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A parallel synthesis approach towards a family of *C*-nucleosides

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Abstract—A synthetic route was devised for a sugar based α-chloroketone, which was subsequently used to generate a family of *C*-nucleosides via parallel synthetic methodology.

1. Introduction

The discovery of new chemotherapeutic treatments for controlling microbial infections is an important topic in clinical medicine.

Many nucleoside analogues of natural origin have been found to be bioactive. Bredinine **1**[1] (Mizoribine) is an imidazole nucleoside antibiotic clinically used as an immunosuppressant;[2] Toyocamycin **2**,[3] Mycalisin A **3**,[4] and Thiosangivamycin **4**[3] are three naturally occurring nucleosides which exert potent antiviral and antineoplastic activity (Fig. 1); Pseudouridine **5**,[5] Showdomycin **6**,[6] Pyrazofurin **7**[7] and Tiazofurin **8**[8] have been shown to possess a wide range of medicinal properties, including antibiotic, antiviral, and anti-tumor activity (Fig. 2).

In recent years a large number of compounds have been prepared modelled on naturally occurring templates and subsequently tested.[9] Triciribine **9**[10a] (Fig. 3) a synthetic tricyclic analogue of Toyocamicin **2** constitutes a valid example. Triciribine monophospate (TCN-P) is now in phase II studies as a potential antineoplastic agent.[10b]

In general, nucleoside analogues can be divided into three classes: (a) nucleosides bearing modification on the sugar moiety, (b) nucleosides bearing modification on the base moiety, (c) nucleosides bearing modification on both the base and the sugar moieties. Typical modifications of class (a) analogues include the alteration of sugar stereochemistry or the removal of one or more stereogenic centre as in

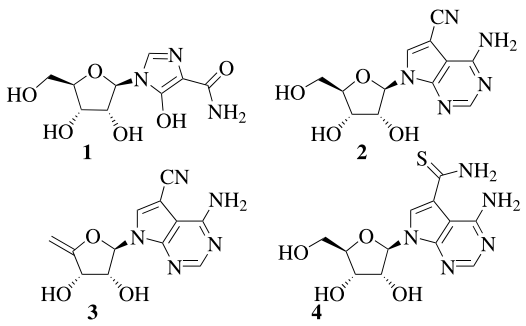

Figure 1. Naturally occurring nucleosides analogues.

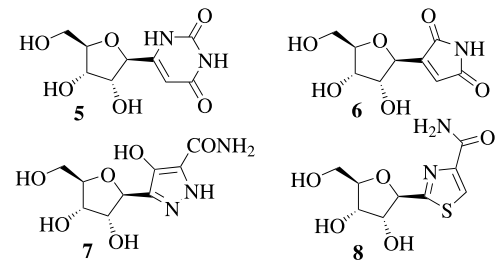

Figure 2. Naturally occurring *C*-nucleosides.

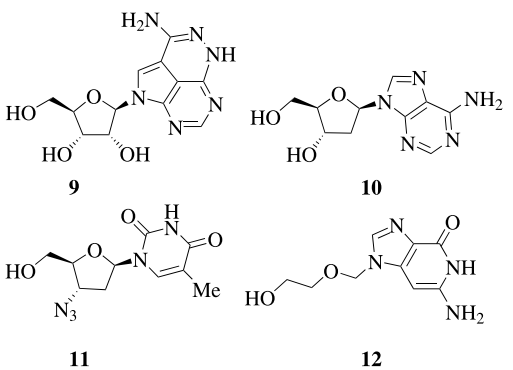

Figure 3. Synthetic nucleosides analogues.

Keywords: *C*-Nucleosides; Parallel synthesis.
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2′-deoxyadenosine **10** (Fig. 3); introduction of a different moiety such as an azido group in Zidovudine **11**, or replacement of the sugar by acyclic structures. Compounds having remarkable antiviral or antitumor activity have been obtained through sugar modification, such as acyclovir **12**.

Typical modifications of class (b) analogues include the addition or removal of structural elements, as in **9**. Modifications for class (c) analogues include all previously mentioned alterations for group (a) and (b). *C*-Nucleosides constitute a category of analogues in which the modification occurred at the linkage between the base and the sugar. In *C*-nucleosides, the sugar and the base are linked through a C–C linkage as opposed to *N*-nucleosides where a C–N bond is present. This structural alteration is believed to increase the nucleoside stability towards nucleoside hydrolase enzymes, and to inhibit in general the cascade of events leading to DNA or RNA formation.[11] Many naturally occurring *C*-nucleosides such as Pseudouridine **5**, Showdomycin **6** and Pyrazofurin **7** have been reported as strong antibiotic agents,[5–7] which has primed research on *C*-nucleoside analogues. However, despite the large amount of data collected, *C*-nucleosides and especially *C*-nucleosides belonging to the 2-deoxy-D-ribose series have scarcely been explored. Additionally, there is no data available on the biological activity of 2-deoxy-*C*-nucleosides belonging to the α-anomeric series. For these reasons, we believe that *C*-nucleosides constitute an ideal template for use in drug discovery.

2. Results and discussion

Our research focuses on the development of parallel synthetic methodologies which generate families of potentially useful drug candidates.[12–15] As part of this research we set out to develop a synthetic route to a family of *C*-nucleoside analogues of the 2-deoxy-D-series (Fig. 4). We choose the following key features to define the new family: (i) the *C*-linkage between the sugar and the heterocyclic moiety; (ii) the presence of multiple heteroatoms, as potential sites for H-bonding recognition; (iii) synthesis in both the α and β anomeric series; (iv) sugar moiety derived from the naturally occurring 2-deoxy-D-ribose **19**.

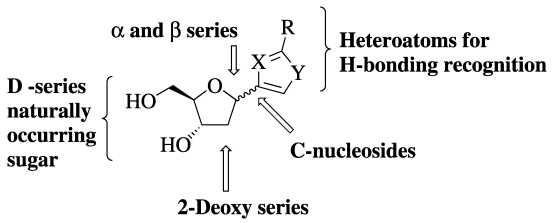
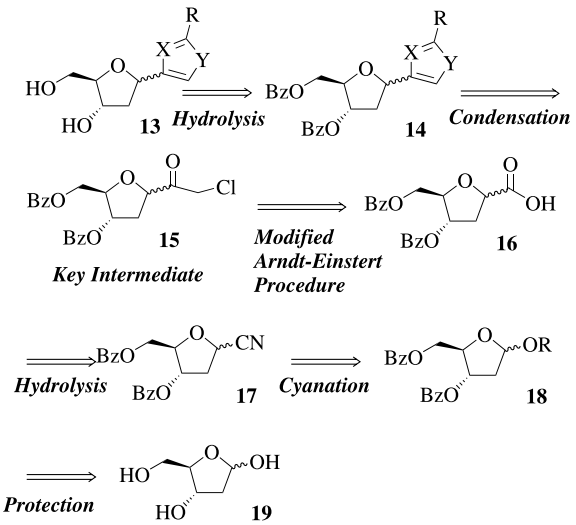


Figure 4. A family of 2-D-deoxy-*C*-nucleosides.

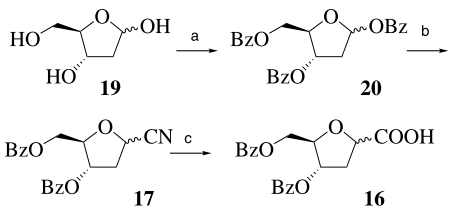
A disconnection analysis towards target **13** placed α-chloroketone **15** as the key intermediate in the synthetic plan (Scheme 1).

