ARTICLE

OBC
www.rsc.org/obc

Synthesis and evaluation of mimetics of UDP and UDP-α-D-galactose, dTDP and dTDP-α-D-glucose with monosaccharides replacing the key pyrophosphate unit

Lluis Ballell,[a] Robert J. Young[b] and Robert A. Field*[a,c]

[a] *Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich, UK NR4 7TJ. E-mail: r.a.field@uea.ac.uk; Fax: +44-1603-592003*

[b] *CVU UK Medicinal Chemistry, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

[c] *Department of Biological Chemistry, John Innes Centre, Norwich Research Park, Norwich, UK NR4 7UH*

Received 1st January 2005, Accepted 27th January 2005
First published as an Advance Article on the web 21st February 2005

A series of 5′-*O*-glycosyl-uridine and thymidine derivatives have been prepared as potential mimics of sugar nucelotides and nucleotide-diphosphates. These compounds proved not to be inhibitors of bovine β-1,4-galactosyltransferase although some showed moderate inhibition of *Salmonella* dTDP-α-D-glucose 4,6-dehydratase (RmlB).

Introduction

In connection with studies on the dTDP-β-L-rhamnose biosynthetic pathway,[1] a potential target for the development of new anti-tuberculosis agents,[2] we had a need to develop inhibitors of sugar-nucleotide processing enzymes. In particular, we wished to devise small molecules capable of inhibiting RmlB, a key dTDP-α-D-glucose 4,6-dehydratase enzyme that converts dTDP-α-D-glucose to dTDP-6-deoxy-α-D-*xylo*-4-hexulose *en route* to dTDP-β-L-rhamnose. Although much crystallographic[3] and mechanistic information[4] is available about RmlB, to date few molecules have been described that inhibit this or other enzymes involved in dTDP-rhamnose biosynthesis.[5]

The development of NDP/NDP-sugar mimetics is not new to medicinal chemistry[6] and many examples based on naturally occurring antibiotics have been noted. These include nucleocidin,[7] an antitumor compound active against a wide variety of gram positive bacteria; uracil/thymine polyoxins,[8] active against phytopathogenic fungi and useful therapeutically against *Candida albicans*; ascamycin,[9] with broad antibacterial activity against various gram-negative and gram-positive bacteria; and nikkomycin Z,[10] an anti-fungal agent based on it's ability to serve as a competitive inhibitor of chitin synthase. An inherent feature of these types of molecules is their lack of charge with respect to NDP/NDP-sugars, rendering them cell membrane permeable at physiological pH. Amongst many recent efforts to prepare NDP/NDP-sugar mimetics,[11] we were intrigued by a report from Wong and coworkers[12] noting lactosyl uridine **1** (Fig. 1) to be an inhibitor (K_i 119.6 μM) of the β-1,4-galactosyltransferase activity present in L1210 leukaemia ascites fluid. The corresponding galactosyl-uridine proved to be a very poor inhibitor (K_i >1 mM) of the same system. Based on analogy with the mode of action of tunicamycin (Fig. 1),[13] it seemed reasonable that the central glucose unit in lactosyl-uridine **1** might also serve as a surrogate for a pyrophosphate–metal ion complex, or as a spacer between sugar and nucleoside units (Fig. 1).

Considering the model explaining the activity of lactosyl uridine (Fig. 1), 5′-*O*-β-cellobiosyl-thymidine **2** might serve as a dTDP-α-D-glucose analogue and, similarly, 5′-*O*-β-D-glucosyl-thymidine **3** might serve as a dTDP analogue (Fig. 2), both potentially with the ability to inhibit RmlB (which recognises the pyrophosphate bridge of its substrate through hydrogen bonding, rather than with the aid of a metal ion).[3] Reflecting the stereochemistry evident in the central unit of tunicamycin, 5′-*O*-β-L-rhamnosyl thymidine **4** might serve as a dTDP mimetic and might also inhibit RmlB (Fig. 2). In order to investigate this notion, and to further investigate the reported inhibition of β-1,4-galactosyltransferase by lactosyl-uridine,[12] glycosyl-nucleosides **1–4** were synthesised and assessed as potential inhibitors of bovine β-1,4-galactosyltransferase and *Salmonella* RmlB.

Results and discussion

Lactosyl-uridine **1** was prepared essentially as described by Wong and co-workers,[12] using an approach described earlier by Lichtenthaler,[14] from the known building blocks 2′,3′-*O*-isopropylidene uridine[15] and acetobromolactose .[12] Cellobiosyl-thymidine **2** was prepared in a similar fashion, using the known donor acetylated cellobiosyl bromide **5**[16] and acceptor 3′-*O*-benzoyl-thymidine **6**,[17] which were coupled together using AgOTf as an activating agent in the presence of 2,4,6-collidine. For ease of purification, after work-up the crude product was treated with sodium methoxide to effect complete de-*O*-acetylation. The deprotected product was purified by gel filtration on Sephadex LH-20 in methanol to give cellobiosyl thymidine **2** in a modest 25% yield (Scheme 1). The beta stereochemistry of the newly formed glycosidic linkage was confirmed by ^{1}H NMR spectroscopy (Glc δ_{H-1} 4.39 ppm; $J_{1,2}$ 8 Hz).

The poor glycosylation yield obtained during the preparation of compound **2** is likely due to two factors: internal hydrogen bonding between the heterocyclic base and the alcohol nucleophile in the acceptor nucleoside, and donor consumption through acetate transfer from the donor to the acceptor hydroxyl group. The former has been addressed in a modification of the Koenigs–Knorr reaction[18] whereby a 5′-*O*-trityl-nucleoside is employed as an acceptor instead of the nucleoside *per se*. The problem of acetyl transfer is overcome by substituting acetates with less prone to migrate benzoate groups.[19] Hence, in the synthesis of glucosyl-thymidine **3** known 3′-*O*-acetyl-5′-*O*-trityl thymidine **7**[20] was coupled with benzobromoglucose **8**[16] in the presence of AgOTf to give protected glucosyl-thymidine **9** in 68% yield (Scheme 2). The use of benzoate in place of acetate protection in the donor improved the coupling yield

DOI: 10.1039/b500418g

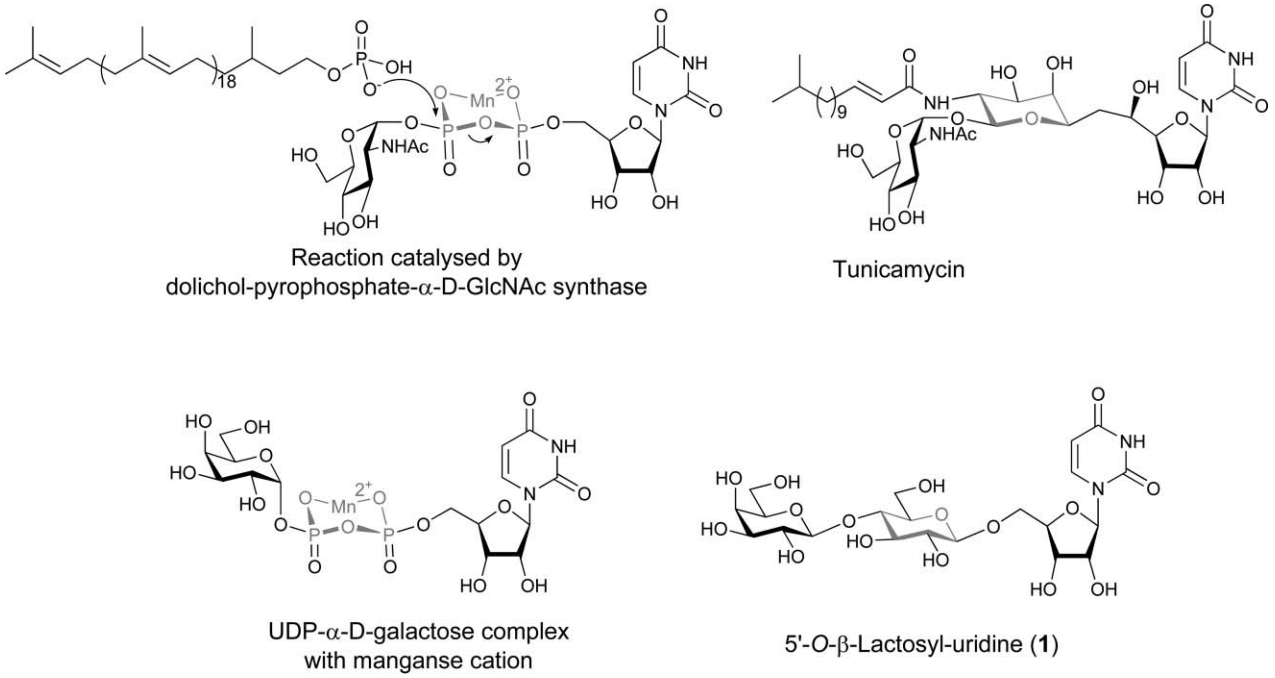


Fig. 1 Monosaccharides as pyrophosphate–metal ion complex mimetics: reaction catalysed by dolichol-pyrophosphoryl-α-D-GlcNAc synthase and its relationship to tunicamycin structure; UDP-α-D-galactose–manganese cation complex and its relationship to 5′-*O*-β-lactosyl-uridine **1**.

