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Selective sulfonylation of 4-*C*-hydroxymethyl-β-L-threo-pento-1,4-furanose: synthesis of bicyclic diazasugars

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Dedicated to Professor N. S. Narasimhan on the occasion of his 75th birthday

Abstract—Hydroxymethylation of α-D-xylo-pentodialdose **6** using excess formaldehyde and sodium hydroxide in THF–water (one pot aldol and crossed Cannizzaro reactions) followed by hydrogenolysis of C3-*O*-benzyl group afforded triol **8**. The regio-selective α- and β-sulfonylation of hydroxymethyl groups in **8** afforded **9a** (α-sulfonylation) and **14** (β-sulfonylation) in good yield. The cleavage of the 1,2-acetonide functionality, individually in **9a** and **14**, followed by reaction with 1,3-diaminopropane gave in situ formation of sugar aminals, that undergo concomitant nucleophilic displacement of the sulfonyloxy group by amino functionality to give hitherto unknown bicyclic diazasugars **4** and **5**, respectively, with a hydroxymethyl substituent at C-7.

1. Introduction

Azasugars, also known as iminosugars, demonstrate significant glycosidase inhibitory activity[1] and are therefore promising substrates in investigating structure-activity relationship of glycoproteins that play an important role in many biochemical processes including carbohydrate metabolic disorders,[2] viral infection,[3] cancer metastasis,[4] and immune response.[5] The search for new natural and unnatural azasugars thus opened a dynamic research field at the interface between glycobiology and synthetic organic chemistry. This resulted in the development of a new class of azasugars namely bicyclic diazasugrs **1** (Fig. 1). In general, the sugar analogues in which both the ring and glycosidic oxygen atoms have been replaced by nitrogen atoms, in a bicyclic system, are known as bicyclic diazasugars. Naturally occurring kifunensine **2**[6] and nagstatin **3**[7] are the bicyclic diazasugars which showed selectivity in enzyme inhibition,[8] enabling us to understand the processes of the intractable diseases such as nephritis, cancer and immune disorders.

In recent years, improved glycosidase inhibition is being examined for each hydroxyl substituent in azasugars and

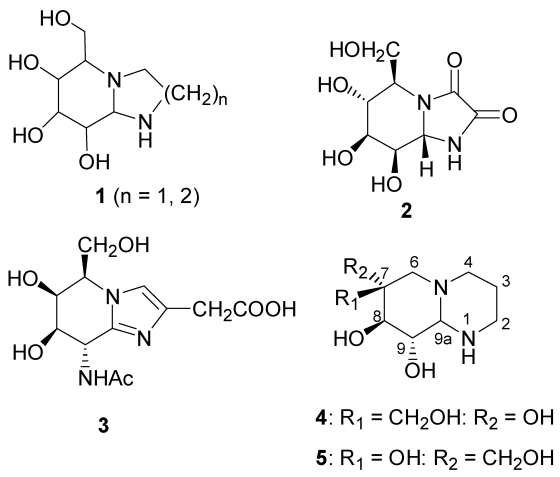

Figure 1. Bicyclic diazasugars.

systematic data of the inhibition of β-glucosidases is documented in the literature.[2,4,9] In this respect, Berges and co-workers have reported a number of new analogues of bicyclic diazasugars with different stereochemical orientation of the –OH functionality at C-6/C-7/C-8/C-9, as well as presence or absence of hydroxymethyl substituent at C-6 and observed that the presence of the hydroxymethyl substituent at C-6 of diazasugars had a significant effect on enzyme substrate activity.[10] Inspired by this observation and as a part of our continuing interest in the synthesis and evaluation of glycosidase inhibitory activities of

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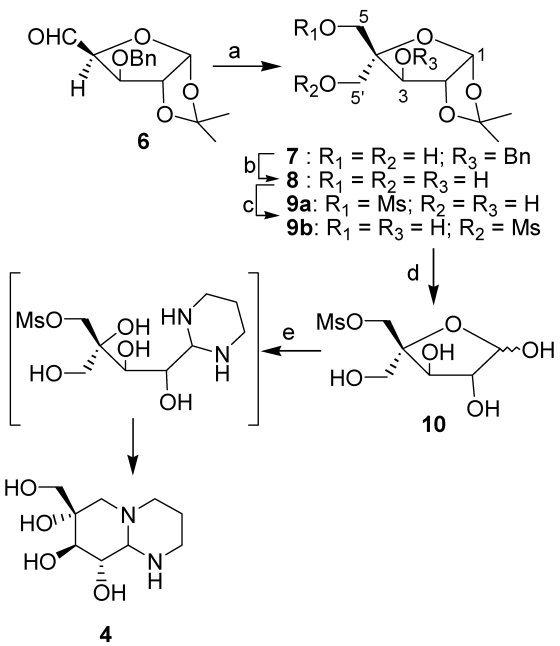
azasugars;[11] we are now reporting an efficient route for the synthesis of hitherto unknown hydroxymethyl bicyclic diazasugars **4** and **5** with both hydroxyl and hydroxymethyl substituents at C-7 (Fig. 1).

