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Highly functionalized glyco-conjugated hexahydroazepindiones from saccharide imides via the Norrish type II reaction

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Abstract—Starting from readily available protected 6-tosylates of D-glucose and D-mannose in both their pyranoside and furanoside forms as well as 6-tosylates of α-D-galactopyranose, the corresponding primary succinimido derivatives were obtained in good yield by nucleophilic displacement with potassium succinimide. These imido sugars were photochemically transformed into hexahydroazepindione derivatives such as by means of a Norrish type II reaction. As expected, the intramolecular alkylation proceeded via an 1,6 H-abstraction leading to a stabilized diradical. The regiochemistry of the photoreaction was controlled by configurational, conformational and electronic features and was sometimes influenced by the protecting groups. Using this route, a facile approach to a novel class of highly functionalized sugar derived heterocycles was developed.

Keywords: Hexahydroazepinediones; Saccharides; Imides; Norrish type II

1. Introduction

Seven-membered aza-heterocycles represent a decisive fragment of a large number of pharmaceutically active compounds.[1] Among them are heterocycles containing the azepindione or azepinone structural elements. For example, benzazepindiones (**1**) or the substituted dipyridino-analogue of a functionalized benzazepinone (**2**) are well-established pharmaceuticals with a wide range of applications (Fig. 1). Furthermore, substituted 6-caprolactams show interesting biological activities and could have particular applications in psychopharmacy.[2,3]

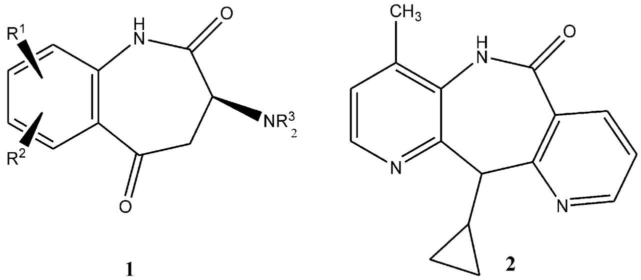

Figure 1. Some seven-membered aza-heterocycles of pharmaceutical interest.

Several strategies have been developed for the construction of azepindione substructures. In the case of aromatic compounds, Friedel–Crafts acylations are widely used but these cannot be applied in carbohydrate chemistry. In recent years, interest in radical carbon–carbon bond formation increased substantially and several excellent methods with broad applicability in organic syntheses were developed.[4–6] Consequently, radical carbon–carbon bond formation has found considerable use in carbohydrate chemistry. By free radical reduction of primary and secondary sugar halides or mercury derivatives with tributyltin hydride in the presence of AIBN, an intermediate carbon radical results, which can be trapped with electron-deficient alkenes to lead to branched-chain sugars with sometimes high diastereo- selectivities.[7–10]

The intra- and intermolecular hydrogen abstraction by an excited carbonyl group via a Norrish type II reaction is well known.[11] If the chromophore is a

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suitably alkylated, cyclic imide, instead of a ketone ring, expanded products are obtained.[12,13] Kanaoka et al.[14,15] were the first to introduce Norrish type II cyclization of alkylated phthalimides and succinimides as a novel ring expansion reaction leading to various medium-sized heterocycles (see also Ref. 16).

The excited carbonyl function of the imide **3** leads to γ-hydrogen abstraction forming the biradical **4**, followed by type II cyclization to give the strained azetidinole **5**. Retro-aldol ring opening furnishes the azepindione derivative **6** containing two carbon units of the side chain. By competing β-cleavage, formation of alkene **7** and succinimide **8** result (Fig. 2). In contrast to the reaction with ketones, for N-alkylated imides cyclization dominates over type II elimination.[17,18] Furthermore, Kanaoka and Hatanaka[17] and others[18] could apply the concept of 'regioselective remote photocyclization' of sulfide-containing phthalimides to the synthesis of macrocyclic systems. This method included a photoinduced electron transfer (PET) from a heteroatom of the side chain to the excited phthalimide chromophore. Later, Griesbeck et al.[19,20] succeeded to use this reaction for *N*-phthaloyl derivatives of substituted amino acids. They observed a direct relation between the multiplicity of the excited state and the regioselectivity of hydrogen abstraction. Depending on the conditions of the irradiation, different products such as benzazepine-1,5-diones, annelation products and the corresponding dehydrated compounds could be obtained.[21]

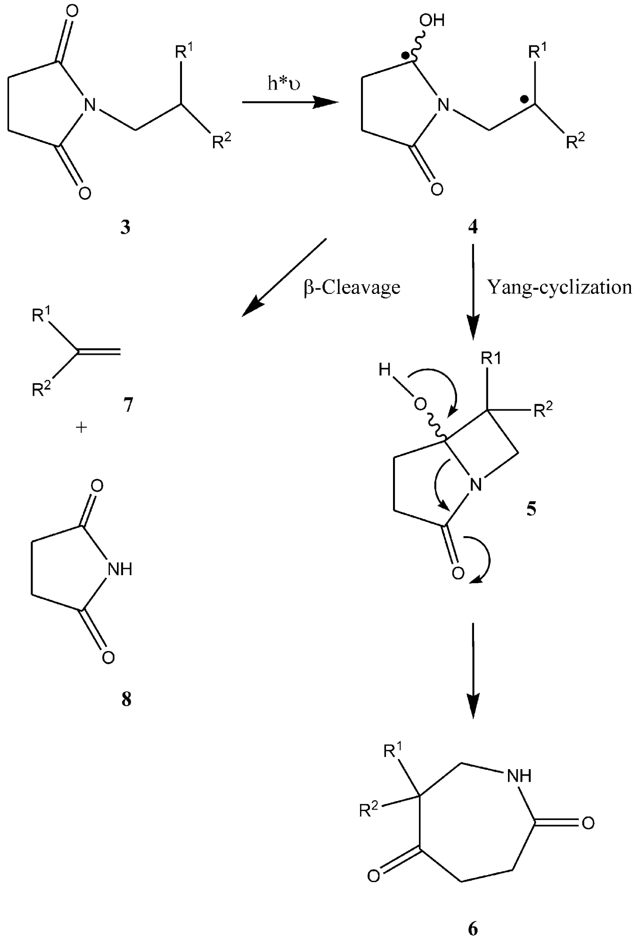


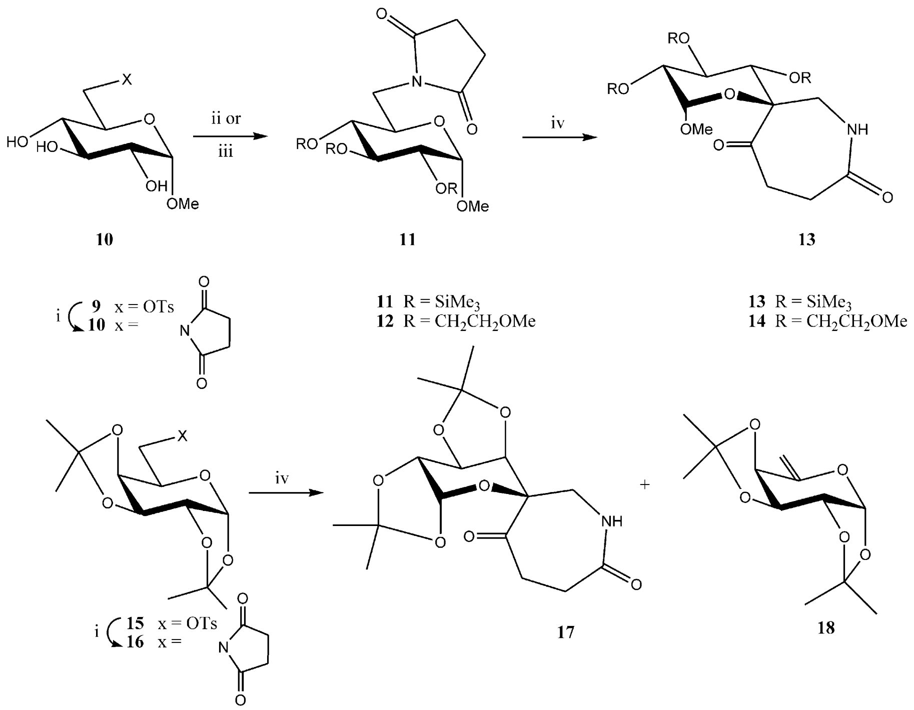
Figure 2. Norrish Type II pathway leading to seven-membered azaheterocycles.

In previous investigations, we demonstrated that Norrish type II reactions proved to be a suitable method to transform 1-*N*-glycosylimides, obtained by addition of *N*-iodo-succinimide to glycals followed by stereoselective reduction, into novel carbohydrate-derived hexahydro-2,5-azepindiones and tricyclic oxolactams.[22,23] Pentopyranose derivatives yielded exclusively the azepindiones whereas hexopyranose components gave the corresponding oxolactam structures, or mixtures, depending on the conformational shapes of the starting material and the availability of hydrogen to be abstracted. These results prompted us to investigate the synthesis of substrates containing an exocyclic imide at C-6 of the carbohydrate. For conformational and electronic reasons, hydrogen abstraction should only take place at the γ-hydrogen attached to C-5.[24] In this paper, we report on the synthesis of various saccharide-imides, their photochemical conversion to hexahydroazepindiones and their spectroscopic properties.

2. Results and discussion

Attempts to prepare the sugar-derived 6-*N*-succinimido compounds using Mitsunobu conditions[25] led to rather low yields of the desired products. In contrast, a simple nucleophilic displacement of the corresponding tosylate at C-6 of the fully, or partially, protected carbohydrate derivative by potassium succinimide offered a clean and simple approach for the introduction of the imide substituent.[24] The protecting groups used have to be stable at elevated temperatures, because the conversion of the tosylate to the succinimide using DMF as solvent requires temperatures of 120–150 °C. Acetonides and *tert*-butyldimethylsilyl ethers are stable under these conditions whereas trimethylsilyl ethers decompose. In the latter case, the imide has to be alkylated by the partially unprotected tosylate and silylated afterwards as outlined in Scheme 1.

Starting from methyl α-D-glucopyranoside the corresponding primary tosylate **9** was synthesized,[26] and treatment with 1.1 equiv of potassium succinimide in DMF at 150 °C gave the desired unprotected alkylated succinimide **10** in 67% yield. This, in turn, could be converted to the fully protected TMS-ether **11**, ready for irradiation.[27] Alternatively, **10** could be reacted to give the MEM-protected component **12** in 62% yield. Transformation of the galactopyranose-derived tosylate **15** gave the 6-*N*-succinimido derivative **16** in 70% yield.

