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**A NEW STEREOSPECIFIC SYNTHESIS OF
1,2,4-TRIDEOXY-1,4-IMINO-D-*erythro*-PENTITOL**

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ABSTRACT

1,2,4-Trideoxy-1,4-imino-D-*erythro*-pentitol [(2*R*,3*S*)-3-hydroxy-2-hydroxymethylpyrrolidine] (**4**) was synthesised from 2,5-di-*O*-tosyl-D-ribo-1,4-lactone in 42 % overall yield. The key steps were deoxygenation at C-2 and a stereospecific inversion of the configuration at C-4. Compound **4** inhibited α -D-glucosidase ($K_i = 25 \mu\text{M}$) and β -D-glucosidase ($K_i = 80 \mu\text{M}$).

INTRODUCTION

Five-membered iminosugars (1,4-dideoxy-1,4-iminoalditols) **1** are potent inhibitors of glycosidases. Recently, the immucillins, 1-*C*-substituted iminoribitols (**2**, **3**, Y = OH), have been shown to be very potent inhibitors of purine nucleoside phosphorylase (PNP).¹ In studies of structure-activity relationships, the 2'-deoxy analogues **2** and **3** (Y = H) have been synthesised by deoxygenation of the parent compounds **2** and **3** (Y = OH).²

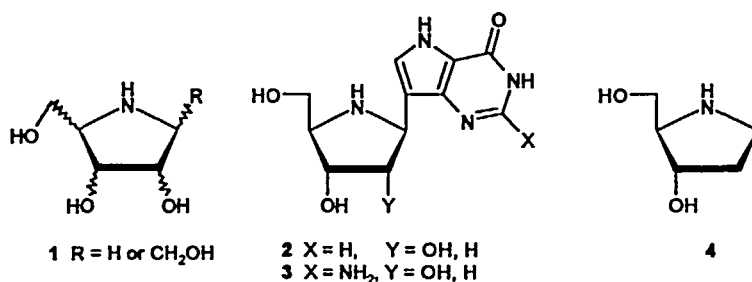


Figure 1

1,2,4-Trideoxy-1,4-imino-D-erythro-pentitol (4), the iminosugar residue in the 2'-deoxyimmucillins (2, 3, Y = H), is a natural product which has been isolated from the seeds of the legume *Castanospermum australe*.³ Recent interest in 4 has centered on its incorporation into DNA oligonucleotide analogues (Figure 2). These analogues have been evaluated as inhibitors of *N*-glycosylases,⁴ and their interactions with complementary DNA and RNA have been examined.⁵