α-Haloketones have been shown to be versatile building blocks for the synthesis of heterocycles,[16–19] therefore we targeted compound **15** as a key intermediate in our synthetic approach. In turn, compound **15** can be accessed from the



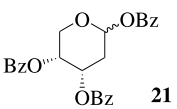
Scheme 1. Synthetic plan.

parent carboxylic acids **16**, through a modified Arndt–Einstert reaction. The synthesis of **16** has been reported from commercially available 2-deoxy-D-ribose **19** (Scheme 2).[20] As a protecting group regime was needed, attention was directed towards groups, which could be cleaved under mild conditions. The benzoyl group was selected, due to its ease of removal with aqueous base or methanolic ammonia. Thus, commercially available 2-deoxy-D-ribose **19** was firstly protected to give a tri-*O*-benzoyl deoxyribose derivative **20**, which in turn, was reacted to give nitrile **17**. Hydrolysis of **17** in mild acidic conditions furnished acid **16**. Conversion of **20** to **17** and of **17** to **16** were very effective processes, leading to high reaction yields.

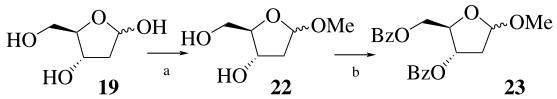


Scheme 2. *Reagents and conditions*: (a) DCM, BzCl (4 equiv.), pyridine (12 equiv.), rt, 1.5 h, 39%; (b) DCM, TMSCN (1.3 equiv.), $BF_3{\cdot}Et_2O$ (3.3 equiv.), 0 °C, 1.5 h, 73%; (c) 1,4-dioxane, HCl (1 mL, 35% HCl in water), 72%.

However, following this route, the overall yield was restricted as compound **20** could be obtained in no more than 39% yield from **19**. This was due to the concomitant formation of tribenzoylpyranose **21**, which affected the efficiency of the whole synthetic route. Furthermore, we found that the purification of **20** from **21** was laborious and time consuming.

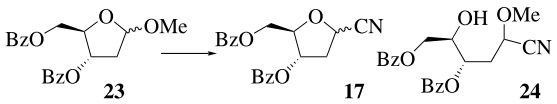


Formation of **21** could be avoided by blocking the anomeric position prior to benzoylation. Hence, selective methoxylation of the anomeric position furnished compound **22**[21] in nearly quantitative yields, which was successively benzoylated to give **23**[22] in 73% yield (Scheme 3).



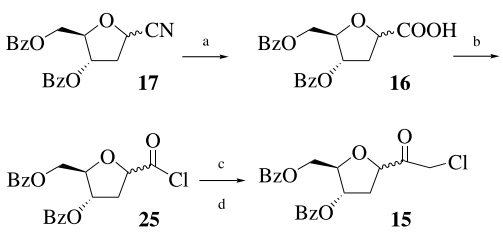
Scheme 3. *Reagents and conditions*: (a) MeOH, AcCl (6.4 mol%), rt, 25 min, 99%; (b) DCM, BzCl (4 equiv.), pyridine (12 equiv.), rt, 1.5 h, 73%.

Compound **23** was then submitted to cyanation using TMSCN in the presence of $BF_3{\cdot}OEt_2$ (Scheme 4) to give nitrile **17**. Although conversion of **23** was complete under the experimental conditions employed, the yields of **17** never exceeded 70–75%, due to the formation of acyclic derivative **24** by product. This behaviour was not observed when **20** was cyanated under similar conditions, and could be rationalised by the fact that benzoate is a better leaving group.



Scheme 4. *Reagents and conditions*: DCM, TMSCN (1.3 equiv.), $BF_3{\cdot}Et_2O$ (3.3 equiv.), 0 °C, 1.5 h, 71%.

The hydrolysis of nitrile **17** proceeded as reported and acid **16** was obtained in 72% yield (Scheme 5).[20]

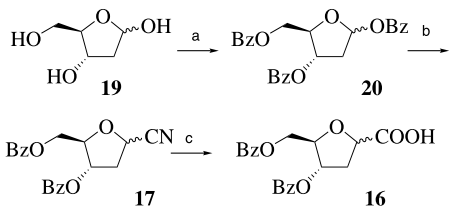


Scheme 5. *Reagents and conditions*: (a) dioxane/HCl, 70 °C, 6 h, 72%; (b) DCM, α,α-dichloromethyl methyl ether (5 equiv.), reflux, 4 h, 99%; (c) Et_2O, CH_2N_2, (3 equiv.); (d) HCl gas, 30 min, 61%.

α-Chloroketone **15** was prepared from **16** through a modified Arndt–Einstert procedure. This method involved the activation of the acid to a mixed anhydride or an acyl chloride such as **25**, followed by displacement of chloride by diazomethane and subsequent quenching with HCl (Scheme 5). With the α-chloroketone **15** in hand we explored its reactivity towards a number of polynucleophiles.

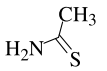
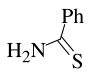
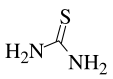
We reacted **15** with various thioamide nucleophiles and found that thiazoles **26**–**28** could be obtained in good yields (Scheme 6 and Table 1).

Importantly, the α and β anomers could be separated at this stage by simple flash chromatography.



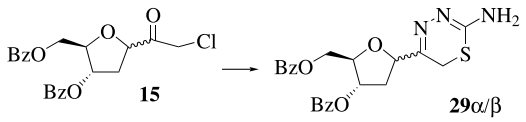
Scheme 6. *Reagents and conditions*: **15**, ethanol, thioamide (1.0 equiv.), or thiourea, reflux, 16 h.

Table 1. Formation of benzoyl nucleosides

Entry	Nucleophile	Product	Yield (%)
1		R=CH_3 **26**α	35
		R=CH_3 **26**β	53
2		R=Ph **27**α	22
		R=Ph **27**β	45
3		R=NH_2 **28**α	35
		R=NH_2 **28**β	55

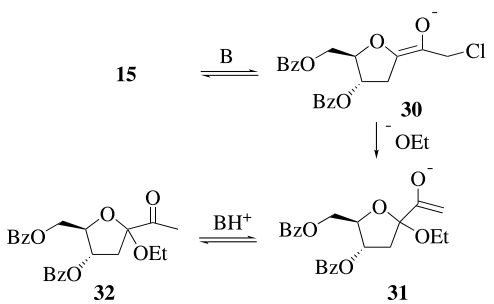
The stereochemistry at the anomeric position was assigned by NOE experiments. Positive NOE was observed between the anomeric H-1′ and H-4′ in the β anomer, and between the H-1′ and H-3′ in the α anomer.

We have also employed **15** to make heterocycles other than thiazoles. When chloroketone **15** was reacted with thiosemicarbazide hydrochloride, rapid condensation occurred and thiazidine **29**α/β was isolated in 81% yield (Scheme 7).



Scheme 7. *Reagents and conditions*: **15**, methanol, thiosemicarbazide hydrochloride (1.0 equiv.), reflux, 1 h, 81%.

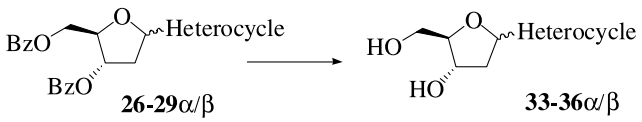
We have attempted to prepare sugar-based imidazoles by reacting α-chloroketone **15** with amidines. In these experiments no heterocycle was formed and repeatedly, compound **32**α/β was isolated in 60–70% yield (Scheme 8).



Scheme 8. *Reagents and conditions*: **15**, ethanol, benzamidine hydrochloride (1 equiv.), $NaHCO_3$ (1 equiv.), reflux, 4 h, 65% yield.

It is possible that the basic character of amidines promotes conversion of **15** to **32**. A mechanism for this reaction is proposed as follows (Scheme 8). It is noteworthy that reaction of α-chloroketones with AcOK/AcOH to give α′-propanones has been reported for substrates bearing an α′-aryloxy, or α′-phenylthio substituent.[23]

Dibenzoyl *C*-nucleosides **26**–**28**α/β, were finally deprotected using either LiOH in THF/H_2O or NH_3/MeOH. These reactions proceeded in high yields and with no epimerization at the anomeric position (Scheme 9 and Table 2).



26-29α/β **33-36**α/β

Scheme 9. *Reagents and conditions*: LiOH·H_2O (1.1 equiv.) THF–H_2O, rt, 24 h; or.MeOH,·NH_3, rt, 24 h.

