Synthesis of sugar-derived spiroaminals *via* lactamization and metathesis reactions†

Adabala Pal John Pal, Parasuraman Kadigachalam, Asadulla Mallick, Venkata Ramana Doddi and Yashwant D. Vankar*

Received 9th August 2010, Accepted 12th October 2010
DOI: 10.1039/c0ob00555j

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 μM), crambescidin natural products,[1c] 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[2] have appeared for its synthesis and also a wide range of analogues.

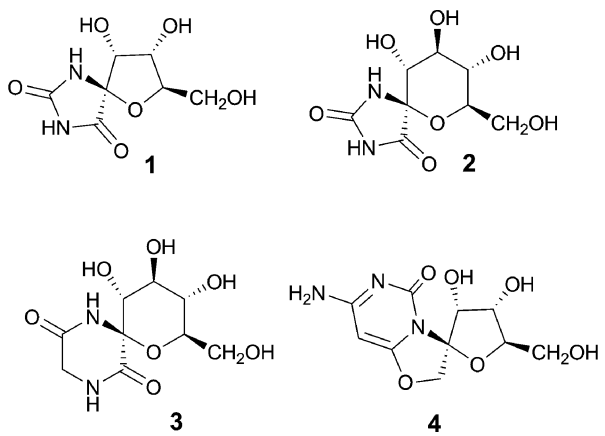


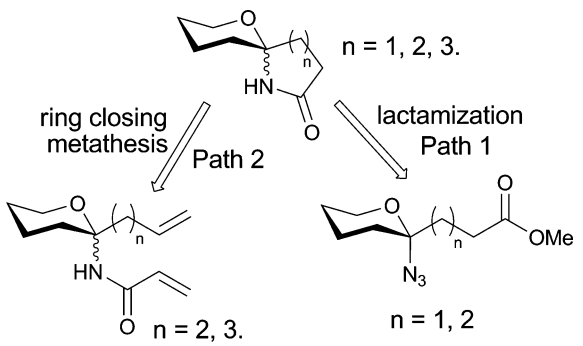
Fig. 1 Some important sugar-derived spiroaminal frameworks.

Department of Chemistry, Indian Institute of Technology, Kanpur, 208 016, India. E-mail: vankar@iitk.ac.in; Fax: +91-512-259 0007; Tel: +91-512-2597169

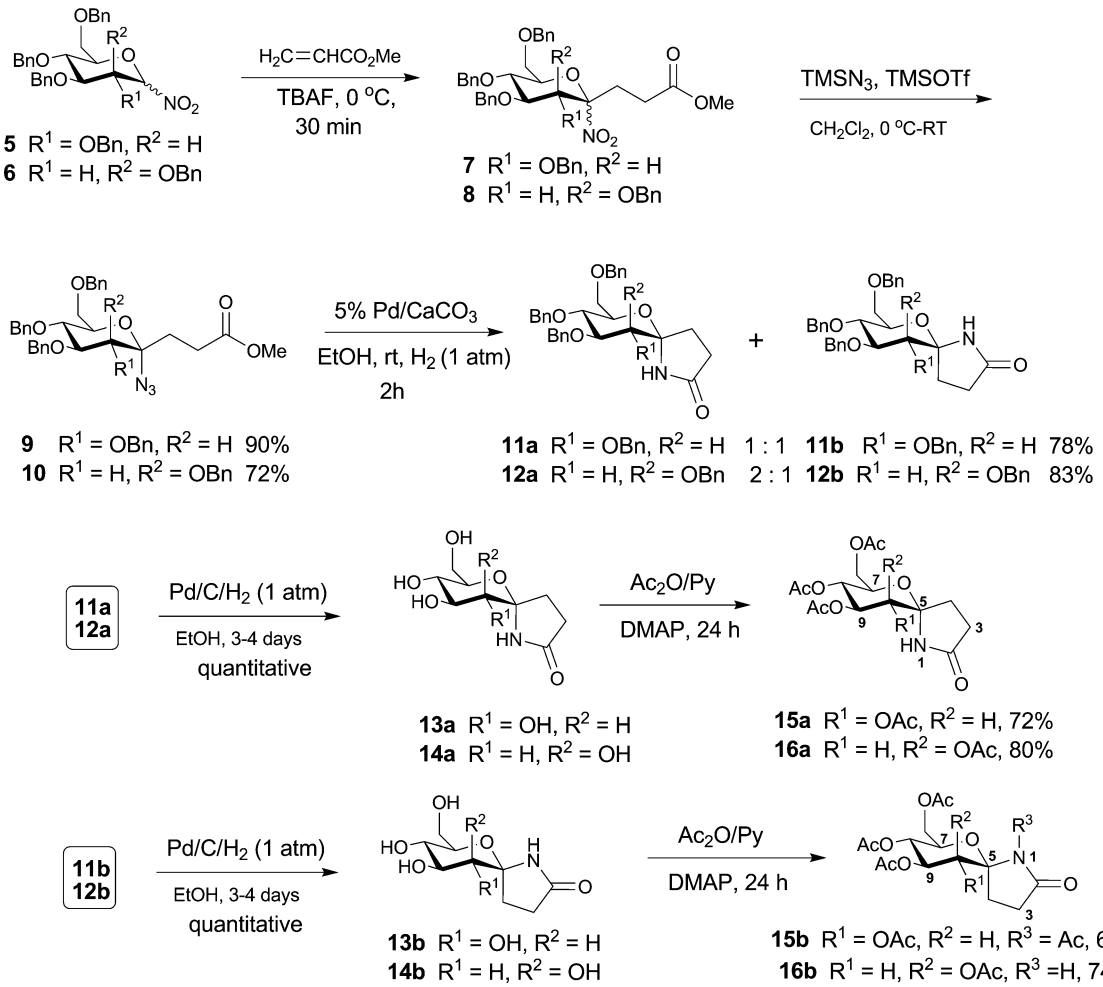
† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR spectra for all new compounds, and 2D-COSY, NOE, DEPT-135 spectra of some selected compounds. See DOI: 10.1039/c0ob00555j

The D-glucopyranose analogue of hydantocidin,[3] 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,[4] 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.*[5] and Compain *et al.*,[6] 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,[7] we reported the 6,5-fused sugar-derived 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.



