Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1535–1549

TETRAHEDRON: *ASYMMETRY*

Amino acid based diastereoselective synthesis of fucosamines

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Received 19 June 2002; accepted 17 July 2002

Abstract—Enantiomerically pure (+)-D-fucosamine **1**, (+)-*N*-methyl-D-fucosamine **2** and (+)-3-*O*-methyl-D-fucosamine **3** (elsaminose) have been synthesised from known building blocks derived from natural amino acids. Direct and diastereoselective construction of the key intermediate **8** was accomplished by a highly *syn*,*anti*-selective aldol reaction between lithiated Schöllkopf's bis-lactim ether **7** and the 1,3-dioxolane-4-carboxaldehyde **5**. Elaboration of the common intermediate required optional methylation, selective hydrolysis of the bis-lactim ether in the presence of an isopropylidene ketal, lactonization and partial reduction of the carboxylic group.

1. Introduction

Amino sugars are an important class of carbohydrates which are ubiquitous in nature and, in the form of glycoproteins, oligosaccharides, or glycolipids, play a fundamental role in various molecular recognition processes.[1] Furthermore, amino sugars are essential units in other compounds of biological interest as aminoglycoside, macrolide, anthracycline and cyclopeptide antibiotics.[2] 2-Amino-2-deoxyhexoses are the most commonly occurring amino sugars and constitute integral components of bioactive natural products of significant pharmacological importance.[3] Thus, *N*-acetyl-D-galactosamine is a constituent of the human breast tumor (Globo-H) antigen oligosaccharide,[4] whereas *N*-acetyl-D-glucosamine and other *N*-acyl derivatives of D-galactosamine are present in tunicamycin, a potent inhibitor of glycosyltransferases.[5] Additionally, D-fucosamine (2-amino-2,6-dideoxy-D-galactose) is a common component of bacterial polysaccharides[6] and its 3-*O*-methyl and *N*-methyl derivatives are present in elsamicin A[7] and neocarzinostatin[8] antibiotics, respectively. These carbohydrate residues seem to be critical in conferring optimum activity to both antibiotics.[9]

Despite the ubiquity of 2-amino sugars in nature, the available methods for the preparation of such structures in enantiomerically pure form are few in number. The most direct synthetic routes to 2-amino sugars usually involve the stereoselective functionalization of glycals which, in turn, can be prepared from natural carbohydrates or by Lewis acid catalyzed diene–aldehyde cyclocondensation.[10] Stereoselective amination of carbocycles which are accessible by enzymatic dihydroxylation of aromatic compounds has also been used in the asymmetric synthesis of 2-amino sugars.[11] Another commonly employed strategy relies on the diastereoselective elongation of acyclic homochiral precursors. Thus, organometallic addition to serine-derived aldehydes[12] or Julia olefination of glyceraldehydes,[13] followed by diastereoselective dihydroxylation constitute efficient examples of this methodology. Aminohomologation of aldehydes by coupling of their nitrones with metalated thiazoles[14] and aldol reaction of chiral glycine imines[15] provided other straightforward approaches to the stereocontrolled construction of the 2-amino sugar skeleton.

In this area, as part of a project directed towards an efficient synthesis of bioactive amino polyol derivatives,[16] we have recently developed a convergent approach to 2-amino-2-deoxyhexoses, where the stereoselective construction of the sugar backbone relied on an aldol reaction using derivatives of natural amino acids as chiral auxiliaries and building blocks. Thus, in this paper we report in full details the application of such methodology to the synthesis of D-fucosamine **1** and its *N*-methyl and 3-*O*-methyl derivatives (**2** and **3**, respectively).[17] Although carbohydrate-based syntheses of these biologically significant

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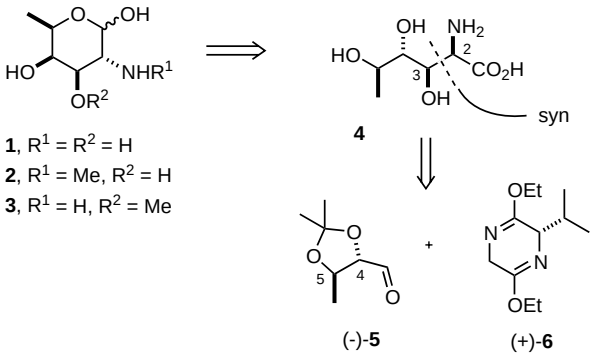
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00376-2

amino sugars have been described,[18] to the best of our knowledge, only *N*-methyl-D-fucosamine has been prepared, previously to this work, by other asymmetric, amino acid-based, approach.[12a] In formulating the synthetic plan, we recognized that the three targeted sugars would originate through reduction of a common polyhydroxylated α-amino acid derived from D-galactonic acid. In this way, disconnection at the C(2)–C(3) bond makes key intermediate **4** accessible via a *syn*-aldol[19] reaction between a chiral glycine equivalent and a C_4-building block with the required configuration at positions 4 and 5 (see Scheme 1).[20] As the addition of organometallic reagents to 1,3-dioxolane-4-carboxaldehyde systems generally proceed with *anti* selectivity,[21] the aldehyde **5**, readily available from L-threonine,[22] was sought as an appropriate precursor.[23] On the other hand, of the various chiral glycine equivalents,[24] we found Schöllkopf's bis-lactim ethers (like **6**) to be very attractive, due to the high *syn*-selectivity shown by these reagents in aldol-type reactions.[25] We anticipated a highly selective formation of the desired 2,3-*syn*-3,4-*anti* configuration in the key step of the synthesis, as the hydroxyaldehyde **5** and the azaenolate derived from **6** would form a matched pair,[26] and their coupling in the aldol reaction should proceed with double asymmetric induction.

2. Results and discussion

2.1. Azaenolate aldol addition to dioxolane-carboxaldehyde

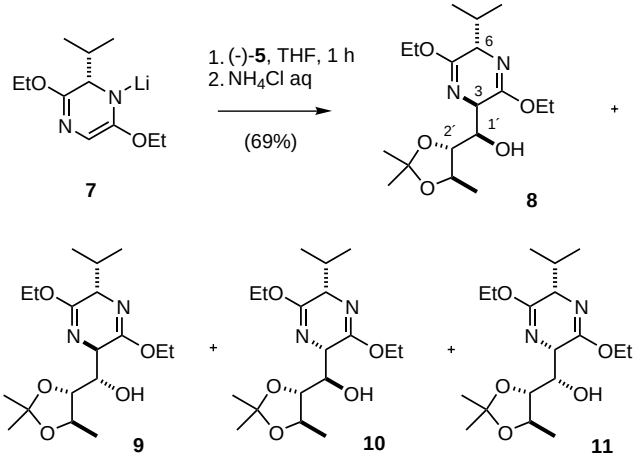
According to the literature,[22] L-threonine was converted into (4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxaldehyde (−)-**5**, while (3*S*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine, (+)-**6** was prepared from glycine and valine.[27,28] A high degree of stereoselection in the aldol addition was essential for a successful execution of our strategy. Nevertheless, taking into account that substrate **5** and reagent **6** should form a matched pair, the reactivity of the more accessible but usually less selective lithium salt of the Schöllkopf's bis-lactim ether was examined.[16,25] Thus, slow addition of freshly distilled[29] **5** over a solution of 1.2 equiv. of **7** at −78°C in THF led, after quenching, aqueous workup, and removal of side products by flash chromatography, to a mixture of adducts **8**, **9**, and **10** in a combined yield of 69% (see Scheme 2).



Scheme 1. Retrosynthetic approach to fucosamines.

Integration of the pairs of doublets corresponding to the isopropyl groups in the ^{1}H NMR spectrum of the mixture of adducts revealed high asymmetric induction in the formation of both new stereocenters, the ratio **8**/**9**/**10** being ca. 50:3.3:<1. Thus, at low temperature, the aldol addition of **7** to **5** is highly stereoselective, and the facial discrimination delivered by aldehyde **5**, with a methyl group at the β-position and *trans* to the carbonyl group, is higher than that reported by Schöllkopf for cyclohexylidene glyceraldehyde.[25f] This trend is in agreement with the results obtained in the addition of other nucleophiles to similar 1,3-dioxolane-4-carboxaldehydes[23c] and also in double stereodifferentiating additions of lithium enolates to β-alkoxy aldehydes.[30] However, the product distribution of the aldol reaction between **5** and **7** was found to be markedly dependent on the reaction temperature. When the addition was performed at 0°C a different mixture of aldol adducts was obtained in similar yield, but containing adducts **8**/**10**/**11** in a 7:3:1 ratio.

Separation of the major components of the mixtures could be achieved by flash chromatography to provide products of high purity, with diastereomeric excess higher than 98%. Evidence supporting the relative configuration on adducts was obtained by NMR analyses. For compounds **8** and **9**, the H-6 resonance appears near to 3.93 ppm, as a triplet with ^5J(H3,H6) close to 3.5 Hz, which is general of the *trans* relationship of substituents at the pyrazine ring. Conversely, the NMR spectrum of adduct **10** shows the absorption corresponding to H-6 at similar δ, as a double doublet with a ^5J(H3,H6) of 6.0 Hz, which is typical of a *cis* relationship at the bis-lactim ring.[31] The assignment of the relative configurations for adduct **8** (3,1′-*syn*-1′,2′-*anti*), for adduct **9** (3,1′-*anti*-1′,2′-*syn*), and for adduct **10** (3,1′-*anti*-1′,2′-*anti*), was made on the basis of X-ray structure determination or analysis by ^{1}H NOE difference spectroscopy of their cyclic derivatives, as will be described below. Absolute configurations follow from the use of aldehyde **5**, as there is ample precedent.[22,23]



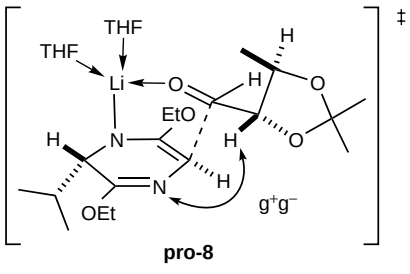
Scheme 2. Addition of lithiated bis-lactim ether **7** to aldehyde (−)-**5**.

Furthermore, stereochemical assignment for major adduct **8** was unambiguously confirmed through its conversion into natural amino sugars of known configuration (vide infra).

The stereochemical course of the addition of azaenolate **7** to aldehyde **5** can be rationalised by extending the proposal of Roush,[32] which combines the Zimmerman–Traxler transition state model[33] and the non-Anh model[34] for 1,2-asymmetric induction. In this manner, an initial lithium–carbonyl coordination to form an intermediate complex should be followed by the rate-determining reorganisation through competitive six-membered transition states. The chair-like transition structure **pro-8**, with *lk* topology arising from the interaction between the *Re* faces of the azaenolate and the carbonyl moieties, would be favoured with respect to other diastereomeric transition structures due to the minimisation of the steric interactions between the isopropyl and ethoxy groups of the bis-lactim and the equatorial aldehyde substituents (see Fig. 1). In addition, an anticlinal relationship between the α-alkoxy and carbonyl groups, determining a non-Anh conformation for the aldehyde moiety, could reduce the unfavourable g^+g^- double *gauche* interaction with one of the bis-lactim nitrogen atoms. In agreement with this qualitative transition state model, ab initio molecular orbital calculations (at the B3LYP/6-31+G*//HF/6-31G* level) showed a chair-like, non-Anh conformation as the most stable transition structure, being preferred by more than 2.1 kcal/mol to the competitive ones.[35]

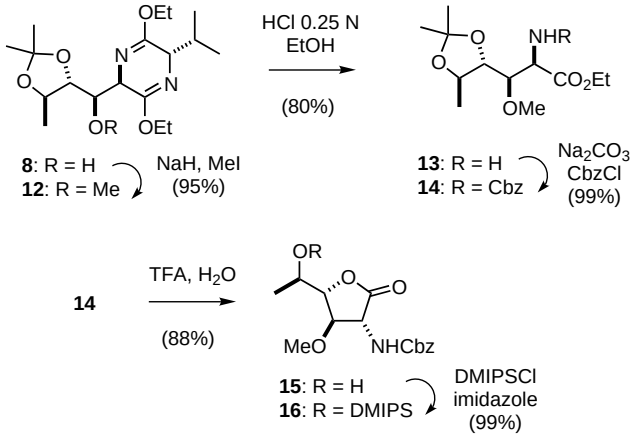
2.2. Synthesis of 2-amino-2,6-dideoxy-3-*O*-methyl-D-galactose (elsaminose, 3)

