

Synthesis of Pyrrolidine-Based Imino Sugars as Glycosidase Inhibitors

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Two pyrrolidine-based imino sugars have been synthesized in an efficient manner, using regiospecific amination, ring closing metathesis, and diastereospecific dihydroxylations as key steps. These azasugars are found to be moderate inhibitors of glycosidases.

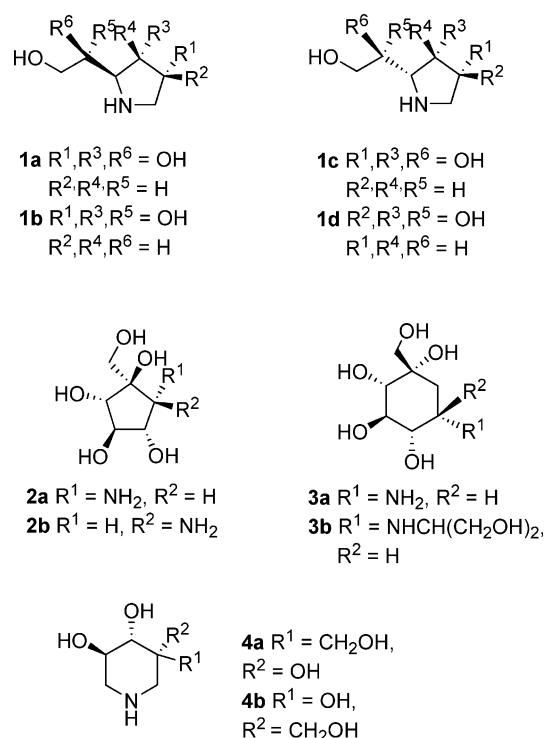
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Introduction

Biosynthesis of oligosaccharides and glycoconjugates is controlled by glycosidases and glycosyltransferases.^[1] These oligosaccharides and glycoconjugates play a major role in various cellular functions such as cell adhesion, cell-cell differentiation, metastasis and other metabolic disorders and diseases. Therefore, development of inhibitors of such enzymes is of immense importance, and as a result there has been explosive growth in the design, synthesis and biological evaluation of new glycosidase inhibitors.^[2]

Among many glycosidase inhibitors, polyhydroxylated nitrogen-containing heterocycles have been the subject of immense interest in recent years.^[3] Some of them such as *N*-hydroxyethyl-1-deoxynojirimycin (miglitol) and *N*-butyl-1-deoxynojirimycin are already marketed against type II diabetes and Gaucher's disease, respectively. Besides these, many other polyhydroxylated five- and six-membered, and bicyclic aza heterocycles and their analogs are potent glycosidase inhibitors. In addition to the use of such inhibitors as potential drugs for the treatment of viral infections, cancer, HIV-AIDS, diabetes, Gaucher's disease and other metabolic disorders,^[4,2b] analysis of their structures vis-à-vis the associated biological activities may provide new mechanistic insight into the glycoside cleavage and formation processes. Many of these glycosidase inhibitors have therefore been designed^[2] to mimic the shape, configuration and charge distribution of the cation liberated during the enzyme-catalyzed processes.

Among the pyrrolidine-based azasugars,^[5] 1,4-dideoxy-1,4-iminoheptitols, **1a**, **1b**, **1c**, **1d** (Figure 1) are more potent glycosidase inhibitors^[6,7] and the biological activity varies depending on substitution patterns of the hydroxy groups. Thus, while compounds **1a**,^[8a] **1b**^[8b,8c] and **1c**^[8d,8e] are inhibitors of α -mannosidases, a stereochemical analog **1d**^[8f] acts as a potent inhibitor of α -galactosidases. One of the characteristic features that these molecules possess is the presence of 1,2-dihydroxyethyl side chain. Likewise, some of the potent glycosidase inhibitors such as trehalosamine **2a**,^[9] 1-epitrehalosamine **2b**,^[9] valiolamine **3a**,^[10] voglibose



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Figure 1. Some of the important glycosidase inhibitors.

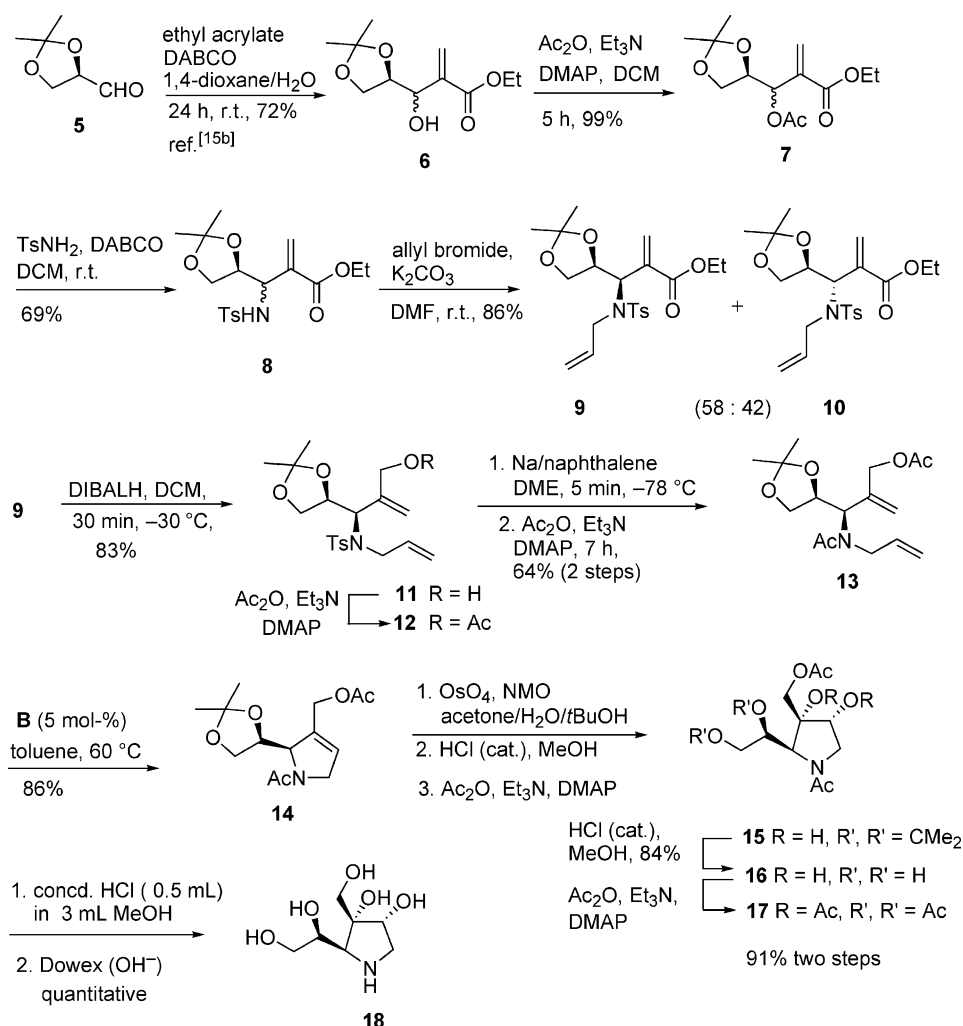
3b^[11] (3*S*,4*R*,5*S*)-3,4,5-trihydroxy-5-(hydroxymethyl)piperidine **4a**^[12a,12b] and its enantiomer,^[12c] (3*S*,4*R*,5*R*)-3,4,5-trihydroxy-5-(hydroxymethyl)piperidine **4b**^[12a] and its enantiomer^[12d] (Figure 1) contain quaternary carbons bearing a hydroxy and a hydroxymethyl group^[12e] as key features.