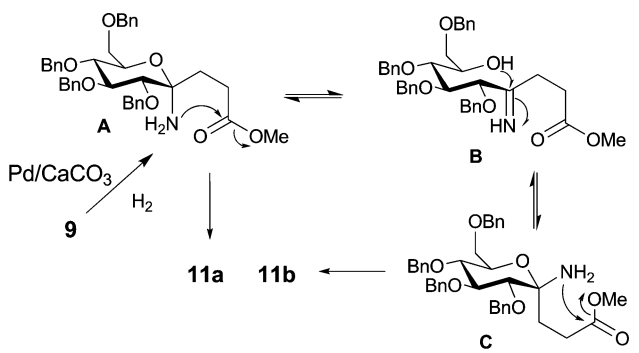
Scheme 1 Strategies used to construct the spiroaminals.



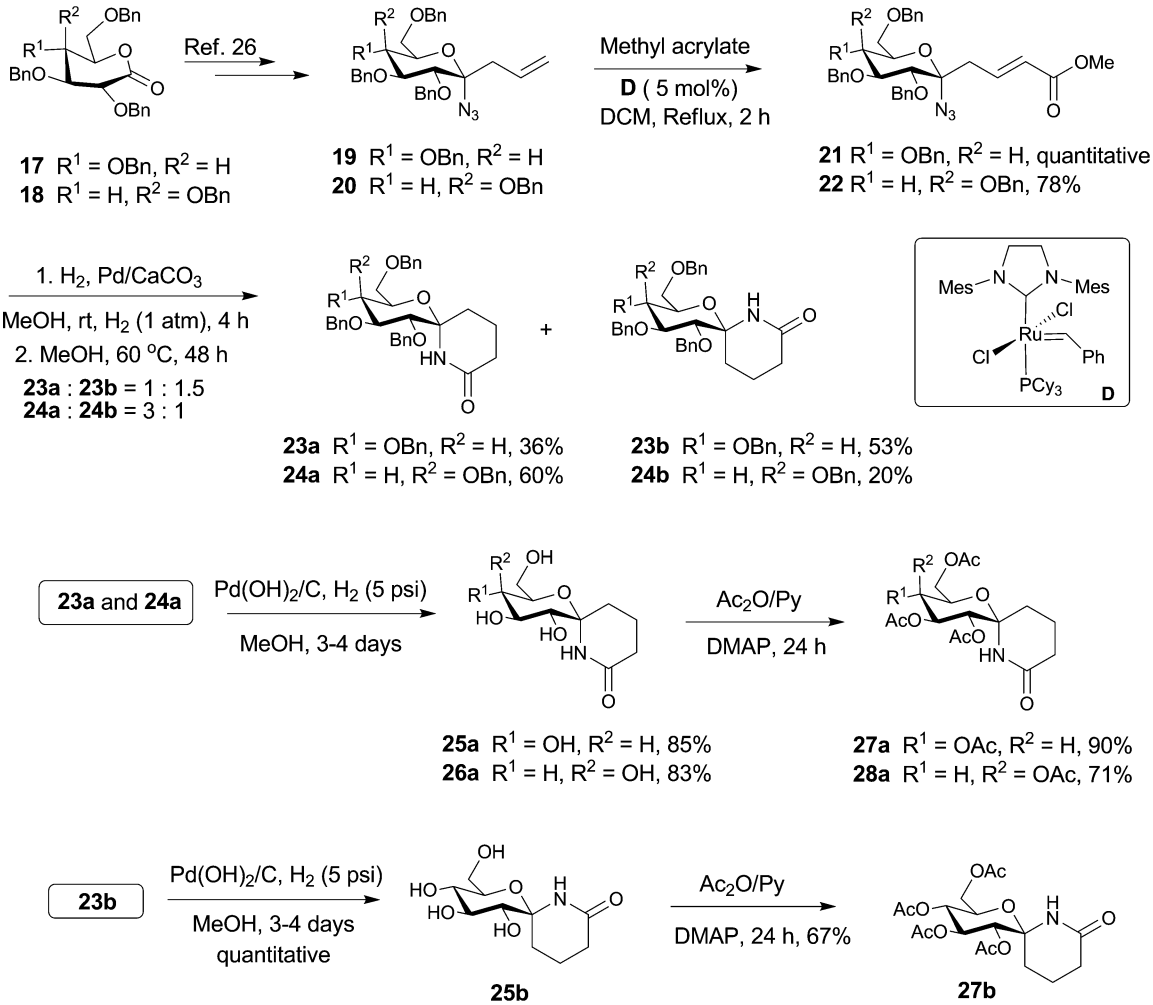
Scheme 2 Synthesis of 6,5-fused bicyclic spirolactams.

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.[7] To convert 1-*C*-alkyl-1-azido sugars into spirolactams, we studied their reductions under different conditions. There are only a few reports[9] in the literature regarding the reduction of *C*-glycosylated-1-azido sugars. Our initial attempts for the reduction of azide **9** with PPh_3 along with H_2O[10] and Zn-AcOH[9a] conditions were unsuccessful. Treatment of ester **9** with Zn-AcOH at room temperature gave a complex mixture, which is not surprising as earlier reports[9a] 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 ^{t}BuOH·H_2O, 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/$CaCO_3$ as a catalyst[11] for the reduction of such azides. Thus, the treatment of azide **9** with Pd/$CaCO_3$ 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[3a] 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, ^{1}H NMR spectra of **11a** and **11b** showed –NH protons as singlets at δ 6.94 and 5.92 and IR spectra showed



