_2. The suspension was plunged into an oil bath at 80 °C and stirred for 25 min when TLC (ethyl acetate/hexane 1:2) showed a new product (R_f 0.7) and a trace of starting material (R_f 0.25). The flask was plunged in an ice bath. The solution was filtered and the sinta funnel eluted with carbon tetrachloride. The solvent was removed under reduced pressure to give the crude bromoester **11**, which was dissolved in dry DMF (10 ml) under N_2, and sodium azide (391 mg, 1.3 equiv) then added. The solution was stirred for 16 h under N_2. The solvent was removed under reduced pressure and coevaporated with toluene (3 × 20 ml). The residue was preadsorbed on silica and purified by flash chromatography (ethyl acetate/hexane 1:5) to afford a mixture of methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-talonate **12α** and methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **12β** as a colourless oil in a 10:1 ratio (891 mg, 74% yield). Careful chromatography enabled to obtain pure samples of both azidoesters.

4.5. Methyl 2,5-anhydro-2-bromo-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 11

$[\alpha]_D^{21} = -199.0$ (*c* 1.60, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1763 (C=O); δ_H (500 MHz, $CDCl_3$): 1.33, 1.41 (6H, 2 × s, $(CH_3)_2C$), 1.47 (3H, d, $J_{5,6}$ 6.5 Hz, CH_3), 3.92 (3H, s, CH_3O_2C), 4.44 (1H, dq, $J_{5,6}$ 6.5 Hz, $J_{5,4}$ 3.9 Hz, H-5), 4.78 (1H, dd, $J_{4,5}$ 3.9 Hz, $J_{4,3}$ 5.7 Hz, H-4), 5.31 (1H, d, $J_{3,4}$ 5.7 Hz, H-3); δ_C (50 MHz, $CDCl_3$): 12.4 (q, CH_3), 25.2 (q, $(CH_3)_2C$), 25.8 (q, $(CH_3)_2C$), 53.4 (q, CH_3O_2C), 79.6, 80.8, 90.6 (3 × d, C-3, C-4, C-5), 99.6 (s, C-2), 113.6 (s, $(CH_3)_2C$), 165.1 (s, C-1); *m*/*z* (CI; NH_3): 312 ($M+NH_4^+$, 100%), 314 ($M+NH_4^+$, 100%), 232 (95%); (Found: C, 40.15; H, 4.94; $C_{10}H_{15}O_5Br$ requires C, 40.70; H, 5.12).

4.6. Methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-talonate 12α

$[\alpha]_D^{22} = -35.3$ (*c* 1.23, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2130 (N_3), 1744 (C=O); δ_H (500 MHz, $CDCl_3$): 1.39 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 1.38, 1.60 (6H, 2 × s, $(CH_3)_2C$), 3.83 (s, CH_3O_2C), 4.13 (1H, dq, $J_{4,5}$ 4.0 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.69 (1H, dd, $J_{3,4}$ 5.9 Hz, $J_{4,5}$ 4.0 Hz, H-4), 4.98 (1H, d, $J_{3,4}$ 5.9 Hz, H-3); δ_H (125 MHz, $CDCl_3$): 13.6 (q, CH_3), 24.6, 25.3 (2 × q, $(CH_3)_2C$), 53.2 (q, CH_3O_2C), 76.4, 81.2, 83.6 (3 × d, C-3, C-4, C-5), 94.4 (s, C-2), 113.7 (s, $C(CH_3)_2$), 168.0 (s, C=O); *m*/*z* per (CI, NH_3): 275 ($M+NH_4^+$, 25%), 232 ($M+NH_4^+-CH_3CO$, 74%), 210 (100%); (Found: C, 46.88; H, 5.89; N, 16.97; $C_{10}H_{15}O_5N_3$ requires C, 46.69; H, 5.88; N, 16.33); (HRMS: Found: 232.1032; Calcd for MH^+-N_2: 230.1028).