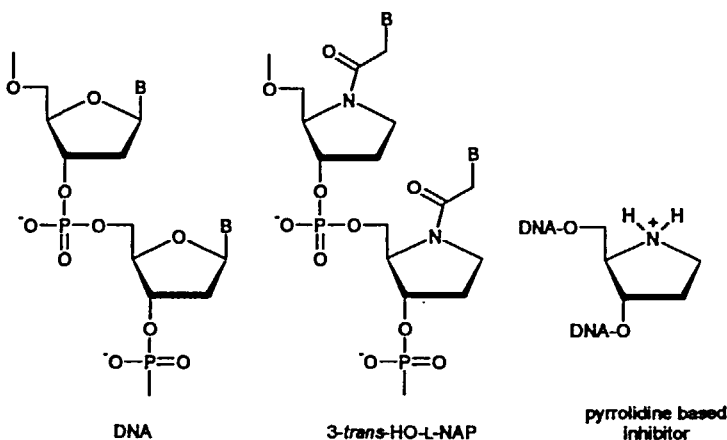


Figure 2

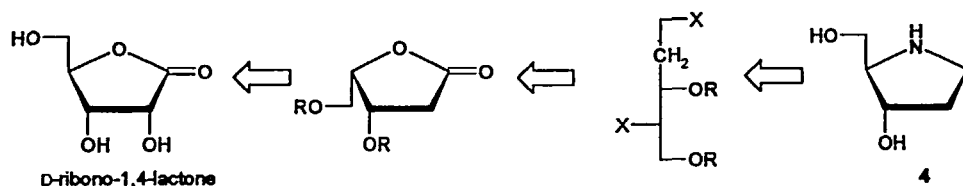
Although several syntheses of 1,2,4-trideoxy-1,4-imino-D-erythro-pentitol (4) have been reported^{4,5,6,7,8} none of them are entirely satisfactory. The two most direct syntheses both use D-serine derivatives as starting materials. The more recent one consists of 8 steps from (*R*)-Garner aldehyde (D-serine derivative) and features a chromium(II) chloride-mediated coupling reaction of (*R*)-Garner aldehyde with allyl bromide to give the corresponding homoallylic alcohol.⁶ The coupling proceeds with moderate diastereoselectivity forming the required alcohol and an isomer in a 6:4 ratio. After sepa-

ration, the diastereomerically pure homoallylic alcohol is transformed into **4** in an overall yield of 21 % from (*R*)-Garner aldehyde.

The other method⁵ was originally reported by Rapoport.⁹ It involves 6 steps from D-serine and proceeds by way of *N*-(phenylsulfonyl)-D-serine to **4** in an overall yield of 13 %. The two steps that cause the low yield are (i) coupling of the serine derivative with vinylmagnesium bromide which proceeds in 50 % average yields, and (ii) the lack of diastereoselectivity in the final reduction step, which necessitates separation of **4** from its C-3 isomer (5:2 ratio).

Our continuing interest in developing efficient syntheses of iminosugars,¹⁰ together with an interest in the application of **4** as the core structure in DNA analogues^{4,5} (Figure 2), led us to develop a stereospecific synthesis of **4** based on a chiral pool starting material. Access to the 2-deoxy-iminoribitol **4** in a suitably protected form would also be of interest, since it might enable a more direct approach to the 2'-deoxyimmucillins (**2**, **3**, Y = H).

Our approach uses D-ribo-1,4-lactone as the starting material, and involves as the key steps deoxygenation at C-2, stereospecific inversion of the configuration at C-4, reduction of the lactone moiety and activation of the hydroxy groups for ring closure with an amine to form the pyrrolidine **4** (Scheme 1).



Scheme 1

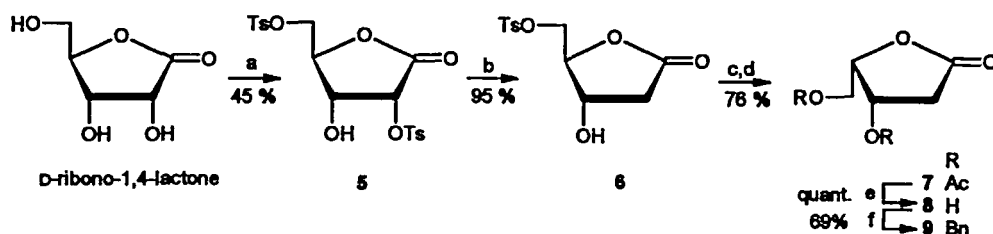
Retrosynthetic analysis of **4**

RESULTS AND DISCUSSION

Selective deoxygenation at C-2 in aldono-lactones is easily performed by sequential treatment of either a 2-bromo-2-deoxy- or a 2-tosyloxylactone with hydrazine followed by bromine.¹¹ Thus, 2,5-di-*O*-tosyl-D-ribo-1,4-lactone (**5**) was the starting material of choice, since it is readily available in 45 % yield as a shelf-stable crystalline solid by selective ditosylation of D-ribo-1,4-lactone.¹² Deoxygenation of **5** gave the 2-deoxylactone **6** in 95 % yield.¹³

Previously we have shown that 5-*O*-mesyl-2,3-di-*O*-isopropylidene-D-ribo-1,4-lactone, by treatment with aqueous base followed by acidification to pH 3, was transformed into the 2,3-di-*O*-isopropylidene-L-lyxono-1,4-lactone.^{11, 14} Thus a stereoselective inversion at C-4 had taken place. The reaction proceeded by formation of a 4,5-epoxide of an open-chain carboxylate derivative, then intramolecular attack by the carboxylate anion opens the epoxide at C-4 with inversion of the configuration. Using this concept, the 5-*O*-tosylated 2-deoxylactone **6** gave the 2-deoxylactone **8** with the *L*-*threo*-configuration by treatment with strong base (Scheme 2). In order to remove the salts, the crude product was acetylated under standard conditions to give 3,5-di-*O*-acetyl-2-deoxy-*L*-*threo*-pentono-1,4-lactone (**7**).