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



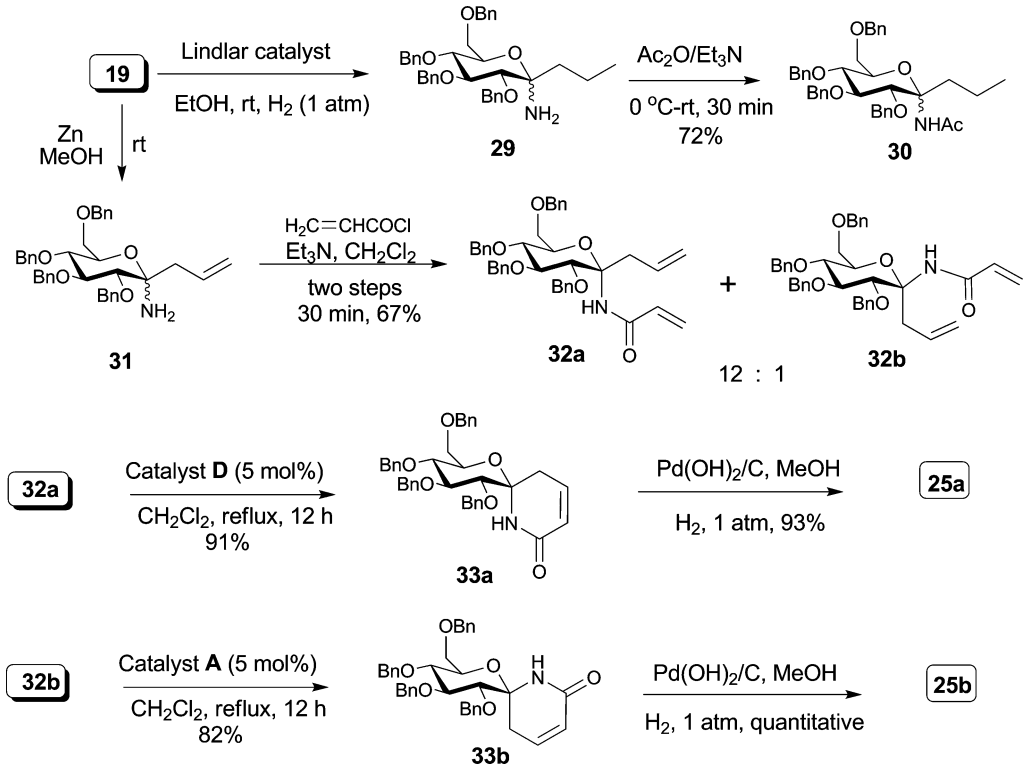
Scheme 4 Synthesis of 6,6-fused bicyclic spirolactams.

the carbonyl group frequency at 1701 and 1705 cm^{-1}, respectively. Likewise, reduction of the mannose-derived azido ester **10** in the presence of $Pd/CaCO_3$ 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_2 (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_2O/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 ^1H, ^{13}C NMR and COSY spectral data.[12]

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,[13] 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[14] 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 ^1H NMR spectrum of **21** showed olefinic protons at δ 6.94 and δ 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 $Pd/CaCO_3$ in MeOH in the presence of H_2 (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 $Pd(OH)_2$ in MeOH in the presence of an H_2 (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_2O and Py. All these compounds were characterized by ^1H, ^{13}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

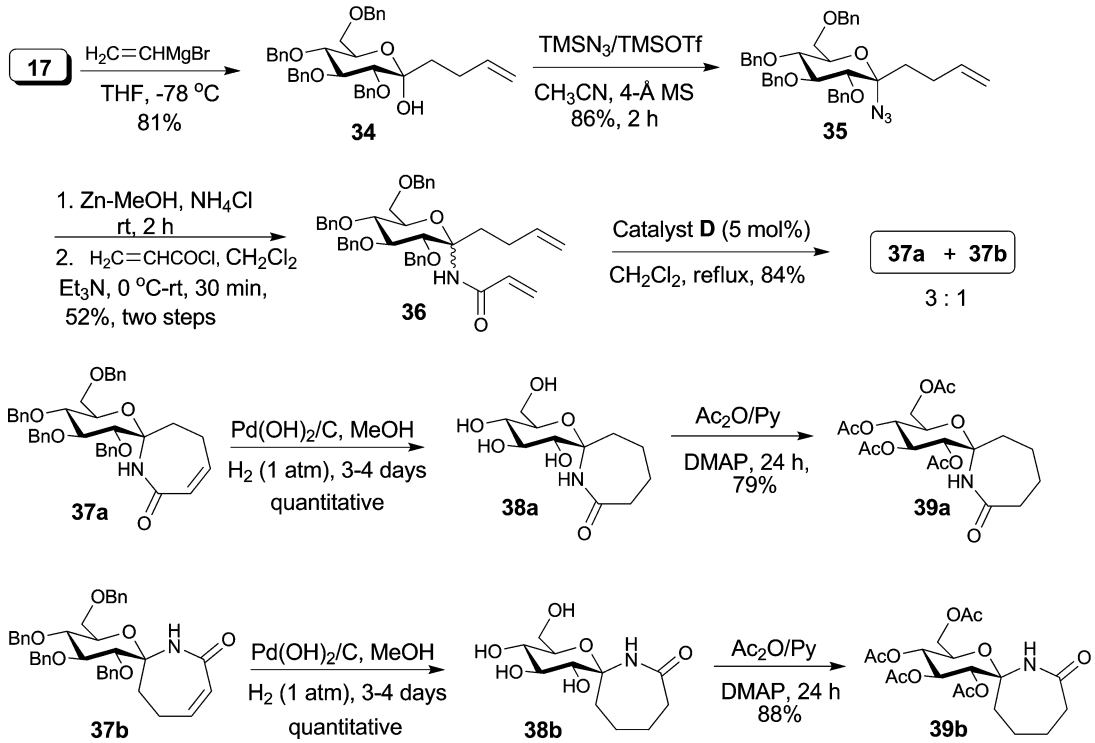


Scheme 5 Ring closing metathesis approach for the synthesis of 6,6-fused bicyclic spirolactams.

(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_4Cl.[15] The acroylation 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 ^{1}H NMR spectrum of compound **33a** showed characteristic peaks of –NH at δ 6.81 as a singlet and olefinic protons at δ 6.55–6.53 and δ 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 $Pd(OH)_2$ 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 α-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.[16] 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.

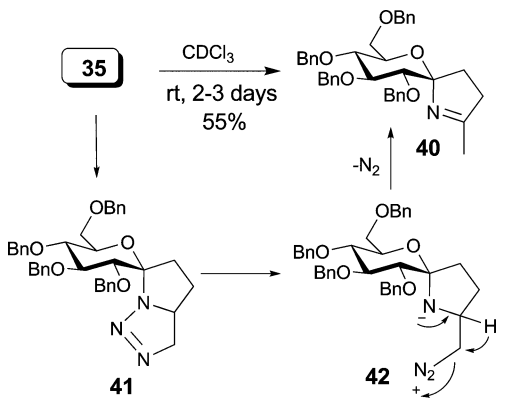
In order to construct the 7-membered aza-cycle at the anomeric center, the required key intermediate, butenyl glycosyl azide **35** was prepared from benzylated lactone **17**. Thus, addition of four equivalents of vinyl magnesium bromide onto lactone **17** produced hemiketal **34** in 81% yield.[17] The glycosylation of ketose **34** using $TMSN_3$ in presence of TMSOTf in CH_3CN 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^{-1} and the four methylene protons as multiplets at δ 2.19–1.90 in its ^{1}H NMR spectrum clearly indicating the formation of the product. The reduction of the glycosyl azide **35** with Zn in presence of NH_4Cl, 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 ^{1}H NMR spectrum of spirolactam **37b** showed the –NH proton appearing at δ 6.21 as a singlet, whereas internal olefinic protons appeared at δ 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.