4.7. Methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 12β

ν_{max} (film)/cm^{-1}: 1766 (C=O), 2116 (N_3); δ_H (500 MHz, $CDCl_3$): 1.32, 1.44 (6H, 2 × s, $(CH_3)_2C$), 1.46 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 3.89 (3H, s, CH_3O_2C), 4.27 (1H, dq, $J_{5,6}$ 6.4 Hz, $J_{5,4}$ 3.5 Hz, H-5), 4.63 (1H, d, $J_{3,4}$ 5.7 Hz, H-3), 4.68 (1H, dd, $J_{4,5}$ 3.5 Hz, $J_{4,3}$ 5.7 Hz, H-4); δ_C (125 MHz, $CDCl_3$): 13.2 (q, CH_3), 25.2 (q, $(CH_3)_2C$), 25.8 (q, $(CH_3)_2C$), 53.1 (q, CH_3O_2C), 78.3, 80.9, 86.6 (3 × d, C-3, C-4, C-5), 98.7 (s, C-2), 113.8 (s, $(CH_3)_2C$), 165.5 (s, C-1).

4.8. 3,4-*O*-Isopropylidene-L-talono-1,5-lactone 13

3,4-*O*-Isopropylidene-L-fucono-1,5-lactone **7** (2.2 g, 10.89 mmol) was dissolved in dry dichloromethane under N_2 and the solution was cooled to −30 °C. Dry pyridine (2.65 ml, 32.67 mmol, 3 equiv) was added followed by the dropwise addition of triflic anhydride (2.2 ml, 13.7 mmol, 1.2 equiv). The solution was stirred at −20 °C under N_2. After 20 min, TLC (ethyl acetate/hexane 1:2) showed some starting material remaining. Some more triflic anhydride (1.1 ml, 0.6 equiv) was added to complete the reaction. The reaction was quenched by the addition of a few drops of water. The solution was filtered through a Celite pad topped with magnesium sulfate and eluted with dichloromethane. The solvent was removed in vacuo and coevaporated with toluene. The crude triflate **8** was then dissolved in dry DMF (20 ml) under N_2 and sodium trifluoroacetate (4.477 g, 32.67 mmol, 3 equiv) was added. The solution was stirred at 70 °C for 43 h. The reaction mixture was then diluted with dry methanol (4 ml) and stirred under N_2 for 18 h at room temperature. The solvent was removed under reduced pressure and coevaporated with toluene (4 × 20 ml) to give a yellow oil, which was dissolved in ethyl acetate (80 ml) and washed with brine (80 ml). The aqueous layer was extracted with ethyl acetate (2 × 80 ml). The organic extracts were combined, dried (magnesium sulfate) and the solution concentrated in vacuo to afford a yellow oil, which was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 2:3 then 1:1 then ethyl acetate) afforded 3,4-*O*-isopropylidene-L-talono-1,5-lactone **13** (1.38 g, 63% yield) as a white solid: mp 144–145 °C; $[\alpha]_D^{21} = -105.4$ (*c* 0.74, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3401 (br, OH), 1746 (C=O); δ_H (500 MHz, benzene-d_6): 1.05 (3H, d, $J_{5,6}$ 6.5 Hz, CH_3), 1.00, 1.29 (6H, 2 × s, $(CH_3)_2C$), 3.11 (1H, dq, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 6.5 Hz, H-5), 3.20 (1H, dd, $J_{3,4}$ 7.7 Hz, $J_{4,5}$ 1.7 Hz, H-4), 3.35 (1H, br, OH), 3.59 (1H, br, H-2), 4.10 (1H, dd, $J_{3,4}$ 7.7 Hz, $J_{2,3}$ 3.5 Hz, H-3); δ_C (50 MHz, $CDCl_3$): 15.5 (q, CH_3), 24.3, 25.8 (2 × q, $(CH_3)_2C$), 68.5, 73.3, 74.8, 75.3 (4 × d, C-2, C-3, C-4, C-5), 110.8 (s, $C(CH_3)_2$), 172.4 (s, C=O); *m*/*z* (CI, NH_3): 220 ($M+NH_4^+$, 100%), 203 (MH^+, 90%), 210 (100%); (Found: C, 53.41; H, 7.16; $C_9H_{14}O_5$ requires C, 53.44; H, 6.98).

