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PII: S0008-6215(20)30106-3

DOI: https://doi.org/10.1016/j.carres.2020.107988

Reference: CAR 107988

To appear in: *Carbohydrate Research*

Received Date: 19 February 2020

Revised Date: 17 March 2020

Accepted Date: 17 March 2020

Please cite this article as: V.K. Harit, N.G. Ramesh, A common strategy towards the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol, deacetyl (+)-anisomycin and amino-substituted piperidine iminosugars, *Carbohydrate Research* (2020), doi: https://doi.org/10.1016/j.carres.2020.107988.

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A Common Strategy towards the Synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol, Deacetyl (+)-anisomycin and Amino-substituted Piperidine Iminosugars

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Abstract:

A strategy towards the synthesis of three different target molecules, namely 1,4-dideoxy-1,4-imino-L-xylitol, deacetyl (+)-anisomycin and amino-substituted piperidine iminosugars, molecules of potential biological and medicinal significance, is reported from a common amino-vicinal diol intermediate derived from tri-*O*-benzyl-D-glucal. Construction of the key pyrrolidine ring present in 1,4-dideoxy-1,4-imino-L-xylitol and (+)-anisomycin was a consequence of thermodynamically driven concomitant intramolecular nucleophilic addition reaction of the amino group to the resultant aldehyde obtained by oxidative cleavage of the amino-vicinal diol. Alternatively, double nucleophilic substitution reaction on the amino-vicinal diol, after mesylation, with various amines delivered amino-substituted piperidine iminosugars in good yields.

Keywords:

1,4-Dideoxy-1,4-imino-L-xylitol

Anisomycin

Iminosugars

Oxidative cleavage

Glycal

1. Introduction

Glycosidase inhibitors have found applications, in the last few decades, as therapeutic agents against several diseases like diabetes, cancer, genetic disorders and viral infections [1]. Iminosugars, derivatives that arise from the replacement of endocyclic oxygen atom of a natural sugar with a nitrogen atom, have emerged as a special class of glycosidase inhibitors

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due to their structural resemblance to natural sugars as well as the mimicry of the transition state involved during the hydrolysis of glycosides [2]. Further, discovery of iminosugar derived marketed drugs such as Glyset® (for type-II diabetes), Zavesca® (for Gaucher's disease) and Galafold® (for Fabry's disease) have established this class of molecules as the most sought after by pharma industries [3]. Iminosugars can be broadly classified based on the size and type of rings, such as pyrrolidines, piperidines, azepanes, indolizidines, and pyrrolizidine derivatives [4]. 1,4-Dideoxy-1,4-imino-D-arabinitol (DAB) **1**, a pyrrolidine iminosugar, first isolated from the fruits of *Angylocalyx boutiqueanus* in 1985, is an α-glucosidase inhibitor and potential AIDS virus replication inhibitor [5]. On the other hand, its enantiomer, 1,4-dideoxy-1,4-imino-L-arabinitol (LAB) which inhibits α–glucosidase to a lesser extent [6] showed prominent inhibition against cytopathic effects of AIDS virus [7]. Glycogen-degrading enzymes regulation and reduction in postprandial glycemia in blood makes DAB and LAB as promising therapeutic agents [8]. 1,4-Dideoxy-1,4-imino-D-xylitol **3**, stereoisomer of **1**, was isolated from marine sponges and found to possess α-glucosidase inhibitory activity [9]. Synthetic 1,4-dideoxy-1,4-imino-L-xylitol **4** (Figure 1), the C-2 epimer of compound **1** [10], has also been found to be a potential glycosidase inhibitor Thus, polyhydroxylated pyrrolidines such as **1**–**4** have become attractive targets for organic chemists due to their wide spectrum of pharmacological and biological activities, especially their anti-cancer activities. 1-Deoxynojirimycin (DNJ) **7**, a piperidine iminosugar, was isolated from the roots of mulberry trees (*Moracae*) in 1976 [11] and was found to be a stable and potent inhibitor of α-glucosidase [12]. Subsequently, several isomers of DNJ have been synthesized and investigated for their biological properties. Continued reserach in this area has also led to the identification that replacement of one or more hydroxyl groups of naturally occurring iminocyclitols by an amino functionality has profound effects on their glycosidase inhibition [4a]. This observation has provided a great impetus to organic chemists for the development of novel amino-modified iminocyclitols possessing better and selective inhibition properties. Iminosugar derivative **8** was found to inhibit human lysosomal β-glucocerebrosidase with an IC_{50} value of 7.5 nM [13] whereas amide derivatives **9** and **10** showed 0.5-0.6 nM inhibition against *α-fucosidase* [14]. In relevance to the part of the work presented in this paper on the synthesis 3-amino-piperidine iminosugars **35-41**, there is only one report in literature and that too on the synthesis of the enantiomer of **36** [15].

(–)-Anisomycin (–)-**5** (Figure 1) is an antibiotic isolated from the fungi *Streptomyces griseolous* and *Streptomyces roseochromogens* by Sobin and Tanner at Pfizer, in 1954 [16].

Wong in 1964, established its stereochemistry as (2*R*,3*S*,4*S*) through chemical derivatization [17]. Later, in 1968, its structure was also confirmed by single crystal X-ray analysis [18]. Both (–)-anisomycin, (–)-**5** and deacetyl (–)-anisomycin, (–)-**6** (Figure 1) have found applications as fungicides [19]. Recently, they have also been found to exhibit antitumour and antiviral activities due to apoptic action, like mammalian cell lines RAS A, HBL 100 and MCF 7 [20]. (–)-Anisomycin (–)-**5** has been found to inhibit protein biosynthesis in rabbit reticulocytes, HeLa cells and *Saccharmyces fragilis*, while not harming *Escherichia coli* [21]. It is also used in therapeutics of trichomoniasis, amoebic dysentery [22]. Many derivatives of anisomycin have been reported to be potent glycosidase inhibitors [23]. The biological activity profile and structural features of anisomycin grabbed the attention of synthetic organic chemists. Several syntheses of both natural (–)-anisomycin (–)-**5** and its enantiomer (+)-anisomycin (+)-**5** are available in literature [24]. The precursors used so far include for the synthesis of (+)-anisomycin are (+)-(2*R*,3*R*) tartaric acid [17], valine based formamidine of dihydropyrrole

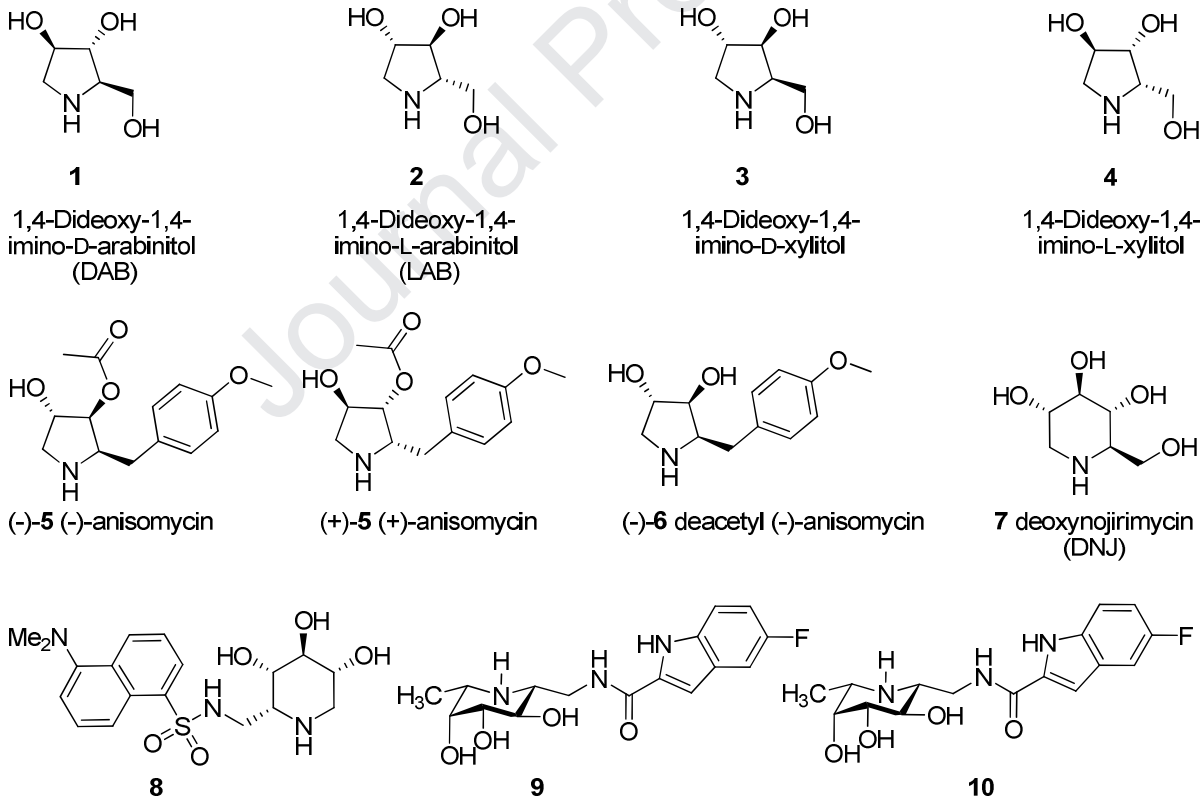
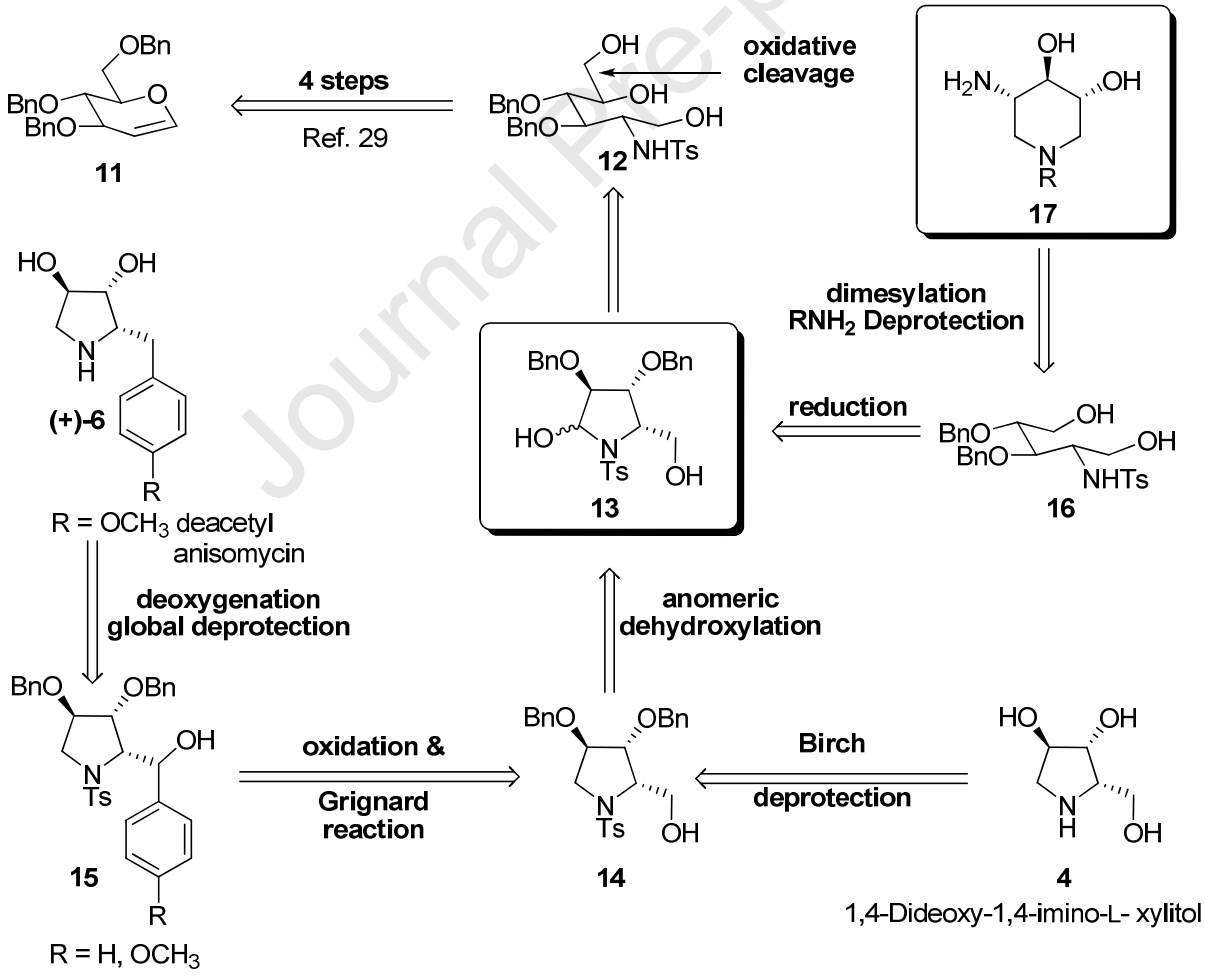


Figure 1. Structures of DAB, LAB, 1,4-Dideoxy-1,4-imino-D-xylitol, 1,4-Dideoxy-1,4-imino-L-xylitol, (-)-anisomycin, deacetyl-(+)-anisomycin, deoxynojirimycin and amino-modified iminocyclitols.