Following the synthetic strategy (Scheme 1), stable protecting groups at C-3 and C-5 were required, and **7** was thus deacetylated and then benzylated. Deacetylation was performed using hydrochloric acid in methanol, benzylation was affected using benzyl trichloroacetimidate¹⁵ in dioxane under slightly acidic conditions,¹⁶ since standard basic conditions would lead to isomerisation and elimination reactions. These steps gave 3,5-di-*O*-benzyl-2-deoxy-*L*-*threo*-pentono-1,4-lactone (**9**) in 69 % yield after chromatography, which was necessary in order to remove trichloroacetamide. The *threo*-configuration was further established since ¹H and ¹³C NMR data were different from those published for the *erythro*-isomer.¹⁶ Thus, $J_{3,4}$ was 5.9 Hz for compound **9** while $J_{3,4}$ was reported to be 2 Hz for the *erythro*-isomer.



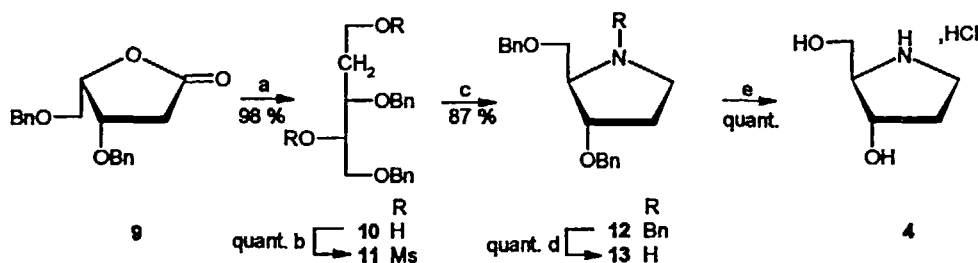
Scheme 2

a) 2.3 eq TsCl, pyridine/acetone, 0 °C; b) 3 eq 80 % aq hydrazine, Br₂, dioxane, 0 °C-rt; c) i: 3 eq KOH, H₂O, ii: conc HCl; d) Ac₂O, cat HClO₄, rt; e) 2 vol % AcCl in MeOH, rt; f) 5 eq benzyl trichloroacetimidate, CF₃SO₃H (pH 3), dioxane, rt.

Reduction of the benzylated lactone **9** using LiAlH₄ in THF (Scheme 3) gave the corresponding diol **10** (98 %) which was converted directly to the dimesylate **11** in quan-

titative yield. The mesylation was performed by slow addition of **10** to the solution of MsCl in pyridine to avoid possible intramolecular ring closure of the intermediate monomesylates. Cyclisation of the dimesylate **11** with benzylamine in DMF gave the protected pyrrolidine **12** in 87 % yield. Selective *N*-debenzylation could be performed by hydrogenation of **12** in MeOH in the presence of catalytic amounts of $\text{Pd}(\text{OH})_2$ and 25 % aq NH_3 to give **13** in quantitative yield.

Finally, complete debenzoylation of **12** by hydrogenation in the presence of 10 % palladium on charcoal gave the natural product 1,2,4-trideoxy-1,4-imino-D-erythro-pentitol (**4**).



Scheme 3

a) LiAlH_4 , THF, 0°C - rt; b) 3 eq MsCl , pyridine; c) BnNH_2 , DMF, $50-60^\circ\text{C}$; d) 10 % $\text{Pd}(\text{OH})_2$, H_2 , cat 25 % aq NH_3 , MeOH, rt; e) 10 % Pd/C , H_2 , cat HCl, EtOH, rt.

