# Synthesis of sugar-derived spiroaminals *via* lactamization and metathesis reactions<sup>†</sup>

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A series of sugar-derived spiroaminals has been synthesized by utilizing cross metathesis, ring closing metathesis and lactamization reactions as key steps from 1-*C*-alkylated glycosyl azides and important correlations in the spectral data between spiroaminals and their respective anomers are reported.

## Introduction

Spiroaminals, also called oxa-aza spirobicyclic frameworks, spiroaminoketals or spiro-N,O-ketals, are substructures present in a number of biologically active compounds, viz. marineosins A and B,1a,b that show significant inhibition of human colon carcinoma (HCT-116,  $IC_{50} = 0.5 \mu M$ ), crambescidin natural products,<sup>1c</sup> that display nanomolar cytotoxicities against several tumor cell lines, pandamarilactone,1d marine toxin azaspiacids,1e and immunosuppressant sanglifehrin.1f,g Not only these spiroaminals, but the sugar-derived spiroaminoketals or spironucleosides have gained considerable importance with the discovery of hydantocidin 1 (Fig. 1). Hydantocidin 1 is a natural spiroaminal, which was isolated from Streptomyces hygroscopicus and has unique structural features, that is, a spirohydantoin ring at the anomeric position of D-ribofuranose. Because of the unique structural features, potent herbicidal and plant growth regulatory activities of hydantocidin 1, several reports<sup>2</sup> have appeared for its synthesis and also a wide range of analogues.



Fig. 1 Some important sugar-derived spiroaminal frameworks.

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<sup>†</sup>Electronic supplementary information (ESI) available: Copies of <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra for all new compounds, and 2D-COSY, NOE, DEPT-135 spectra of some selected compounds. See DOI: 10.1039/c0ob00555j

The D-glucopyranose analogue of hydantocidin,<sup>3</sup> compound **2** (Fig. 1), is the most powerful inhibitor of glycogen phosphorylase (GP), and glucopyranosyl spirodiketopiperazine **3** has been shown to be a highly specific inhibitor of GP. The anomeric spironucleosides,<sup>4</sup> which were synthetic derivatives of psiconucleosides, were also an important class of spiroaminals for structure– activity relationship studies. Because of their pharmacological importance, together with intrinsic complexity in the construction and the novelty of their frameworks, we planned to synthesize sugar-derived spiroaminals as potentially biologically important fused sugars.

The synthesis of sugar-derived oxa-aza spirobicycles, were reported by Suarez et al.<sup>5</sup> and Compain et al.,<sup>6</sup> who used an intramolecular hydrogen abstraction as a key step in the promotion of the cyclisation. In their synthesis, the spiroaminal precursors, viz. C-glycosyl amines, were synthesized in a multistep process. We have devised a new strategy, in which we have utilized 1-C-alkyl glycosyl azides as spiroaminal precursors and mainly used two main pathways (Scheme 1), viz. reduction of azide, followed by spontaneous lactamization and ring closing metathesis reaction for the construction of core oxa-aza spirobicycles. In our previous communication,<sup>7</sup> we reported the 6,5-fused sugarderived spiroaminals as glycosidase inhibitors from the azido esters obtained via the nucleophilic substitution reactions of unstable Michael adducts derived from 1-nitrosugars. Because of the significant inhibition activity of spiroaminals, we report herein a full account of the synthesis of a series of spiroaminals and also provide some interesting spectral correlations between anomeric spiroaminals.



Scheme 1 Strategies used to construct the spiroaminals.



Scheme 2 Synthesis of 6,5-fused bicyclic spirolactams.

## **Results and discussion**

For the synthesis of 6,5-fused spiroaminals, we chose to utilize the chemistry of anomeric nitrosugars.8 The required glycosyl azido esters 9 and 10 were prepared (Scheme 2) from nitrosugars 5 and 6 using our earlier developed method.<sup>7</sup> To convert 1-Calkyl-1-azido sugars into spirolactams, we studied their reductions under different conditions. There are only a few reports9 in the literature regarding the reduction of C-glycosylated-1-azido sugars. Our initial attempts for the reduction of azide 9 with PPh<sub>3</sub> along with H<sub>2</sub>O<sup>10</sup> and Zn-AcOH<sup>9a</sup> conditions were unsuccessful. Treatment of ester 9 with Zn-AcOH at room temperature gave a complex mixture, which is not surprising as earlier reports<sup>9a</sup> for the reduction of anomeric azides with Zn-AcOH have led to N,O-acetals in lower yields. Dondoni et al.9d have reported the reduction of C-glycosylated-1-azido sugars with  $Pd/C-H_2$  in <sup>t</sup>BuOH·H<sub>2</sub>O, and the use of these conditions in the reduction of 9 led to a mixture of products. To overcome these problems we chose to utilize Pd/CaCO<sub>3</sub> as a catalyst<sup>11</sup> for the reduction of such azides. Thus, the treatment of azide 9 with Pd/CaCO<sub>3</sub> in EtOH in the presence of  $H_2$  (1 atm) at room temperature afforded the spiroaminals 11a and 11b (Scheme 2) in 1:1 ratio and in 78% yield. It is likely that under these conditions the azide group gets

first reduced<sup>3a</sup> to a free amine which undergoes tautomerization accompanied by pyranose ring opening to form a species having a free alcohol and an imine **B** (Scheme 3). Reclosure to form the pyranose ring leads to two anomeric amines **A**, **C** each of which cyclizes leading to two spiroaminals, *viz*. **11a** and **11b**. The formation of **11a** and **11b** was confirmed through their spectral analysis. Thus, <sup>1</sup>H NMR spectra of **11a** and **11b** showed –NH protons as singlets at  $\delta$  6.94 and 5.92 and IR spectra showed



Scheme 3 Anomerization of glycosyl amine for the formation of anomeric spiroaminals 11a and 11b.



Scheme 4 Synthesis of 6,6-fused bicyclic spirolactams.

the carbonyl group frequency at 1701 and 1705 cm<sup>-1</sup>, respectively. Likewise, reduction of the mannose-derived azido ester **10** in the presence of Pd/CaCO<sub>3</sub> gave a 2:1 ratio of products **12a** and **12b** in 83% yield.

These benzylated spirolactams 11a, 11b, 12a, and 12b were deprotected using Pd/C in EtOH in the presence of H<sub>2</sub> (1 atm) at room temperature to afford fully deprotected spirolactams 13a, 13b, 14a and 14b, respectively, in quantitative yields, whose structures were confirmed by the spectral analysis of the corresponding acetates obtained from acetylation with Ac<sub>2</sub>O/Py (Scheme 2). Interestingly, while compound 13b produced a pentaacetate 15b, other compounds 13a, 14a and 14b gave the tetraacetates 15a, 16a, and 16b, respectively. All these compounds were characterized by <sup>1</sup>H, <sup>13</sup>C NMR and COSY spectral data.<sup>12</sup>

After the successful synthesis of 6,5-fused spiroaminals, our synthetic plan focused on the construction of 6,6-fused spiroaminals. For this purpose we chose D-glucono-1,5-lactone 17 and D-galactono-1,5-lactone 18 as the starting materials. According to the literature procedures,<sup>13</sup> we have prepared allyl azides 19 and 20 from allyl Grignard addition on lactones 17 and 18, followed by azidation of the obtained hemiketals (Scheme 4). In order to extend the aglycon part carbon chain of allyl azides 19 and 20 to construct the 6-membered aza-cycles, we have utilized the

cross metathesis<sup>14</sup> reaction. Thus, the cross metathesis reaction of allyl azide 19 with methyl acrylate in the presence of 5 mol% of Grubbs' second generation catalyst D produced trans azido olefin 21 in quantitative yield. The <sup>1</sup>H NMR spectrum of 21 showed olefinic protons at  $\delta$  6.94 and  $\delta$  5.85 with coupling constant J =15.8 Hz, clearly indicating the trans olefin formation. Similarly, cross metathesis reaction of allyl azide 20 gave trans azido ester 22 in 78% yield and with 84% conversion. Reduction of the azide group in azido ester 21 using Pd/CaCO<sub>3</sub> in MeOH in the presence of H<sub>2</sub> (1 atm), followed by heating of the crude amine in MeOH at 60 °C gave a mixture of spirolactams 23a and 23b in 1:1.5 ratio. Similarly, reduction of azide 22 also gave a mixture of spiroaminals 24a and 24b in 3:1 ratio. The global debenzylation of all these lactams was carried out using Pd(OH)<sub>2</sub> in MeOH in the presence of an H<sub>2</sub> (5 psi) atmosphere. Thus, the spirolactams 23a, 23b and 24a successfully produced the hydroxy lactams 25a, 25b and 26a, respectively. Further, the structures of these hydroxy lactams were confirmed through their acetates 27a, 27b and 28a, obtained from the acetylation of aminals 25a, 25b and 26a in the presence of Ac<sub>2</sub>O and Py. All these compounds were characterized by <sup>1</sup>H, <sup>13</sup>C-NMR, COSY and nOe spectroscopic data.