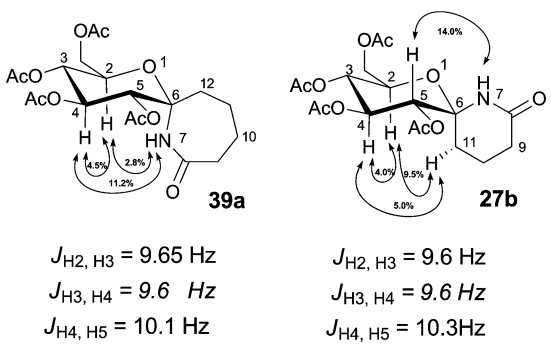
and **38b** were converted into their acetyl derivatives **39a** and **39b** using Ac_2O/Py.

During these studies it was observed that the glycosyl azidoalkene **35** was unstable and was easily converted to a new sugar-derived spiroiminal **40** (Scheme 7), even in the NMR tube in $CDCl_3$, 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[18] 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.[1a–b] The extension of this work is currently in progress.



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

The ^{1}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 $^4C_1$ chair conformation[19] of the pyranose ring in these spiroaminals (Fig. 2).[12] In case of mannose-derived spiroaminals **16a** and **16b**, the large coupling constants for $J_{7,8}$ and $J_{8,9}$ = 10.4 Hz and coupling constant between axial-equatorial protons, $J_{9,10}$ = 3.05 Hz with interproton nOe effects between H-7/H-9 clearly established the $^4C_1$ chair conformation of the pyranose ring.[12] In a similar manner, in galactose-derived



$J_{H2, H3}$ = 9.65 Hz
$J_{H3, H4}$ = 9.6 Hz
$J_{H4, H5}$ = 10.1 Hz

$J_{H2, H3}$ = 9.6 Hz
$J_{H3, H4}$ = 9.6 Hz
$J_{H4, H5}$ = 10.3Hz

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

Table 1 Spectroscopic correlations between α- and β-spirolactams

S. No	Compound	^{1}H NMR (ppm) –NH chemical shift	^{13}C NMR (ppm) 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 $^4C_1$ chair conformation of their pyranose ring.

In glucose-derived 6,7-fused spiroaminal **39a**, irradiation of the –NH proton signal at δ 6.12 enhanced the H-2 proton signal at δ 4.0 and the H-4 proton signal at δ 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 δ 6.43 enhanced only the H-5 proton signal at δ 4.97 (14.0% nOe) and irradiation of the H-2 proton signal at 3.77 enhanced the H-11 proton signal at δ 2.24 and the H-4 proton signal at δ 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†).

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 ^{13}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 δ 6.48 and the anomeric carbon peak at δ 85.9 ppm. But in the case of its anomer, *viz*. compound **23b**, the –NH proton peak appeared at δ 6.01 and the anomeric carbon peak at δ 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,[20] and there are a number of drugs currently in the market which are used in the treatment of several diseases.[21] As a result, numerous classes of sugar-mimicking glycosidase inhibitors have been developed.[22–24] As part of our ongoing programme towards the design, synthesis and biological evaluation of novel carbohydrate entities such as hybrid sugars,[25] iminosugars[26]and aminocyclitols,[27] 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.[28] However, these molecules showed poor inhibition toward all tested enzymes.[29] 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, azido-esters, were prepared from 1-nitrosugars, and the precursors for the synthesis of 6,6 and 6,7-fused spiroaminals were prepared from sugar-derived δ-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. ^{1}H and ^{13}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 $CDCl_3$ 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 obtained 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% $Pd(OH)_2/C$ (50 mg) was added to it. The reaction mixture was stirred under 1 atm or 5 psi H_2 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 $MgSO_4$, concentrated *in vacuo*, and purified by silica gel chromatography to give the pure acetylated spiro sugars.

(*E*)-Methyl4-((2*S*,3*R*,4*S*,5*R*,6*R*)-2-azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-2-yl)but-2-enoate (21). To a solution of azide **19** (100 mg, 0.163 mmol) in anhydrous CH_2Cl_2 (3 mL) under N_2 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_f: 0.4 (hexane–ethyl acetate, 9 : 1), $[\alpha]_D^{28}$ = +61.0 (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max}: 3030, 2920, 2863, 2119, 1724, 1453, 1273, 1090, 735, 697 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.19 (m, 20H, *Ar-H*), 6.94–6.88 (m, 1H, *CH*═CHCO$_2$Me), 5.83 (d, 1H, *J* = 15.8 Hz, CH═*CH*CO$_2$Me), 4.95 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.91 (d, 1H, *J* = 10.6 Hz, Ph*CH*), 4.86–4.82 (m, 2H, 2 × Ph*CH*), 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, –O*CH*$_3$), 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{39}H_{41}N_3O_7$ [M + Na]$^+$ 686.2842, Found: 686.2846.

