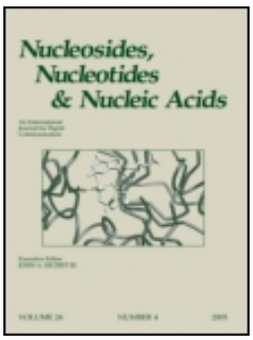

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NOVEL TRIAZOLE 2'-DEOXY-4'-THIONUCLEOSIDES : STEREOSELECTIVE SYNTHESIS AND BIOLOGICAL EVALUATION

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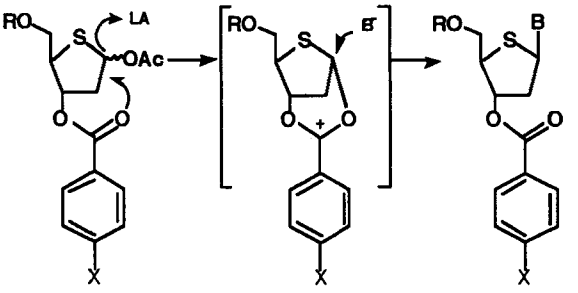
Abstract

A study on the use of protecting groups led to the employment of the *para*-methoxybenzoyl (pMB) group as a directing group in the synthesis of novel triazole 2'-deoxy-4'-thionucleosides. Use of the pMB group gave α:β ratios of 1:6 in the glycosylation step with azidotrimethylsilane. A series of novel triazoles were generated for *in vitro* antiviral evaluation.

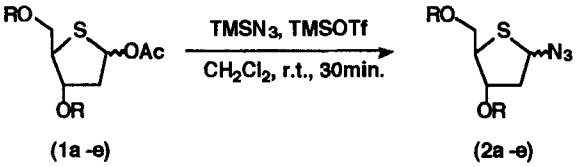
Introduction

The synthesis of 2'-deoxy-4'-thionucleosides is hampered by poor anomeric selectivity in the glycosylation step. This problem is circumvented in the synthesis of 2'-deoxy-4'-oxonucleosides by the use of a halo-sugar, often 2-deoxy-3,5-di-*O-para*-toluoyl-D-ribofuranosyl chloride,[1] and the sodium salt of a nucleobase, however employing the same strategy for the preparation of 2'-deoxy-4'-thionucleosides has not been successful owing to elimination of the 4-thio-chlorosugar.[2] It has been demonstrated in the literature[3,4] that stereocontrolled glycosylation is possible in the synthesis of 2'-deoxy-pyrimidine nucleosides by the use of a suitable 3'-directing group. A study was therefore undertaken using primarily acyl groups at the 3-position to determine whether this approach could be applied to the synthesis of 2'-deoxy-4'-thio-triazole nucleosides, and to determine whether the proposed mechanism[4] of participation also occurs with thiosugars (Scheme 1) .

If the intramolecular cation intermediate forms after treatment with a Lewis acid (LA), stabilization of this cation, through the employment of suitable electron-releasing **X** groups should lead to an increase in the percentage of β-anomer formed on reaction with the nucleophile/nucleobase (B^-), conversely if **X** is an electron-withdrawing group, more α-anomer would be formed (Scheme 1) owing to destabilization of the intermediate cation.



Scheme 1



(1a -e) (2a -e)