We also investigated an alternative method for the synthesis of 6,6-fused spiroaminals (Scheme 5) *via* ring closing metathesis



Scheme 5 Ring closing metathesis approach for the synthesis of 6,6-fused bicyclic spirolactams.

(RCM). Our attempts to procure the metathesis precursors 32a and 32b by selective reduction of azide in the presence of a double bond using the hydrogenation reaction of allyl azide 19 in the presence of Lindlar catalyst (poisoned with Pb) were unsuccessful and afforded the N,O-acetal 29 via saturation of the double bond. However, after examination of different reaction conditions, we finally obtained the desired aminal **31** upon treatment of the allyl azide 19 with Zn in MeOH in the presence of NH<sub>4</sub>Cl.<sup>15</sup> The acrovlation reaction of crude amine 31 with acryloyl chloride furnished the anomeric aminals 32a and 32b in 12:1 ratio in 67% overall yield. The ring closing metathesis reaction of dienes 32a and 32b using Grubbs' second generation catalyst D successfully produced spirolactams 33a and 33b in 91% and 82% yield, respectively, whose structures were confirmed through their spectral analysis. Thus, the <sup>1</sup>H NMR spectrum of compound 33a showed characteristic peaks of -NH at  $\delta$  6.81 as a singlet and olefinic protons at  $\delta$  6.55–6.53 and  $\delta$  5.94 as a multiplet and a doublet (J = 9.9 Hz), respectively. The global debenzylation along with saturation of the double bond of 33a and 33b using Pd(OH)<sub>2</sub> in MeOH in the presence of  $H_2$  (1 atm) afforded fully deprotected spirolactams 25a and 25b in good yields. The advantage of this RCM route is that we can get 6,6-fused  $\alpha$ -spiroaminal with high diastereoselectivity.

Next we turned our attention to synthesize 6,7-fused spiroaminals. Earlier we had observed spontaneous lactamization (intramolecular amine-ester cyclisation) at room temperature in the construction of 6,5-fused spiroaminals (Scheme 2). But in the case of 6,6-fused spiroaminals, spontaneous lactamization was not observed, the lactamization reactions took longer time (7–8 days) at room temperature, whereas they took 2–3 days (Scheme 4) at higher temperatures. In general, 7-membered lactam formation required harsh basic and heating conditions.<sup>16</sup> To overcome these problems in the construction of larger aza-cycles and due to the above success (Scheme 5), we chose only the ring closing metathesis approach for the synthesis of 6,7-fused spiroaminals.

In order to construct the 7-membered aza-cycle at the anomeric center, the required key intermediate, butenyl glycosyl azide 35 was prepared from benzylated lactone 17. Thus, addition of four equivalents of vinyl magnesium bromide onto lactone 17 produced hemiketal 34 in 81% yield.<sup>17</sup> The glycosylation of ketose 34 using TMSN<sub>3</sub> in presence of TMSOTf in CH<sub>3</sub>CN furnished the required butenyl glycosyl azide 35 in 86% yield (Scheme 6). The IR spectrum of compound 35 showed an intense peak at 2218 cm<sup>-1</sup> and the four methylene protons as multiplets at  $\delta$  2.19–1.90 in its <sup>1</sup>H NMR spectrum clearly indicating the formation of the product. The reduction of the glycosyl azide 35 with Zn in presence of NH<sub>4</sub>Cl, followed by the acroylation reaction of crude amine with acryloyl chloride provided inseparable anomeric aminals 36 in 52% overall yield. Subsequent subjection of the mixture of aminals 36 to RCM reaction using Grubbs' second generation catalyst D, in refluxing methylene chloride, afforded spiroaminals 37a and 37b in 3:1 ratio in 84% yield (Scheme 6). The isomers were separated by column chromatography and their structures were confirmed through spectral analysis. Thus, the <sup>1</sup>H NMR spectrum of spirolactam **37b** showed the –NH proton appearing at  $\delta$  6.21 as a singlet, whereas internal olefinic protons appeared at  $\delta$  6.36–6.33 and 5.92 as a multiplet and a doublet, respectively. The debenzylation and saturation of double bonds of spirolactams 37a and 37b with  $Pd(OH)_2$  in MeOH in the presence of  $H_2$  (1 atm) gave the fully deprotected spiroaminals 38a and 38b in quantitative yields. For the structural confirmation, these free hydroxy compounds 38a



Scheme 6 Synthesis of 6,7-fused bicyclic spirolactams.

and **38b** were converted into their acetyl derivatives **39a** and **39b** using  $Ac_2O/Py$ .

During these studies it was observed that the glycosyl azidoalkene **35** was unstable and was easily converted to a new sugarderived spiroiminal **40** (Scheme 7), even in the NMR tube in CDCl<sub>3</sub>, by merely keeping it at room temperature. The column chromatography of the crude product gave the spiroiminal **40** as a major isolable product in 55% yield. The formation of the product could be explained based on Huisgen intramolecular 1,3-dipolar cycloaddition<sup>18</sup> between the azide and olefin of **35** followed by the loss of nitrogen from **42** or from the corresponding diradical, furnishing spiroiminal **40**, which was found as a core structure of biologically active natural products, marineosins A and B.<sup>1a-b</sup> The extension of this work is currently in progress.

The <sup>1</sup>H NMR, 2D-COSY and nOe experiments helped to unambiguously establish the configurations of the newly generated anomeric center (spiroaminal center) in all the synthesized spirolactams. To assign the stereochemistry at the anomeric center, initially we examined the conformation of the pyranose ring by spectral studies of the all acetylated derivatives. In the case of glucose-derived spiroaminals 15a, 15b, 27a, 27b, 39a and **39b**, the large coupling constants for  $J_{2,3}$ ,  $J_{3,4}$  and  $J_{4,5} >$ 9.5 Hz along with positive nOe observations between H-2/H-4 unambiguously established the  ${}^{4}C_{1}$  chair conformation<sup>19</sup> of the pyranose ring in these spiroaminals (Fig. 2).<sup>12</sup> In case of mannosederived spiroaminals 16a and 16b, the large coupling constants for  $J_{7,8}$  and  $J_{8,9} = 10.4$  Hz and coupling constant between axialequatorial protons,  $J_{9,10} = 3.05$  Hz with interproton nOe effects between H-7/H-9 clearly established the <sup>4</sup>C<sub>1</sub> chair conformation of the pyranose ring.12 In a similar manner, in galactose-derived



Scheme 7 Intramolecular [2 + 3] cycloaddition of azidoolefin 35.



Fig. 2 nOe observations and vicinal proton coupling constants of compounds **39a** and **27b**.

		<sup>1</sup> H NMR (ppm)	<sup>13</sup> C NMR (ppm)
S. No	Compound	-NH chemical shift	anomeric carbon
1	23a	6.48	85.9
2	23b	6.01	87.4
3	24a	6.51	86.5
4	24b	5.92	88.7
5	27a	6.94	85.1
6	27b	6.43	86.6
7	11a	6.93	91.8
8	11b	5.92	92.4
9	16a	8.9	90.7
10	16b	6.5	90.4
11	33a	6.81	86.1
12	33b	5.85	87.9
13	37a	6.41	84.8
14	37b	6.28	85.5

spiroaminals **24a** and **24b**, the large coupling constant for  $J_{4,5} > 10.0$  Hz and coupling constants between axial-equatorial protons  $J_{2,3}$  and  $J_{3,4} < 3.0$  Hz confirmed the <sup>4</sup>C<sub>1</sub> chair conformation of their pyranose ring.

In glucose-derived 6,7-fused spiroaminal 39a, irradiation of the -NH proton signal at  $\delta$  6.12 enhanced the H-2 proton signal at  $\delta$  4.0 and the H-4 proton signal at  $\delta$  5.24 (2.8% and 11.2%) nOe, respectively, Fig. 2), clearly indicating the axial orientation of the -NH position in compound 39a. Similarly, we confirmed the stereochemistry of spiroaminals 15a, 16a, 27a, 24a and 33a as isomers having the -NH group in the axial position. In the case of compound 27b, irradiation of the –NH proton at  $\delta$  6.43 enhanced only the H-5 proton signal at  $\delta$  4.97 (14.0% nOe) and irradiation of the H-2 proton signal at 3.77 enhanced the H-11 proton signal at  $\delta$  2.24 and the H-4 proton signal at  $\delta$  5.32 (9.5% and 4.0%) nOe, respectively, Fig. 2). These results clearly indicated that the -NH group in spiroaminal 27b was in the equatorial orientation. In a similar manner the stereochemistry of the anomeric center of spiroaminals 15b, 16b, 24b, 39b and 33b were also confirmed as isomers with the -NH group in the equatorial position (see the ESI<sup>†</sup>).

An interesting spectral difference was observed between spiroaminals and their respective anomers. In general, the spiroaminals, having the –NH group in the axial orientation, showed the –NH proton chemical shifts at slightly lower fields, and in their <sup>13</sup>C-NMR spectra, anomeric carbon chemical shifts were observed at slightly higher fields than their respective anomers. Thus, compound **23a** showed the –NH proton as a singlet at  $\delta$ 6.48 and the anomeric carbon peak at  $\delta$  85.9 ppm. But in the case of its anomer, *viz.* compound **23b**, the –NH proton peak appeared at  $\delta$  6.01 and the anomeric carbon peak at  $\delta$  87.4. Likewise, the remaining pairs of anomers showed a similar pattern in their spectral data. It appears that the stereoelectronic differences between the anomers directly reflect a regular pattern in spectral data, from which one can easily predict the stereochemistry of these spirolactams. These results are summarized in Table 1.