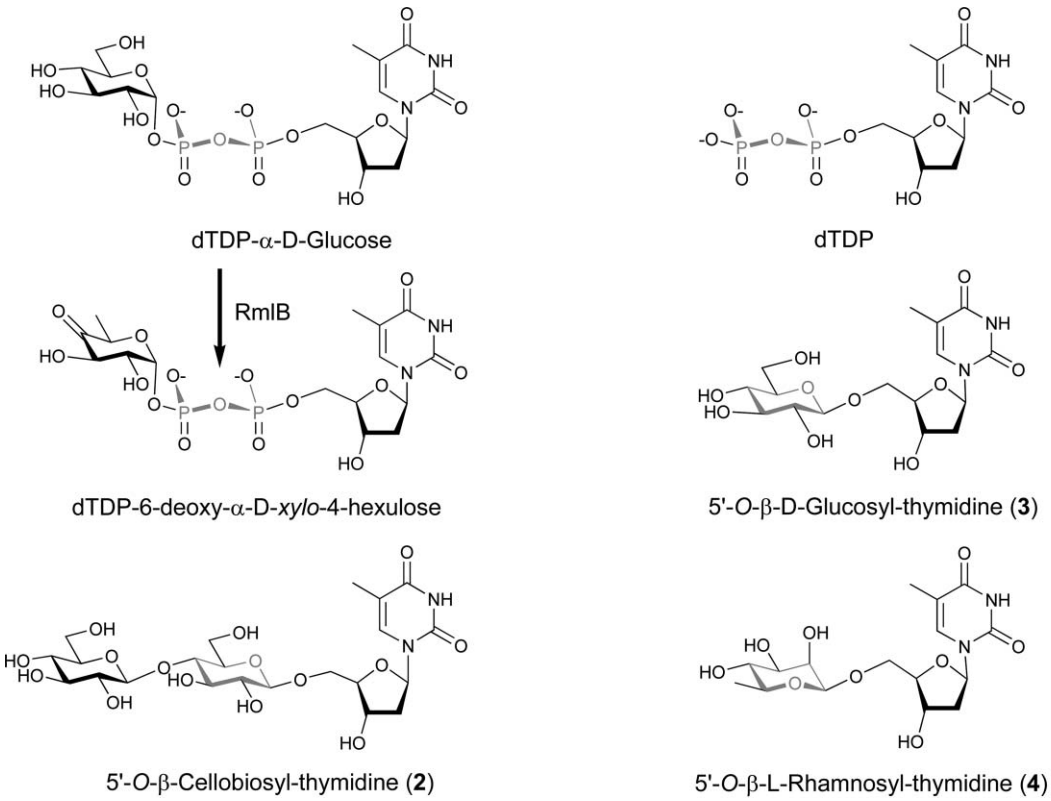
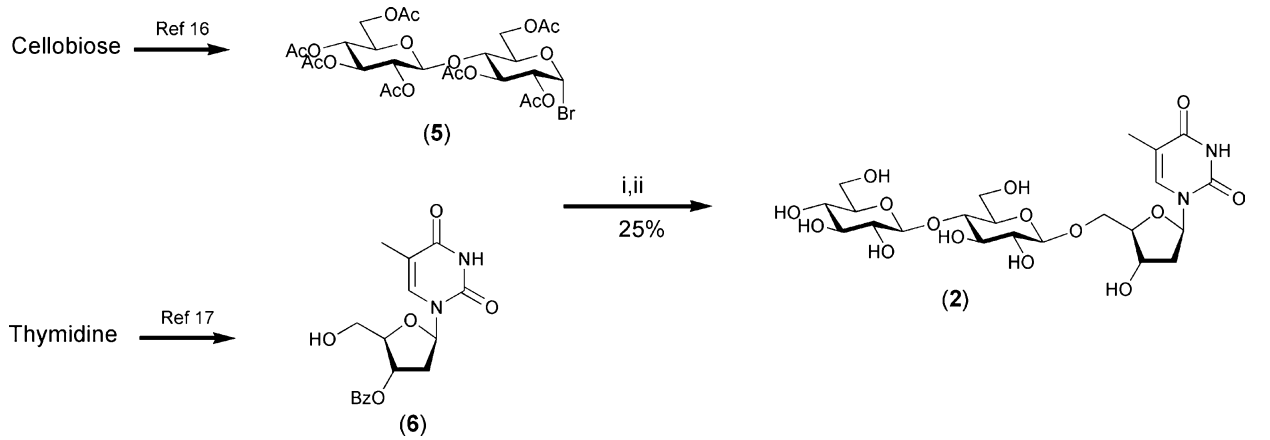


Fig. 2 Reaction catalysed by RmlB, putative dTDP-glucose and dTDP analogues **2**–**4**.

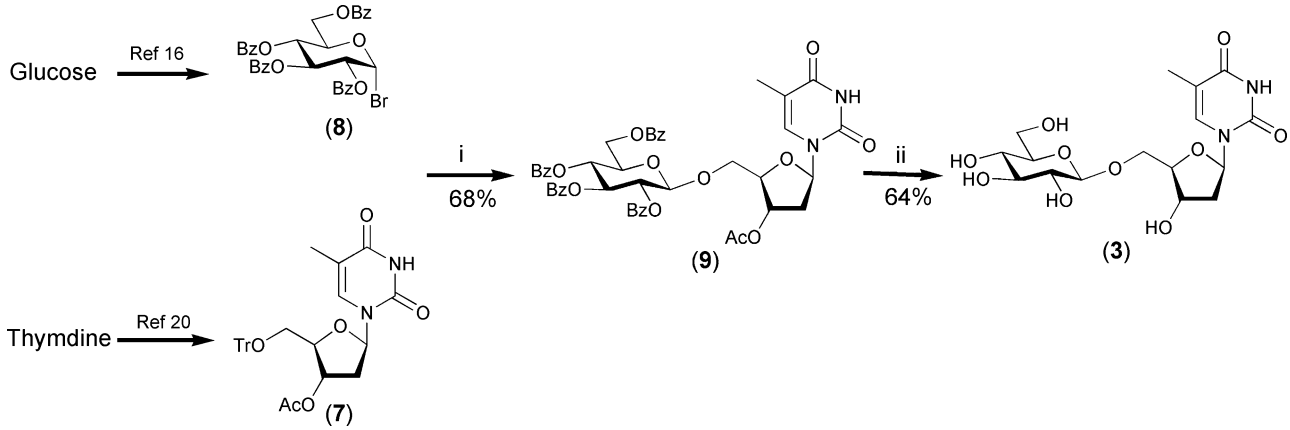
substantially.[21] Deacetylation of **9**, silica column chromatography and crystallisation then gave a 64% yield of the deprotected 5′-*O*-β-D-glucopyranosyl thymidine **3**,[21] the structure of which was confirmed by ^{1}H NMR spectroscopy (Glc $\delta_{H-1''}$ 4.34 ppm, $J_{1'',2''}$ 7.7 Hz) and through comparison with literature data.[21]

In the preparation of glycosyl-nucleosides **2** and **3** there is the potential issue of regiocontrol arising from the possibility of *O*-3′-ester migration under (acidic) glycosylation conditions to *O*-5′, followed by *O*-3′ glycosylation. However, extensive NMR studies on the related deprotected 3′- and 5′-β-D-galactosyl thymidines by Schmid and co-workers[22] provides diagnostic information about regioisomers (glycosylation of O-5′ results in resolved H-5′a/b ^{1}H NMR signals; *O*-3′ glycosylation results in distinctive shifts of ^{13}C NMR signals of C-3′ to lower field and C-5′ to higher field).