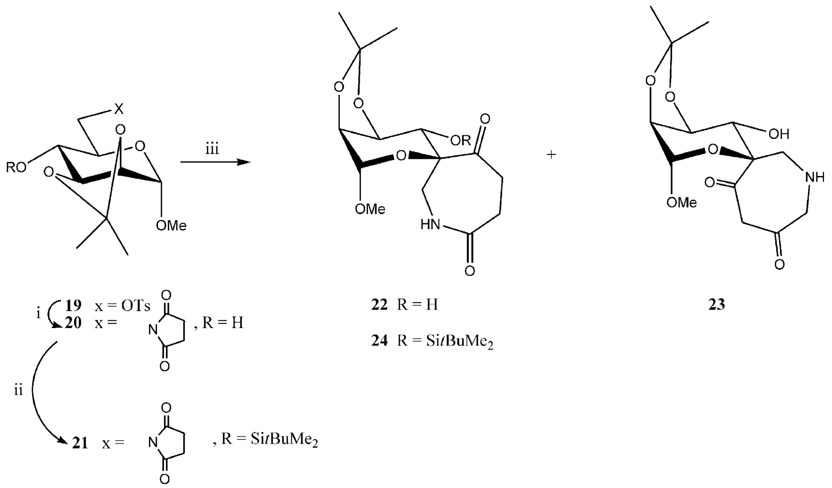


Scheme 1. Reagents and conditions: (i) potassium succinimide, DMF; (ii) TMS imidazole, Py; (iii) MEMCl, *i*Pr_2NEt; (iv) 254 nm, CH_3CN.

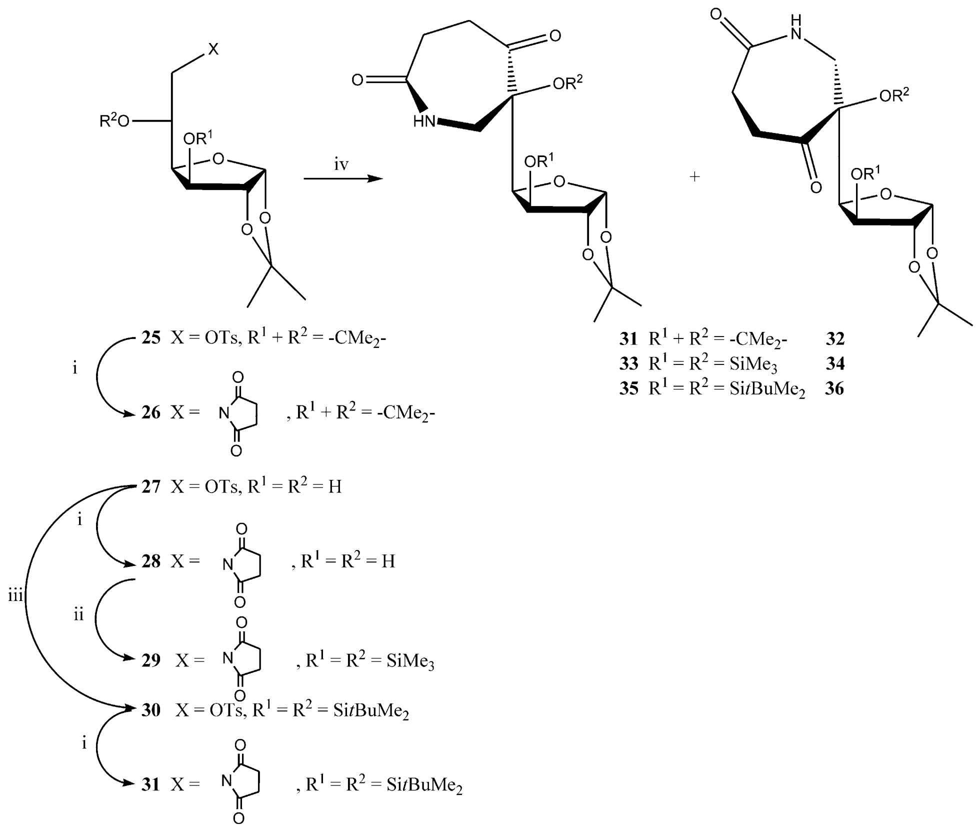
In the mannopyranose case, the 6-*O*-tosylate **19** could be transformed into the 6-*N*-succinimido compound **20** (60%) and further silylated to give the derivative **21** (63%) ready for irradiation (Scheme 2).

In the furanose series, the 6-*O*-tosylate of the diisopropylidene derivative **25** could be facilely converted into the 6-*N*-succinimido compound **26**. Similarly, the monoisopropylidene tosylate **27** was transformed into **28** and further silylated to give **29**. For carbohydrate derivatives with thermally stable protecting groups, the preparation of the corresponding imides can be carried out as described for methyl 6-deoxy-2,3-*O*-isopropylidene-6-*N*-succinimido-5-*O*-(*tert*-butyldimethylsilyl)-α-D-glucofuranose (**31**). Treatment of the tosylate **27** with TBDMSOTf gave **30** in quantitative yield,[28] and upon reaction with potassium succinimide this compound yielded the sugar derived imide **31** in 70% yield (Scheme 3). Following the same route, the *manno*-configured furanoside 6-*N*-succinimido sugar **39** could be obtained (Scheme 4).

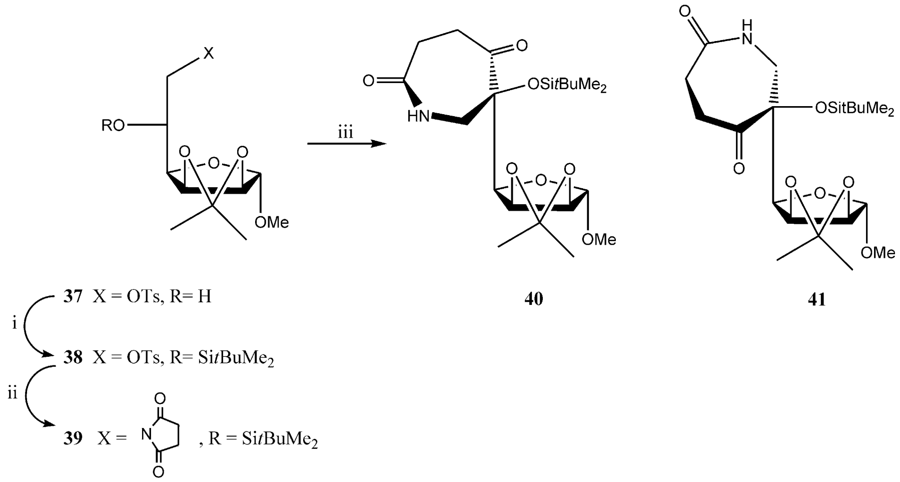
Succinimide derivatives absorb UV light at ~190–215 nm, and N-alkylated cyclic imides have a shoulder at ca. 240 nm. With its low molar absorption (ε ~ 140) and its solvent dependency, this band represents an nπ* transition.[14–16] The UV spectra of all *N*-succinimido substrates are consistent with this and thus irradiation



Scheme 2. Reagents and conditions: (i) potassium succinimide, DMF; (ii) TBDMSOTf, Py; (iii) 254 nm, CH_3CN.



Scheme 3. Reagents and conditions: (i) potassium succinimide, DMF; (ii) TMS imidazole, Py; (iii) TBDMSOTf, Py; (iv) 254 nm, CH_3CN.



Scheme 4. Reagents and conditions: (i) TBDMSOTf, Py; (ii) potassium succinimide. DMF; (iii) 254 nm, CH_3CN.

was carried out in dry, degassed acetonitrile with a low pressure mercury lamp emitting UV light of 254 nm. Under these conditions, only photochemically-inert hydroxyl protecting groups such as silyl- or alkylethers and acetonides could be employed. The N-alkylated galactopyranose-derived succinimide **16** was irradiated at four different temperatures and at four different concentrations to determine optimal reaction conditions. The highest yields were obtained at 20 °C with the best ratio between the desired azepindione **17**, the exocyclic galactal **18** and recovered starting material **16**. In contrast, the concentration had no significant influence on the distribution of the products in the investigated range (0.035–0.007 M).

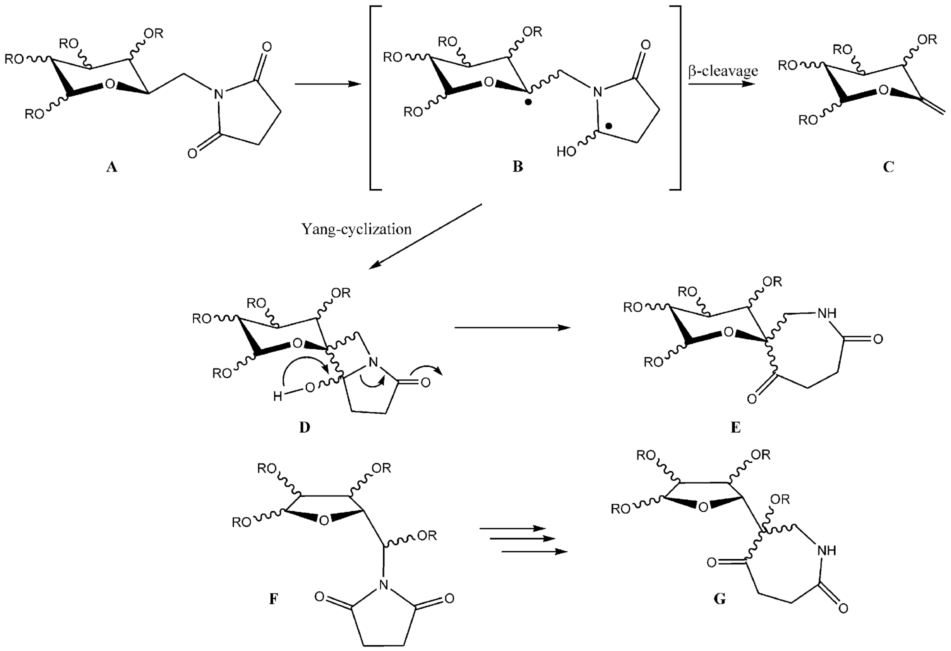
The glucofuranoside substrates **26, 28, 29** and **31** as well as the 6-*N*-succinimido-mannose derivative **20** with a free hydroxyl group in the 4-position led to both diastereomers of the hexahydroazepin-1,5-diones **31**–**36** and **22**–**23**. In the case of the pyranoside substrates of glucose **11**, **12** and galactose **16** an increase in selectivity was observed, because only the spiroannelated products **13**, **14** and **17** were obtained, whereas the corresponding diastereomers could not be detected. Formation of the exocyclic galactal **18** as side product of the alternative β-cleavage pathway (17%) was observed only for galactose derivative **16**. Interestingly, the fully protected mannose pyranoside derivative **21** gave diastereomer **24** exclusively as one of the two possible products. As expected for alicyclic imides, in all cases cyclization to the intermediate azetidinol with subsequent ring enlargement was clearly dominant over the cleavage in contrast to keto systems. Furthermore, the formation of dimers was not observed.

Intra- and intermolecular hydrogen abstractions are among the best known photochemical reactions of carbonyl groups. Like ketones, aldehydes and esters, cyclic imides can undergo this reaction intramolecularly if the structure allows a close approach between the excited carbonyl group and a hydrogen atom within the same molecule.[29] The abstraction of hydrogen from the γ-C atom is generally favoured, because the Norrish type II reaction can proceed via an unstrained six-membered chair-like transition state. Should there be no hydrogen in the γ-position, the abstraction will occur at δ-, ε- or another more distant carbon atom if a close proximity to the excited carbonyl group is possible.[30] Furthermore, heteroatoms, for example, sulfur or oxygen, stabilize carbon radicals in the α-position and the abstraction at this site is usually favoured.[31,32] Indeed, 6-succinimido sugar derivatives combine these effects for a regioselective reaction as shown in Scheme 5.