[25], D and L-tyrosine [26], mannitol derivatives [27], D-glucose [28] etc. It may be noted that most of these synthesis employ pre-installed 4-methoxyaryl group before the final formation of the pyrrolidine ring through an intramolecular nucleophilic substitution reaction.

2. Results and Discussion

Our retrosynthesis towards 1,4-Dideoxy-1,4-imino-L-xylitol, (+)-anisomycin and piperidine iminosugars is given in Scheme 1. As depicted, all three targets could be synthesized from a common intermediate **13**, which in turn, could be obtained from triol **12** through $NaIO_4$ mediated oxidative cleavage of vicinal diol of **12**. 3,4,6-tri-*O*-benzyl-D-glucal **11** could be converted to triol **12** following the procedure reported from our lab earlier [29]. The hemiaminal **13** on deoxygenation would afford compound **14**, the common precursor for both

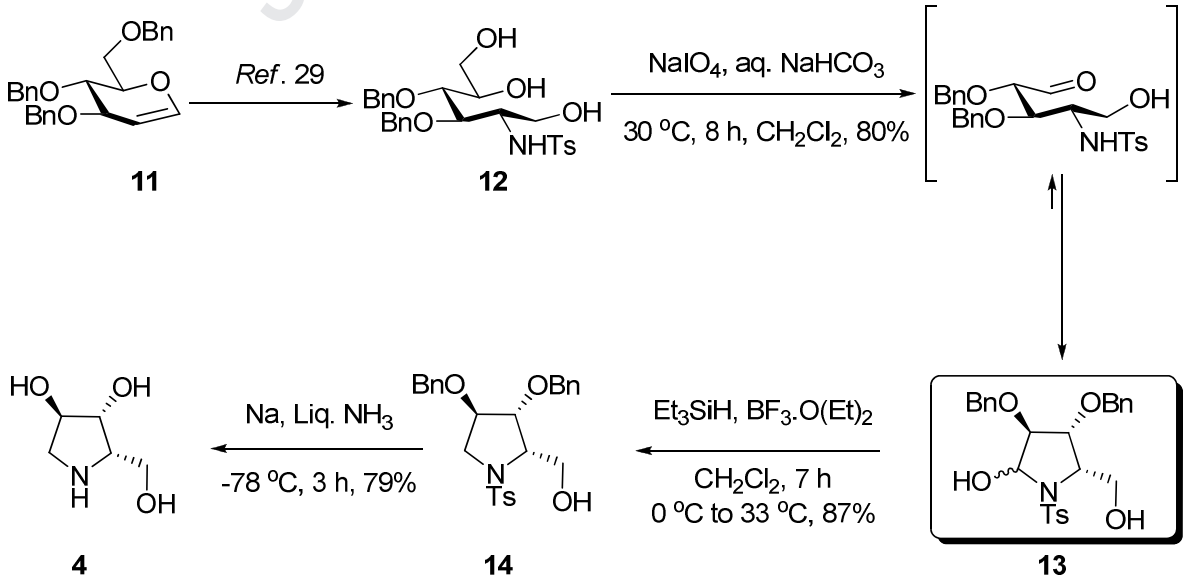


Scheme 1. Retrosynthsis of 1,4-Dideoxy-1,4-imino-L-xylitol, (+)-anisomycin and piperidine iminosugars.

1,4-Dideoxy-1,4-imino-L-xylitol **4** and deacetyl-(+)-anisomycin (+)-**6**. Global deprotection of compound **14** would directly deliver 1,4-Dideoxy-1,4-imino-L-xylitol **4**. On the other hand, oxidation of primary hydroxyl group of **14** and exposure of the resulting aldehyde to aryl Grignard reagents would provide the corresponding benzyl alcohols **15**. Subsequent deprotection of various protecting groups in two steps would then lead to deacetyl (+)-anisomycin (+)-**6**. The hemiaminal **13** could also be converted to diol **16** through $NaBH_4$ mediated reduction that would provide an opportunity for the synthesis of piperidine iminosugars **17** after dimesylation and heating with appropriate amines.

2.1 Synthesis of common intermediate 13.

Synthesis of common intermediate **13** commenced with the conversion of readily available tri-*O*-benzyl-D-glucal **11** to triol **12**, in three steps following the procedure developed in our lab earlier [29]. Triol **12** was next subjected to $NaIO_4$ mediated oxidative cleavage of its vicinal hydroxyl groups. The reaction proceeded smoothly to completion in 8 h at 30 ^{o}C to give the amino-aldehyde in 80% yield, which was found to exist only in the hemiaminal form **13** as revealed from the absence of signal due to the aldehydic proton in its ^{1}H-NMR spectrum. Compound **13** was found to exist as a mixture of diastereomers in a ratio of 2:1 which was evidenced from the appearance of two signals, in its ^{1}H-NMR spectrum, resonating as doublets at δ 5.57 and 5.81 ppm, and integrating for 0.31 and 0.61 proton respectively. These signals



Scheme 2: Total synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol **4**.

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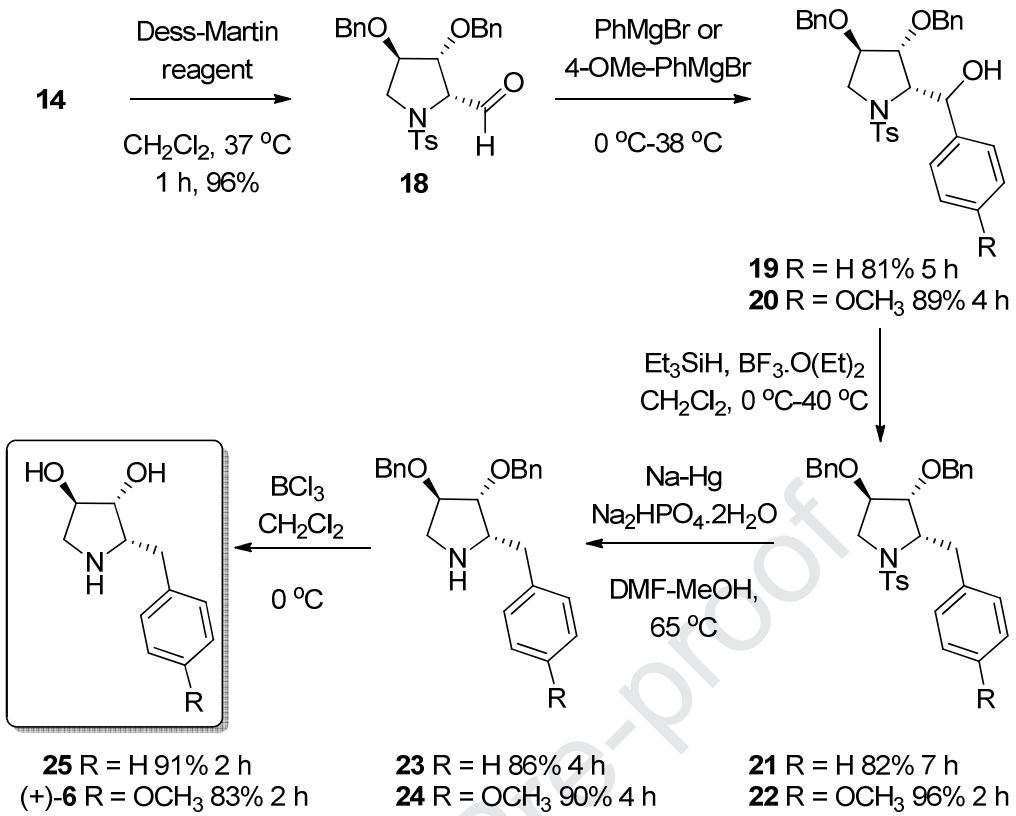
were exchangeable with D_2O and thus are assigned to the signals of hemiaminal –OH protons of the two diastereomers of **13**. Moreover, absence of signal due to carbonyl carbon and appearance of signals due to hemiaminal carbon at δ 93.3 and 91.8 ppm (for two diastereomers) in its ^{13}C-NMR spectrum confirmed the existence of compound **13** in the cyclic form.

2.2 Synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol.

Towards the synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol, initial deoxygenation of hemiaminal **13** was carried out by reacting it with triethylsilane in presence of $BF_3.O(Et)_2$ in CH_2Cl_2. The deoxygenation reaction proceeded smoothly to give compound **14** in 87% yield. Compound **14** possessing benzyl and tosyl groups was ideally suited for a global deprotection under Birch condition. Thus, exposing **14** to sodium in liq. ammonia at –78 ^oC resulted in a facile deprotection to afford directly 1,4-Dideoxy-1,4-imino-L-xylitol **4** in 3 h in 79% yield, whose spectral data were found to be identical with those reported in literature [30] (Scheme 2).

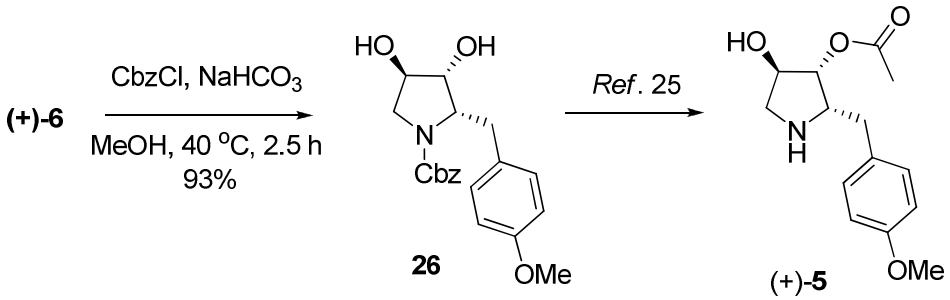
2.3 Formal synthesis of (+)-anisomycin.