2. Results and discussion

2.1. Synthesis of bicyclic diazasugar 4

The aldol-crossed Cannizzaro reactions of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo-petodialdo-1,4-furanose (**6**)[12] with excess formaldehyde and sodium hydroxide in THF–water afforded diol **7** and triol **8** in the ratio 2:1 (Scheme 1). Selective sulfonylation of α- or β-hydroxymethyl group in **7** using either methane- or *p*-toluenesulfonyl chloride, under variety of reaction conditions, and also by use of dibutyltin oxide[13] afforded inseparable mixture in poor selectivity. In an attempt to achieve the selective α- or β-sulfonylation, we performed the reactions with triol **8** in which the bulky –OBn group at C3 is replaced by an –OH group. The formation of **8** (C-3 debenzylated product), as a minor product, under aldol-crossed Cannizzaro reactions in the basic medium is uncommon. We believe that the initially formed aldol-adduct **A** undergoes intra-molecular hydride delivery, assisted by the lone pair of electrons on the benzyloxy oxygen via a six membered transition state, to give intermediate ion pair **B**. Hydration of **B** followed by the loss of benzaldehyde, as shown in Figure 2, affords triol **8**.

The triol **8** in high yield, however, was obtained by hydrogenolysis of **7** with 10% Pd/C in methanol. Treatment of **8** with methanesulfonyl chloride (0.95 equiv.) in pyridine at −10 °C gave a mixture of mono-mesylated products **9a** and **9b** in the 3:1 ratio (Scheme 1). The major product **9a**



Scheme 1. Reagents and conditions: (a) HCHO, NaOH, THF–H_2O, rt, 10 h, (**7**, 41%), (**8**, 21%); (b) 10% Pd/C, MeOH, H_2, rt, 24 h, 93%; (c) MsCl, pyridine, −10 °C, 4 h, (**9a**, 44%); (d) TFA–H_2O, 0 °C to rt, 3 h, 93%; (e) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 81%.

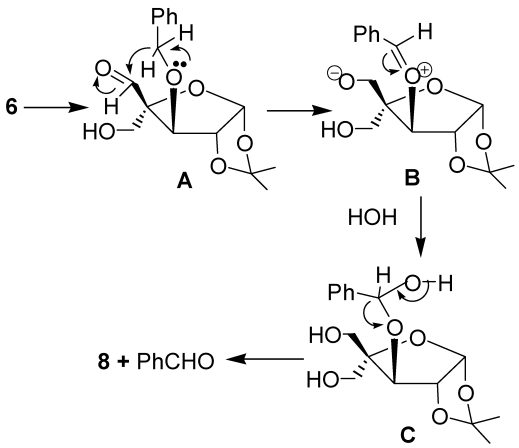


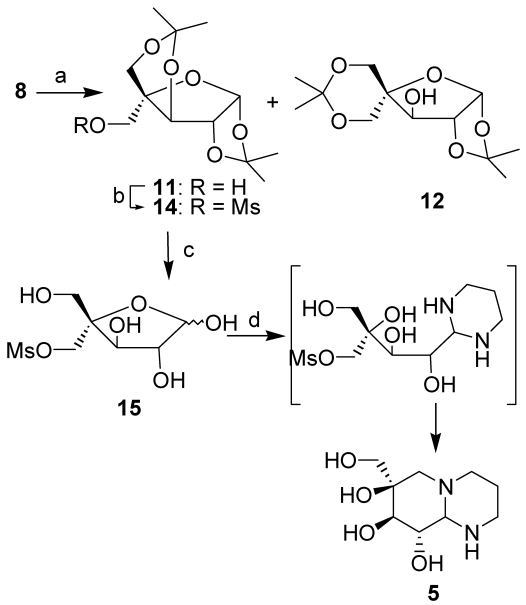
Figure 2. Mechanism for the formation of **8**.

was crystallized out from the binary solvent system (chloroform/hexane=1/1) on keeping the solution at 0 °C for 24 h.[14] The formation of the mono-mesylated product **9a** was evident from the ^{1}H NMR spectrum wherein one of the methylene protons, appeared at δ 4.33 as a AB quartet,[15] were assigned to the $-CH_2OMs$ group while; the other methylene protons, appeared at δ 3.59 as a singlet, were assigned to the $-CH_2OH$ functionality. The assignment of α or β-mesylated product was established by 1D-NOESY experiments. Thus, in compound **9a**, irradiation of a signal at δ 3.59 ($-CH_2OH$) showed NOE for the methylene protons at δ 4.33 ($-CH_2OMs$) and for a singlet at δ 4.19 corresponding to C-3 Hα. This indicated that the mesylation had occurred at the β-CH_2OH group resulting in (4*R*) absolute configuration at C-4. The good selectivity in the favor of **9a** could be attributed to the presence of α-oriented 1,2-acetonide functionality that hindered the mesylation of α-CH_2OH group. In the subsequent steps, the de-protection of the 1,2-acetonide functionality in **9a** (TFA/water=3/2) followed by reaction with 1,3-diaminopropane (1 equiv.) in methanol–water for 12 h afforded diazasugar **4** as a hygroscopic semi-solid in good yield.