Table 2. Deprotection of dibenzoyl nucleosides

Entry	Protected nucleoside	Nucleoside	Yield (%)
1[a]	**26**α	**33**α	71
2[a]	**26**β	**33**β	78
3[a]	**27**α	**34**α	82
4[a]	**27**β	**34**β	86
5[b]	**28**α	**35**α	65
6[b]	**28**β	**35**β	68
7[b]	**29**α/β	**36**α/β	75

[a] Reagents and conditions: LiOH·H_2O (1.1 equiv.) THF–H_2O, rt, 24 h.
[b] Reagents and conditions: MeOH·NH_3, rt, 24 h.

In conclusion, parallel synthetic methodology towards a family of *C*-nucleosides has been developed. This route made use of an α-chloroketone as the key intermediate derived from a naturally occurring sugar, which led to a number of synthetic nucleosides.

3. Experimental

3.1. General

Anhydrous DCM was obtained by stirring over calcium hydride for 24 h followed by distillation under nitrogen. All water used was distilled.

^1H and ^{13}C Spectra were recorded on, Brüker DPX200 (200 MHz), Varian Gemini 200 (200 MHz), Brüker DPX 250 (250 MHz), Brüker DQX 400 (400 MHz), Brüker DPX400 (400 MHz) and Brüker AMX 500 (500 MHz) spectrometers at ambient temperatures. ^1H NMR spectral assignments are supported by ^1H–^1H COSY where necessary. For ^1H NMR recorded in $CDCl_3$ chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet, d, doublet, t, triplet, dd, doublet of doublets, ddd, doublet of doublet of doublets, dt, doublet of triplets, m, multiplet and br, broad. Coupling constants (*J*) were recorded in Hertz (Hz) to the nearest 0.5 Hz. Carbon spectra are supported by DEPT analysis where necessary.

Infrared (IR) spectra were recorded as thin films between NaCl plates on a Perkin–Elmer Paragon Fourier Transform spectrometer. Absorption maximum (ν_{max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. The following abbreviations are used: w, weak, m, medium, s, strong and br, broad.

Low-resolution mass spectra (*m/z*) were recorded using a V.G.TRIO (GCMS) spectrometer, a Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a Micromass ZAB spectrometer (CI^+, EI). Only molecular ion (M^+) and other major peaks are reported. High-resolution mass spectra were recorded on a Micromass Autospec spectrometer and are accurate to ±5 ppm.

Melting points were obtained using a Büchi 510 Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected.

Specific optical rotations were recorded using a Perkin–Elmer 241 automatic polarimeter with a cell of path length 1 dm. All concentrations are given in grams per 100 mL.

Flash chromatography was carried out using silica gel 60 0.040–0.063 mm, 230–400 mesh as the stationary phase. Thin layer chromatography was carried out on aluminium backed plates pre-coated with Merck silica gel 60 F_{254} (1.05554), which were visualized by quenching of UV fluorescence (λ_{max}=254 nm) or by staining with either 10% (w/v) ammonium molybdate in 2 M sulphuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to ±0.5.

All reactions were carried out under anhydrous conditions and an argon atmosphere unless otherwise indicated.

3.1.1. 2*R*-Hydroxymethyl-5-methoxytetrahydrofuran-3*S*-ol, 22.[21] To a stirred solution of 2-deoxy-D-ribose (5.00 g, 37.3 mmol) in methanol (60 mL) was added 1% methanolic hydrogen chloride solution (prepared by adding 170 μL acetyl chloride to 10 mL MeOH). The reaction mixture was stirred at room temperature under an Argon atmosphere (25 min) then sodium bicarbonate (2 g) added and the reaction stirring continued for further 10 min. The solids were filtered and the solvent removed in vacuo to give **22** as an orange oil (5.46 g, 99% yield). This product was found pure enough to be used without further purification; δ_H (400 MHz, $CDCl_3$) 5.11–5.08 (1H, m, CH_3O–C*H*–O), 4.50–4.01 (2H, m, $HOCH_2CHCHO$), 3.75–3.71 (2H, m, $HOCH_2CHCHOH$), 3.38 (3H, s, CH_3OCHO), 2.17–1.83 (2H, m, $MeOCHCH_2CH$).[21]

3.1.2. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5-methoxytetrahydrofuran, 23.[22] To a stirred solution of **22** (5.46 g, 36.9 mmol) in dichloromethane (90 mL) was added benzoyl chloride (17.2 mL, 147 mmol, 4 equiv.) and the reaction mixture cooled to 0 °C by ice bath cooling. A mixture of dichloromethane (88 mL) and pyridine (44 mL) was added dropwise and the reaction mixture was then stirred at room temperature under Ar atmosphere (1.5 h). The reaction mixture was washed with 10% sulphuric acid (4×300 mL), then with saturated potassium bicarbonate solution (2×200 mL) and finally with water (2×200 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with dichloromethane to give the title compound **23** as a colourless oil (9.63 g, 73% yield, α/β=40:60);[24] R_f 0.2, dichloromethane.

Compound **23**α. δ_H (500 MHz, $CDCl_3$) 8.16–8.08 (4H, m, Ar); 7.62–7.59 (2H, m, Ar), 7.50–7.45 (4H, m, Ar), 5.52–5.49 (1H, m, BzOC*H*CH_2), 5.25 (1H, d, CH_3OCHO *J*=4.5 Hz), 4.72–4.42 (3H, m, BzOCH_2CHO, BzOCH_2-C*H*O), 3.48 (3H, s, CH_3OCHO), 2.59 (1H, m, CHOHCH_2) 2.27 (1H, m, CHOHCH_2); δ_C (125.8 MHz, $CDCl_3$) 105.51

(CH_3OCHO), 81.37 ($BzOCH_2CHO$), 75.26 ($BzOCHCHO$), 64.93 ($BzOCH_2CHO$), 55.58 (CH_3OCHO), 39.54 ($OCHCH_2CHOBz$).

Compound **23**β. δ_H (500 MHz, $CDCl_3$) 8.16–8.08 (4H, m, Ar); 7.62–7.59 (2H, m, Ar), 7.50–7.45 (4H, m, Ar), 5.70–5.67 (1H, m, $BzOCHCH_2$), 5.29 (1H, dd, CH_3OCHO, J=2, 5.5 Hz), 4.72–4.42 (3H, m, $BzOCH_2CHO$, $BzOCH_2CHO$), 3.42 (3H, s, CH_3OCHO), 2.63 (1H, m, $CHOHCH_2$) 2.41 (1H, m, $CHOHCH_2$); δ_C (125.8 MHz, $CDCl_3$) 105.89 (CH_3OCHO), 82.12 ($BzOCH_2CHO$), 76.04 ($BzOCHCHO$), 65.74 ($BzOCH_2CHO$), 55.67 (CH_3OCHO), 39.85 ($OCHCH_2CHOBz$).

Compound **23**α/β. δ_C (125.8 MHz, $CDCl_3$) 166.49, 166.64, 166.69, 166.86 (PhCO); 133.76, 133.69, 133.58, 133.50, 130.37, 130.27, 130.22, 130.20, 130.13, 130.10, 130.04, 129.06, 128.99, 128.89, 128.86, 128.82 (Ar); ν_{max}/cm^{-1} (neat film) 1723s, 1602m; *m/z* (GC–CI[NH_3]) 374 (MNH_4^+, 30%), 325 (100%); HRMS found: MNH_4^+ 374.1620 ($C_{20}H_{24}NO_6$ requires 374.1604).