Synthesis of β-L-rhamnosyl-thymidine **4** presents the classical 1,2-*cis*-β-glycosylation problem evident in β-mannoside and β-rhamnoside chemistry. Incisive work from Crich and Sun,[23] exploiting torsional control of reactivity,[24] has led to a practical solution to the synthesis the former. A recent elegant variation



Scheme 1 i). AgOTf–collidine, 4 Å molecular sieves, DCM, −20 °C; ii). NaOMe–MeOH.



Scheme 2 i). AgOTf–collidine, 4 Å molecular sieves, DCM, −78→0 °C; ii). NaOMe–MeOH.

on this theme by Crich and Yao also provides access to β-rhamnosides.[25] In the context of our work, a report from Silva and Sofia[26] on the 5-*O*-L-mannosylation of a uridine derivative with an appropriately 4,6-*O*-benzylidenated mannosyl sulfoxide donor gave an α/β selectivity of only a 1 : 1.8. These authors suggest that the lack of stereoselectivity may be due to particular stereoelectronic characteristics of the uridyl acceptor.[26] We were therefore discouraged from preparing elaborate donor molecules and considered other options. In recent work on the synthesis of β-L-rhamnosyl apiose, we have exploited 2,3-carbonate protection in a rhamosyl donor[27] and, in other studies, we have demonstrated apparent S_N2 reactions of a benzylated α-mannosyl sulfoxide donor, giving rise to β-mannosides in excess in (some) glycosylation reactions.[28] Based on the related work of Silva and Sofia,[26] the separability of anomeric rhamnosyl-nucleosides seemed likely, encouraging us to employ a benzylated α-L-rhamnosyl sulfoxide donor in glycosylation studies. Suitably protected uridine was initally investigated as an acceptor, followed by thymidine.

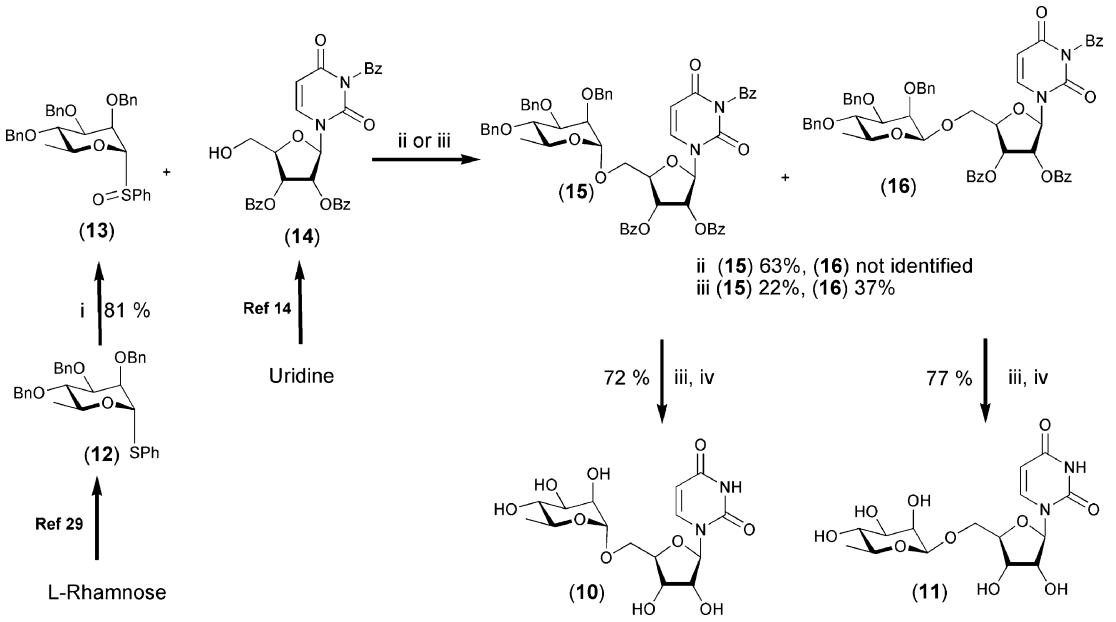
To generate the required donor, known benzyl protected L-thiorhamnoside **12**[29] was oxidised with hydrogen peroxide–acetic anhydride–silica in dichloromethane[30] to give 2,3,4-tri-*O*-benzyl-1-(phenylsulfinyl)-α-L-rhamnose **13**, in 81% yield. As expected for a reaction that is likely to proceed *via* an S_N1-like fragmentation, and where the β-face of the resulting oxocarbenium ion is more hindered, reaction of donor **13** with the known glycosyl acceptor 3-*N*-benzoyl-2′,3′-di-*O*-benzoyl uridine **14**[31] in the presence of Tf_2O–DTBMP[23] gave α-linked disaccharide **15** in 63% yield with no sign of the β-anomer. The anomeric configuration of **15** was confirmed using the distinct J_{C1-H1} coupling constants of α and β glycosides.[32] In contrast, iodine-promoted reaction of sulfoxide donor **13** and uridine acceptor **14** gave α/β-disaccharides **15**/**16** in a 3 : 5 ratio and a combined 59% yield. The α and β anomers were easily separable by column chromatography to give pure **15** (H-1α $J_{C1''-H1''}$ 167 Hz) and **16** (H-1β $J_{C1''-H1''}$ 157 Hz). Methanolic liquid ammonia deesterification and palladium-mediated hydrogenation gave the deprotected counterparts **10** (H-1α $J_{C1''-H1''}$ 169 Hz) and **11** (H-1β $J_{C1''-H1''}$ 159 Hz) in 72% and 77% yield, respectively (Scheme 3).

The same glycosylation conditions employed for the synthesis of rhamnosyl uridines **15** and **16** were used for synthesis of the related thymidine derivatives **18** and **19**. Reaction of known acceptor **17**[19] with the benzylated rhamnosyl sulfoxide **13** in the presence of iodine gave a mixture of α- and β-rhamnosides (2 : 3) in a 71% combined yield. The separated stereoisomers **18** (H-1α $J_{C1''-H1''}$ 167 Hz) and **19** (H-1β $J_{C1''-H1''}$ 157 Hz) were fully deprotected as described above, giving α-rhamnoside **20** (H-1α $J_{C1''-H1''}$ 171 Hz) and β-rhamnoside **4** (H-1β $J_{C1''-H1''}$ 161 Hz), respectively (Scheme 4).

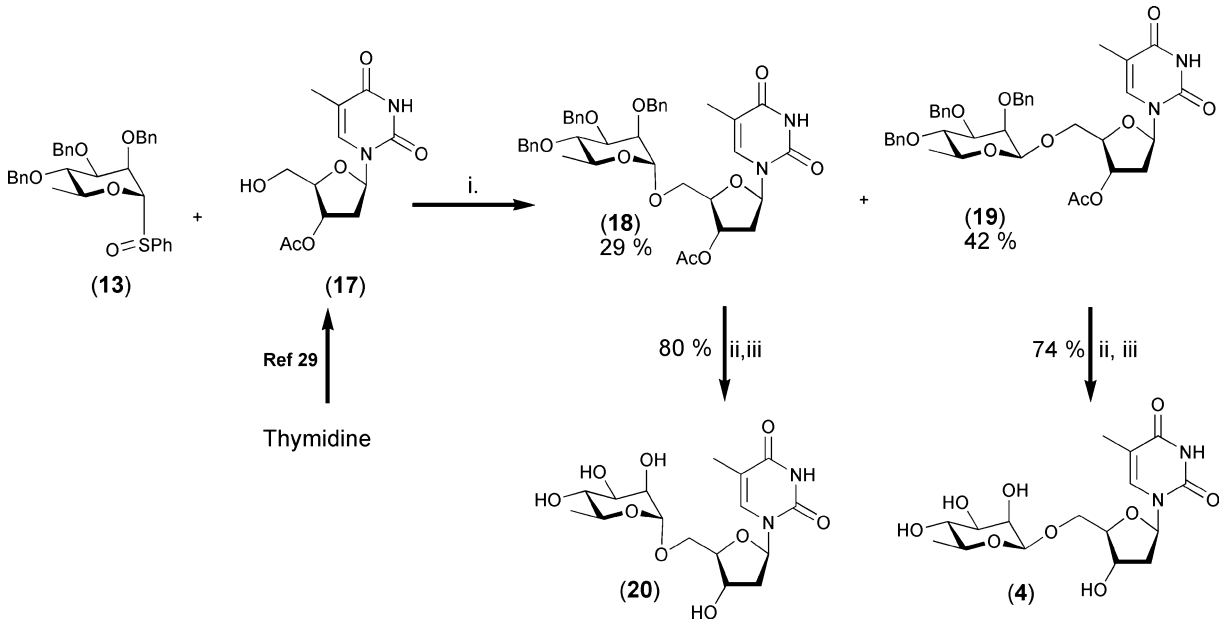
Synthetic glycosyl-nucleosides were assessed for their ability to inhibit bovine β-1,4-galactosyltransferase.[33] None of the compounds showed more than 10% inhibition at 500 μM concentration, where UDP showed 90% inhibition. The same compounds were also assessed as inhibitors of recombinant *Salmonella enterica* serovar typhimurium LT2.[34,35] Some moderate inhibition was found at the concentration assayed (1 mM) for some compounds, although unexpectedly for an enzyme that utilises a dTDP-sugar substrate, uridine derivatives **1** and **11** proved more active than the thymidine derivatives investigated in this study (Table 1).