2.2. Synthesis of bicyclic diazasugar 5

For the synthesis of C-7 epimeric diazasugar **5**, it was necessary to have α-sulfonyloxy methylene group at C-4 of **8**. This was visualized by prior protection of C3-βOH and C4 β-CH_2OH groups in **8** as an acetonide group.

Therefore, the regio-selective acetonide formation of triol **8** under various reaction conditions (e.g. change of catalyst and solvent) was studied (Scheme 2). As shown in Table 1, the reaction of acetone (as a reagent and solvent) in the presence of *p*-TSA afforded two products **11** and **12** in the ratio 15:85 in 78% yield (entry 1).[16] The use of CSA as a catalyst led to the poor selectivity (entry 2); while the copper sulphate afforded exclusive formation of undesired acetonide **12** albeit in low yield (entry 3). Alternatively, the reaction of triol **8** using 2,2-dimethoxypropane as a reagent was studied. The reaction of triol **8** with 2,2-dimethoxypropane (1 equiv.) in acetone using *p*-TSA as a catalyst, afforded two products **11** and **12** in the ratio 68:32 in 87% yield (entry 4).[17] Again, the use of CSA had no effect on regio-selectivity (entry 5), and in copper sulphate the



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxypropane, MeOH, *p*-TSA, 25 °C, 5 min, 97%; (b) MsCl, pyridine, 0 °C, 4 h, 92%; (c) TFA–H_2O, 0 °C to rt, 3 h, 97%; (d) $NH_2(CH_2)_3NH_2$, MeOH–H_2O, rt, 12 h, 79%.

reaction of **14** with TFA–water (3:2) furnished a hemiacetal, that on reaction with 1,3-diaminopropane in methanol–water gave the bicyclic diazasugar **5** as a semi-solid.

2.3. Conformational assignment

The bicyclic diazasugars are known to exist in $^4C_1$ and $^1C_4$ conformations (Fig. 3).[10] The presence of $-CH_2OH$ and $-OH$ groups on the same carbon atom (C-7), in compounds **4** and **5**, decides their conformation and configuration at C-7. Therefore, three structures **A**, **B** and **C** and **A′**, **B′**, and **C′** for compounds **4** and **5**, respectively, were considered. The coupling constant information, determined from the ^1H NMR spectra and decoupling experiments in D_2O, was used to assign the conformations for compounds **4** and **5** (Table 2). In case of **4**, appearance of a doublet of doublet at δ 3.49 and a doublet at δ 3.40 ($J_{9,9a}$=8.9 Hz; $J_{9,8}$=9.6 Hz) for H-9 and H-8, respectively, clearly indicated the *trans*-diaxial relationship between the H-8, H-9 and H-9a and thus ruled out the possibility of structure **C** with $^1C_4$ conformation. The coupling constant $J_{9,9a}$ was informative for the determination of the configuration at C-9a and the appearance of a doublet at δ 2.95, corresponding to H-9a,

Table 1. Selective acetonide formation in **8**

Entry	Reagent (equiv.)	Solvent	Catalyst	Reaction conditions		Product	Yield[a] (%)	Ratio[b] (**11**:**12**)
				Temperature (°C)	Time			
1	Acetone (30)		*p*-TSA	25	30 min	**11**, **12**	78	15:85
2	Acetone (30)		CSA	25	1.5 h	**11**, **12**	79	42:58
3	Acetone (30)		$CuSO_4$	30	2 days	**12**	19[c]	
4	2,2-Dimethoxy propane (1.1)	Acetone	*p*-TSA	20	5 min	**11**, **12**	87	68:32
5	2,2-Dimethoxy propane (1.1)	Acetone	CSA	25	40 min	**11**, **12**	78	10:90
6	2,2-Dimethoxy propane (1.1)	Acetone	$CuSO_4$	30	15 h	**11**, **12**	55[c]	55:45[17]
7	2,2-Dimethoxy propane (1.1)	DMF	*p*-TSA	25	5 min	**11**, **12**	89	39:61
8	2,2-Dimethoxy propane (1.1)	Methanol	*p*-TSA	25	5 min	**11**	89	100:00