(*E*)-Methyl4-((2*S*,3*R*,4*S*,5*S*,6*R*)-2-azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-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_f: 0.4 (hexane–ethyl acetate, 9 : 1), $[\alpha]_D^{28}$ = +59.5 (c 2.0, CH_2Cl_2). IR (neat) ν_{max}: 3088, 3063, 2920, 2867, 2118, 1724, 1659, 1605, 1435, 1273, 1101, 982, 736, 697 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.25 (m, 20H, *Ar-H*), 6.96–6.90 (m, 1H, *CH*═CHCO$_2$Me), 5.83 (d, 1H, *J* = 14.4 Hz, CH═*CH*CO$_2$Me), 4.98–4.93 (m, 2H, 2 × Ph*CH*), 4.73 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.67 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.64 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.58 (d, 1H, *J* = 11.6 Hz, Ph*CH*), 4.49–4.41 (ABq, 2H, *J* = 11.7 Hz, Ph*CH*$_2$), 4.01–3.93 (m, 3H), 3.90 (dd, 1H, *J* = 2.4, 9.6 Hz), 3.69 (s, 3H, -*OCH*$_3$), 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$_2$Me), 2.71 (ddd, 1H, *J* = 1.4, 7.5, 8.9 Hz, C(Ha*H*$_b$)═CHCO$_2$Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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/$CaCO_3$ (125 mg). The reaction mixture was stirred for 3–4 h under H_2 (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_f: 0.4 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = +40.0 (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max}: 3220, 3063, 2923, 2854, 1669, 1496, 1453, 1363, 1085, 735, 698 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{39}H_{41}N_3O_7$ [M + Na]$^+$ 686.2842, Found: 686.2840, calcd [M + H]$^+$ 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_f: 0.3 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = −12.7 (*c* 0.55, CH_2Cl_2). IR (neat) ν_{max}: 3213, 2923, 2854, 1671, 1495, 1085, 737, 689 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{38}H_{41}NO_6$ [M + H]$^+$ 608.3012, Found: 608.3019.

(2*R*,3*S*,4*S*,5*R*,6*S*)-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_f: 0.4 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = +40.7 (*c* 0.65, CH_2Cl_2). IR (neat) ν_{max}: 3230, 3063, 2924, 2854, 1662, 1496, 1495, 1454, 1396, 1082, 1026, 734, 697 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 20H, *Ar-H*), 6.51 (s, 1H, *–NH*), 4.99 (d, 1H, *J* = 11.6, Ph*CH*). 4.91 (d, 1H, *J* = 11.3 Hz, Ph*CH*), 4.72 (d, 1H, *J* = 11.6, Ph*CH*), 4.69 (d, 1H, *J* = 11.7 Hz, Ph*CH*), 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, Ph*CH*$_2$), 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*$_a$H$_b$OBn), 3.45 (dd, 1H, *J* = 5.5, 8.9 Hz, *CH*$_a$*H*$_b$OBn), 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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_f: 0.3 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = −8.67 (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max}: 3224, 3062, 2923, 2854, 1671, 1453, 1366, 1087, 1025, 734, 697 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 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*$_a$H$_b$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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{38}H_{41}NO_6$ $[M + H]^+$ 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). ^{1}H NMR (500 MHz, D_2O): δ 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). ^{13}C NMR (125 MHz, D_2O): δ 178.0, 86.0, 74.4, 72.7, 72.5, 69.8, 60.7, 30.8, 30.4, 14.9. HRMS calcd for $C_{10}H_{17}NO_6$ $[M + Na]^+$ 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, $[\alpha]_D^{28}$ = +6.8 (*c* 1.35, MeOH). ^{1}H NMR (500 MHz, D_2O): 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). ^{13}C NMR (125 MHz, D_2O): δ 177.4, 87.6, 74.9, 73.1, 69.7, 60.9, 30.5, 20.8, 14.5. HRMS calcd for $C_{10}H_{17}NO_6$ $[M + Na]^+$ 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). ^{1}H NMR (500 MHz, D_2O): δ 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). ^{13}C NMR (125 MHz, D_2O): δ 178.1, 86.4, 71.7, 71.4, 69.0, 68.9, 61.3, 30.8, 30.4, 14.9. HRMS calcd for $C_{10}H_{17}NO_6$ $[M + Na]^+$ 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), $[\alpha]_D^{28}$ = +38.0 (*c* 0.5, CH_2Cl_2). IR (neat) ν_{max}: 3332, 2923, 2853, 1748, 1673, 1369, 1221, 1033, 901 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 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_aH_bOAc), 4.05 (dd, 1H, J = 2.0, 12.3 Hz, CH_aH_bOAc), 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, COCH_3), 2.05(s, 3H, COCH_3), 2.01 (s, 3H, COCH_3), 1.99 (s, 3H, COCH_3) 1.91–1.89 (m, 1H), 1.77–1.73 (m, 1H), 1.67–1.40 (m, 1H). ^{13}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 $C_{18}H_{25}NO_{10}$ $[M + Na]^+$ 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_f: 0.30 (hexane–ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = − 27.5 (*c* 0.4, CH_2Cl_2). IR (neat) ν_{max}: 2953, 1752, 1682, 1370, 1225, 1036, 822 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 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_aH_bOAc), 4.09 (dd, 1H, J = 2.7, 12.4 Hz, CH_aH_bOAc), 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_3), 2.04 (s, 3H, COCH_3), 2.01 (s, 3H, COCH_3), 1.98 (s, 3H, COCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{18}H_{25}NO_{10}$ $[M + H]^+$ 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_f: 0.40 (hexane–ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = +72.7 (*c* 0.55, CH_2Cl_2). IR (neat) ν_{max}: 3331, 2924, 2853, 1750, 1672, 1436, 1372, 1226, 1129, 1078 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 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, COCH_3), 2.07(s, 3H, COCH_3), 2.02 (s, 3H, COCH_3), 1.97 (s, 3H, COCH_3), 1.97–1.94 (m, 1H), 1.75–1.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{18}H_{25}NO_{10}$ $[M + H]^+$ 416.1557, Found: 416.1551.

***N*-((3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-propyltetrahydro-2*H*-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_3N, 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) ν_{max}: 3328, 2924, 1672, 1538, 1372, 1496 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): 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_3, major), 1.92–1.85 (m, 1H, minor), 1.77 (s, 3H, COCH_3, 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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*-((2*S*,3*R*,4*S*,5*R*,6*R*)-2-Allyl-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)acrylamide (32a).** To a solution of azide **19** (300 mg, 0.495 mmol) in methanol (20 ml) was added NH_4Cl (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 × 30 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_2Cl_2 (4.0 mL) at 0 °C was added dropwise Et_3N (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_2Cl_2). IR (neat) ν_{max}: 3405, 2921, 1672, 1615, 1497, 1453 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): 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_2), 5.98–5.88 (m, 1H, –*CH*=CH_2), 5.62 (d, 1H, *J* = 9.9 Hz, –CH=CH_aH_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, Ph*CH*), 4.88 (d, 1H, *J* = 10.7 Hz, Ph*CH*), 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 × Ph*CH*), 4.66 (d, 1H, *J* = 10.3 Hz, Ph*CH*), 4.56 (d, 1H, *J* = 11.5 Hz, Ph*CH*), 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_aH_bCH=CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 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_f: 0.40 (hexane–ethyl acetate, 7 : 3), $[\alpha]_D^{28}$ = –4.17 (*c* 0.6, CH_2Cl_2). IR (neat) ν_{max}: 3405, 2924, 1728, 1694, 1453 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.17 (m, 20H, *Ar–H*), 6.18 (d, 1H, *J* = 16.9 Hz, –CH=CH_aH_b), 6.08 (s, 1H, –*NH*), 5.92–5.83 (m, 2H, 2 × *CH*=CH_2), 5.55 (d, 1H, *J* = 10.5 Hz, –CH=CH_aH_b), 5.26–5.24 (m, 1H, –CH=CH_aH_b), 5.23 (d, 1H, *J* = 11.0 Hz, –CH=CH_aH_b), 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_2CH=CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{40}H_{43}NO_6$ $[M + H]^+$ 634.3169, Found: 634.3169.