Results and Discussions

As part of on going research project in our laboratory towards the synthesis of natural and unnatural azasugars and hybrid sugars,^[13] we became interested in synthesizing new pyrrolidine-based azasugars with combined structural features as pointed above viz. having 1,2-dihydroxyethyl side chains and a quaternary C atom holding a hydroxy and a hydroxymethyl group. This was perceived from the point of view in finding out if these combined features make any difference in selective and/or improved inhibition. Thus, we wish to report the synthesis of two new polyhydroxylated azasugars **18** and **26**. The key steps in their synthesis in-

volved the use of the Baylis–Hillman adduct **6**, obtained from the aldehyde **5** as a masked diol, and ring closing metathesis to form the key five-membered ring core.

Accordingly, the Baylis–Hillman reaction of (*R*)-2,3-*O*-isopropylidene-glyceraldehyde (**5**)^[14] (Scheme 1) with ethyl acrylate in the presence of DABCO gave **6** as a mixture of two diastereomers^[15] which was acetylated to obtain a mixture of diastereomeric acetates **7**. Treatment of **7** with *p*-toluenesulfonamide and DABCO underwent successive S_N2'–S_N2' displacement reactions regioselectively to give the amine **8** whose treatment with allyl bromide yielded two chromatographically separable dienes **9** and **10** in 58:42 ratio in 86% yield. Separation of the dienes by column chromatography led to the isolation of the more polar compound **9** as a crystalline solid and subsequent recrystallization from CH₂Cl₂ and hexane (1:9) at 0 °C followed by X-ray analysis permitted its structural characterization.^[16] Based on the structure of **9**, the other diastereomer was assigned structure **10**. Reduction of the unsaturated ester **9**



Scheme 1. Synthesis of imino sugar **18**.

with DIBAL-H at $-30\text{ }^{\circ}\text{C}$ gave the primary alcohol **11** in 76% yield which was characterized as its acetate **12**. Alcohol **11** was subjected to desotylation with sodium naphthalenide solution in DME^[17] followed by acetylation to form the diacetate **13**.

Initially the diacetate **13** was treated with catalytic amount of Grubbs' first-generation ruthenium complex **A**,^[16] but no reaction was observed even not in refluxing toluene. On the other hand, treatment of diene **13** with the more reactive second-generation Grubbs' catalyst **B**^[16] (5 mol-%) in toluene at $60\text{ }^{\circ}\text{C}$ for 3 h gave one single product **14** in 89% yield. Dihydroxylation of **14** was performed by using a catalytic amount of OsO_4 in the presence of NMO which afforded exclusively one diastereomeric diol **15**. It appears that the bulky acetonide group blocks the β -face of the trisubstituted double bond of the pyrrolidine ring and is responsible for high diastereoselectivity. Subsequent cleavage of the acetonide group gave the tetrahydroxy compound **16** which was subjected to acetylation affording hexaacetate **17**. Treatment of this hexaacetate with 6 N HCl followed by treatment with basic Dowex gave the expected product **18** in quantitative yield.

Likewise, the diastereomer **26** was synthesized from the diene **10** similar to the synthesis of compound **18** (from compound **9**) using the same synthetic sequence and reaction conditions as shown in Scheme 2. Since the stereocenters at C-2 and C-7 of compound **18** were already established by the X-ray crystal structure of compound **9**, the overall stereochemistry of both **18** and **26** was confirmed from the COSY and NOE (Figure 2) experimental data^[16] of the corresponding pentaacetates viz. **17** and **25**, respectively. Thus, the NOE correlation between H-4 and H-5 of

compound **17** revealed that they are in *cis* relationship. Likewise, protons H-7 and H-6 and H-5 were also found to be *cis* to each other which indicated that the carbon side chains are *cis* to each other and oriented in β -fashion whereas the acetoxy groups at C-3 and C-4 are α -oriented. This obviously confirms that the dihydroxylation had taken place on the face opposite to the acetonide moiety. In a similar fashion, the structure of compound **25** was established for which the NOE correlations are shown in Figure 2.