Scheme 2

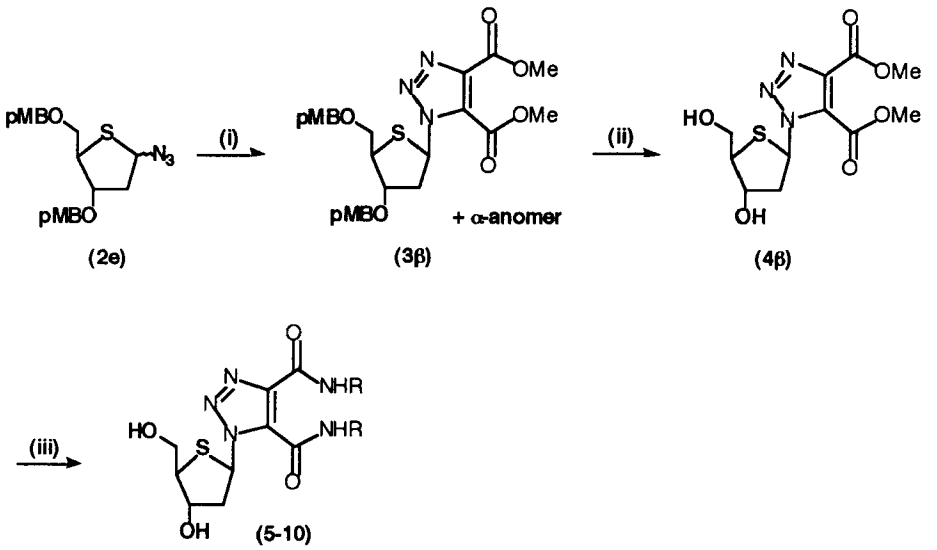
Chemistry

Compounds **1a-e** were prepared from benzyl 2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside following the general procedure described by Walker *et al*.[5] Treatment of the acetyl sugars with azidotrimethylsilane and trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave the azides **2a-e** (Scheme 2) with varying anomeric ratios (Table 1). TMSOTf was used in preference to $SnCl_4$ as the presence of tin residues complicated the work-up. Anomeric assignment was based on the shift of the H-1 proton (further downfield for the β-anomer) and the $J_{1,2exo}$ coupling (larger for the β-anomer).

Synthesis of compound **2a** (R = *para*-nitrobenzoyl, pNB) gave the α-anomer as the major product, this was owing to destabilization of the intermediate cation by the electron withdrawing capacity of the nitro group in the *para*-position. The 2:1 α:β ratio observed for compound **2b** (R = acetyl, Ac) is primarily owing to steric factors. Compound **2c** (R = benzyl, Bn) and **2d** (R = *para*-toluoyl, pTol) gave identical 1:1 α:β ratios, indicating that the steric bulk of the benzyl group is comparable with the stability confered to the intermediate cation by the *para*-toluoyl group. The best ratio was obtained with a more powerful electron releasing group in the *para*-position of the benzene ring, as shown in the synthesis of **2e** (R = *para* -methoxybenzoyl, pMB) which resulted in a consistent ratio of 1:6 α:β (Table 1).

Table 1 : The effect of varying 3'-groups on the anomeric ratios

Compound	R	Yield %	% α : β
2a	pNB	90	75 : 25
2b	Ac	85	67 : 33
2c	Bn	77	50 : 50
2d	pTol	79	50 : 50
2e	pMB	99	14 : 86



Reagents and conditions : (i) dimethylacetylene dicarboxylate, toluene, 80°C, 22 hours (ii) NaOMe, MeOH, r.t., 18 hours (iii) R = H, NH_3, MeOH, r.t. 16 hours; R = Me, $MeNH_2$, MeOH, r.t., 10 min.; R = Et, $EtNH_2$, MeOH, r.t. 3 hours; R = Pr, $PrNH_2$, MeOH, r.t. 3 hours; R = Bu, $BuNH_2$, MeOH, r.t. 3 hours; R = cyclopropyl, cyclopropylamine, MeOH, r.t. 16 hours.

Scheme 3

Separation of the anomers of **2e** was not very efficient by column chromatography, however anomeric separation was successful with the triazole **3**. Reaction of **2e** with the symmetrical alkene, dimethylacetylenedicarboxylate, gave the 1,3-dipolar cycloaddition product **3**, as an anomeric mixture (α:β 1:6), which after recrystallization from methanol gave the pure β anomer **3β** as a white crystalline solid in 87% yield. Deprotection of triazole **3β** with sodium methoxide gave **4β** in only a moderate yield of 58% owing to the formation of polar by-products during the course of the reaction (Scheme 3). A small amount of **3α** was also deprotected to give the α-anomer **4α**.