Conversion of adduct **8** into 2-amino-2,6-dideoxy-3-*O*-methyl-D-galactose **3** required methylation of the free hydroxyl group, removal of the chiral auxiliary, and partial reduction of the carboxylic group. Attempts to obtain the methylated adduct **12** (see Scheme 3) by quenching the aldol reaction with methyl iodide were unsuccessful. Thus, after 24 h at room temperature and aqueous workup, only traces of **12** were isolated, along with the adduct **8** and the 3-methyl derivative of the Schöllkopf's reagent that was present in excess during the aldol addition. Methylation was finally accomplished in high yield by treatment of **8** with sodium hydride and methyl iodide. Selective hydrolysis of the pyrazino moiety of methyl ether **12** in the presence of



pro-8

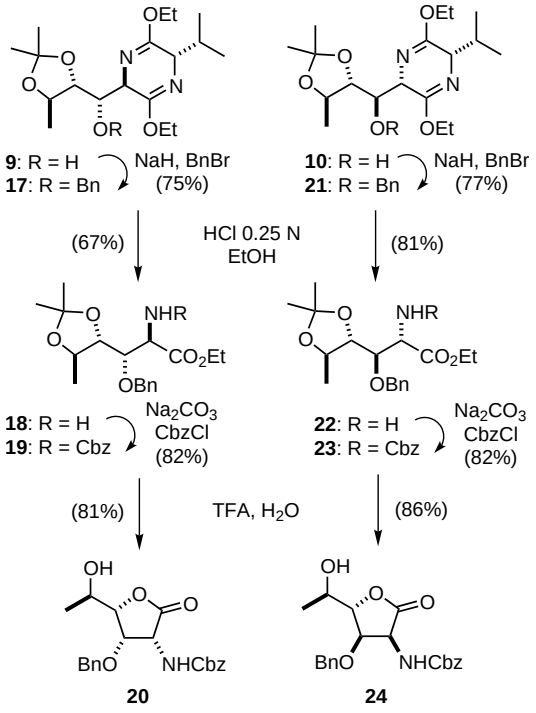
Figure 1. Proposed transition state model for the addition of **7** to **5**.



Scheme 3. Synthesis of elsaminose: transformation of adduct **8** into the intermediate lactone **16**.

the isopropylidene ketal required some experimentation: treatment of a solution of **12** in THF with TFA at room temperature led to an intractable mixture, while the reaction with aqueous 0.25N HCl or Dowex 50WX8 (H^+ form) under the same conditions resulted in a complete hydrolysis to the corresponding galactonic acid, which was isolated in low yield. Eventually, a clean conversion of **12** to the desired amino ester was accomplished employing 0.25N HCl in EtOH at room temperature, and thus, amino ester **13** could be isolated in good yield after removal of the chiral auxiliary by flash chromatography. In order to avoid the manipulation of compounds with the α-amino aldehyde function, of well documented configurational instability,[36] we decided to postpone the partial reduction of the carboxyl group until the lactonization of **13** was achieved. Thus, quantitative protection of the amino group of **13** as a benzylcarbamate under standard conditions was followed by the hydrolysis of the isopropylidene ketal (of **14**) in acidic media, which led to the simultaneous formation of the desired lactone **15** in high yield. Treatment of lactone **15** with isopropyldimethylsilyl chloride (DMIPSCl) in the presence of imidazole then afforded the corresponding silyl ether **16** in excellent yield.

In order to allow the stereochemical assignment of the minor adducts, compounds **9** and **10** were also transformed into the cyclic derivatives **20** and **24** (see Scheme 4). As was previously observed for other aldol adducts derived from Schöllkopf's reagents,[25c] the hydrolysis of the pyrazino moiety of compounds **9** and **10** required the protection of the hydroxyl group to proceed with acceptable yields. Thus, after benzylation of **9** and **10**, the selective hydrolysis of the intermediates **17** and **21** with 0.25N HCl in EtOH led to the corresponding amino esters **18** and **22**. Subsequent formation of the benzylcarbamates **19** and **23** was followed by the TFA-catalysed lactonization, to afford compounds **20** and **24** in good yields. The IR spectra of compounds **15**, **16**, **20**, and **24** included bands at 1775, 1785, 1770, and 1760 cm^{-1}, respectively, clearly indicating the formation of γ-lactones in these cyclizations.



Scheme 4. Transformation of adducts **9** and **10** into lactones **20** and **24**.

In contrast to **15**, the ^{1}H NMR spectra of lactones **16**, **20** and **24** showed a pattern of signals suitable for the study of their conformation and relative stereochemistry by ^{1}H NOE difference spectroscopy. After corroborating the ^{1}H NMR assignments by COSY experiments, the analysis of the sets of observed NOEs confirmed the formation of γ-lactones and allowed assignment of the relative configuration of the stereogenic centers formed in the aldol reaction (see Fig. 2).[37–43] Thus, the stereochemistry of lactone **16**, derived from the major aldol adduct **8**, was determined as 3,4-*trans*-4,5-*trans*, while lactones **20** and **24** showed a 3,4-*cis*-4,5-*cis*- and 3,4-*cis*-4,5-*trans*-configuration, respectively.

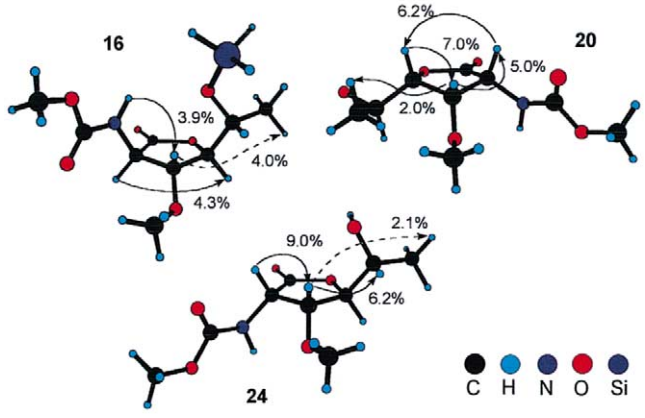
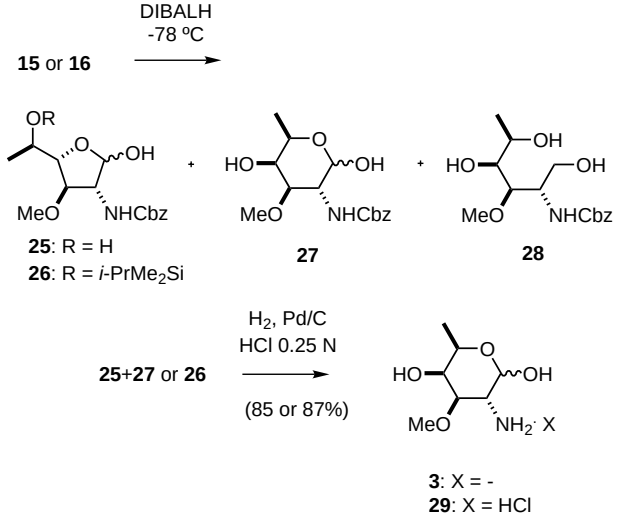


Figure 2. PM3-optimized minimum energy conformations located for models of γ-lactones **16**, **20** and **24** (MMX force field), showing characteristic NOEs.

Partial reduction of the lactone with the required configuration and a final deprotection step were necessary to complete the synthesis of elsaminose. Although no reaction was observed when lactone **15** was treated with 2.5 equiv. of DIBALH in THF or CH_2Cl_2 at low temperature, the use of a 2:1 mixture of toluene/THF as solvent gave rise to lactols **25**+**27**, along with unreacted starting material and alcohol **28**, which were isolated in 43, 28 and 7% yields, respectively (see Scheme 5). Attempts to improve the conversion of **15** to the lactols using a larger excess of DIBALH resulted in increased over-reduction to the alcohol **28**. Although hydrogenation of the mixture of pyranose and furanose anomers **25**+**27** afforded elsaminose with acceptable efficiency (16% yield for the seven steps), better yields were obtained by performing the reduction of the fully protected lactone. Thus, when **16** was treated with 2.0 equiv. of DIBALH in toluene/THF (2:1) at low temperature, a 65% conversion to a 2:1 mixture of furanoses **26** was achieved. As the undesirable reduction to the alcohol was not observed in this case, the yield of **26** could be increased to 85% by subjecting recovered starting material to these reduction conditions. Finally, deprotection of **26** by catalytic hydrogenation in acidic media allowed, after chromatography on acidic ion-exchange resin, the isolation of the free amino sugar in a global yield of 31% over eight steps from the starting building blocks. Treatment of **3** with HCl and purification by reversed-phase flash chromatography afforded elsaminose as its hydrochloride salt **29** in almost quantitative yield. Analysis of the ^{1}H NMR spectrum (500 MHz, D_2O) of **29** showed the presence of a 2:1 mixture of α- and β-pyranoses, with vicinal coupling constants characteristic for the galacto configuration. The specific rotation value determined for **29** was in good agreement with that reported in the literature: $[\alpha]_D^{22} = +92.1$ (*c* 0.6, H_2O), (lit. $[\alpha]_D = +85.3$ (*c* 1.1, H_2O)).[18d]

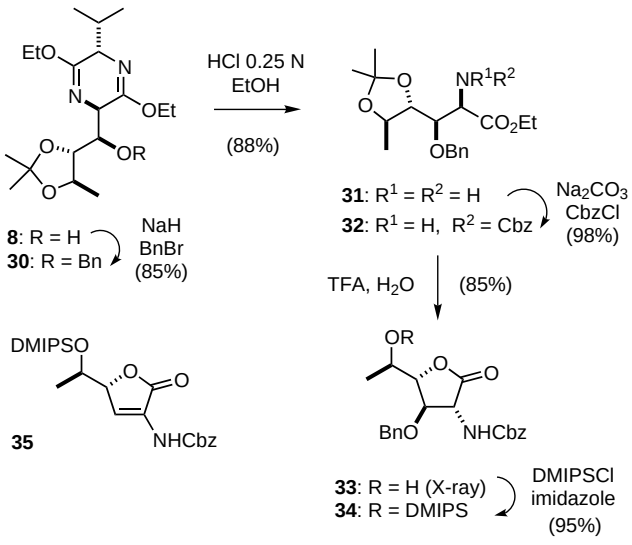


Scheme 5. Transformation of lactones **15** and **16** into elsaminose **3**.

2.3. Synthesis of D-fucosamine and *N*-methyl-D-fucosamine 1 and 2

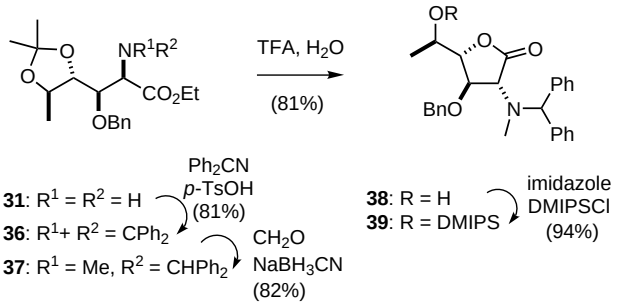
Conversion of key intermediate **8** to fucosamines **1** and **2** required the removal of the chiral auxiliary and partial reduction of the carboxylate, in addition to an

optional and selective monomethylation of the amino group. After the protection of the hydroxyl group at position 1′, the selective hydrolysis of the pyrazino moiety in the presence of the isopropylidene ketal should give rise to intermediates capable of undergoing the *N*-monomethylation. Using the conditions previously developed for the preparation of lactones **20** and **24**, the benzylation of **8**, followed by selective hydrolysis of the pyrazino moiety of **30**, gave the amino ester **31** in high yield (see Scheme 6). After protection of the amino group of **31** as the benzylcarbamate, cyclization in acidic media led to lactone **33**, which was isolated in high yield as a colorless solid. Upon crystallisation on a ligroin/ether mixture, lactone **33** yielded crystals amenable to X-ray structure determination, allowing the confirmation of its 2,3-*trans*-3,4-*trans*-stereochemistry. The fully protected lactone **34** was obtained by *O*-silylation of **33**.