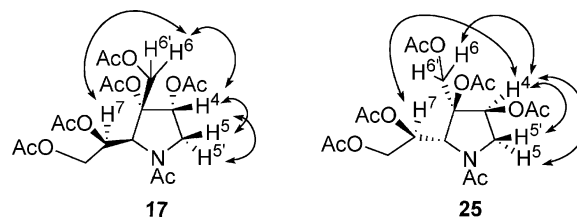
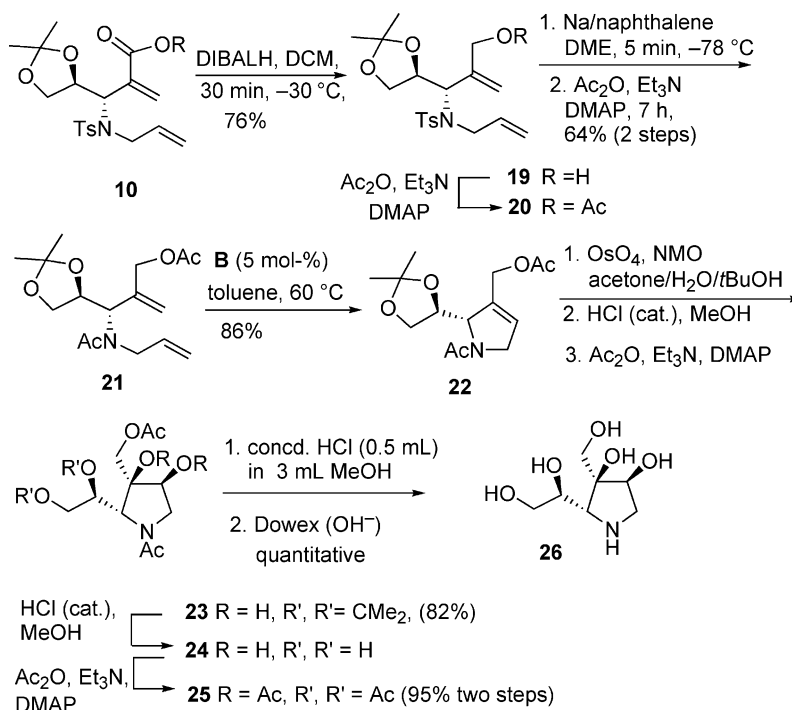


Figure 2. NOE correlations of compounds **17** and **25**.

The inhibitory activity of iminosugars **18** and **26** were tested against a few glycosidases^[18] and the same is shown in Table 1. Thus, pyrrolidine **18** was specifically found to show moderate inhibition of β -galactosidase and showed no inhibition of α -glucosidase, β -glucosidase, α -galactosidase and α -mannosidase. On the other hand, pyrrolidine **26** showed no inhibition of α -glucosidase, β -glucosidase and β -galactosidase but reasonable inhibition of α -galactosidase and α -mannosidase at 0.1 and 0.22 mM concentrations, respectively.



Scheme 2. Synthesis of imino sugar **26**.

Table 1. IC₅₀ values for compounds **18** and **26**.

Enzyme	18	26
α -Glucosidase (rice)	NI ^[a]	NI ^[a]
β -Glucosidase (almonds)	NI ^[a]	NI ^[a]
α -Galactosidase (coffee beans)	NI ^[a]	0.1 mM
β -Galactosidase (bovine liver)	0.28 mM	NI ^[a]
α -Mannosidase (jack beans)	NI ^[a]	0.22 mM

[a] NI: no inhibition at 3 mM concentration, inhibition studies were carried out at 0.1 mM concentrations, optimal pH of the enzymes, at 37 °C.

It is noteworthy that a compound similar to that of **18** but devoid of the hydroxymethyl side chain at C-3 showed^[19a] inhibition against α -mannosidase at 0.12 mM concentration. Likewise, a similar analog of **26** devoid of hydroxymethyl side chain at C-3 was reported^[19b] to be active against β -glucosidase at 0.32 mM concentration. Similarly, 5-hydroxy-*ribo*-isofagomine and its enantiomer, each bearing a quaternary carbon bonded to a hydroxy and a hydroxymethyl group have been reported^[12a] to inhibit α - and β -glucosidases whereas compounds **18** and **26** show no inhibition of these enzymes. Clearly there is a change both in terms of specificity as well as the inhibition constant values as a result of the combination of the structural features as aimed in the present studies.

Conclusions

In conclusion, we have described efficient methods for the synthesis of iminosugars **18** and **26** which are moderate inhibitors of β -galactosidase, and α -galacto- and α -mannosidases, respectively. It is expected that further structural variations of these pyrrolidines could improve inhibition values.

Experimental Section

(R)-Ethyl 2-[Acetoxy(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]acrylate (7): To a solution of **6** (1 g, 4.34 mmol) in 3 mL of dry CH₂Cl₂ were added Ac₂O (0.5 mL, 5.2 mmol), Et₃N (0.9 mL, 5.2 mmol) and catalytic amount of DMAP. After stirring for 3 h at ambient temperature, usual workup with water and CH₂Cl₂ gave a crude product which was purified by column chromatography to give **7** as a mixture of two diastereomers (69:31) (1.15 g, 98% yield). ¹H NMR (400 MHz, CDCl₃): δ = 6.40 (s, 1 H, both isomers), 5.90 (s, 1 H, minor), 5.88 (s, 1 H, major), 5.78 (d, J = 4.16 Hz, 1 H, major), 5.68 (d, J = 5.12 Hz, 1 H, major), 4.45–4.40 (m, 1 H, both isomers), 4.27–4.22 (m, 2 H, both isomers), 4.01–3.96 (m, 1 H both isomers), 3.89 (dd, J = 8.80, 5.88 Hz, 1 H, major), 3.80 (dd, J = 8.52, 5.88 Hz, 1 H, minor), 2.12 (s, 3 H, minor), 2.11 (s, 3 H, major), 1.46 (s, 3 H, minor), 1.40 (s, 3 H, minor), 1.35–1.25 (m, 6 H, both isomers) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.4, 164.9, 137.1, 137.0, 127.9, 127.6, 110.1, 109.9, 76.0, 75.9, 71.7, 70.9, 65.7, 65.2, 61.1, 26.3, 26.1, 25.4, 25.2, 20.1, 20.0, 14.1 ppm. ESMS: m/z = 295 [M + Na]⁺. C₁₃H₂₀O₆ (272.29): calcd. C 57.34, H 7.40, O 35.25; found C 57.35, H 7.42.