3.1.3. 4*S*-Benzoyloxy-5*R*-benzoyloxymethyltetrahydrofuran-2*R*/*S*-carbonitrile, 17.[20] To a stirred solution of **23** (9.62 g, 27.0 mmol) in dry dichloromethane (160 mL) was added TMSCN (5.47 mL, 38.4 mmol, 1.4 equiv.) and $BF_3{\cdot}OEt_2$ (11.9 mL, 96.0 mmol, 3.6 equiv.). The reaction mixture was stirred at 0 °C under an Argon atmosphere for 1.5 h. After this time, a saturated aqueous $NaHCO_3$ solution (300 mL) was slowly added and the reaction mixture stirred until evolution of CO_2 was finished. The product was extracted with dichloromethane (2×300 mL), the organic layer dried over Na_2SO_4 and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with chloroform/ethyl acetate (40:1) to give the title compound **17** as a yellow oil (6.72 g, 71% yield); R_f 0.85; δ_H (250 MHz, $CDCl_3$) 8.12–8.00 (4H, m, Ar), 7.51–7.47 (6H, m, Ar), 5.65 (1H, m, $BzOCHCH_2$) 5.08 (0.4H, dd, J=2, 7 Hz, OCHCN), 4.94 (0.6H, dd, J=6.5, 9 Hz, OCHCN), 4.71–4.52 (3H, m, $BzOCH_2CHO$), 2.81–2.60 (2H, m, $CHCH_2CHCN$); δ_C (62.5 MHz, $CDCl_3$) 166.56 (PhCO), 166.45 (PhCO), 166.11 (PhCO), 134.19 (Ar), 134.14 (Ar), 133.84 (Ar), 130.37 (Ar), 130.17 (Ar), 130.13 (Ar), 130.05 (Ar), 129.79 (Ar), 129.34 (Ar), 129.06 (Ar), 129.02 (Ar), 128.98 (Ar), 118.84 (NCCHO), 118.29 (NCCHO), 84.64 ($CNCHCH_2CHOBz$), 84.17 ($CNCHCH_2CHOBz$), 75.94 ($BzOCH_2CHO$), 75.42 ($BzOCH_2CHO$), 66.98 (NCCHO), 66.30 (NCCHO), 64.32 ($BzOCH_2CHO$), 64.20 ($BzOCH_2CHO$), 38.33 ($NCCHCH_2CH$), 38.22 ($NCCHCH_2CHOBz$); ν_{max}/cm^{-1} (neat film), 1722s, 1602s,; *m/z* [CI(NH_3)] 369 (MNH_4^+, 100%); HRMS found: MNH_4^+ 369.1438 ($C_{20}H_{21}N_2O_5$ requires 369.1450), and 4*S*,5*R*,6-tribenzoyloxy-2*R*/*S*-methoxy-hexanenitrile **24**: yellow oil (2.25 g, 22% yield); R_f 0.25, chloroform/ethyl acetate (40:1); δ_H (200 MHz, $CDCl_3$), 8.09–8.01 (4H, m, Ar), 7.61–7.40 (6H, m, Ar), 5.51–5.42 (1H, m, $NCCHOCH_3$), 4.61–4.17 (4H, m, $BzOCH_2CHO$, $BzOCHCH_2$), 3.45 and 3.48 (3H, 2×s, OCH_3), 2.58–2.38 (2H, m, $BzOCHCH_2CHCN$); δ_C (50.3 MHz, $CDCl_3$) 167.0 (PhCO), 166.0 (PhCO), 133.7 (Ar), 133.6 (Ar), 133.4 (Ar), 129.8 (Ar), 129.8 (Ar), 129.4 (Ar), 128.7 (Ar), 128.5 (Ar), 117.7 (NCCHOMe), 71.2 and 71.1 (NCCHOMe), 70.9 and 70.7 ($BzOCHCHOH$), 67.8 and 67.0 ($BzOCH_2CHOH$), 65.7 and 65.6 ($BzOCH_2CHOH$), 58.4 and 58.2 ($BzOCHCH_2CHCN$), 34.9 and 34.5 (CH_3OCHCN); ν_{max}/cm^{-1} (neat film) 3477m br, 1202s, 1126s; *m/z* (electrospray) 401 (MNH_4^+, 100%); HRMS found: MH^+ 384.1463 ($C_{21}H_{22}NO_6$ requires 384.1447).

3.1.4. 4*S*-Benzoyloxy-5*R*-benzoyloxymethyltetrahydrofuran-2*R*/*S*-carboxylic acid 16.[20] To a stirred solution of **17** (4.81 g, 13.7 mmol) in 1,4-dioxane (112 mL) was added conc. HCl (11 mL). The reaction mixture was refluxed at 80 °C (6 h) and then the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/petrol/acetic acid (70:30:2) to give **16** as a yellow oil (3.64 g, 72% yield); R_f 0.4, ethyl acetate/petrol/acetic acid (70:30:2); δ_H (200 MHz, $CDCl_3$) 8.90 (1H, br s, HOOCCH), 8.08–8.01 (3H, m, Ar), 7.96–7.92 (1H, m, Ar), 7.62–7.37 (6H, m, Ar), 5.58–5.54 (1H, m, $BzOCHCH_2$) 4.48–4.71 (1H, m, HO_2CCHO) 4.70–4.51 (3H, m, $BzOCH_2CHO$), 2.82–2.43 (2H, m, $BzOCHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 177.03 (HOOCCH), 166.74 (PhCO), 165.90 (PhCO), 133.65 (Ar), 133.54 (Ar), 133.47 (Ar), 133.37 (Ar), 129.76 (Ar), 129.71 (Ar), 129.66 (Ar), 129.46 (Ar), 129.32 (Ar), 129.11 (Ar), 128.57 (Ar), 128.54 (Ar), 128.50 (Ar), 84.26 and 83.73 ($BzOCHCH_2$), 75.86 and 75.34 ($BzOCH_2CHO$), 67.04 (OCHCOOH), 64.43 and 64.17 ($BzOCH_2CHO$), 36.37 ($BzOCHCH_2CHO$); ν_{max}/cm^{-1} (neat film) 1721s, 1271s; *m/z* (electrospray) 393 (MNa^+, 100%); HRMS found: MNa^+ 393.0943 ($C_{20}H_{18}O_7Na$ requires 393.0950).

3.1.5. 4*S*-Benzoyloxy-5*R*-benzoyloxymethyl-tetrahydrofuran-2*R*/*S*-carbonyl chloride, 25. To a mixture of the **16** (100 mg, 0.27 mmol) in dry dichloromethane (5 mL) was added α,α-dichloromethyl methyl ether (122 μL, 1.35 mmol, 5 equiv.). The mixture was then refluxed for 4 h, allowed to cool and concentrated in vacuo to yield the desired acid chloride **25** as a light yellow oil (103 mg, 99% yield); δ_H (400 MHz, $CDCl_3$) 8.05–7.96 (4H, m, Ar), 7.62–7.55 (2H, m, Ar), 7.48–7.45 (4H, m, Ar), 5.59 (1H, app s, $BzOCHCH_2$), 5.04 (1H, app t, $ClCOCHO$, J=9 Hz), 4.61–4.51 (3H, m, $BzOCH_2CHO$), 2.79–2.64 (2H, m, $ClCOCHCH_2$); δ_C (50.3 MHz, $CDCl_3$) 175.22 ($ClCOCHO$), 173.67 ($ClCOCHO$), 166.36 (PhCO), 166.01 (PhCO), 135.25 (Ar), 133.87 (Ar), 133.50 (Ar), 129.88 (Ar), 129.73 (Ar), 129.36 (Ar), 129.25 (Ar), 128.78 (Ar), 84.36 ($BzOCHCH_2$), 83.89 ($BzOCHCH_2$), 75.38 ($ClCOCHO$), 74.95 ($ClCOCHO$), 68.02 ($BzOCH_2CHO$), 64.05 ($BzOCH_2CHO$), 53.51 ($BzOCH_2CHO$), 52.63 ($BzOCH_2CHO$), 36.62 ($BzOCHCH_2CHO$), 36.26 ($BzOCHCH_2CHO$); ν_{max}/cm^{-1} 3021 m, 2401 w, 1811 m, 1773s; this compound gave unsatisfactory mass spectral data.