Because of the potential therapeutic applications of glycosidase inhibitors, in recent years great effort has been made, not only in the synthesis of naturally occurring glycodiase inhibitors but also their chemically modified analogues,<sup>20</sup> and there are a number of drugs currently in the market which are used in the treatment of several diseases.<sup>21</sup> As a result, numerous classes of sugarmimicking glycosidase inhibitors have been developed.<sup>22-24</sup> As part of our ongoing programme towards the design, synthesis and biological evaluation of novel carbohydrate entities such as hybrid sugars,<sup>25</sup> iminosugars<sup>26</sup> and aminocyclitols,<sup>27</sup> we became interested in exploring the glycosidase inhibitory activities of the hydroxy spiroaminals reported in the present study. Thus, the inhibitory activities of compounds **13a**, **13b**, **14a**, **14b**, **25a**, **25b**, **26a**, **38a** and **38b** were tested against a few commercially available enzymes.<sup>28</sup> However, these molecules showed poor inhibition toward all tested enzymes.<sup>29</sup> But, it is possible that structural variations of these molecules may improve the activity and selectivity of inhibition.

#### Conclusions

In conclusion, we have successfully synthesized a series of spiroaminals from 1-C-alkyl-1-azido sugars. The synthesis of these spirolactams was achieved in two main pathways, *viz*. reduction of azide, followed by spontaneous lactamization, and ring closing metathesis reaction to construct the core oxa-aza spirobicycles. For the synthesis of 6,5-fused spiroaminals, the precursors, azidoesters, were prepared from 1-nitrosugars, and the precursors for the synthesis of 6,6 and 6,7-fused spiroaminals were prepared from sugar-derived  $\delta$ -lactones. Because of the occurrence of spiroaminal frameworks in natural products of pharmacological importance, we studied the enzyme inhibition activities of hydroxy spiroaminals. Further work to extend the scope of the study is in progress.

## Experimental

Infrared spectra were recorded on a Bruker FT/IR Vector 22 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL LA-400 (400 and 100 MHz, respectively) spectrometer or a JEOL ECX-500 spectrometer (500 and 125 MHz, respectively) in solutions of CDCl<sub>3</sub> using tetramethylsilane as the internal standard. The mass spectra were recorded on a Waters HAB 213 Q Tof Premier Micromass spectrometer. Optical rotations were recorded on an Autopol II automatic polarimeter at the wavelength of sodium D-line (589 nm) at 28 °C. Column chromatography was performed on silica gel (100–200 mesh) and thin layer chromatography (TLC) was performed on silica gel plates made by using grade G silica gel optained from s.d.fine-chem Ltd., Mumbai or on Merck silica gel pre-coated plates. All solvents and common reagents were purified by established procedures.

General procedure (A). Deprotection of benzyl groups. The benzyl-protected spiro sugar (0.1 mmol) was dissolved in 2 mL of MeOH and 20% Pd(OH)<sub>2</sub>/C (50 mg) was added to it. The reaction mixture was stirred under 1 atm or 5 psi H<sub>2</sub> pressure for 3–4 days at room temperature. The catalyst was filtered off through Celite, and concentrated *in vacuo* to obtain polyhydroxylated spirosugars.

General procedure (B). Acetylation of hydroxy spiro sugars. Polyhydroxy spiro sugar derivative (20 mg) in acetic anhydride (0.5 mL) and pyridine (0.5 mL) in the presence of a catalytic amount of DMAP was stirred for 24 h at room temperature. The reaction mixture was dissolved in  $CH_2Cl_2$  (3 × 10 mL) and washed with water (5 mL) and brine (3 mL), dried with MgSO<sub>4</sub>, concentrated *in vacuo*, and purified by silica gel chromatography to give the pure acetylated spiro sugars.

(E)-Methyl4-((2S,3R,4S,5R,6R)-2-azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2H-pyran-2-yl)but-2-enoate (21). To a solution of azide 19 (100 mg, 0.163 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL) under N<sub>2</sub> atmosphere, was added methyl acrylate (44 µL, 0.489 mmol, 3 equiv.). Grubbs' catalyst D (7.0 mg, 0.016 mmol, 0.05 equiv.) was added and the mixture was heated at 40 °C. After 2 h, the solvent was evaporated under reduced pressure. Purification of the residual product by silica gel chromatography (AcOEt-petroleum ether) afforded azido ester 21 (108 mg, quantitative) as a colourless oil.  $R_{\rm f}$ : 0.4 (hexane-ethyl acetate, 9:1),  $[\alpha]_{D}^{28} = +61.0$  (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat) v<sub>max</sub>: 3030, 2920, 2863, 2119, 1724, 1453, 1273, 1090, 735, 697 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.36–7.19 (m, 20H, Ar-H), 6.94–6.88 (m, 1H, CH=CHCO<sub>2</sub>Me), 5.83 (d, 1H, J = 15.8 Hz, CH= $CHCO_2Me$ ), 4.95 (d, 1H, J = 11.3 Hz, PhCH), 4.91 (d, 1H, J = 10.6 Hz, PhCH), 4.86–4.82 (m, 2H, 2 × PhCH), 4.65 (d, 1H, J = 11.3 Hz, Ph*CH*), 4.63–4.59 (m, 2H, 2 × Ph*CH*), 4.52 (d, 1H, J = 12.0 Hz, Ph*CH*), 3.99 (t, 1H, J = 9.2 Hz), 3.88 (dd, 1H, J = 1.4, 9.6 Hz), 3.77 (dd, 1H, J = 3.4, 11.0 Hz), 3.71–3.67 (m, 2H), 3.70 (s, 3H,  $-OCH_3$ ), 3.48 (d, 1H, J = 9.3 Hz), 2.83 (dd, 1H, J = 6.9, 14.7 Hz), 2.73 (dd, 1H, J = 7.9, 14.7 Hz). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 166.3, 141.4, 138.3, 138.2, 138.0, 137.7, 128.6-127.8 (m, Ar-C), 125.3, 93.2, 83.7, 81.6, 77.7, 75.8, 75.5, 75.2, 74.0, 73.5, 68.3, 51.7, 38.4. HRMS calcd for C<sub>39</sub>H<sub>41</sub>N<sub>3</sub>O<sub>7</sub> [M + Na]+ 686.2842, Found: 686.2846.

(E)-Methyl4-((2S,3R,4S,5S,6R)-2-azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)but-2-enoate (22). A procedure similar to that described for the synthesis of 21 was employed (oil, 170 mg from 200 mg, 0.327 mmol of 20; Yield: 77%).  $R_{\rm f}: 0.4$  (hexane-ethyl acetate, 9:1),  $[\alpha]_{\rm D}^{28} = +59.5$  (c 2.0, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat) v<sub>max</sub>: 3088, 3063, 2920, 2867, 2118, 1724, 1659, 1605, 1435, 1273, 1101, 982, 736, 697 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ 7.35–7.25 (m, 20H, Ar-H), 6.96–6.90 (m, 1H, CH=CHCO<sub>2</sub>Me), 5.83 (d, 1H, J = 14.4 Hz, CH=CHCO<sub>2</sub>Me), 4.98–4.93 (m, 2H, 2× PhCH), 4.73 (d, 1H, J = 11.3 Hz, PhCH), 4.67 (d, 1H, J = 11.3 Hz, PhCH), 4.64 (d, 1H, J = 11.3 Hz, PhCH), 4.58 (d, 1H, J = 11.6 Hz, Ph*CH*), 4.49–4.41 (ABq, 2H, J = 11.7 Hz, Ph*CH*<sub>2</sub>), 4.01–3.93 (m, 3H), 3.90 (dd, 1H, J = 2.4, 9.6 Hz), 3.69 (s, 3H, -OCH<sub>3</sub>), 3.59 (dd, 1H, J = 7.6, 9.3 Hz), 3.54 (dd, 1H, J = 5.8, 9.3 Hz), 2.84 (ddd, 1H, J = 1.7, 7.2, 9.3 Hz, C( $H_a$ Hb)=CHCO<sub>2</sub>Me), 2.71 (ddd, 1H, J =1.4, 7.5, 8.9 Hz,  $C(HaH_b) = CHCO_2Me$ ). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  166.3, 141.6, 138.8, 138.1, 137.9, 137.9, 128.6–124.9 (m, Ar-C), 124.9, 93.8, 81.0, 78.3, 75.6, 74.5, 73.9, 73.6, 72.6, 72.5, 68.3, 51.6, 38.6. HRMS calcd for  $C_{39}H_{41}N_3O_7[M + Na]^+$  686.2842, Found: 686.2840.