[a] Yields refer to the isolated combined yields after chromatography.
[b] Ratio has been determined by ^1H NMR of the crude mixture.
[c] Starting recovered 40~50%.

reaction was found to be sluggish with poor regio-selectivity (entry 6). The change of solvent to DMF in the presence of *p*-TSA decreased the selectivity (entry 7). However, the use of methanol in the presence of *p*-TSA afforded **11** exclusively in a short reaction time and high yield (entry 8). We believe that a protic solvent like methanol increases the acidity of the *p*-TSA catalyst due to intermolecular hydrogen bonding. Under these conditions the initially formed spirocyclic acetonide **12** is likely to be unstable and the more stable bicyclic acetonide, derived from primary and secondary hydroxyl, affords acetonide **11** as the only isolable product.[18] This fact was confirmed by recording the ^1H NMR of **12** in methanol-d_4 before and after addition of catalytic amount of *p*-TSA wherein compound **12** was found to be completely converted to **11** within 5 min.

In the subsequent steps, the mesylation of the α-CH_2OH in 1,2:3,5-bis-acetonide **11** afforded the mesylate **14** in good yield (Scheme 2). The α-mesylated product **14** was confirmed by 1D-NOESY spectra wherein irradiation of signal at δ 4.17 for C3-Hα showed NOE for the methylene protons at δ 4.39 and 4.53 (C4-α-CH_2OMs). In the next step,

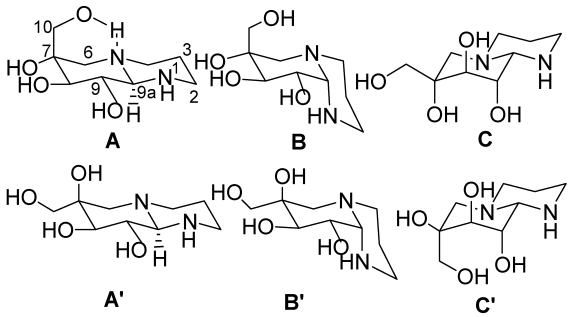


Figure 3. Conformational structures of **4** and **5**.

Table 2.

Compound	*J* (Hz)					
	$J_{2a,2e}$	$J_{4a,4e}$	$J_{6a,6e}$	$J_{8,9}$	$J_{9,9a}$	$J_{10a,10b}$
4	12.3	11.4	13.2	9.6	8.9	9.7
5	11.4	12.3	13.0	9.6	8.8	

with large coupling constant for ($J_{9,9a}$=8.9 Hz) indicated the structure **A** with $^4C_1$ conformation. The initial geometry in the precursor **9a** ensures that in the product **4** the −OH substituents at C-9, C-8 and C-8, C-7 should be *trans* and therefore the $-CH_2OH$ substituent was assigned the axial orientation with (7*S*) absolute configuration. Furthermore, we believe that the intra-molecular hydrogen bonding between $-CH_2OH$ and a lone pair of electrons on a fused ring nitrogen atom, in a six-membered transition state, stabilize the conformation **A**.

Since the ^{1}H NMR spectrum of **5** is different from **4**, it was thought that **5** could exist in different conformation. However, the appearance of one doublet of doublet at δ 3.59 ($J_{9,9a}$=8.9 Hz and $J_{9,8}$=9.8 Hz) and a doublet at δ 3.42 ($J_{8,9}$=9.6 Hz) for H-9 and H-8, respectively, indicated the *trans*-diaxial relationship of H-8, H-9 and H-9a. In addition, the appearance of a doublet at δ 3.21 for H-9a with large coupling constant ($J_{9a,9}$=8.9 Hz) indicated the $^4C_1$ conformation as shown in structure **A′**. Since the relative stereochemistry of substituents at C-9, C-8 and C-7 in precursor **15** is retained in the product formation, the $-CH_2OH$ substituent was assigned the equatorial orientation with (7*R*) absolute configuration.

2.4. Conclusion

In conclusion, we have demonstrated the utility of the aldol-crossed Cannizzaro reactions of α-D-xylo-pentodialdose **6** for the synthesis of hitherto unknown diazasugars **4** and **5** with hydroxymethylene substituents. In addition, a convenient method for the selective acetonide formation between the primary and secondary hydroxyl functionalities, in the presence of two primary hydroxymethylene groups, was developed using 2,2-dimethoxypropane and *p*-TSA in the presence of methanol as a solvent. A study of orientation of the hydroxymethylene group at C-7, in **4** and **5**, on the glycosidase inhibitory activity is in progress.