Conclusion

In contrast to the observations of Wong *et al*. on the inhibition of the β-1,4-galactosyltransferase activity present in L1210 leukaemia ascites fluid by lactosyl-uridine,[12] none of the



Scheme 3 i). 30% H_2O_2–Ac_2O–SiO_2 in DCM; ii). Tf_2O–DTBMP in DCM at −78 °C; iii). I_2–K_2CO_3 in DCM; iv). MeOH–NH_3; v). H_2–10% Pd/C in EtOH.



Scheme 4 i). I_2–K_2CO_3 in DCM; ii). MeOH–NH_3; iii). H_2–10% Pd/C in EtOH.

Table 1 Inhibition of RmlB by glycosyl-nucleosides (data are accurate to ± ~10%)

Compound	Inhibition at 1 mM concentration (%)
β-Lactosyl-uridine **1**	43
β-Cellobiosyl-thymidine **2**	3
β-D-Glucosyl-thymidine **3**	27
β-L-Rhamnosyl-thymidine **4**	7
α-L-Rhamnosyl-uridine **10**	27
β-L-Rhamnosyl-uridine **11**	47
α-L-Rhamnosyl-thymidine **20**	0

compounds prepared in this study showed significant inhibition of the bovine β-1,4-galactosyltransferase. This may highlight structural differences between β-1,4-galactosyltransferases from different species. Although reasonable inhibition of *Salmonella* RmlB was noted for β-lactosyl-uridine **1** and β-L-rhamnosyl-uridine **11**, none of the compounds reported in this study gave >50% inhibition at 1 mM concentration. Whilst our work was in progress, a report on attempts to prepare chitin synthase inhibitors using sugars to replace the pyrophosphate group in UDP-GlcNAc analogues also demonstrated only very weak inhibition of chitin synthase.[36] We conclude that the notion that sugars might serve as generic surrogates for pyrophosphate–metal ion complexes, or as spacers between sugar and nucleoside moieties in sugar-nucleotide mimics, should be treated with caution. However, in relation to RmlB inhibition, in particular, the moderate inhibition observed warrants further investigation.

Experimental

General information

TLC was performed on Silica Gel 60 F_{254} (Merck) detected by immersion in a 5% ethanolic solution of H_2SO_4, followed by heating (>100 °C). Column chromatography was performed using Silica Gel 60 (0.063–0.200 mm). Concentration of organic extracts was typically carried out below 40 °C and at water pump pressure. Unless otherwise stated, NMR spectra were obtained

in $CDCl_3$ (referenced to δ 77.0 or residual $CHCl_3$ at δ 7.27 ppm for ^{13}C and ^1H, respectively) or D_2O (referenced to added acetone at δ 31.00 or 2.25 ppm for ^{13}C and ^1H, respectively).

5′-*O*-β-D-Galactopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-uridine 1. This compound was prepared essentially as described in the literature.[12]

5′-*O*-β-D-Glucopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-thymidine 2. α-*D*-Hepta-*O*-acetylcellobiosyl bromide **5**[16] (302 mg, 0.43 mmol) and 3′-*O*-benzoyl thymidine **8**[17] (100 mg, 0.29 mmol) were suspended in dry DCM (4 ml) together with 4 Å molecular sieves and the reaction mixture was cooled to −20 °C. 2,4,6-Collidine (64 mg, 0.53 mmol) and AgOTf (133 mg, 0.52 mmol) were added and the mixture was allowed to warm slowly to room temperature whilst protected from light. The mixture was then diluted with DCM (50 ml) and washed with equal volumes of saturated $NaHCO_3$ solution (2 ×) and H_2O (2 ×). The organic extract was dried ($MgSO_4$), concentrated *in vacuo* and subjected to column chromatography (DCM : acetone, 6 : 1). Without further characterisation, the resulting crude, fully protected trisaccharide was dissolved in anhydrous MeOH (4 ml), NaOMe (35 mg, 0.576 mmol) was added and the mixture was stirred at room temperature for 1 h. When tlc showed deprotection to be complete, the mixture was concentrated *in vacuo* and the crude mixture was purified on a Sephadex LH-20 column eluted with MeOH. The required cellobiosyl-thymidine **2** was obtained as a white powder (40 mg, 25%); mp 146–148 °C (MeOH–Et_2O); $[a]_D^{25}$ 4.7 (*c* 0.42, MeOH); δ_H (MeOD): 7.57 (1 H, s, *H-6*), 6.21 (1 H, t, $J_{1,2}$ 7 Hz, *H-1′*), 4.63 (1 H, d, *J* 8.5 Hz, H-1″), 4.44 (1 H, d, $J_{1‴,2‴}$ 8 Hz, H-1‴), 4.42 (1 H, m, H-3′), 4.10 (2 H, m), 3.87 (2 H, m), 3.79 − 3.50 (8 H, m), 3.39 (2 H, m), 3.29 (1 H, m, H-5″ or H-5‴) 3.22 (2 H, m), 2.29 (2H, m, *H-2a′,2b′*), 1.81 (3 H, s, CH_3 Thy); δ_C (MeOD): 164.6 (*C-4*), 150.5 (*C-2*), 137.7 (*C-6*), 112.5 (*C-5*), 102.6, 102.3 (*C-1″*, *C-1‴*), 85.5, 85.3 (*C-1′*, *C-4′*), 78.9, 76.0, 75.5, 74.8, 74.4, 73.2, 71.5, 71.0 (*C-2″-C-5″*, *C-2‴-C-5‴*), 69.5, 69.3 (*C-3′*, *C-5′*), 61.8, 60.6 (*C-6″*, *C-6‴*), 38.2 (*C-2′*), 11.6 (CH_3 Thy); ES-MS $C_{28}H_{35}N_2O_{15}^+$ requires 567.2037, found $(M + H)^+$ 567.2041.