4.9. 2-Trifluoromethanesulfonyl-3,4-*O*-isopropylidene-L-talono-1,5-lactone 14

3,4-*O*-Isopropylidene-L-talono-1,5-lactone **13** (1.86 g, 9.2 mmol) was dissolved in dry dichloromethane (30 ml) under N_2 and the solution cooled to −40 °C. Dry pyridine (1.49 ml, 18.4 mmol, 2 equiv) was added followed by dropwise addition of triflic anhydride (1.86 ml, 11.0 mmol, 1.2 equiv) over 5 min. The solution was stirred at −30 °C under N_2. After 40 min, TLC (ethyl acetate/hexane 1:1) showed no starting material. The reaction was quenched by addition of three drops of water. The solution was filtered through a Celite pad topped with magnesium sulfate and eluted with dichloromethane. The organic layer was concentrated in vacuo and coevaporated with toluene. The resulting solid was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 1:2 then 1:1) afforded 2-trifluoromethanesulfonyl-3,4-*O*-isopropylidene-talono-1,5-lactone **14** (2.648 g, 86% yield) as a white solid: mp 142–145 °C; $[\alpha]_D^{23} = -56.9$ (*c* 0.91, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1777 (C=O); δ_H (500 MHz, $CDCl_3$): 1.40, 1.50 (6H, 2 × s, $(CH_3)_2C$), 1.50 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 4.43 (1H, dq, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.50 (1H, dd, $J_{3,4}$ 7.7 Hz, $J_{4,5}$ 1.7 Hz, H-4), 4.88 (1H, dd, $J_{3,4}$ 7.7 Hz, $J_{2,3}$ 3.3 Hz, H-3), 3.59 (1H, d, $J_{2,3}$ 3.3 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 15.6 (q, CH_3), 24.5, 25.8 (2 × q, $(CH_3)_2C$), 73.7, 73.8, 75.6, 78.9 (4 × d, C-2, C-3, C-4, C-5), 112.2 (s, $C(CH_3)_2$), 162.7 (s, C=O); *m*/*z* (CI, NH_3): 352 ($M+NH_4^+$, 100%); (Found: C, 35.86; H, 3.86; $C_{10}H_{13}O_7SF_3$ requires C, 35.93; H, 3.92).

4.10. Methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 15

3,4-*O*-Isopropylidene-L-talono-1,5-lactone **13** (1.38 g, 6.83 mmol) was dissolved in dry dichloromethane (50 ml) under N_2 and the solution was cooled to −25 °C. Dry pyridine (1.65 ml, 20.5 mmol, 3 equiv) was added followed by the dropwise addition of triflic anhydride (1.38 ml, 8.2 mmol, 1.2 equiv) over 3 min. The solution was stirred at −20 °C under N_2. After 20 min, TLC (ethyl acetate/hexane 1:1) showed some starting material remaining. Some more triflic anhydride (0.5 ml, 0.4 equiv) was added to complete the reaction. After 50 min, the reaction was quenched by the addition of 4 drops of water. The solution was filtered through a Celite pad topped with magnesium sulfate and eluted with dichloromethane. The solvent was removed in vacuo and coevaporated with toluene. The crude triflate **14** was dissolved in 3% HCl in methanol (20 ml) under N_2 and the solution was stirred at room temperature. After 64 h, TLC (ethyl acetate/hexane 1:1)

showed a trace of starting material. The solution was then stirred at 55 °C for 8 h. The reaction mixture was diluted with ethyl acetate (20 ml) and neutralized with sodium bicarbonate. The solution was filtered through a Celite pad eluted with ethyl acetate and concentrated in vacuo to afford an oil, which was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 1:2 then 1:1 then ethyl acetate) afforded methyl 2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **15** (1.069 g, 74% yield) as a colourless oil: $[\alpha]_D^{22} = -53.9$ (*c* 1.21, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1766 (C=O); δ_H (500 MHz, benzene-d_6): 0.74 (3H, d, $J_{5,6}$ 6.8 Hz, CH_3), 1.14, 1.48 (6H, 2 × s, $(CH_3)_2C$), 3.43 (3H, s, CH_3O_2C), 3.89 (1H, dd, $J_{4,5}$ 2.2 Hz, $J_{4,3}$ 6.2 Hz, H-4), 4.28 (1H, d, $J_{2,3}$ 5 Hz, H-2), 4.39 (1H, dq, $J_{5,6}$ 6.3 Hz, $J_{5,4}$ 2.2 Hz, H-5), 4.51 (1H, app t, *J* 5.6 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 16.9 (q, CH_3), 25.2, 26.2 (2 × q, $(CH_3)_2C$), 52.1 (q, CH_3O_2C), 79.3, 80.4, 81.7, 85.5 (4 × d, C-2, C-3, C-4, C-5), 113.7 (s, $C(CH_3)_2$), 168.7 (s, C-1); *m*/*z* (CI; NH_3): 234 ($M+NH_4^+$, 100%), 217 (MH^+, 55%), 201 (22%); (Found: C, 55.36; H, 7.74; $C_{10}H_{16}O_5$ requires C, 55.53; H, 7.46).