Ethyl (S)-2-[(2,2-Dimethyl-1,3-dioxolan-4-yl)(4-methylphenylsulfon-ylamino)methyl]acrylate (8): To a stirred solution of the Baylis–Hillman acetate **7** (1.1 g, 4.04 mmol) in 5 mL of dry CH₂Cl₂ at 0 °C

was added DABCO (985 mg, 8.8 mmol). Tosylamide (759 mg, 4.4 mmol) was then added slowly and stirred it for 4 h at room temperature. Usual workup and column chromatographic purification gave **8** as a mixture of two diastereomers (58:42) (1.06 g, 69% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.47 (d, major, J = 8.32 Hz, 2 H, Ar-H), 7.64 (d, minor, J = 8.32 Hz, 2 H, Ar-H), 7.28–7.22 (m, both isomers, 4 H, Ar-H), 6.25 (s, 1 H, major), 6.03 (s, 1 H, minor), 5.80 (s, 1 H, major), 5.75 (d, J = 10.24 Hz, 1 H, minor), 5.51 (s, 1 H, minor), 5.35 (d, J = 7.56 Hz, 1 H, major), 4.26–4.05 (m, 3 H, both isomers), 3.99–3.87 (m, 2 H, both isomers), 3.52 (dd, J = 8.56, 5.12 Hz, 1 H, major), 2.41 (s, 3 H, Ar-CH₃, minor), 2.40 (s, 3 H, ArCH₃, major), 1.36 [s, 3 H, C(CH₃)₂, major], 1.34 [s, 3 H, C(CH₃)₂, minor], 1.29–1.21 [m, 3 H, C(CH₃)₂, 3 H, OCH₂CH₃, both isomers] ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 165.6, 143.4, 137.6, 137.2, 137.1, 135.1, 130.0, 129.6, 129.5, 129.4, 128.4, 127.2, 110.2, 109.8, 76.2, 75.6, 67.4, 66.2, 61.1, 59.9, 55.8, 26.7, 26.2, 25.0, 24.7, 21.5, 14.0, 13.9 ppm. ESMS: m/z = 406 [M + Na]⁺. C₁₈H₂₅NO₆S (383.46): calcd. C 56.38, H 6.57, N 3.65, O 25.03, S 8.36; found C 56.41, H 6.58, N 3.67.

Procedure for the Allylation of Compound 8: A mixture of **8** (900 mg, 0.42 mmol) and allyl bromide (0.042 mL, 0.5 mmol) in 3 mL of dry DMF was treated with K₂CO₃ (115 mg, 0.84 mmol) and stirred at room temperature for 2 h. Usual workup and column chromatographic purification gave a mixture of two diastereomers (**9:10**, 58:42) (854 mg, 86% yield).

Ethyl 2-[(R)-(N-Allyl-4-methylphenylsulfon-ylamino)](4S)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl]acrylate (9): White crystalline solid. [α]_D²⁸ = +36.25 (c = 0.8, CH₂Cl₂), m.p. 154 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (d, J = 8.32 Hz, 2 H, Ar-H), 7.23 (d, J = 8.32 Hz, 2 H, Ar-H), 6.41 (s, 1 H, 1-H), 5.92 (s, 1 H, 1-H), 5.74 (merged tdd, J = 10.24, 17.08, 4.16 Hz, 1 H, 2'-H), 5.10 (dd, J = 17.32, 1.48 Hz, 1 H, 3'-H), 5.03 (dd, J = 10.24, 1.24 Hz, 1 H, 3'-H), 4.82 (d, J = 9.28 Hz, 1 H), 4.77–4.71 (m, 1 H, 5-H), 4.14 (q, J = 7.32 Hz, 2 H, OCH₂CH₃), 3.99–3.95 (m, 3 H), 3.55 (dd, 1 H, 8.54, 6.84), 2.40 (s, 3 H, Ar-CH₃), 1.39 [s, 3 H, C(CH₃)₂], 1.33 [s, 3 H, C(CH₃)₂], 1.29 (t, J = 7.28 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 166.0, 142.8, 138.1, 137.6, 135.6, 129.8, 129.0, 128.0, 117.1, 109.9, 74.9, 67.5, 61.3, 59.6, 49.1, 26.4, 25.3, 21.4, 14.0 ppm. ESMS: m/z = 446 [M + Na]⁺. C₂₁H₂₉NO₆S (423.52): calcd. C 59.55, H 6.90, N 3.31, O 22.67, S 7.57; found C 59.89, H 6.92, N 3.34.

Ethyl 2-[(S)-(N-Allyl-4-methylphenylsulfon-ylamino)](4S)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl]acrylate (10): White solid. [α]_D²⁸ = +180 (c = 1.15, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.64 (d, J = 8.32 Hz, 2 H, Ar-H), 7.23 (d, J = 8.32 Hz, 2 H, Ar-H), 6.46 (s, 1 H, 1-H), 5.98 (s, 1 H, 1-H), 5.86–5.78 (m, 1 H, 2'-H), 5.24–5.16 (m, 2 H), 4.75 (br. s, 2 H), 4.16–4.08 (m, 2 H), 4.05–3.98 (m, 2 H), 3.91 (dd, J = 6.56, 1.00 Hz, 2 H), 2.40 (s, 3 H, Ar-CH₃), 1.37 [s, 3 H, C(CH₃)₂], 1.33 [s, 3 H, C(CH₃)₂], 1.98 (t, J = 7.32 Hz, 3 H, OCH₂CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 166.3, 143.1, 137.4, 135.9, 135.2, 130.0, 129.2, 127.7, 118.8, 109.9, 74.9, 67.5, 61.0, 58.5, 49.8, 26.8, 25.7, 21.4, 14.0 ppm. ESMS: m/z = 446 [M + Na]⁺. C₂₁H₂₉NO₆S (423.52): calcd. C 59.55, H 6.90, N 3.31, O 22.67, S 7.57; found C 59.01, H 6.92, N 3.30.