3.1.6. 2-Chloro-1-(4*S*-benzoyloxy-5*R*-benzoyloxymethyltetrahydrofuran-2*R*/*S*-yl)-ethanone, 15. The crude acid chloride **25**, obtained from **16** (3.56 g, 9.62 mmol), was taken up in dry diethyl ether (100 mL) and an ethereal solution of freshly generated alcohol free diazomethane added (6.18 g Diazald, 28.9 mmol, 3 equiv.). The reaction mixture was stirred for 15 min and then bubbled through with dry HCl gas for 30 min. The solution was diluted with diethyl ether (125 mL) and the organic phase washed with water (300 mL), then with saturated aqueous $NaHCO_3$ solution (2×300 mL) and finally with water (300 mL). The

reaction mixture was dried over $CaCl_2$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/petrol (30:70) to give **15** as a white solid (2.38 g, 61% yield), m.p 122 °C; R_f 0.55, ethyl acetate/petrol (30:70); δ_H (400 MHz, $CDCl_3$) 8.17–7.90 (4H, m, Ar) 7.64–7.59 (2H, m, Ar), 7.55–7.44 (4H, m, Ar), 5.58–5.55 (1H, m, BzOC*H*CH_2), 4.88–4.83 (1H, m, C*H*$COCH_2Cl$), 4.64 (2H, d, *J*=5 Hz, BzOC*H*$_2$CHO), 4.48 (2H, 2×s, $COCH_2Cl$), 4.65–4.47 (1H, m, $BzOCH_2CHO$), 2.77–2.37 (1H, m, $BzOCHCH_2CH$); δ_C (100.6 MHz, $CDCl_3$) 203.31 and 201.02 ($COCH_2Cl$), 166.08, 165.85 and 165.52 (Ph*C*O); 133.65, 133.57, 133.43, 133.37, 129.66, 129.63, 129.59, 129.53, 129.44, 129.32, 129.20, 128.88, 128.62, 128.54 and 128.52 (Ar); 83.95 and 83.76 (BzO*C*HCH_2), 83.20 and 82.54 ($ClCH_2CO$*C*), 75.80 and 75.65 ($BzOCH_2$C*H*), 64.27 and 64.15 (BzO*C*H_2CH), 47.56 and 46.51 (Cl*C*H_2CO), 35.82 and 35.72 (BzOCH*C*H_2); ν_{max}/cm^{-1} (neat film) 1719s, 1269s, 1101s; *m*/*z* (electrospray) 403 (MH^+, 30%); HRMS found: 403.0944 ($C_{21}H_{20}O_6Cl$ requires 403.0948).

3.2. General procedure for the preparation of compounds 26α/β, 27α/β, 28α/β

To a solution of **15** (556 mg, 1.38 mmol) in ethanol (10.4 mL) was added the corresponding thioamide (1.38 mmol, 1 equiv.) and the reaction mixture refluxed for 20 h. Then the solvent was removed and the residue purified by flash chromatography.

3.2.1. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*R*-(2-methylthiazol-4-yl)-tetrahydrofuran, 26β. Colourless oil, 310 mg, 53% yield from **15**, R_f 0.4 ethyl acetate/petrol (30:70); δ_H (400 MHz, $CDCl_3$) 8.09–8.07 (4H, m, Ar), 7.61–7.55 (2H, m, Ar), 7.48–7.40 (4H, m, Ar), 7.12 (1H, s, =C*H*S), 5.65 (1H, d, *J*=6 Hz, BzOC*H*CH_2), 5.41 (1H, dd, *J*=5.5, 10 Hz, OC*H*C=), 4.64 (2H, d, *J*=2 Hz, BzOC*H*$_2$-CH), 4.56–4.55 (1H, m, $BzOCH_2CH$), 2.68 (3H, s, CH_3C=), 2.68–2.65 (1H, m, $BzOCHCH_2$), 2.50 (1H, ddd, *J*=6, 10, 14 Hz, $BzOCHCH_2$); δ_C (100.6 MHz, $CDCl_3$) 166.51 and 166.26 (Ph*C*=O), 165.99 (CH_3C), 155.49 (OCHC=*C*H), 133.29 133.01, 129.87, 129.72, 129.69, 129.43, 128.33, 128.27 (Ar), 114.34 (OCH*C*=CH), 82.88 (BzO*C*HCH_2), 78.14 (O*C*HC=CH), 76.69 ($BzOCH_2$ *C*HO), 64.74 (BzO*C*H_2CHO), 39.71 (BzOCH*C*H_2), 19.12 (CH_3C); ν_{max}/cm^{-1} (neat film) 1722s, 1602 w, *m*/*z* (electrospray) 446 (MNa^+, 100%); HRMS found: MNa^+ 446.1042 ($C_{23}H_{21}NO_5SNa$ requires 446.1038); $[\alpha]_D^{20}$ −68.0 [*c* 1.0, $CHCl_3$].

3.2.2. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*S*-(2-methylthiazol-4-yl)-tetrahydrofuran, 26α. Colourless oil, 205 mg, 35% yield from **15**, R_f 0.2 ethyl acetate/petrol (30:70); δ_H (400 MHz, $CDCl_3$) 8.10–8.05 (2H, m, Ar), 7.84–7.81 (2H, m, 2H, Ar), 7.58–7.39 (6H, m, Ar), 7.14 (1H, s, =CHS), 5.62 (1H, ddd, *J*=9, 7, 3 Hz, BzOC*H*CH_2), 5.47 (1H, dd, *J*=6, 5 Hz, OC*H*C=), 4.71 (1H, m, BzOC*H*$_2$CH), 4.61 (2H, d, *J*=5 Hz, BzOC*H*$_2$CH), 2.91 (1H, dd, *J*=9, 7 Hz, $BzOCHCH_2$), 2.69–2.60 (1H, m, $BzOCHCH_2$), 2.67 (3H, s, CH_3); δ_C (100.6 MHz, $CDCl_3$) 166.27 and 166.26 (Ph*C*O), 165.99 (CH_3C=N), 156.21 (OCHC=*C*H), 133.16, 133.11, 129.68, 129.65, 129.58, 129.21, 128.41, 128.27 (Ar), 113.72 (OCH*C*=CH), 82.13 (BzO*C*HCH_2), 77.71 (O*C*HC=CH), 76.43 ($BzOCH_2$*C*HO), 65.80 (BzO*C*H_2CHO), 38.27 (BzOCH*C*H_2), 19.22 (CH_3C=N); ν_{max}/cm^{-1} (neat film) 1722s, 1275s; *m*/*z* (electrospray) 446 (MNa^+, 100%); HRMS found: MNa^+ 446.1047 ($C_{23}H_{21}NO_5SNa$ requires 446.1038); $[\alpha]_D^{20}$ +10.0 [*c* 1.0, $CHCl_3$].

3.2.3. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*R*-(2-phenylthiazol-4-yl)-tetrahydrofuran, 27β. Colourless oil, 301 mg, 45% yield from **15**, R_f 0.65 ethyl acetate/petrol (10:90); δ_H (500 MHz, $CDCl_3$) 8.17–8.13 (4H, m, *Ph*), 7.98–7.96 (2H, m, *Ph*), 7.60–7.45 (9H, m, *Ph*), 7.35 (1H, s, OCHC=C*H*S), 5.76 (1H, d, *J*=5.5 Hz, BzOC*H*CH_2), 5.56 (1H, dd, *J*=10, 5.5 Hz, OC*H*C=), 4.80–4.66 (2H, m, BzOC*H*$_2$CHO), 4.61 (1H, app d, *J*=6.5 Hz, $BzOCH_2$C*H*O), 2.78 (1H, dd, *J*=14, 5.5 Hz, BzOCH*C*H_2), 2.67 (1H, ddd, *J*=14, 10, 5.5 Hz, BzOCH*C*H_2); δ_C (125.8 MHz, $CDCl_3$) 168.65 (Ph*C*=N); 166.21 (Ph*C*O), 165.97 (Ph*C*O), 156.90 (OCHC=C*H*S), 133.45, 133.26, 132.98, 129.94, 129.73, 129.61, 128.78, 128.74, 128.38, 128.33, 128.29, 126.42 (Ar), 114.83 (OCH*C*=CHS), 82.89 (BzO*C*HCH_2), 77.90 (O*C*HC=CH), 77.64 ($BzOCH_2$*C*HO), 64.69 ($BzOCH_2$ *C*HO), 39.10 (BzOCH*C*H_2); ν_{max}/cm^{-1} 1722s, 1602m; *m*/*z* (electrospray) 486 (MH^+, 100%); HRMS found: MH^+ 486.1373 ($C_{28}H_{24}NO_5S$ requires 486.1375); $[\alpha]_D^{20}$ −30.0 [*c* 1.0, $CHCl_3$].