Based both on the studies of Kanaoka et al. on *N*-alkylphthalimides and -succinimides and on our own investigations, we assume that absorption of a photon by the carbonyl chromophore of **A** results in a nπ^*-transition leading to a biradical. The excited oxygen atom with the electron-deficient n-orbital causes a hydrogen abstraction at C-5 for which no differentiation between the singlet and the triplet nπ^* state can be assumed. Thus, the intermediate biradical **B** is formed, which is tertiary at C-5 of the carbohydrate moiety and in addition stabilized by the ring oxygen. This can fragment to the alkene **C** and succinimide, as it is partially observed in case of the 6-*N*-succinimido-galactopyranose **16**, or cyclize via formation of a new C–C bond to the highly strained azetidinol **D**. By a subsequent aza-analogous retroaldol ring opening, the corresponding carbohydrate derived azepindione **E** is formed. Corresponding to this pathway (**A**→**E**) in the pyranose series, an analogous sequence in the furanose series **F**→**G** can be assumed to proceed.[17,18]

All novel 6-*N*-succinimido compounds showed the expected singlet of the two methylene groups for the succinimide substituent at $\sim\delta = 2.7$ ppm in the ^{1}H NMR spectra, and a quarternary signal in the ^{13}C NMR spectra belonging to the carbonyl group of the imide at $\sim\delta = 177$ ppm. IR- and mass spectroscopy supported the structures and also X-ray crystallography proved the structure of **16**.[33]

Determination of the structure and the relative configuration of the hexahydroazepindione derivatives required HMBC- and 2D-NOESY NMR techniques. First, structural hints were obtained from IR-spectroscopy. Apart from a NH-band in the expected region ($\nu \sim 3370\ \mathrm{cm}^{-1}$) two carbonyl absorptions appear at $\nu \sim 1710$ and $\nu \sim 1670\ \mathrm{cm}^{-1}$, classified as keto- and



Scheme 5.

cyclic lactam groups. FABMS experiments and in some cases EIMS data proved the proposed mass of all compounds. These results were supported by NMR spectroscopy showing the amide proton $\sim\delta = 7.0$–5.5 ppm. Through coupling with the α-methylene group, this signal appeared usually as a triplet ($^2J \sim 5.0$–7.5 Hz). The singlet of the methylene groups of the former succinimide moiety is split into discrete signals of an ABD-system, which proves a loss of rotational freedom. Due to removal of the hydrogen at the C-5, a simplification of the coupling pattern with respect to H-4 and both H-6 protons of the carbohydrate backbone is observed. In the ^{13}C NMR spectra, the expected quarternary carbon atoms of the new keto group showed resonances at approximately $\delta = 205$ ppm and the lactam group at $\delta = 175$ ppm. Decisive hints with regard to the assigned structure were obtained from the third new quarternary carbon atom. Due to the γ-hydrogen abstraction at C-5 of the sugar, this quarternary centre is formed and shows a signal around $\delta = 80$ ppm which is evident for the spiro carbon atom.

For further proof of the supposed structures, HMBC (heteronuclear multiple bond correlation) experiments were performed. By this special pulse sequence long-range H,C correlations such as $^2J_{\mathrm{C,H}}$ and $^3J_{\mathrm{C,H}}$ couplings with a spin coupling constant between 3 and 10 Hz are observed, whereas $^1J_{\mathrm{C,H}}$ correlations resulting from the widely used HMQC (hetero multinuclear quantum coherence) technique are suppressed.[34,35] The formation of the new spiroannelated ring at the former 5-position of the carbohydrate is supported by the $^3J_{\mathrm{C,H}}$ coupling of H-5 with C-7 and the quarternary carbon atom belonging to the keto functionality. As proven by a $^3J_{\mathrm{C,H}}$ coupling between H-1 and C-5, the galactose unit still adopts the pyranoside structure. Of particular interest is the rather unexpected $^4J_{\mathrm{C,H}}$ coupling between C-1 and one H-6 proton of the azepindione **17**. Such a long range coupling was previously only reported for aromatic and conjugated sterically fixed systems under the conditions that the nuclei coupling are w-, or m-shaped.[36] Nishida et al. used the Hadamard experiment to examine long-range proton-carbon couplings in 1,6-anhydro-β-D-galactopyranoside. In addition to all expected $^3J_{\mathrm{C,H}}$-couplings, a $^4J_{\mathrm{C,H}}$-coupling between C-2 and H-6*S* with a coupling constant of 2.99 Hz was observed.[37] To prove our results, a HMBC-spectra of 1,6-anhydro-2-*O*-tosyl-β-D-galactopyranose was measured. As expected the $^4J_{\mathrm{C,H}}$ coupling between C-2 and H-6*S* could be clearly observed. It should be mentioned that only the sterically fixed compounds show this effect, which strongly supports the proposed structure. The relative configuration could be determined by 2D-NOESY experiments, for example, in the case of the crucial assignment of the correct configuration at C-5 of the mannopyranose azepindione **35**, there is an NOE between H-5 and H-7 consistent with an (*S*)-configuration. In case of the non-spiroannelated azepindiones such as **35** and **36**, the assignment of the data and the appropriate diastereomer is based on the comparison of their ^{1}H NMR-spectra with the ^{1}H NMR-spectra of the structurally known compounds **26a** and **b** (NOESY experiments). Structures with the (*S*)-configuration at C-6 are related with a shift of H-7* to lower field, due to the anisotropic effect of the keto group.

3. Conclusion

The intramolecular alkylation of readily available 6-*N*-succinimido saccharides by means of the Norrish type II reaction could be elaborated into a synthetic approach that offers a general route to a novel class of highly functionalized carbohydrate-derived hexahydroazepindiones.

4. Experimental

4.1. General methods

NMR spectra were recorded with Bruker AMX-400 or DRX-500 instruments with $(CH_3)_4Si$, $CHCl_3$ (in $CDCl_3$) or acetone (in acetone-d_6) as internal standards. Chemical shifts (δ) are reported in parts per million (ppm) and signals are quoted as s (singlet), d (doublet), dd (doublet of doublet), t (triplet). Carbon multiplicities were determined by DEPT. IR spectra were recorded on ATI Mattson FTIR (Genesis series) spectrophotometer. Optical rotations were recorded on Perkin–Elmer 243 and 341 polarimeters. Mass spectra (EI) were recorded with Varian 331 A (70 eV) and by FAB with a VG 70-250S mass spectrometer. All melting points were determined with an Olympus BH-polarization microscope (heating: Mettler FP 82). Combustion analyses were done at the Zentrale Elementanalytik of the Department of Chemistry. For all photochemical reactions, a 60W low-pressure mercury lamp (Heraeus, 254 nm) was used. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Merck, silica gel 60 GF 245). Detection was under UV light and by spraying with 20% ethanolic sulfuric acid and subsequent heating to 200 °C. Merck Silica Gel 60 (230–400 mesh, particle size 0.040–0.063 mm) was used for all flash column chromatography. Dry acetonitrile was distilled from calcium hydride under an argon atmosphere prior to use.

4.2. General procedure for the synthesis of 6-*N*-succinimido-saccharide derivatives

To a solution of the corresponding tosylate in DMF was added 1.2 equivalents potassium succinimide. The mixture was heated under vigorous stirring to 140 °C until no starting material could be detected by TLC (3–7 h). After evaporation of the solvent (80 °C, 60 mbar) the brown residue was taken up with EtOAc/H_2O (1:1). The organic layer was separated and washed with water (3 × 20–50 mL depending on the amount of starting material). The combined aqueous layers were extracted with EtOAc (3 × 20–50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography or re-crystallization from 2-propanol yielded the pure products.

4.3. General procedure for irradiation

A solution of the 6-*N*-succinimido derivative in dry and degassed freshly distilled CH_3CN was irradiated ($\lambda = 254$ nm) at 18 °C under an argon atmosphere until the reaction was complete as monitored by TLC (2.5–7 h). After removal of the solvent at reduced pressure (40 °C), the resulting yellowish syrup was purified by flash column chromatography.

4.4. Synthesis of precursors

4.4.1. Methyl 6-deoxy-6-*N*-succinimido-α-D-glucopyranoside (10). Compound **10** was synthesized from methyl 6-*O*-tosyl-α-D-glucopyranoside (**9**, 10.0 g, 28.71 mmol) following the procedure outlined in Section 4.2. After evaporation, the crude, brown solid was purified directly by flash column chromatography (8:1→5:1, CH_2Cl_2/CH_3OH) to give the product as light yellowish syrup (4.16 g, 15.12 mmol, 53%). $R_f = 0.21$ (silica gel, 4:1, toluene/EtOAc); IR (neat): 3471.35 (O–H), 2967.90, 2888.07, 2827.82 (C–H), 1775.26, 1719.70 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 2.78 (s, 4H, –CH_2–, imide), 3.24 (s, 3H, –OMe), 3.28 (m, $J_{3,4} = 9.0$ Hz, H-4), 3.50 (dd, $J_{2,3} = 9.5$ Hz, H-2), 3.56 (dd, H-3), 3.65–3.80 (m, 2H, $J_{5,6a} = 2.0$, $J_{6,6a} = 12.5$ Hz, H-5, H-6), 3.84 (dd, H-6a), 4.66 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, D_2O): δ 28.34 (2C, –CH_2–, imide), 40.31 (–CH_2–, C-6), 55.23 (–OMe), 68.58, 71.50, 72.52, 73.31 (C-2, C-3, C-4, C-5), 99.46 (C-1), 181.83 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+–OCH_3, –H_2O]: *m/z* 226 (2%); [$C_{11}H_{17}NO_7$]: 275.3.

4.4.2. Methyl 6-deoxy-2,3,4-tri-*O*-trimethylsilyl-6-*N*-succinimido-α-D-glucopyranoside (11). Compound **10** (0.71 g, 2.6 mmol) was dissolved in dry pyridine (10 mL), then trimethylsilylimidazole (1.7 mL, 11.6 mmol) was added at 0 °C under argon atmosphere and stirred for 3 h at rt. After removal of the solvent, the residue was taken up into CH_2Cl_2 (20 mL) and washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (6:1, toluene/EtOAc) gave **11** as a colourless syrup (0.85 g, 1.73 mmol, 67%). $R_f = 0.45$ (silica gel, 1:1, toluene/acetone); $[\alpha]_D^{20}$ +44 (*c* 0.5, $CHCl_3$); IR (neat): 2957.35, 2916.80 (C–H), 1775.22, 1704.30 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.12, 0.14, 0.18 (3s, 27H, –$SiCH_3$, TMS), 2.70 (s, 4H, –CH_2–, imide), 3.15 (s, 3H, –OMe), 3.30 (dd, $J_{4,5} = 9.0$ Hz, H-4), 3.48 (dd, $J_{2,3} = 9.0$ Hz, H-2), 3.63–3.76 (m, 3H, $J_{3,4} = 9.5$, $J_{5,6a} = 12.5$, $J_{5,6} = 3.0$ Hz, H-3, H-6, H-6a), 3.87 (ddd, H-5), 4.53 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.09, 0.51, 0.96 (9C, –$SiCH_3$, TMS), 27.58 (2C, –CH_2–, imide), 40.46 (–CH_2–, C-6), 53.87 (–OMe), 67.11, 73.13, 74.24, 74.69 (C-2, C-3, C-4, C-5), 99.11 (C-1), 177.98 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+−CH_3]: *m/z* 476 (8%). Anal Calcd for $C_{20}H_{41}NO_7Si_3$: C, 48.84; H, 8.40; N, 2.85. Found: C, 49.02; H, 8.43; N, 2.83.