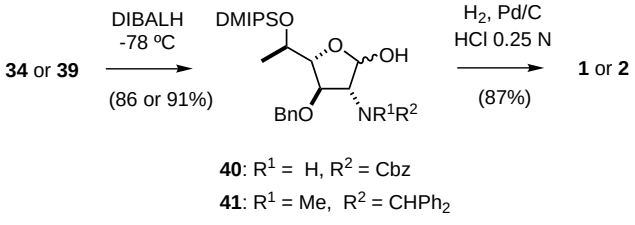
Scheme 6. Synthesis of D-fucosamine: transformation of adduct **8** into the intermediate lactone **34**.

For the synthesis of *N*-methyl-D-fucosamine, we studied the direct methylation of carbamates **32** and **34**. Attempts to achieve the *N*-methylation of **32** under the conditions described by Cheung and Benoiton[44] for the preparation of *N*-methylated α-amino acids (NaH, MeI, THF, 5°C, 15 h) resulted in recovered starting material, while higher reaction temperatures and prolonged reaction times led only to decomposition products. Treatment of lactone **34** with sodium hydride and methyl iodide (THF, −15°C, 15 min) led to the exclusive formation of the butenolide **35** by *syn*-elimination[45] of the 4-benzyloxy group. These disappointing results led us to examine a slightly longer, but ultimately practical route for *N*-monomethylation of the intermediate **31**, based on the reduction of its O'Donnell's Schiff base followed by reductive methylation of the corresponding secondary amine (Scheme 7).[12a] Thus, the imino ester **36** was obtained in good yield by treatment of amino ester **31** with diphenylketimine and anhydrous *p*-TsOH acid as catalyst.[46] Reduction of the Schiff base under anhydrous acidic conditions to generate a benzhydryl secondary amine and subsequent reductive methylation[47] enabled the isolation of the monomethylamine **37**. Treatment of this compound in aqueous acidic media resulted in rapid hydrolysis of the isopropylidene ketal, but proceeded slowly to the lactone **38**. Complete lactonization of the corresponding γ,δ-dihydroxy ester, with the bulky *N*-methyl-*N*-diphenylmethylamino group at the α-position, required prolonged reaction times. Silylation of the secondary hydroxyl group of compound **38** afforded the fully protected *N*-methylated lactone **39** in excellent yield.



Scheme 7. Synthesis of *N*-methyl-D-fucosamine: *N*-monomethylation of intermediate **31** and lactonization.

Completion of the synthesis of fucosamines **1** and **2** followed the same reaction sequence as described for elsaminose. Partial reduction of lactones **34** and **39** led to the mixtures of furanoses **40** and **41**, respectively, within combined yields higher than 80% (see Scheme 8). Finally, deprotection of lactols by catalytic hydrogenation in acidic media allowed, after chromatography on acidic ion-exchange resin, the isolation of the free amino sugars **1** and **2**, with 28 and 19% overall yields, respectively. The hydrochloride salt of D-fucosamine was prepared to make comparisons with the reported physical and spectral data. Optical rotations for both amino sugars were in good agreement with those reported: D-fucosamine hydrochloride: $[\alpha]_D^{23}=+76.1$ (final, *c* 0.6, H_2O), (lit $[\alpha]_D^{25}=+81.0$ (final, *c* 0.2, H_2O))[18c]; *N*-methyl-D-fucosamine: $[\alpha]_D^{23}=+69.0$ (final, *c* 0.1, H_2O), (lit $[\alpha]_D^{25}=+73.1$ (final, *c* 0.1, H_2O)).[8b] ^1H NMR spectral data obtained for both fucosamines were also in accordance with the literature values.[6,12a]



Scheme 8. Synthesis of D-fucosamine and *N*-methyl-D-fucosamine from lactones **34** and **39**.

3. Conclusion

We have developed a practical, chemically efficient, and diastereoselective synthesis of D-fucosamine **1** and its

N-methyl and 3-*O*-methyl derivatives (**2** and **3**, respectively), three amino sugars not readily available from natural sources. Direct and diastereoselective construction of the common key intermediate **8**, with the complete backbone and the proper stereochemical configuration, was accomplished by a *syn*,*anti*-aldol type reaction between Schöllkopf's bis-lactim ether **6** and the 1,3-dioxolane-4-carboxaldehyde **5**, both derived from natural amino acids. One of the attractive features of the present approach to 2-deoxy-2-aminosugars lay in its inherent flexibility since a variety of 2-aminopolyols could be available by simply altering the stereochemistry or the pattern of substitution in the starting aldehyde. Additionally, the syntheses require rather inexpensive reagents, require straightforward reaction conditions, and the overall yields for the targeted sugars were high and compare well or favourably with those in the literature.

4. Experimental

4.1. General methods

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Reagents and solvents were purchased and used without further purification unless otherwise stated. THF and toluene were distilled from sodium/benzophenone. CH_2Cl_2 and CH_3CN were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualising agent and cerium sulfate/ammonium molybdate in 10% sulfuric acid or ninhydrin in a 3% HOAc/*n*-BuOH solution as developing agents. E. Merck silica gel 60 and RP-18 (both 230–400 mesh) were used for liquid chromatography separations and Dowex 50WX8 resin (100–200 mesh) for ion-exchange chromatography. Melting points are uncorrected. IR spectra were obtained as liquid film or as KBr pellets. Unless otherwise indicated, ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra were recorded at 50 MHz with broad-band ^{1}H decoupling at 25°C. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C spectra rests on the *J*-modulated spin-echo sequence. ^{1}H or ^{13}C assignments were confirmed with the aid of homonuclear or heteronuclear two-dimensional experiments. FABMS spectra were recorded using thioglycerol as a matrix. High-resolution FAB mass spectra were obtained using 3-nitrobenzyl alcohol as a matrix. Elemental analyses were performed at Servicios Xerais de Apoio á Investigación of Universidade da Coruña.

4.2. 2,5-Diethoxy-3,6-dihydro-3-(1-hydroxy-2,3-isopropylidenedioxybutyl)-6-isopropylpyrazines, 8, 9 and 10

A solution of *n*-BuLi (2.5 M in hexane, 11.3 mL, 28.3 mmol) was added to a stirred solution of the bis-lactim ether (+)-**6** (6 g, 28.3 mmol) in THF (160 mL) at −78°C and the mixture was stirred for 1 h. Then, a solution of the aldehyde (−)-**5** (3.3 g, 22.9 mmol) in THF (25 mL) was added dropwise over a period of 40 min. After stirring at −78°C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The crude reaction mixture was warmed to room temperature, and the solvent was removed in vacuo. The resulting material was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by gradient flash chromatography (silica gel, EtOAc/hexanes, 1:9–1:3) to yield pure **8** (5.2 g, 64%) and pure **9** (348 mg, 4%). When the addition was carried out at 0°C, starting from 1 g of **5**, pure **8** (632 mg, 26%) and pure **10** (472 mg, 19%) along with a 3:1 mixture of adducts **8**/**11** (624 mg, 25%) were obtained after column chromatography.

4.2.1. (3*R*,6*S*,1′*R*,2′*S*,3′*R*)-Adduct 8. Colorless oil: R_f 0.48 (silica gel, EtOAc/hexanes, 1:2.3); $[\alpha]_D^{22}=+14.5$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.76 (d, $J=6.9$ Hz, 3H), 1.02 (d, $J=6.9$ Hz, 3H), 1.29 (t, $J=6.9$ Hz, 3H), 1.30 (t, $J=6.9$ Hz, 3H), 1.39 (d, $J=5.9$ Hz, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 1.67 (d, $J=9.3$ Hz, 1H), 2.20 (dsp, $J=6.9$, 3.7 Hz, 1H), 3.77 (dd, $J=8.6$, 7.2 Hz, 1H), 3.97 (t, $J=3.7$ Hz, 1H), 4.00–4.30 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.2, 19.1, 19.8, 27.0, 27.6 (CH_3), 32.5, 56.4 (CH), 61.0, 61.1 (CH_2), 61.3, 72.9, 77.0, 81.1 (CH), 108.4 (C), 161.3, 166.6 (C=N); IR (film) ν 3460, 2995, 1690, 1380, 1300, 1230, 1030 cm^{-1}; FABMS m/z 357 (MH^+, 97). Anal. calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.56; H, 9.09; N, 7.65%.

4.2.2. (3*R*,6*S*,1′*S*,2′*S*,3′*R*)-Adduct 9. Colorless oil: R_f 0.40 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=+8.9$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.68 (d, $J=6.9$ Hz, 3H), 1.02 (d, $J=6.9$ Hz, 3H), 1.20–1.35 (m, 15H), 2.26 (dsp, $J=6.9$, 3.3 Hz, 1H), 3.27 (d, $J=10.0$ Hz, 1H), 3.42 (dd, $J=8.5$, 1.5 Hz, 1H), 3.85 (dd, $J=4.9$, 1.5 Hz, 1H), 3.88 (t, $J=3.3$ Hz, Hz, 1H), 4.00–4.22 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.2, 16.5, 17.0, 19.0, 26.5, 27.4 (CH_3), 31.5, 58.7 (CH), 60.6, 60.7 (CH_2), 60.9, 69.0, 73.4, 81.6 (CH), 108.4 (C), 160.5, 163.8 (C=N); IR (film) ν 2977, 1695, 1237 cm^{-1}; FABMS m/z 357 (MH^+, 100). Anal. calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.32; H, 9.27; N, 7.80%.

4.2.3. (3*S*,6*S*,1′*R*,2′*S*,3′*R*)-Adduct 10. Colorless oil: R_f 0.36 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=+62.4$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.74 (d, $J=6.8$ Hz, 3H), 1.07 (d, $J=6.8$ Hz, 3H), 1.20–1.40 (m, 15H), 2.41 (dsp, $J=6.8$, 3.7 Hz, 1H), 2.95 (brd, 1H), 3.55 (t, $J=7.7$ Hz, 1H), 3.90 (dd, $J=6.0$, 3.7 Hz, 1H), 3.95–4.25 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.1, 19.4, 19.5, 26.7, 27.2 (CH_3), 31.1, 57.9, 60.4 (CH), 60.5, 60.7 (CH_2), 73.7, 75.8, 80.8 (CH), 108.2 (C), 159.6, 164.0 (C=N); IR (film) ν 3500, 2995, 1690, 1370, 1230 cm^{-1}; FABMS m/z 357 (MH^+, 100). Anal. calcd for $C_{18}H_{32}N_2O_5$: C, 60.65; H, 9.05; N, 7.86. Found: C, 60.60; H, 9.27; N, 7.88%.

4.3. General procedure for the protection of the hydroxyl group of adduct 8

A solution of adduct **8** (2.2 g, 6.18 mmol) in THF (30 mL) was added to a stirred suspension of NaH (210

mg, 80% dispersion in mineral oil, 7.0 mmol) in THF (60 mL) at 0°C. After 30 min, MeI (1.9 mL, 30.5 mmol) was added, and the resulting solution was stirred at room temperature for a further 12 h. The reaction mixture was cooled to 0°C and quenched by the addition of CH_3OH (2 mL). The solvents were removed in vacuo and the resulting material was diluted with water and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by gradient flash chromatography (silica gel, EtOAc/hexane, 1:18–1:9) to yield **12** (2.17 g, 95%) as a colorless oil.