3.2.4. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*S*-(2-phenylthiazol-4-yl)-tetrahydrofuran, 27α. Colourless oil, 147 mg, 22% yield from **15**, R_f 0.62 ethyl acetate/petrol (10:90); δ_H (500 MHz, $CDCl_3$) 8.10–8.09 (2H, m, Ar), 7.96–7.92 (2H, m, Ar), 7.80–7.78 (2H, m, Ar), 7.60–7.58 (1H, m, Ar), 7.50–7.26 (9H, m, *Ar*), 5.61 (1H, dd, *J*=6, 3 Hz, BzOC*H*CH_2), 5.58 (1H, dd, *J*=4, 8 Hz, OC*H*C=), 4.74–4.73 (1H, m, $BzOCH_2$C*H*), 4.63 (2H, d, BzOC*H*$_2$CH, *J*=4 Hz), 2.97 (1H, dt, *J*=14, 7 Hz, BzOCHC*H*$_2$),), 2.81 (1H, dt, *J*=14, 4 Hz, BzOCHC*H*$_2$); δ_C (100.6 MHz, $CDCl_3$) 168.11 (Ph*C*=N), 166.24 (Ph*C*O), 165.88 (Ph*C*O), 158.73 (OCHC=*C*HS), 133.50, 133.07, 166.06, 129.92, 129.62, 129.47, 128.79, 128.37, 128.17, 126.42 (Ar), 114.10 (OCH*C*=CHS), 82.37 (BzO*C*HCH_2), 77.92 (O*C*HC=CH), 76.44 ($BzOCH_2$*C*HO), 64.71 (BzO*C*H_2CHO), 38.17 (BzO*C*H_2CH); ν_{max}/cm^{-1} (neat film) 1722s; *m*/*z* (electrospray) 486 (MH^+, 100%); HRMS found: 486.1366 ($C_{28}H_{24}NO_5S$ requires 486.1375); $[\alpha]_D^{20}$ +6.4 [*c* 1.0, $CHCl_3$].

3.2.5. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*R*-(2-aminothiazol-4-yl)-tetrahydrofuran, 28β. Colourless oil, 322 mg, 55% yield from **15**, R_f 0.55 ethyl acetate/petrol (50:50); δ_H (400 MHz, $CDCl_3$) 8.10–8.07 (4H, m, Ar), 7.67–7.56 (2H, m, Ar), 7.49–7.37 (4H, m, Ar), 6.51 (1H, s, C=C*H*), 5.61 (1H, d, *J*=5 Hz, BzOC*H*CH_2), 5.19 (1H, dd, *J*=10, 6 Hz, C*H*C=CH), 5.01 (2H, br, NH_2), 4.65–4.62 (2H, m, BzOC*H*$_2$CHO), 4.53 (1H, app s, $BzOCH_2$C*H*O), 2.56–2.45 (2H, m, BzOCHC*H*$_2$); δ_C (100.6 MHz, $CDCl_3$) 168.41 (=*C*NH_2), 166.77 (Ph*C*O), 166.48 (Ph*C*O), 151.78 (CHC=*C*H), 133.77, 133.66, 130.37, 130.24, 130.14, 128.91, 128.87, and 128.81 (Ar), 105.25 (CH*C*=CH), 83.17 (BzO*C*HCH_2), 77.93 (*C*HC=CH), 77.20 ($BzOCH_2$-*C*H), 65.23 (BzO*C*H_2CH), 39.02(BzOCH*C*H_2); ν_{max}/cm^{-1} (neat film) 3367 br m, 1721s; *m*/*z* (EI) 425 (MH^+, 100%); HRMS found: MH^+ 425.1178 ($C_{22}H_{21}N_2O_5S$ requires 425.1171); $[\alpha]_D^{20}$ −53 [*c* 1.0, $CHCl_3$].

3.2.6. 3*S*-Benzoyloxy-2*R*-benzoyloxymethyl-5*S*-(2-aminothiazol-4-yl)-tetrahydrofuran, 28α. Colourless oil, 205 mg, 35% yield from **15**, R_f 0.45 ethyl acetate/petrol (50:50) δ_H (400 MHz, $CDCl_3$) 8.08–8.05 (2H, m, Ar), 7.93–7.90 (2H, m, Ar), 7.59–7.53 (2H, m, Ar), 7.45–7.39 (4H, m, Ar), 6.49 (1H, s, C=C*H*), 5.60 (1H, ddd, *J*=10, 7, 4 Hz, BzOC*H*CH_2), 5.24 (1H, dd, *J*=8, 6 Hz, C*H*C=CH), 5.19 (2H, br, NH_2), 4.67 (1H, dd, *J*=8, 4 Hz, BzOCH_2C*H*), 4.58 (2H, d, *J*=8 Hz, BzOC*H*$_2$CH), 2.83 (1H, dd, *J*=13, 8 Hz, BzOCHC*H*$_2$), 2.53 (1H, ddd, *J*=13, 7, 6 Hz, BzOCHC*H*$_2$); δ_C (100.6 MHz, $CDCl_3$) 168.15 (=*C*NH_2), 166.32 (Ph*C*O), 166.06 (Ph*C*O), 152.64 (CHC=*C*H), 133.22, 133.14, 129.75, 129.68, 129.67, 129.62, 128.43 and 128.45 (Ar), 103.97 (CH*C*=CH), 81.87 (BzO*C*HCH$_2$), 77.46 (*C*HC=CH), 76.28 (BzOCH$_2$*C*H), 64.82 (BzO*C*H$_2$CH), 37.82(BzOCH*C*H$_2$); ν_{max}/cm^{-1} (neat film) 3367 br m, 1721s; *m*/*z* (EI) 425 (MH^+, 100%); HRMS found: MH^+ 425.1172 ($C_{22}H_{21}N_2O_5S$ requires 425.1171); $[\alpha]_D^{20}$ +4.5 [*c* 1.0, $CHCl_3$].

3.2.7. Preparation of 3*S*-benzoyloxy-2*R*-benzoyloxymethyl-5*R*/*S*-[6*H*-(1,3,4)-thiadiazin-2-amine-5-yl]-tetrahydro-furan 29α/β. To a solution of **15** (556 mg, 1.38 mmol) in methanol (20 mL) was added thiosemicarbazide hydrochloride (175 mg, 1.38 mmol, 1 equiv.) and the reaction mixture refluxed for 1 h. Then the solvent was removed and the residue purified by flash chromatography, to yield **29**α/β as a colourless oil, 490 mg, 81% yield from **15**, R_f 0.65 ethyl acetate/methanol (50:50); δ_H (400 MHz, $CDCl_3$) 8.07–7.96 (4H, m, Ar), 7.62–7.55 (2H, m, Ar), 7.49–7.42 (4H, m, Ar), 5.59 (1H, m, BzOC*H*CH_2), 5.15 (1H, m, C*H*C=N), 4.65–4.51 (3H, m, BzOCH_2C*H*), 3.41 (0.4H, d, *J*=14 Hz, N=CCH_2), 3.30 (0.4H, d, *J*=14 Hz, N=CCH_2), 3.29 (0.6H, d, *J*=14 Hz, N=CCH_2), 3.20 (0.6H, d, *J*=14 Hz, N=CCH_2), 2.92–2.84 (0.4H, m, BzOCHCH_2), 2.72–2.66 (0.4H, m, BzOCHCH_2), 2.58–2.31 (1.2H, m, BzOCHCH_2); δ_C (100.6 MHz, $CDCl_3$) 166.15(Ph*C*O), 166.05(Ph*C*O), 150.56 (=*C*NH_2), 133.46, 133.32, 133.24, 129.70, 129.66, 129.54, 129.45 and 128.59 (Ar), 95.67 (CH*C*=N), 83.36 and 82.60 (BzO*C*HCH$_2$), 80.53 and 80.08 (*C*HC=CH), 76.69 and 76.33 (BzOCH$_2$-*C*H), 64.73 and 64.54 (BzO*C*H$_2$CH), 37.37 and 36.29 (BzOCH*C*H$_2$), 20.58 and 20.36, (*C*H_2S); ν_{max}/cm^{-1} (neat film) 3320 br m, 1716s; *m*/*z* (AP^+) 439 (M^+, 100%); HRMS found: MH^+ 440.1281 ($C_{22}H_{22}N_3O_5S$ requires 440.1280).