(2*R*,3*R*,4*S*,5*R*,6*S*)-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_2Cl_2 (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_f: 0.40 (hexane–ethyl acetate, 1 : 1), $[\alpha]_D^{28}$ = +74.61 (*c* 0.65, CH_2Cl_2). IR (neat) ν_{max}: 3241, 2921, 2852, 1678, 1614, 1453, 1414 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 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, Ph*CH*), 4.81 (d, 1H, *J* = 11.1 Hz, Ph*CH*), 4.69 (d, 1H, *J* = 11.8 Hz, Ph*CH*), 4.58 (d, 2H, *J* = 11.4 Hz, 2 × Ph*CH*), 4.44 (d, 1H, *J* = 12.2 Hz, Ph*CH*), 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_aH_bOBn, *H-2*), 3.56 (d, 1H, *J* = 10.3 Hz, CH_aH_bOBn), 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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.

2*R*,3*R*,4*S*,5*R*,6*R*)-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_2Cl_2). IR (neat) ν_{max}: 3442, 2956, 1687, 1618, 1464, 1363 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.14 (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, Ph*CH*), 4.57 (d, 1H, *J* = 12.2 Hz, Ph*CH*), 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_aH_bOBn, *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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{38}H_{39}NO_6$ $[M + H]^+$ 606.2856, Found: 606.2855.

(2*S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)tetrahydro-2*H*-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_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give the corresponding hemiketal **34**. Yield: 82% (1.8 g). R_f: 0.5 (hexane–ethyl acetate, 4 : 1), $[\alpha]_D^{28}$ = +22.94 (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max}: 3440, 3063, 3030, 2923, 2863, 1640, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 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 × Ph*CH*), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{38}H_{42}O_6$ $[M + NH_4]^+$ 612.3325, Found: 612.3325.

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-Azido-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)tetrahydro-2*H*-pyran (35). The hemiketal **34** (1.2 g, 2.02 mmol) was dissolved in CH_2Cl_2 (15.0 mL) and treated with activated 4 Å powdered molecular sieves (500 mg). To this reaction mixture, $TMSN_3$ (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_3N, diluted with CH_2Cl_2, filtered through Celite, and concentrated. Column chromatography of this residue afforded the desired azide **35**. Yield: 86% (1.1 g). R_f: 0.50 (hexane–ethyl acetate, 9 : 1), $[\alpha]_D^{28}$ = +68.46 (*c* 0.65, CH_2Cl_2). IR (neat) ν_{max}: 2922, 2118, 1642, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.19 (m, 20H, *Ar-H*), 5.77–5.70 (m, 1H, –*CH*=CH_2), 4.98 (d, 1H, *J* = 15.8 Hz, –CH=CH_aH_b), 4.94–4.84 (m, 4H, –CH=CH_aH_b 3 × 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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_4]$^+$ 637.3390, Found: 637.3393.

***N*-((3*R*,4*S*,5*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)tetrahydro-2*H*-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_f: 0.4 (hexane–ethyl acetate, 7 : 3), $[\alpha]_D^{28}$ = +40.75 (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max}: 3411, 2924, 1737, 1463 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.17 (m, 20H, *Ar-H*), 6.23 (d, 1H, *J* = 16.8 Hz, –CH=C*H*$_a$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$_a$*H*$_b$), 4.98–4.90 (m, 4H, *J* = 9.9 Hz, –CH=*CH*$_2$, 2 × Ph*CH*), 4.84 (d, 1H, *J* = 10.0 Hz, Ph*CH*), 4.77 (d, 1H, *J* = 10.7 Hz, Ph*CH*), 4.73–4.70 (m, 2H, 2 × Ph*CH*), 4.66 (d, 1H, *J* = 10.3 Hz, Ph*CH*), 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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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.