(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (23a). To a solution of azido ester 21 (250 mg, 0.105 mmol) in MeOH (4.0 mL) was added 5% Pd/CaCO<sub>3</sub> (125 mg). The reaction mixture was stirred for 3–4 h under H<sub>2</sub> (1 atm) at rt. The catalyst was filtered through Celite, washed with EtOAc and the filtrate was concentrated. The crude amine was dissolved in 5.0 mL of MeOH and heated at 60 °C for 48 h. MeOH was evaporated and purification of the residual product by silica gel chromatography afforded spiroaminals 23a and 23b (1:1.5) in 89% yield. 23a: (83 mg, yield: 36%, oil) *R*<sub>f</sub>: 0.4 (hexane–ethyl acetate, 3:2),  $[\alpha]_{D}^{28} = +40.0$  (*c* 0.75, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 3220, 3063, 2923, 2854, 1669, 1496, 1453, 1363, 1085, 735, 698 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.34–7.16 (m, 20H, *Ar-H*), 6.48 (s, 1H, -NH), 4.93 (d, 1H, J = 11.3, Ph*CH*). 4.87–4.79 (m, 3H, 3 × Ph*CH*), 4.68 (d, 1H, J = 11.3 Hz, Ph*CH*), 4.60–4.57 (m, 2H, 2 × Ph*CH*), 4.50 (d, 1H, J = 12.0 Hz, Ph*CH*), 3.77–3.70 (m, 3H), 3.63–3.59 (m, 2H), 3.45 (d, 1H, J = 9.2), 2.47–2.43 (m, 1H), 2.32–2.25 (m, 1H), 2.12–2.09 (m, 1H), 1.87 (dt, 1H, J = 4.4, 13.0), 1.76–1.68 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  173.5, 138.0, 137.7, 128.5–127.5 (m, *Ar-C*), 85.9, 82.9, 82.0, 78.0, 75.6, 74.7, 73.3, 71.3, 68.5, 31.6, 30.9, 15.7. HRMS calcd for C<sub>39</sub>H<sub>41</sub>N<sub>3</sub>O<sub>7</sub> [M + Na]<sup>+</sup> 686.2842, Found: 686.2840, calcd [M + H]<sup>+</sup> 608.3012, Found: 608.3018.

(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (23b). 124 mg, Yield: 53%, oil, *R*<sub>f</sub>: 0.3 (hexane–ethyl acetate, 3:2),  $[\alpha]_D^{28} = -12.7$  (*c* 0.55, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat) *v*<sub>max</sub>: 3213, 2923, 2854, 1671, 1495, 1085, 737, 689 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.35–7.12 (m, 20H, *Ar*-*H*), 6.01 (s, 1H, –*NH*), 4.88 (d, 1H, *J* = 11.0, Ph*CH*). 4.83–4.72 (m, 4H, 4 × Ph*CH*), 4.60 (d, 1H, *J* = 12.0 Hz, Ph*CH*), 4.53–4.50 (m, 2H, 2 × Ph*CH*), 3.74 (t, 1H, *J* = 9.2 Hz), 3.69–3.63 (m, 3H), 3.53–3.50 (m, 1H), 3.29 (d, 1H, *J* = 9.6 Hz), 2.46-2.43 (m, 1H), 2.31–2.24 (m, 1H), 2.04–1.96 (m, 2H), 1.89–1.87 (m, 1H), 1.77– 1.73 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  172.9, 138.7, 137.9, 137.6, 128.4–127.7 (m, *Ar*-*C*), 87.4, 84.4, 83.0, 77.9, 75.6, 75.0, 73.6, 73.0, 68.9, 31.7, 22.6, 15.6. HRMS calcd for C<sub>38</sub>H<sub>41</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 608.3012, Found: 608.3019.

(2R,3S,4S,5R,6S)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (24a). A procedure similar to that described for the synthesis of 23a and 23b was employed. Spiroaminals 24a and 24b were obtained in 3:1 ratio (377 mg from 510 mg, of 22, Yield: 80%). 24a: 283 mg, Yield: 60%, oil, R<sub>f</sub>: 0.4 (hexane–ethyl acetate, 3:2),  $[\alpha]_{D}^{28} = +40.7$  (c 0.65, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat) v<sub>max</sub>: 3230, 3063, 2924, 2854, 1662, 1496, 1495, 1454, 1396, 1082, 1026, 734, 697 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.35-7.26 (m, 20H, Ar-H), 6.51 (s, 1H, -NH), 4.99 (d, 1H, J = 11.6, PhCH). 4.91 (d, 1H, J = 11.3 Hz, PhCH), 4.72 (d, 1H, J = 11.6, PhCH), 4.69 (d, 1H, J = 11.7 Hz, PhCH), 4.64 (d, 1H, J = 11.7 Hz, Ph*CH*), 4.60 (d, 1H, J = 11.7 Hz, Ph*CH*), 4.46–4.40 (ABq, 2H, J = 11.7 Hz, PhCH<sub>2</sub>), 4.02 (d, 1H, J = 1.7 Hz, H-3), 3.89 (d, 1H, J = 10.3 Hz, H-5), 3.77 (dd, 1H, J = 6.2, 7.5 Hz, H-2), 3.67 (dd, 1H, J = 2.7, 9.9 Hz, H-4), 3.58 (t, 1H, J = 8.9 Hz,  $CH_aH_bOBn$ ),  $3.45 (dd, 1H, J = 5.5, 8.9 Hz, CH_aH_bOBn), 2.42 (ddd, 1H, J = 2.7,$ 6.5, 9.3 Hz), 2.35-2.22 (m, 1H), 2.07-2.00 (m, 1H), 1.89 (td, 1H, J = 4.8, 13.0 Hz), 1.76–1.72 (m, 1H), 1.75–1.60 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 174.0, 138.6, 138.1, 137.9, 128.6–127.7 (m, Ar-C), 86.5, 79.9, 78.6, 75.9, 74.7, 73.9, 73.5, 72.5, 69.9, 68.4, 31.7, 30.9, 15.6. HRMS calcd for  $C_{38}H_{41}NO_6 [M + H]^+$  608.3012, Found: 608.3016.

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (24b). 94 mg, Yield: 20%, oil,  $R_{\rm f}$ : 0.3 (hexane–ethyl acetate, 3:2),  $[\alpha]_{\rm D}^{28} = -8.67$  (*c* 0.75, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\rm max}$ : 3224, 3062, 2923, 2854, 1671, 1453, 1366, 1087, 1025, 734, 697 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.36– 7.25 (m, 20H, *Ar-H*), 5.92 (s, 1H, –*NH*), 4.94 (d, 1H, *J* = 9.3, Ph*CH*). 4.83 (d, 1H, *J* = 10.6 Hz, Ph*CH*), 4.73–4.71 (m, 3H, 3 × Ph*CH*), 4.59 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.46 (d, 1H, *J* = 11.7 Hz, Ph*CH*), 4.40 (d, 1H, *J* = 11.6 Hz, Ph*CH*), 3.94 (d, 1H, *J* = 2.4 Hz, *H*-3), 3.74 (d, 1H, *J* = 10.0 Hz, *H*-5), 3.64 (dd, 1H, *J* = 2.7, 9.9 Hz, *H*-4), 3.61–3.57 (m, 2H, H-2, *CH*<sub>a</sub>H<sub>b</sub>OBn), 3.51(dd, 1H, J = 4.1, 7.5 Hz,  $CH_aH_bOBn$ ), 2.44–2.40 (m, 1H), 2.39–2.23 (m, 1H), 2.04–1.71 (m, 4H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  172.9, 138.6, 138.2, 138.0, 137.9, 128.5–127.6 (m, *Ar-C*), 88.1, 81.2, 80.6, 75.9, 74.8, 74.1, 73.7, 72.9, 72.0, 69.0, 31.9, 22.2, 16.1. HRMS calcd for C<sub>38</sub>H<sub>41</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 608.3012, Found: 608.3018.

(2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (25a). Yield: 85%, oil,  $[\alpha]_{D}^{28} = +50.0$ (*c* 0.4, MeOH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta$  3.7 (dd, 1H, *J* = 2.4, 12.0 Hz), 3.63 (t, 1H, *J* = 10.0 Hz), 3.58 (dd, 1H, *J* = 5.5, 12.3 Hz), 3.42–3.89 (m, 1H), 3.31–3.20 (m, 2H), 2.32–2.18 (m, 2H), 1.95–1.87 (m, 2H), 1.67–1.63 (m, 2H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta$  178.0, 86.0, 74.4, 72.7, 72.5, 69.8, 60.7, 30.8, 30.4, 14.9. HRMS calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>6</sub> [M + Na]<sup>+</sup> 270.0954, Found: 270.0954.

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-1 - oxa-7-azaspiro[5.5]undecan-8-one (25b). Yield: quantitative, oil,  $[α]_D^{28} = +6.8$  (*c* 1.35, MeOH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O): δ 3.68 (d, 1H, *J* = 12.0 Hz), 3.55 (dd, 1H, *J* = 4.8, 12.0 Hz), 3.49 (t, 1H, *J* = 9.2 Hz), 3.38–3.35 (m, 1H), 3.28–3.24 (m, 2H), 2.28–1.99 (m, 3H), 1.70–1.48 (m, 3H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O): δ 177.4, 87.6, 74.9, 73.1, 69.7, 60.9, 30.5, 20.8, 14.5. HRMS calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>6</sub> [M + Na]<sup>+</sup> 270.0954, Found: 270.0955.