(3R)-3-(N-Allyl-4-methylphenylsulfon-ylamino)-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylene-propyl Acetate (12): A solution of unsaturated ester **9** (800 mg, 1.891 mmol) in 10 mL of dry CH₂Cl₂ was cooled to –78 °C under N₂ before slowly adding DIBAL (5.67 mL, 1 M in toluene, 5.67 mmol). After addition of DIBAL, the temperature was slowly raised to –30 °C and stirred at that temperature for 30 min. The reaction mixture was quenched by slow addition of MeOH until evolution of gas bubbles ceased, con-

concentrated at reduced pressure followed by column chromatographic purification to get the desired product **11** (595 mg, 83% yield). To the solution of **11** (50 mg, 0.13 mmol) in 1 mL of dry CH_2Cl_2 were added Ac_2O (0.015 mL, 0.156 mmol), Et_3N (0.021 mL, 0.156 mmol) and catalytic amount of DMAP. After stirring for 2 h at ambient temperature, usual workup gave the crude product which was purified by column chromatography to give **12** colorless oil (53.28 mg, 96% yield). $[\alpha]_D^{25} = -53.3$ ($c = 0.15$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.81$ (d, $J = 8.32$ Hz, 2 H, Ar-H), 7.24 (d, $J = 8.32$ Hz, 2 H, Ar-H), 5.69–5.62 (m, 1 H, 2'-H), 5.37 (s, 1 H, 1-H), 5.12 (s, 1-H), 5.07 (dd, $J = 1.44$, 17.32 Hz, 1 H, 3'-H), 4.97 (dd, $J = 1.24$, 10.00 Hz, 1 H, 3'-H), 4.56–4.50 (m, 4 H, 2H- CH_2OAc , 3-H, 4-H), 4.05–3.97 (m, 2 H, 5-H, 1'-H), 3.77 (dd, $J = 1.44$, 16.8 Hz, 1 H, 1'-H), 3.54 (dd, $J = 8.52$, 6.8 Hz, 1 H, 5-H), 2.41 (s, 3 H, Ar- CH_3), 2.11 (s, 3 H, COCH_3), 1.58 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 1.37 [s, 3 H, $\text{C}(\text{CH}_3)_2$] ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.4$, 143.0, 140.0, 138.1, 135.2, 129.0, 128.1, 117.8, 117.1, 109.6, 73.9, 68.0, 65.4, 60.34, 47.2, 26.4, 25.0, 21.5, 20.9 ppm. ESMS: $m/z = 446$ [$\text{M} + \text{Na}$] $^+$. $\text{C}_{21}\text{H}_{29}\text{NO}_6\text{S}$ (423.52): calcd. C 59.55, H 6.90, N 3.31, O 22.67, S 7.57; found C 59.57, H 6.91, N 3.30.

(3R)-3-(N-Allylacetamido)-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylenepropyl Acetate (13): To a solution of naphthalene (512 mg, 4 mmol) in 10 mL of dry DME was added Na (85.2 mg, 4 mmol) and solution stirred at room temperature for 2 h under N_2 atmosphere to give sodium naphthalenide solution (0.4 M). To a solution of **11** (500 mg, 1.31 mmol) in 3 mL of dry DME was added freshly prepared sodium naphthalenide solution (7 mL, 2.8 mmol) was added at -78°C until decolorization of reagent stops in solution. After stirring at -78°C for 5 min, the solution was quenched with saturated NH_4Cl solution and the organic layer was washed with brine, and dried with Na_2SO_4 . After removal of the solvent the residue was subjected to acetylation in 5 mL of dry CH_2Cl_2 using Ac_2O (0.47 mL, 5 mmol), Et_3N (0.7 mL, 5 mmol) and catalytic amount of DMAP. After stirring for 8 h at ambient temperature, usual workup and chromatographic purification gave **13** as a colorless oil (195 mg, 63% overall yield for 2 steps). $[\alpha]_D^{25} = -40.923$ ($c = 3.25$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta =$ mixture of rotamers (67:33): $\delta = 5.87$ –5.80 (m, 1 H, 2'-H), 5.43 (s, 1 H, 1-H, minor), 5.35 (s, 1 H, 1-H), 5.23–5.03 (m, 4 H, 1-H, 3-H, 3'-H), 4.53–4.40 (m, 3 H, CH_2OAc , 4-H), 4.41 (d, $J = 5.4$ Hz, 1 H, 4-H, minor), 4.13 (dd, $J = 8.52$, 6.56 Hz, 1 H, 5-H, minor), 4.08 (dd, $J = 8.52$, 6.32 Hz, 1 H, 5-H), 3.91–3.88 (m, 2 H, 1'-H), 3.63 (dd, $J = 8.56$, 6.60 Hz, 1 H, 5-H), 3.51 (dd, $J = 8.52$, 7.08 Hz, 1 H, 5-H, minor), 2.25 (s, 3 H, COCH_3 , minor), 2.17 (s, 3 H, COCH_3), 2.09 (s, 3 H, COCH_3 , minor), 2.09 (s, 3 H, COCH_3), 1.45 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.42 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 1.34 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 1.33 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor] ppm. ^{13}C NMR (400 MHz, CDCl_3): $\delta = 172.2$, 170.5, 141.0, 135.0, 116.9, 116.8, 109.5, 74.4, 67.3, 65.2, 54.9, 47.9, 26.4, 25.2, 22.3, 20.9 ppm. Minor isomer: 171.6, 170.2, 139.9, 134.9, 118.1, 116.1, 109.4, 73.5, 67.8, 65.6, 61.8, 44.3, 24.4, 22.0 ppm. ESMS: $m/z = 334$ [$\text{M} + \text{Na}$] $^+$. $\text{C}_{16}\text{H}_{25}\text{NO}_5$ (311.37): calcd. C 61.72, H 8.09, N 4.50, O 25.69; found C 61.76, H 8.10, N 4.79.