(2*R*,3*R*,4*S*,5*R*,6*S*)-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_2Cl_2 (2.0 mL) at room temperature was added the Grubbs' second generation catalyst (5 mol%, 7.2 mg). The mixture was refluxed in CH_2Cl_2 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_f: 0.25 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = +29.41 (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max}: 3250, 2920, 1669, 1619, 1453 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.18 (m, 20H, *Ar-H*), 6.41 (s, 1H, –*NH*), 6.25 (dt, 1H, *J* = 3.7, 12.7 Hz, –CH=*CH*–CH$_2$), 5.84 (d, 1H, *J* = 12.4 Hz, –*CH*=CHCH$_2$), 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 × Ph*CH*), 4.73 (d, 1H, *J* = 11.2 Hz, Ph*CH*), 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, Ph*CH*), 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). ^{13}C NMR (125 MHz, $CDCl_3$): 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_f: 0.2 (hexane–ethyl acetate, 3 : 2), $[\alpha]_D^{28}$ = +5.0 (*c* 0.0.4, CH_2Cl_2). IR (neat) ν_{max}: 3397, 2924, 1669, 1618, 1453 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.15 (m, 20H, *Ar-H*), 6.36–6.33 (m, 1H, CH=*CH*–CH$_2$), 6.21 (s, 1H, –*NH*), 5.92 (d, 1H, *J* = 12.2 Hz, –*CH*=CH–CH$_2$), 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*$_a$H$_b$OBn), 3.60–3.57 (m, 2H, *H-2*, *H-3*), 3.52 (dd, 1H, *J* = 4.2, 13.7 Hz, CH$_a$*H*$_b$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). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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, $[\alpha]_D^{28}$ = +39.09 (*c* 0.55, MeOH). ^{1}H NMR (500 MHz, D_2O): 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). ^{13}C NMR (125 MHz, D_2O): 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 $C_{11}H_{19}NO_6$ [M + H]$^+$ 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, $[\alpha]_D^{28}$ = −3.33 (*c* 0.45, MeOH). ^{1}H NMR (500 MHz, D_2O): δ 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 ^{13}C NMR MHz, D_2O): δ 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 $C_{11}H_{19}NO_6$ [M + H]$^+$ 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_f: 0.35 (hexane–ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = +66.0 (*c* 0.75, CH_2Cl_2). IR (neat) ν_{max}: 3386, 2926, 1755, 1673, 1434, 1368 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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*$_a$H$_b$OAc), 4.15 (dd, 1H, *J* = 2.3, 12.4 Hz, CH$_a$*H*$_b$OAc), 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, CO*CH*$_3$), 2.06 (s, 3H, CO*CH*$_3$), 2.02 (s, 3H, CO*CH*$_3$), 1.97 (s, 3H, CO*CH*$_3$), 1.97–1.94 (m, 1H), 1.87–1.83 (m, 1H), 1.75–1.68 (m, 2H), 1.54–1.45 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{19}H_{27}NO_{10}$ [M + H]$^+$ 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_f: 0.35 (hexane–ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = +15.0 (*c* 0.3, CH_2Cl_2). IR (neat) ν_{max}: 3368, 2922, 1738, 1662, 1459, 1381 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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*$_2$OAc), 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*$_3$), 2.08 (s, 3H, CO*CH*$_3$), 2.02 (s, 3H, CO*CH*$_3$), 2.00 (s, 3H, CO*CH*$_3$), 1.91–1.83 (m, 3H), 1.69–1.64 (m, 1H), 1.59–1.52 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{19}H_{27}NO_{10}$ [M + H]$^+$ 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_f: 0.4 (hexane–ethyl acetate, 1 : 4), $[\alpha]_D^{28}$ = +26.25 (*c* 0.4, CH_2Cl_2). IR (neat) ν_{max}: 2918, 1595, 1413 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 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×PhC*H*), 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, COCH_3), 1.89–1.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{38}H_{41}NO_5$ $[M + H]^+$ 592.3063, Found: 592.3069.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi for financial support [Grant No. 01(2298)/09/EMR-II]. A.P.J.P. thanks the University Grant Commission, New Delhi, for a Senior Research Fellowship and A.M. thanks the CSIR, New Delhi, for a Junior Research Fellowship.

Notes and references

1 (*a*) C. Boonlarppradab, C. A. Kauffman, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 5505–5508; (*b*) X.-C. Cai, X. Wu and B. B. Snider, *Org. Lett.*, 2010, **12**, 1600–1603; (*c*) L. E. Overman and Y. H. Rhee, *J. Am. Chem. Soc.*, 2005, **127**, 15652–15658; (*d*) R. M. Karmer, B. Johansen, C. Hession and R. B. Pepinsky, *Adv. Exp. Med. Biol.*, 1990, **275**, 35–53; (*e*) M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke and T. Yasumoto, *J. Am. Chem. Soc.*, 1998, **120**, 9967–9968; (*f*) J.-J. Sanglier, V. Quesniaux, T. Fehr, H. Hofmann, M. Mahnke, K. Memmert, W. Schuler, G. Zenke, L. Gschwind, C. Mauer and W. Schilling, *J. Antibiot.*, 1999, **52**, 466–473; (*g*) M. E. Sinibaldi and I. Canet, *Eur. J. Org. Chem.*, 2008, 4391–4399.

2 (*a*) S. Moi, R. Inchinose, K. Goto and S. Sugai, *Tetrahedron*, 1991, **47**, 2111–2120; (*b*) H. Sano and S. Sugai, *Tetrahedron*, 1995, **51**, 4635–4646; (*c*) S. Hanessian, J. Y. Sanceau and P. Chemla, *Tetrahedron*, 1995, **51**, 6669–6678.

3 (*a*) C. J. F. Bichard, E. P. Mitchell, M. R. Wormald, K. A. Watson, L. N. Johnson, S. E. Zographos, D. D. Koutra, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 2145–2148; (*b*) C. de la Fuente, T. M. Krülle, K. A. Watson, M. Gregoriou, L. N. Johnson, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos and G. W. J. Fleet, *Synlett*, 1997, 485–487.

4 (*a*) T. Gimisis, C. Castellari and C. Chatgilialoglu, *Chem. Commun.*, 1997, 2089–2090; (*b*) C. Chatgilialoglu, T. Gimisis and G. P. Spada, *Chem.–Eur. J.*, 1999, **5**, 2866–2876.

5 (*a*) A. Martin, I. Perez-Martin and E. Suarez, *Org. Lett.*, 2005, **7**, 2027–2030; (*b*) R. Freire, A. Martin, I. Perez-Martin and E. Suarez, *Tetrahedron Lett.*, 2002, **43**, 5113–5116.

6 S. Toumieux, P. Compain and O. R. Martin, *Tetrahedron Lett.*, 2005, **46**, 4731–4735.

7 A. P. John Pal and Y. D. Vankar, *Tetrahedron Lett.*, 2010, **51**, 2519–2524.

8 L. Somsak, *Chem. Rev.*, 2001, **101**, 81–135 (In this review, see the references regarding 1-nitro sugars chemistry).

9 (*a*) K. Czifrak, P. Szilagyi and L. Somsak, *Tetrahedron: Asymmetry*, 2005, **16**, 127–141; (*b*) K. Czifrak, L. Kovacs, K. E. Kover and L. Somsak, *Carbohydr. Res.*, 2005, **340**, 2328–2334; (*c*) L. Somsak, K. Czifrak and E. Veres, *Tetrahedron Lett.*, 2004, **45**, 9095–9097; (*d*) A. Dondoni, M. C. Scherrmann, A. Marra and J. L. Delepine, *J. Org. Chem.*, 1994, **59**, 7517–7520.

10 B. Gopal Reddy, K. P. Madhusudanan and Y. D. Vankar, *J. Org. Chem.*, 2004, **69**, 2630–2633.

11 (*a*) T. Suzuki, S. T. Suzuki, I. Yamada, Y. Kaoshi, K. Yamada and N. Chida, *J. Org. Chem.*, 2002, **67**, 2874–2880; (*b*) A. Aravind, M. G. Sankar, B. Varghese and S. Baskaran, *J. Org. Chem.*, 2009, **74**, 2858–2861.