(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-1-oxa-7-azaspiro[5.5]undecan-8-one (26a). Yield: 83%, oil,  $[\alpha]_D^{28} = +59.0$ (*c* 1.0, MeOH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta$  3.80 (d, 1H, *J* = 2.7 Hz), 3.74 (dd, 1H, *J* = 3.4, 10.3 Hz), 3.62–3.60 (m, 1H), 3.53– 3.50 (m, 3H), 2.24–2.17 (m, 2H), 1.90–1.86 (m, 2H), 1.68–1.58 (m, 2H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta$  178.1, 86.4, 71.7, 71.4, 69.0, 68.9, 61.3, 30.8, 30.4, 14.9. HRMS calcd for C<sub>10</sub>H<sub>17</sub>NO<sub>6</sub> [M + Na]<sup>+</sup> 270.0954, Found: 270.0954.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-8-oxo-1-oxa-7-aza-spiro-[5.5]undecane-3,4,5-triyltriacetate (27a). Yield: 90%, Rf: 0.30 (hexane–ethyl acetate, 1 : 4),  $[α]_D^{28} = +38.0 (c 0.5, CH_2Cl_2)$ . IR (neat)  $v_{max}$ : 3332, 2923, 2853, 1748, 1673, 1369, 1221, 1033, 901 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.94 (s, 1H, -*NH*), 5.38 (dd, 1H, *J* = 9.6, 10.3 Hz, *H*-4), 5.09 (dd, 1H, *J* = 4.1, 10.3 Hz, *H*-3), 5.07 (d, 1H, *J* = 9.6 Hz, *H*-5), 4.27 (dd, 1H, *J* = 4.4, 12.3 Hz, *CH*<sub>a</sub>H<sub>b</sub>OAc), 4.05 (dd, 1H, *J* = 2.0, 12.3 Hz, CH<sub>a</sub>H<sub>b</sub>OAc), 3.93–3.90 (m, 1H, *H*-2), 2.52–2.47 (m, 1H), 2.36–2.28 (m, 1H), 2.16–2.07 (m, 1H), 2.06 (s, 3H, CO*CH*<sub>3</sub>), 2.05(s, 3H, CO*CH*<sub>3</sub>), 2.01 (s, 3H, CO*CH*<sub>3</sub>), 1.99 (s, 3H, CO*CH*<sub>3</sub>) 1.91–1.89 (m, 1H), 1.77–1.73 (m, 1H), 1.67– 1.40 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl3): δ 173.2, 170.6, 170.1, 169.6, 169.4, 85.1, 71.8, 70.4, 68.4, 68.2, 61.9, 31.5, 30.8, 20.7, 20.6, 20.5, 20.4, 15.4. HRMS calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>10</sub> [M + Na]<sup>+</sup> 438.1376, Found: 438.1376.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-8-oxo-1-oxa-7-aza-spiro-[5.5]undecane-3,4,5-triyltriacetate (27b). Yield: 67%. *R*<sub>i</sub>: 0.30 (hexane–ethyl acetate, 1:4),  $[\alpha]_D^{28} = -27.5$  (*c* 0.4, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 2953, 1752, 1682, 1370, 1225, 1036, 822 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.43 (s, 1H, *-NH*), 5.32 (dd, 1H, *J* = 9.6, 10.3 Hz, *H*-4), 5.03 (t, 1H, *J* = 9.6 Hz, *H*-3), 4.97 (d, 1H, *J* = 10.3 Hz, *H*-5), 4.14 (dd, 1H, *J* = 4.8, 12.0 Hz, *CH*<sub>a</sub>H<sub>b</sub>OAc), 4.09 (dd, 1H, *J* = 2.7, 12.4 Hz, CH<sub>a</sub>H<sub>b</sub>OAc), 3.78–3.75 (m, 1H, *H*-2), 2.49-2.45 (m, 1H), 2.32–2.23 (m, 2H), 1.91–1.78 (m, 3H), 2.08 (s, 3H, COCH<sub>3</sub>), 2.04 (s, 3H, COCH<sub>3</sub>), 2.01 (s, 3H, COCH<sub>3</sub>), 1.98 (s, 3H, COCH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  175.5, 172.9, 170.6, 170.1, 169.4, 86.6, 72.4, 70.6, 70.1, 68.8, 62.4, 31.2, 22.4, 20.7, 20.6, 20.5, 20.5, 15.0. HRMS calcd for  $C_{18}H_{25}NO_{10}$  [M + H]<sup>+</sup> 416.1557, Found: 416.1554.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-8-oxo-1-oxa-7-aza-spiro-[5.5]undecane-3,4,5-triyltriacetate (28a). Yield: 71%. *R*<sub>f</sub>: 0.40 (hexane–ethyl acetate, 1:4),  $[\alpha]_D^{28} = +72.7$  (*c* 0.55, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 3331, 2924, 2853, 1750, 1672, 1436, 1372, 1226, 1129, 1078 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.59 (s, 1H, -*NH*), 5.44–5.41 (m, 2H), 5.29 (dd, 1H, *J* = 1.3, 12.0 Hz), 4.19–4.16 (m, 1H), 4.08–4.07 (m, 2H), 2.51–2.46 (m, 1H), 2.34–2.27 (m, 1H), 2.11–2.06 (m, 1H), 2.14 (s, 3H, CO*CH*<sub>3</sub>), 2.07(s, 3H, CO*CH*<sub>3</sub>), 2.02 (s, 3H, CO*CH*<sub>3</sub>), 1.97 (s, 3H, CO*CH*<sub>3</sub>), 1.97–1.94 (m, 1H), 1.75–1.62 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  173.8, 170.4, 170.3, 170.2, 169.9, 85.6, 69.4, 67.7, 67.2, 61.5, 31.8, 30.9, 20.7, 20.6, 20.5, 15.3. HRMS calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>10</sub> [M + H]<sup>+</sup> 416.1557, Found: 416.1551.

N-((3R,4S,5R)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2propyltetrahydro-2H-pyran-2-yl)acetamide (30). To a solution of azido olefin 19 (70 mg, 0.115 mmol) in EtOH (1.5 mL) was added 5% Lindlar's catalyst (poisoned with Pb, 35 mg). The reaction mixture was stirred for 15 h under  $H_2$  (1 atm) at rt. The catalyst was filtered through Celite, washed with EtOAc and the filtrate was concentrated. Acetylation of the crude amine 29 was carried out conventionally using acetic anhydride and Et<sub>3</sub>N, to give glycosyl acetamide **30**. Yield: 72%, oil,  $R_f$ : 0.40 (hexane-ethyl acetate, 3:2),  $[\alpha]_{D}^{28} = +31.18 \ (c \ 0.85, \ CH_2Cl_2)$ . IR (neat)  $v_{max}$ : 3328, 2924, 1672, 1538, 1372, 1496 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 2:1 ratio of anomers: δ 7.34–7.16 (m, 40H, Ar-H, both isomers), 5.93 (s, 1H, -NH, major), 5.78 (s, 1H, -NH, minor), 4.97 (d, 1H, J = 10.3 Hz, major), 4.89–4.52 (m, 15H, both isomers), 3.88 (dd, 1H, J = 2.7, 11.7 Hz, major), 3.83-3.59 (m, 11H, both isomers), 2.38-2.36 (m, 1H, major), 2.17–2.07 (m, 2H, both isomers), 1.96 (s, 3H, COCH<sub>3</sub>, major), 1.92–1.85 (m, 1H, minor), 1.77 (s, 3H, COCH<sub>3</sub>, minor), 1.62–1.42 (m, 2H, both isomers), 1.35–1.15 (m, 2H, both isomers), 0.95 (t, 3H, J = 7.5, minor), 0.85 (t, 3H, J = 6.8 Hz, major). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.4, 169.2, 138.6, 138.5, 138.5, 138.5, 138.1, 137.6, 128.7–127.7 (m, Ar-C), 88.4, 88.1, 84.4, 83.9, 79.9, 79.3, 78.2, 77.6, 75.8, 75.7, 75.1, 74.8, 74.7, 74.5, 73.5, 73.1, 72.3, 69.3, 68.7, 37.6, 32.4, 29.8, 24.9, 24.7, 16.8, 14.9, 14.2. HRMS calcd for  $C_{39}H_{45}NO_6 [M + H]^+$  624.3325, Found: 624.3328.