4.3.1. (3*R*,6*S*,1′*R*,2′*S*,3′*R*)-2,5-Diethoxy-3,6-dihydro-3-(2,3-isopropylidenedioxy-1-methoxybutyl)-6-isopropylpyrazine, 12. Following the general procedure, adduct **8** (2.2 g, 6.18 mmol) gave **12** (2.17 g, 95%) as a colorless oil: R_f 0.66 (silica gel, EtOAc/hexanes, 1:9); $[\alpha]_D^{22}=-41.2$ (*c* 2.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.68 (d, $J=6.8$ Hz, 3H), 1.04 (d, $J=6.8$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 1.32 (t, $J=7.1$ Hz, 3H), 1.37 (d, $J=5.9$ Hz, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 2.30 (dsp, $J=6.8$, 3.4 Hz, 1H), 3.34 (s, 3H), 3.78 (dd, $J=8.1$, 1.9 Hz, 1H), 3.92 (dd, $J=8.2$, 8.1 Hz, 1H), 3.96 (dd, $J=3.4$, 3.5 Hz, 1H), 4.08–4.32 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 16.5, 19.1, 19.6, 27.1, 27.5 (CH_3), 31.5 (CH), 56.3, 60.2, 60.4 (CH, OCH_3), 60.6, 60.7 (CH_2), 76.1, 80.4, 83.7 (CH), 108.2 (C), 161.4, 163.8 (C=N); IR (film) ν 2950, 1700, 1380, 1370, 1230, 1100, 1040 cm^{-1}; FABMS m/z 371 (MH$^+$, 100). Anal. calcd for $C_{19}H_{34}N_2O_5$: C, 61.60; H, 9.25; N, 7.56. Found: C, 61.83; H, 9.21; N, 7.56%.

4.3.2. (3*R*,6*S*,1′*S*,2′*S*,3′*R*)-3-(1-Benzyloxy-2,3-isopropylidenedioxybutyl)-2,5-diethoxy-3,6-dihydro-6-isopropylpyrazine, 17. Prepared from adduct **9** (300 mg, 0.84 mmol), according to the general procedure, but *n*-Bu_4NI (0.1 equiv.) and BnBr (2.0 equiv.) were added instead of MeI. Purification by gradient flash chromatography (silica gel, EtOAc/hexanes, 1:19–1:12) afforded **17** (282 mg, 75%) as a colorless oil: R_f 0.60 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=-13.3$ (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.65 (d, $J=6.9$ Hz, 3H), 1.03 (d, $J=6.9$ Hz, 3H), 1.25 (t, $J=6.9$ Hz, 3H), 1.27 (t, $J=7.1$ Hz, 3H), 1.36 (d, $J=5.6$ Hz, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 2.40 (dsp, $J=6.9$, 3.3 Hz, 1H), 3.69 (dd, $J=7.7$, 2.0 Hz, 1H), 3.82 (t, $J=3.3$ Hz, 1H), 3.90–4.25 (m, 7H), 4.60 (d, $J=11.7$ Hz, 1H), 4.80 (d, $J=11.7$ Hz, 1H), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 16.4, 19.1, 19.5, 27.1, 27.4 (CH_3), 30.7, 57.4, 60.2 (CH), 60.7 (CH_2), 73.9 (CH), 74.4 (CH_2), 83.5, 83.8 (CH), 108.0 (C), 127.3, 128.0, 128.1 (aromatic CH), 138.06 (aromatic C), 159.7, 165.0 (C=N); IR (film) ν 2948, 1734, 1672, 1378, 1332, 1095 cm^{-1}; FABMS m/z 447 (MH$^+$, 100). Anal. calcd for $C_{25}H_{38}N_2O_5$: C, 67.24; H, 8.58; N, 6.27. Found: C, 67.27; H, 8.27; N, 6.02%.

4.3.3. (3*S*,6*S*,1′*R*,2′*S*,3′*R*)-3-(1-Benzyloxy-2,3-isopropylidenedioxybutyl)-2,5-diethoxy-3,6-dihydro-6-isopropylpyrazine, 21. Prepared from adduct **10** (400 mg, 1.12 mmol), according to the general procedure, but *n*-Bu_4NI (0.1 equiv.) and BnBr (2.0 equiv.) were added instead of MeI. Purification by gradient flash chromatography (silica gel, EtOAc/hexane, 1:19–1:12) afforded **21** (386 mg, 77%) as a colorless oil: R_f 0.34 (silica gel, EtOAc/hexanes, 1:9); $[\alpha]_D^{23}=+26.1$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, $J=6.7$ Hz, 3H), 1.05 (d, $J=6.7$ Hz, 3H), 1.20–1.35 (m, 15H), 2.25 (dsp, $J=6.7$, 4.3 Hz, 1H), 3.81 (dd, $J=6.0$, 4.3 Hz, 1H), 3.85–4.07 (m, 3H), 4.07–4.30 (m, 4H), 4.31 (dd, $J=6.0$, 3.0 Hz, 1H), 4.57 (d, $J=11.7$ Hz, 1H), 4.73 (d, $J=11.7$ Hz, 1H), 7.28–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 17.8, 19.6, 19.8, 26.7, 27.1 (CH_3), 31.6, 56.7, 60.4 (CH), 60.5, 60.6, 73.0 (CH_2), 76.1, 80.6, 81.9 (CH), 107.9 (C), 127.6, 128.0, 128.2 (aromatic CH), 138.0 (aromatic C), 160.4, 163.6 (C=N); IR (film) ν 2980, 1700, 1360, 1250 cm^{-1}; FABMS m/z 447 (MH$^+$, 100). Anal. calcd for $C_{25}H_{38}N_2O_5$: C, 67.24; H, 8.58; N, 6.27. Found: C, 67.45; H, 8.27; N, 6.09%.

4.3.4. (3*R*,6*S*,1′*R*,2′*S*,3′*R*)-3-(1-Benzyloxy-2,3-isopropylidenedioxybutyl)-2,5-diethoxy-3,6-dihydro-6-isopropylpyrazine, 30. Prepared from adduct **8** (1.6 g, 4.49 mmol), according to the general procedure, but *n*-Bu_4NI (0.1 equiv.) and BnBr (2.0 equiv.) were added instead of MeI. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:16) to give **30** (1.70 g, 85%) as a colorless oil: R_f 0.62 (silica gel, EtOAc/hexanes, 1:9); $[\alpha]_D^{22}=-65.2$ (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.69 (d, $J=6.8$ Hz, 3H), 1.06 (d, $J=6.8$ Hz, 3H), 1.23–1.35 (m, 9H), 1.41 (s, 3H), 1.44 (s, 3H), 2.32 (dsp, $J=6.8$, 3.6 Hz, 1H), 3.91 (t, $J=3.6$ Hz, 1H), 3.98–4.41 (m, 8H), 4.44 (d, $J=11.0$ Hz, 1H), 4.51 (d, $J=11.0$ Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.4, 16.4, 19.2, 19.9, 27.1, 27.5 (CH_3), 31.3, 56.5, 60.3 (CH), 60.6, 73.7 (CH_2), 75.9, 80.6, 81.2, (CH), 108.2 (C), 127.7, 128.0, 128.2 (aromatic CH), 138.0 (aromatic C), 161.4, 163.6 (C=N); IR (film) ν 2980, 2960, 1690, 1370, 1240 cm^{-1}; FABMS m/z 447 (MH$^+$, 29), 169 (100). Anal. calcd for $C_{25}H_{38}N_2O_5$: C, 67.24; H, 8.58; N, 6.27. Found: C, 67.47; H, 8.44; N, 6.18%.

4.4. General procedure for the hydrolysis of the bis-lactim ether

A solution of compound **12** (1.76 g, 4.75 mmol) in EtOH (60 mL) and 0.25N HCl (38 mL) was stirred at room temperature for 5 h. Then the solution was diluted with water (40 mL) and concentrated to half its initial volume. The aqueous solution was made basic (pH ~ 10) by the addition of $NaHCO_3$ followed by concentrated ammonia. The aqueous layer was extracted with CH_2Cl_2 (7×50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude mixture of ethyl valinate and amino ester **13** was purified by flash chromatography (silica gel, EtOAc) to yield amino ester **13** (995 mg, 80%) as a colorless oil.

4.4.1. Ethyl (2*R*,3*R*,4*S*,5*R*)-2-amino-4,5-isopropylidenedioxy-3-methoxyhexanoate (13). Following the general procedure, compound **12** (1.76 g, 4.75 mmol) gave **13** (995 mg, 80%) as a colorless oil: R_f 0.56 (silica gel, EtOAc); $[\alpha]_D^{22}=-15.0$ (*c* 1.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.32 (t, $J=6.8$ Hz, 3H), 1.37 (d, $J=6.0$ Hz, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 1.63 (brs, 2H), 3.36 (s, 3H, OCH_3), 3.7–3.8 (m, 3H), 4.1 (quintuplet, $J=6.0$ Hz, 1H), 4.24 (q, $J=6.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.2, 27.1, 27.5 (CH_3), 54.7 (CH), 59.4 (OCH_3), 61.1 (CH_2), 76.2, 80.2, 83.6 (CH), 108.3 (C), 174.6 (C=O); IR (film) *v* 3000, 1740, 1090 cm^{-1}; FABMS *m*/*z* 262 (MH^+, 100). Anal. calcd for $C_{12}H_{23}NO_5$: C, 55.16; H, 8.87; N, 5.36. Found: C, 54.91; H, 8.57; N, 5.61%.

4.4.2. Ethyl (2*R*,3*S*,4*S*,5*R*)-2-amino-3-benzyloxy-4,5-isopropylidenedioxyhexanoate, 18. Prepared from compound **17** (260 mg, 0.58 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc) to give **18** (131 mg, 67%) as a colorless oil: R_f 0.41 (silica gel, EtOAc/hexanes, 2:1); $[\alpha]_D^{22}=-13.3$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, $J=6.1$ Hz, 3H), 1.24 (t, $J=7.1$ Hz, 3H), 1.34 (s, 6H), 2.23 (brs, 2H), 3.58–3.66 (m, 1H), 3.71 (dd, $J=8.2$, 3.0 Hz, 1H), 3.80–3.93 (m, 1H), 4.05–4.23 (m, 3H), 4.55 (d, $J=11.7$ Hz, 1H), 4.69 (d, $J=11.7$ Hz, 1H), 7.28–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.6, 26.7, 27.3 (CH_3), 55.8 (CH), 61.1, 73.2 (CH_2), 72.6, 78.0, 82.3 (CH), 108.5 (C), 127.8, 127.9, 128.4 (aromatic CH), 137.6 (aromatic C), 173.4 (C=O); IR (film) *v* 3390, 3330, 2980, 2934, 1736, 1380, 1214 cm^{-1}; FABMS *m*/*z* 338 (MH^+, 90). Anal. calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.42; H, 7.96; N, 4.21%.

4.4.3. Ethyl (2*S*,3*R*,4*S*,5*R*)-2-amino-3-benzyloxy-4,5-isopropylidenedioxyhexanoate, 22. Prepared from compound **21** (350 mg, 0.78 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc) to give **22** (214 mg, 81%) as a colorless oil: R_f 0.43 (silica gel, EtOAc/hexanes, 1:1); $[\alpha]_D^{26}=-4.0$ (*c* 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.20–1.40 (m, 12H), 1.82 (brs, 2H), 3.75–3.92 (m, 2H), 3.98 (dd, $J=7.2$, 6.0 Hz, 1H), 4.02–4.30 (m, 3H), 4.56 (d, $J=11.4$ Hz, 1H), 4.68 (d, $J=11.4$ Hz, 1H), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.4, 26.5, 27.2 (CH_3), 55.0 (CH), 60.1, 72.4 (CH_2), 76.4, 79.5, 82.3 (CH), 108.4 (C), 128.0, 128.4 (aromatic CH), 137.4 (aromatic C), 172.7 (C=O); IR (film) *v* 2934, 1730, 1380, 1250 cm^{-1}; FABMS *m*/*z* 338 (MH^+, 47), 306 (100). Anal. calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.95; H, 8.32; N, 4.23%.

4.4.4. Ethyl (2*R*,3*R*,4*S*,5*R*)-2-amino-3-benzyloxy-4,5-isopropylidenedioxyhexanoate, 31. Prepared from compound **30** (1.5 g, 3.36 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc) to give **31** (1.0 g, 88%) as a colorless oil: R_f 0.43 (silica gel, EtOAc/hexanes, 1:1); $[\alpha]_D^{24}=-20.7$ (*c* 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.30 (t, $J=7.0$ Hz, 3H), 1.33 (d, $J=5.9$ Hz, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.67 (brs, 2H), 3.75 (d, $J=1.9$ Hz, 1H), 3.82 (t, $J=7.6$ Hz, 1H), 3.97–4.10 (m, 2H), 4.22 (dq, $J=7.0$, 2.0 Hz, 2H), 4.46 (d, $J=11.3$ Hz, 1H), 4.55 (d, $J=11.3$ Hz, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.6, 27.1, 27.5 (CH_3), 55.3 (CH), 61.2, 73.6 (CH_2), 76.4, 80.6, 81.6 (CH), 108.4 (C), 127.9, 128.0, 128.4 (aromatic CH), 137.4 (aromatic C), 175.1 (C=O); IR (film) *v* 3392, 3337, 2984, 2934, 1736, 1378, 1216 cm^{-1}; FABMS *m*/*z* 338 (MH^+, 100). Anal. calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.28; H, 7.96; N, 4.14%.