Towards the formal synthesis of (+)-anisomycin, the primary hydroxyl group of compound **14** was oxidized to the corresponding aldehyde **18** (96%) using Dess-Martin periodinane in CH_2Cl_2 at 37 ^oC. Initially, in order to check the feasibility of Grignard reaction, aldehyde **18** was treated with phenylmagnesium bromide at 0 ^oC. The reaction proceeded smoothly to provide a 1:9 diastereomeric mixture of benzylic alcohol **19** in 81% yield. Attempts were not made to improve the diastereoselectivity as the next step was to perform the deoxygenation of the hydroxyl group. Encouraged by the success of the reaction, it was extended to the synthesis of *p*-methoxyphenyl derivative by reacting aldehyde **18** with 4-methoxyphenylmagnesium bromide. The nucleophilic addition proceeded with equal ease in this case also to give alcohol **20** as a mixture of diastereomers in 89% yield in 4 h. Deoxygenation of compounds **19** and **20** was achieved with triethylsilane in presence of $BF_3.OEt_2$ to get compounds **21** and **22** in 82% and 96% yields respectively. *N*-Detosylation of compounds **21** and **22** to the corresponding amines **23** (86%) and **24** (90%) was performed with Na-Hg in DMF. Next, the benzyloxy groups in **23** and **24** were cleaved through their reaction with BCl_3 at 0 ^oC to obtain deacetyl (+)-anisomycin (+)-**6** and its phenyl analogue **25** and in 83% and 91% yields respectively (Scheme 3).



Scheme 3: Synthesis of deacetyl (+)-anisomycin (+)-6 and its phenyl derivative **25**.

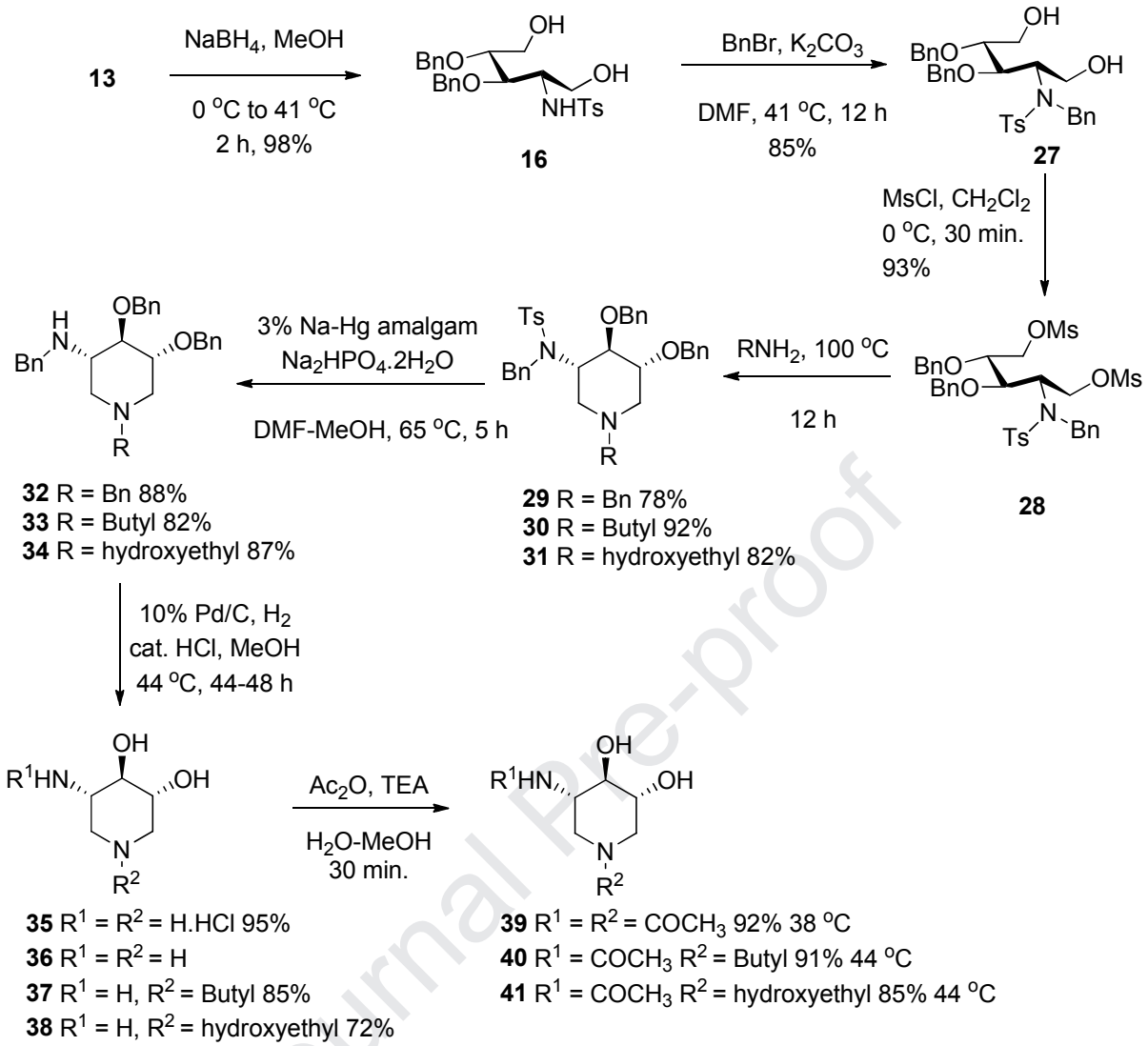
In order to accomplish a formal synthesis of (+)-anisomycin (+)-**5**, compound (+)-**6** was converted to its Cbz derivative by reacting it with CbzCl in the presence of $NaHCO_3$ to get the carbamate **26** in 93% yield. The spectral data and specific rotation of **26** was found to be in full agreement with the literature reported values [31]. Transformation of compound **26** to (+)-anisomycin (+)-**5** has already been reported in literature [25] and thus our present approach constitutes a formal synthesis of (+)-anisomycin (+)-**5** (Scheme 4).



Scheme 4. Formal synthesis of (+)-anisomycin (+)-**5**.

2.4 Synthesis of amino-substituted piperidine iminosugars.

It was envisioned that the common intermediate **13** could also be utilized for the synthesis of amino-piperidine iminosugars in which case, it requires the reductive ring cleavage of the hemiaminal **13**. Towards this direction, hemiaminal **13** was reduced with sodium borohydride in methanol to diol **16** in 98% yield. Chemoselective benzylation of the amino group of compound **16** was achieved through its reaction with benzyl bromide in the presence of K_2CO_3 at 41 ^oC to get compound **27** in 85% yield. Both the free hydroxyl groups of compound **27** were then mesylated to the corresponding dimesyl derivative **28** in 93% yield, by treating it with mesyl chloride and triethylamine at 0 ^oC. In order to synthesize piperidine core, dimesylate **28** was initially heated with benzylamine at 100 ^oC. A double nucleophilic substitution reaction took place to provide the amino-substituted piperidine **29** in 78% yield [29]. Similar reaction of **28** with butylamine and hydroxyethylamine also afforded the corresponding piperidines **30** and **31** in 92% and 82% yields respectively. Protected piperidines **29–31** were then detosylated by their treatment with 3% Na-Hg amalgam to get compounds **32–34** in 82–88% yields. Final deprotection to get the free amino-substituted piperidine iminocyclitols **35** and **36–38**, was then achieved through Pd/C catalyzed hydrogenolysis in presence of catalytic amount of HCl. Under this condition, compound **35** was obtained as hydrochloride salt in 95% yield, which was found to be pure enough and did not require any further purification. The spectral data of compound **35** were found to be identical with the values reported in literature [15] for its enantiomer. The specific rotation was also found to match except the sign. The dihydrochloride **35** was also neutralized by passing it through silica gel column and eluting with NH_4OH and acetonitrile (4:1) to get free amine **36**. On the other hand, compounds **37** and **38** required purification by column chromatography using NH_4OH and acetonitrile (4:1) as eluent and compounds **37** and **38** were isolated, as free amines, in 85% and 72% yields respectively. The C-5 amino group of compounds **37** and **38** were then selectively acetylated by their treatment with acetic anhydride in presence of Et_3N and water to get acetamido derivatives **40** and **41** in 91% and 85% yields respectively. However, in the case of compound **35**, formation of diacetate **39** was the sole product irrespective of equivalents of acetic anhydride used in the reaction (Scheme 5). Hence the acetylation reaction of **35** was carried out with an excess of acetic anhydride to get directly the diacetate **39** in 92% yield.



Scheme 5: Synthesis of amino-substituted piperidine iminosugars.

3. Conclusion

In summary, we have developed a divergent approach utilizing tri-*O*-benzyl-D-glucal derived common intermediate for successful synthesis of three distinct target molecules of biological and medicinal significance. We have achieved the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol, formal synthesis of (+)-anisomycin and its unsubstituted phenyl analogue. The strategy also provided amino-modified piperidine iminosugars in a very efficient manner with high yields.

4. Experimental Section

General Experimental Methods. All experiments were performed in oven–dried apparatus and in dry solvents unless otherwise mentioned. Commercial grade solvents were distilled

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and dried as per standard procedures and were stored over 4 Å molecular sieves wherever applicable. IR spectra were recorded as a KBr pellet or neat (ATR) and expressed in cm^{-1}. High resolution mass spectra were recorded on a Q–TOF instrument using electrospray ionization (ESI) as the source. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded using $CDCl_3$, CD_3OD or D_2O as a solvent. Chemical shifts have been reported in ppm downfield to tetramethylsilane and coupling constants are expressed in Hertz (Hz). Optical rotations were measured at indicated temperature and solvents. Commercial TLC plates were used and the spots were visualized by exposure to the required developing agent/reagent. Column chromatography was performed over silica gel (230–400 mesh).

*4.1 (3S,4R,5S)-3,4-Bis-benzyloxy-2-hydroxy-5-hydroxymethyl-N-tosyl-pyrrolidine (**13**):*

Triol **12** (1.0 g, 1.94 mmol) was dissolved in dichloromethane (10 mL). $NaIO_4$ (0.83 g, 3.88 mmol) was added to it followed by 1 mL of aturated sodium bicarbonate solution. The biphasic reaction mixture was stirred at 30 ^{o}C and the progress of reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated under vacuum. Ethyl acetate (100 mL) and water (100 mL) were added to the residue. The layers were separated and aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. The resulting crude reaction mixture was purified by column chromatography over silica gel using a mixture of ethyl acetate and hexane (3:2) as an eluent to get the pyrrolidine derivative as an inseparable mixture of diastereomers **13** (0.75 g, 80%) with a *dr* of 1:2 as a white solid. M.P: 97–100 ^{o}C; R_f : 0.20 (hexane-ethyl acetate, 3:2); Specific rotation: $[\alpha]_D^{26}$ –19.8 (*c* 0.58, $CHCl_3$); [mixture of stereoisomers] IR (KBr): $\bar{\upsilon}$ 3452, 3032, 2924, 2863, 1453, 1335, 1159, 1086, 813, 741, 698, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ mixture of diastereomers) δ 7.69–7.65 (overlapped signals, 2H), 7.36–7.19 (overlapped signals, 12H), 5.81 (d, *J* = 9.0 Hz, 0.31H exchangeable with D_2O), 5.57 (d, *J* = 9.6 Hz, 0.61H exchangeable with D_2O), 4.96 (d, *J* = 9.6 Hz, 0.32H), 4.85 (d, *J* = 10.2 Hz, 0.63H), 4.15 (dd, *J* = 12.3, 2.1 Hz, 0.32H), 3.86–3.76 (overlapped signals, 1.44H), 3.77 (t, *J* = 3.3 Hz, 0.52H), 3.60–3.33 (overlapped signals, 4H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ mixture of stereoisomers) δ 143.46 (s), 137.98 (s), 137.37 (s), 136.89 (s), 136.64 (s), 136.53 (s), 129.78 (d), 128.77 (d), 128.65 (d), 128.60 (d), 128.48 (d), 128.24 (d), 128.13 (d), 127.99 (d), 127.94 (d), 127.82 (d), 126.96 (d), 93.36 (d), 91.88 (d), 76.50 (d), 74.97 (d), 74.20 (d), 74.08 (d), 73.25 (t), 73.14 (t), 72.79 (t), 72.75 (t), 64.40 (t), 59.38 (t), 50.18 (d), 49.72 (d), 21.56 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{29}NNaO_6S$: 506.1608, found 506.1612.