N-((2S,3R,4S,5R,6R)-2-Allyl-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)acrylamide (32a). To a solution of azide 19 (300 mg, 0.495 mmol) in methanol (20 ml) was added NH<sub>4</sub>Cl (262 mg, 4.95 mmol), and Zn (dust) (575 mg, 4.95 mmol) and the reaction mixture was stirred vigorously for 2 h at room temperature. After completion of the reaction, the reaction mixture was concentrated, and the residue was triturated with ether  $(5 \times 30 \text{ mL})$  and the combined ether fractions were filtered through small pad of silica to afford 245 mg of 31 as an oil which was used directly in the next step. To a stirred solution of amine **31** (245 mg, 0.423 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) at 0 °C was added dropwise Et<sub>3</sub>N (0.07 mL, 0.507 mmol) followed by acryloyl chloride (0.04 mL, 0.507 mmol). The reaction mixture was stirred for 30 min and after completion of reaction (TLC monitoring), it was extracted with  $CH_2Cl_2$  (2 × 40 mL). Usual work-up gave a crude product which was purified by column chromatography to give dienes 32a and 32b in 67% overall yield. **32a**: 193 mg, oil,  $R_f$ : 0.35 (hexane-ethyl acetate, 7:3),

 $[\alpha]_{D}^{28} = +55.0 \ (c \ 0.4, \ CH_{2}Cl_{2}). \ IR \ (neat) \ v_{max}: 3405, \ 2921, \ 1672,$ 1615, 1497, 1453 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37–7.17 (m, 20H, Ar-H), 6.24 (d, 1H, J = 16.8 Hz,  $-CH = CH_aH_b$ ), 6.08– 6.04 (m, 2H, -NH, -CH=CH<sub>2</sub>), 5.98-5.88 (m, 1H, -CH=CH<sub>2</sub>), 5.62 (d, 1H, J = 9.9 Hz,  $-CH = CH_a H_b$ ), 5.12 (d, 1H, J = 9.9 Hz,  $-CH = CH_aH_b$ ), 5.06 (d, 1H, J = 17.2 Hz,  $-CH = CH_aH_b$ ), 4.95 (d, 1H, J = 10.7 Hz, PhCH), 4.88 (d, 1H, J = 10.7 Hz, PhCH), 4.81 (d, 1H, J = 11.1 Hz, Ph*CH*), 4.77 (d, 1H, J = 10.7 Hz, Ph*CH*), 4.74–4.69 (m, 2H,  $2 \times$  Ph*CH*), 4.66 (d, 1H, J = 10.3 Hz, PhCH), 4.56 (d, 1H, J = 11.5 Hz, PhCH), 3.84-3.62 (m, 6H), 3.39 (d, 1H, J = 10.7 Hz,  $-CH_aH_bCH=CH_2$ ), 2.61 (dd, 1H, J =10.3, 14.5 Hz, -CH<sub>a</sub>H<sub>b</sub>CH=CH<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 164.7, 138.6, 138.4, 138.0, 137.8, 133.5, 131.4, 128.7–127.6(m, Ar-C), 127.1, 118.8, 83.3, 84.4, 79.8, 78.0, 75.8, 75.5, 75.1, 73.6, 72.6, 68.6, 40.12. HRMS calcd for  $C_{40}H_{43}NO_6 [M + H]^+$  634.3169, Found: 634.3165.

*N*-((2*R*,3*R*,4*S*,5*R*,6*R*)-2-Allyl-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)acrylamide (32b). 17 mg, oil,  $R_{\rm f}$ : 0.40 (hexane–ethyl acetate, 7:3),  $[\alpha]_{\rm D}^{28} = -4.17$  (*c* 0.6, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\rm max}$ : 3405, 2924, 1728, 1694, 1453 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.45–7.17 (m, 20H, *Ar*–*H*), 6.18 (d, 1H, *J* = 16.9 Hz, -CH=*CH*<sub>a</sub>*H*<sub>b</sub>), 6.08 (s, 1H, *-NH*), 5.92–5.83 (m, 2H, 2 × *CH*=*C*H<sub>2</sub>), 5.55 (d, 1H, *J* = 10.5 Hz, -CH=*C*H<sub>a</sub>*H*<sub>b</sub>), 5.26–5.24 (m, 1H, -CH=*CH*<sub>a</sub>*H*<sub>b</sub>), 5.23 (d, 1H, *J* = 11.0 Hz, -CH=*C*H<sub>a</sub>*H*<sub>b</sub>), 4.82 (d, 1H, *J* = 11.5 Hz, Ph*CH*), 4.79–4.70 (m, 4H, 4 × Ph*CH*), 4.61–4.52 (m, 3H, 3 × Ph*CH*), 3.81–3.68 (m, 6H), 2.89–2.78 (m, 2H, -*CH*<sub>2</sub>CH=*C*H<sub>2</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  164.7, 138.6, 138.3, 138.1, 131.7, 128.5–127.7 (m, *Ar*-*C*), 126.6, 120.3, 87.4, 83.8, 79.2, 77.6, 74.8, 74.7, 74.6, 73.7, 73.4, 69.3, 35.1. HRMS calcd for C<sub>40</sub>H<sub>43</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 634.3169, Found: 634.3169.

(2R,3R,4S,5R,6S)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undec-9-en-8-one (33a). To a stirred solution of compound 32a (400 mg, 0.63 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5-6 mL) at room temperature was added the second generation Grubbs' catalyst (26.8 mg, 0.031 mmol). The mixture was refluxed for 24 h and after completion of reaction, the solvent was evaporated and residue was purified by column chromatography. Yield: 91% (347 mg).  $R_{\rm f}$ : 0.40 (hexane-ethyl acetate, 1:1),  $[\alpha]_{\rm D}^{28} = +74.61$ (c 0.65, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat) v<sub>max</sub>: 3241, 2921, 2852, 1678, 1614, 1453, 1414 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.32-7.16 (m, 20H, Ar-H), 6.81 (s, 1H, -NH) 6.56-6.52 (m, 1H, -CH=CH-), 5.94 (d, 1H, J = 9.9 Hz, -CH = CH-), 4.96 (d, 1H, J = 11.4 Hz, Ph*CH*), 4.92 (d, 1H, J = 10.7 Hz, Ph*CH*), 4.85 (d, 1H, J = 10.2 Hz, PhCH), 4.81 (d, 1H, J = 11.1 Hz, PhCH), 4.69 (d, 1H, J = 11.8 Hz, Ph*CH*), 4.58 (d, 2H, J = 11.4 Hz,  $2 \times$  Ph*CH*), 4.44 (d, 1H, J =12.2 Hz, PhCH), 3.93 (t, 1H, J = 9.5 Hz, H-4), 3.76 (t, 1H, J = 9.5 Hz, H-3), 3.75–3.71 (m, 2H, CH<sub>a</sub>H<sub>b</sub>OBn, H-2), 3.56 (d, 1H, J = 10.3 Hz, CH<sub>a</sub> $H_b$ OBn), 3.45 (d, 1H, J = 9.5 Hz, H-5), 2.70 (d, 1H, J = 18.3 Hz,  $-CH_aH_bCH=CH_2$ ), 2.31 (dd, 1H, J = 5.7, 17.9 Hz,  $-CH_aH_bCH=CH_2$ ). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ 165.6, 139.9, 138.0, 137.9, 137.8, 137.5, 128.4-127.5 (m, Ar-C), 122.7, 86.1, 82.9, 80.7, 77.9, 75.6, 75.3, 74.6, 73.3, 70.7, 68.2, 33.6. HRMS calcd for  $C_{38}H_{39}NO_6 [M + H]^+$  606.2856, Found: 606.2859.

2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.5]undec-9-en-8-one (33b). The same procedure was employed, as used for the synthesis of 33a. Yield: 82%(60 mg from 80 mg, 0.0315 mmol of 32b).  $R_f$ : 0.40 (hexane-ethyl acetate, 1:1),  $[\alpha]_{D}^{28} = +12.0$  (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 3442, 2956, 1687, 1618, 1464, 1363 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ7.31–7.14 (m, 20H, Ar-H), 6.55–6.52 (m, 1H, –CH=CH–), 6.00 (d, 1H, J = 9.9 Hz, -CH=CH-), 5.85 (s, 1H, -NH), 4.87 (d, 1H, J = 11.1 Hz, Ph*CH*), 4.81 (d, 1H, J = 10.7 Hz, Ph*CH*), 4.80 (d, 1H, J = 11.0 Hz, Ph*CH*), 4.79 (d, 1H, J = 10.7 Hz, Ph*CH*), 4.75 (d, 1H, J = 11.1 Hz, PhCH), 4.57 (d, 1H, J = 12.2 Hz, PhCH), 4.51(d, 1H, J = 10.7 Hz, Ph*CH*), 4.49 (d, 1H, J = 12.2 Hz, Ph*CH*), 3.70–3.66 (m, 3H, CH<sub>a</sub>H<sub>b</sub>OBn, H-3, H-4), 3.61 (dd, 1H, J = 1.9, 11.1 Hz,  $CH_aH_bOBn$ ), 3.53–3.49 (m, 1H, H-2), 3.33 (d, 1H, J = 9.5 Hz, *H*-5), 2.93 (dt, 1H, J = 2.6, 19.1 Hz,  $-CH_aH_bCH=CH_2$ ), 2.66 (dd, 1H, J = 5.7, 19.1 Hz,  $-CH_aH_bCH=CH_2$ ). <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta$  166.0, 138.7, 138.3, 138.1, 137.9, 137.5, 128.6–127.8 (m, Ar-C), 123.3, 87.9, 83.9, 82.8, 77.8, 75.7, 75.3, 75.1, 73.2, 68.8, 24.9. HRMS calcd for C<sub>38</sub>H<sub>39</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 606.2856, Found: 606.2855.