Table 2 : ^{1}H n.m.r. data for compounds **4α** and **4β**

Compd	H-1'	$J_{1',2'}$	H-2'a	H-2'b	H-3'	H-4'	H-5'a	H-5'b
4α	6.45,dd	3.8, 7.0	3.13,dt	2.62,dt	4.78,ddd	3.15,m	3.89,dd	3.60,dd
4β	6.48,dd	6.0, 7.6	3.05,ddd	2.91,ddd	4.33,ddd	3.68	3.91,dd	3.68

Table 3 : Yields and H-1' n.m.r. data for compounds **5-10**

Compound	R	H-1' ppm	$J_{1',2'}$	Yield %
5	H	6.87, t	7.5[a]	90
6	Me	7.14, dd	5.2,7.9 [b]	91
7	Et	7.13, dd	5.2, 7.9[b]	96
8	Pr	7.14, dd	5.2, 7.9[b]	89.5
9	Bu	7.14, dd	5.2, 7.9[b]	99.5
10	cyclopropyl	7.10, dd	5.3, 7.9[b]	95

N.m.r. solvents : (a) DMSO-d_6 (b) CD_3OD.

On deprotection the anomeric assignment was further confirmed by ^{1}H n.m.r. A study[6] on configurational assignments in 2'-deoxy-4'-thionucleosides has shown that when the 3'-substituent is a hydroxy group, coupling to the anomeric proton follows established trends noted for the 4'-O-nucleosides, that is the $J_{1',2'exo}$ coupling in α-anomers is small (0-4Hz) and larger (5-7.5Hz) in the β-anomer. For compound **4β**, the H-1' is observed as a doublet of doublets at 6.48ppm, with the anomeric coupling $J_{1',2'}$ = 6.0, 7.6Hz. For compound **4α**, the H-1' is observed as a doublet of doublets at 6.45ppm, with the anomeric coupling $J_{1',2'}$ = 3.8, 7.0Hz (Table 2). NOe and X-ray studies were performed on the triazole nucleosides to further clarify the anomeric assignment, however no additional information was obtained.

Reaction of **4β** with a range of amines produced a library of novel triazole 2'-deoxy-4'-thionucleosides, all of which were obtained in high yields. Treatment of **4β** with a large excess of ammonia, methylamine, ethylamine, propylamine, butylamine and cyclopropylamine in methanol gave the triazoles **5-10** respectively (Table 3).

The choice of amines was restricted to ammonia and primary amines, reactions with secondary amines, *e.g.* dimethylamine, were unsuccessful presumably owing to steric limitations.

Biological Results

The antiviral activity of compounds **4β** and **5-10** were evaluated against HSV-1 and HSV-2, HCMV, VZV, and HIV-1. All of the compounds were inactive at 100μM with the

exception of **9**, which had poor activity against HIV-1 (12.9% inhibition at 80μM). None of the compounds displayed toxicity up to a concentration of 100μM.

Experimental section

^1H and ^{13}C NMR spectra were recorded with a Brucker Avance DPX300 spectrometer operating at 300 and 75MHz respectively, with Me_4Si as internal standard. Mass spectra and HRMS were determined by the EPSRC mass spectrometry centre, Swansea, U.K. Microanalyses were determined at the department of chemistry, Cardiff University. IR spectra were recorded with a Perkin Elmer 1600 series FTIR spectrophotometer. Flash column chromatography was performed with silica gel 60 (230-400mesh) (Merck) and t.l.c. were carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Melting points were determined on an electrothermal instrument and are uncorrected.

General procedure for the synthesis of compounds 2a-e. To a solution of **1a-e** (4.5mmol) in dry dichloromethane (50ml) was added azidotrimethylsilane (13.5mmol), followed by the dropwise addition of trimethylsilyltrifluoromethane sulfonate (0.7mmol). The reaction was stirred under nitrogen at room temperature for 30 minutes then diluted with dichloromethane (50ml). This solution was washed with water (50ml), saturated aqueous sodium hydrogen carbonate (50ml), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether - ethyl acetate 4:1v/v) to give a yellow syrup.