{(2R)-1-Acetyl-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-dihydro-1H-pyrrol-3-yl}methyl Acetate (14): To a stirred solution of compound **13** (150 mg, 0.482 mmol) in dry toluene at room temperature was added the Grubbs' 2nd generation catalyst (5 mol-%). The mixture was heated up to 60°C and stirred for 3 h and after completion of the reaction, the solvent was evaporated under reduced pressure and the crude product purified by column chromatography to obtain compound **14** (116 mg, 86% yield) as a viscous liquid. $[\alpha]_D^{25} = +70.40$ ($c = 2.94$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta =$ [mixture of rotamers (89:11)]: $\delta = 6.00$ (s, 1 H, 4-H,

minor) 5.88 (s, 1 H, 4-H, major), 5.09 (s, 1 H, 2-H, major), 4.81 (d, major, $J = 14.16$ Hz, 1 H, 6-H), 4.72 (d, major, $J = 14.16$ Hz, 1 H, 6'-H), 4.63 (td, major, $J = 2.92$, 6.84 Hz, 1 H, 7-H), 4.48 (d, major, $J = 17.36$ Hz, 1 H, minor), 4.36 (m, 1 H, minor), 4.24 (d, major, $J = 14.64$ Hz, 1 H, 5-H), 4.15 (dd, major, $J = 1.92$, 14.64 Hz, 1 H, 5'-H), 3.95 (dd, major, $J = 6.60$, 8.32 Hz, 1 H, 8-H), 3.74 (merged dd, major, $J = 7.32$, 8.28 Hz, 1 H, 8'-H), 3.62 (merged dd, major, $J = 7.32$, 8.04 Hz, 1 H, minor), 2.18 (s, 3 H, COCH_3 , minor), 2.11 (s, 3 H, COCH_3 , minor), 2.09 (s, 3 H, COCH_3 , major), 2.07 (s, 3 H, COCH_3 , major), 1.44 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.39 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major], 1.34 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.32 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major] ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.1$, 170.0, 136.5, 132.7, 108.8, 74.6, 65.2, 63.3, 60.9, 54.5, 25.9, 24.7, 22.4, 20.8 ppm. ESMS: $m/z = 306$ [$\text{M} + \text{Na}$] $^+$. $\text{C}_{14}\text{H}_{21}\text{NO}_5$ (283.32): calcd. C 59.35, H 7.47, N 4.94, O 28.24; found C 59.41, H 7.39, N 4.98.

(2S,3R,4R)-3-(Acetoxymethyl)-1-acetyl-2-[(1S)-1,2-diacetoxyethyl]-pyrrolidine-3,4-diyl Diacetate (17): To a stirred solution of compound **14** (100 mg, 0.353 mmol) in acetone/water/ $t\text{BuOH}$ (1:1:0.4) at room temperature, were added $\text{NMO} \cdot \text{H}_2\text{O}$ (57 mg, 0.423 mmol) and OsO_4 (4 μL , 0.004 equiv.). The reaction mixture was stirred for 16 h and then treated with $\text{Na}_2\text{S}_2\text{O}_5$ (80.4 mg, 0.423 mmol). The reaction mixture was stirred for further 1 h and extracted with AcOEt (2×15 mL). The organic layer was washed with 1 N HCl , water and finally with brine. Usual workup thereafter gave a crude product which was purified by column chromatography to give the diol **15** (94 mg, 84% yield). To a solution of diol **15** (60 mg, 0.189 mmol) in 2 mL of MeOH was added catalytic amount of HCl , stirred for 5 min and then passed the reaction mixture through DOWEX (50X) basic resin column. Concentration under reduced pressure to get the tetrahydroxy compound followed by acetylation with excess of triethylamine and Ac_2O (1:1, 4 mL) and catalytic amount of DMAP at room temperature for 8 h gave a crude product which was purified by column chromatography to give hexaacetate **17** (76 mg, 91% yield two steps) as colorless oil. $[\alpha]_D^{25} = +20.01$ ($c = 0.45$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): $\delta =$ mixture of rotamers (87:13): $\delta = 5.59$ (dd, $J = 8.32$, 8.28 Hz, 1 H, 4-H), 5.34–5.33 (m, 1 H, 7-H), 5.07 (d, $J = 1.48$ Hz, 1 H, 2-H), 4.84 (d, $J = 12.68$ Hz, 1 H, 6-H), 4.51 (d, $J = 12.7$ Hz, 1 H, 6'-H), 4.33 (dd, $J = 11.72$, 4.88 Hz, 1 H, 8-H), 4.05–3.96 (m, 2 H, 5-H, 8'-H), 3.41 (dd, $J = 9.52$, 8.04 Hz, 1 H, 5'-H) ppm. 2.15 (s, 3 H, COCH_3), 2.11 (s, 3 H, COCH_3), 2.08 (s, 3 H, COCH_3), 2.05 (s, 3 H, COCH_3), 2.03 (br. s, 6 H, COCH_3). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 171.0$, 170.5, 170.1, 169.7, 169.6, 169.3, 85.6, 71.6, 70.3, 63.8, 60.7, 60.6, 49.4, 21.9, 21.6, 21.1, 20.7, 20.6, 20.5 ppm. ESMS: $m/z = 468$ [$\text{M} + \text{Na}$] $^+$. $\text{C}_{19}\text{H}_{27}\text{NO}_{11}$ (445.42): calcd. C 51.23, H 6.11, N 3.14, O 39.51; found C 51.13, H 6.25, N 3.00.

N-Allyl-N-[(S)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(ethoxymethyl)allyl]-4-methylbenzenesulfonamide (20): A solution of unsaturated ester **10** (800 mg, 1.891 mmol) in 10 mL of CH_2Cl_2 was cooled to -78°C under N_2 before slowly adding of DIBAL (5.67 mL, 1 M in toluene, 5.67 mmol). After addition of DIBAL, the temperature was slowly raised to -30°C and stirred at that temperature for 30 min. The reaction mixture was quenched by slow addition of MeOH until evolution of gas bubbles ceased, concentrated at reduced pressure followed by column chromatographic purification to get the desired product **19** (544 mg, 1.48 mmol, 76% yield). To the solution of **19** (50 mg, 0.13 mmol) in 1 mL of dry CH_2Cl_2 were added Ac_2O (0.015 mL, 0.156 mmol), Et_3N (0.021 mL, 0.156 mmol) and catalytic amount of DMAP. After stirring for 2 h at ambient temperature, usual workup gave the crude product which was purified by column chromatography to give **20** (53.28 mg, 0.125 mmol, 96% yield). $[\alpha]_D^{25} = +48.4$ ($c = 2.05$,

CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ = 7.71 (d, J = 8.32 Hz, 2 H, Ar-H), 7.31 (d, J = 8.32 Hz, 2 H, Ar-H), 5.78–5.68 (m, 1 H, 2'-H), 5.48 (s, 1 H, 1-H), 5.41 (s, 1 H, 1'-H), 5.15–5.10 (m, 2 H, 3'-H), 4.51–4.50 (m, 2 H, 3-H, 4-H), 4.26 (d, J = 13.40 Hz, 1 H, CH_2OAc), 4.12–4.06 (m, 2 H, 5-H), 4.02 (d, J = 13.40 Hz, 1 H, CH_2OAc), 3.91 (dd, J = 5.12, 16.12 Hz, 1 H, 1'-H), 3.58 (dd, J = 8.32, 16.12 Hz, 1 H, 1'-H), 2.43 (s, 3 H, Ar- CH_3), 2.05 (s, 3 H, COCH_3), 1.42 [s, 3 H, $\text{C}(\text{CH}_3)_2$], 1.35 [s, 3 H, $\text{C}(\text{CH}_3)_2$] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.1, 143.8, 138.1, 137.3, 135.5, 129.7, 127.4, 119.5, 118.4, 110.0, 74.5, 67.5, 65.5, 59.7, 47.4, 26.7, 25.7, 21.5, 20.8 ppm. ESMS: m/z = 446 $[\text{M} + \text{Na}]^+$. $\text{C}_{21}\text{H}_{29}\text{NO}_6\text{S}$ (423.52): calcd. C 59.55, H 6.90, N 3.31, O 22.67, S 7.57; found C 59.59, H 6.91, N 3.35.

(3S)-3-(N-Allylacetamido)-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylenepropyl Acetate (21): To a solution of naphthalene (512.8 mg, 4 mmol) in 10 mL of dry DME was added Na (85.2 mg, 4 mmol) and solution stirred at room temperature for 2 h under N_2 atmosphere to give sodium naphthalenide solution (0.4 M). To a solution of **19** (500 mg, 1.31 mmol) in 3 mL of dry DME was added freshly prepared sodium naphthalenide solution (7 mL, 2.8 mmol) at -78°C until decolorization of reagent stops in solution. After stirring at -78°C for 5 min, the solution was quenched with saturated NH_4Cl solution and the organic layer was washed with brine, and dried with Na_2SO_4 . After removal of the solvent the residue was subjected to acetylation in 5 mL of dry CH_2Cl_2 using Ac_2O (0.47 mL, 5 mmol), Et_3N (0.7 mL, 5 mmol) and catalytic amount of DMAP. After stirring for 8 h at ambient temperature, usual workup and chromatographic purification gave **21** as a colorless oil (195 mg, 0.627 mmol, 63% overall yield for 2 steps). $[\alpha]_D^{28}$ = +45.07 (c = 3.15, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ = [mixture of rotamers (78:22)]: δ = 5.82–5.79 (m, 1 H, 2'-H, minor), 5.78–5.68 (m, 1 H, 2-H, major), 5.56 (s, 1 H, minor), 5.48 (s, 1 H, 1-H, major), 5.47 (s, 1 H, 1-H, major), 5.24–5.07 (m, 3 H, 3'-H, 3-H, major), 4.53–4.40 (m, 3 H, CH_2OAc , 4-H, major), 4.02 (dd, major, J = 8.32, 6.12 Hz, 1 H, 5-H), 3.83–3.79 (m, 5-H, 1'-H, major), 2.23 (s, 3 H, COCH_3 , minor), 2.11 (s, 3 H, COCH_3 , major), 2.08 (s, 3 H, COCH_3 , major), 2.07 (s, 3 H, COCH_3 , minor), 1.38 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major], 1.37 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.32 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.30 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 171.8, 170.5, 139.6, 134.2, 117.9, 117.8, 109.9, 74.3, 67.3, 65.1, 56.3, 47.7, 26.5, 25.4, 22.1, 20.8 ppm. Minor isomer: 170.8, 170.1, 138.7, 134.4, 119.4, 117.4, 110.3, 74.3, 66.5, 65.9, 60.8, 45.1, 27.2, 25.2, 25.1, 21.8 ppm. ESMS: m/z = 334 $[\text{M} + \text{Na}]^+$. $\text{C}_{16}\text{H}_{25}\text{NO}_5$ (311.37): calcd. C 61.72, H 8.09, N 4.50, O 25.69; found C 61.78, H 8.11, N 4.6.

{(2S)-1-Acetyl-2-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,5-dihydro-1H-pyrrol-3-yl}methyl Acetate (22): To a stirred solution of compound **21** (150 mg, 0.482 mmol) in dry toluene at room temperature was added the Grubbs' 2nd generation catalyst (5 mol-%). The mixture was heated up to 60°C and stirred for 3 h and after completion of the reaction, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography to obtain compound **22** (116 mg, 0.409 mmol, 86% yield) as a viscous liquid. $[\alpha]_D^{28}$ = -55.93 (c = 2.95, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ = [mixture of rotamers (80:20)]: δ = 5.95 (s, 1 H, H-4, minor), 5.85 (s, 1 H, H-4, major), 4.90 (d, 1 H, CHHOAc , J = 13.40 Hz, major), 4.83 (br. s, 1 H, H-2, major), 4.63 (d, 1 H, CHHOAc , J = 13.9 Hz, major), 4.35 (dd, 1 H, H-7, J = 6.36, 4.88 Hz, major), 4.23 (m, 2 H, H-5, major), 4.09 (dd, 1 H, H-8, J = 6.84, 9.04 Hz, major), 4.01 (dd, 1 H, H-8', J = 6.36, 9.28 Hz, major), 2.23 (s, 3 H, minor), 2.12 (s, 3 H, COCH_3 , minor), 2.09 (s, 3 H, COCH_3 , major), 2.07 (s, 3 H, COCH_3 , major), 1.38 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major], 1.37 [s, 3 H, $\text{C}(\text{CH}_3)_2$, minor], 1.32 [s, 3 H,

$\text{C}(\text{CH}_3)_2$, minor], 1.30 [s, 3 H, $\text{C}(\text{CH}_3)_2$, major] ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.4, 169.4, 137.3, 127.1, 123.8, 109.1, 67.4, 64.9, 61.4, 53.8, 26.1, 24.9, 22.3, 20.8 ppm. ESMS: m/z = 306 $[\text{M} + \text{Na}]^+$. $\text{C}_{14}\text{H}_{21}\text{NO}_5$ (283.32): calcd. C 59.35, H 7.47, N 4.94, O 28.24; found C 59.79, H 7.96, N 4.86.