1,2,4-Trideoxy-1,4-imino-D-erythro-pentitol (**4**) was evaluated as an inhibitor of a set of commercially available glycosidases. It showed activity towards α - and β -glucosidases, only. The α -glucosidase (yeast) was inhibited with a K_i of 25 μM and β -glucosidase (almonds) with a K_i of 80 μM . Compared to the two 1,4-dideoxy-1,4-imino-pentitols having a hydroxy group at C-2, the inhibition was in the same range for α -glucosidase as for the *D-ribo*-isomer (K_i of 23 μM)¹⁷ while the 1,4-dideoxy-1,4-imino-D-arabinitol showed an IC_{50} of 0.18 μM .¹⁸ The 2-deoxy-1,4-iminopentitol **4** was a stronger inhibitor of the β -glucosidase than the *D-arabino*-analogue which had an IC_{50} value of 200 μM .¹⁸

CONCLUSION

In this paper, the first stereospecific synthesis of 1,2,4-trideoxy-1,4-imino-D-erythro-pentitol (**4**) has been described. From the readily available 2,5-di-*O*-tosyl-D-

ribo-1,4-lactone, compound **4** was obtained in 42 % overall yield. All the reactions were easily performed on a multi-gram scale, which makes this route an attractive alternative to the existing methods.

Further work on the applications of 1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol is in progress.

EXPERIMENTAL

General methods. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz, referenced to the solvent peak (CDCl_3 : δ 7.27 for ^1H , 77.4 for ^{13}C ; D_2O : δ 4.63 for ^1H) or dioxane (δ = 67.4 for ^{13}C) as internal standard. NMR spectra were assigned using HH and CH correlated spectra. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. TLC was performed on Merck 60 F254 precoated plates. Flash column chromatography was performed with silica gel 60 (Merck, 40–63 μm). All solvents were distilled before use. All evaporations were performed in vacuo below 40 °C.

Inhibition analysis. α -D-Glucosidase from Bakers yeast, β -D-glucosidase from almonds, α -D-galactosidase from green coffee beans, β -D-galactosidase from *Eschericia coli*, α -D-mannosidase from jack bean, β -D-mannosidase from snail and α -L-fucosidase from bovine kidney were purchased from Sigma. K_i determination were run at 25 °C for the α -glycosidases and at 35 °C for the β -glycosidases using the corresponding *p*-nitrophenyl α - or β -glycosides at various concentrations, ranging from 3×10^{-3} to 7×10^{-4} M at pH 6.8 (0.12 M phosphate buffer). For the inhibition studies, inhibitors were incorporated in the buffer to give a final concentration of 2×10^{-5} M. Enzymes were incorporated in the buffer to give a final concentration of 0.2 units/mL. Dissociation constants for inhibition were calculated from a Hanes-plot ($[\text{S}]/v$ against $[\text{S}]$) from the rates of substrate hydrolysis in the absence and presence of inhibitor.

2-Deoxy-5-O-tosyl-D-*erythro*-pentono-1,4-lactone (6**).** Ditosyl lactone **5**¹² (10.0 g, 21.9 mmol) was dissolved in dioxane (100 mL) and cooled to 0 °C. NH_2NH_2 (80 % aq 6.4 mL) was added and stirring was continued for 30 min at rt. After cooling to 0 °C, Br_2 (ca 8 mL) was added dropwise until N_2 evolution ceased. The reaction mixture was concentrated. The residue was dissolved in H_2O (50 mL), neutralised with sat NaHCO_3 and

extracted with CHCl_3 (4×40 mL). The extract was dried (NaSO_4) and concentrated to give **6** as a colourless crystalline residue (6.0 g, 95 %); mp 53–55 °C, $[\alpha]_{\text{D}}^{20} +32.1^\circ$ (c 3.2, CH_2Cl_2). Lit¹⁹: mp 55–57 °C, $[\alpha]_{\text{D}}^{20} +39.6^\circ$ (c 5.3, CH_2Cl_2). ^1H NMR (CDCl_3 , 300 MHz): δ 2.45 (3H, s, CH_3), 2.51 (1H, dd, $J = 18.0, 3.0$, H-2), 2.87 (1H, dd, $J = 18.0, 7.0$, H-2'), 3.23 (1H, br. s, OH), 4.18 (1H, dd, $J = 11.0, 3.0$, H-5), 4.26 (1H, dd, $J = 11.0, 3.0$, H-5'), 4.55 (2H, m, H-3, H-4), 7.47 (2H, arom. H), 7.75 (2H, arom. H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.3 (CH_3), 37.3 (C-2), 67.9, 68.1 (C-3, C-5), 84.0 (C-4), 127.5, 129.9, 131.3, 145.4 (arom. C), 175.2 (C-1).