4.11. Methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate 16α and methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate 16β

Methyl 2,5-anhydro-2-azido-6-deoxy-3,4-*O*-isopropylidene-L-talonate **12α** (222 mg, 0.863 mmol) was dissolved in HPLC grade methanol (10 ml). Palladium black (52 mg) was added. The solution was degassed three times and air was replaced by H_2. The solution was stirred at room temperature under an atmosphere of H_2. After 19 h, TLC (ethyl acetate/hexane 1:2) showed no trace of starting material (R_f 0.7) and a new product (R_f 0.3). The solution was filtered through a Celite plug eluted with methanol (50 ml). The solvent was removed under reduced pressure to give an oil. Purification by flash chromatography (ethyl acetate/hexane 1:2) afforded a mixture of methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **16α** and methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **16β** (143 mg, 72% yield) as a colourless oil.

Data for the major epimer: $[\alpha]_D^{23} = -27.7$ (*c* 0.95, $CHCl_3$); ν_{max} (film)/cm^{-1}: 1737 (C=O), 3401 (NH_2); δ_H (500 MHz, $CDCl_3$): 1.27 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3), 1.36, 1.52 (6H, 2 × s, $(CH_3)_2C$), 2.45 (2H, br, NH_2), 3.77 (3H, s, CH_3O_2C), 3.85 (1H, dq, $J_{5,6}$ 6.3 Hz, $J_{5,4}$ 3.8 Hz, H-5), 4.64 (1H, dd, $J_{4,5}$ 3.8 Hz, $J_{4,3}$ 6.0 Hz, H-4), 4.88 (1H, d, $J_{3,4}$ 6.0 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 13.8 (q, CH_3), 24.7 (q, $(CH_3)_2C$), 26.0 (q, $(CH_3)_2C$), 52.4 (q, CH_3O_2C), 74.4, 81.6, 81.8 (3 × d, C-3, C-4, C-5), 92.1 (s, C-2), 112.3 (s, $(CH_3)_2C$), 169.3 (s, C-1); *m*/*z* (APCI+): 232 (MH^+, 82%), 215 (100%); (HRMS: Found: 232.1184; Calcd for MH^+: 232.1184).

4.12. Methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-talonate 17 and methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-galactonate 18

DCC (305 mg, 1.48 mmol, 1.3 equiv) was suspended in dry DMF (10 ml) at 0 °C under N_2. *Z*-Glycine (310 mg, 1.48 mmol, 1.3 equiv) and 1-hydroxybenzotriazole (300 mg, 1.48 mmol, 1.3 equiv) were added at 0 °C. The white suspension was sonicated and stirred for 15 min at 0 °C and then allowed to warm up to room temperature and stirred for a further 30 min at room temperature. Methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **16α** and methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **16β** (265 mg, 1.14 mmol) were dissolved in dry DMF (5 ml) under N_2 and then added dropwise to the suspension stirred at room temperature. After 18 h, TLC (ethyl acetate/hexane 1:1) showed a trace of starting material and three new spots. The solvent was removed under reduced pressure and coevaporated with toluene to give a white solid, which was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 1:1 then ethyl acetate) afforded methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-talonate **17** (85 mg, 0.201 mmol, 17% yield) as a white solid: mp 94–96 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = -3.2$ (*c* 1.19, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3399 (NH), 2937 (NH), 1733 (C=O), 1697 (C=O); δ_H (500 MHz, $CDCl_3$): 1.37 (3H, d, $J_{5,6}$ 6.5 Hz, CH_3), 1.37, 1.51 (6H, 2 × s, $(CH_3)_2C$), 3.78 (s, CH_3O_2C), 3.96 (2H, m, $NHCH_2C=O$), 4.32 (1H, dq, $J_{4,5}$ 3.5 Hz, $J_{5,6}$ 6.5 Hz, H-5), 4.62 (1H, dd, $J_{3,4}$ 5.8 Hz, $J_{4,5}$ 3.5 Hz, H-4), 4.76 (1H, d, $J_{3,4}$ 5.8 Hz, H-3), 5.14 (2H, s, CH_2Ph), 5.33 (1H, br, NH), 7.20 (1H, br, NH), 7.32–7.38 (5H, m, ArH); δ_C (125 MHz, $CDCl_3$): 13.6 (q, CH_3), 25.0, 25.8 (2 × q, $(CH_3)_2C$), 44.4 (t, $NHCH_2C=O$), 53.1 (q, CH_3O_2C), 67.2 (t, CH_2Ph), 75.9, 81.3, 83.8 (3 × d, C-3, C-4, C-5), 88.2 (s, C-2), 113.8 (s, $C(CH_3)_2$), 128.1, 128.2, 128.6 (3 × d, $Ph_{o,m,p}$), 136.1 (s, Ph_{ipso}), 156.2 (s, C=O), 168.3 (s, C=O), 169.5 (s, C=O); *m*/*z* (APCI+): 423 (MH^+, 100%); (Found: C, 56.79; H, 6.30; N, 6.63; $C_{20}H_{26}O_8N_2$ requires C, 56.87; H, 6.20; N, 6.63).