4.4.3. Methyl 6-deoxy-2,3,4-tri-*O*-methoxyethoxymethyl-6-succinimido-α-D-glucopyranoside (12). To a suspension of **10** (1.22 g, 4.45 mmol) in CH_2Cl_2 (10 mL) was added diisopropylethylamine (3.03 mL, 17.8 mmol) and 1-chloro-2-methoxyethane (2.44 mL, 17.8 mmol) at rt. The mixture was stirred for 4 h, then diluted with EtOAc (20 mL) and washed with brine (2 × 50 mL). After drying over $MgSO_4$ and filtering, the solution was concentrated and purified by flash column chromatography (3:1, toluene/acetone). The product **12** was obtained as a labile lightly yellow syrup (1.49 g, 2.76 mmol, 62%); $R_f = 0.32$ (silica gel, 1:1, toluene/acetone); IR (neat): 2932.43, 2891.13 (C–H), 1775.45, 1705.64 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 4H, imide), 3.18 (s, 3H, –OCH_3), 3.35 (3s, 9H, –OCH_3, MEM), 3.46–3.92 (m, 18H, H-2, H-3, H-4, H-5, H-6, H-6a, 3CH_3–O–CH_2–CH_2–O–CH_2–O–), 4.72–4.87 (m, 6H, 3CH_3–O–CH_2–CH_2–O–CH_2–O–), 4.98 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.08 (2C, –CH_2–, imide), 39.39 (–CH_2–, C-6), 53.64 (–OMe), 58.06 (3C, CH_3–O–CH_2–CH_2–O–CH_2–O–), 66.28, 66.90, 67.17, 70.57, 70.70, 70.78 (6C, CH_3–O–CH_2–CH_2–O–CH_2–O–), 65.53, 77.48, 77.72, 78.39 (C-2, C-3, C-4, C-5), 95.51, 96.35, 96.63 (3C, CH_3–O–CH_2–CH_2–O–CH_2–O–), 97.48 (C-1), 175.94 (q, 2C, C=O, imide).

4.4.4. 6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-*N*-succinimido-α-D-galactopyranose (16). Compound **16** was prepared from 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (**15**, 7.0 g, 16.94 mmol) according to the procedure outlined in Section 4.2. The crude product was crystallized from 2-propanol to yield **16** (4.06 g, 11.90 mmol, 70%) as colourless crystals; mp 149.6 °C. $R_f = 0.26$ (silica gel, 20:1, CH_2Cl_2/acetone); $[\alpha]_D^{20}$ +1.1 (*c* 1.0, $CHCl_3$); IR (KBr): 2981.75, 2936.54, 2915.14 (C–H), 1774.69, 1703.50 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29, 1.34, 1.46, 1.50 (4s, 12H, –CH_3, isopropylidene), 2.72 (s, 4H, –CH_2–, imide), 3.39 (dd, $J_{4,5} = 2.5$, $J_{5,6a} = 13.5$, $J_{5,6} = 11.0$ Hz, H-5), 4.07–4.30 (m, 4H, $J_{3,4} = 5.0$ Hz, H-4, H-6a, H-6, H-3), 4.61 (dd, $J_{2,3} = 7.5$ Hz, H-2), 5.45 (d, $J_{1,2} = 4.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.62, 25.03, 25.80, 26.04 (4C, $-CH_3$, isopropylidene), 28.10 (2C, $-CH_2-$, imide) 39.27 ($-CH_2-$, C-6), 64.24, 70.51, 71.00, 71.56 (C-2, C-3, C-4, C-5), 96.56 (C-1), 108.80, 109.90 (q, 2C, isopropylidene), 177.17 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m/z* 326 (26%). Anal Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.05; H, 6.81; N, 4.05.

4.4.5. Methyl 6-deoxy-2,3-*O*-isopropylidene-6-*N*-succinimido-α-D-mannopyranoside (20). Compound **20** was synthesized from methyl 6-deoxy-2,3-*O*-isopropylidene-6-*O*-tosyl-α-D-mannopyranoside (**19**, 2.42 g, 4.13 mmol) according to the procedure outlined in Section 4.2. Flash column chromatography yielded **20** as a colourless foam (1.3 g, 4.13 mmol, 66%). $R_f = 0.2$ (silica gel, 5:1, toluene/acetone); $[\alpha]_D^{20}$ +31.8 (*c* 1.0, $CHCl_3$); IR (KBr): 3462.51 (O–H), 2990.05, 2940.1 (C–H), 1775.53, 1704.72 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29, 1.46 (2s, 6H, $-CH_3$, isopropylidene), 2.71 (s, 4H, $-CH_2-$, imide), 3.32–3.38 (m, 4H, $J_{4,5} = 9.0$ Hz, $-OCH_3$, H-4), 3.61 (d, $J_{4,OH} = 4.5$ Hz, 4-OH), 3.66–3.70 (m, H-5), 3.76 (dd, $J_{5,6} = 4.5$, $J_{6,6a} = 14.0$ Hz, H-6), 3.87 (dd, $J_{5,6a} = 4.0$ Hz, H-6a), 4.06–4.10 (m, $J_{2,3} = 3.5$, $J_{3,4} = 5.5$ Hz, H-2, H-3), 4.80 (s, $J_{1,2} = 0$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.53, 27.51 (2C, $-CH_3$, isopropylidene), 27.68 (2C, $-CH_2-$, imide), 38.89 ($-CH_2-$, C-6), 54.56 ($-OCH_3$), 67.04 (C-5), 70.23 (C-4), 75.15 (C-2), 77.11 (C-3), 98.04 (C-1), 109.00 (q, isopropylidene), 163.50 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m/z* 300 (1%). Anal Calcd for $C_{14}H_{21}NO_7$: C, 53.33; H, 6.71; N, 4.45. Found: C, 53.92; H, 6.90; N, 4.55.

4.4.6. Methyl 4-*O*-*tert*-butyldimethylsilyl-6-deoxy-2,3-*O*-isopropylidene-6-*N*-succinimido-α-D-mannopyranoside (21). A solution of compound **20** in dry THF/pyridine (5:1) was cooled to −40 °C and TBDMSOTf (0.42 mL, 3.31 mmol) was added under vigorous stirring. The reaction mixture was allowed to warm to rt with continued stirring for 3 h. After evaporation of the solvent, the crude product was dissolved in water (20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous solution was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with water (20 mL), separated, dried ($MgSO_4$), filtered and evaporated in vacuo (40 °C) to dryness. The crude product was recrystallized from 2-propanol to give **21** as colourless needles (1.7 g, 3.96 mmol, 63%); mp 164 °C; $R_f = 0.43$ (silica gel, 5:1, toluene/acetone); $[\alpha]_D^{2}$ +58.2 (*c* 1.0, $CHCl_3$); IR (KBr): 2985.99, 2953.47, 2935.84, 2895.39, 2856.17 (C–H), 1769.74, 1704.44 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11, 0.16 (2s, 6H, $-SiCH_3$), 0.91 (s, 9H, $-SiC(CH_3)_3$), 1.32, 1.50 (2s, 6H, $-CH_3$, isopropylidene), 2.71 (s, 4H, $-CH_2-$, imide), 3.19 (s, 3H, –OMe), 3.50 (dd, $J_{4,5} = 9.5$ Hz, H-4), 3.73 (dd, $J_{5,6} = 10.5$, $J_{6,6a} = 13.0$ Hz, H-6), 3.78–3.86 (m, 2H, H-5, H-6), 3.99 (dd = t, $J_{2,3} = 5.5$, $J_{3,4} = 7.0$ Hz, H-3), 4.05 (d, H-2), 4.80 (s, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.93 (2C, $-SiCH_3$), 17.62 (q, $-SiC(CH_3)_3$), 24.84 (3C, $-SiC(CH_3)_3$), 25.24, 26.98 (2C, $-CH_3$, isopropylidene), 27.08 (2C, $-CH_2-$, imide), 39.20 ($-CH_2-$, C-6), 53.41 ($-OCH_3$), 65.73 (C-5), 72.25 (C-4), 74.87 (C-2), 77.79 (C-3), 97.12 (C-1), 108.74 (q, isopropylidene), 176.41 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-OCH_3]: *m/z* 399 (2%). Anal Calcd for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found: C, 55.67; H, 8.17; N, 3.30.

4.4.7. 6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-*N*-succinimido-α-D-glucofuranose (26). Compound **26** was synthesized from 1,2:3,5-di-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**25**, 5.43 g, 13.1 mmol) following the procedure outlined in Section 4.2 and purified by flash column chromatography (10:1, toluene/acetone). The product was obtained as colourless needles (2.43 g, 7.12 mmol, 54%); mp 100.6 °C; $R_f = 0.52$ (silica gel, 3:1, toluene/acetone); $[\alpha]_D^{25}$ −20 (*c* 1.0, $CHCl_3$); IR (KBr): 2987.61, 2966.52, 2939.55 (C–H), 1701.43 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99, 1.01, 1.03, 1.14 (4s, 12H, $-CH_3$, isopropylidene), 2.40 (s, 4H, $-CH_2-$, imide), 3.38–3.43 (m, 2H, H-6, H-6a), 3.52 (dd, $J_{4,5} = 7.0$ Hz, H-5), 3.91 (d, $J_{3,4} = 4.0$ Hz, H-3), 3.99 (dd, H-4), 4.24 (d, $J_{2,3} = 0$ Hz, H-2), 5.68 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.29, 23.48, 26.35, 26.79 (4C, $-CH_3$, isopropylidene), 27.60 (2C, $-CH_2-$, imide), 40.33 ($-CH_2-$, C-6), 67.62 (C-5), 74.45 (C-3), 81.13 (C-4), 83.45 (C-2), 106.10 (C-1), 100.70, 111.80 (q, 2C, isopropylidene), 176.74 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m/z* 326 (3%). Anal Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.30; H, 6.88; N, 4.00.