3,5-Di-O-acetyl-2-deoxy-L-threo-pentono-1,4-lactone (7). Tosyl lactone **6** (10.57 g, 36.9 mmol) was dissolved in H_2O (200 mL) containing KOH (6.2 g, 110.8 mmol) and stirred overnight at rt. The reaction mixture was acidified with conc HCl to pH 1, concentrated and co-concentrated with toluene to a yellow residue of 2-deoxy-L-threo-pentono-1,4-lactone (**8**) mixed with salts. The crude product was acetylated using Ac_2O (120 mL) and 5 drops of HClO_4 for 3 h at rt. The reaction was quenched with ice (200 mL), stirred for 1.5 h and extracted with CH_2Cl_2 (3×100 mL). The organic phase was washed with H_2O (3×100 mL), sat NaHCO_3 (100 mL), dried (NaSO_4), filtered and concentrated to a yellow oil of sufficient purity for further reaction (6.07 g, 76 % from **6**). An analytical sample (colourless oil) was obtained by column chromatography (EtOAc /pentane 2:1, $R_f = 0.33$); $[\alpha]_{\text{D}}^{25} -33.8^\circ$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 2.08 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.64 (1H, dd, $J = 18.3, 2.3$, H-2), 2.93 (1H, dd, $J = 18.3, 6.6$, H-2'), 4.32 (1H, dd, $J = 11.5, 2.0$, H-5), 4.37 (1H, d, $J = 11.5$, H-5'), 4.79 (1H, m, H-4), 5.56 (1H, ddd, $J = 6.6, 4.9, 2.3$, H-3). ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.0 (CH_3), 36.3 (C-2), 61.8 (C-5), 69.8 (C-3), 82.4 (C-4), 170.2, 170.7 (C=O), 173.5 (C-1).

Anal. Calcd for $\text{C}_9\text{H}_{12}\text{O}_6$ (216.19): C, 50.00; H 5.59. Found: C, 49.70; H, 5.48.

2-Deoxy-L-threo-pentono-1,4-lactone (8). The lactone **7** (5.13 g, 23.7 mmol) was dissolved in 2 vol % AcCl in MeOH (150 mL) and stirred overnight at rt. The solution was concentrated and co-concentrated with toluene to give **8** as colourless oil in quantitative yield. ^1H NMR (D_2O , 300 MHz): δ 2.45 (1H, dd, $J = 18.0, 1.5$, H-2), 2.94 (1H, dd, $J = 18.0, 6.0$, H-2'), 3.80 (2H, m, H-5, H-5'), 4.56 (2H, m, H-3, H-4). ^{13}C NMR (D_2O , 75 MHz): δ 39.1 (C-2), 60.1 (C-5), 68.2 (C-3), 86.1 (C-4), 179.9 (C-1).

3,5-Di-*O*-benzyl-2-deoxy-*L*-threo-pentono-1,4-lactone (9). Lactone **8** (3.39 g, 17 mmol) was dissolved in anhydrous dioxane (80 mL) under argon. Benzyl-2,2,2-trichloroacetimidate^{15,16} (22.0 mL, 119 mmol) and CF₃SO₃H (0.4 mL, pH 2.5-3) were added, and the solution was stirred at rt overnight. The solution was concentrated, and the residue was partitioned between H₂O (100 mL) and CH₂Cl₂ (100 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic phases were washed with water, dried (NaSO₄) and concentrated to a crystalline residue, which was dissolved in CH₂Cl₂ (50 mL) and pentane (50 mL) and cooled to 0 °C to crystallise the trichloroacetimidate. Filtration, washing of the residue with CH₂Cl₂/pentane 1:1 followed by concentration of the combined filtrates gave a residue (25 g), which was further purified by column chromatography (d = 6 cm, h = 18 cm, EtOAc/pentane 1:2, R_f = 0.24). This gave **9** as an oil (3.64 g, 69 % yield). Further chromatography afforded an analytical sample; [α]_D²⁷ -2.0 °, [α]_D²⁷ -7.0 ° (c 1.7, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ 2.61 (1H, dd, *J* = 17.3, 5.9, H-2), 2.70 (1H, dd, *J* = 17.3, 2.9, H-2'), 3.84 (1H, dd, *J* = 10.7, 5.1, H-5), 3.87 (1H, dd, *J* = 10.7, 5.1, H-5'), 4.31 (1H, ddd, *J* = 5.9, 5.1, 2.9, H-3), 4.43, 4.54, 4.57, 4.59 (4H, 4 × d, *J* = 12.0, CH₂Ph), 4.61 (1H, q, *J* = 5.1, H-4), 7.22-7.36 (10H, arom. H). ¹³C NMR (CDCl₃, 125 MHz): δ 35.9 (C-2), 68.1 (C-5), 72.1, 74.1 (2 × CH₂Ph), 74.9 (C-3), 82.3 (C-4), 128.0-138.2 (arom. C), 175.1 (C-1).