3′-*O*-Acetyl-5′-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-thymidine 9. 3′-*O*-Acetyl-5′-*O*-trityl-thymidine **7**[20] (400 mg, 0.76 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **8**[16] (752 mg, 1.14 mmol) were dissolved in 5 ml of dry DCM and 4 Å molecular sieves were added (500 mg). The reaction mixture was then cooled to −78 °C under N_2. AgOTf (475 mg, 1.14 mmol) was then added and the reaction mixture was allowed to slowly warm −10 °C, when tlc showed the reaction to be complete. The reaction was then quenched with collidine (200 µl), concentrated *in vacuo* and the crude product was subjected to column chromatography (EtOAc : hex, 1 : 1) to give glycoside **9** (446 mg, 68%) as a colourless syrup; δ_H ($CDCl_3$): 7.20–8.02 (20 H, m, *Ar*), 7.64 (1 H, s, *H-6*), 6.34 (1H, dd, $J_{1′,2a″}$ 6.0 Hz, $J_{1′,2b′}$ 9 Hz, *H-1′*), 5.97 (1 H, t, $J_{3″,4″}$ 9.7 Hz, *H-3″*), 5.69 (1 H, t, $J_{3″,4″}$, *H-4″*), 5.50 (1 H, dd, $J_{1,2}$ 5.9 Hz $J_{2,3}$ 8.1 Hz, *H-2*), 4.90 (2 H, m, *H-1″β*, *H-5:″*), 4.67 (1 H, dd, $J_{5″,6b″}$ 3.1 Hz, $J_{6a″,6b″}$ 12.2 Hz, *H-6a″*), 4.50 (1 H, dd, $J_{5″,6b″}$ 5.2 Hz, $J_{6a″,6b″}$, *H-6b″*), 4.32 (1 H, dd, $J_{4″,5a″}$ 2.1 Hz, $J_{5a″,5b″}$ 10.5 Hz, *H-5a″*), 4.20 (1 H, m, *H-4′*), 4.08 (1 H, br s, *H-3′*), 3.78 (1 H, dd, $J_{4″,5b″}$ 1.8 Hz, $J_{5a″,5b″}$, *H-5b′*), 2.08 (2 H, m, *H-2a′*, *H-2b′*), 1.20 (3 H, s, CH_3Thy); δ_C ($CDCl_3$): 171.2 (*C*OCH_3), 165.7, 166.0, 166.4, 166.7 (4 × *C*OPh), 164.1 (*C-4*), 150.9 (*C-6*), 133.8, 133.9, 134.1, 134.3 (*quat. Ar*) 128.9–130.4 (*Ar*), 112.0 (*C-5*), 101.9 (*C-1″*), 85.0 (*C-1′*), 84.0 (*C-4′*), 75.9, 73.1, 72.8, 72.4, 70.3, 70.1 (*C-3′-5′* and *C-2″-5″*), 63.3 (*C-6″*), 36.9 (*C-2′*), 21.2 (CO*C*H_3), 12.9 (CH_3 Thy); FAB-MS $C_{46}H_{42}N_2NaO_{15}^+$ requires 885.2483, found $(M + Na)^+$ 885.2486. The compound was used in the synthesis of **3** without further characterisation.

5′-*O*-β-D-Glucopyranosyl-thymidine 3[21]**.** The esterified glucopyranosyl thymidine **9** (300 mg, 0.35 mmol) was dissolved in dry MeOH (5 ml), NaOMe (20 mg) was added and the mixture was stirred until tlc showed the reaction to be complete. Dowex-50X8 (H^+) resin was then added to neutralise the reaction mixture. Removal of the resin by filtration, concentration *in vacuo* and column chromatography (DCM : MeOH, 10 : 3) gave glucopyranosyl-thymidine **3** (92 mg, 64%) as a white solid; mp 118–120 °C (lit.[21] 119–120 °C); $[a]_D^{20}$ 12.5 (*c* 0.5, MeOH) (lit.[21] 12.2); δ_H (CD_3OD): 7.83 (1 H, s, *H-6*), 6.32 (1 H, m, *H-1′*), 4.51 (1 H, m, *H-3′*), 4.34 (1 H, d, $J_{1″,2″}$ 7.7 Hz, *H-1″*), 4.23 (1 H, dd, $J_{4′,5a′}$ 3 Hz, $J_{5a′,5b′}$ 11 Hz, *H-5a′*), 4.08 (1 H, dd, $J_{3′,4′}$ 5.3, Hz, $J_{4′,5′}$ 3 Hz, *H-4′*), 3.87 (1 H, dd, $J_{5″,6a″}$ 2 Hz, $J_{6a″,6b″}$ 12 Hz, *H-6a″*), 3.71 (1 H, dd, $J_{4′,5b′}$ 3, Hz, $J_{5a′,5b′}$, *H-5b′*), 3.65 (1 H, dd, $J_{5″,6b″}$ 5.9 Hz, $J_{6a″,6b″}$, *H-6b′*), 3.26–3.36 (3 H, m, *H-2′*, *H-3″*,*4″*), 3.20 (1 H, m, *H-5″*), 2.55 (2 H, m, *H-2a″*, *2b″*), 1.89 (3 H, s, CH_3 Thy); δ_C ($CDCl_3$): 165.5 (*C-4*), 151.5 (*C-2*), 137.3 (*C-6*), 110.5 (*C-5*), 103.4 (*C-1″*), 86.6, 85.6 (*C-1′*, *C-4′*), 77.2 (*C-5″*), 74.2 (*C-2″*), 72.1, 70.7, 69.4, 69.2 (*C-3″*, *C-4″*,*C-3′*, *C-5′*), 61.8 (*C-6″*), 40.1 (*C-2′*), 11.5 (CH_3 Thy). NMR data are in accordance with literature data;[21] ES-MS $C_{16}H_{25}N_2O_{10}$ requires 405.1509, found $(M + H)^+$ 405.1514.

2,3,4-Tri-*O*-benzyl-1-(phenylsulfinyl)-α-L-rhamnopyranoside 13. To a stirred solution of known thioglycoside **12**[29] (5 g, 9.5 mmol), Ac_2O (1.05 ml, 11 mmol) and silica 220–240 mesh (2 g) in DCM (40 ml) was added aqueous 30% H_2O_2 solution (2 g, 1.80 ml). The resulting mixture was stirred vigorously until tlc (EtOAc : hex, 1 : 1) showed the reaction to be complete. The mixture was then diluted with DCM (150 ml), washed with aqueous $Na_sS_2O_5$ solution (2 × 100 ml) and brine (2 × 100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude mixture was subjected to column chromatography (EtOAc : hex, 1 : 2) to give rhamnosyl-sulfoxide **13** as a colourless oil (4.22 g, 82%); $[a]_D^{25}$ 57.6 (*c* 1.14, $CHCl_3$); δ_H ($CDCl_3$): 7.48–7.57 (5H, m, *Ar SPh*), 7.21–7.39 (15H, m, *Ar Bn*), 5.27 (1 H, d, $J_{1,2}$ 1.4 Hz, *H-1*), 4.97 (1 H, d, $J_{4,5}$ 11 Hz, *H-4*), 4.48–4.67 (6 H, m, 3 × −CH_2-), 4.16 (1 H, m, *H-3*), 3.97 (1 H, m, *H-5*), 3.71 (1H, m, *H-2*), 1.30 (3 H, d, $J_{5,6}$ 6.3 Hz, *6-*CH_3); δ_C ($CDCl_3$): 142.3, 138.5, 138.3, 137.8 (*4 × quat. Ar*), 131.6, 131.0, 129.5, 129.1, 128.9, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.1, 124.6 (*Ar*), 96.9 (*C-1*), 79.8, 79.4, 75.6, 74.6, 72.9, 72.4, 72.1 (*C-2-5* and *3 × -CH*$_2$–Ph), 18.5 (*C-6*); CI $C_{33}H_{35}O_5S^+$ requires 543.2205, found $(M + H^+)$ 542.2211.

3-*N*-Benzoyl-2′,3′-di-*O*-benzoyl-5′-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-uridine 15. Rhamnosyl-sulfoxide **13** (347 mg, 0.64 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (395 mg, 1.9 mmol) were dissolved in dry DCM (5 ml) and the resulting solution was cooled to −78 °C. Tf_2O (90 mg, 54 µl, 0.32 mmol) was added and the reaction was allowed to reach −60 °C over a period of 15 min. 3-*N*-Benzoyl-2′,3′-di-*O*-benzoyl uridine **14**[31] (88 mg, 0.16 mmol) in dry DCM (5 ml) was added drop-wise and the resulting solution was stirred for another 10 min. The reaction mixture was then allowed to warm to −5 °C over a period of 1 h, at which point the reaction was quenched by the addition of saturated $NaHCO_3$ solution (1 ml). The organic extract was separated, dried (MgSO4), concentrated *in vacuo* and the resulting crude product was subjected to column chromatography (acetone : hex, 1 : 5→1 : 3) to protected rhamnosyl-uridine **15** (97 mg, 63%); δ_H ($CDCl_3$): 7.12–7.98 (31 H, *3 × Ph* and *H-6*), 6.6 (1 H, d, $J_{1′,2′}$ 7.3 Hz, *H-1′*), 5.73 (1 H, m, *H-3′*), 5.63 (1 H, d, $J_{5,6}$ 8.2 Hz, *H-5*), 5.37 (1 H, dd, $J_{1′,2′}$, $J_{2′,3′}$, 5.8 Hz, *H-2′*), 4.91 (1 H, s, *H-1″*), 4.44–4.85 (6 H, m, 3 × CH_2–*Bn*), 4.58 (1H, m, *H-4′*), 3.98–4.15 (2H, m, *H-3″*, *H-4″*), 3.61–3.82 (4 H, m, *H-5a′*, *5b′* and *H-2″*, *H-5″*), 1.36 (3H, d, $J_{5″,6′}$ 4.8 Hz, *6″-*CH_3); δ_C ($CDCl_3$): 168.4, 165.7, 165.6, 164.0, 161.7 (*C*O), 149.6 (*C-6*), 126.7–138.7 (*aromatic*), 104.5 (*C-5*), 99.2 (*C-1″* J_{C1-H1} 167 Hz), 85.8 (*C-1′*), 82.6 (*C-4′*), 80.2 (*C-2″*), 78.7 (*C-4″*), 76.0 (–CH_2–Ph 74.2 (*C-3″*), 74.1 (*C-2′*), 73.8 (–CH_2–Ph 72.3 (*C-3′*), 71.8 (–CH_2–Ph 69.3 (*C-5′*), 67.8 (*C-5′*), 18.3 (*C-6″*); ES-MS $C_{57}H_{56}N_3O_{13}^+$ requires 990.3813, found $(M + NH_4^+)$ 990.3809.