4.5. General procedure for the protection of the amino group as *N*-benzylcarbamate

A solution of amino ester **13** (800 mg, 3.06 mmol), Na_2CO_3 (324 mg, 3.06 mmol) and $NaHCO_3$ (261 mg, 3.11 mmol) in dioxane (32 mL) and H_2O (32 mL) at 0°C was treated with CbzCl (0.5 mL, 3.49 mmol). The mixture was stirred at room temperature for 1 h, and then was concentrated to half its initial volume and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6–1:3) to give **14** (1.20 g, 99%) as a colorless oil.

4.5.1. Ethyl (2*R*,3*R*,4*S*,5*R*)-2-[*N*-(benzyloxycarbonyl)-amino]-4,5-isopropylidenedioxy-3-methoxyhexanoate, 14. Following the general procedure, amino ester **13** (800 mg, 3.06 mmol) gave **14** (1.20 g, 99%) as a colorless oil: R_f 0.37 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=-5.3$ (*c* 2.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.29 (t, $J=7.1$ Hz, 3H), 1.31 (d, $J=6.0$ Hz, 3H), 1.38 (s, 6H), 3.36 (s, 3H), 3.54 (dd, $J=8.3$, 7.0 Hz, 1H), 3.77 (dd, $J=8.3$, 1.5 Hz, 1H), 4.06 (dq, $J=7.0$, 6.0 Hz, 1H), 4.24 (q, $J=7.1$ Hz, 2H), 4.62 (dd, $J=9.5$, 1.5 Hz, 1H), 5.29 (s, 2H), 5.50 (brd, $J=9.5$ Hz, 1H), 7.28–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.3, 26.9, 27.3 (CH_3), 54.4 (CH), 59.5 (OCH_3), 61.5, 66.9 (OCH_2), 76.0, 80.2, 82.8 (CH), 108.7 (C), 127.5, 127.9, 128.4 (aromatic CH), 136.3 (aromatic C), 156.3, 171.4 (C=O); IR (film) *v* 2980, 1730, 1500, 1250, 1200 cm^{-1}; FABMS *m*/*z* 396 (MH^+, 100). Anal. calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.84; H, 7.35; N, 3.44%.

4.5.2. Ethyl (2*R*,3*S*,4*S*,5*R*)-3-benzyloxy-2-[*N*-(benzyloxycarbonyl)amino] - 4,5 - isopropylidenedioxyhexanoate, 19. Prepared from amino ester **18** (100 mg, 0.30 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6) to give **19** (116 mg, 82%) as a colorless oil: R_f 0.35 (silica gel, EtOAc/hexanes, 1:6); $[\alpha]_D^{21}=-5.4$ (*c* 0.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.11 (d, $J=6.0$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 1.39 (s, 6H), 3.52 (dd, $J=8.2$, 2.6 Hz, 1H), 3.79 (dd, $J=4.3$, 2.6 Hz, 1H), 4.10–4.20 (m, 1H), 4.23 (q, 2H, $J=7.1$ Hz, 2H), 4.50 (d, $J=11.7$ Hz, 1H), 4.77 (d, $J=11.7$ Hz, 1H), 4.89 (dd, $J=8.7$, 4.3 Hz, 1H), 5.13 (s, 2H), 6.17 (brd, $J=8.7$ Hz, 1H), 7.29–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.2, 17.2, 26.5, 27.4 (CH_3), 55.0 (CH), 61.6, 66.9, 71.7 (CH_2), 72.4, 73.6, 82.6 (CH), 109.1 (C), 128.0, 128.2, 128.4 (aromatic CH), 136.4, 137.1 (aromatic C),

156.6, 170.0 (C=O); IR (film) ν 3343, 2962, 1728, 1689, 1549, 1260, 1089, 1020 cm^{-1}; FABMS m/z 472 (MH^+, 10), 181 (100). Anal. calcd for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 65.82; H, 7.10; N, 2.97%.

4.5.3. Ethyl (2*S*,3*R*,4*S*,5*R*)-3-benzyloxy-2-[*N*-(benzyloxycarbonyl)amino] - 4,5 - isopropylidenedioxyhexanoate, 23. Prepared from amino ester **22** (180 mg, 0.53 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:9) to give **23** (206 mg, 82%) as a colorless oil: R_f 0.50 (silica gel, EtOAc/hexanes, 1:3); $[\alpha]_D^{21} = -1.4$ (c 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.23–1.34 (m, 12H), 3.59 (t, $J=8.1$ Hz, 1H), 3.90 (dq, $J=6.2$, 1.0 Hz, 1H), 4.02 (dd, $J=8.1$, 2.2 Hz, 1H), 4.05–4.03 (m, 2H), 4.49 (d, $J=11.1$ Hz, 1H), 4.84 (d, $J=11.1$ Hz, 1H), 5.00 (dd, $J=9.2$, 2.2 Hz, 1H), 5.16 (s, 2H), 5.55 (brd, $J=9.2$ Hz, 1H), 7.30–7.41 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.1, 26.3, 27.3 (CH_3), 54.0 (CH), 61.5, 67.2, 71.8 (CH_2), 77.0, 80.0, 80.8 (CH), 108.7 (C), 128.0, 128.2, 128.4, 128.5 (aromatic CH), 136.1, 137.0 (aromatic C), 156.5, 169.8 (C=O); IR (film) ν 3340, 2980, 1730, 1500 cm^{-1}; FABMS m/z 472 (MH^+, 7), 181 (74), 165 (100). Anal. calcd for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.46; H, 7.18; N, 3.08%.

4.5.4. Ethyl (2*R*,3*R*,4*S*,5*R*)-3-benzyloxy-2-[*N*-(benzyloxycarbonyl)amino] - 4,5 - isopropylidenedioxyhexanoate, 32. Prepared from amino ester **31** (700 mg, 2.08 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4) to give **32** (961 mg, 98%) as a colorless oil: R_f 0.35 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{21} = -14.6$ (c 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.28 (t, $J=7.0$ Hz, 3H), 1.28 (d, $J=5.8$ Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 3.62 (t, $J=7.6$ Hz, 1H), 3.94–4.10 (m, 2H), 4.15–4.30 (m, 2H), 4.42 (d, $J=11.0$ Hz, 1H), 4.56 (d, $J=11.0$ Hz, 1H), 4.70 (dd, $J=8.3$, 1.0 Hz, 1H), 5.15 (s, 2H), 5.56 (brd, $J=9.5$ Hz, 1H), 7.20–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 26.9, 27.3 (CH_3), 54.7 (CH), 61.7, 67.1, 73.7 (CH_2), 75.8, 80.2, 82.5 (CH), 108.7 (C), 128.1, 128.3, 128.5 (aromatic CH), 136.1, 136.7 (aromatic C), 156.4, 171.4 (C=O); IR (film) ν 3439, 3343, 2984, 2936, 1728, 1501, 1212, 1062 cm^{-1}; FABMS m/z 472 (MH^+, 13), 181 (100). Anal. calcd for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.23; H, 7.25; N, 2.97%.

4.5.5. Ethyl (2*R*,3*R*,4*S*,5*R*)-3-benzyloxy-4,5-isopropylidenedioxy - 2 - [*N* - (diphenylmethylene)amino]hexanoate, 36. Benzophenone imine (0.25 mL, 1.49 mmol), amino ester **31** (381 mg, 1.13 mmol) and anhydrous p-TsOH (63 mg) in dry CH_2Cl_2 (15 mL) were stirred under an argon atmosphere at room temperature for 14 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:11) to give **36** (458 mg, 81%) as a colorless oil: R_f 0.40 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{25} = +91.4$ (c 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.20 (d, $J=6.1$ Hz, 3H), 1.26 (t, $J=7.1$ Hz, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 3.54–3.61 (m, 1H), 4.03 (dq, $J=6.2$, 1.3 Hz, 1H), 4.14 (q, $J=7.1$ Hz, 2H), 4.30–4.40 (m, 2H), 4.66 (d, $J=10.8$ Hz, 1H), 4.83 (d, $J=10.8$ Hz, 1H), 7.12–7.18 (m, 2H), 7.25 (s, 5H), 7.27–7.46 (m, 6H), 7.70–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.2, 26.6, 27.3 (CH_3), 61.0 (CH_2), 68.7 (CH), 74.8 (CH_2), 75.2, 81.4, 81.7 (CH), 108.1 (C), 127.6, 128.0, 128.2, 128.4, 128.9, 130.4 (aromatic CH), 136.2, 138.1, 139.4 (aromatic C), 170.5, 171.9 (C=O, C=N); IR (film) ν 3000, 1745, 1625, 1450, 1370, 1250, 700 cm^{-1}; FABMS m/z 502 (MH^+, 27), 206 (95), 193 (87), 165 (100). Anal. calcd for $C_{31}H_{35}NO_5$: C, 74.23; H, 7.03; N, 2.79. Found: C, 73.87; H, 6.72; N, 2.70%.

4.5.6. Ethyl (2*R*,3*R*,4*S*,5*R*)-3-benzyloxy-4,5-isopropylidenedioxy - 2 - [*N* - methyl - *N* - (diphenylmethyl)amino]-hexanoate, 37. Schiff base ester **36** (250 mg, 0.50 mmol) in anhydrous CH_3CN (8 mL) was added to solid $NaBH_3CN$ (51 mg, 0.81 mmol), and glacial HOAc was added to keep the pH near to neutrality. After the reduction was complete (15 min by TLC, silica gel, EtOAc/hexanes, 1:4), 37% aqueous formaldehyde (0.78 mL, 9.7 mmol) and additional $NaBH_3CN$ (190 mg, 3.0 mmol) were added. The resulting exothermic reaction was allowed to cool to room temperature and glacial HOAc was added until the solution was neutral to wet pH paper. After 4 h, the reaction mixture was diluted with Et_2O and then washed with aqueous saturated $NaHCO_3$ and then H_2O. The organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:12) to give **37** (212 mg, 82%) as a white solid: R_f 0.50 (silica gel, EtOAc/hexanes, 1:9); mp 86–87°C; $[\alpha]_D^{24} = +77.1$ (c 1.9, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.21 (d, $J=5.9$ Hz, 3H), 1.31 (t, $J=7.1$ Hz, 3H), 1.36 (s, 3H), 1.49 (s, 3H), 2.55 (s, 3H), 3.68 (d, $J=6.1$ Hz, 1H), 3.91 (dd, $J=7.9$, 6.6 Hz, 1H), 4.10–4.34 (m, 4H), 4.69 (d, $J=11.1$ Hz, 1H), 4.83 (d, $J=11.1$ Hz, 1H), 5.00 (s, 1H), 7.10–7.50 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.2, 26.9, 27.3, 36.8 (CH_3), 59.7 (CH_2), 60.1, 74.6 (CH), 74.8 (CH_2), 75.0, 81.0, 81.4 (CH), 107.8 (C), 126.7, 127.3, 127.5, 127.8, 128.2, 128.3, 128.4, 128.9 (aromatic CH), 138.4, 142.1, 144.0 (aromatic C), 171.4 (C=O); IR (KBr) ν 3000, 1730, 1500 cm^{-1}; FABMS m/z 518 (MH^+, 7), 168 (45), 167 (100). Anal. calcd for $C_{32}H_{39}NO_5$: C, 74.25; H, 7.59; N, 2.71. Found: C, 74.12; H, 7.28; N, 2.70%.

4.6. General procedure for lactonization

A solution of compound **14** (1.17 g, 2.96 mmol) in THF/H_2O (6:1) (28 mL) at 0°C was treated with TFA (24 mL) and stirred at room temperature for 3 h. The solvents were removed in vacuo and the crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:1) to give lactone **15** (808 mg, 88%) as a white solid.