3. Experimental

3.1. General

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with FTIR as a thin film or in nujol mull or using KBr pellets and are expressed in cm^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in Hz. The assignments of the signals were confirmed by decoupling, DEPT and ^{1}H–^{1}H COSY experiments. Elemental analyses were carried out with C,H-analyzer. Optical rotations were measured using a Bellingham Stanley-ADP digital polarimeter using sodium light (D line 589.3 nm) at 25 °C. Thin layer chromatography was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh) and in some cases with ammonia solution. Amberlite A-21 anion exchange resin (OH^- form, weak base) was used for neutralization. The reactions were carried out in oven-dried glassware under dry N_2. Methanol, pyridine, THF, were purified and dried before use. Petroleum ether (PE) that was used is a distillation fraction between 40–60 °C. 1,3-Diaminopropane and 10% Pd/C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves-washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure. The suitably protected α-D-xylopentodialdose **6** was prepared as per the reported procedure.[12]

3.1.1. 1,2-*O*-Isopropylidene-3-*O*-benzyl-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (7) and 1,2-*O*-isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (8). To a solution of the aldehyde **6** (1.0 g, 3.60 mmol) in THF–water (30 mL, 2:1) was added sodium hydroxide (0.288 g, 7.20 mmol) in water (10 mL), formaldehyde solution (37–41% w/v, Merck) (0.238 g, 7.925 mmol), respectively and the reaction mixture was stirred at 25 °C for 10 h. The reaction mixture was neutralized with formic acid (0.5 mL) and evaporated to dryness. The residue thus obtained was extracted with ethyl acetate (3×30 mL), dried ($MgSO_4$) and concentrated. Purification of syrupy residue by column chromatography (20% ethyl acetate/PE) gave diol **7** (0.456 g, 41%) as a pale yellow solid, mp 70–71 °C; [Found: C, 62.08; H, 7.31. $C_{16}H_{22}O_6$ requires C, 61.92; H, 7.14%]; R_f (60% ethyl acetate/*n*-hexane) 0.34; $[\alpha]_D$=−42.5 (*c* 0.8, $CHCl_3$); ν_{max} (KBr) 3400–3250 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (3H, s, *Me*), 1.54 (3H, s, *Me*), 2.35–2.60 (2H, br s, O*H*, exchange with D_2O), 3.57–3.77 (4H, m, 2×CH_2OH), 4.10 (1H, d, *J*=1.6 Hz, *H*3), 4.54 (1H, d, *J*=11.8 Hz, *O*-CH_2Ph), 4.74 (1H, d, *J*=11.8 Hz, *O*-CH_2Ph), 4.76 (1H, dd, *J*=1.6, 4.4 Hz, *H*2), 6.00 (1H, d, *J*=4.4 Hz, *H*1), 7.26–7.39 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 26.8, 27.3, 63.1, 63.4, 72.5, 84.7, 85.7, 89.8, 104.8, 113.0, 127.5, 128.1, 128.5, 136.7.

Further elution with 60% ethyl acetate/PE gave **8** (0.166 g, 21%) as white solid, mp 98–99 °C (lit.[19a] mp 98–100 °C).

3.1.2. 1,2-*O*-Isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (8). Diol **7** (1.0 g, 3.22 mmol) and 10% Pd/C (0.22 g) in dry methanol was hydrogenolyzed under hydrogen (at 78 psi) at 25 °C for 24 h. The reaction mixture was filtered through celite, washed with methanol, concentrated and purified by chromatography (60% ethyl acetate/PE) to give triol **8** (0.652 g, 93%) as a white solid, mp 98–99 °C (lit.[19a] mp 98–100 °C); [Found: C, 49.19; H, 7.48. $C_9H_{16}O_6$ requires C, 49.08; H, 7.32]; R_f (60% ethyl acetate/*n*-hexane) 0.15; $[\alpha]_D$=−5.71 (*c* 0.35, MeOH) (lit.[19b] $[\alpha]_D$=−7.5, *c* 4, ethanol); ν_{max}(KBr) 3480–3300 (br band) cm^{-1}; δ_H (300 MHz, D_2O) 1.22 (3H, s, *Me*), 1.42 (3H, s, *Me*), 3.42–3.70 (4H, m, 2×CH_2OH), 4.11 (1H, br s, *H*3), 4.64 (1H, obscure with D_2O signal, *H*2) (confirmed by ^{1}H–^{1}H COSY experiments), 5.89 (1H, d, *J*=4.4 Hz, *H*1); δ_C (75 MHz, D_2O) 25.6, 26.1, 60.6, 61.2, 76.0, 87.5, 90.7, 104.5, 113.5.