Azido 3,5-di-*O*-*para*-nitrobenzoyl-2-deoxy-4-thio-α/β-D-*erythro*-pento furanoside (2a). Obtained as a mixture of anomers, α:β 3:1, in a yield of 90%. T.l.c. system : petroleum ether - ethyl acetate 2:1v/v; R_F α 0.53, β R_F 0.48. *α-anomer*: ^1H n.m.r. ($CDCl_3$) δ 8.27 (m, 8, 2 x Ph), 5.86 (dd, $J_{1,2}$ = 5.6, 10.6Hz, 1, H-1), 5.43 (t, J = 5.0, 10.1Hz, 1, H-3), 4.65 (t, J = 1.6, 7.7Hz, 2, H-5), 4.06 (m, 1, H-4), 2.63 (t, $J_{2,1}$ = 5.4, 11.4Hz, 2, H-2); ^{13}C n.m.r. ($CDCl_3$) δ 164.19 and 164.65 (C=O), 151.12 and 151.24 (C, C-NO_2), 134.89 and 135.21 (C, C=O), 131.29 (*meta*-CH, Ph), 124.04, 124.09 (*ortho*-CH, Ph), 78.70 (CH, C-3), 68.06 (CH, C-1), 66.55 (CH_2, C-5), 51.38 (CH, C-4), 41.96 (CH_2, C-2). *β-anomer* ^1H n.m.r. ($CDCl_3$) δ 8.34 (m, 8, 2 x Ph), 5.85 (d, J = 7.3Hz, 1, H-1), 5.42 (m, 1, H-3), 4.48 (m, 2, H-5), 4.23 (m, 1, H-4), 2.64 (m, 2, H-2); ^{13}C n.m.r. ($CDCl_3$) δ 164.44 and 164.70 (C=O), 151.20 and 151.26 (C, C-NO_2), 135.06 and 135.17 (C, C=O), 131.29, 131.37 and 131.49 (*meta*-CH, Ph), 124.09, 124.14 (*ortho*-CH, Ph), 79.56 (CH, C-3), 69.21 (CH, C-1), 66.03 (CH_2, C-5), 53.69 (CH, C-4), 42.14 (CH_2, C-2). IR (CH_2Cl_2) 2105 cm^{-1} (N_3), 1722 cm^{-1} (C=O).

Azido 3,5-di-*O*-acetyl-2-deoxy-4-thio-α/β-D-*erythro*-pento furanoside (2b). Obtained as an inseparable mixture of anomers, α:β 2:1, in a yield of 85%. T.l.c. system : petroleum ether - ethyl acetate 2:1v/v; R_F 0.51. ^1H n.m.r. ($CDCl_3$) δ 5.42 (m, H-

1α and β),5.22 (t, J = 5.4Hz, H-3β), 5.09 (dd, J = 2.8, 5.2Hz, H-3α), 4.26 (dd, J = 4.1, 7.1Hz, H-5β and H-5'β), 4.14 (dd, $J_{5,4}$ = 5.8, $J_{5,5'}$ = 11.4Hz, H-5α), 4.03 (dd, $J_{5',4}$ = 8.3, $J_{5',5}$ = 11.4Hz, H-5'α), 3.89 (dt, $J_{4,5}$ = 6.0, $J_{4,5'}$ = 8.2Hz, H-4α), 3.70 (dt, J = 4.6, 6.2Hz, H-4β), 2.43 (m, H-2α and β), 2.16 (s, 3, CH_3), 2.13 (s, 3, CH_3); ^{13}C n.m.r. ($CDCl_3$) δ 170.70 and 171.02 (C, C=O), 77.27* and 77.91 (CH, C-3), 67.88* and 68.61 (CH, C-1), 64.99 and 65.55* (CH_2, C-5), 51.54* and 53.85 (CH, C-4), 41.73* and 42.35 (CH_2, C-2), 21.18 and 21.65 (CH_3, Ac) *β-anomer. IR (CH_2Cl_2) 2104 cm^{-1} (N_3), 1735 cm^{-1} (C=O).