3.2.8. 1-(2*R*/*S*-Ethoxy-4*S*-benzoyloxy-5*R*-benzoyloxymethyl-tetrahydrofuran-2-yl)-ethanone 32. To a solution of **15** (556 mg, 1.38 mmol) in ethanol (10.4 mL) was added benzamidine hydrochloride (215 mg, 1.38 mmol, 1 equiv.) and $NaHCO_3$ (115 mg, 1.38 mmol, 1 equiv.). The reaction mixture was refluxed for 4 h, then the solvent was removed and the residue purified by flash chromatography to yield **32** as a colourless oil, 370 mg (65% yield), R_f 0.45 ethyl acetate/petrol (20:80); δ_H (400 MHz, $CDCl_3$) 8.10–7.99 (4H, m, Ar), 7.62–7.56 (2H, m, Ar), 7.48–7.42 (4H, m, Ar), 5.63 (0.3H, ddd, *J*=3.5, 4.5, 7 Hz, BzOC*H*CH_2), 5.54 (0.7H, ddd, *J*=8, 5.5, 2.5 Hz, BzOC*H*CH_2), 4.71–4.53 (3H, m, BzOCH_2C*H*), 3.65 (1H, m, *J*=7 Hz, CH_3CH_2OC), 3.49 (0.7H, m, CH_3CH_2OC), 3.40 (0.3H, m, CH_3CH_2OC), 2.77 (0.3H, dd, *J*=14, 7 Hz, BzOCHCH_2), 2.63 (0.7H, dd, *J*=14, 7 Hz, BzOCHCH_2), 2.49 (0.3H, dd, *J*=15, 5 Hz, BzOCHCH_2), 2.42 (0.7H, dd, *J*=15, 2 Hz, BzOCHCH_2), 2.33 (0.9H, s, CH_3C=O), 2.24 (2.1H, s, CH_3C=O), 1.26 (2.1H, t, *J*=7 Hz, C$H_3$$CH_2$OC), 1.17 (0.9H, t, *J*=7 Hz, C$H_3$$CH_2$OC); δ_C (100.6 MHz, $CDCl_3$) 204.95 and 204.29 (CH_3*C*=O), 166.15, 166.12, 166.10, 165.82 (Ph*C*=O), 133.45, 133.38, 133.24, 133.18, 139.72, 129.68, 129.64, 129.56, 129.49, 129.22, 128.48, 128.44, 128.38, 128.26 (Ar), 109.43 and 109.15 (*C*–OCH_2CH_3), 83.30 and 83.06 (BzO*C*HCH$_2$), 74.85 and 74.72 (BzOCH$_2$*C*H), 64.34 and 64.06 (BzO*C*H$_2$CH), 59.57 and 59.23 (CO*C*$H_2$$CH_3$), 40.25 and 39.56 (BzOCH*C*H$_2$), 25.43 and 25.37 (CH_3C=O), 15.58 and 15.21 (COCH_2*C*H_3); ν_{max}/cm^{-1} (neat film) 1724s; *m*/*z* (electrospray) 430 (MNH_4^+, 100%); HRMS found: MNH_4^+ 430.1870 ($C_{23}H_{28}NO_7$ requires 430.1866).

3.3. General procedure for the preparation of compounds 33α, 33β, 34α and 34β

To solution of the benzoylated nucleoside **26**α, **26**β, **27**α and **27**β (0.4 mmol) in THF (20 mL) and water (20 mL) was added LiOH·H_2O (19 mg, 1.1 equiv.) and the solution stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to leave a cloudy water phase, which was extracted with ethyl acetate (3×10 mL). The organic layer was dried Na_2SO_4 and concentrated in vacuo to give pure **33**α, **33**β, **34**α and **34**β.

3.3.1. 2*R*-Hydroxymethyl-5*R*-(2-methylthiazol-4-yl)-tetrahydrofuran-3*S*-ol, 33β. Colourless oil, 67 mg, 78% yield; δ_H (500 MHz, $CDCl_3$) 7.06 (1H, s, C=C*H*S), 5.24 (1H, dd, *J*=9, 1.5 Hz, HOC*H*CH_2), 4.32–4.30 (2H, m, HOCH$_2$C*H*OC*H*C=N), 3.69 (1H, dd, *J*=11.5, 4 Hz, HOCH_2CHO), 3.58 (1H, dd, *J*=11.5, 6 Hz, HOCH_2CHO), 2.70 (3H, s, CH_3C=N), 2.58 (1H, ddd, *J*=14, 9, 6.5 Hz, HOCHCH_2CHO), 2.17 (1H, m, HOCHCH_2CHO); δ_C (125.8 MHz, $CDCl_3$) 167.7 (CH_3*C*=N), 156.4 (OCHC=*C*HS), 115.8 (OCH*C*=CHS), 89.2 (HO*C*HCH$_2$), 76.4 (O*C*HCN=C), 73.7 (HOCH$_2$*C*HO), 63.6 (HO*C*H$_2$-CH), 39.7 (HOCH*C*H$_2$CHO), 19.0 (*C*H_3C=N); ν_{max}/cm^{-1} (neat film) 3366 br, *m*/*z* (electrospray) 216 (MH^+,100%); HRMS found: MH^+ 216.0684 ($C_9H_{14}NO_3S$ requires 216.0694); $[\alpha]_D^{20}$ +50.0 [*c* 1.0, $CHCl_3$].

3.3.2. 2*R*-Hydroxymethyl-5*S*-(2-methylthiazol-4-yl)tetrahydrofuran-3*S*-ol, 33α. Colourless oil, 61 mg (71% yield); δ_H (500 MHz, $CDCl_3$) 7.00 (1H, s, C=C*H*S), 5.30 (1H, dd, *J*=9.5, 6.5 Hz, HOC*H*CH_2), 4.66 (1H, d, *J*=5 Hz, OC*H*C=CH), 4.16 (1H, app s, HOCH$_2$C*H*O), 3.93 (1H, dd, *J*=12.5, 2.5 Hz, HOCH_2CHO), 3.72 (1H, d, *J*=12.5 Hz, HOCH_2CHO), 2.69 (3H, s, CH_3C=N), 2.56 (1H, ddd, *J*=13.5, 9.5, 5.5 Hz), 2.26 (1H, dd, *J*=13.5, 6.5 Hz, CH_2CHO); δ_C (125.8 MHz, $CDCl_3$) 167.7 (CH_3*C*=N), 156.7 (OCHC=*C*H), 114.9 (OCH*C*=CH), 88.9 (O*C*HCH$_2$), 76.2 (O*C*HC=CH), 75.4 (HOCH$_2$*C*HO), 64.10 (HO*C*H$_2$CH), 42.7 (HOCH*C*H$_2$O), 19.1 (*C*H_3C=N); ν_{max}/cm^{-1} (neat film) 3367 br; *m*/*z* (electrospray) 216 (MH^+, 100%); HRMS found: MH^+ 216.0694 ($C_9H_{14}NO_3S$ requires 216.0694); $[\alpha]_D^{20}$ +4.1 [*c* 1.0, $CHCl_3$].