3.1.3. 1,2-*O*-Isopropylidene-4-(*R*)-*C*-(hydroxymethyl)-5-*O*-methanesulfonyl-β-L-threo-pento-1,4-furanose (9a). To a cooled solution of triol **8** (1.0 g, 4.54 mmol) at −10 °C in dry pyridine (1.5 mL) was added methanesulfonyl chloride (0.49 g, 4.27 mmol) and stirring was

continued at −10 °C for 4 h. The reaction was decomposed by addition of ice water. Pyridine was co evaporated with toluene (2×3 mL). Chromatographic purification (10% ethyl acetate/PE) gave a mixture of monomesyl derivatives **9a** and **9b** (1.10 g, 81%). The isomeric mixture was dissolved in chloroform–hexane (30 mL, 1:1) and refrigerated at 0 °C for 24 h to afford **9a** (0.594 g, 44%) as a white solid, mp 139–140 °C; [Found: C, 40.19; H, 6.33. $C_{10}H_{18}SO_8$ requires C, 40.26; H, 6.08]; R_f (60% ethyl acetate/*n*-hexane) 0.22; $[\alpha]_D$=−53.3 (*c* 0.15, MeOH); ν_{max} (nujol) 3460–3200 (br), 1356 cm^{-1}; δ_H (300 MHz, D_2O) 1.23 (3H, s, *Me*), 1.46 (3H, s, *Me*), 3.12 (3H, s, *Me*), 3.59 (2H, s, C*H*$_2$OH), 4.19 (1H, br s, *H*3), 4.33 (2H, AB quartet, *J*=10.5 Hz, C*H*$_2$OMs), 4.68 (1H, obscure with D_2O signal, *H*2) (confirmed by $^1H-^1H$ COSY experiments), 5.94 (1H, d, *J*=4.1 Hz, *H*1); δ_C (75 MHz, D_2O) 24.8, 25.4, 36.5, 59.4, 67.8, 75.0, 86.7, 88.5, 104.9, 113.4. [For NOE experiment, 0.011 g of **9a** was dissolved in 0.8 mL of D_2O and the solution was purged with N_2 for 15 min].

3.1.4. (7*S*,8*R*,9*S*,9a*R*)-Octahydro-7-hydroxymethyl-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]pyrimidine (4). A solution of **9a** (0.5 g, 1.67 mmol) in TFA–H_2O (6 mL, 3:2) was stirred at 25 °C for 3 h. TFA was evaporated in vacuo and co evaporated with water (2×2 mL). The hemiacetal **10** thus obtained (0.398 g, 93%) was dissolved in water (6 mL) and 1,3-diaminopropane (0.057 g, 0.769 mmol; 0.5 equiv.) was added carefully with stirring. After 30 min a second lot of 1,3-diaminopropane (0.057 g, 0.5 equiv.) in MeOH (10 mL) was added dropwise at room temperature. After 12 h amberlite A-21 anion exchange resin (OH^- form, weak base) was added to neutralize methanesulfonic acid. The solution was filtered and the solvent was evaporated to give a gum that was dissolved in ethanol (1 mL) and precipitated with diethyl ether (15 mL). The precipitate thus obtained was filtered, washed with diethyl ether and dried. Chromatographic purification of the residue with chloroform/methanol/ammonia (80/19/1) afforded **4** (0.272 g, 81%) as a hygroscopic semi-solid mass; [Found: C, 35.25; H, 9.01. $C_9H_{18}N_2O_4{\cdot}5H_2O$ requires C, 35.06; H, 9.15]; R_f (66% methanol/chloroform) 0.14; $[\alpha]_D$=−4.0 (*c* 0.5, MeOH); ν_{max} (nujol) 3460–3150 (br), 2858 and 2735 cm^{-1}; δ_H (300 MHz, D_2O) 1.62–1.78 (2H, m, *H*3), 2.24 (1H, ddd, *J*=11.4, 10.5, 4.1 Hz, *H*2a), 2.32 (1H, d, *J*=3.2 Hz, *H*6a), 2.67 (1H, ddd, *J*=12.3, 10.5, 4.3 Hz, *H*4a), 2.71 (1H, d, *J*=13.2 Hz, *H*6e), 2.88 (1H, ddd, *J*=11.4, 3.8, 3.0 Hz, *H*2e), 2.95 (1H, d, *J*=8.9 Hz, *H*9a), 3.17 (1H, br d, *J*=12.3 Hz, *H*4e), 3.40 (1H, d, *J*=9.6 Hz, *H*8), 3.46 (2H, s, C*H*$_2$OH), 3.49 (1H, dd, *J*=9.8, 8.9 Hz, *H*9); δ_C (75 MHz, D_2O) 23.0, 42.9, 52.3, 57.6, 63.8, 71.0, 72.3, 72.4, 77.4.