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*4.2 (2S,3R,4R)-3,4-Bis-benzyloxy-2-hydroxymethyl-N-tosyl –pyrrolidine (**14**):*

Compound **13** (0.5 g, 1.03 mmol) was dissolved in dichloromethane (5 mL). Triethylsilane (0.33 mL, 2.07 mmol) was added to it dropwise followed by addition of $BF_3.OEt_2$ (0.638 mL, 2.33 mmol) at 0 ^oC (bath temperature). The reaction mixture was then stirred at 33 ^oC under argon atmosphere. After 7 h, the reaction was stopped and solvent was concentrated under vacuum. Ethyl acetate (100 mL) and water (50 mL) were added to the reaction mixture. Then solid sodium bicarbonate solution was added to the reaction mixture until the effervescence stopped. The layers were separated and aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. The resulting crude reaction mixture was purified by column chromatography over silica gel using a mixture of ethyl acetate and hexane (1:4) as an eluent to get the deoxy compound **14** (0.42 g, 87%) as a white solid. M.P: 61–65 °C; R_f : 0.17 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{29}$ +19.7 (*c* 0.28, $CHCl_3$); IR (KBr): ῡ 3513, 3032, 2926, 1598, 1454, 1336, 1157, 1089, 797, 741, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.33–7.05 (overlapped signals, 12H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.27 (overlapped signals, 2H), 4.03–3.90 (overlapped signals, 3H), 3.86–3.83 (m, 1H), 3.74–3.69 (overlapped signals, 2H), 3.33 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.59 (br m, 1H exchangeable with D_2O), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.74 (s), 137.29 (s), 137.12 (s), 133.88 (s), 129.61 (d), 128.62 (d), 128.40 (d), 128.19 (d), 127.85 (d), 127.81 (d), 127.76 (d), 127.33 (d), 82.58 (d), 79.02 (d), 72.87 (t), 71.48 (t), 62.69 (t), 62.58 (d), 51.58 (t), 21.52 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{29}NNaO_5S$: 490.1659, found 490.1641.

*4.3 (2S,3R,4R)-2-Hydroxymethyl-pyrrolidine-3,4-diol, (1,4-dideoxy-1,4-imino-L-xylitol) (**4**):*

Ammonia gas was condensed (about 10 mL) in a three necked 50 mL reaction flask at –78 ^oC. Finely divided sodium pieces were added to it until the colour of the solution turned dark blue. Compound **14** (0.196 g, 0.42 mmol) was added to the reaction mixture. When the blue colour of the solution disappeared, a few more fine pieces of sodium were added and the blue color resurfaced. This procedure was repeated until the blue color of the solution persists (without fading) for 3 h, which required a total 0.193 g (8.4 mmol) of sodium. The reaction mixture was then quenched at −78 ^oC by slow addition of benzene (3 mL) followed by dropwise addition of water (3 mL) to the reaction mixture at −78 ^oC. It was allowed to warm to room temperature and stirred until the excess ammonia got evaporated.

Benzene layer was then separated and the aqueous layer was directly loaded onto the silica gel column and eluted with a mixture of acetonitrile and ammonium hydroxide (4:1) to get 1,4-dideoxy-1,4-imino-L-xylitol **4** (0.044 g, 79%) as a colorless viscous liquid. R_f : 0.11 (CH_3CN-NH_4OH, 4:1); Specific rotation: $[\alpha]_D^{30}$ −7.1 (*c* 0.21, H_2O); IR (neat): ῡ 3399, 2930, 1633, 1447, 1412, 1316, 1115, 1045, 979, 617 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.39–4.38 (m, 1H), 4.32 (br s, 1H), 4.05–3.97 (m, 1H), 3.93–3.86 (overlapped signals, 2H), 3.66 (dd, *J* = 12.9, 3.9 Hz, 1H), 3.29 (d, *J* = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 74.30 (d), 74.29 (d), 62.94 (d), 57.22 (t), 50.45 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_5H_{11}NO_3$: 134.0812, found 134.0808.

4.4 *(2S,3R,4R)-3,4-Bis-benzyloxy-N-tosyl-pyrrolidine-2-carbaldehyde (**18**):*

Compound **14** (0.5 g, 1.07 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). Dess Martin reagent (0.544, 1.28 mmol) was added to the reaction mixture and stirred for 1 h at 37 ^oC. The reaction was then stopped and solvent was evaporated under vacuum. The resulting residue was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate (4:1) to get the aldehyde **18** (0.48 g, 96%) as a white solid. M.P: 93–96 ^oC; R_f : 0.35 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{30}$ +77.8 (*c* 0.62, $CHCl_3$); IR (KBr): ῡ 3033, 2924, 2850, 1730, 1595, 1455, 1393, 1343, 1216, 1158, 1120, 1079, 1018, 811, 740, 668, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.30–7.15 (overlapped signals, 10H), 6.87–6.86 (overlapped signals, 2H), 4.43 (br m, 2H), 4.20 (d, *J* = 4.8 Hz, 1H), 4.06 (br m, 2H), 3.95–3.92 (m, 1H), 3.87–3.83 (overlapped signals, 2H), 2.01 (d, *J* = 12.0 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.55 (s), 144.12 (s), 136.89 (s), 136.64 (s), 133.36 (s), 129.71 (d), 128.59 (d), 128.31 (d), 128.25 (d), 127.84 (2 x d), 127.78 (d), 127.02 (d), 84.15 (d), 79.13 (d), 72.83 (t), 70.72 (t), 68.85 (d), 52.36 (t), 21.54 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{27}NNaO_5S$: 488.1502, found 488.1518.

*4.5 (2S,3R,4R,2'S)-2-(Benzyl-2'-hydroxy)-3,4-bis-benzyloxy-N-tosyl-pyrrolidine and (2S,3R,4R,2'R)-2-(Benzyl-2'-hydroxy)-3,4-bis-benzyloxy-N-tosyl-pyrrolidine (**19**):*

Compound **18** (0.43 g, 0.86 mmol) was dissolved in dry THF (4 mL). Phenylmagnesium bromide (1.11 mL, 1 M solution in THF, 1.11 mmol) was added dropwise to it at 0 ^oC (bath temperature) under argon atmosphere. The reaction mixture was then allowed to warm and stirred at 38 ^oC for 5 h. Saturated ammonium chloride solution (10 mL) and water (100 mL) were then added successively to the reaction mixture and it was extracted

with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. Purification of crude compound was done by column chromatography over silica gel (230–400 mesh) using a mixture of ethyl acetate and hexane (1:4) as an eluent to get (~1:9) diasteromeric mixture of **19** (0.41 g, 81%) as transparent viscous liquid. R_f : 0.27 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{30}$ −20.6 (*c* 0.53, $CHCl_3$); IR (KBr): ῡ 3446, 3032, 2925, 2872, 1597, 1494, 1454, 1399, 1336, 1213, 1157, 1093, 1029, 786, 758, 702, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers): δ 9.74 (d, *J* = 3.0 Hz, 0.04H exchangeable with D_2O), 7.77–7.71 (overlapped signals, 2H), 7.40–6.96 (overlapped signals, 17H), 5.29 (dd, *J* = 10.2, 3.6 Hz, 0.1H), 5.02 (dd, *J* = 6.6, 4.2 Hz, 0.82H), 4.43 (d, *J* = 4.5 Hz, 1H exchangeable with D_2O), 4.28–3.94 (overlapped signals, 5H), 3.84–3.58 (overlapped signals, 2H), 3.52–3.39 (overlapped signals, 2H), 2.38 and 2.36 (s, 3H two signals for 2 diastereomers); ^{13}C NMR (75 MHz, $CDCl_3$) (mixture of diastereomers): δ 143.89 (s), 143.84 (s), 141.65 (s), 141.43 (s), 137.42 (s), 137.30 (s), 137.25 (s), 136.67 (s), 134.82 (s), 134.08 (s), 129.81 (d), 129.67 (d), 128.64 (d), 128.52 (d), 128.45 (d), 128.42 (d), 128.30 (d), 128.18 (d), 128.01 (d), 127.86 (d), 127.77 (d), 127.72 (d), 127.64 (d), 127.47 (d), 127.34 (d), 126.50 (d), 83.64 (d), 83.58 (d), 78.82 (d), 78.60 (d), 74.03 (d), 73.29 (t), 73.20 (d), 72.81 (t), 71.56 (t), 71.34 (t), 67.19 (d), 65.67 (d), 53.37 (t), 51.32 (t), 21.63 (q); HRMS (ESI): $[M + K]^+$ calcd for $C_{32}H_{33}KNO_5S$: 582.1711; found: 582.1721.

*4.6 (2S,3R,4R,2'S)-2-(4-Methoxybenzyl-2'-hydroxy)-3,4-bis-benzyloxy-N-tosyl-pyrrolidine and (2S,3R,4R,2'R)-2-(4-Methoxybenzyl-2'-hydroxy)-3,4-bis-benzyloxy-N-tosyl-pyrrolidine (**20**):*

Compound **18** (0.4 g, 0.86 mmol) was dissolved in dry THF (4 mL). 4-methoxyphenylmagnesium bromide (1.03 mL, 1 M solution in THF, 1.03 mmol) was added dropwise to it at 0 ^oC (bath temperature) under argon atmosphere. The reaction mixture was then allowed to warm and stirred at 38 ^oC for 4 h. Saturated ammonium chloride solution (10 mL) and water (100 mL) were then added successively to the reaction mixture and it was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. Purification of crude compound was done by column chromatography over silica gel (230–400 mesh) using a mixture of ethyl acetate and hexane (1:4) as an eluent to get a diastereomeric mixture of **20** (0.44 g, 89%) in a ratio of ~1:2 as a transparent viscous liquid. The spectral data and specific rotation reported here is for a mixture of diastereomers. R_f : 0.27 (hexane-ethyl

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acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ −11.0 (*c* 0.98, $CHCl_3$); IR (KBr): ῡ 3482, 3027, 2928, 1603, 1507, 1454, 1335, 1247, 1159, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (mixture of diastereomers) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.32–6.80 (overlapped signals, 16H), 5.19 (br m, 0.41H), 4.98 (d, *J* = 6.6 Hz, 0.7H), 4.50–4.47 (br m, 1H exchangeable with D_2O), 4.40–4.33 (m, 1H), 4.29–4.09 (overlapped signals, 3H), 4.02–3.96 (m, 1H), 3.81 and 3.80 (2 s, for the methyloxy protons), 3.74–3.25 (overlapped signals, 4H), 2.39 and 2.37 (2 s, for the methyl protons of tosyl group); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.10 (s), 158.91 (s), 143.88 (s), 137.40 (s), 137.29 (s), 136.78 (s), 134.61 (s), 134,07 (s), 133.60 (s), 133.50 (s), 129.83 (d), 129.65 (d), 128.74 (d), 128.62 (d), 128.50 (d), 128.40 (d), 128.25 (d), 127.99 (d), 127.92 (d), 127.84 (d), 127.71 (d), 127.66 (d), 127.60 (d), 127.46 (d), 113.54 (d), 83.62 (d), 83.42 (d), 78.69 (d), 78.59 (d), 73.54 (d), 73.24 (t), 72.78 (t), 72.57 (d), 71.67 (t), 71,30 (t), 67.18 (q), 65.59 (q), 55.29 (d), 53.36 (t), 51.12 (t), 21.62 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{33}H_{35}NNaO_6S$: 596.2077; found: 596.2079.