Azido 3,5-di-*O*-benzyl-2-deoxy-4-thio-α/β-D-*erythro*-pentofuranoside (2c). Obtained in a 1:1 α:β ratio, in a yield of 77%. T.l.c. system : petroleum ether - ethyl acetate 4:1v/v, R_F α 0.65, β 0.71. *α-anomer* ^{1}H n.m.r. ($CDCl_3$) δ 7.37 (m, 10, 2 x Ph), 5.06 (dd, $J_{1,2a}$ = 1.7, $J_{1,2b}$ = 6.5Hz, 1, H-1), 4.59 (m, 4, 2 x CH_2Ph), 4.30 (quintet, J = 2.1, $J_{3,2b}$ = 4.3Hz, 1, H-3), 4.00 (dt, J = 1.5, $J_{4,5a}$ = 5.5, $J_{4,5b}$ = 7.6Hz, 1, H-4), 3.49 (dd, $J_{5a,4}$ = 5.5, $J_{5a,5b}$ = 10.0Hz, 1, H-5a), 3.39 (dd, $J_{5b,4}$ = 8.3, $J_{5b,5a}$ = 9.8Hz, 1, H-5b), 2.43 (dt, $J_{2a,1}$ = 1.8, 3.3, $J_{2a,2b}$ = 14.3Hz, 1, H-2a), 2.26 (ddd, $J_{2b,3}$ = 4.7, $J_{2b,1}$ = 6.5, $J_{2b,2a}$ = 14.3Hz, 1, H-2b); ^{13}C n.m.r. ($CDCl_3$) δ 138.17 and 138.20 (C, Ph), 128.06, 128.15 , 128.25, 128.35, 128.83 and 128.90 (CH, Ph), 83.05 (CH, C-3), 73.56 and 72.19 (CH_2, CH_2Ph), 71.45 (CH_2, C-5), 68.81 (CH, C-1), 54.35 (CH, C-4), 42.05 (CH_2, C-2). *β-anomer* ^{1}H n.m.r. ($CDCl_3$) δ 7.38 (m, 10, 2 x Ph), 5.21 (br.s, 1, H-1),4.60 (m, 4, 2 x CH_2Ph), 4.27 (dd, $J_{3,2a}$ = 4.7, 10.6Hz, 1, H-3), 3.69 (m, 3, H-5 and H-4), 2.37 (dt, J = 6.1, $J_{2a,2b}$ = 13.1Hz, 1, H-2b), 2.26 (dt, $J_{2a,3}$ = 4.8, 9.5, $J_{2a,2b}$ = 13.2Hz, 1, H-2a); ^{13}C n.m.r. ($CDCl_3$) δ 138.20 and 138.30 (C, Ph),128.09, 128.16 , 128.29, 128.86 and 128.90 (CH, Ph), 82.91 (CH, C-3), 73.64 (CH_2, 2 x CH_2Ph), 72.37 (CH_2, C-5), 67.99 (CH, C-1),52.80 (CH, C-4), 42.02 (CH_2, C-2). MS (FAB), *m/z* : 355 $(M + H)^+$, 378 $(M + Na)^+$. IR (CH_2Cl_2) 2107 cm^{-1} (N_3).

Azido 3,5-di-*O*-*para*-toluoyl-2-deoxy-4-thio-α/β-D-*erythro*-pentofuranoside (2d). Obtained in a 1:1 α:β ratio, in a yield of 79%. T.l.c. system : petroleum ether - ethyl acetate 4:1v/v; R_F α 0.61, β R_F 0.55. *α-anomer* ^{1}H n.m.r. ($CDCl_3$) δ 8.01 (t, J = 8.5Hz, 4, Ph), 7.30 (m, 4, Ph), 5.77 (dt, J = 2.4, 4.4Hz, 1, H-1), 5.33 (dd, J = 2.5, $J_{3,2}$ = 5.6Hz, 1, H-3), 4.44 (dt, J = 5.0, $J_{5,4}$ = 8.9, 11.5Hz, 2, H-5), 4.22 (dt, J = 1.8, 7.1, 8.7Hz, 1, H-4), 2.62 (dd, $J_{2,3}$ = 5.6, 7.6Hz, 2, H-2), 2.47 (s, 6, 2 x $C\underline{H}_3$Ph); ^{13}C n.m.r. ($CDCl_3$) δ 166.58 and 166.32 (C, 2 x C=O), 144.61 and 144.49 (C, $\underline{C}$-CH_3), 130.38, 130.21 130.00, 129.65, 129.60 129.40, 129.28 and 128.94 (CH, Ph), 127.16 and 127.07 (C, C=O), 79.33 (CH, C-3), 68.90 (CH, C-1), 65.47 (CH_2, C-5), 54.00 (CH, C-4), 42.46 (CH_2, C-2), 22.15 (CH_3, *p*-toluoyl). *β-anomer* ^{1}H n.m.r. ($CDCl_3$) δ 7.95 (dd, J = 8.2, 11.4Hz, 4, Ph), 7.26 (dd, J = 8.2, 11.3Hz, 4, Ph), 5.79 (dd, J = 5.6, 11.1Hz, 1, H-1), 5.35 (t, J = 5.4Hz, 1, H-3), 4.57 (d, $J_{5,4}$ = 7.0Hz, 2, H-5), 4.04 (dt, J = 4.9, $J_{4,5}$ = 6.9Hz, 1, H-4), 2.58 (m, 2, H-2), 2.46 (s, 3, $C\underline{H}_3$Ph), 2.43 (s, 3, $C\underline{H}_3$Ph); ^{13}C n.m.r.