3.1.5. 1,2:3,5-Di-*O*-isopropylidene-4-(*R*)-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (11). To a suspension of triol **8** (0.5 g, 2.27 mmol) in methanol (10 mL) was added 2,2-dimethoxypropane (0.380 g, 2.49 mmol) followed by *p*-toluenesulfonic acid (0.01 g, cat.) at 20 °C. The mixture became homogeneous after 5 min and tlc analysis indicated that the reaction was complete. The solution was concentrated, diluted with DCM (20 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4) and concentrated. Chromatography with 5% ethyl acetate/PE gave **11** (0.524 g, 89%) as colourless needles, mp 94–95 °C; [Found: C, 55.58; H, 7.92. $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.74]; R_f (33% ethyl acetate/*n*-hexane) 0.40; $[\alpha]_D$=+32.0 (*c* 0.25, $CHCl_3$); ν_{max}(KBr) 3500–3410 (br) cm^{-1}; δ_H (300 MHz, $CDCl_3$+D_2O) 1.34 (3H, s, *Me*), 1.39 (3H, s, *Me*), 1.41 (3H, s, *Me*), 1.58 (3H, s, *Me*), 3.68 (1H, d, *J*=12.1 Hz, OC*H*$_2$), 3.70 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.86 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.93 (1H, d, *J*=12.1 Hz, OC*H*$_2$), 4.14 (1H, s, *H*3), 4.64 (1H, d, *J*=4.1 Hz, *H*2), 6.06 (1H, d, *J*=4.1 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 21.5, 25.5, 26.1, 26.3, 63.0, 63.8, 74.7, 85.4, 85.7, 99.1, 105.8, 112.2.

3.1.6. 1,2:5,5′-Di-*O*-isopropylidene-4-*C*-(hydroxymethyl)-β-L-threo-pento-1,4-furanose (12). *p*-Toluenesulfonic acid (0.01 g, cat.) was added to a suspension of triol **8** (0.4 g, 1.82 mmol) and 2,2-dimethoxypropane (0.208 g, 1.99 mmol) in acetone (5 mL) at 20 °C. The mixture became homogeneous after 5 min and tlc analysis indicated that the reaction was complete. The solution was concentrated, diluted with DCM (20 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL), dried (Na_2SO_4) and concentrated. The crude product on chromatography with 5% ethyl acetate/PE gave **11** (0.279 g, 59%). Further elution with 10% ethyl acetate/PE gave **12** (0.132 g, 28%) as a clear syrup; [Found: C, 55.66; H, 7.86. $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.74]; R_f (33% ethyl acetate/*n*-hexane) 0.39; $[\alpha]_D$=−10.7 (*c* 1.5, $CHCl_3$); ν_{max} (nujol) 3418 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.29 (3H, s, *Me*), 1.40 (3H, s, *Me*), 1.49 (3H, s, *Me*), 1.51 (3H, s, *Me*), 3.30–3.51 (1H, br s, exchange with D_2O, O*H*), 3.74 (1H, d, *J*=12.0 Hz, OC*H*$_2$), 3.91 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 3.99 (1H, d, *J*=11.5 Hz, OC*H*$_2$), 4.03 (1H, d, *J*=12.0 Hz, OC*H*$_2$), 4.52 (1H, s, *H*3), 4.60 (1H, d, *J*=4.0 Hz, *H*2), 5.89 (1H, d, *J*=4.0 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 19.3, 25.5, 26.4, 27.5, 61.7, 65.7, 75.3, 82.0, 86.7, 98.2, 105.0, 111.9.

3.1.7. 1,2:3,5-Di-*O*-isopropylidene-4-(*S*)-*C*-(methanesulfonyloxymethyl)-β-L-threo-pento-1,4-furanose (14). To a solution of **11** (0.2 g, 0.77 mmol) in anhydrous pyridine (0.5 mL) was added methanesulfonyl chloride (0.106 g, 0.93 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Usual work-up and chromatography (10% ethyl acetate/PE) provided monomesylate **14** (0.24 g, 92%) as a white solid, mp 99–100 °C; [Found: C, 46.23; H, 6.57. $C_{13}H_{22}SO_8$ requires C, 46.14; H, 6.55]; R_f (25% ethyl acetate/*n*-hexane) 0.38; $[\alpha]_D$=+10.0 (*c* 0.2, $CHCl_3$); ν_{max}(KBr) 1352 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.34 ((3H, s, *Me*), 1.40 (3H, s, *Me*), 1.42 (3H, s, *Me*), 1.64 (3H, s, *Me*), 3.17 (3H, s, *Me*), 3.72 (1H, d, *J*=12.6 Hz, OC*H*$_2$), 3.98 (1H, d, *J*=12.6 Hz, OC*H*$_2$), 4.17 (1H, s, *H*3), 4.39 (1H, d, *J*=11.1 Hz, C*H*$_2$OMs), 4.53 (1H, d, *J*=11.1 Hz, C*H*$_2$OMs), 4.64 (1H, d, *J*=3.8 Hz, *H*2), 6.09 (1H, d, *J*=3.8 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 21.0, 25.3, 26.0, 26.2, 38.1, 62.1, 69.7, 74.4, 82.9, 84.8, 99.0, 106.5, 112.5.