4.6.1. (3*R*,4*R*,5*S*,1′*R*)-3-[*N*-(Benzyloxycarbonyl)-amino]-5-(1-hydroxyethyl)-4-methoxytetrahydrofuran-2-one, 15. Following the general procedure, **14** (1.17 g, 2.96 mmol) gave **15** (808 mg, 88%) as a white solid; R_f 0.23

(silica gel, EtOAc/hexanes, 2:3); mp 89–90°C (CH_2Cl_2/hexanes); $[\alpha]_D^{20}=-28.2$ (c 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.33 (d, $J=6.4$ Hz, 3H, CH_3CH), 3.10 (brs, 1H, OH), 3.45 (s, 3H, OCH_3), 4.00 (m, 1H, H-1′), 4.07–4.15 (m, 2H, H-4, H-5), 4.46 (m, 1H, H-3), 5.14 (s, 2H, CH_2Ph), 5.87 (brd, $J=8.6$ Hz, 1H, NH), 7.35 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.3 (CH_3), 57.5, 58.1 (OCH_3, C-3), 67.1 (CH), 67.6 (CH_2), 81.9, 84.7 (CH), 128.2, 128.3, 128.6 (aromatic CH), 135.6 (aromatic C), 156.0, 172.9 (C=O); IR (KBr) ν 3300, 1775, 1700, 1540 cm^{-1}; FABMS m/z 310 (MH^+, 25), 266 ([M–CO_2]H$^+$, 100). Anal. calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 57.95; H, 5.86; N, 4.52%.

4.6.2. (3*R*,4*S*,5*S*,1′*R*)-4-Benzyloxy-3-[*N*-(benzyloxycarbonyl)amino]-5-(1-hydroxyethyl)tetrahydrofuran-2-one, 20. Prepared from **19** (70 mg, 0.15 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:1) to give **20** (47 mg, 81%) as a white solid: R_f 0.30 (silica gel, EtOAc/hexanes, 1:3); mp 167–169°C (EtOH); $[\alpha]_D^{23}=-53.4$ (c 0.9, acetone); ^{1}H NMR ([D_6]acetone) δ 1.13 (d, $J=6.3$ Hz, 3H, CH_3CH), 4.08–4.2 (m, 1H, H-1′), 4.13 (d, $J=2.7$ Hz, 1H, OH), 4.38 (dd, $J=7.0$, 3.8 Hz, 1H, H-5), 4.50 (dd, $J=5.0$, 3.8 Hz, 1H, H-4), 4.52 (d, $J=11.3$ Hz, 1H, CH_2Ph), 4.57 (d, $J=11.3$ Hz, 1H, CH_2Ph), 4.91 (dd, $J=8.5$, 5.0 Hz, 1H, H-3), 5.13 (d, $J=12.5$ Hz, 1H, CH_2Ph), 5.19 (d, $J=12.5$ Hz, 1H, CH_2Ph), 7.00 (brd, $J=8.5$ Hz, 1H, NH), 7.26–7.44 (m, 10H, ArH); ^{13}C NMR ([D_6]acetone) δ 18.7 (CH_3), 56.3, 65.9 (CH), 67.2, 74.8 (CH_2), 77.4, 85.7 (CH), 128.5, 128.6, 128.7, 128.8, 129.1, 129.2 (aromatic CH), 137.9, 138.5 (aromatic C), 157.0, 174.0 (C=O); IR (KBr) ν 3400, 3300, 1770, 1690, 1500 cm^{-1}; FABMS m/z 386 (MH^+, 10), 342 ([M–CO_2]H$^+$, 100); HRFABMS calcd for $C_{21}H_{23}NO_6$: (M+H)$^+$ 386.1604. Found: 386.1607.

4.6.3. (3*S*,4*R*,5*S*,1′*R*)-4-Benzyloxy-3-[*N*-(benzyloxycarbonyl)amino]-5-(1-hydroxyethyl)tetrahydrofuran-2-one, 24. Prepared from **23** (100 mg, 0.21 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:1) to give **24** (70 mg, 86%) as a white solid: R_f 0.40 (silica gel, EtOAc/hexanes, 1:1.8); mp 90–91°C (CH_2Cl_2/hexanes); $[\alpha]_D^{21}=+4.3$ (c 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, $J=6.5$ Hz, 3H, CH_3CH), 2.93 (brs, 1H, OH), 3.9 (dq, $J=6.5$, 2.7 Hz, 1H, H-1′), 4.22 (d, $J=6.0$ Hz, 1H, H-4), 4.29 (d, $J=2.7$ Hz, 1H, H-5), 4.54 (d, $J=11.8$ Hz, 1H, CH_2Ph), 4.60 (d, $J=11.8$ Hz, 1H, CH_2Ph), 5.02 (dd, $J=8.9$, 6.0 Hz, 1H, H-3), 5.10 (d, $J=12.1$ Hz, 1H, CH_2Ph), 5.16 (d, $J=12.1$ Hz, 1H, CH_2Ph), 5.53 (brd, $J=8.9$ Hz, 1H, NH), 7.23–7.38 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_3), 52.7, 67.4 (CH), 67.4, 72.4 (CH_2) 76.4, 86.5 (CH), 127.9, 128.1, 128.2, 128.5, 128.6 (aromatic CH), 135.9, 136.5 (aromatic C), 156.3, 174.5 (C=O); IR (KBr) ν 3400, 3240, 1760, 1700 cm^{-1}; FABMS m/z 386 (MH^+, 10), 342 ([M–CO_2]H$^+$, 100). Anal. calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.54; H, 6.02; N, 3.62%.

4.6.4. (3*R*,4*R*,5*S*,1′*R*)-4-Benzyloxy-3-[*N*-(benzyloxycarbonyl)amino]-5-(1-hydroxyethyl)tetrahydrofuran-2-one, 33. Prepared from compound **32** (650 mg, 1.38 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 2:3) to give **33** (452 mg, 85%) as a colorless solid. Crystallization from ligroin/ether afforded colorless needles: R_f 0.50 (silica gel, EtOAc/hexanes, 1:1); mp 97–99°C; $[\alpha]_D^{24}=-23.6$ (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, $J=6.4$ Hz, 3H), 2.10 (brs, 1H), 3.8–4.00 (m, 1H), 4.10–4.21 (m, 1H), 4.32 (brt, $J=6.1$ Hz, 1H), 4.40–4.75 (m, 3H), 5.11 (d, $J=12.2$ Hz, 1H), 5.18 (d, $J=12.2$ Hz, 1H), 5.6 (brd, $J=8.5$ Hz, 1H), 7.32 (s, 5H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 19.3 (CH_3), 57.9, 67.0 (CH), 67.5, 72.4 (CH_2), 79.9, 84.7 (CH), 128.0, 128.2, 128.4, 128.6 (aromatic CH), 135.8 (aromatic C), 155.9, 172.6 (C=O); IR (KBr) ν 3544, 3414, 2985, 1789, 1710, 1505, 1250, 1128 cm^{-1}; FABMS m/z 386 (MH^+, 10), 342 ([M–CO_2]H$^+$, 100). Anal. calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.32; H, 6.04; N, 3.65%.

4.6.5. X-Ray crystallographic data of lactone 33. X-Ray crystal analysis was performed on a Siemens Smart CCD diffractometer with $Mo_{k\alpha}$ radiation ($\lambda=0.71073$ Å). Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-175830. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). $C_{21}H_{23}NO_6$; $M=385.4$; colorless needles; crystal dimensions $=0.50\times0.35\times0.30$ mm; space group $P2_12_12_1$; orthorhombic; $a=5.6870(7)$ Å, $b=11.4549(13)$ Å, $c=30.439(3)$ Å; $V=1982.9(4)$ Å^3; $Z=4$; $T=298(2)$ K; $\rho_{calcd}=1.291$ Mg m^{-3}; $\mu=0.095$ mm^{-1}; reflections total: 14106, unique: 4930 (R_{int} 0.0685), observed: 2695 ($I>2\sigma(I)$); R indices (all data), $R1=0.1243$, w$R2=0.1126$; final R indices ($I>2\sigma(I)$), $R1=0.0530$, w$R2=0.0935$; GOF $=0.998$.

4.6.6. (3*R*,4*R*,5*S*,1′*R*)-4-Benzyloxy-5-(1-hydroxyethyl)-3-[*N*-methyl-*N*-(diphenylmethyl)amino]tetrahydrofuran-2-one, 38. Prepared from compound **37** (163 mg, 0.31 mmol) following the general procedure. Lactonization required 16 h of stirring at room temperature. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:3) to give **38** (108 mg, 81%) as a colorless oil: R_f 0.37 (silica gel, EtOAc/hexanes, 1:3); $[\alpha]_D^{22}=+12.1$ (c 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.26 (d, $J=6.5$ Hz, 3H), 2.4 (s, 3H), 3.15 (brs, 1H), 3.85 (dq, $J=6.5$, 2.4 Hz, 1H), 3.96 (dd, $J=6.6$, 2.4 Hz, 1H), 4.04 (d, $J=7.9$ Hz, 1H), 4.60 (t, $J=7.5$ Hz, 1H), 4.75 (d, $J=11.2$ Hz, 1H), 5.04 (d, $J=11.2$ Hz, 1H), 5.41 (s, 1H), 7.15–7.61 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 19.3 (CH_3), 36.1 (NCH_3), 66.4, 66.7 (CH), 72.8 (CH_2), 73.1 76.1, 84.0 (CH), 127.4, 127.6, 127.9, 128.0, 128.2, 128.5, 128.7, 129.0 (aromatic CH), 137.4, 141.0, 141.8 (aromatic C), 172.0 (C=O); IR (film) ν 3300, 3414, 1765, 1495, 1450 cm^{-1}; FABMS m/z (%): 431 (M^+, 20), 167 (100). Anal. calcd

for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.26; H, 6.82; N, 3.35%.

4.7. General silylation procedure

A solution of lactone **15** (470 mg, 1.52 mmol) and imidazole (207 mg, 3.04 mmol) in THF (25 mL) was treated with isopropyldimethylsilyl chloride (0.30 mL, 1.91 mmol) and stirred at room temperature for 3 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, EtOAc/hexanes, 1:6–1:4) of the crude material gave lactone **16** (615 mg, 99%) as a colorless oil.

4.7.1. (3*R*,4*R*,5*S*,1′*R*)-3-[*N*-(Benzyloxycarbonyl)-amino]-5-[1-(isopropyldimethylsilanyloxy)ethyl)]-4-methoxytetrahydrofuran-2-one, 16. Following the general procedure lactone **15** (470 mg, 1.52 mmol) gave lactone **16** (615 mg, 99%) as a colorless oil: R_f 0.50 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=-34.1$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H; $(CH_3)_2Si$), 0.70–0.90 (m, 7H, $(CH_3)_2CHSi$), 1.27 (d, $J=6.9$ Hz, 3H, CH_3CH), 3.45 (s, 3H, OCH_3), 3.90 (t, $J=5.8$ Hz, 1H, H-4), 4.00–4.10 (m, 1H, H-1′), 4.10–4.17 (m, 1H, H-5), 4.50 (dd, $J=8.5$, 5.8 Hz, 1H, H-3), 5.16 (s, 2H, CH_2Ph), 5.30 (brd, $J=8.5$ Hz, 1H, NH), 7.36 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −3.7, −3.6 ($(CH_3)_2Si$), 14.6, 16.8, 19.4 ($(CH_3)_2CHSi$, CH_3CH), 57.3, 57.8 (CH, OCH_3), 67.4 (CH_2), 67.9, 82.4, 85.3 (CH), 128.1, 128.2, 128.5 (aromatic CH), 135.7 (aromatic C), 155.7, 172.5 (C=O); IR (film) *v* 3340, 2950, 2860, 1785, 1720, 1420, 1250 cm^{-1}; FABMS *m*/*z* 410 (MH^+, 42), 366 ($[M-CO_2]H^+$, 100). Anal. calcd for $C_{20}H_{31}NO_6Si$: C, 58.65; H, 7.63; N, 3.42. Found: C 58.95, H; 7.31; N, 3.25%.