*4.7 (2S,3R,4R)-2-Benzyl-3,4-bis-benzyloxy-N-tosyl-pyrrolidine (**21**):*

Compound **19** (0.4 g, 0.73 mmol) was dissolved in dry CH_2Cl_2 (4 mL). Et_3SiH (0.24 mL, 1.47 mmol) and $BF_3.O(Et)_2$ (0.45 mL, 1.66 mmol) were added successively at 0 ^oC under argon atmosphere. The reaction mixture was stirred at 40 ^oC for 7 h, after which the reaction was stopped and the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. Purification of crude compound was done by column chromatography over silica gel (230–400 mesh) using a mixture of ethyl acetate and hexane (1:4) as an eluent to get compound **21** (0.32 g, 82%) as a transparent viscous liquid**.** R_f : 0.46 (hexane-ethyl acetate, 7:3; Specific rotation: $[\alpha]_D^{30}$ + 30.1 (*c* 0.61, $CHCl_3$); IR (KBr): ῡ 3030, 2923, 1598, 1495, 1453, 1394, 1340, 1215, 1158, 1094, 1030, 737, 700, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.36–6.94 (overlapped signals, 17H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 4.12 (d, *J* = 12.0 Hz, 1H), 4.07 (d, *J* = 12.3 Hz, 1H), 3.94–3.87 (m, 1H), 3.68–3.65 (m, 1H), 3.61 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.52–3.41 (overlapped signals, 3H), 3.16 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.42 (s), 138.85 (s), 137.60 (s), 137.42 (s), 134.77 (s), 129.65 (d), 129.58 (d), 128.51 (d), 128.38 (d), 128.35 (d), 127.92 (d), 127.78 (d), 127.75 (d), 127.66 (d), 127.32 (d), 126.29 (d), 81.80 (d), 78.12 (d), 72.49 (t), 70.99 (t), 63.82 (d), 51.81 (t), 35.52 (t), 21.58 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{32}H_{33}NNaO_4S$: 550.2023; found: 550.2034.

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*4.8 (2S,3R,4R)-2-(4-Methoxybenzyl)-3,4-bis-benzyloxy-N-tosyl-pyrrolidine (**22**):*

Compound **20** (0.5 g, 0.87 mmol) was dissolved in dry CH_2Cl_2 (5 mL). Et_3SiH (487.2 µL, 3.05 mmol) and $BF_3.O(Et)_2$ (537.81 µL, 1.96 mmol) were added successively at 0 ^oC under argon atmosphere. The reaction mixture was stirred at 40 ^oC for 2 h, after which the reaction was stopped and the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum. Purification of crude compound was done by column chromatography over silica gel (230–400 mesh) using a mixture of ethyl acetate and hexane (1:4) as an eluent to get compound **22** (0.47 g, 96%) as a transparent viscous liquid. R_f : 0.36 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ +34.1 (*c* 1.87, $CHCl_3$); IR (KBr): ῡ 2993, 2847, 1603, 1508, 1453, 1341, 1245, 1161, 1100, 1029, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.33–7.19 (overlapped signals, 10H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.97–6.95 (overlapped signals, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.13 (d, *J* = 12.0 Hz, 1H), 4.09 (d, *J* = 12.4 Hz, 1H), 3.85 (qui, *J* = 5.2 Hz, 1H), 3.76 (s, 3H), 3.65–3.63 (m, 1H), 3.56 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.49 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.41 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.32 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.08 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.18 (s), 143.46 (s), 137.71 (s), 137.51 (s), 134.78 (s), 130.80 (s), 130.67 (d), 129.62 (d), 128.54 (d), 128.36 (d), 127.94 (d), 127.77 (d), 127.69 (d), 127.35 (d), 113.82 (d), 81.87 (d), 78.16 (d), 72.49 (t), 71.03 (t), 63.94 (q), 55.29 (d), 51.87 (t), 34.61 (t), 21.59 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{33}H_{35}NNaO_5S$: 580.2128; found: 580.2126.

General procedure for N-detosylation reaction: N-Tosylated derivative (1 equiv.) was dissolved in a solvent mixture of DMF and methanol. Sodium dihydrogen phosphate (5 equiv.) was added to the reaction mixture followed by 3% Na–Hg (10 equiv.). The reaction mixture was allowed to stir at 65 ^oC. After completion of the reaction, as revealed by TLC, ethyl acetate was added to the reaction mixture and it was washed with water. The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was concentrated under vacuum. Purification of the product was done by column chromatography over silica gel to get the *N*-detosylated derivatives.

*4.9 (2S,3R,4R)-2-Benzyl-3,4-bis-benzyloxy-pyrrolidine (**23**):*

Compound **21** (0.3 g, 0.57 mmol) was subjected to *N*-detosylation reaction for 4 h as per the general procedure described earlier in DMF (10 mL) and methanol (5 mL), in presence of $Na_2HPO_4.2H_2O$ (0.506 g, 2.84 mmol) and 3% Na–Hg (4.36 g, 5.69 mmol). Product was purified by column chromatography using a mixture of chloroform and methanol (19:1) to get **23** (0.184 g, 86%) as a colorless viscous liquid. R_f : 0.41 (chloroform-methanol, 9:1); Specific rotation**:** $[\alpha]_D^{30}$ + 31.5 (*c* 0.41, $CHCl_3$); IR (KBr): ῡ 3035, 2923, 2851, 1596, 1450, 1307, 1092, 1025, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.17 (overlapped signals, 15H), 4.51–4.33 (overlapped signals, 4H), 4.00 (d, *J* = 4.8 Hz, 1H), 3.73–3.68 (overlapped signals, 2H), 3.55 (dd, *J* = 12.6, 5.4 Hz, 1H), 3.17–3.09 (overlapped signals, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.08 (s), 137.50 (s), 137.38 (s), 129.08 (d), 128.58 (d), 128.56 (d), 127.98 (d), 127.81 (d), 127.77 (d), 126.54 (d), 81.19 (d), 80.15 (d), 71.71 (t), 71.51 (t), 63.03 (d), 49.89 (t), 33.27 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{25}H_{28}NO_2$: 374.2115, found 374.2126.

*4.10 (2S,3R,4R)-2-(4-Methoxybenzyl)-3,4-bis-benzyloxy-pyrrolidine (**24**):*

Compound **22** (0.4 g, 0.71 mmol) was subjected to *N*-detosylation reaction for 4 h as per the general procedure described earlier in DMF (10 mL) and methanol (5 mL), in presence of $Na_2HPO_4.2H_2O$ (0.638 g, 3.59 mmol) and 3% Na–Hg (5.5 g, 7.17 mmol). Product was purified by column chromatography using a mixture of chloroform and methanol (19:1) to get **24** (0.26 g, 90%) as a colorless viscous liquid**.** R_f : 0.5 (chloroform-methanol, 9:1); Specific rotation: $[\alpha]_D^{32}$ + 52.5 (*c* 1.25, $CHCl_3$); IR (KBr): ῡ 3031, 2921, 2851, 1608, 1507, 1452, 1246, 1088, 1033, 745, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (overlapped signals, 10H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 8.1 Hz, 2H), 4.55–4.39 (overlapped signals, 4H), 4.01–3.99 (m, 1H), 3.85 (br m, 1H exchangeable with D_2O), 3.75 (s, 3H), 3.69–3.68 (m, 1H), 3.49–3.40 (overlapped signals, 2H), 2.96–2.90 (overlapped signals, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.09 (s), 138.02 (s), 137.88 (s), 131.40 (s), 129.96 (d), 128.51 (d), 127.84 (d), 127.81 (d), 127.67 (d), 113.91 (d), 82.58 (d), 81.94 (d), 71.48 (t), 71.39 (t), 63.40 (q), 55.27 (d), 51.11 (t), 33.55 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{26}H_{30}NO_3$: 404.2220, found 404.2222.

*4.11 (2S,3R,4R)-2-Benzyl-3,4-dihydroxy-pyrrolidine (**25**):*

Compound **23** (0.15 g, 0.4 mmol) was dissolved in dry dichloromethane (2 mL) and the reaction vessel was cooled to 0 ^oC (bath temperature). Boron trichloride (2.01 mL of 1 M solution in CH_2Cl_2, 2.01 mmol) was added dropwise under argon atmosphere and the reaction

mixture was allowed to stir at 0 ^{o}C for 2 h. The reaction mixture was quenched by the addition of MeOH (3 mL) and the solvent was concentrated under vacuum. The resulting residue was directly loaded on to a silica gel column and the product was purified by eluting using a mixture of NH_4OH and acetonitrile (1:9) to get product **25** (0.071 g, 91%) as a transparent viscous liquid. R_f : 0.41 (NH_4OH-acetonitrile, 1:4); Specific rotation: $[\alpha]_D^{30}$ –4.0 (*c* 0.52, MeOH); IR (neat): $\bar{\upsilon}$ 3252, 2935, 1591, 1405, 1311, 1296, 1196, 1074, 973, 701, 620 cm^{-1}. ^{1}H NMR (300 MHz, D_2O) δ 7.37–7.21 (overlapped signals, 5H), 4.26 (d, *J* = 5.1 Hz, 1H), 4.02 (br m, 1H), 3.78–3.72 (m, 1H), 3.51 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.07 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.95–2.84 (overlapped signals, 2H); ^{13}C NMR (75 MHz, D_2O) δ 137.56 (s), 128.95 (2 x d), 127.06 (d), 75.71 (d), 75.21 (d), 63.00 (d), 50.93 (t), 32.32 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{16}NO_2$: 194.1176; found: 194.1178.

*4.12 (2S,3R,4R)-3,4-Dihydroxy-2-(4-methoxybenzyl)pyrrolidine, (+)-deacetyl anisomycin **(+)-6**:*

Compound **24** (0.2 g, 0.49 mmol) was dissolved in dry dichloromethane (2 mL) and the reaction vessel was cooled to 0 ^{o}C (bath temperature). Boron trichloride (4.96 mL of 1 M solution in CH_2Cl_2, 4.96 mmol) was added dropwise under argon atmosphere and the reaction mixture was allowed to stir at 0 ^{o}C for 2 h. The reaction mixture was quenched by the addition of MeOH (3 mL) and solvent was concentrated under vacuum. The resulting residue was directly loaded on to a silica gel column and the product was purified by eluting using a mixture of NH_4OH and acetonitrile (1:9) to get product (+)-**6** (0.092 g, 83%) as a white solid. M.P: 176–178 ^{o}C; R_f : 0.38 (NH_4OH-acetonitrile, 1:4); Specific rotation: $[\alpha]_D^{29}$ +17.6 (*c* 0.51, MeOH); IR (neat): $\bar{\upsilon}$ 3350, 3268, 2919, 1605, 1510, 1450, 1295, 1247, 1180, 1076, 1027, 957, 902, 825, 749 cm^{-1}. ^{1}H NMR (400 MHz, D_2O) δ 7.22 (d, *J* = 6.8 Hz, 2H), 6.92 (d, *J* = 7.2 Hz, 2H), 4.16 (br m, 1H), 3.89 (br m, 1H), 3.76 (s, 3H), 3.38–3.29 (overlapped signals, 2H), 2.90–2.85 (m, 1H), 2.72–2.63 (overlapped signals, 2H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.16 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.80 (br s, 2H exchangeable with D_2O), 3.88 (d, *J* = 5.0 Hz, 1H), 3.70 (s, 3H), 3.52 (d, *J* = 3.0 Hz, 1H), 3.20 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.08 (td, *J* = 7.5, 3.0 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.57 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.45 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 157.35 (s), 131.19 (s), 129.97 (d), 114.06 (d), 76.50 (d), 76.26 (d), 62.37 (q), 55.25 (d), 50.94 (t), 32.23 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$: 224.1281; found: 224.1280.