3.1.8. (7*R*,8*R*,9*S*,9a*R*)-Octahydro-7-hydroxymethyl-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]pyrimidine (5). A solution of **14** (0.135 g, 0.326 mmol) in TFA-H_2O (4 mL, 3:2) was stirred for 3 h. TFA was evaporated under vacuum and co evaporated with water (3×2 mL) to leave a hemiacetal **15** (0.106 g, 97%). The hemiacetal **15** (0.105 g, 0.314 mmol) was dissolved in water (3 mL) and 1,3-diaminopropane (0.012 g, 0.161 mmol) (0.5 equiv.) was

added carefully with stirring. After 0.5 h extra 0.5 equiv. of 1,3-diaminopropane (0.012 g, 0.161 mmol) in MeOH (7 mL) was added dropwise at room temperature. Stirring was continued for 12 h and the solution was treated with amberlite A-21 anion exchange resin (OH^- form, weak base) to remove sulfonic acid. The solvent was filtered and evaporated to give a gum that was dissolved in ethanol (1 mL) and then ether was added with shaking. The precipitate thus obtained again washed with ether and dried. Column chromatographic purification of the residue with chloroform/methanol/ammonia (Merck, 25% solution)=70/29/1 afforded **5** (0.054 g, 79%) as a hygroscopic semi-solid mass; [Found: C, 37.71;H, 9.53. $C_9H_{18}N_2O_4{\cdot}4H_2O$ requires C, 37.23; H, 9.02%]; R_f (66% methanol/chloroform) 0.10; $[\alpha]_D$=+26.7 (*c* 0.15, MeOH); ν_{max} (nujol) 3500–3220 (br), 2832 and 2737 cm^{-1}; δ_H (300 MHz, D_2O) 1.72–1.87 (2H, m, *H*3), 2.34 (1H, ddd, *J*=11.4, 10.5, 4.1 Hz, *H*2a), 2.43 (1H, d, *J*=13.2 Hz, *H*6a), 2.80 (1H, d, *J*=13.2 Hz, *H*6e), 2.80–3.02 (2H, m, *H*2e and *H*4a), 3.21 (1H, d, *J*=8.9 Hz, *H*9a), 3.33 (1H, br d, *J*=12.3 Hz, *H*4e), 3.42 (1H, d, *J*=9.6 Hz, *H*8), 3.46 (2H, s, C*H*$_2$OH), 3.59 (1H, dd, *J*=9.8, 8.9 Hz, *H*9); δ_C (75 MHz, D_2O) 21.6, 42.7, 51.4, 57.4, 63.5, 70.1, 71.9, 72.4, 76.7.

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14. The mother liquor was found to be a mixture of **9a** and **9b**. Attempts to separate the mixture by flash chromatography were unsuccessful.
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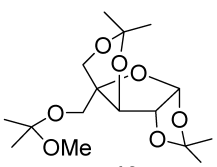
16. The structure of compounds **11** and **12** were confirmed by their conversion to monotosylate derivatives and NMR studies. In the tosylate derivative of **12** H-3 showed considerable downfield shift.



13

17. In the reactions of 2,2-dimethoxypropane (entry 4) we isolated ~10% of **13** as a white solid, mp 72–73 °C; [Found: C, 58.03; H, 8.31. $C_{16}H_{28}O_7$ requires C, 57.81;H, 8.49%]; R_f (33% ethyl acetate/*n*-hexane) 0.75; $[\alpha]_D=-13.3$ (*c* 0.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3+D_2O$) 1.28 (3H, s, *Me*), 1.32 (3H, s, *Me*), 1.33 (3H, s, *Me*), 1.35 (3H, s, *Me*), 1.42 (3H, s, *Me*), 1.56 (3H, s, *Me*), 3.20 (3H, s, O*Me*), 3.31 (1H, d, *J*=12.2 Hz, CH_2), 3.66 (1H, d, *J*=11.5 Hz, CH_2), 3.70 (1H, d, *J*=11.5 Hz, CH_2), 4.12 (1H, d, *J*=12.2 Hz, CH_2), 4.39 (1H, s, *H*3), 4.56 (1H, d, *J*=4.0 Hz, *H*2), 5.99 (1H, d, *J*=4.0 Hz, *H*1); δ_C (75 MHz, $CDCl_3$) 19.8, 24.3 (strong), 25.3, 26.0, 27.6, 48.8, 61.1, 62.7, 74.2, 82.2, 85.7, 97.6, 100.0, 105.5, 111.7. This **13** on treatment with *p*-TSA in methanol gave **11** only.
18. The formation of acetonide between α-CH_2OH and βC3-OH (*trans* fusion) is less favored than between β-CH_2OH and βC3-OH (*cis* fusion) and also hindered due to the 1,2-*O*-isopropylidene functionality.
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