($CDCl_3$) δ 166.60 and 166.03 (C, 2 x C=O), 144.62 and 144.33 (C, C-CH_3), 130.19, 129.57, and 129.52 (CH, Ph), 127.16 and 127.03 (C, 2 x C-C=O), 67.97 (CH, C-1), 66.16 (CH_2, C-5), 51.48 (CH, C-4), 42.00 (CH_2, C-2), 22.14 and 22.11 (CH_3, *p*-toluoyl), C-3 is obscured by the $CDCl_3$ signal. MS (FAB), *m/z* : 411 $(M + H)^+$, 434 $(M + Na)^+$. IR (CH_2Cl_2) 2108 cm^{-1} (N_3), 1717 cm^{-1} (C=O).

Azido 3,5-di-*O*-*para*-methoxybenzoyl-2-deoxy-4-thio-α/β-D-*erythro*-pentofuranoside (2e). Obtained in a 1:6 α:β ratio as an inseparable mixture, in a yield of 65%. T.l.c. system : petroleum ether - ethyl acetate 4:1v/v; R_F α/β 0.48. Enriched α- and β-fractions were obtained for characterisation. *α-anomer* ^1H n.m.r. ($CDCl_3$) δ 7.99 (m, 4, CH-Ph), 6.90 (m, 4, CH-Ph), 5.77 (m, 1, H-1), 5.33 (t, 1, J = 4.9 and 10.2Hz, H-3), 4.54 (m, 2, H-5), 4.01 (dd, 1, J = 6.5, 11.5Hz, H-4), 3.88 (d, 6, J = 6.6Hz, 2 x OCH_3), 2.55 (m, 2, H-2); ^{13}C n.m.r. ($CDCl_3$) δ 163.79 and 164.35 (CO, COPh), 162.04 and 162.21 (C, Ph), 130.36 (CH, Ph), 127.20 and 127.56 (CH, Ph), 120.23 and 120.39 (C, CPh), 112.14 and 112.20 (CH, Ph), 76.04 (CH, C-3), 66.04 (CH_2, C-5), 64.20 (CH, C-4), 53.93 and 54.00 (CH_3, OCH_3), 49.50 (CH, C-4), 40.15 (CH_2, C-2). *β-anomer* ^1H n.m.r. ($CDCl_3$) δ 8.07 (m, 4, Ph), 6.97 (m, 4, Ph), 5.76 (m, 1, H-1), 5.32 (m, 1, H-3), 4.42 (t, 2, J = 6.9 and 13.1Hz, H-5), 4.20 (m, 1, H-4), 3.9 (s, 6, 2 x OCH_3), 2.61(m, 2, H-2); ^{13}C n.m.r. ($CDCl_3$) δ 166.26 (CO, COPh), 164.05 and 164.13 (C, Ph), 132.24 and 132.43 (CH, Ph), 122.24 (C, Ph), 114.12 and 114.17 (CH, Ph), 78.52 (CH, C-3), 68.87 (CH_2, C-5), 65.37 (CH, C-1), 55.89 (CH_3, OCH_3), 54.03 (CH, C-4), 42.46 (CH_2, C-2). MS (FAB), *m/z* : 444 $(M + H)^+$, 466 $(M + Na)^+$. IR (CH_2Cl_2) 2108 cm^{-1} (N_3), 1712 cm^{-1} (C=O).