4.4.8. 6-Deoxy-1,2-*O*-isopropylidene-6-*N*-succinimido-α-D-glucofuranose (28). Compound **28** was prepared from 1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**27**, 3.82 g, 10.2 mmol) according to the procedure outlined in Section 4.2. After evaporation, the crude, brown solid was purified by flash column chromatography (2:1, toluene/acetone) to give the product **28** as colourless needles (2.85 g, 9.5 mmol, 93%); mp 123.3 °C; $R_f = 0.27$ (silica gel, 1:1, toluene/acetone); $[\alpha]_D^{25}$ −11 (*c* 1.0, $CHCl_3$); IR (KBr): 3372.28 (O–H), 2988.01, 2967.24, 2941.86, 2881.57 (C–H), 1774.72, 1764.26, 1706.09 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26, 1.43 (2s, 6H, $-CH_3$, isopropylidene), 2.69 (s, 4H, $-CH_2-$, imide), 3.70 (dd, $J_{5,6} = 8.5$, $J_{6,6a} = 13.5$ Hz, H-6), 3.78 (dd, $J_{5,6a} = 4.0$ Hz, H-6a), 3.94–3.95 (m, 2H, 3,5-OH), 3.97 (d, $J_{4,5} = 8.0$ Hz, H-4), 4.08–4.11 (m, H-

5), 4.29–4.31 (m, $J_{3,4} = 2.5$ Hz, H-3), 4.45 (d, $J_{2,3} = 0$ Hz, H-2), 5.88 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.82, 26.34 (2C, $-CH_3$, isopropylidene), 27.75 (2C, $-CH_2-$, imide), 42.31 ($-CH_2-$, C-6), 67.25 (C-5), 74.67 (C-3), 80.61 (C-4), 84.55 (C-2), 104.67 (C-1), 111.41 (q, isopropylidene), 177.71, 177.84 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m*/*z* 286 (9%). Anal Calcd for $C_{13}H_{19}NO_7$: C, 51.80; H, 6.36; N, 4.65. Found: C, 51.35; H, 6.28; N, 5.30.

4.4.9. 6-Deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-trimethylsilyl-6-*N*-succinimido-α-D-glucofuranose (29). Compound **28** (2.55 g, 8.5 mmol) was dissolved in dry pyridine (20 mL) at 0 °C under argon atmosphere. To the stirred solution, trimethylsilylimidazole (3.1 mL, 21.2 mmol) was added and stirring was continued for 1 h at rt. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (30 mL). After washing with water (3 × 20 mL), the organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the remaining brown residue by column chromatography (5:1, toluene/acetone) yielded **29** as a pale yellow foam (1.05 g, 2.35 mmol, 89%). $R_f = 0.43$ (silica gel, 5:1, toluene/acetone); $[\alpha]_D^{25}$ −15.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.075, 0.19 (2s, 18H, $-SiCH_3$, TMS), 1.28, 1.47 (2s, 6H, $-CH_3$, isopropylidene), 2.65 (s, 4H, $-CH_2-$, imide), 3.68 (dd, $J_{5,6} = 5.0$, $J_{6,6a} = 13.5$ Hz, H-6), 3.82 (dd, $J_{5,6a} = 8.5$ Hz, H-6a), 4.04 (dd, $J_{4,5} = 6.5$ Hz, H-4), 4.20 (d, $J_{3,4} = 2.5$ Hz, H-3), 4.23–4.25 (m, H-5), 4.34 (d, $J_{2,3} = 0$ Hz, H-2), 5.81 (d, $J_{1,2} = 3.5$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.32 (6C, $-SiCH_3$, TMS), 26.29, 26.37 (2C, $-CH_3$, isopropylidene), 27.65 (2C, $-CH_2-$, imide), 42.04 ($-CH_2-$, C-6), 67.77 (C-5), 75.34 (C-3), 83.32 (C-4), 83.63 (C-2), 104.41 (C-1), 111.47 (q, isopropylidene), 176.79 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m*/*z* 430 (0.5%). Anal Calcd for $C_{19}H_{35}NO_7Si_2$: C, 51.20; H, 7.91; N, 3.14. Found: C, 51.34; H, 7.89; N, 3.43.

4.4.10. 1,2-*O*-Isopropylidene-3,5-di-*O*-*tert*-butyldimethylsilyl-6-*O*-tosyl-α-D-glucofuranose (30). A solution of 1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**27**, 2.87 g, 7.7 mmol) in dry THF/pyridine (5:1, 45 mL) was cooled to −40 °C and TBDMSOTf (6.7 mL, 29.4 mmol) was added under vigorous stirring. The reaction mixture was allowed to warm to rt with continued stirring for 5 h. The solvent was evaporated and the crude product was dissolved in water (30 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous solution was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed again with water (20 mL), separated, dried ($MgSO_4$), filtered and evaporated in vacuo (40 °C) to dryness. The crude product was purified by flash column chromatography (30:1, toluene/EtOAc) to give the product as a light yellow oil (3.27 g, 5.4 mmol, 71%). $R_f = 0.29$ (silica gel, 30:1, toluene/acetone); $[\alpha]_D^{20}$ −12.3 (*c* 1.0, $CHCl_3$); IR (neat): 2953.49, 2931.32, 2895.10, 2858.04 (C–H), 1470.92, 1463.62 (S=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06, 0.08, 0.11, 0.13 (4s, 12H, $-SiCH_3$), 0.84, 0.88 (2s, 18H, $-SiC(CH_3)_3$), 1.29, 1.44 (2s, 6H, $-CH_3$, isopropylidene), 2.43 (s, 3H, Ar–CH_3, tosyl), 3.97 (dd, $J_{5,6} = 7.5$, $J_{6,6a} = 10.0$ Hz, H-6), 4.09 (dd, $J_{4,5} = 1.5$ Hz, H-4), 4.14–4.20 (m, 2H, $J_{2,3} = 0$, $J_{3,4} = 3.0$ Hz, H-3, H-5), 4.31 (d, H-2), 4.34 (dd, $J_{5,6a} = 1.5$, H-6a), 5.77 (d, $J_{1,2} = 3.5$ Hz, H-1), 7.30, 7.77 (2d, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.95, 4.54 (4C, $-SiCH_3$), 17.64 (2q, $-SiC(CH_3)_3$), 21.16 (Ar–CH_3), 25.26, 25.34 (6C, $-SiC(CH_3)_3$), 26.05, 26.47 (2C, $-CH_3$, isopropylidene), 72.30 ($-CH_2-$, C-6), 68.45, 75.58, 83.26, 84.26 (C-2, C-3, C-4, C-5), 104.17 (C-1), 111.48 (q, isopropylidene), 127.78, 129.25 (4C, Ar), 132.47 (q, $-C-CH_3$), 144.04 (q, $-C-SO_2-$). Anal Calcd for $C_{28}H_{49}NO_8SSi_2$: C, 55.87; H, 8.21. Found: C, 55.83; H, 8.32.

4.4.11. 6-Deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-*tert*-butyldimethylsilyl-6-*N*-succinimido-α-D-glucofuranose (31). Compound **31** was prepared from **30** (3.15 g, 5.2 mmol) according to the procedure outlined in Section 4.2 and purified by crystallization from 2-propanol. The product was obtained as colourless needles (1.61 g, 3.0 mmol, 58 %); mp 169 °C; $R_f = 0.22$ (silica gel, 20:1, toluene/EtOAc); $[\alpha]_D^{20}$ −0.5 (*c* 0.41, $CHCl_3$); IR (KBr): 2987.56, 2953.48, 2932.20, 2893.77, 2857.66 (C–H), 1779.12, 1703.88 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.06, 0.04, 0.19, 0.2 (4s, 12H, $-SiCH_3$), 0.83, 0.92 (2s, 18H, $-SiC(CH_3)_3$), 1.30, 1.46 (2s, 12H, $-CH_3$, isopropylidene), 2.65 (s, 4H, $-CH_2-$, imide), 3.58 (dd, $J_{5,6} = 4.5$, $J_{6,6a} = 14.0$ Hz, H-6), 4.09 (dd, $J_{5,6a} = 3.5$ Hz, H-6a), 4.17 (dd, $J_{4,5} = 3.0$ Hz, H-4), 4.20 (d, $J_{3,4} = 2.5$ Hz, H-3), 4.33 (d, $J_{2,3} = 0$ Hz, H-2), 4.40–4.44 (m, H-5), 5.87 (d, $J_{1,2} = 4.0$ Hz, H-1); ^{13}C NMR (63 MHz, $CDCl_3$): δ −4.65, −4.50, −4.17 (4C, $-SiCH_3$), 17.97, 18.26 (2q, $-SiC(CH_3)_3$), 25.76, 26.13 (6C, $-SiC(CH_3)_3$), 26.70, 27.04 (2C, $-CH_3$, isopropylidene), 28.29 (2C, $-CH_2-$, imide), 41.58 ($-CH_2-$, C-6), 66.55 (C-5), 76.54 (C-3), 84.39 (C-4), 85.11 (C-2), 104.69 (C-1), 111.84 (q, isopropylidene), 177.34 (q, 2C, C=O, imide); MS (70 eV, EI) [M^+-CH_3]: *m*/*z* 514 (0.5%). Anal Calcd for $C_{25}H_{47}NO_7Si_2$: C, 56.67; H, 8.94; N 2.64. Found: C, 56.78; H, 9.11; N, 2.59.

4.4.12. Methyl 4-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-6-deoxy-α-D-mannofuranoside (38). To a cooled (−50 °C) solution of the tosylate **37** in dry THF/pyridine (5:1, 40 mL), TBDMSOTf (1.44 mL, 11.4 mmol) was added under vigorous stirring. The solution was allowed to warm to rt and stirring was continued for an additional 30 h. The work up procedure was the same as for **30** without further purification. The product was obtained as a light yellow syrup (2.55 g, 5.07 mmol, 98%).

$R_f = 0.64$ (silica gel, 20:1, toluene/EtOAc); $[\alpha]_D^{20}$ +26 (*c* 1.0, $CHCl_3$); IR (neat): 2951.33, 2933.49, 2896.30, 2857.17 (C–H), 1426.71, 1471.16 (S=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.02, 0.05 (2s, 6H, $-SiCH_3$), 0.82 (s, 9H, $-SiC(CH_3)_3$), 1.27, 1.39 (2s, 6H, $-CH_3$, isopropylidene), 2.43 (s, 3H, Ar–CH_3, tosyl), 3.23 (s, 3H, –OMe), 3.84 (dd, $J_{4,5} = 9.0$, $J_{3,4} = 3.0$ Hz, H-4), 4.07 (dd, $J_{5,6} = 5.5$, $J_{6,6a} = 10.0$ Hz, H-6), 4.13–4.16 (m, H-5), 4.21 (dd, $J_{5,6a} = 2.0$ Hz, H-6a), 4.49 (d, H-2), 4.65 (dd, $J_{2,3} = 5.5$ Hz, H-3), 4.78 (s, $J_{1,2} = 0$ Hz, H-1), 7.32, 7.79 (2d, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.75, −4.51 (2C, $-SiCH_3$), 17.61 (q, $-SiC(CH_3)_3$), 25.28 (3C, $-SiC(CH_3)_3$), 24.22, 25.56 (2C, $-CH_3$, isopropylidene), 53.96 ($-OCH_3$), 67.81 (C-5), 71.98 ($-CH_2-$,C-6), 78.61 (C-4), 78.72 (C-2), 84.32 (C-3), 106.79 (C-1), 111.83 (q, isopropylidene), 127.56, 132.70 (4C, tosyl), 129.29, 144.17 (q, 2C, tosyl); MS (70 eV, EI) $[M^+-CH_3]$: *m*/*z* 487 (5%). Anal Calcd for $C_{23}H_{38}O_8SSi$: C, 54.95; H, 7.62; S, 6.38. Found: C, 55.14; H, 7.38; S, 5.96.