*4.13 (2S,3R,4R)-N-(Benzyloxycarbonyl)-3,4-dihydroxy-2-(4-methoxybenzyl)pyrrolidine (**26**):*

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Compound (+)-**6** (0.03 g, 0.134 mmol) was dissolved in dry methanol (1 mL). Sodium bicarbonate (0.0226 g, 0.268 mmol) and benzyl chloroformate (28.77 µL of 1 M solution in CH_2Cl_2, 0.201 mmol) was added dropwise under argon atmosphere and the reaction mixture was allowed to stir at 40 ^oC. When TLC indicated the disappearance of starting material (2.5 h), reaction was stopped and the reaction mixture was concentrated under vacuum. The resulting residue was directly loaded on to a silica gel column and the product was eluted using a mixture of ethyl acetate and hexane (3:2) to get **26** (0.045 g, 93%) as a white solid. M.P: 125–128 ^oC; R_f : 0.31 (hexane-ethyl acetate, 1:4); Specific rotation: $[\alpha]_D^{32}$ +8.1 (*c* 0.22, MeOH); IR (neat) ῡ 3551, 3440, 3375, 2930, 1674, 1613, 1511, 1423, 1337, 1246, 1186, 1115, 1030, 970, 816, 760, 696, 608 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (br m, 5H), 7.23–7.10 (overlapped signals, 2H), 6.81 (br m, 2H), 5.22–5.12 (overlapped signals, 2H), 4.22 (br s, 1H), 4.01 (br s, 1H), 3.93 (br s, 1H), 3.78 (s, 3H), 3.59 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.41–3.33 (overlapped signals, 2H, 1H exchangeable with D_2O), 3.28–3.25 (m, 1H), 2.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): mixture of rotamers: δ 158.02 (s), 155.91 (s), 136.13 (s), 130.75 (d), 130.65 (d), 128.55 (d), 128.14 (d), 113.78 (d), 76.34 (d), 73.81 (d), 67.54 (t), 66.96 (t), 61.21 (q), 55.21 (d), 51.23 (t), 33.36 (t), 32.35 (t); HRMS (ESI): $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_5$: 380.1468; found: 380.1484.

*4.14 (2R,3R,4S)-2,3-Bis-benzyloxy-4-(p-toluenesulfonamido)-pentane-1,5-diol (**16**):*

Compound **13** (1.6 g, 3.31 mmol) was dissolved in dry methanol (20 mL). Sodium borohydride (0.188 g, 4.96 mmol) was added to the reaction mixture portion wise at 0 ^oC (bath temperature). After addition, ice bath was removed and the reaction mixture was stirred at 41 ^oC under nitrogen atmosphere for 2 h. Solvent was then concentrated under vaccum. Water (100 mL) was added to the residue and it was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. The crude residue was then subjected to column chromatography over silica gel and eluted using a mixture of hexane and ethyl acetate (2:3) to obtain **16** (1.58 g, 98%) as a white solid. R_f : 0.2 (hexane-ethyl acetate, 3:7); Specific rotation: $[\alpha]_D^{32}$ −16.4 (*c* 0.44, $CHCl_3$); IR (neat): ῡ 3404, 2915, 1592, 1403, 1324, 1151, 1075, 740, 651, 556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.38–7.13 (overlapped signals, 12H), 5.44 (d, *J* = 8.7 Hz, 1H exchangeable with D_2O), 4.74 (d, *J* = 11.1 Hz, 1H), 4.55 (s, 2H), 4.50 (d, *J* = 11.1 Hz, 1H), 3.88 (dd, *J* = 7.2, 2.1 Hz, 1H), 3.64–3.40 (overlapped signals, 5H), 3.30 (dd, *J* = 10.8, 7.5 Hz, 1H), 2.90 (br s, 1H exchangeable with D_2O), 2.73 (br s, 1H exchangeable with D_2O), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.60 (s), 138.07 (s), 137.91 (s),

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137.89 (s), 129.80 (d), 128.57 (d), 128.54 (d), 128.29 (d), 128.07 (d), 127.98 (d), 127.91 (d), 126.99 (d), 80.15 (d), 77.65 (d), 75.17 (t), 72.87 (t), 62.17 (t), 60.83 (t), 54.95 (d), 21.54 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{26}H_{31}NNaO_6S$: 508.1764, found 508.1749.

*4.15 (2R,3R,4S)-2,3-Bis-benzyloxy-4-(N-benzyl-N-p-toluenesulfonyl)amino-pentane-1,5-diol (**27**):*

Compound **16** (1.4 g, 2.88 mmol) was dissolved in dry DMF (15 mL). K_2CO_3 (0.797 g, 5.77 mmol) and benzyl bromide (0.377 mL, 3.17 mmol) were added successively under argon atmosphere. The reaction mixture was then allowed to stirr at 41 °C for 12 h. The reaction was stopped and ethyl acetate (200 mL) was added to the reaction mixture. It was then washed with water several times to remove DMF. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum. Purification by column chromatography over silica gel using a mixture of hexane and ethyl acetate (1:1) as an eluent afforded the *N*-benzyl derivative **27** (1.41 g, 85%) as a colorless viscous liquid. R_f : 0.33 (hexane-ethyl acetate, 3:7); Specific rotation: $[\alpha]_D^{32}$ +12 (*c* 0.57, $CHCl_3$); IR (neat): ῡ 3534, 3414, 3033, 2934, 2868, 1597, 1449, 1331, 1211, 1153, 1048, 912, 757, 700, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.2 Hz, 2H), 7.26–7.09 (overlapped signals, 17H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.45–4.33 (overlapped signals, 4H), 4.06–4.03 (m, 1H), 3.93–3.89 (m, 1H), 3.72–3.59 (overlapped signals, 4H), 3.47 (dd, *J* = 11.4, 5.7 Hz, 1H), 2.68 (br m, 2H exchangeable with D_2O), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.43 (s), 138.05 (s), 137.63 (s), 129.64 (d), 128.90 (d), 128.56 (d), 128.41 (d), 128.39 (d), 128.27 (d), 128.00 (d), 127.94 (d), 127.82 (d), 127.57 (d), 127.41 (d), 79.30 (d), 77.39 (d), 74.60 (t), 73.13 (t), 61.29 (2 x t), 60.87 (d), 49.91 (t), 21.56 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{33}H_{37}NNaO_6S$: 598.2234, found 598.2247.

*4.16 (2R,3R,4S)-2,3-Bis-benzyloxy-4-(N-benzyl-N-p-toluenesulfonyl)amino-1,5-di-O-(methanesulfonyl)- pentane-1,5-diol (**28**):*

Diol **27** (1.42 g, 2.47 mmol) was dissolved in dry dichloromethane (15 mL). Triethylamine (750.12 µL, 5.43 mmol) was added to it at room temperature followed by DMAP (0.030 g, 10 mol%). The reaction mixture was cooled to 0 ^oC and mesyl chloride (420 µl, 5.43 mmol) was slowly added to it. After 30 min, when TLC indicated the disappearance of starting material, reaction was stopped and the reaction mixture was directly concentrated under vacuum. The crude residue was then subjected to column chromatography over silica gel and eluted using a mixture of hexane and ethyl acetate (7:3) to obtain **28** (1.68 g, 93%) as

a colorless viscous liquid. R_f : 0.5 (hexane-ethyl acetate, 2:3); Specific rotation: $[\alpha]_D^{32}$ +12.4 (*c* 1.03, $CHCl_3$); IR (neat): ῡ 3031, 2923, 2855, 1597, 1454, 1348, 1168, 1096, 965, 829, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.30–7.16 (overlapped signals, 17H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.49–4.21 (overlapped signals, 9H), 3.98 (br s, 1H), 3.89 (br s, 1H), 3.75 (br s, 1H), 2.95 (s, 3H), 2.72 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.08 (s), 137.36 (s), 137.31 (s), 137.09 (s), 136.73 (s), 129.85 (d), 129.02 (d), 128.73 (d), 128.57 (d), 128.52 (d), 128.41 (d), 128.15 (d), 128.07 (d), 127.77 (d), 127.74 (d), 77.14 (d), 76.56 (d), 74.91 (t), 73.16 (t), 68.33 (t), 65.77 (t), 57.88 (d), 49.99 (t), 37.36 (q), 37.18 (q), 21.56 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_{35}H_{41}NNaO_{10}S_3$: 754.1785, found 754.1812.

*4.17 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl-N-p-tolunesulfonyl)amino-1-N-benzyl-piperidine (**29**):*

Compound **28** (0.4 g, 0.54 mmol) was dissolved in freshly distilled benzylamine (4 mL) and the reaction mixture was stirred at 100 ^oC for 12 h. It was then cooled to room temperature and ethyl acetate (150 mL) was added to it. The reaction mixture was washed with water (4 x 50 mL) and with 10% HCl (3 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was concentrated under vacuum. The product was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate (4:1) to get **29** (0.276 g, 78%) as a viscous pale yellow liquid. R_f : 0.27 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ −8.66 (*c* 0.85, $CHCl_3$); IR (neat): ῡ 3030, 2926, 2868, 2806, 1597, 1494, 1452, 1335, 1158, 1097, 1021, 927, 888, 746, 700, 661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.25–7.01 (overlapped signals, 22H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.51–4.42 (overlapped signals, 4H), 3.99–3.83 (overlapped signals, 2H), 3.65–3.51 (overlapped signals, 2H), 3.41 (d, *J* = 13.2 Hz, 1H), 3.31 (d, *J* = 13.2 Hz, 1H), 2.96 (m, 1H), 2.74 (m, 1H), 2.28 (s, 3H), 1.81 (br m, 1H), 1.68 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.81 (s), 138.79 (s), 138.08 (s), 138.03 (s), 137.96 (s), 137.53 (s), 129.34 (d), 128.76 (d), 128.51 (d), 128.45 (d), 128.42 (d), 128.34 (d), 128.17 (d), 127.92 (d), 127.81 (d), 127.77 (d), 127.70 (d), 127.52 (d), 127.30 (d), 127.17 (d), 81.43 (d), 79.45 (d), 73.29 (t), 72.36 (t), 61.59 (t), 58.98 (d), 57.19 (t), 55.13 (t), 48.99 (t), 21.57 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_{40}H_{43}N_2O_4S$: 647.2938, found 647.2932.