3-*N*-Benzoyl-2′,3′-di-*O*-benzoyl-5′-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-uridine 15 and 3-*N*-benzoyl-2′,3′-di-*O*-benzoyl-5′-*O*-(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)-uridine 16. 3-*N*-Benzoyl-2′,3′-di-*O*-benzoyl uridine **14**[31] (88 mg, 0.16 mmol) and 2,3,4-tri-*O*-benzyl-1-(phenylsulfinyl)-α-L-rhamnose **13** (347 mg, 0.64 mmol) were dissolved in dry DCM (5 ml). K_2CO_3 (23 mg, 0.16 mmol) and iodine (61 mg, 0.24 mmol) were added to the solution and the reaction mixture was flushed under N_2. The reaction was monitored by tlc (acetone : hex, 1 : 2) until it was complete, concentrated *in vacuo* to ~1 ml and subjected to column chromatography (acetone : hex, 1 : 5→1 : 3). The first compound to elute from the column was the α-anomer **15** (34 mg, 22%) followed by the β-anomer **16** (57 mg, 37%). α-anomer **15**: data as reported above. β-anomer **16**: δ_H ($CDCl_3$): 7.12–8.04 (31 H, *6* × *Ph*, and *H-6*), 6.41 (1 H, d, $J_{1',2'}$ 7.0 Hz, *H-1′*), 5.94 (1 H, dd, $J_{2',3'}$ 5.6 $J_{3',4'}$ 2.2 Hz, *H-3′*), 5.67 (2 H, m, *H-5* and *H-2′*), 4.63–4.98 (6 H, m, 3 × -CH_2–Bn), 4.55 (1 H, s, *H-1″*), 4.50 (1H, d, $J_{3',4'}$,*H-4′*), 4.28 (1H, dd, $J_{4',5a'}$ 2.2 Hz $J_{5a',5b'}$ 11.4 Hz, *H-5a′*), 3.96 (1 H, m, *H-2″*), 3.91 (1H, dd, $J_{4',5b'}$ 2.5 Hz $J_{5a',5b'}$, *H-5b′*), 3.68 (1H, d, $J_{3'',4''}$ 8.8 Hz *H-4″*), 3.60 (1H, dd, $J_{2'',3''}$ 2.9 Hz $J_{3'',4''}$, *H-3″*), 3.45 (1H, m, *H-5″*), (3H, d, $J_{5'',6''}$ 6.2 Hz, *6′-CH*$_3$); δ_C ($CDCl_3$): 168.4, 165.7, 165.6, 164.0, 161.7 (*C*O), 149.6 (*C-6*), 126.5–138.8 (*aromatic*), 103.3 (*C-5*), 100.5 (*C-1″* J_{C1-H1} 157 Hz), 83.0 (*C-1′*), 82.3 (*C-4′*), 80.2 (*C-2″*), 75.9, 75.7, 74.5, 74.4, 73.5, 73.0, 72.8, 72.3 (–CH_2–Ph × 3, *C-2′*, *3′*, *5′* and *C-3″*,*4″*), 69.0 (*C-5″*), 18.4 (*C-6″*), ESI-MS $C_{57}H_{56}N_3O_{13}^+$ requires 990.3813, found ($M + NH_4^+$) 990.3810.

5′-*O*-α-L-Rhamnopyranosyl-uridine 10. Protected α-rhamnosyl-uridine **15** (80 mg, 0.08 mmol) was dissolved in methanol (2 ml) and aqueous ammonia was added (2 ml). After 48 h, tlc (DCM : MeOH, 5 : 1) showed the reaction to be complete. The solution was then concentrated *in vacuo*, the resulting crude product was dissolved in ethanol (5 ml) and AcOH–H_2O (1 ml of 1 : 1 v/v solution) and 10% Pd/C (50 mg) were added and the mixture was placed under a hydrogen atmosphere for 16 h. The mixture was then filtered, neutralised with NH_4OAc and concentrated to dryness. Purificaton on a Sephadex LH-20 column eluted with MeOH gave the α-glycoside **10** as a white powder (21 mg, 65%); mp 122–124 °C (DCM : MeOH); $[\alpha]_D^{25}$ −31.9 (*c* 0.68, MeOH); δ_H (DMSO): 10.24 (1H, br s, *NH*), 7.84 (1H, d, $J_{5,6}$ 7.1 Hz, *H-6*), 7.42 (1H, d, $J_{5,6}$ 7.1 Hz, *H-5*), 5.71 (1H, s, *H-1′*), 4.55 (1H, s, *H-1″*), 3.02–3.94 (9H, m, *H-2″-5″* and *H-2′-4′*, *5a′*,*5b′*), 1.10 (1H, d, $J_{5'',6''}$ 5.9 Hz, *6-CH*$_3$); δ_C (DMSO): 171.9, 154.3 (2 × NH*C*O), 129.4, 128.7 (*C-5*,*6*), 101.4 (*C-1″* J_{C1-H1}169 Hz), 88.7 (*C-1′*), 82.5 (*C-2′*), 73.0, 71.9, 71.7, 71.5, 71.4, 69.5, 68.1 (*C-3′-5′* and *C-2″-5″*), 20.0 (*C-6″*); ES-MS $C_{15}H_{22}N_2NaO_{10}^+$ requires 413.1172, found ($M + Na^+$) 413.1181.

5′-*O*-β-L-Rhamnopyranosyl-uridine 11. Protected β-rhamnsoyl-uridine **16** (80 mg, 0.1 mmol) was deprotected and purified as described in the preparation of the α-anomer **10** to give the β-glycoside **11** as a colourless syrup (30 mg, 77%); $[\alpha]_D^{25}$ <5 (*c* 0.11, MeOH); δ_H (DMSO): 10.21 (1H, br s, *NH*), 7.87 (1H, d, $J_{5,6}$ 7.7 Hz, *H-6*), 7.42 (1H, d, $J_{5,6}$ 7.6 Hz, *H-5*), 5.74 (1H, s, *H-1′*), 4.35 (1H, s, *H-1″*), 3.02–3.94 (8H, m, *H-2″-4″* and *H-2′-4′*, *5a′*,*5b′*), 3.01 (1H, m, H-5″), 1.13 (1H, d, $J_{5'',6''}$ 5.9 Hz, *6-CH*$_3$); δ_C (DMSO): 171.7, 154.1 (2 × NH*C*O), 129.2, 128.5 (*C-5*,*6*), 102.4 (*C-1″* J_{C1-H1}159 Hz), 88.4 (*C-1′*), 81.5 (*C-2′*), 73.5, 72.1, 71.7, 71.4, 71.3, 69.1, 67.5 (*C-3′-5′* and *C-2″-5″*), 19.8 (*C-6″*); ES-MS $C_{15}H_{22}N_2NaO_{10}^+$ requires 413.1172, found ($M + Na^+$) 413.1181.