(2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)tetrahydro-2H-pyran-2-ol (34). To a cold (-78 °C) solution of lactone 17 (2.0 g, 3.72 mmol) in THF (15.0 mL) under nitrogen atmosphere was added dropwise freshly prepared vinylmagnesium bromide (1.95 g in 15.0 mL THF, 14.86 mmol). After 2 h of stirring at -78 °C, the reaction mixture was quenched with saturated NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), and concentrated to give the corresponding hemiketal 34. Yield: 82% (1.8 g).  $R_{\rm f}$ : 0.5 (hexane-ethyl acetate, 4:1),  $[\alpha]_{\rm D}^{28} = +22.94$  (c 0.85,  $CH_2Cl_2$ ). IR (neat)  $v_{max}$ : 3440, 3063, 3030, 2923, 2863, 1640, 1453 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.85–7.18 (m, 20H, Ar-H), 5.84-5.77 (m, 1H,  $-CH = CH_2$ ), 5.00 (dd, 1H, J = 4.0, 16.0 Hz, - $CH = CH_aH_b$ , 4.96–4.82 (m, 5H, – $CH = CH_aH_b$ , 4×Ph*CH*), 4.70– 4.52 (m, 4H, 4×PhCH), 4.02–3.96 (m, 2H), 3.76 (dd, 1H, J = 4.0, 8.0 Hz), 3.69–3.63 (m, 2H), 3.41(d, 1H, J = 8.0 Hz), 2.72 (s, 1H, OH), 2.24-2.21(m, 1H) 2.13-2.09 (m, 1H), 1.85-1.77 (m, 1H), 1.75–1.69 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 138.5, 138.4, 138.3, 128.4-127.5 (m, Ar-C), 114.8, 98.2, 83.8, 81.8, 78.4, 75.6, 75.4, 74.8, 73.3, 71.5, 68.8, 37.4, 26.8. HRMS calcd for C<sub>38</sub>H<sub>42</sub>O<sub>6</sub>  $[M + NH_4]^+$  612.3325, Found: 612.3325.

(2S,3R,4S,5R,6R)-2-Azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)tetrahydro-2H-pyran (35). The hemiketal 34 (1.2 g, 2.02 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15.0 mL) and treated with activated 4 Å powdered molecular sieves (500 mg). To this reaction mixture, TMSN<sub>3</sub> (0.8 mL, 6.06 mmol) and TMSOTf (0.2 mL, 0.44 mL) were added at -40 °C and the reaction mixture was stirred at the same temperature for 2.0 h. It was then neutralized with Et<sub>3</sub>N, diluted with CH<sub>2</sub>Cl<sub>2</sub>, filtered through Celite, and concentrated. Column chromatography of this residue afforded the desired azide 35. Yield: 86% (1.1 g).  $R_f$ : 0.50 (hexaneethyl acetate, 9:1),  $[\alpha]_{D}^{28} = +68.46$  (c 0.65, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 2922, 2118, 1642, 1453 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.35– 7.19 (m, 20H, Ar-H), 5.77-5.70 (m, 1H, -CH=CH<sub>2</sub>), 4.98 (d, 1H,  $J = 15.8 \text{ Hz}, -\text{CH} = CH_aH_b), 4.94 - 4.84 \text{ (m, 4H, -CH} = CH_aH_b 3 \times$ Ph*CH*), 4.81 (d, 1H, *J* = 10.7 Hz, Ph*CH*), 4.70 (d, 1H, *J* = 11.2 Hz, Ph*CH*), 4.63–4.58 (m, 2H, 2 × Ph*CH*), 4.52 (d, 1H, J = 12.2 Hz, Ph*CH*), 3.99 (t, 1H, *J* = 9.2 Hz), 3.85 (dd, 1H, *J* = 1.9, 10.7 Hz), 3.75 (dd, 1H, J = 3.6, 11.2 Hz), 3.69–3.64 (m, 2H), 3.49 (d, 1H, J = 9.2 Hz), 2.19–2.17 (m, 1H), 2.09–2.01 (m, 2H), 1.93–1.88 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): *δ* 138.4, 138.2, 138.1, 137.8, 137.5, 128.6-127.2 (m, Ar-C), 115.2, 93.9, 83.8, 81.8, 77.8, 75.9, 75.5,

75.2, 73.6, 73.4, 68.4, 34.7, 27.2. HRMS calcd for  $C_{38}H_{41}N_3O_5$  [M + NH<sub>4</sub>]<sup>+</sup> 637.3390, Found: 637.3393.

N-((3R,4S,5R)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-envl)tetrahydro-2H-pyran-2-yl)acrylamide (36). A procedure similar to that described for the synthesis of 32a and 32b was employed. Yield: 52% (oil, 271 mg from 500 mg, 0.807 mmol of azide 35). Data have given for the major separable isomer.  $R_{\rm f}$ : 0.4 (hexane-ethyl acetate, 7:3),  $[\alpha]_{D}^{28} = +40.75$  (c 0.75, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\text{max}}$ : 3411, 2924, 1737, 1463 cm<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.49–7.17 (m, 20H, Ar-H), 6.23 (d, 1H, J = 16.8 Hz,  $-CH = CH_a H_b$ ), 6.10–6.03 (m, 2H, -NH,  $-CH = CH_2$ ), 5.79–5.72 (m, 1H,  $-CH = CH_2$ ), 5.61 (d, 1H, J = 9.9 Hz,  $-CH = CH_aH_b$ ), 4.98–4.90 (m, 4H, J = 9.9 Hz,  $-CH = CH_2$ ,  $2 \times PhCH$ ), 4.84 (d, 1H, J = 10.0 Hz, PhCH), 4.77 (d, 1H, J = 10.7 Hz, PhCH), 4.73-4.70 (m, 2H,  $2 \times PhCH$ ), 4.66 (d, 1H, J = 10.3 Hz, PhCH), 4.54 (d, 1H, J = 12.2 Hz, Ph*CH*), 3.89–3.76 (m, 4H), 3.63–3.59 (m, 2H), 2.56-2.49 (m, 1H), 2.35-2.30 (m, 1H), 2.02-1.83 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  164.4, 138.6, 138.5, 138.1, 138.0, 137.4, 131.5, 128.7–127.6 (m, Ar-C), 126.9, 114.8, 88.3, 84.4, 79.5, 78.0, 75.7, 75.1, 75.1, 73.6, 72.6, 68.6, 34.8, 27.9. HRMS calcd for  $C_{41}H_{45}NO_6 [M + H]^+ 648.3325$ , Found: 648.3321.

(2R,3R,4S,5R,6S)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.6]dodec-9-en-8-one (37a). To a stirred solution of compound 36 (110 mg, 0.17 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at room temperature was added the Grubbs' second generation catalyst (5 mol%, 7.2 mg). The mixture was refluxed in CH<sub>2</sub>Cl<sub>2</sub> and stirred for overnight under nitrogen atmosphere. After completion of the reaction, the solvent was evaporated under reduced pressure and the column chromatography of the crude product gave two anomeric spiroaminals 37a and 37b in 3:1 ratio with 84% yield. **37a**: (51 mg),  $R_{\rm f}$ : 0.25 (hexane–ethyl acetate, 3 : 2),  $[\alpha]_{\rm D}^{28} = +29.41$  (c 0.85, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\text{max}}$ : 3250, 2920, 1669, 1619, 1453 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ7.34–7.18 (m, 20H, Ar-H), 6.41 (s, 1H, -*NH*), 6.25 (dt, 1H, *J* = 3.7, 12.7 Hz, -CH=*CH*-CH<sub>2</sub>), 5.84 (d, 1H, J = 12.4 Hz, -CH=CHCH<sub>2</sub>), 4.89 (d, 1H, J = 11.2 Hz, Ph*CH*), 4.87 (d, 1H, J = 10.5 Hz, Ph*CH*), 4.81(d, 2H, J = 10.2 Hz,  $2 \times PhCH$ ), 4.73 (d, 1H, J = 11.2 Hz, PhCH), 4.60 (d, 1H, J =10.9 Hz, Ph*CH*), 4.55 (d, 1H, *J* = 12.4 Hz, Ph*CH*), 4.48 (d, 1H, J = 12.2 Hz, PhCH), 3.80–3.70 (m, 4H), 3.55 (d, 1H, J = 10.0 Hz), 3.47 (d, 1H, J = 9.0 Hz), 2.79-2.71 (m, 1H), 2.37-2.26 (m, 2H), 1.96–1.92 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 169.4, 143.1, 138.3, 138.2, 137.6, 128.6–127.7 (m, Ar-C), 124.1, 84.8, 84.0, 83.8, 78.1, 75.9, 75.8, 74.8, 73.4, 71.6, 68.5, 36.7, 26.8. HRMS calcd for  $C_{39}H_{41}NO_6 [M + H]^+$  620.3012, Found: 620.3011.