Anal. Calcd for C₁₉H₂₀O₄ (312.36): C, 73.06; H, 6.45. Found: C, 72.97; H, 6.38.

3,5-Di-*O*-benzyl-2-deoxy-*L*-threo-pentitol (10). The dibenzylloxylactone **9** (0.60 g, 1.92 mmol) was dissolved in THF (15 mL, anal grade) and cooled to 0 °C. LiAlH₄ (300 mg, 7.9 mmol) was added in one portion and stirring was continued at 0 °C for 15 min and at rt for 1 h. The reaction was quenched by adding H₂O (300 μL), 15 % aq NaOH (300 μL) and H₂O (900 μL), successively. The mixture was filtered through celite, and the residue washed with EtOAc (3 × 30 mL). Concentration afforded **10** as colourless oil (0.61 g, 98 % yield). Column chromatography (EtOAc, R_f = 0.43) afforded an analytical sample. [α]_D²⁴ +3.50° (c 0.9, CHCl₃). ¹H NMR (CDCl₃, 500 MHz): δ 1.81 (1H, m, H-2), 1.93 (1H, m, H-2'), 3.56 (1H, dd, *J* = 10.0, 1.5, H-5), 3.59 (1H, d, *J* = 10.0, H-5'), 3.72, 3.77 (3H, m, H-1, H-1', H-4), 3.91 (1H, m, H-3), 4.54 (2H, 2 × d, *J* = 12.0, CH₂Ph), 4.56 (1H, d, *J* = 11.5, CH₂Ph), 4.63 (1H, d, *J* = 11.5, CH₂Ph), 7.20-7.40 (10H, arom. H). ¹³C NMR (CDCl₃, 75 MHz): δ 33.7 (C-2), 59.7 (C-1), 71.5 (CH₂), 72.3 (C-3), 73.1 (CH₂), 73.9 (CH₂), 77.4 (C-4), 126.5-138.4 (arom. C).

Anal. Calcd for C₁₉H₂₄O₄ (316.40): C, 72.13; H, 7.65. Found: C, 71.81; H, 7.44.

3,5-Di-*O*-benzyl-2-deoxy-1,4-di-*O*-mesyl-1-*threo*-pentitol (11). To a solution of MsCl (2.20 mL, 28.44 mmol) in pyridine (75 mL) was added dropwise the diol **10** (2.99 g, 9.48 mmol) in pyridine (36 mL) during 30 min at 0 °C. Stirring was continued at 0 °C for 50 min and at rt for further 40 min. After concentration the residue was dissolved in CH_2Cl_2 (100 mL), washed with H_2O (3×50 mL), dried (MgSO_4), filtered and concentrated to give a light yellow oil in quantitative yield. The crude product **11** was sufficiently pure for further synthesis. Purification by column chromatography (EtOAc /pentane 1:1, $R_f = 0.42$) afforded an analytical sample **11** as a colourless oil; $[\alpha]_D^{25} -27.4^\circ$ (c 0.9, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 1.91 (1H, m, H-2), 2.08 (1H, m, H-2'), 2.93 (3H, Ms), 3.01 (3H, Ms), 3.73 (2H, dd, $J = 10.5, 5.0$, H-5, H-5'), 3.89 (1H, m, H-3), 4.30 (2H, m, H-1, H-1'), 4.52 (2H, $2 \times d$, $J = 11.7$, CH_2Ph), 4.61 (2H, $2 \times d$, $J = 11.3$, CH_2Ph), 4.86 (1H, q, $J = 5.0$, H-4), 7.23-7.40 (10H, arom. H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 30.4 (C-2), 37.8, 38.9 ($2 \times \text{CH}_3$), 66.4 (C-1), 68.9 (C-5), 73.7, 74.0 ($2 \times \text{CH}_2\text{Ph}$), 74.6 (C-3), 81.8 (C-4), 128.3-137.7 (arom. C).

Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_8\text{S}_2$ (472.57): C, 53.37, H, 5.97, S, 13.57. Found: C, 53.94; H, 6.25; S, 13.33.

***N*-Benzyl-3,5-di-*O*-benzyl-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol (12).** To dimesylate **11** (0.57 g, 1.21 mmol) in anhydrous DMF (10 mL) was added BnNH_2 (6 mL). The solution was stirred at 50-60 °C for 16 h. Concentration afforded an oil, which was purified by column chromatography (EtOAc /pentane 1:3, $R_f = 0.34$) to give a colourless oil (0.39 g, 87 %); $[\alpha]_D^{25} -23.3^\circ$ (c 1.5, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 1.85 (2H, m, H-2, H-2'), 2.55 (1H, dd, $J = 17.8, 8.6$, H-1), 2.88 (2H, m, H-1', H-4), 3.35 (1H, dd, $J = 9.8, 6.8$, H-5), 3.45 (1H, dd, $J = 9.8, 4.7$, H-5'), 3.54 (1H, d, $J = 13.0$, NCH_2Ph), 3.93 (1H, m, H-3), 4.04 (1H, d, $J = 13.0$, NCH_2Ph), 4.50, 4.51 (4H, OCH_2Ph), 7.2-7.4 (15H, arom. H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 31.0 (C-2), 52.7 (C-1), 60.2 (NCH_2Ph), 70.3 (C-4), 70.9 (OCH_2Ph), 72.0 (C-5), 73.7 (OCH_2Ph), 82.4 (C-3), 126.5-139.9 (arom. C).

Anal. Calcd for $\text{C}_{26}\text{H}_{29}\text{O}_2\text{N}$ (387.52): C, 80.59; H, 7.54; N, 3.61. Found: C, 80.59; H, 7.58; N, 3.59.

3,5-Di-*O*-benzyl-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol (13). The *N*-benzylamine **12** (2.65 g, 7.06 mmol) was dissolved in MeOH (70 mL) and 25 % aq NH_3 (0.7 mL) and 10 % $\text{Pd}(\text{OH})_2$ (280 mg) were added. The mixture was hydrogenated at rt

and 1 atm for 2 days. The solution was filtered through celite, the residue washed with MeOH and the combined filtrate concentrated to give **13** as a colourless oil in quantitative yield (sufficiently pure for further synthesis). Purification by column chromatography (EtOAc/ MeOH 9:1, 1 vol % NEt₃) afforded an analytical sample of amine **13**; $[\alpha]_D^{25} +11.7^\circ$ (*c* 0.8, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.85 (1H, s, NH), 1.88 (2H, m, H-2, H-2'), 3.02 (2H, m, H-1, H-1'), 3.31 (1H, dt, *J* = 5.5, 3.8, H-4), 3.47 (2H, 2 \times dd, *J* = 10.7, 5.5, H-5, H-5'), 3.91 (1H, ddd, *J* = 5.6, 3.8, 3.8, H-3), 7.2-7.4 (10H, arom. H). ¹³C NMR (CDCl₃, 75 MHz): δ 31.3 (C-2), 44.2 (C-1), 63.0 (C-4), 70.1 (CH₂Ph), 70.4 (C-5), 72.2 (CH₂Ph), 80.3 (C-3), 126.5-137.4 (arom. C).

Anal. Calcd for C₁₉H₂₃O₂N (297.40): C, 76.74; H, 7.79; N, 4.71. Found: C, 76.87; H, 7.68; N, 4.42.