*4.18 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl-N-p-tolunesulfonyl)amino-1-N-butyl-piperidine (**30**):*

Compound **28** (0.4 g, 0.546 mmol) was dissolved in butylamine (4 mL) and the reaction mixture was stirred at 100 ^{o}C for 12 h. It was then cooled to room temperature and ethyl acetate (150 mL) was added to it. The reaction mixture was washed with water (4 x 50 mL) followed by 10% HCl (3 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was concentrated under vacuum. The product was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate (4:1) to get **30** (0.31 g, 92%) as a viscous colorless liquid. R_f : 0.27 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ −15.6 (*c* 1.1, $CHCl_3$); IR (neat): ῡ 3031, 2947, 2869, 2812, 1598, 1491, 1454, 1335, 1157, 1092, 1033, 926, 889, 804, 742, 700, 661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.29–7.03 (overlapped signals, 17H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.55–4.51 (overlapped signals, 3H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.99–3.91 (overlapped signals, 2H), 3.60–3.51 (overlapped signals, 2H), 2.97 (d, *J* = 7.6 Hz, 1H), 2.73 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H), 2.16 (br m, 2H), 1.68 (overlapped signals, 2H), 1.22–1.17 (overlapped signals, 4H), 0.85 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.84 (s), 138.82 (s), 138.16 (s), 138.06 (s), 138.01 (s), 129.36 (d), 128.49 (d), 128.15 (d), 127.97 (d), 127.84 (d), 127.67 (d), 127.56 (d), 127.26 (d), 81.55 (d), 79.53 (d), 73.21 (t), 72.47 (t), 58.94 (d), 57.18 (t), 57.06 (t), 55.89 (t), 48.90 (t), 29.15 (t), 21.56 (q), 20.54 (t), 14.07 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_{37}H_{45}N_2O_4S$: 613.3095, found 613.3095.

*4.19 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl-N-p-tolunesulfonyl)amino-1-N-(2'-hydroxyethyl)piperidine (**31**):*

Compound **28** (0.4 g, 0.54 mmol) was dissolved in hydroxyethylamine (4 mL) and the reaction mixture was stirred at 100 ^{o}C for 12 h. It was then cooled to room temperature and ethyl acetate (150 mL) was added to it. The reaction mixture was washed with water (4 x 50 mL) followed by with 10% HCl (3 x 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was concentrated under vacuum. The product was purified by column chromatography over silica gel using a mixture of hexane and ethyl acetate (1:1) to get **31** (0.271 g, 82%) as a viscous colorless liquid. R_f : 0.34 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ −10.33 (*c* 0.74, $CHCl_3$); IR (neat): ῡ 3417, 3034, 2939, 2878, 2810, 1598, 1486, 1453, 1332, 1158, 1089, 928, 887, 750, 701, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.28–7.02 (overlapped signals, 17H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.55–4.45 (overlapped signals, 4H), 3.95–3.90 (overlapped signals, 2H), 3.65–3.57 (overlapped signals, 2H), 3.44 (t, *J* = 5.1 Hz, 2H), 3.00 (m, 1H), 2.75 (m, 1H), 2.42 (br s, 1H exchangeable with D_2O), 2.36 (t, *J* = 5.4 Hz, 2H), 2.31 (s, 3H), 1.80 (t, *J* = 10.5

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Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.00 (s), 138.59 (s), 137.94 (s), 137.85 (s), 137.79 (s), 129.40 (d), 128.55 (d), 128.51 (d), 128.44 (d), 128.18 (d), 127.94 (d), 127.92 (d), 127.80 (d), 127.74 (d), 127.54 (d), 127.35 (d), 81.37 (d), 79.21 (d), 73.33 (t), 72.56 (t), 58.78 (d), 58.33 (t), 58.31 (t), 57.20 (t), 55.52 (t), 49.00 (t), 21.55 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_{35}H_{41}N_2O_5S$: 601.2731, found 601.2742.

*4.20 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl)amino-1-N-benzyl-piperidine (**32**):*

Compound **29** (0.7 g, 1.08 mmol) was subjected to *N*-detosylation reaction for 5 h as per the general procedure described earlier in DMF (10 mL) and methanol (5 mL), in presence of $Na_2HPO_4.2H_2O$ (0.963 g, 5.41 mmol) and 3% Na–Hg (8.29 g, 10.82 mmol). Product was purified by column chromatography using a mixture of hexane and ethyl acetate (4:1) to get **32** (0.47 g, 88%) as a colorless viscous liquid. R_f : 0.22 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ + 17.3 (*c* 0.61, $CHCl_3$); IR (neat): $\bar{\upsilon}$ 3332, 3031, 2894, 2809, 1596, 1455, 1365, 1181, 1081, 908, 741, 701, 617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.14 (overlapped signals, 20H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.57 (s, 1H), 3.73–3.62 (overlapped signals, 3H), 3.58–3.54 (overlapped signals, 2H), 3.32 (t, *J* = 8.7 Hz, 1H), 3.07–2.96 (overlapped signals, 2H), 2.79 (td, *J* = 9.3, 4.2 Hz, 1H), 2.11–2.04 (overlapped signals, 2H), 1.94 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.40 (s), 138.88 (s), 138.52 (s), 138.09 (s), 128.90 (d), 128.52 (d), 128.44 (d), 128.37 (d), 128.03 (d), 127.97 (d), 127.78 (d), 127.72 (d), 127.69 (d), 127.19 (d), 126.90 (d), 84.08 (d), 79.62 (d), 74.67 (t), 72.27 (t), 62.28 (t), 57.91 (d), 56.32 (t), 55.81 (t), 51.88 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{33}H_{37}N_2O_2$: 493.2850, found 493.2852.

*4.21 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl)amino-1-N-butyl-piperidine (**33**):*

Compound **30** (0.6 g, 0.98 mmol) was subjected to *N*-detosylation reaction for 5 h as per the general procedure described earlier in DMF (10 mL) and methanol (3 mL), in presence of $Na_2HPO_4.2H_2O$ (0.871 g, 4.90 mmol) and 3% Na–Hg (7.50 g, 9.79 mmol). Product was purified by column chromatography using a mixture of hexane and ethyl acetate (4:1) to get **33** (0.368 g, 82%) as colorless viscous liquid. R_f : 0.19 (hexane-ethyl acetate, 7:3); Specific rotation: $[\alpha]_D^{32}$ + 20.0 (*c* 1.20, $CHCl_3$); IR (neat): $\bar{\upsilon}$ 3331, 3032, 2941, 1596, 1457, 1365, 1255, 1187, 1088, 904, 825, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (overlapped signals, 15H), 4.95 (d, *J* = 11.7 Hz, 1H), 4.73–4.61 (overlapped signals, 3H), 3.78 (d, *J* = 12.9 Hz, 1H), 3.69–3.62 (overlapped signals, 2H), 3.29 (t, *J* = 9.0 Hz, 1H), 3.10–2.99 (overlapped signals, 2H), 2.82–2.74 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.07 (br m, 1H

exchangeable with D_2O), 1.99 (t, *J* = 10.8 Hz, 1H), 1.86 (t, *J* = 10.5 Hz, 1H), 1.42 (qui, *J* = 7.8 Hz, 2H), 1.29 (sextet, *J* = 7.5 Hz, 2H), 0.90 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.43 (s), 138.88 (s), 138.57 (s), 128.52 (d), 128.47 (d), 128.04 (d), 128.02 (d), 127.85 (d), 127.72 (d), 126.94 (d), 84.46 (d), 79.84 (d), 74.75 (t), 72.44 (t), 58.16 (d), 57.89 (t), 56.82 (t), 56.29 (t), 52.07 (t), 29.19 (t), 20.75 (t), 14.14 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_{30}H_{39}N_2O_2$: 459.3006, found 459.3016.

*4.22 (3R,4R,5S)-3,4-Bis-benzyloxy-5-(N-benzyl)amino-1-N-(2'-hydroxyethyl)piperidine (**34**):*

Compound **31** (0.65 g, 1.08 mmol) was subjected to *N*-detosylation reaction for 5 h as per the general procedure described earlier in DMF (10 mL) and methanol (5 mL), in presence of $Na_2HPO_4.2H_2O$ (0.963 g, 5.41 mmol) and 3% Na–Hg (8.29 g, 10.82 mmol). Product was purified by column chromatography using a mixture of chloroform and methanol (19:1) to get **34** (0.421 g, 87%) as a colorless viscous liquid. R_f : 0.42 (Chloroform-methanol, 9:1); Specific rotation: $[\alpha]_D^{32}$ +15.8 (*c* 0.76, $CHCl_3$); IR (neat): ῡ 3341, 3030, 2880, 1597, 1456, 1364, 1182, 1078, 900, 741, 699, 608 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (overlapped signals, 15H), 4.92 (d, *J* = 11.4 Hz, 1H), 4.65–4.61 (overlapped signals, 3H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.69–3.61 (overlapped signals, 2H), 3.55 (t, *J* = 5.4 Hz, 2H), 3.53 (t, *J* = 8.4 Hz, 1H), 3.06–2.95 (overlapped signals, 2H), 2.78 (td, *J* = 9.0, 4.2 Hz, 1H), 2.60 (br m, 2H exchangeable with D_2O), 2.53 (t, *J* = 5.4 Hz, 2H), 2.17 (t, *J* = 10.5 Hz, 1H), 2.06 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.03 (s), 138.67 (s), 138.33 (s), 128.55 (d), 128.53 (d), 128.06 (d), 127.99 (d), 127.83 (d), 127.07 (d), 83.24 (d), 79.34 (d), 74.65 (t), 72.44 (t), 58.96 (t), 58.28 (t), 57.89 (d), 56.23 (t), 55.79 (t), 51.94 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_{28}H_{35}N_2O_3$: 447.2642, found 447.2645.

*4.23 (3R,4R,5S)-5-Amino-3,4-dihydroxy-piperidine dihydrochloride (**35**):*

Compound **32** (0.2 g, 0.406 mmol) was dissolved in methanol (4 mL). 10% Palladium on charcoal (0.04 g) was added to the reaction mixture under argon atmosphere followed by slow addition of HCl (0.169 µL, 2.03 mmol). Argon gas was stopped and hydrogen gas was bubbled slowly in to the reaction mixture continuously while stirring at 44 ^{o}C for 48 h. The reaction mixture was filtered through a celite bed and the filtrate was concentrated to get **35** (0.079 g, 95%) as a pale yellow viscous liquid. The product was found to be pure enough as revealed from its NMR spectrum. R_f : 0.14 (acetonitrile-ammonium hydroxide, 7:3); Specific rotation: $[\alpha]_D^{30}$ +1.1 (*c* 0.18, CH_3OH) lit. for enantiomer $[\alpha]_D^{30}$ –1.05 (*c* 0.01, CH_3OH]; IR (neat): ῡ 3443, 3217, 2924, 1598, 1417, 1245, 1100, 879, 738, 601 cm^{-1}; ^{1}H NMR (400 MHz,

D_2O) δ 3.99–3.93 (m, 1H), 3.84–3.80 (overlapped signals, 2H), 3.66–3.58 (overlapped signals, 2H), 3.34 (dd, *J* = 12.4, 11.2 Hz, 1H), 3.10 (dd, *J* = 12.8, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 70.96 (d), 66.81 (d), 48.74 (d), 46.07 (t), 42.85 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_5H_{13}N_2O_2$: 133.0972, found 133.0968.

*4.24 (3R,4R,5S)-5-Amino-3,4-dihydroxy-piperidine (**36**):*

The crude *bis*-hydrochloride salt **35** obtained earlier was purified by column chromatography over silica gel using NH_4OH and acetonitrile (4:1) to get the free amine **36**. R_f : 0.21 (acetonitrile-ammonium hydroxide, 4:1); Specific rotation: $[\alpha]_D^{30}$ +1.5 (*c* 0.19, CH_3OH); IR (neat): $\bar{\upsilon}$ 3404, 2928, 1615, 1525, 1463, 1225, 1113, 884, 795, 615 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.57 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 3.42 (t, *J* = 9.2 Hz, 1H), 3.33 (ddd, *J* = 12.4, 4.4, 0.8 Hz, 1H), 3.21 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.12 (ddd, *J* = 14.8, 10.0, 4.8 Hz, 1H), 2.76 (dd, *J* = 12.8, 11.2 Hz, 1H), 2.59 (dd, *J* = 12.8, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 73.27 (d), 68.81 (d), 50.63 (d), 47.53 (t), 44.76 (t); HRMS (ESI): $[M + H]^+$ calcd for $C_5H_{13}N_2O_2$: 133.0972, found 133.0967.