(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-1-oxa-7-azaspiro[5.6]dodec-9-en-8-one (37b). 28 mg,  $R_{\rm f}$ : 0.2 (hexane–ethyl acetate, 3:2),  $[\alpha]_{\rm D}^{28} = +5.0$  (*c* 0.0.4, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\rm max}$ : 3397, 2924, 1669, 1618, 1453 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.33–7.15 (m, 20H, *Ar-H*), 6.36–6.33 (m, 1H, CH=*CH*–CH<sub>2</sub>), 6.21 (s, 1H, –*NH*), 5.92 (d, 1H, *J* = 12.2 Hz, –*CH*=*C*H–CH<sub>2</sub>), 4.88–4.79 (m, 5H, 5×Ph*CH*), 4.58–4.51 (m, 3H, 3×Ph*CH*), 3.77 (t, 1H, *J* = 8.8 Hz, *H*-4), 3.70 (d, 1H, *J* = 10.7 Hz, *CH*<sub>a</sub>H<sub>b</sub>OBn), 3.60–3.57 (m, 2H, *H*-2, *H*-3), 3.52 (dd, 1H, *J* = 4.2, 13.7 Hz, CH<sub>a</sub>H<sub>b</sub>OBn), 3.41 (d, 1H, *J* = 8.8 Hz, *H*-5), 2.53–2.49 (m, 1H), 2.39–2.38 (m, 2H), 2.26–2.23 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  168.7, 143.4, 138.1, 137.7, 137.4, 128.6–127.6 (m, *Ar-C*), 125.2, 85.5, 85.2, 83.8, 78.0, 75.7, 75.4, 75.0, 73.4, 73.2, 68.9, 27.2, 24.4. HRMS calcd for  $C_{39}H_{41}NO_6 [M + H]^+$  620.3012, Found: 620.3015.

(2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-1-oxa-7-azaspiro[5.6]dodecan-8-one (38a). Yield: quantitative, oil,  $[α]_{12}^{28} = +39.09$  (*c* 0.55, MeOH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O): δ 3.73 (d, 1H, *J* = 12.4 Hz), 3.60 (dd, 1H, *J* = 5.5, 12.4 Hz), 3.46 (t, 1H, *J* = 9.1 Hz), 3.39–3.36 (m, 1H), 3.28–3.23 (m, 2H), 2.66 (t, 1H, *J* = 13.3 Hz), 2.13 (dd, 1H, *J* = 6.4, 13.7 Hz), 1.92–1.85 (m, 2H), 1.76–1.70 (m, 2H), 1.61–1.60 (m, 1H), 1.34–1.29 (m, 1H). <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O): δ 182.2, 85.7, 76.6, 73.1, 72.7, 69.5, 60.4, 36.9, 35.8, 22.6, 22.4. HRMS calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 262.1291, Found: 262.1292.

(2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-2-(hydroxymethyl)-1-oxa-7-azaspiro[5.6]dodecan-8-one (38b). Yield: quantitative, oil,  $[\alpha]_{2^8}^{2^8} = -3.33$  (*c* 0.45, MeOH). <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O):  $\delta$  3.79 (d, 1H, *J* = 12.3 Hz), 3.58 (dd, 1H, *J* = 3.7, 15.1 Hz), 3.52 (t, 1H, *J* = 10.1 Hz), 3.38–3.21 (m, 3H), 2.70 (t, 1H, *J* = 13.5 Hz), 2.29–2.23 (m, 1H), 2.12(d, 1H, *J* = 15.6 Hz), 1.83–1.58 (m, 3H), 1.43–1.37 (m, 1H), 1.19–1.14 (m, 1H). (125 <sup>13</sup>C NMR MHz, D<sub>2</sub>O):  $\delta$  182.0, 86.8, 76.7, 74.0, 73.8, 69.7, 60.8, 36.2, 27.6, 22.3, 21.6. HRMS calcd for C<sub>11</sub>H<sub>19</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 262.1291, Found: 262.1291.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-8-oxo-1-oxa-7-azaspiro-[5.6]dodecane-3,4,5-triyl triacetate (39a). Yield: 79%,  $R_i$ : 0.35 (hexane–ethyl acetate, 1:4),  $[\alpha]_D^{28} = +66.0$  (*c* 0.75, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{max}$ : 3386, 2926, 1755, 1673, 1434, 1368 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  6.15 (s, 1H, –NH), 5.25 (t, 1H, J = 9.6 Hz, H-4), 5.04 (t, 1H, J = 9.6 Hz, H-3), 5.00 (d, 1H, J = 10.1 Hz, H-5), 4.21 (dd, 1H, J = 5.9, 12.4 Hz,  $CH_aH_bOAc$ ), 4.15 (dd, 1H, J = 2.3, 12.4 Hz,  $CH_aH_bOAc$ ), 4.02–3.99 (m, 1H, H-2), 2.63 (td, 1H, J =2.3, 13.3 Hz), 2.42 (dd, 1H, J = 6.0, 13.3 Hz), 2.07–2.02 (m, 1H), 2.07 (s, 3H, COCH<sub>3</sub>), 2.06 (s, 3H, COCH<sub>3</sub>), 2.02 (s, 3H, COCH<sub>3</sub>), 1.97 (s, 3H, COCH<sub>3</sub>), 1.97–1.94 (m, 1H), 1.87–1.83 (m, 1H), 1.75– 1.68 (m, 2H), 1.54–1.45 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ 177.6, 170.4, 169.9, 169.5, 168.9, 84.6, 74.3, 70.8, 68.5, 62.1, 37.9, 36.4, 22.9, 20.7, 20.5, 20.4. HRMS calcd for C<sub>19</sub>H<sub>27</sub>NO<sub>10</sub> [M + H]<sup>+</sup> 430.1713, Found: 430.1715.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-8-oxo-1-oxa-7-azaspiro-[5.6]dodecane-3,4,5-triyl triacetate (39b). Yield: 88%,  $R_i$ : 0.35 (hexane–ethyl acetate, 1:4),  $[\alpha]_D^{28} = +15.0 (c 0.3, CH_2Cl_2)$ . IR (neat)  $v_{max}$ : 3368, 2922, 1738, 1662, 1459, 1381 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl\_3):  $\delta$  6.56 (s, 1H, –NH), 5.35 (t, 1H, J = 9.6 Hz, H-4), 5.00 (t, 1H, J = 9.6 Hz, H-3), 4.93 (d, 1H, J = 9.6 Hz, H-5), 4.21–4.13 (m, 2H,  $CH_2OAc$ ), 3.74–3.72 (m, 1H, H-2), 2.69 (t, 1H, J = 12.8 Hz), 2.46 (dd, 1H, J = 5.9, 14.3 Hz), 2.39 (d, 1H, J = 14.2 Hz), 2.09 (s, 3H, CO*CH*<sub>3</sub>), 2.08 (s, 3H, CO*CH*<sub>3</sub>), 2.02 (s, 3H, CO*CH*<sub>3</sub>), 2.00 (s, 3H, CO*CH*<sub>3</sub>), 1.91–1.83 (m, 3H), 1.69–1.64 (m, 1H), 1.59–1.52 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  177.4, 170.8, 170.6, 170.1, 169.5, 85.9, 75.1, 71.1, 70.0, 69.0, 62.6, 37.2, 29.6, 22.9, 22.6, 20.8, 20.7, 20.6, 20.6. HRMS calcd for C<sub>19</sub>H<sub>27</sub>NO<sub>10</sub> [M + H]<sup>+</sup> 430.1713, Found: 430.1711.

(5*S*,7*R*,8*R*,9*S*,10*R*) - 8,9,10 - Tris(benzyloxy) - 7 - (benzyloxymethyl)-2-methyl-6-oxa-1-azaspiro[4.5]dec-1-ene (40). Yield: 55%,  $R_{\rm f}$ : 0.4 (hexane–ethyl acetate, 1 : 4),  $[\alpha]_{\rm D}^{28} = +26.25$  (*c* 0.4, CH<sub>2</sub>Cl<sub>2</sub>). IR (neat)  $v_{\rm max}$ : 2918, 1595, 1413 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.35–7.17 (m, 20H, *Ar*–*H*), 4.89 (d, 1H, *J* = 10.72 Hz, Ph*CH*), 4.90–4.83 (m, 3H, 3×Ph*CH*), 4.65 (d, 1H, *J* = 11.7 Hz, Ph*CH*), 4.62–4.48 (m, 3H, 3×Ph*CH*), 4.29–4.27 (m, 1H), 4.23 (t, 1H, J = 9.2 Hz), 3.77 (t, 1H, J = 9.5 Hz), 3.71 (dd, 1H, J = 4.6, 11.0 Hz), 3.62 (m, 1H), 3.56 (d, 1H, J = 9.5 Hz), 2.53–2.45 (m, 1H), 2.42–2.33 (m, 1H), 2.07 (s, 3H, CO*CH*<sub>3</sub>), 1.89–1.78 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  179.0, 138.9, 138.8, 138.6, 138.3, 128.4–127.4 (m, *Ar*-C), 106.9, 84.6, 83.6, 79.2, 75.5, 75.5, 75.4, 74.7, 73.5, 69.1, 39.1, 33.6, 20.5. HRMS calcd for C<sub>38</sub>H<sub>41</sub>NO<sub>5</sub> [M + H]<sup>+</sup> 592.3063, Found: 592.3069.

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