3.3.3. 2*R*-Hydroxymethyl-5*R*-(2-phenylthiazol-4-yl)-tetrahydrofuran-3*S*-ol, 34β. Colourless oil, 95 mg, 86% yield; δ_H (400 MHz, $CDCl_3$) 7.88–7.85 (2H, m, Ph), 7.49–7.39 (3H, m, Ph), 7.37 (1H, s, OCHC=C*H*S), 5.32 (1H, dd, *J*=1.5, 9 Hz), 4.39–4.37 (2H, m HOCH$_2$

C*H*OC*H*C═CH), 3.73 (1H, dd, *J*=11, 4 Hz, HOC*H*$_2$CHO), 3.62 (1H, dd, *J*=11, 5.5 Hz, HOC*H*$_2$CHO), 2.63 (1H, ddd, *J*=14, 9, 6.5 Hz, HOCHC*H*$_2$CHO), 2.34 (1H, m, HOCHC*H*$_2$CHO); δ_C (125.8 MHz, $CDCl_3$) 169.88 (Ph*C*═N), 157.68 (OCHC═*C*H), 132.64, 130.11, 128.21, 126.34 (Ar), 116.10 (OCH*C*═CH), 89.10 (O*C*HCH$_2$), 76.22 (O*C*HC═CH), 74.10 (HOCH$_2$*C*HO), 63.71 (HO*C*H$_2$CH), 40.01(HOCH*C*H$_2$O); ν_{max}/cm^{-1} (neat film) 3030 br; *m*/*z* (electrospray) 278 (MH$^+$, 100%); HRMS found: MH$^+$ 278.0848 ($C_{14}H_{16}NO_3S$ requires 278.0851). $[\alpha]_D^{20}$ +45.0 [*c* 1.0, $CHCl_3$].

3.3.4. 2*R*-Hydroxymethyl-5*S*-(2-phenylthiazol-4-yl)tetrahydrofuran-3*S*-ol, 34α. Colourless oil, 91 mg (82% yield); δ_H (400 MHz, $CDCl_3$) 7.94–7.88 (2H, m, Ph), 7.49–7.39 (3H, m, Ph), 7.16 (1H, s, OCHC═C*H*S), 5.39 (1H, dd, *J*=9, 7 Hz, HOC*H*CH$_2$), 4.70 (1H, d, *J*=5 Hz, OC*H*C═CH), 4.21 (1H, app s, HOCH$_2$C*H*O), 3.97 (1H, dd, *J*=2.5, 12 Hz, HOC*H*$_2$CHO), 3.76 (1H, dd, *J*=9, 2 Hz, HOC*H*$_2$CHO), 2.65 (1H, ddd, *J*=14, 9, 5.5 Hz), 2.30 (1H, dd, *J*=14, 6.5 Hz, C*H*$_2$CHO); δ_C (80 MHz, $CDCl_3$) 169.88 (Ph*C*═N), 157.99 (OCHC═*C*H), 132.71, 130.34, 128.97 and 126.34 (Ar), 115.26 (OCH*C*═CH), 88.71 (O*C*HCH$_2$), 76.31 (O*C*HC═CH), 75.19 (HOCH$_2$*C*HO), 64.07 (HO*C*H$_2$CH), 42.67(HOCH*C*H$_2$O); ν_{max}/cm^{-1} (neat film) 3015 br; *m*/*z* (electrospray) 278 (MH$^+$, 100%); HRMS found: MH$^+$ 278.0854 ($C_{14}H_{16}NO_3S$ requires 278.0851). $[\alpha]_D^{20}$ +10.8 [*c* 1.0, $CHCl_3$].

3.4. General procedure for the preparation of compounds 35α, 35β, and 36α/β

A stream of NH_3 was bubbled through a solution of the benzoylated nucleoside **28**α, **28**β, and **29**α/β (0.4 mmol) in methanol (20 mL) for 5 min. The reaction mixture was stirred at room temperature for 24 h, then the solvent removed in vacuo. The residue was dissolved in water (1 mL) and washed with dichloromethane (3×2 mL). The aqueous phase was evaporated to give **35**α, **35**β, and **36**α/β.

3.4.1. 2*R*-Hydroxymethyl-5*R*-(2-aminothiazol-4-yl)tetrahydrofuran-3*S*-ol, 35β. Colourless oil, 59 mg, 68% yield; δ_H (200 MHz, D_2O) 6.33 (1H, s, OCHC═C*H*S), 4.72 (1H, t, HOC*H*CH$_2$, *J*=8 Hz), 4.09 (1H, dd, *J*=5, 2.5 Hz, OC*H*C═CH), 3.67 (1H, dd, *J*=8, 5 Hz, HOCH$_2$C*H*O), 3.45–3.31 (2H, m, HOC*H*$_2$CHO), 1.93–1.86 (2H, m, C*H*$_2$CHO); δ_C (80 MHz, $CDCl_3$) 173.82 (*C*NH$_2$), 152.88 (OCH*C*═CH), 108.67 (C═*C*–S), 89.82 (O*C*HCH$_2$), 79.16 (O*C*HC═CH), 75.60 (HOCH$_2$*C*HO), 65.10 (HO*C*H$_2$CH), 42.55 (HOCH*C*H$_2$); ν_{max}/cm^{-1} (neat film) 3030 br; *m*/*z* (electrospray) 217 (MH$^+$, 100%); HRMS found: MH$^+$ 217.0647 ($C_8H_{13}N_2O_3S$ requires 217.0647); $[\alpha]_D^{20}$ +42.0 [*c* 1.0, H_2O].

3.4.2. 2*R*-Hydroxymethyl-5*S*-(2-aminothiazol-4-yl)tetrahydrofuran-3*S*-ol, 35α. Colourless oil, 56 mg, 65% yield; δ_H (200 MHz, D_2O) 6.34 (1H, s, OCHC═C*H*S), 4.74 (1H, t, HOC*H*CH$_2$, *J*=7 Hz), 4.08 (1H, dd, *J*=7, 5 Hz, OC*H*C═N), 3.82–3.72 (1H, m, HOCH$_2$C*H*O), 3.48–3.30 (2H, m, HOC*H*$_2$CHO), 2.31 (1H, m, C*H*$_2$CHO), 1.86 (1H, m, C*H*$_2$CHO); δ_C (80 MHz, $CDCl_3$), 170.08 (*C*NH$_2$), 149.41 (OCH*C*═CH), 104.71 (C═*C*–S), 85.10 (O*C*HCH$_2$), 75.06 (O*C*HC═CH), 71.24 (HOCH$_2$*C*HO), 60.69 (HO*C*H$_2$CH), 38.06 (HOCH*C*H$_2$); ν_{max}/cm^{-1} (neat film) 3030 br; *m*/*z* (electrospray) 217 (MH$^+$, 100%); HRMS found: MH$^+$ 217.0654 ($C_8H_{13}N_2O_3S$ requires 217.0647); $[\alpha]_D^{20}$ +5.6 [*c* 1.0, H_2O].

3.4.3. 5-*R*/*S* (2-Amino-6*H*-[1,3,4]thiadiazin-5-yl)-2*R*-hydroxymethyltetrahydrofuran-3*S*-ol, 36α/β. Colourless oil, 69 mg, 75% yield; δ_H (200 MHz, D_2O) 4.86 (1H, t, HOC*H*CH$_2$, *J*=8 Hz), 4.32–4.28 (1H, m, OC*H*C═N), 3.96–3.93 (1H, m, HOCH$_2$C*H*O), 3.64–3.51 (2H, m, HOC*H*$_2$CHO), 3.32–3.19 (2H, m, C*H*$_2$S), 3.24 (2H, s, NH$_2$), 2.13–2.08 (2H, m, C*H*$_2$CHO); δ_C (80 MHz, D_2O), 171.65 (*C*NH$_2$), 154.55 (OCH*C*═N), 87.86 (O*C*HCH$_2$), 79.89 (O*C*HC═CH), 72.72 (HOCH$_2$*C*HO), 62.26 (HO*C*H$_2$CH), 38.92 (HOCH*C*H$_2$), 20.10 (*C*H$_2$S); ν_{max}/cm^{-1} (neat film) 3050 br; *m*/*z* (electrospray) 232 (MH$^+$, 35%); HRMS found: MH$^+$ 232.0764 ($C_8H_{14}N_3O_3S$ requires 232.0756).

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