2'-Deoxy-3',5'-di-*O*-*para*-methoxybenzoyl-4'-thio-1'-[4,5-bis (methyloxy)carbonyl-1,2,3-triazole]-β-D-*erythro*-pentofuranoside (3β). To a solution of **2e** (557mg, 1.25mmol) in dry toluene (25ml) was added dimethylacetylene dicarboxylate (0.23ml, 1.88mmol), the reaction was then stirred at 80°C under nitrogen for 22 hours. The reaction was allowed to cool to room temperature then concentrated under reduced pressure, and the resulting brown syrup purified by flash column chromatography (petroleum ether-ethyl acetate 4:1v/v) to give compound **3β** after recrystallization from methanol as a white solid. Yield : 0.646mg (87%). T.l.c. system : petroleum ether-ethyl acetate 4:1 v/v, R_F : 0.28. m.p.: 123-124°C. ^1H n.m.r. ($CDCl_3$) δ 8.02 (d, J = 8.7Hz, 2, Ph), 7.91(d, 2, J = 8.8, Ph), 6.93 (dd, J = 3.4, 8.8Hz, 2, Ph), 6.55 (dd, J = 3.6, 7.6Hz, 1, H-1'), 5.76 (dd, J = 5.2, 10.5Hz, 1, H-3'), 4.62 (m, 1, H-5'), 4.50 (m, 1, H-5'), 4.32 (m, 1, H-4'), 4.07 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 3.90 (s, 6, 2 x $COOCH_3$), 3.57 (dt, J = 4.2, 8.5Hz, 1, H-2'), 3.15 (m, 1, H-2'); ^{13}C n.m.r. ($CDCl_3$) δ 166.31 and 166.12 (C=O, 2 x OCOPh), 164.29 and 164.21 (2 x C), 160.92 and 159.78 (C=O, 2 x $OCOCH_3$), 140.76 (C, C4/C5), 132.50 and 132.39 (2 x CH, Ph), 130.79 (C, C-4/C-5), 122.58 and

122.05 (2 x C, Ph), 114.29 and 114.26 (2 x CH, Ph), 77.56 (CH, C-3'), 65.66 (CH, C-1'), 64.65 (CH_2, C-5'), 56.02 (CH_3, 2 x OCH_3), 54.30 (CH, C-4'), 53.18 and 53.11 (CH_3, 2 x $OCOCH_3$), 39.94 (CH_2, C-2'). Anal. $C_{27}H_{27}N_3O_{10}S$ requires C 55.00%, H 4.61%, N 7.12%, found C 54.97%, H 4.61%, N 7.02%.

2'-Deoxy-4'-thio-1'-[4,5-bis-carbamoyl-1,2,3-triazole]-β-D-erythro-pentofuranoside (4β). To a solution of **3β** (3.18g, 5.39mmol) in dry methanol (100ml) was added sodium methoxide (174mg, 3.24mmol) and the reaction stirred at room temperature under nitrogen overnight. Additional sodium methoxide (289mg, 5.39mmol) was then added and the reaction stirred for a further 24 hours. The reaction was neutralized with amberlite (H^+ resin), then concentrated under reduced pressure to give a yellow syrup/foam. Purification by column chromatography (chloroform-methanol 95:5 v/v) gave the product **4β** as a pale yellow syrup. Yield : 983mg (58%), t.l.c. system : chloroform-methanol 9:1 v/v , vanillin stain; R_F : 0.28. ^1H n.m.r. ($CDCl_3$) δ 6.36 (dd, $J_{1,2b}$ = 6.0, $J_{1,2a}$ = 7.5Hz, 1, H-1'), 4.21 (dd, J = 6.2, $J_{3,2b}$ = 13.5Hz, 1, H-3'), 3.91 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.80 (dd, J = 4.4, 10.8Hz, 1, H-4'), 3.56 (m, 2, H-5'), 2.94 (ddd, $J_{1,2b}$ = 6.0, 7.3, $J_{2b,3}$ = 13.6Hz, H-2'b), 2.80 (ddd, $J_{2a,3}$ = 5.9, $J_{2a,1}$ = 7.5, 13.0Hz, H-2'a); ^{13}C n.m.r. ($CDCl_3$) δ 161.87 and 160.61 (2 x C=O), 140.70 and 132.30 (C), 76.44 (CH, C-3'), 65.12 (CH, C-1'), 64.54 (CH_2, C-5'), 59.84 (CH, C-4'), 54.49 and 53.43 (CH_3, 2 x OCH_3), 43.23 (CH_2, C-2'). MS (FAB), *m/z* : 318 $(M + H)^+$, 340 $(M + Na)^+$. HRMS (CI) Calcd for $C_{11}H_{16}N_3O_6S$; 318.3299 $(M + H)^+$. Found: 318.0759 (error 0.26ppm).