12 For the spectral copies and data of 6,5-fused spiroaminals, see the supporting information of ref. 7.

13 (*a*) M. D. Lewis, J. K. Cha and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976–4978; (*b*) Y. Oda and T. Yamanoi, *Synthesis*, 2007, 3021–3031.

14 (*a*) A. K. Chatterjee, T. L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370; (*b*) G. Godin, P. Compain and O. R. Martin, *Org. Lett.*, 2003, **5**, 3269–3272.

15 A. N. Rai and A. Basu, *Org. Lett.*, 2004, **6**, 2861–2863.

16 (*a*) C. J. O'Donnell, R. A. Singer, J. D. Brubaker and J. D. McKinley, *J. Org. Chem.*, 2004, **69**, 5756–5759; (*b*) D. M. Floyd, R. V. Moquin, K. S. Atwal, S. Z. Ahmed, S. H. Spergel, J. Z. Gougoutas and M. F. Malley, *J. Org. Chem.*, 1990, **55**, 5572–5579.

17 (*a*) J. Xie, F. Durrat and J.-M. Valeary, *J. Org. Chem.*, 2003, **68**, 7896–7898; (*b*) L. Cipolla and F. Nicotra, *Tetrahedron*, 1997, **53**, 6163–6170.

18 (*a*) A. Hassner, A. S. Amarasekara and D. Andisik, *J. Org. Chem.*, 1988, **53**, 27–30; (*b*) Y. Zhou and P. V. Murphy, *Org. Lett.*, 2008, **10**, 3777–3780.

19 K. Zhang and F. Schweizer, *Synlett*, 2005, 3111–3115.

20 For some excellent accounts on glycosidases and their inhibitors, see: (*a*) B. G. Davis, *Tetrahedron: Asymmetry*, 2009, **20**, 652–671; (*b*) P. Compain, V. Chagnault and O. R. Martin, *Tetrahedron: Asymmetry*, 2009, **20**, 672–711; (*c*) V. H. Lillelund, H. H. Jensen, X. Liang and M. Bols, *Chem. Rev.*, 2002, **102**, 515–553; (*d*) K. Afarinkia and A. Bahar, *Tetrahedron: Asymmetry*, 2005, **16**, 1239–1287; (*e*) D. L. Zechel and S. G. Withers, *Acc. Chem. Res.*, 2000, **33**, 11–18; (*f*) T. D. Heightman and A. T. Vasella, *Angew. Chem., Int. Ed.*, 1999, **38**, 750–770; (*g*) G. M. Gloster and G. J. Davies, *Org. Biomol. Chem.*, 2010, **8**, 305–320; (*h*) Y. Ichikawa, Y. Igarashi, M. Ichikawa and Y. Suhara, *J. Am. Chem. Soc.*, 1998, **120**, 3007–3018.

21 (*a*) B. G. Winchester, *Tetrahedron: Asymmetry*, 2009, **20**, 645–651; (*b*) D. Sailer and G. Roder, *Arzneimittelforschung*, 1980, **30**, 2182–2185; (*c*) N. Katsilambros, P. Philippides, T. Toskas, J. Protopapas, D. Frangaki, M. Marangos, P. Siskoudis, K. Anastasopoulou, H. Xefteri and I. Hillebrand, *Arzneimittelforschung*, 1986, **36**, 1136–1138; (*d*) F. G. Hayden, J. J. Treanor, R. F. Betts, M. Lobo, J. D. Esinhart and E. K. Hussey, *JAMA, J. Am. Med. Assoc.*, 1996, **275**, 295–299; (*e*) C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.*, 1997, **119**, 681–690.

22 A. E. Stuetz, *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*, Wiley-VCH, Weinheim, Germany, 1999 and see ref. 6a–d.

23 H. Yuasa, M. Izumi and H. Hashimoto, *Curr. Top. Med. Chem.*, 2009, **9**, 76–86.

24 A. Berecibar, C. Grandjean and A. Siriwardena, *Chem. Rev.*, 1999, **99**, 779–844.

25 (*a*) B. Gopal Reddy and Y. D. Vankar, *Angew. Chem., Int. Ed.*, 2005, **44**, 2001–2004; (*b*) K. Jayakanthan and Y. D. Vankar, *Tetrahedron Lett.*, 2006, **47**, 8667–8671; (*c*) V. R. Doddi, H. P. Kokatla, A. P. John Pal, R. K. Basak and Y. D. Vankar, *Eur. J. Org. Chem.*, 2008, 5731–5739; (*d*) A. Kumar, G. K. Rawal and Y. D. Vankar, *Tetrahedron*, 2008, **64**, 2379–2390.

26 (*a*) V. R Doddi and Y. D. Vankar, *Eur. J. Org. Chem.*, 2007, 5583–5589; (*b*) M. A. Alam, A. Kumar and Y. D. Vankar, *Eur. J. Org. Chem.*, 2008, 4972–4980; (*c*) M. A. Alam and Y. D. Vankar, *Tetrahedron Lett.*, 2008, **49**, 5534–5536; (*d*) P. Gupta and Y. D. Vankar, *Eur. J. Org. Chem.*, 2009, 1925–1933; (*e*) N. Kumari, B. G. Reddy and Y. D. Vankar, *Eur. J. Org. Chem.*, 2009, 160–169; (*f*) A. Kumar, M. A. Alam, S. Rani and Y. D. Vankar, *Carbohydr. Res.*, 2010, **345**, 1142–1148.

27 (*a*) K. Jayakanthan and Y. D. Vankar, *Org. Lett.*, 2005, **7**, 5441–5444; (*b*) Y. S. Reddy, P. Kadigachalam, V. R. Doddi and Y. D. Vankar, *Tetrahedron Lett.*, 2009, **50**, 5827–5830; (*c*) V. R. Doddi, A. Kumar and Y. D. Vankar, *Tetrahedron*, 2008, **64**, 9117–9122.

28 We have used α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (coffee beans), β-galactosidase (bovine) and α-mannosidase (jack beans) enzymes for enzyme inhibition studies.

29 Y.-T. Li, S.-C. Li, *Methods in Enzymology*, ed. V. Ginsberg, Academic Press, 1972, pp. 702.