4.7.2. (3*R*,4*R*,5*S*,1′*R*)-4-Benzyloxy-3-[*N*-(benzyloxycarbonyl)amino] - 5 - [1 - (isopropyldimethylsilanyloxy)ethyl)-]tetrahydrofuran-2-one, 34. Prepared from lactone **33** (440 mg, 1.14 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4) to give **34** (525 mg, 95%) as a colorless oil: R_f 0.38 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{22}=-26.7$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.70–0.96 (m, 7H), 1.26 (d, $J=6.4$ Hz, 3H), 3.91–4.12 (m, 1H), 4.10 (t, $J=5.4$ Hz, 1H), 4.21–4.25 (m, 1H), 4.50–4.60 (m, 1H), 4.55 (d, $J=11.9$ Hz, 1H), 4.76 (d, $J=11.9$ Hz, 1H), 5.13 (d, $J=12.2$ Hz, 1H), 5.21 (d, $J=12.2$ Hz, 1H), 5.21 (brd, 1H), 7.31 (s, 5H), 7.37 (s, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ −3.7, −3.6 ($(CH_3)_2Si$), 14.6, 16.8, 19.4 ($(CH_3)_2CHSi$, CH_3CH), 57.6 (CH), 67.4 (CH_2), 67.9 (CH), 71.9 (CH_2), 79.9, 85.6 (CH), 128.1, 128.3, 128.5 (aromatic CH), 135.8, 136.9 (aromatic C), 155.7, 172.5 (C=O); IR (film) *v* 3340, 2953, 2865, 1789, 1722, 1515, 1254 cm^{-1}; FABMS *m*/*z* 486 (MH^+, 5), 442 ($[M-CO_2]H^+$, 17), 181 (100). Anal. calcd for $C_{26}H_{35}NO_6Si$: C, 64.30; H, 7.26; N, 2.88. Found: C, 63.95; H, 7.04; N, 2.88%.

4.7.3. (3*R*,4*R*,5*S*,1′*R*) - 4 - Benzyloxy - 5 - [1 - (isopropyldimethylsilanyloxy)ethyl)] - 3 - [*N* - methyl - *N* - (diphenylmethyl)amino]tetrahydrofuran-2-one, 39. Prepared from lactone **38** (100 mg, 0.23 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:13) to give **39** (116 mg, 94%) as a colorless oil: R_f 0.5 (silica gel, EtOAc/hexanes, 1:9); $[\alpha]_D^{22}=+8.5$ (*c* 2.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.70–0.91 (m, 1H), 0.91–1.04 (m, 6H), 1.26 (d, $J=6.7$ Hz, 3H), 2.40 (s, 3H), 3.90–4.05 (m, 3H), 4.49 (dd, $J=8.0$, 6.6 Hz, 1H), 4.70 (d, $J=11.3$ Hz, 1H), 5.11 (d, $J=11.3$ Hz, 1H), 5.42 (s, 1H), 7.20–7.56 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.5 ($(CH_3)_2Si$), 14.7, 15.5, 19.8 ($(CH_3)_2CHSi$, CH_3CH), 35.9 (NCH_3), 66.3, 66.6 (CH), 72.4 (CH_2), 72.8, 75.8, 83.9 (CH), 127.9, 127.5, 128.2, 128.5, 128.6, 128.7 (aromatic CH), 137.0, 142.0, 143.0 (aromatic C), 172.7 (C=O); IR (film) *v* 2960, 1775, 1450 cm^{-1}; FABMS *m*/*z* 531 (M^+, 4), 530 (20), 167 (100). Anal. calcd for $C_{32}H_{41}NO_4Si$: C, 72.28; H, 7.77; N, 2.63. Found: C, 72.45; H, 7.72; N, 2.70%.

4.7.4. (5*S*,1′*R*)-3-[*N*-(Benzyloxycarbonyl)amino]-5-[1-(isopropyldimethylsilanyloxy)ethyl)]-5*H*-furan-2-one, 35. Sodium hydride (8 mg, 60% dispersion in mineral oil, 0.21 mmol) was added to a solution of lactone **34** (68 mg, 0.14 mmol) and MeI (0.07 mL, 1.12 mmol) in dry THF (5 mL) at −15°C. After the reaction was complete (15 min by TLC, silica gel, EtOAc/hexanes, 1:4), MeOH (0.3 mL) was added and the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated, and the crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6) to give **35** (36 mg, 68%) as a colorless oil: R_f 0.57 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{24}=-5.1$ (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.70–1.0 (m, 7H), 1.16 (d, $J=6.3$ Hz, 3H), 3.97 (quintuplet, $J=6.3$ Hz, 1H), 4.9 (dd, $J=5.8$, 2.0 Hz, 1H), 5.2 (s, 2H), 7.04 (brd, $J=9.2$ Hz, 1H), 7.10–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$) δ −4.0, −3.8 ($(CH_3)_2Si$), 14.6, 16.7, 19.4 ($(CH_3)_2CHSi$, CH_3CH), 67.8 (CH_2), 68.7, 84.8, 123.9 (CH), 126.9 (C), 128.2, 128.6, 128.7 (aromatic CH), 135.0 (aromatic C), 153.0, 169.0 (C=O); IR (film) *v* 2954, 1768, 1738, 1666, 1536, 1320, 1216 cm^{-1}; FABMS *m*/*z* 378 (MH^+, 28), 334 ($[M-CO_2]H)^+$, 18), 181 (100). Anal. calcd $C_{19}H_{27}NO_5Si$: C, 60.45; H, 7.21; N, 3.71. Found: C, 60.58; H, 6.96; N, 3.49%.

4.8. General procedure for the DIBALH reduction

DIBALH (1.5 M solution in toluene, 2 mL, 3.0 mmol) was added dropwise to a stirred solution of lactone **16** (592 mg, 1.45 mmol) in toluene/THF (2:1) (45 mL) at −78°C. After stirring for 6 h at −78°C, the reaction was quenched with cold CH_3OH (2 mL). Then, an ice-cold aqueous saturated NH_4Cl solution (8 mL) was slowly added, and the suspension was allowed to reach to room temperature. The mixture was extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mate-

rial was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6–1:3) to give lactols **26** (385 mg, 65%; 85% based on recovered starting material) and starting lactone **16** (186 mg, 31%) unchanged in $[\alpha]_D$.

4.8.1. 2-[*N*-(Benzyloxycarbonyl)amino]-2,6-dideoxy-3-*O*-methyl-D-galactose, 25 and 27 and alcohol 28. Prepared from lactone **15** (300 mg, 0.97 mmol) following the general procedure but using 2.5 equiv. of DIBALH. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 2:3 to EtOAc) to give a 7:3:1 mixture of lactols **25** and **27** (130 mg, 43%), starting lactone **15** (84 mg, 28%) unchanged in $[\alpha]_D$ and alcohol **28** (21 mg, 7%). Data for **25** and **27**: colorless oil: R_f 0.33 (silica gel, EtOAc/hexanes, 3:1); $[\alpha]_D^{24}=+2.7$ (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ (7:3:1 anomeric mixture) 1.21 (d, $J=6.4$ Hz, 9H), 1.27 (d, $J=6.4$ Hz, 21H), 1.29 (d, $J=6.3$ Hz, 3H), 3.35–3.45 (m, 44H), 3.76–3.90 (m, 11H), 4.00–4.35 (m, 22H), 5.00–5.38 (m, 33H), 5.45 (brd, $J=6.8$ Hz, 1H), 5.79 (brd, $J=9.2$ Hz, 7H), 5.95 (brd, $J=8.6$ Hz, 3H), 7.30–7.40 (m, 55H); ^{13}C NMR ($CDCl_3$) δ (7:3:1 anomeric mixture) 16.4, 19.6, 19.9 (CH_3), 50.1, 54.9, 57.7, 57.9, 59.7, 60.5 (CH, OCH_3), 66.9, 67.2 (CH_2), 67.6, 68.1, 70.4, 78.4, 80.1, 84.7, 86.0, 87.6, 92.1, 95.5, 96.4, 102.2 (CH), 128.1, 128.3, 128.4 (aromatic CH), 135.9, 136.3 (aromatic C), 155.9, 156.6, 157.8 (C–O); IR (film): $\nu=3330$, 2950, 1700, 1540, 1260, 1200 cm^{-1}; FABMS *m*/*z* 312 (MH^+, 22), 294 ($[M-H_2O]H^+$, 82), 241 (100). Anal. calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.99; H, 6.80; N, 4.73%. Data for **28**: colorless oil: R_f 0.25 (silica gel, EtOAc); $[\alpha]_D^{23}=-17.7$ (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.27 (d, $J=5.9$ Hz, 3H), 3.23 (brd, $J=8.8$ Hz, 1H), 3.42–3.54 (m, 1H), 3.50 (s, 3H), 3.55–3.70 (m, 3H), 3.75–4.00 (m, 1H), 4.00–4.20 (m, 1H), 5.11 (s, 2H), 5.37 (brd, $J=9.2$ Hz, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 52.8, 60.4 (CH, OCH_3), 63.0 (CH_2), 66.2 (CH), 67.3 (CH_2), 77.6, 80.4 (CH), 128.1, 128.3, 128.6 (aromatic CH), 136.1 (aromatic C), 157.7 (C=O); IR (film) ν 3382, 2948, 1694, 1519, 1260, 1051 cm^{-1}; FABMS *m*/*z* 314 (MH^+, 20), 270 (100). Anal. calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.19; H, 7.35; N, 4.14%.

4.8.2. 2-*N*-[(Benzyloxycarbonyl)amino]-2,6-dideoxy-5-*O*-(isopropyldimethylsilyl)-3-*O*-methyl-D-galactofuranose, 26. Prepared from lactone **16** (592 mg, 1.45 mmol) following the general procedure. The crude product was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6–1:3) to give lactols **26** (385 mg, 65%, 85% based on recovered starting material) as a colorless solid and starting lactone **16** (186 mg, 31%) unchanged in $[\alpha]_D$. Data for **26**: R_f 0.26 (silica gel, EtOAc/hexanes, 1:3); mp 61–62°C; $[\alpha]_D^{22}=-22.4$ (*c* 2.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ (1.5:1 anomeric mixture) 0.07 (s, 3H), 0.08 (s, 3H), 0.15 (s, 4.5H), 0.16 (s, 4.5H), 0.80–1.03 (m, 17.5H), 1.27 (d, $J=6.4$ Hz, 4.5H), 1.29 (d, $J=6.3$ Hz, 3H), 3.42 (s, 4.5H), 3.45 (s, 3H), 3.40–3.55 (m, 1H), 3.62–3.68 (m, 2.5H), 3.85–3.97 (m, 2.5H), 4.00–4.11 (m, 1H), 4.20–4.33 (m, 3H), 5.08–5.24 (m, 7.5H), 5.35 (brd, $J=8.5$ Hz, 1.5H), 5.84 (brd, $J=8.5$ Hz, 1H), 7.32–7.43 (m, 12.5H); ^{13}C NMR ($CDCl_3$) δ (1.5:1 anomeric mixture) −3.8, −3.6 ($(CH_3)_2Si$), 14.3, 14.6, 16.7, 20.0, 20.1 ($(CH_3)_2CHSi$, CH_3CH), 57.7, 57.9, 58.3, 60.5 (CH, OCH_3), 66.9, 67.0 (CH_2), 68.7, 68.8, 85.0, 86.9, 87.0, 87.9, 96.1, 102.2 (CH), 128.1, 128.3, 128.4 (aromatic CH), 136.2 (aromatic C), 155.4, 155.7 (C=O); IR (film) ν 2960, 1720, 1260, 1100, 1020 cm^{-1}; FABMS *m*/*z* 394 ($[M-H_2O]H^+$, 100). Anal. calcd for $C_{20}H_{33}NO_6Si$: C, 58.37; H, 8.08; N, 3.40. Found: C, 58.64; H, 7.88; N, 3.18%.