3′-*O*-Acetyl-5′-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-thymidine 18 and 3′-*O*-acetyl-5′-*O*-(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)-thymidine 19. *3′-O*-Acetyl-thymidine **17**[19] (42 mg, 0.16 mmol) and 2,3,4-tri-*O*-benzyl-1-(phenylsulfinyl)-α-L-rhamnose **13** (347 mg, 0.64 mmol) were dissolved in dry DCM (5 ml). K_2CO_3 (23 mg, 0.16 mmol) and iodine (61 mg, 0.24 mmol) were added to the solution and the reaction mixture was flushed with N_2. The reaction was monitored by tlc (acetone : hex, 1 : 2) until it was complete, concentrated *in vacuo* to ~1 ml and subjected to column chromatography (acetone : hex, 1 : 2). The mixture was then concentrated to ~1 ml *in vacuo* and subjected to column chromatography (acetone : hex, 1 : 5→1 : 3) for purification. The first compound to be eluted from the column was the α-anomer **18** (33 mg, 29%), followed by the β-anomer **19** (48 mg, 42%). α-anomer **18**: δ_H ($CDCl_3$): 9.02 (1H, br s, *NH*), 7.24–7.41 (15 H, *3* × *Ph*), 7.08 (1 H, s, *H-6*), 6.22 (1 H, m, *H-1′*), 5.07 (1 H, m, *H-3′*), 4.57–4.98 (8 H, m, 3 × −CH_2–Bn, *H-1″*,*2″*), 4.09 (1 H, br s, *H-4′*), 3.93 (1H, dd, $J_{4',5a'}$ 2.2 Hz, $J_{5a',5b'}$ 11.0 Hz, *H-5a′*), 3.72 (1H, br s, *H-4″*), 3.65 (2 H, m, *H-3″*,*5″*), 3.53 (1H, dd, $J_{4',5b'}$ 3.4 Hz $J_{5a',5b'}$, *H-5b′*), 2.26 (1H, m, *H-2a′*), 2.10 (3H, s, CO*CH*$_3$), 1.75 (3H, s, *CH*$_3$ *Thy*), 1.69 (3H, m, *H-2b′*), 1.33 (3H, d, $J_{5'',6''}$ 4.9 Hz, *6″*-C*H*$_3$); δ_C ($CDCl_3$): 170.7, 163.7, 150.5 (*C*O), 138.4, 138.2, 138.1 (*quat. Ar*), 134.2 (*C-6*), 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6 (*Ar*), 111.9 (*quat. Thy*), 99.2 (*C-1″* $J_C{}^1$-$_H{}^1$ 167 Hz), 84.4 (*C-1′*), 83.2 (*C-4′*), 80.2, 78.7 (*C-3″*,*5″*), 76.6 (*CH*$_2$*Bn*), 75.5, 74.8 (2 × −CH_2–Bn), 74.5, 72.9, 71.9 (*C-3′* and *C-2″*,*4″*), 37.5 (*C-2′*), 20.9 (CO*CH*$_3$), 17.9 (*C-6″*), 12.4 (*CH*$_3$ *Thy*); ES-MS $C_{39}H_{48}N_2O_{10}^+$ requires 718.3340, found ($M + NH_4^+$) 718.3344. β-anomer **19**: δ_H ($CDCl_3$): 8.84 (1H, br s, *NH*), 7.22–7.39 (16 H, *3* × *Ph* and *H-6*), 6.27 (1 H, m, *H-1′*), 5.35 (1 H, m, *H-3′*), 4.93 (2H, m, −CH_2–Bn), 4.61–4.77 (4H, m, 2 × −CH_2–Bn), 4.27 (1 H, s, *H-1″*), 4.19 (1 H, br s, *H-4′*), 4.13 (1H, dd, $J_{4',5a'}$ 3.1 Hz, $J_{5a',5b'}$ 10.8 Hz, *H-5a′*), 3.90 (1H, d, $J_{2'',3''}$ 2.5 Hz, *H-2″*), 3.72 (1H, dd, $J_{4',5a'}$ 2.4 Hz, $J_{5a',5b'}$, *H-5b′*), 3.64 (1H, t, $J_{3'',4''}$ 9.2 Hz, *H-4″*), 3.52 (1H, dd, $J_{2'',3''}$ $J_{3'',4''}$, *H-3″*), 3.35 (1H, m, *H-5″*), 2.30 (1H, m, *H-2a′*), 2.10 (3H, s, CO*CH*$_3$), 1.81 (3H, s, *CH*$_3$ *Thy*), 1.69 (3H, m, *H-2b′*), 1.35 (3H, d, $J_{5'',6''}$ 6.0 Hz, *6″*-C*H*$_3$); δ_C ($CDCl_3$): 170.5, 163.7, 150.6 (*C*O), 138.4, 138.1 (*quat. Ar*), 135.4 (*C-6*), 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.7 (*Ar*), 111.2 (*quat. Thy*), 101.2 (*C-1″* J_{C1-H1} 157 Hz), 85.4 (*C-1′*), 83.8 (*C-4′*), 82.9 (*C-3″*), 80.1 (*C-4″*), 76.7, 76.1, 76.0, 75.4, 74.3 (3 × −CH_2–Bn and *C-2″*,*3′*), 72.4 (*C-5″*), 69.1 (*C-5′*), 37.8 (*C-2′*), 21.4 (CO*CH*$_3$), 18.3 (*C-6″*), 13.2 (*CH*$_3$ *Thy*); ES-MS $C_{39}H_{48}N_2O_{10}^+$ requires 718.3340, found ($M + NH_4^+$) 718.3343.

5′-*O*-α-L-Rhamnopyranosyl-thymidine 20. Protected α-rhamnosyl-thymidine **18** (80 mg, 0.1 mmol) was deprotected and purified as described for compound **10** to give α-rhamnosyl-thymidine **20** as a colourless syrup (31 mg, 80%); $[\alpha]_D^{25}$ −7.0 (*c* 0.41, MeOH); δ_H (MeOD): 7.43 (1H, br s, *H-6*), 6.19 (1H, s, *H-1′*), 4.62 (1H, s, *H-1″*), 3.02–4.13 (9H, m, *H-2″-5″* and *H-3′-5a′*,*5b′*), 2.11 (1H, m, *H-2a′*), 1.95 (1 H, m, *H-2b′*), 1.91 (3H, s, *CH*$_3$ *Thy*), 1.19 (1H, br s, $J_{5'',6''}$ 5.9 Hz, *6-CH*$_3$); δ_C (MeOD): 166.1, 152.1 (2 × NH*C*O), 137.0 (*C-6*), 111.5 (*quat. Thy*), 101.9 (*C-1″* J_{C1-H1}171 Hz), 86.5, 85.7, 73.3, 71.9, 71.7, 71.4 (*C-1′*, *C-4′* and *C-2″-5″*), 69.7, 68.1 (*C-3′*, *C-5′*), 40.2 (*C-2′*), 17.4 (*C-6″*), 12.1 (*C*H$_3$ *Thy*): ES-MS $C_{16}H_{28}N_3O_9^+$ requires 406.1826, found ($M + NH_4^+$) 406.1827.

5′-*O*-β-L-Rhamnopyranosyl thymidine 4. Protected β-rhamnosyl-thymidine **19** (70 mg, 0.09 mmol) was deprotected and purified as described for compound **10** to give β-rhamnosyl-thymidine **4** as a colourless syrup (25 mg, 74%); $[\alpha]_D^{25}$ +8.2 (*c* 0.37, MeOH); δ_H (MeOD): 7.60 (1H, s, *H-6*), 6.23 (1H, dd, $J_{1',2a'}$ 8 Hz $J_{1',2b'}$ 6.2 Hz, *H-1′*), 4.47 (1H, s, *H-1″*), 4.41 (1H, m, *H-3′*), 3.94 (2H, m, *H-4′*,*5a′*), 3.81 (1H, d, $J_{2'',3''}$ 2.9 Hz, *H-2″*), 3.70 (1H, dd, $J_{4',5a''}$ 2.3 Hz $J_{5a',5b''}$ 10.1 Hz, *H-5b′*), 3.36 (1H, dd, $J_{2'',3''}$ $J_{3'',4''}$ 9.1 Hz, *H-3″*), 3.24 (2H, m, *H-4″*,*5″*), 2.24 (1H, ddd, $J_{1',2a'}$ $J_{2a',2b'}$ 13 Hz $J_{2a',3'}$ 6 Hz, *H-2a′*), 2.24 (1H, ddd, $J_{1',2b'}$ $J_{2a',2b'}$ $J_{2b',3'}$ 2.7 Hz, *H-2b′*), 1.81 (3H, s, *CH*$_3$ *Thy*), 1.23 (1H, br s, $J_{5'',6''}$ 5.9 Hz, *6-CH*$_3$), δ_C (MeOD) 166.1, 152.1 (2 × NH*C*O), 137.6 (*C-6*), 111.3 (*q Thy*), 101.0 (*C-1″* J_{C1-H1}161 Hz), 86.9 (*C-4′*), 86.0 (*C-1′*), 74.5, 73.3, 72.7, 72.3, 72.0 (*C-2′*,*C-2″-5″*), 69.5, 67.8 (*C-3′*, *C-5′*), 40.2 (*C-2′*) 17.4 (*C-6″*), 11.9 (*C*H$_3$ *Thy*); ES-MS $C_{16}H_{28}N_3O_9^+$ requires 406.1826, found ($M + NH_4^+$) 406.1828.