*4.25 (3R,4R,5S)-5-Amino-3,4-dihydroxy-1-N-butyl-piperidine (**37**):*

Compound **33** (0.216 g, 0.47 mmol) was dissolved in methanol (5 mL). 10% Palladium on charcoal (0.043 g, 20% w/w) was added to the reaction mixture under argon atmosphere. Argon gas was stopped and hydrogen gas was bubbled slowly in to the reaction mixture continuously while stirring at 44 ^{o}C for 48 h. Hydrogen supply was stopped, the reaction mixture was filtered through a celite bed and the filtrate was concentrated under vacuum. Product was purified by column chromatography over silica gel using a mixture of acetonitrile and aqueous ammonium hydroxide solution (9:1) to get **37** (0.076 g, 85%) as a colorless viscous liquid. R_f : 0.3 (acetonitrile-ammonium hydroxide, 4:1); Specific rotation: $[\alpha]_D^{30}$ +2.7 (*c* 0.33, MeOH); IR (neat): $\bar{\upsilon}$ 3371, 2927, 1596, 1458, 1376, 1259, 1073, 897, 765, 711, 621 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.48 (td, *J* = 9.6, 4.8 Hz, 1H), 3.10 (t, *J* = 9.6 Hz, 1H), 2.99 (td, *J* = 11.6, 4.8 Hz, 2H), 2.79 (td, *J* = 10.8, 4.4 Hz, 1H), 2.39 (dd, *J* = 8.0, 8.0 Hz, 2H), 1.98 (t, *J* = 11.2 Hz, 2H), 1.39 (qui, *J* = 7.2 Hz, 2H), 1.20 (sextet, *J* = 7.2 Hz, 2H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 77.38 (d), 69.70 (d), 56.80 (t), 56.77 (t), 55.70 (t), 51.10 (d), 27.65 (t), 20.07 (t), 13.21 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_9H_{21}N_2O_2$: 189.1598, found 189.1597.

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*4.26 (3R,4R,5S)-5-Amino-3,4-dihydroxy-1-N-(2-hydroxyethyl)-piperidine (**38**):*

Compound **34** (0.21 g, 0.47 mmol) was dissolved in methanol (5 mL). 10% Palladium on charcoal (0.04 g) was added to the reaction mixture under argon atmosphere. Argon gas was stopped and hydrogen gas was bubbled slowly in to the reaction mixture continuously while stirring at 44 ^{o}C for 48 h. Hydrogen supply was stopped, the reaction mixture was filtered through celite bed and the filtrate was concentrated under vacuum. Product was purified by column chromatography over silica gel using a mixture of acetonitrile and aqueous ammonium hydroxide solution (4:1) to get **38** (0.06 g, 72%) as a colorless viscous liquid. R_f : 0.52 (acetonitrile-ammonium hydroxide, 4:1); Specific rotation: $[\alpha]_D^{30}$ +6.1 (*c* 0.65, MeOH); IR (neat): $\bar{\upsilon}$ 3391, 2923, 1597, 1470, 1360, 1121, 891, 710, 621 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.59 (t, *J* = 6.0 Hz, 2H), 3.47 (td, *J* = 9.6, 4.8 Hz, 1H), 3.15 (t, *J* = 9.6 Hz, 1H), 3.01–2.95 (overlapped signals, 2H), 2.88 (td, *J* = 10.4, 4.0 Hz, 1H), 2.53 (t, *J* = 6.0 Hz, 2H), 2.11 (t, *J* = 11.2 Hz, 1H), 2.04 (t, *J* = 11.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 76.04 (d), 69.62 (d), 58.15 (t), 57.94 (t), 57.01 (t), 54.92 (t), 51.17 (d); HRMS (ESI): $[M + Na]^+$ calcd for $C_7H_{16}N_2NaO_3$: 199.1053, found 199.1051.

General procedure for acetylation reactions:

Triethyl amine dissolved in MeOH was added to a solution of compound to be acetylated in water. Acetic anhydride dissolved in MeOH was then added dropwise to the reaction mixture and it was stirred at the specified temperature for 30 min. The reaction mixture was then concentrated under vacuum and the resulting residue was directly loaded on to a silica gel column for purification.

*4.27 (3R,4R,5S)-5-(N-acetyl)Amino-3,4-dihydroxy-1-N-acetylpiperidine (**39**):*

Compound **35** (0.032 g, 0.156 mmol) was acetylated in water (1.0 mL)/MeOH (1.0 mL) using triethylamine (0.0347 g, 0.343 mmol) and acetic anhydride (0.035 g, 0.343 mmol) at 38 ^{o}C following the general procedure to get the di-*N*-acetylated derivative **39** (0.025 g, 92%) as a colorless viscous liquid after purification by column chromatography using a mixture of acetonitrile and aqueous ammonium hydroxide solution (9:1). R_f : 0.36 (CH_3CN-NH_4OH, 4:1); Specific rotation: $[\alpha]_D^{30}$ +13.9 (*c* 0.48, MeOH); IR (neat): $\bar{\upsilon}$ 3685, 3264, 1644, 1560, 1441, 1312, 1254, 1100, 1040, 699, 613 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) (mixture of rotamers) δ 4.39–4.27 (m, 1H), 3.94–3.84 (m, 1H), 3.70 (m, 0.5H), 3.64–3.53 (m, 1H), 3.45–

3.41 (overlapped signals, 1.5H), 3.04–2.94 (m, 1H), 2.62–2.56 (m, 1H), 2.10, 2.09 (s, 3H, two signals for rotamers), 1.96, 1.95 (s, 3H, two signals for rotamers); ^{13}C NMR (75 MHz, D_2O) (mixture of rotamers) δ 174.50 (s), 174.35 (s), 172.97 (s), 172.96 (s), 75.01 (d), 69.74 (d), 69.27 (d), 50.80 (d), 50.10 (d), 49.96 (t), 48.11 (t), 45.47 (t), 43.57 (t), 22.07 (q), 22.06 (q), 20.42 (q), 20.39 (q); HRMS (ESI): $[M + Na]^+$ calcd for $C_9H_{16}N_2NaO_4$: 239.1002, found 239.1010.

*4.28 (3R,4R,5S)-5-(N-acetyl)Amino-3,4-dihydroxy-1-N-butyl-piperidine (**40**):*

Compound **37** (0.041 g, 0.217 mmol) was acetylated in water (1.0 mL)/MeOH (1.0 mL) using triethylamine (0.0242 g, 0.239 mmol) and acetic anhydride (0.0244 g, 0.239 mmol) at 44 ^oC following the general procedure to get the *N*-acetylated derivative **40** (0.0458 g, 91%) as a colorless viscous liquid after purification by column chromatography using a mixture of acetonitrile and aqueous ammonium hydroxide solution (9:1). R_f : 0.61 (CH_3CN-NH_4OH, 4:1); Specific rotation: $[\alpha]_D^{30}$ +32.6 (*c* 0.60, MeOH); IR (neat): $\bar{\upsilon}$ 3338, 3286, 3094, 2924, 2861, 1650, 1562, 1438, 1372, 1313, 1150, 1065, 730, 607 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.80 (td, *J* = 10.8, 4.4 Hz, 1H), 3.61 (td, *J* = 10.4, 4.8 Hz, 1H), 3.30 (t, *J* = 9.6 Hz, 1H), 3.15 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.06 (dd, *J* = 11.6, 3.2 Hz, 1H), 2.57 (overlapped signals, 2H), 2.21 (q, *J* = 11.6 Hz, 2H), 1.93 (s, 3H), 1.44 (qui, *J* = 7.6 Hz, 2H), 1.22 (sextet, *J* = 7.6 Hz, 2H), 0.81 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 174.27 (s), 74.77 (d), 69.17 (d), 56.75 (t), 55.97 (t), 54.13 (t), 49.72 (d), 27.12 (t), 22.03 (q), 19.84 (t), 13.09 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{23}N_2O_3$: 231.1703, found 231.1701.

*4.29 (3R,4R,5S)-5-(N-acetyl)Amino-3,4-dihydroxy-1-N-(2-hydroxyethyl)-piperidine (**41**):*

Compound **38** (0.038 g, 0.215 mmol) was acetylated in water (1.0 mL)/MeOH (1.0 mL) using triethylamine (0.024 g, 0.237 mmol) and acetic anhydride (0.0242 g, 0.237 mmol) at 44 ^oC following the general procedure to get the *N*-acetylated derivative **41** (0.04 g, 85%) as a colorless viscous liquid after purification by column chromatography using a mixture of acetonitrile and aqueous ammonium hydroxide solution (4:1). R_f : 0.33 (CH_3CN-NH_4OH, 7:3); Specific rotation: $[\alpha]_D^{30}$ +8.5 (*c* 0.35, H_2O); IR (neat): $\bar{\upsilon}$ 3497, 3411, 3331, 2939, 1645, 1556, 1433, 1376, 1317, 1044, 958, 611 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ 3.76 (td, *J* = 10.8, 4.4 Hz, 1H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.58 (td, *J* = 10.0, 4.8 Hz, 1H), 3.24 (t, *J* = 9.6 Hz, 1H), 3.06 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.97 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.13 (t, *J* = 11.2 Hz, 1H), 2.09 (t, *J* = 11.2 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ

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174.32 (s), 75.41 (d), 69.68 (d), 57.99 (t), 57.91 (t), 56.89 (t), 54.98 (t), 50.24 (d), 22.04 (q); HRMS (ESI): $[M + H]^+$ calcd for $C_9H_{19}N_2O_4$: 219.1339, found 219.1341.

Acknowledgements

The authors are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial support in the form of a reserach grant (02(243)/15/EMR-II). The authors also thank the Department of Science and Technology (DST) and the Indian Institute of Technology Delhi (IITD) for funding of the ESI-HRMS at IIT Delhi. V.K.H thanks the Department of Science and Technology, New Delhi, for the INSPIRE Fellowship.

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A Common Strategy towards the Synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol, Deacetyl (+)-anisomycin and Amino-substituted Piperidine Iminosugars.

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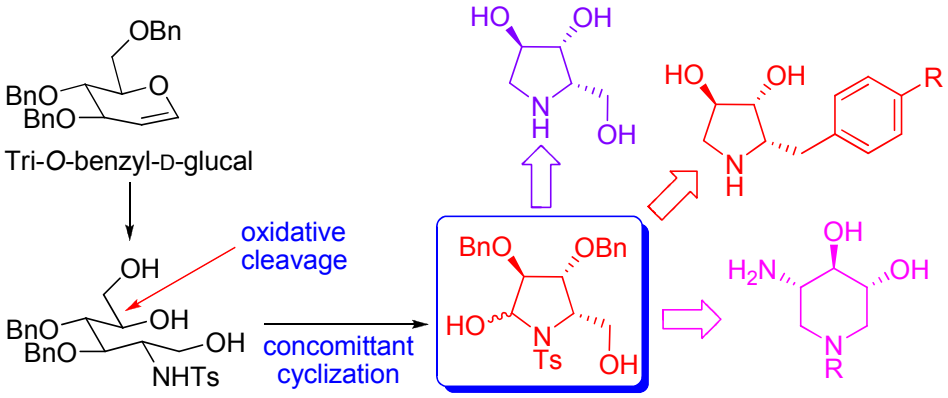

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HIGHLIGHTS

Anisomycin is an antibiotic that exhibit antitumour and antiviral activities.

A divergent strategy from a glycal provides access to three classes of compounds.

Oxidative cleavage of vicinal diol provides access to pyrrolidine skeleton.

Synthesis of compounds of biological relevance through a carbohydrate based approach.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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