1,2,4-Trideoxy-1,4-imino-D-erythro-pentitol (4). Amine **13** (110 mg, 0.39 mmol) was dissolved in EtOH (5 mL) and Pd/C (50 mg) and 3 drops of conc HCl were added. The mixture was hydrogenated at rt and 1 atm for 24 hours. The solution was filtered through celite, the residue washed with EtOH and the combined filtrate concentrated to give the hydrochloride salt of **4** as oil in quantitative yield; $[\alpha]_D^{25} +46.2^\circ$ (*c* 0.49, H₂O) (ref³: $[\alpha]_D^{20} +46.5$ (H₂O)). ¹H NMR (D₂O, 500 MHz): δ 1.99 (1H, dddd, *J* = 17.1, 7.3, 5.9, 3.8, H-2), 2.22 (1H, dddd, *J* = 17.1, 8.5, 8.5, 5.9, H-2'), 3.42 (2H, m, H-1, H-1'), 3.56 (1H, dt, *J* = 7.3, 4.3, H-4), 3.68 (1H, dd, *J* = 12.4, 7.3, H-5), 3.86 (1H, dd, *J* = 12.4, 4.3, H-5'), 4.33 (1H, dt, *J* = 5.9, 4.3). ¹³C NMR (D₂O, 75 MHz): δ 32.7 (C-2), 44.6 (C-1), 59.2 (C-4), 67.9 (C-5), 71.6 (C-3). The NMR data were in accordance with literature data.²⁰

REFERENCES

1. R.W. Miles, P.C. Tyler, R.H. Furneaux, C.K. Bagdassarian and V.L. Schramm, *Biochemistry*, **37**, 8615 (1998).
2. R.W. Miles, P.C. Tyler, G.B. Evans, R.H. Furneaux, D.W. Parkin and V.L. Schramm, Iminoribitol Transition State Analogue Inhibitors of Protozoan Nucleoside Hydrolases, *Biochemistry*, in press.
3. R.J. Nash, A. Bell, G.W.J. Fleet, R.H. Jones and J.M. Williams, *J. Chem. Soc., Chem. Commun.*, 738 (1985).
4. O.D. Schärer, J.-Y. Ortholand, A. Ganesan, K. Ezaz-Nikpay and G.L. Verdine, *J. Am. Chem. Soc.*, **117**, 6623 (1995).
5. G. Ceulemans, A. Van Aerschot, J. Rozenski and P. Herdewijn, *Tetrahedron*, **53**, 14957 (1997).

6. Y. Aoyagi, H. Inaba, Y. Hiraiwa, A. Kuroda and A. Ohta, *J. Chem. Soc., Perkin Trans. 1*, 3975 (1998).
7. C.M. Huwe and S. Blechert, *Synthesis*, 61 (1997).
8. N.D. Uomo, M.C.D. Giovanni, D. Misiti, G. Zappia and G.D. Monache, *Tetrahedron: Asymmetry*, 7, 181 (1996).
9. R.C. Roemmele and H. Rapoport, *J. Org. Chem.*, 54, 1866 (1989).
10. I. Lundt and R. Madsen in *Iminosugars as Glycosidase Inhibitors*, A. E. Stütz, Ed; Wiley-VCH: Weinheim, pp 93-111 (1999).
11. I. Lundt, *Top. Curr. Chem.*, 187, 117, (1997).
12. I. Lundt and R. Madsen, *Synthesis*, 1129 (1992).
13. K. Bock, I. Lundt and C. Pedersen, *Acta Chem. Scand.*, B 38, 555 (1984).
14. M. Godskesen, I. Lundt, R. Madsen and B. Winchester, *Bioorg. Med. Chem.*, 4, 1857 (1996).
15. H.P. Wessel, T. Iversen and D.R. Bundle, *J. Chem. Soc., Perkin Trans. 1*, 2247 (1985).
16. H.S. Jensen, G. Limberg and C. Pedersen, *Carbohydr. Res.*, 302, 109 (1997).
17. J.F. Witte and R.W. McClard, *Tetrahedron Lett.*, 32, 3927 (1991).
18. G.W.J. Fleet, S.J. Nichlas, P.W. Schmith, S.V. Evans, L.E. Fellows and R.J. Nash, *Tetrahedron Lett.*, 26, 3127 (1985).
19. J. Cardellach, J. Font and R.M. Ortuño, *J. Heterocycl. Chem.*, 327 (1984).
20. C. Herdeis, H.P. Hubmann and H. Lotter, *Tetrahedron: Asymmetry*, 5, 119 (1994).