Further elution afforded methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-galactonate **18** (333 mg, 0.789 mmol, 69% yield) as a white solid: mp 191–193 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = -49.0$ (*c* 0.42, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3330 (NH), 2951 (NH), 1740 (C=O), 1687 (C=O); δ_H (500 MHz, $CDCl_3$): 1.36 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 1.30, 1.45 (6H, 2 × s, $(CH_3)_2C$), 3.81 (s, CH_3O_2C), 3.86 (2H, m, $NHCH_2C=O$), 4.26 (1H, dq, $J_{4,5}$ 3.6 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.69 (1H, app t, $J_{3,4}$ 5.7 Hz, $J_{4,5}$ 3.6 Hz, H-4), 4.90 (1H, d, $J_{3,4}$ 5.7 Hz, H-3), 5.13 (2H, s, CH_2Ph), 5.53 (1H, br, NH), 7.29 (1H, br, NH), 7.31–7.40 (5H, m, ArH); δ_C (125 MHz, $CDCl_3$): 13.3 (q, CH_3), 25.0, 25.5 (2 × q, $(CH_3)_2C$), 44.4 (t, $NHCH_2C=O$), 52.8 (q, CH_3O_2C), 67.1 (t, CH_2Ph), 77.1, 81.6, 87.2 (3 × d, C-3, C-4, C-5), 92.3 (s, C-2), 113.7 (s, $C(CH_3)_2$), 128.1, 128.4, 128.7 (3 × d, $Ph_{o,m,p}$), 136.4 (s, Ph_{ipso}), 157.1 (s, C=O), 168.0 (s, C=O), 170.0 (s, C=O); *m*/*z* (APCI+): 423 (MH^+, 53%), 215 (M−*Z*-Gly, 100%); (Found: C, 56.76; H, 6.29; N, 6.55; $C_{20}H_{26}O_8N_2$ requires C, 56.87; H, 6.20; N, 6.63).

4.13. (2*S*,3*R*,4*R*,5*R*)-3,4-*O*-Isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione 19

Methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-talonate **17** (85 mg,