4.4.13. Methyl 4-*O*-*tert*-butyldimethylsilyl-6-deoxy-2,3-*O*-isopropylidene-6-*N*-succinimido-α-D-mannofuranoside (39). Compound **39** was synthesized from **38** following procedure outlined in Section 4.2. The pure product (0.95 g, 2.22 mmol, 63%) was obtained after flash column chromatography (20:1, toluene/EtOAc) as a clear syrup. $R_f = 0.07$ (silica gel, 20:1, toluene/EtOAc); $[\alpha]_D^{20}$ +36 (*c* 1.0, $CHCl_3$); IR (neat): 2951.47, 2935.06, 2896.43, 2857.18 (C–H), 1775.34, 1707.73 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.09, 0.1 (2s, 6H, $-SiCH_3$), 0.85 (s, 9H, $-SiC(CH_3)_3$), 1.27, 1.41 (2s, 6H, $-CH_3$, isopropylidene), 2.65 (s, 4H, $-CH_2-$, imide), 3.27 (s, 3H, –OMe), 3.63 (dd, $J_{5,6} = 6.0$, $J_{6,6a} = 14.0$ Hz, H-6), 3.78–3.83 (m, 2H, $J_{4,5} = 6.0$ Hz, H-4, H-5), 4.38 (dd, $J_{5,6a} = 7.0$ Hz, H-6a), 4.45 (d, $J_{2,3} = 6.0$ Hz, H-2), 4.67 (dd, $J_{3,4} = 3.5$ Hz, H-3), 4.77 (s, $J_{1,2} = 0$ Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.63, −4.55 (2C, $-SiCH_3$), 17.52 (q, $-SiC(CH_3)_3$), 25.41 (3C, $-SiC(CH_3)_3$), 24.38, 25.67 (2C, $-CH_3$, isopropylidene), 27.74 (2C, $-CH_2-$, imide), 42.90 ($-CH_2-$, C-6), 54.20 ($-OCH_3$), 4.91 (C-5), 79.30 (C-4), 82.53 (C-2), 83.90 (C-3), 107.4 (C-1), 111.76 (q, isopropylidene), 176.67 (q, 2C, C=O, imide); MS (70 eV, EI) $[M^+-CH_3]$: *m*/*z* 414 (0.5%). Anal Calcd for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found: C, 56.59; H, 8.42; N, 2.85.

4.5. Photochemical reactions

4.5.1. (2*S*,3*R*,4*S*,5*R*,6*R*)-8-Aza-2-methoxy-3,4,5-tris-*O*-(trimethylsilyl)-1-oxa-spiro[5.6]dodecan-9,12-dione (13). Compound **13** was synthesized from **11** (2.0 g, 4.07 mmol) following the procedure outlined in Section 4.3 and purified by flash column chromatography (5:1→3:1, toluene/EtOAc). The product was obtained as a colourless foam (1.33 g, 2.7 mmol, 66%) in addition to the starting material **11** (151 mg, 15%). $R_f = 0.56$ (silica gel, 1:1, toluene/acetone); $[\alpha]_D^{20}$ +67 (*c* 0.7, $CHCl_3$); IR (KBr): 3340.16, 3241.05 (N–H), 2957.47, 2902.15 (C–H), 1722.74, 1678.31 (C=O) cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 0.18, 0.22, 0.31 (3s, 27H, $-SiCH_3$), 2.04 (ddd, $J_{10,10a} = 14.0$, $J_{10,11a} = 2.5$, $J_{10,11} = 13.5$ Hz, $-CH_2-$, H-10), 2.14 (ddd, $J_{11,11a} = 14.0$ Hz, $-CH_2-$, H-11), 2.33 (ddd, $-CH_2-$, H-10a), 2.94 (ddd, H-11a), 3.22 (dd, $J_{NH,7} = 7.5$, $J_{7,7a} = 15.0$ Hz, H-7_{ax}), 3.32 (dd, $J_{NH,7} = 5.5$ Hz, H-7_{eq}), 3.42 (d, $J_{4,5} = 8.0$ Hz, H-5), 3.48 (s, 3H, –OMe), 3.51 (dd, $J_{3,4} = 8.0$ Hz, H-3), 4.52 (d, $J_{2,3} = 3.5$ Hz, H-2), 4.53 (dd, H-4), 7.48 (dd, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.06, 0.50, 1.25 (9C, $-SiCH_3$), 31.71 ($-CH_2-$, C-11), 36.30 ($-CH_2-$, C-10), 47.96 ($-CH_2-$, C-7), 58.79 (–OMe), 71.70 (C-5), 74.10 (C-3), 77.04 (C-4), 81.05 (q, C-6), 100.11 (C-2), 178.60 (q, –NH–C=O), 205.70 (q, C=O). Anal Calcd for $C_{20}H_{41}NO_7Si_3$: C, 48.84; H, 8.40; N, 2.85. Found: C, 49.28; H, 8.33; N, 2.71.

4.5.2. (2*S*,3*R*,4*S*,5*R*,6*R*)-8-Aza-2-methoxy-3,4,5-tris-*O*-(methoxyethoxymethyl)-1-oxa-spiro[5.6]dodecan-9,12-dione (14). Compound **14** was prepared from **12** (1.4 g, 2.6 mmol) according to the procedure outlined in Section 4.3 and purified by flash column chromatography (2:1→1:1, toluene/acetone). The product was obtained as a colourless labile syrup (998 mg, 1.85 mmol, 71%). $R_f = 0.11$ (silica gel, 1:1, toluene/acetone); ^1H NMR (400 MHz, $CDCl_3$): δ 2.31–2.36, 2.51–2.67, 2.96–3.06 (3m, 4H, $-CH_2-$, H-10, H-10a, H-11, H-11a), 3.46–3.92, 4.30–4.33 (2m, 29H, H-3, H-4, H-5, H-7, H-7a, $3CH_3-O-CH_2-CH_2-O-CH_2-O-$, $3CH_3-O-CH_2-CH_2-O-CH_2-O-$, $-OCH_3$), 4.66–4.90 (m, 7H, $3CH_3-O-CH_2-CH_2-O-CH_2-O-$, H-2), 6.18 (t, –NH–); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.51$, 35.31 (2C, $-CH_2-$, C-10, C-11), 48.38 ($-CH_2-$, C-7), 58.42, 58.55, 58.62 (4C, $CH_3-O-CH_2-CH_2-O-CH_2-O-$, –OMe), 66.92, 67.50, 67.66, 71.17, 71.20, 71.36 (6C, $CH_3-O-CH_2-CH_2-O-CH_2-O-$), 74.64, 78.76, 82.44 (C-3, C-4, C-5), 78.51 (q, C-6), 96.27, 96.73, 97.82 (3C, $CH_3-O-CH_2-CH_2-O-CH_2-O-$), 101.04 (C-2), 175.11 (q, –NHCO–), 204.53 (q, –CO–).

4.5.3. (2*S*,3*R*,4*S*,5*R*,6*R*)-8-Aza-2,3:4,5-di-*O*-isopropylidene-1-oxa-spiro[5.6]dodecan-9,12-di-one (17). Compound **17** (0.99 g, 2.89 mmol, 39.5%) was obtained from **16** according to the procedure outlined in Section 4.3, in addition to **18** (296 mg, 1.22 mmol, 17%) and starting material **16** (215 mg, 0.63 mmol, 8.6%), by flash column chromatography as a white foam; mp 79.1 °C. $R_f = 0.16$ (silica gel, 10:1, CH_2Cl_2/CH_3OH); $[\alpha]_D^{20}$ −4.6 (*c* 1.0, $CHCl_3$); IR (KBr): 3378.92 (N–H), 2987.53, 2940.68 (C–H), 1708.21, 1679.36 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25, 1.31, 1.36, 1.44 (4s, 12H, $-CH_3$, isopropylidene), 2.42 (m, 2H, $-CH_2-$, H-10a, H-11), 2.56 (m, 1H, $-CH_2-$, H-11a), 3.24 (dd,

$J_{NH,7}$ = 5.5, $J_{7,7a}$ = 15.5 Hz, –CH$_2$–, H-7), 3.49 (ddd, H-10a), 3.83 (dd, H-7a), 4.17 (d, H-3), 4.60 (dd, $J_{4,5}$ = 4.5 Hz, H-4), 4.70 (d, H-5), 5.64 (d, $J_{2,3}$ = 6.0 Hz, H-2), 5.80 (dd = t, NH); ^{13}C NMR (63 MHz, CDCl$_3$): δ 23.77, 24.17, 26.37 (4C, –CH$_3$, isopropylidene), 31.34 (–CH$_2$–, C-10), 36.25 (–CH$_2$–, C-11), 45.35 (–CH$_2$–, C-7), 68.40 (C-5), 71.30 (C-3), 71.77 (C-4), 78.17 (q, C-6), 96.04 (C-2), 107.39, 108.14 (q, 2C, isopropylidene), 175.52 (q, –NH–C=O), 208.21 (q, C=O); MS (70 eV, EI) [M$^+$–CH$_3$]: *m/z* 326 (7%); FAB [M$^+$]: *m/z* 342. Anal Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 54.68; H, 6.65; N, 4.12 (hygroscopic material).