(2R,3S,4S)-3-(Acetoxymethyl)-1-acetyl-2-[(1S)-1,2-diacetoxyethyl]-pyrrolidine-3,4-diyl Diacetate (25): To a stirred solution of compound **22** (100 mg, 0.353 mmol) in acetone/water/ $t\text{BuOH}$ (1:1:0.4) at room temperature, were added $\text{NMO}\cdot\text{H}_2\text{O}$ (57 mg, 0.423 mmol) and OsO_4 (4 μL , 0.004 equiv.). The reaction mixture was stirred for 16 h and then it was treated with $\text{Na}_2\text{S}_2\text{O}_5$ (80.4 mg, 0.423 mmol). The reaction mixture was stirred for further 1 h and extracted with AcOEt (2×15 mL). The organic layer was washed with 1 N HCl, water and finally with brine. Usual workup thereafter gave a crude product which was purified by column chromatography to give the diol **23** (91.8 mg, 0.289 mmol, 82% yield). To the solution of diol **23** (60 mg, 0.189 mmol) in 2 mL of MeOH was added catalytic amount of HCl and stirred for 5 min and then passed the reaction mixture through DOWEX (50X) basic resin column and concentrate under reduced pressure to get the tetra hydroxy compound followed by acetylation with excess of triethylamine and Ac_2O (1:1, 4 mL) and catalytic amount of DMAP at room temperature for 8 h. The usual workup gave a crude product which was purified by column chromatography to give hexaacetate **25** (79.8 mg, 0.179 mmol, 95% yield two steps). Colorless oil, $[\alpha]_D^{28}$ = -5.01 (c = 0.6, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3): δ = [mixture of rotamers (95:5)]: δ = 5.55 (t, 1 H, 4-H), 5.41 (m, 1 H, 7-H), 5.02 (d, J = 5.36 Hz, 1 H, 2-H), 4.85 (d, J = 12.2 Hz, 1 H, 6-H), 4.73 (d, J = 12.2 Hz, 1 H, 6'-H), 4.30 (dd, J = 12.2, 4.16 Hz, 1 H, 8-H), 4.14 (dd, J = 11.96, 7.32 Hz, 1 H, 8'-H), 3.92 (dd, J = 9.52, 8.52 Hz, 1 H, 2-H), 3.37 (dd, J = 9.28, 9.00 Hz, 1 H, 5'-H), 2.11–2.04 (6 s, 18 H, 6OAc) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 170.5, 170.5, 169.9, 169.8, 169.6, 169.4, 85.0, 71.6, 70.2, 63.1, 61.0, 60.8, 48.1, 22.0, 21.6, 20.9, 20.7, 20.6, 20.5 ppm. ESMS: m/z = 468 $[\text{M} + \text{Na}]^+$. $\text{C}_{19}\text{H}_{27}\text{NO}_{11}$ (445.42): calcd. C 51.23, H 6.11, N 3.14, O 39.5; found C 51.10, H 6.20, N 3.12.

(2S,3R,4R)-2-[(1S)-1,2-Dihydroxyethyl]-3-(hydroxymethyl)pyrrolidine-3,4-diol (18): To the solution of hexaacetate **17** (50 mg, 0.111 mmol) in 3 mL of MeOH was added concd. HCl (0.5 mL) and stirred for 12 h and then passed the reaction mixture through DOWEX (50X) basic resin column and concentrate under reduced pressure to get the imino sugar **18** in quantitative yield. Light brownish solid, $[\alpha]_D^{28}$ = +3.06 (c = 0.1, H_2O). ^1H NMR (400 MHz, D_2O): δ = 4.07 (br. s, 1 H), 3.80 (br. s, 1 H), 3.56–3.47 (m, 4 H), 3.20 (br. s, 1 H), 2.89 (br. m, 1 H), 2.59 (br. s, 1 H) ppm. ESMS: m/z = 194 $[\text{M} + \text{H}]^+$. $\text{C}_7\text{H}_{15}\text{NO}_5$ (193.20): calcd. C 43.52, H 7.83, N 7.25, O 41.4; found C 43.23, H 7.97, N 7.19.

(2R,3S,4S)-2-[(1S)-1,2-Dihydroxyethyl]-3-(hydroxymethyl)pyrrolidine-3,4-diol (26): To the solution of hexaacetate **25** (50 mg, 0.111 mmol) in 3 mL of MeOH was added concd. HCl (0.5 mL) and stirred for 12 h and then passed the reaction mixture through DOWEX (50X) basic resin column and concentrate under reduced pressure to get the imino sugar **26** in quantitative yield. white solid, $[\alpha]_D^{28}$ = -2.32 (c = 0.1, H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.80 (t, J = 5.36 Hz, 1 H), 3.69 (d, J = 12.20 Hz, 1 H), 3.58 (m, 2 H), 3.43 (d, J = 12.44 Hz, 1 H), 3.40 (m, 1 H), 3.05 (dd, J = 11.96, 6.12 Hz, 1 H), 2.86 (d, J = 9.52 Hz, 1 H), 2.58 (dd, J = 11.96, 4.88 Hz, 1 H) ppm. ESMS: m/z = 194 $[\text{M} + \text{H}]^+$. $\text{C}_7\text{H}_{15}\text{NO}_5$ (193.20): calcd. C 43.52, H 7.83, N 7.25, O 41.4; found C 43.27, H 7.89, N 7.30.

CCDC-646079 (for compound **9**) contains the supplementary crystallographic data for this paper. These data can be obtained free

of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): X-ray data for compound **9**, copies of spectra for all new compounds **7**, **8**, **9**, **10**, **12**, **13**, **14**, **17**, **18**, **20**, **21**, **22**, **25**, **26**.

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