0.20 mmol) was dissolved in HPLC methanol (10 ml). Palladium black (30 mg) was then added. The suspension was degassed three times and air replaced with H_2. The solution was stirred at room temperature under an H_2 atmosphere. After 24 h, the suspension was filtered through Celite, which was eluted with methanol. The solvent was removed under reduced pressure and the residue dried on the vacuum line for 2 h. The residue was then dissolved in dry THF (5 ml) under N_2. Potassium *tert*-butoxide (28 mg, 0.25 mmol) was added and the solution stirred at room temperature. After 24 h, TLC (ethyl acetate) showed a major spot (R_f 0.45). The reaction mixture was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 1:1 then ethyl acetate) afforded (2*S*,3*R*,4*R*,5*R*)-3,4-*O*-isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **19** (36 mg, 70% yield) as a white solid: mp 203–205 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = -56.1$ (*c* 0.51, $CHCl_3$); ν_{max} (KBr)/cm^{-1}: 3436 (NH), 1697 (C=O), 1787 (C=O); δ_H (500 MHz, $CDCl_3$): 1.33 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 1.44, 1.60 (6H, 2 × s, $(CH_3)_2C$), 3.95 (1H, dd, $J_{NH,7}$ 4.2 Hz, $J_{7',7}$ 17.4 Hz, H-7), 4.20 (1H, dq, $J_{4,5}$ 3.7 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.27 (1H, d, $J_{7,7'}$ 17.4 Hz, H-7′), 4.81 (1H, dd, $J_{3,4}$ 5.9 Hz, $J_{4,5}$ 3.7 Hz, H-4), 5.02 (1H, d, $J_{3,4}$ 5.9 Hz, H-3), 6.07 (1H, br, NH), 6.84 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 13.5 (q, CH_3), 24.6, 26.0 (2 × q, $(CH_3)_2C$), 44.9 (t, NHCH_2C=O), 75.5, 80.5, 81.9 (3 × d, C-3, C-4, C-5), 86.2 (s, C-2), 113.2 (s, $C(CH_3)_2$), 165.0 (s, C=O), 166.0 (s, C=O); *m*/*z* (APCI+): 257 (MH$^+$, 100%), 156 (57%); (HRMS; Found: 257.1134; Calcd for MH$^+$: 257.1137).

4.14. (2*S*,3*R*,4*R*,5*S*)-3,4-*O*-Isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione 20

Methyl *N*-2-(benzyloxycarbonylglycylamino)-2,5-anhydro-3,4-*O*-isopropylidene-6-deoxy-L-galactonate **18** (333 mg, 0.789 mmol) was dissolved in HPLC methanol (25 ml). Palladium black (102 mg) was added. The suspension was degassed three times and air replaced with H_2. The solution was stirred at room temperature under H_2 atmosphere. After 24 h, TLC (ethyl acetate) showed only a trace amount of starting material (R_f 0.7) and a new product (R_f 0.0). The suspension was filtered through Celite, which was eluted with methanol. The solvent was removed under reduced pressure. The residue was then dissolved in dry THF (20 ml) under N_2. Potassium *tert*-butoxide (98 mg, 0.868 mmol) was added and the solution stirred at room temperature. After 24 h, the reaction mixture was preadsorbed on silica. Purification by flash chromatography (ethyl acetate then 10% methanol in ethyl acetate) afforded (2*S*,3*R*,4*R*,5*S*)-3,4-*O*-isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **20** (148 mg, 0.578 mmol, 73% yield) as a white solid: mp 284–288 °C decomposed (ethyl acetate/hexane); $[\alpha]_D^{25} = -152.1$ (*c* 0.61, CH_3OH); ν_{max} (KBr)/cm^{-1}: 3394 (NH), 3255 (NH), 1711 (C=O), 1686 (C=O), δ_H (500 MHz, CD_3CN): 1.31 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3), 1.27, 1.40 (6H, 2 × s, $(CH_3)_2C$), 3.68 (1H, dd, $J_{NH,7}$ 5.0 Hz, $J_{7',7}$ 17.5 Hz, H-7), 3.97 (1H, d, $J_{7,7'}$ 17.5 Hz, H-7′), 4.30 (1H, dq, $J_{4,5}$ 3.4 Hz, $J_{5,6}$ 6.3 Hz, H-5), 4.74 (1H, dd, $J_{3,4}$ 5.6 Hz, $J_{4,5}$ 3.4 Hz, H-4), 4.83 (1H, d, $J_{3,4}$ 5.6 Hz, H-3), 6.51 (1H, br, NH), 7.02 (1H, br, NH); δ_C (50 MHz, CD_3OD): 13.1 (q, CH_3), 24.5, 25.2 (2 × q, $(CH_3)_2C$), 45.4 (t, NHCH_2C=O), 78.5, 82.5, 89.6 (3 × d, C-3, C-4, C-5), 92.2 (s, C-2), 114.8 (s, $C(CH_3)_2$), 167.3 (s, C=O), 169.4 (s, C=O); *m*/*z* (APCI+): 257 (MH$^+$, 100%), 183 (57%), 115 (42%); (Found: C, 51.66; H, 6.48; N, 10.79; $C_{11}H_{16}O_5N_2$ requires C, 51.56; H, 6.29; N, 10.93).