4.5.4. (2*S*,3*S*,4*S*,5*R*,6*R*)-8-Aza-2-methoxy-3,4-*O*-isopropylidene-1-oxa-spiro[5.6]dodecan-9,12-dione (22) and (2*S*,3*S*,4*S*,5*R*,6*S*)-8-Aza-2-methoxy-3,4-*O*-isopropylidene-1-oxa-spiro[5.6]dodecan-9,12-dione (23). Compounds **22** and **23** were obtained from **20** (1.17 g, 3.7 mmol) following the procedure outlined in Section 4.3. Although starting material was still present after 3 h of irradiation, the reaction was stopped because of the formation of larger amounts of decomposition products and the mixture was purified by flash column chromatography (2:1→1:1, toluene/EtOAc). The products were obtained as a light yellow foam; **22** (241 mg, 0.76 mmol, 21%) and **23** (89 mg, 0.28 mmol, 8%) in addition to starting material **20** (522 mg, 45%). *Major diastereomer* (**22**): mp 91 °C; R_f = 0.18 (silica gel, 2:1, toluene/acetone); $[\alpha]_D^{20}$ +20.4 (*c* 1.0, CHCl$_3$); IR (KBr): 3415.31 (O–H), 3235.96 (N–H), 2985.26, 2937.05 (C–H), 1724.04, 1710.55 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.33, 1.51 (2s, 6H, –CH$_3$, isopropylidene), 2.51–2.58 (m, 2H, –CH$_2$–, H-10, H-10a), 2.67–2.74 (m, –CH$_2$–, H-11), 2.80–2.88 (m, H-11a), 3.40 (dd, $J_{NH,7}$ = 6.5 Hz, –CH$_2$–, H-7), 3.55 (dd, $J_{NH,7a}$ = 7.5, $J_{7,7a}$ = 15.5 Hz, –CH$_2$–, H-7a), 3.68 (s, 3H, –OMe), 4.27 (dd, $J_{4,5}$ = 3.0 Hz, H-3), 4.38 (br s, 1H, H-4), 4.53 (dd, $J_{3,4}$ = 8.0 Hz, H-4), 4.88 (d, $J_{2,3}$ = 1.5 Hz, H-2), 6.43 (dd = t, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 22.7, 24.98 (2C, –CH$_3$, isopropylidene), 30.82 (–CH$_2$–, C-11), 36.45 (–CH$_2$–, C-10), 47.13 (–CH$_2$–, C-7), 57.21 (–OCH$_3$), 64.06 (C-5), 71.83 (C-3), 72.76 (C-4), 83.96 (q, C-6), 98.45 (C-2), 108.82 (q, 1C, isopropylidene), 175.0 (q, –NH–C=O), 204.35 (q, C=O); FAB [M$^+$] 316. *Minor diastereomer* (**23**): R_f = 0.075 (silica gel, 2:1, toluene/acetone); $[\alpha]_D^{20}$ +45.8 (*c* 1.0, CHCl$_3$); IR (KBr): 3386.38 (O–H), 2987.19, 2937.05 (C–H), 1712.47, 1695.12 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28, 1.35 (2s, 6H, –CH$_3$, isopropylidene), 2.51–2.57 (m, 2H, –CH$_2$–, H-10, H-10a), 2.74–2.84 (m, 2H, –CH$_2$–, H-11, H-11a), 3.35 (dd, $J_{NH,7}$ = 6.0, $J_{7,7a}$ = 15.0 Hz, –CH$_2$–, H-7), 3.46 (dd, $J_{NH,7a}$ = 7.0 Hz, H-7a), 3.55 (s, 3H, –OMe), 4.02 (br s, 1H, 4-OH), 4.24 (dd, $J_{2,3}$ = 7.5 Hz, H-2), 4.41 (d, $J_{3,4}$ = 3.5 Hz, H-4a), 4.46 (dd, H-3), 5.00 (d, $J_{1,2}$ = 2.0 Hz, H-1), 6.31 (dd = t, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 23.45, 24.08 (2C, –CH$_3$, isopropylidene), 31.56 (–CH$_2$–, C-11), 36.46 (–CH$_2$–, C-10), 46.86 (–CH$_2$–, C-7), 56.33 (–OCH$_3$), 65.59 (C-5), 72.35 (C-3), 72.48 (C-4), 83.01 (q, C-6), 98.84 (C-2), 109.82 (q, 1C, isopropylidene), 174.97 (q, –NH–C=O), 204.42 (q, C=O); MS (70 eV, EI) [M$^+$–CH$_3$]: *m/z* 300 (0.5%); FAB [M$^+$]: *m/z* 316.

4.5.5. (2*S*,3*S*,4*S*,5*R*,6*R*)-8-Aza-2-methoxy-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-1-oxaspiro[5.6]dodecan-9,12-dione (24). Compound **24** was synthesized from **21** (401 mg, 0.933 mmol) following the procedure outlined in Section 4.3. The resulting yellow syrup gave **24** (144 mg, 0.335 mmol, 36%) as a colourless foam after flash column chromatography (5:1, toluene/acetone); mp 59 °C; R_f = 0.42 (silica gel, 1:1, toluene/acetone); $[\alpha]_D^{20}$ +34.2 (*c* 1.0, CHCl$_3$); IR (KBr): 3235.54 (N–H), 2982.29, 2954.06, 2934.19, 2907.08, 2858.17 (C–H), 1730.89, 1676.62 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.13, 0.16 (2s, 6H, –SiCH$_3$), 0.87 (s, 9H, –SiC(CH$_3$)$_3$), 1.31, 1.48 (2s, 6H, –CH$_3$, isopropylidene), 2.48–2.56 (m, 1H, –CH$_2$–, H-10), 2.67–2.85 (m, 3H, –CH$_2$–, H-10a, H-11, H-11a), 3.28 (dd, $J_{NH,7}$ = 7.0, $J_{7,7a}$ = 15.5 Hz, –CH$_2$–, H-7), 3.50 (s, 3H, OCH$_3$), 3.87 (d, $J_{3,4}$ = 6.5 Hz, H-4), 3.93 (dd, $J_{NH,7a}$ = 6.0 Hz, H-7a), 4.24 (dd, $J_{2,3}$ = 7.0 Hz, H-2), 4.39 (dd = t, H-3), 4.67 (d, $J_{1,2}$ = 5.5 Hz, H-1), 6.35 (dd = t, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ −5.49, −4.49 (6C, –SiCH$_3$), 17.62 (q, –SiC(CH$_3$)$_3$), 24.09, 26.52 (2C, –CH$_3$, isopropylidene), 25.38 (3C, –SiC(CH$_3$)$_3$), 29.97 (–CH$_2$–, C-11), 37.26 (–CH$_2$–, C-10), 47.12 (–CH$_2$–, C-7), 56.43 (–OCH$_3$), 73.42 (C-5), 74.74 (C-3), 75.66 (C-4), 81.36 (q, C-6), 99.80 (C-2), 108.84 (q, 1C, isopropylidene), 174.43 (q, –NH–C=O), 205.43 (q, C=O); MS (70 eV, EI) [M$^+$]: *m/z* 430 (0.5%); FAB [M$^+$]: *m/z* 430. Anal Calcd for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found C, 55.91; H, 8.31; N, 2.88.

4.5.6. (1′*S*,2′*S*,3′*S*,4′*S*,6*S*)-6,3′-Isopropylidenedioxy-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (31) and (1′*S*,2′*S*,3′*S*,4′*S*,6*R*)-6,3′-isopropylidenedioxy-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (32). Compounds **31** and **32** were prepared according to the procedure outlined in Section 4.3 from **26** (805 mg, 2.36 mmol). The crude product was purified by flash column chromatography yielding the two diastereomers **31** (95.6 mg, 0.28 mmol, 12%) and **32** (194 mg, 0.57 mmol, 24%). *Minor diastereomer* (**31**): mp 165 °C (decomp.); R_f = 0.34 (silica gel, 20:1, CH$_2$Cl$_2$/CH$_3$OH); $[\alpha]_D^{20}$ −10.8 (*c* 1.0, CHCl$_3$); IR (KBr): 3265.99 (N–H), 2990.73, 2940.94 (C–H), 1734.49, 1687.88 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.29, 1.45, 1.46 (3s, 12H, –CH$_3$, isopropylidene), 2.49–2.52 (m, 2H, –CH$_2$–, H-3, H-3a), 2.70–2.75 (m, –CH$_2$–, H-4), 2.82–2.86 (m, –CH$_2$–, H4a), 3.38–3.42 (m, 2H, H-7, H-7a), 4.36 (s, H-3′, H-4′), 4.55 (d, $J_{2',3'} = 0$ Hz, H-2′), 5.87 (d, $J_{1',2'} = 4.0$ Hz, H-1′), 6.55 (br s = t, NH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.56, 25.84, 26.40, 29.49 (4C, $–CH_3$, isopropylidene), 31.43 ($–CH_2–$, C-3), 35.92 ($–CH_2–$, C-4), 47.22 ($–CH_2–$, C-7), 71.85 (C-4’), 71.88 (C-3′), 80.09 (q, C-6), 83.41 (C-2′), 99.17, 111.85 (q, 2C, isopropylidene), 104.74 (C-1′), 175.73 (q, –NH–C=O), 203.66 (q, C=O); MS (70 eV, EI) [$M^+–CH_3$]: *m*/*z* 326 (1%). Anal Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.10; H, 6.90; N, 3.90. *Major diastereomer* (**32**): mp 215 °C; $R_f = 0.44$ (silica gel, 20:1 CH_2Cl_2/CH_3OH); $[\alpha]_D^{20}$ −8.8 (*c* 1.0, $CHCl_3$); IR (KBr): 3373.92 (N–H), 2978.03, 2952.60, 2935.88 (C–H), 1706.00, 1679.01 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): *δ* 1.29, 1.30, 1.34, 1.43 (4s, 12H, $–CH_3$, isopropylidene), 2.39–2.47 (m, 2H, $–CH_2–$, H-3, H-4), 2.52–2.55 (m, $–CH_2–$, H-3a), 3.20 (ddd, $–CH_2–$, H4a), 3.39 (dd, $J_{NH,7} = 5.5$, $J_{7,7a} = 15.5$ Hz, H-7), 3.75 (dd, $J_{NH,7a} = 7.0$ Hz, H-7a), 4.28 (d, $J_{3',4'} = 1.5$ Hz, H-3′), 4.45 (d, H-4′), 4.50 (d, $J_{2',3'} = 0$ Hz, H-2′), 5.87 (d, $J_{1',2'} = 3.5$ Hz, H-1′), 6.80 (br s = t, NH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 21.30, 25.73, 26.21 29.55 (4C, $–CH_3$, isopropylidene), 31.17 ($–CH_2–$, C-3), 35.16 ($–CH_2–$, C-4), 45.86 ($–CH_2–$, C-7), 68.61 (C-4′), 71.59 (C-3′), 77.30 (q, C-6), 83.69 (C-2′), 98.81, 111.77 (q, 2C, isopropylidene), 103.86 (C-1′), 174.77 (q, –NH–C=O), 212.00 (q, C=O); MS (70 eV, EI) [$M^+–CH_3$]: *m*/*z* 326 (8%); FAB [$M^+–CH_3$]: *m*/*z* 326. Anal Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.10; H, 6.75; N, 4.10.

4.5.7. (1′*S*,2′*S*,3′*S*,4′*S*,6*R*)-6,3′-Di-*O*-trimethylsilyl-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (33) and (1′*S*,2′*S*,3′*S*,4′*S*,6*S*)-6,3′-di-*O*-trimethylsilyl-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (34). The inseparable diastereomeric mixture was synthesized from **29** (1.0 g, 2.24 mmol) following the procedure outlined in Section 4.3. Purification was performed by flash column chromatography (5:1, toluene/acetone) to obtain **33** and **34** (485 mg, 1.09 mmol, 48.5%) as a light yellow foam; mp 58–61 °C; $R_f = 0.16$ (silica gel, 5:1, toluene/acetone); IR (KBr): 3328.93 (N–H), 2956.51, 2904.54 (C-H), 1719.84, 1630.93 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.05, 0.06, 0.07, 0.096 (4s, 36H, $–SiCH_3$), 1.22, 1.30, 1.34, 1.43 (4s, 12H, $–CH_3$, isopropylidene), 2.15–2.90 (m, 8H, $–CH_2–$, H-3, H-4), 3.23, 3.38 (2dd, 2H, $–CH_2$, H-7), 3.57–3.67 (m, 2H, H-7a), 4.20, 4.28 (2d, 2H, H-3′), 4.36–4.46 (m, 4H, H-2′, H-4′), 5.89, 5.94 (2d, H-1′), 6.39–6.45 (m, NH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −0.19, 0.10, 2.36, 3.09 (4C, $–SiCH_3$), 26.24, 26.69, 27.11, 27.37 (4C, $–CH_3$, isopropylidene), 30.92, 31.14 ($2–CH_2–$, C-3), 36.47, 37.16 ($2–CH_2–$, C-4), 45.86 ($2–CH_2–$, C-7), 76.13, 77.38, 81.81, 84.10, 84.86, 86.31 (6C, 2C-4′, 2C-3′, 2C-2′), 81.90, 84.20 (q, C-6), 104.34, 105.27 (2C-1′), 111.70, 112.83 (q, 2C, isopropylidene), 175.18, 175.83 (q, 2–NH–C=O), 206.10, 207.25 (q, 2C=O); MS (70 eV, EI) [$M^+–CH_3$]: *m*/*z* 430 (0.5%). Anal Calcd for $C_{19}H_{35}NO_7Si_2$: C, 51.20; H, 7.91; N, 3.14. Found: C, 51.34; H, 7.89; N, 3.43.