4.8.3. 3-*O*-Benzyl-2-*N*-(benzyloxycarbonyl)amino-2,6-dideoxy-5-*O*-(isopropyldimethylsilyl)-D-galactofuranose, 40. Prepared from lactone **34** (140 mg, 0.29 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:4–1:3) to give lactols **40** (95 mg, 67%, 86% based on recovered starting material) as a colorless oil and starting lactone **34** (40 mg, 29%). Data for **40**: R_f 0.40 (silica gel, EtOAc/hexanes, 1:1.8); $[\alpha]_D^{20}=-54.1$ (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ (1.5:1 anomeric mixture) 0.07 (s, 6H), 0.14 (m, 9H), 0.72–0.94 (m, 17.5H), 1.24 (d, $J=6.4$ Hz, 3H), 1.27 (d, $J=6.4$ Hz, 4.5H), 3.66–3.92 (m, 4H), 3.99 (dd, $J=1.5$, 1.1 Hz, 1.5H), 4.14 (t, $J=2.1$ Hz, 1H), 4.31–4.43 (m, 3.5H), 4.53 (dd, $J=7.7$, 1.8 Hz, 2.5H), 4.8 (d, $J=12.0$ Hz, 2.5H), 5.10–5.30 (m, 7.5H), 5.36 (brd, $J=8.0$ Hz, 1.5H), 5.36 (brd, $J=8.0$ Hz, 1H), 7.20–7.45 (m, 25H); ^{13}C NMR ($CDCl_3$) δ (1.5:1 anomeric mixture) −4.1, −4.0, −3.7 ($(CH_3)_2Si$), 14.2, 14.6, 16.7, 19.9, 20.1 ($(CH_3)_2CHSi$, CH_3CH), 58.8, 61.1 (CH), 66.9, 67.0 (CH_2), 68.3, 68.4 (CH), 71.4, 71.7 (CH_2), 82.3, 83.5, 87.6, 88.0, 96.3, 102.3 (CH), 127.8, 128.0, 128.2, 128.4, 128.5, 128.6 (aromatic CH), 136.3, 136.7, 137.6 (aromatic C), 155.4, 155.6 (C–O); IR (film) ν 2965, 1485, 1478, 1260 cm^{-1}; FABMS *m*/*z* 470 ($[M-H_2O]H^+$, 20), 181 (100). Anal. calcd for $C_{26}H_{37}NO_6Si$: C, 64.04; H, 7.65; N, 2.87. Found: C, 64.35; H, 7.46; N, 2.56%.

4.8.4. 3-*O*-Benzyl-2,6-dideoxy-5-*O*-(isopropyldimethylsilyl)-2-[*N*-methyl-*N*-(diphenylmethyl)amino]-D-galactofuranoses, 41. Prepared from lactone **39** (80 mg, 0.15 mmol) following the general procedure. The crude material was purified by flash chromatography (silica gel, EtOAc/hexanes, 1:6) to give lactols **41** (62 mg, 77%, 91% based on recovered starting material) as a colorless oil and starting lactone **39** (14 mg, 18%). Data for **41**: R_f 0.35 (silica gel, EtOAc/hexanes, 1:4); $[\alpha]_D^{24}=-33.0$ (*c* 2.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ (1:1 anomeric mixture) 0.01–0.20 (m, 12H), 0.80–0.11 (m, 14H), 1.28 (d, $J=3.7$ Hz, 3H), 1.27 (d, $J=3.8$ Hz, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 3.49 (dd, $J=6.8$, 4.7 Hz, 1H), 3.57 (dd, $J=4.7$, 2.2 Hz, 1H), 3.89–4.12 (m, 3H), 4.27 (dd, $J=6.8$, 4.7 Hz, 1H), 4.40 (dd, $J=6.8$, 4.7 Hz, 1H), 4.60–4.90 (m, 6H), 5.10 (brs, 1H), 5.20 (brd, $J=4.5$ Hz, 1H), 5.57 (brs, 1H), 7.20–7.60 (m, 30H); ^{13}C NMR ($CDCl_3$) δ (1:1 anomeric mixture) −3.8, −3.7, −3.5 ($(CH_3)_2Si$), 14.7, 16.8, 16.9, 20.2, 20.4 ($(CH_3)_2CHSi$, CH_3CH), 35.7, 36.7 (NCH_3), 61.1, 67.6, 69.3 (CH), 71.8 (CH_2), 72.4, 73.4, 74.4, 78.3, 81.0, 84.4, 86.3, 96.1, 97.6 (CH), 126.8, 126.9, 127.2, 127.7, 128.0, 128.4 (aromatic CH), 138.0, 138.1, 141.7, 142.2, 142.4 (aromatic C); IR (film) ν 2960, 1490, 1470, 1260 cm^{-1}; FABMS *m*/*z* 533 (MH^+, 9), 532 (14), 167 (100). Anal. calcd for

$C_{32}H_{43}NO_4Si$: C, 72.00; H, 8.12; N, 2.62. Found: C, 72.28; H, 8.15; N, 2.44%.

4.9. General procedure for the final deprotection

A mixture of lactols **26** (100 mg, 0.24 mmol) in THF (8 mL) and 0.25N HCl (4 mL) was stirred with 10% Pd/C (10 mg) under H_2 (1 atm) for 6 h at room temperature. The catalyst was removed by filtration through a short pad of Celite, and the filtrate was concentrated in vacuo. The crude product was dissolved in 1 M NaOH (2 mL) and loaded onto a column (1.5×7.0 cm) of Dowex-50WX8 (H^+ form), the column was washed with H_2O, and the product was eluted with a 1% aqueous NH_3 solution. Evaporation of the solvent gave free amino sugar **3** as a pale yellow solid (37 mg, 87%).

4.9.1. 2-Amino-2,6-dideoxy-3-*O*-methyl-D-galactose hydrochloride, 29. Deprotection of lactols **26** (100 mg, 0.24 mmol) following the general procedure gave free amino sugar **3** as a pale yellow solid (37 mg, 87%). Treatment of **3** with 0.25N HCl until pH 2, and purification by reversed-phase flash chromatography (RP-18, H_2O) afforded **29** in an almost quantitative yield. Data for **29**: pale yellow oil: R_f 0.34 (silica gel, *n*-BuOH/AcOH/H_2O, 12:3:5); $[\alpha]_D^{22}=+92.1$ ($c=0.6$, H_2O) (lit. $[\alpha]_D=+85.3$ ($c=1.1$, H_2O));[18d] a 1.4:1 (α/β) anomeric mixture was observed in D_2O solution. For α-anomer: ^{1}H NMR (500 MHz, D_2O, 25°C) δ 1.01 (d, $J=6.6$ Hz, 3H, CH_3CH), 3.21 (dd, $J=11.0$, 3.8 Hz, 1H, H-2), 3.22 (s, 3H, OCH_3), 3.54 (dd, $J=11.0$, 3.0 Hz, 1H, H-3), 3.91 (d, $J=3.0$ Hz, 1H, H-4), 4.00 (q, $J=6.6$ Hz, 1H, H-5), 5.17 (d, $J=3.8$ Hz, 1H, H-1); ^{13}C NMR (125 MHz, D_2O, 25°C) δ 16.6 (C-6), 50.9 (C-2), 56.8 (OCH_3), 67.0 (C-4), 67.4 (C-5), 76.5 (C-3), 90.2 (C-1). For β-anomer: ^{1}H NMR (500 MHz, D_2O, 25°C) δ 1.06 (d, $J=6.4$ Hz, 3H, CH_3CH), 2.90 (dd, $J=11.0$, 8.6 Hz, 1H, H-2), 3.22 (s, 3H, OCH_3), 3.35 (dd, $J=11.0$, 3.0 Hz, 1H, H-3), 3.60 (q, $J=6.4$ Hz, 1H, H-5), 3.87 (d, $J=3.0$ Hz, 1H, H-4), 4.63 (d, $J=8.6$ Hz, 1H, H-1); ^{13}C NMR (125 MHz, D_2O, 25°C) δ 16.7 (C-6), 54.1 (C-2), 57.1 (OCH_3), 66.4 (C-4), 72.3 (C-5), 79.4 (C-3), 94.0 (C-1); IR (film) ν 3410, 1630, 1200 cm^{-1}; FABMS m/z 178 (MH^+, 42), 160 ($[M-H_2O]H^+$, 100).

4.9.2. D-Fucosamine, 1. Prepared from lactols **40** (50 mg, 0.10 mmol) following the general procedure. The crude product was dissolved in 1 M NaOH (2 mL) and loaded onto a column (1.5×7.0 cm) of Dowex-50WX8 (H^+ form), the column was washed with H_2O, and the product was eluted with a 1% aqueous NH_3 solution. Evaporation of the solvent gave free amino sugar **1** as a pale yellow solid (14 mg, 87%). Treatment of **1** with 1 M HCl until pH 2 and purification by reversed-phase flash chromatography (RP-18, H_2O) afforded fucosamine hydrochloride as a colorless solid in an almost quantitative yield: R_f 0.35 (silica gel, *n*-BuOH/AcOH/H_2O, 12:3:5); mp 175–178°C (dec.) (lit. mp 174–176°C (dec.));[18c] $[\alpha]_D^{23}=+76.1$ (final, c 0.6, H_2O) (lit. $[\alpha]_D^{25}=+81.0$ (final, c 0.24, H_2O));[18c] a mixture of α/β anomers 1.5:1 was observed in D_2O solution. ^{1}H NMR (D_2O) δ (for α-anomer) 1.20 (d, $J=6.6$ Hz, 3H), 3.39 (dd, $J=10.9$, 3.6 Hz, 1H), 3.80 (m, 1H), 4.05 (dd, $J=10.9$, 3.3 Hz, 1H), 4.23 (q, $J=6.6$ Hz, 1H), 5.39 (d, $J=3.6$ Hz, 1H); ^{1}H NMR (D_2O) δ (for β-anomer) 1.24 (d, $J=6.6$ Hz, 3H), 3.09 (dd, $J=10.9$, 8.6 Hz, 1H), 3.74–3.82 (m, 2H), 3.84 (dd, $J=10.9$, 3.3 Hz, 1H), 4.84 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (D_2O) δ (anomeric mixture) 16.5, 52.0, 55.3, 67.5, 70.5, 71.3, 71.8, 72.3, 90.2, 93.9; FABMS m/z 164 (MH^+, 49), 146 ($[M-H_2O]H^+$, 69), 57 (100).

4.9.3. *N*-Methyl-D-fucosamine, 2. Prepared from lactols **41** (53 mg, 0.10 mmol) following the general procedure. The crude product was dissolved in 1 M NaOH (1 mL) and loaded onto a column (1.5×7.0 cm) of Dowex-50WX8 (H^+ form), the column was washed with H_2O, and the product was eluted with MeOH/3 M NH_4OH/H_2O (2:5:3).[8b,12a] Evaporation of the solvent followed by purification by reversed-phase flash chromatography (RP-18, H_2O) afforded free amino sugar **2** as a colorless solid (15 mg, 87%): R_f 0.60 (silica gel, *n*-BuOH/AcOH/H_2O, 1:1:1); mp 158–162°C (dec.) (lit. mp 158–161°C (dec.));[8b] $[\alpha]_D^{25}=+69.0$ (final, c 0.1, H_2O) (lit. $[\alpha]_D^{25}=+73.1$ (final, c 0.1, H_2O)).[8b] A mixture of pyranose and furanose anomers was observed in D_2O solution. ^{1}H NMR (D_2O) δ (major anomer) 1.21 (d, $J=6.5$ Hz, 3H), 2.67 (s, 3H), 3.03 (dd, $J=11.0$, 3.5 Hz, 1H), 3.75 (m, 1H), 3.92 (dd, $J=11.0$, 3.0 Hz, 1H), 4.18 (q, $J=6.5$ Hz, 1H), 5.48 (d, $J=3.5$ Hz, 1H); ^{13}C NMR (D_2O) δ (major anomers) 16.6, 32.7, 34.7, 59.1, 62.3, 67.2, 68.6, 71.8, 72.1, 89.8, 96.7; FABMS m/z 178 (MH^+, 99), 160 ($[M-H_2O]H^+$, 94).

Acknowledgements

We gratefully acknowledge the Ministerio de Ciencia y Tecnología (BQU2000-0236), the Xunta de Galicia (PGIDT00PXI10305PR), and the Universidade da Coruña for financial support. We also thank Dr. M. A. Maestro for resolving the X-ray structure. The authors are indebted to Centro de Supercomputación of Galicia for providing the computer facilities.

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