4.15. (2*S*,3*R*,4*R*,5*R*)-3,4-*O*-Isopropylidene-2-methyl-6,8-diaza-1-oxaspiro-[4.4]-nonane-7,9-dione 21

Methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-talonate **15α** and methyl 2-amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-galactonate **15β** (143 mg, 0.619 mmol) were dissolved in glacial acetic acid (5 ml). Potassium cyanate (150 mg, 1.85 mmol, 3 equiv) was added to the solution, which was stirred at 65 °C under N_2. After 4 h, TLC (ethyl acetate/hexane) showed no starting material (R_f 0.65) and a new spot (R_f 0.75). The solvent was removed in vacuo and coevaporated with toluene (3 × 5 ml). The residue was preadsorbed on silica. Purification by flash chromatography (ethyl acetate/hexane 1:2 then 1:1 then ethyl acetate) afforded (2*S*,3*R*,4*R*,5*R*)-3,4-*O*-isopropylidene-2-methyl-6,8-diaza-1-oxaspiro-[4.4]-nonane-7,9-dione **21** (111 mg, 74% yield) as a foam: $[\alpha]_D^{22} = -72.6$ (*c* 0.58, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3272 (NH), 1790 (C=O), 1739 (C=O); δ_H (500 MHz, $CDCl_3$): 1.32 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 1.37, 1.53 (6H, 2 × s, $(CH_3)_2C$), 4.50 (1H, dq, $J_{4,5}$ 3.4 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.74–4.78 (2H, m, H-3 and H-4), 6.22 (1H, br, NH), 8.49 (1H, br, NH); δ_C (125 MHz, $CDCl_3$): 13.5 (q, CH_3), 24.6, 26.0 (2 × q, $(CH_3)_2C$), 75.0, 80.2, 81.6 (3 × d, C-3, C-4, C-5), 91.6 (s, C-2), 113.6 (s, $C(CH_3)_2$), 155.2 (s, C=O), 172.5 (s, C=O); *m*/*z* (electrospray, −ve): 241 (M−H$^-$, 100%); (Found: C, 49.41; H, 5.76; N, 11.03; $C_{11}H_{16}O_5N_2$ requires C, 49.58; H, 5.83; N, 11.26).

4.16. (2*S*,3*R*,4*R*,5*R*)-2-Methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione 3

(2*S*,3*R*,4*R*,5*R*)-3,4-*O*-Isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **19** (20 mg, 0.078 mmol) was dissolved in water (1 ml) and trifluoroacetic acid (1 ml). The solution was stirred at room temperature. After 90 min, TLC (5% methanol in ethyl acetate) showed no starting material (R_f 0.7) and a new product (R_f 0.2). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 3 ml). The resulting solid was preadsorbed on silica. Purification by flash chromatography (ethyl acetate then 5% methanol in ethyl acetate) afforded (2*S*,3*R*,4*R*,5*R*)-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **3** (17 mg, quantitative yield) as a white solid: mp 110–113 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = -1.1$ (*c* 0.43, CH_3OH); ν_{max} (KBr)/cm^{-1}: 3520 (NH, OH), 1672 (C=O); δ_H (500 MHz, CD_3OD): 1.26 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 3.90 (1H, d, *J* 18.2 Hz, H-7), 4.02 (1H, d, *J* 18.2 Hz, H-7′), 4.05 (1H, dd, $J_{4,5}$ 2.9 Hz, $J_{3,4}$ 4.3 Hz, H-4), 4.15 (1H, dq, $J_{4,5}$ 2.9 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.72 (1H, d, $J_{3,4}$ 4.3 Hz, H-3); δ_C (125 MHz, CD_3OD): 15.2 (q, CH_3), 45.4 (t, NHCH_2C=O), 74.0, 75.8, 79.2 (3 × d, C-3, C-4, C-5), 89.3 (s, C-2), 168.3 (s, C=O), 169.2 (s, C=O); *m*/*z* (APCI+): 338 (29%), 231 (18%), 217 (MH$^+$, 100%); HRMS (CI, NH_3): Calcd for $C_8H_{13}N_2O_5$ (M+H$^+$): 217.0824, Found 217.0820.