4.5.8. (1′*S*,2′*S*,3′*S*,4′*S*,6*R*)-6,3′-Di-*O*-*tert*-butyldimethylsilyl-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (35) and (1′*S*,2′*S*,3′*S*,4′*S*,6*S*)-6,3′-di-*O*-trimethylsilyl-6-(1′,2′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (36). Compounds **35** and **36** were prepared from **31** (772 mg, 1.46 mmol) following the procedure outlined in Section 4.3. The crude product was purified by flash column chromatography (1:1, toluene/EtOAc) to yield the two diastereomers **35** (231 mg, 0.44 mmol, 30%) and **36** (203 mg, 0.38 mmol, 26 %) as crystalline solids. *Major diastereomer* (**35**): mp 48 °C; $R_f = 0.17$ (silica gel, 8:1, toluene/acetone); $[\alpha]_D^{20}$ −21.2 (*c* 1.0, $CHCl_3$); IR (KBr): 3424.24, 3330.98 (N–H), 2953.79, 2932.19, 2895.05, 2857.82 (C–H), 1723.67, 1679.26 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): *δ* 0.03, 0.15, 0.19, 0.25 (4s, 12H, $–SiCH_3$), 0.87, 0.91 (2s, 18H, $–SiC(CH_3)_3$), 1.32, 1.43 (2s, 6H, $–CH_3$, isopropylidene), 2.45–2.52 (m, $–CH_2–$, H-3), 2.67–2.81 (m, 2H, $–CH_2–$, H-3a, H-4), 2.98–3.05 (m, $–CH_2–$, H-4a), 3.47 (dd, $J_{NH,7} = 6.5$, $J_{7,7a} = 15.5$ Hz, $–CH_2–$, H-7), 3.86 (dd, $J_{NH,7a} = 6.5$ Hz, $–CH_2–$, H-7a), 4.16 (d, $J_{3',4'} = 3.0$ Hz, H-4′), 4.39 (dd, $J_{2',3'} = 1.5$ Hz, H-2′), 4.48 (dd, H-3′), 5.86 (br s = t, NH), 5.92 (d, $J_{1',2'} = 4.0$ Hz, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.80, −2.72, −2.62 (4C, $–SiCH_3$), 17.53, 18.5 (2q, $–SiC(CH_3)_3$), 25.76, 26.47 (6C, $–SiC(CH_3)_3$), 29.15, 29.24 (2C, $–CH_3$, isopropylidene), 30.14 ($–CH_2–$, C-3), 36.94 ($–CH_2–$, C-4), 46.76 ($–CH_2–$, C-7), 76.92 (C-4′), 81.98 (C-3′), 83.46 (q, C-6), 84.90 (C-2′), 104.29 (C-1′), 112.23 (q, isopropylidene), 174.30 (q, –NH–C=O), 207.32 (q, C=O); MS (70 eV, EI) [M^+]: *m*/*z* 529 (0.5%). Anal Calcd for $C_{25}H_{46}NO_7Si$ (528.8): C, 56.78; H, 8.77; N, 2.65. Found: C, 57.19; H, 8.90; N, 2.65. *Minor diastereomer* (**36**): mp 221 °C; $R_f = 0.22$ (silica gel, 8:1, toluene/acetone); $[\alpha]_D^{20}$ −2.6 (*c* 0.5, $CHCl_3$); IR (KBr): 3350.55 (N–H), 2953.50, 2931.75, 2894.32, 2857.55 (C–H), 1713.40, 1677.15 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.00, 0.11, 0.16, 0.22 (4s, 12H, $–SiCH_3$), 0.86, 0.97 (2s, 18H, $–SiC(CH_3)_3$), 1.30, 1.47 (2s, 6H, $–CH_3$, isopropylidene), 2.50–2.57 (m, 3H, $–CH_2–$, H-3, H-3a, H-4), 2.98–3.08 (m, $–CH_2–$, H-4a), 3.53 (dd, $J_{NH,7} = 7.0$, $J_{7,7a} = 16.0$ Hz, H-7), 3.66 (dd, $J_{NH,7a} = 6.0$ Hz, H-7a), 4.30–4.32 (m, H-2′, H-4′), 4.64 (d, $J_{3',4'} = 3.0$ Hz, H-3′), 5.77 (br s = t, NH), 5.87 (d, $J_{1',2'} = 3.5$ Hz, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* −4.73, −3.65, −3.28 (4C, $–SiCH_3$), 17.35, 18.15 (2q, $–SiC(CH_3)_3$), 25.48, 25.72 (6C, $–SiC(CH_3)_3$), 26.07, 26.46 (2C, $–CH_3$, isopropylidene), 30.23 ($–CH_2–$, C-3), 35.37 ($–CH_2–$, C-4), 44.45 ($–CH_2–$, C-7), 76.63 (C-3′), 80.56 (q, C-6), 82.52 (C-4′), 85.33 (C-2′), 103.31 (C-1′), 111.20 (q, isopropylidene), 174.79 (q, –NH–C=O), 205.37 (q, C=O); MS (70 eV, EI) [M$^+$]: *m/z* 529 (2%), [M$^+$–CH$_3$]: *m/z* 514 (8%). Anal Calcd for $C_{25}H_{46}NO_7Si$: C, 56.78; H, 8.77; N, 2.65. Found: C, 56.97; H, 8.89; N, 2.64.

4.5.9. (1′*S*,2′*R*,3′*S*,4′*S*,6*S*)-1-Methoxy-6-*O*-*tert*-butyldimethylsilyl-6-(2′,3′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (40) and (1′*S*,2′*R*,3′*S*,4′*S*,6*R*)-1-methoxy-6-*O*-*tert*-butyldimethylsilyl-6-(2′,3′-isopropylidenedioxy-tetrahydrofuran-6-yl)-3,3,4,4,7,7-hexahydroazepin-2,5-dione (41). Compounds **40** and **41** were synthesized from **39** (797 mg, 1.86 mmol) according to the procedure outlined in Section 4.3. The crude product was purified by flash column chromatography (5:1, toluene/EtOAc) giving the two diastereomers **40** (78 mg, 0.182 mmol, 10%) and **41** (185 mg, 0.43 mmol, 23%). *Minor diastereomer* (**40**): mp 149–152 °C; $R_f = 0.16$ (silica gel, 2:1, toluene/EtOAc); $[\alpha]_D^{20}$ +13.4 (*c* 1.0, CHCl$_3$); IR (KBr): 3439.76, 3217.79 (N–H), 2952.73, 2936.79, 2858.95 (C–H), 1719.33, 1684.57 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.00, 0.20 (2s, 6H, –SiCH$_3$), 0.86 (s, 9H, –SiC(CH$_3$)$_3$), 1.26, 1.47 (2s, 6H, –CH$_3$, isopropylidene), 2.46–2.53 (m, –CH$_2$–, H-3), 2.64–2.72 (m, –CH$_2$–, H-4), 2.91–2.99 (m, –CH$_2$–, H-4a), 3.1–3.16 (m, 1H, –CH$_2$–, H-3a), 3.21 (s, 3H, –OCH$_3$), 3.64 (dd, $J_{NH,7} = 7.0$, $J_{7,7a} = 16.0$ Hz, H-7), 3.72 (d, $J_{3',4'} = 3.0$ Hz, H-4′), 4.13 (dd, $J_{NH,7a} = 6.0$ Hz, H-7a), 4.45 (d, $J_{2',3'} = 5.5$ Hz, H-2′), 4.77 (dd, H-3′), 4.91 (s, $J_{1',2'} = 0$ Hz, H-1′), 6.04 (br s = t, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ −3.35, −3.07 (6H, –SiCH$_3$), 18.41 (q, –SiC(CH$_3$)$_3$), 23.55, 25.56 (2C, –CH$_3$, isopropylidene), 29.21 (–CH$_2$–, C-3), 36.41 (–CH$_2$–, C-4), 45.56 (–CH$_2$–, C-7), 54.49 (–OCH$_3$), 79.98 (C-3′), 81.18 (C-4′), 83.39 (q, C-6), 83.58 (C-2′), 107.47 (C-1′), 112.16 (q, isopropylidene), 174.26 (q, –NH–C=O), 208.25 (q, C=O); MS (70 eV, EI) [M$^+$]: *m/z* 429 (0.5%), [M$^+$–CH$_3$]: *m/z* 414. Anal Calcd for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found: C, 55.78; H, 8.12; N, 3.26. *Major diastereomer* (**41**): mp 67 °C; $R_f = 0.2$ (silica gel, 2:1, toluene/EtOAc); $[\alpha]_D^{20}$ +40.7 (*c* 1.0, CHCl$_3$); IR (KBr): 3421.91, 3237.20 (N–H), 2951.84, 2934.34, 2895.75, 2855.28 (C–H), 1721.66, 1680.82 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.09, 0.22 (2s, 6H, –SiCH$_3$), 0.87 (s, 9H, –SiC(CH$_3$)$_3$), 1.23, 1.38 (2s, 6H, –CH$_3$, isopropylidene), 2.43–2.51 (m, –CH$_2$–, H-3), 2.69–2.80 (m, 2H, –CH$_2$–, H-3a, H-4), 2.96–3.03 (m, –CH$_2$–, H4a), 3.38 (s, 3H, –OCH$_3$), 3.38 (dd, $J_{NH,7} = 7.0$, $J_{7,7a} = 15.5$ Hz, H-7), 3.79 (dd, $J_{NH,7a} = 6.5$ Hz, H-7a), 4.17 (d, $J_{3',4'} = 3.0$ Hz, H-4′), 4.49 (d, $J_{2',3'} = 5.5$ Hz, H-2′), 4.80 (dd, H-3′), 4.93 (s, $J_{1',2'} = 0$ Hz, H-1′), 5.87 (dd = t, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ −3.52, −3.39 (6H, –SiCH$_3$), 18.30 (q, –SiC(CH$_3$)$_3$), 23.84, 24.95 (2C, –CH$_3$, isopropylidene), 30.26 (–CH$_2$–, C-3), 36.59 (–CH$_2$–, C-4), 48.02 (–CH$_2$–, C-7), 55.17 (–OCH$_3$), 79.20 (C-3′), 81.29 (q, C-6), 83.02 (C-4′), 83.76 (C-2′), 107.55 (C-1′), 112.0 (q, isopropylidene), 174.89 (q, –NH–C=O), 205.23 (q, C=O); MS (70 eV, EI) [M$^+$–CH$_3$]: *m/z* 414 (4%). Anal Calcd for $C_{20}H_{35}NO_7Si$: C, 55.92; H, 8.21; N, 3.26. Found: C, 55.46; H, 8.12; N, 3.18.

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