Enzyme assays

Bovine β-1,4-galactopyranosyltransferase[33] (Sigma) was assayed essentially as described previously, with both donor and acceptor substrates concentrations at their respective K_M values. Under these conditions $IC_{50} \sim 2K_i$ for a competitive inhibitor.

Recombinant *Salmonella enterica* serovar typhimurium LT2 RmlB[34,35] was also assayed essentially as described previously, with $[S] \sim 3K_M$. Under these conditions $IC_{50} \sim 4K_i$ for a competitive inhibitor.

Acknowledgements

These studies were supported by the GlaxoSmithKline Action TB programme and the Weston Foundation. We thank Dr James Errey for assistance with enzyme assays, Professor Jim Naismith (University of St Andrews) for kindly providing the RmlB expression construct and the EPSRC Mass Spectrometry Service Centre, Swansea for invaluable support.

References

1 M.-F. Giraud and J. H. Naismith, *Curr. Opin. Chem. Biol.*, 2000, **10**, 687–696.
2 Y. F. Ma, F. Pan and M. McNeil, *J. Bacteriol.*, 2002, **184**, 3392–3395; J. A. Mills, K. Motichka, M. Jucker, H. P. Wu, B. C. Uhlik, R. J. Stern, M. S. Scherman, V. D. Vissa, F. Pan, M. Kundu, Y. Fang Ma and M. McNeil, *J. Biol. Chem.*, 2004, **279**, 43540–43546.
3 S. T. M. Allard, M.-F. Giraud, C. Whitfield, M. Graninger, P. Messner and J. H. Naismith, *J. Mol. Biol.*, 2001, **307**, 283–295.
4 K. Beis, S. T. M. Allard, A. D. Hegeman, G. Murshudov, D. Philp and J. H. Naismith, *J. Am. Chem. Soc.*, 2003, **125**, 11872–11878; S. T. M. Allard, K. Beis, M. F. Giraud, A. D. Hegeman, J. W. Gross, R. C. Wilmouth, C. Whitfield, M. Graninger, P. Messner, A. G. Allen, D. J. Maskell and J. H. Naismith, *Structure*, 2002, **10**, 81–92.
5 For instance: K. Babaoglu, M. A. Page, V. C. Jones, M. R. McNeil, C. J. Dong, J. H. Naismith and R. E. Lee, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3227–3230; Y. F. Ma, R. J. Stern, M. S. Scherman, V. D. Vissa, W. X. Yan, V. C. Jones, F. Q. Zhang, S. G. Franzblau, W. H. Lewis and M. R. McNeil, *Antimicrob. Agents Chemother.*, 2001, **45**, 1407–1416; J. P. Shilvock, J. R. Wheatley, R. J. Nash, A. A. Watson, R. C. Griffiths, T. D. Butters, M. Müller, D. J. Watkin, D. A. Winkler and G. W. J. Fleet, *J. Chem. Soc., Perkin Trans. 1*, 1999, **45**, 2735–2745.
6 S. Rachakonda and L. Cartee, *Curr. Med. Chem.*, 2004, **11**, 775–793.
7 A. R. Maguire, W. D. Meng, S. M. Roberts and A. J. Willets, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1795–1808 and references cited therein.
8 H. A. Dondas, C. W. G. Fishwick, R. Grigg and C. Kilner, *Tetrahedron*, 2004, **60**, 3473–3485 and references cited therein.
9 D. Heacock, C. J. Forsyth, K. Shiba and K. Musier-Forsyth, *Bioorg. Chem.*, 1996, **24**, 273–289 and references cited therein.
10 J. D. More and N. S. Finney, *Synlett*, 2003, 1307–1310; A. Suda, A. Ohta, M. Sudoh, T. Tsukuda and N. Shimma, *Heterocycles*, 2001, **55**, 1023–1028 and references cited therein.
11 P. Compain and O. R. Martin, *Bioorg. Med. Chem.*, 2001, **9**, 3077–3092.
12 R. Wang, D. H. Steensma, Y. Takoaka, J. W. Yun, T. Kajimoto and C.-H. Wong, *Bioorg. Med. Chem.*, 1997, **5**, 661–672.
13 Reviewed in:K. Kimura and T. D. H. Bugg, *Nat. Prod. Rep.*, 2003, **20**, 252–273.
14 F. W. Lichtenthaler and K. Kitahara, *Angew. Chem., Int. Edn. Engl.*, 1975, **14**, 815–816.
15 K. K. Ogilvie and D. Iwacha, *Can. J. Chem.*, 1974, **52**, 1787–1797.
16 S. A. Mitchell, M. R. Pratt, V. J. Hruby and R. Polt, *J. Org. Chem*, 2001, **66**, 2327–2342.
17 T. Wada, A. Ohkubo, A. Mochizuki and M. Sekine, *Tetrahedron Lett.*, 2001, **42**, 1069–1072.
18 H. Bredereck, A. Wagner, H. Kuhn and H. Ott, *Chem. Ber.*, 1960, **93**, 1201–1206.
19 D. M. Whitfield, S. P. Douglas, T.-H. Tang, I. G. Csizmadia, H. Y. S. Pang, F. L. Moolten and J. J. Krepinsky, *Can. J. Chem.*, 1994, **72**, 2225–2238.
20 N. C. Bar, R. Patra, B. Achari and S. B. Mandal, *Tetrahedron*, 1997, **53**, 4727–4738.
21 N. D. Chkanikov, V. N. Tolkachev and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 1978, **4**, 1620–1626.
22 W. H. Binder, H. Kählig and W. Schmid, *Tetrahedron: Asymmetry*, 1995, **6**, 1703–1710.
23 D. Crich and S. Sun, *J. Org. Chem.*, 1996, **61**, 4506–4507; D. Crich and S. Sun, *J. Org. Chem.*, 1997, **62**, 1198–1199.
24 B. Fraser-Reid, Z. F. Wu, C. W. Andrews, E. Skowronski and J. P. Bowen, *J. Am. Chem. Soc.*, 1991, **113**, 1434–1435.
25 D. Crich and Q. L. Yao, *J. Am. Chem. Soc.*, 2004, **126**, 8232–8236.
26 D. J. Silva and M. J. Sofia, *Tetrahedron Lett.*, 2000, **41**, 855–858.
27 A.-L. Chauvin, S. A. Nepogodiev and R. A. Field, *Carbohydr. Res.*, 2004, **339**, 21–27; for a recent thorough investigation of carbonate-protected rhamnosides in glycosylation chemistry see:; D. Crich, A. U. Vinod and J. Picione, *J. Org. Chem.*, 2003, **68**, 8453–8458.
28 S. J. Marsh, K. P. R. Kartha and R. A. Field, *Synlett*, 2003, 1376–1379.
29 J. Furukawa, S. Kobayashi, M. Nomizu, N. Nishi and N. Sakairi, *Tetrahedron Lett.*, 2000, **41**, 3453–3457.
30 R. Kakarla, R. G. Dulina, N. T. Hatzenbuhler, Y. W. Hui and M. J. Sofia, *J. Org. Chem*, 1996, **61**, 8347–8349.
31 X. Liu and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2227–2236.
32 K. Bock and C. Pedersen, *J. Chem. Soc., Perkin Trans. 1*, 1974, 293–297.
33 R. A. Field, D. C. A. Neville, R. W. Smith and M. A. J. Ferguson, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 391–394.
34 M. Graninger, B. Nidetzky, D. E. Heinrichs, C. Whitfield and P. Messner, *J. Biol. Chem.*, 1999, **274**, 25069–25077.
35 J. A. Vara and C. R. Hutchinson, *J. Biol. Chem.*, 1988, **263**, 14992–14995.
36 J.-B. Behr, T. Gourlain, A. Helimi and G. Guillerm, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1713–1716.