4.17. (2*S*,3*R*,4*R*,5*S*)-2-Methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione 4

(2*S*,3*R*,4*R*,5*S*)-3,4-*O*-Isopropylidene-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **20** (27 mg, 0.105 mmol) was dissolved in water (1 ml) and trifluoroacetic acid (1 ml). The solution was stirred at room temperature. After 1 h, TLC (5% methanol in ethyl acetate, double elution) showed no starting material (R_f 0.3) and a new product (R_f 0.2). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 3 ml). The resulting solid was preadsorbed on silica.

Purification by flash chromatography (ethyl acetate then 10% methanol in ethyl acetate) afforded (2*S*,3*R*,4*R*,5*S*)-2-methyl-6,9-diaza-1-oxaspiro-[4.5]-decane-7,10-dione **4** (23 mg, quantitative yield) as a white solid: mp 184–186 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = -0.3$ (*c* 0.41, CH_3OH); ν_{max} (KBr)/cm^{-1}: 3422 (NH, OH), 1675 (C=O); δ_H (CD_3OD, 500 MHz): 1.25 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 3.90 (1H, dd, $J_{3,4}$ 2.9 Hz, $J_{4,5}$ 5.8 Hz, H-4), 3.98 (2H, d, *J* 4.2 Hz, H-7 and H-7′), 4.39 (1H, dq, $J_{4,5}$ 2.9 Hz, $J_{5,6}$ 6.4 Hz, H-5), 4.40 (1H, d, $J_{3,4}$ 5.8 Hz, H-3); δ_C (125 MHz, D_2O + dioxan): 14.3 (q, CH_3), 44.6 (t, NH*C*H$_2$C=O), 74.0, 80.6, 80.8 (3 × d, C-3, C-4, C-5), 91.2 (s, C-2), 167.7 (s, C=O), 168.8 (s, C=O); *m*/*z* (APCI+): 217 (MH^+, 46%), 143 (100%); HRMS (CI, NH_3): Calcd for $C_8H_{13}N_2O_5$ ($M+H^+$): 217.0824, Found 217.0828.

4.18. (2*S*,3*R*,4*R*,5*R*)-2-Methyl-6,8-diaza-1-oxaspiro-[4.4]-nonane-7,9-dione 5

(2*S*,3*R*,4*R*,5*R*)-3,4-*O*-Isopropylidene-2-methyl-6,8-diaza-1-oxaspiro-[4.4]-nonane-7,9-dione **21** (23 mg, 0.095 mmol) was dissolved in water/trifluoroacetic acid (1:1, 2 ml) and the solution was stirred at room temperature for 7 h by which time (ethyl acetate/hexane 1:1) showed no starting material and a new product. The solvent was removed under reduced pressure and coevaporated with toluene (3 × 5 ml). The residue was preadsorbed on silica and purified by flash chromatography (ethyl acetate) to afford (2*S*,3*R*,4*R*,5*R*)-2-methyl-6,8-diaza-1-oxaspiro-[4.4]-nonane-7,9-dione **5** (18 mg, 94% yield) as a white solid: mp 133–135 °C; $[\alpha]_D^{23} = -23.2$ (*c* 0.57, CH_3OH); ν_{max} (KBr)/cm^{-1}: 3392 (OH, NH), 1770 (C=O), 1733 (C=O); δ_H (500 MHz, D_2O): 1.19 (3H, d, $J_{5,6}$ 6.4 Hz, CH_3), 4.12 (1H, dd, $J_{3,4}$ 3.7 Hz, $J_{4,5}$ 2.6 Hz, H-4), 4.25 (1H, dq, $J_{5,6}$ 6.4 Hz, $J_{5,4}$ 2.6 Hz, H-5), 4.45 (1H, d, $J_{3,4}$ 3.7 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 14.3 (q, CH_3), 72.3, 74.4, 79.4 (3 × d, C-3, C-4, C-5), 92.1 (s, C-2), 157.9 (s, C=O), 176.4 (s, C=O); *m*/*z* (electrospray, −ve): 201 ($M-H^-$, 100%); (Found: C, 41.76; H, 5.16; N, 13.75; $C_7H_{10}O_5N_2$ requires C, 41.59; H, 4.99; N, 13.86).

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