2'-Deoxy-4'-thio-1'-[4,5-bis(carbamoyl)-1,2,3-triazole]-β-D-erythro-pentofuranoside (5). A solution of **4β** (32mg, 0.1mmol) in saturated methanolic ammonia (3ml) was stirred at room temperature under nitrogen for 16 hours, then the reaction concentrated under reduced pressure and purified by flash column chromatography (chloroform-methanol 95:5 v/v) to give **5** as an off-white solid. Yield : 26mg (90%). T.l.c. system : chloroform-methanol 90:10 v/v, R_F : 0.16. m.p.: 169°C. ^1H n.m.r. (DMSO-d_6) δ 10.17 (s, 1, NH, ex), 8.50 (s, 1, NH, ex), 8.21 (s, 1, NH, ex), 8.14 (s, 1, NH, ex), 6.87 (t, J = 7.6, 15.0Hz, 1, H-1'), 5.42 (d, J = 6.2Hz, 1, OH, ex), 4.93 (t, J = 5.4, 10.4Hz, 1, OH, ex), 4.03 (dt, J = 4.0, 8.5Hz, 1, H-4'). 3.51 (m, 1, H-5'), 3.38 (m, 1, H-5'), 2.95 (m, 1, H-2'), 2.77 (m, 1, H-2'); ^{13}C n.m.r. (DMSO-d_6) δ 163.67 and 159.02 (2 x C=O), 139.99 and 131.79 (C), 74.72 (CH, C-3'), 63.44 (CH_2, C-2'), 62.17 (CH, C-1'), 58.19 (CH, C-4'), 40.96 (CH_2, C-2'). MS (FAB), *m/z* : 288 $(M + H)^+$, 310 $(M + Na)^+$. Anal. $C_9H_{13}N_5O_4S$ requires C 37.62%, H 4.56%, N 24.37%, found C 37.60%, H 4.35%, N 24.56%.

2'-Deoxy-4'-thio-1'-[4,5-bis(*N*-methyloxycarbamoyl)-1,2,3-triazole] -β-D-erythro-pentofuranoside (6). A solution of **4β** (34mg, 0.1mmol) in methylamine (33% w/w in industrial methylated spirit, 15ml) was stirred at room temperature for 10

minutes then concentrated under reduced pressure and purified by column chromatography (chloroform-methanol 95:5 v/v) to give **6** as a white crystalline solid. Yield : 31mg (91%). T.l.c. system : chloroform-methanol 90:10 v/v, R_F : 0.42. m.p.: 92°C. ^{1}H n.m.r. (CD_3OD) δ 7.14 (dd, J = 5.2, 7.8Hz, 1, H-1'), 4.36 (dd, J = 6.0, 12.1Hz, 1, H-3'), 3.85 (dd, J = 4.5, 10.3Hz, 1, H-4'), 3.65 (ddd, J = 6.5, 12.2, 16.9Hz, 2, H-5'), 3.05 (m, 1, H-2'), 2.90 (m, 7, 2 x OMe and H-2'); ^{13}C n.m.r. (CD_3OD) δ 162.31 and 158.33 (2 x C=O), 139.74 and 130.94 (2 x C), 75.76 (CH, C-3'), 64.36 (CH, C-4'), 63.56 (CH_2, C-5'), 58.58 (CH, C-1'), 41.56 (CH_2, C-2'), 25.36 and 25.17 (CH_3, 2 x OCH_3); MS (FAB), *m/z* : 316 $(M + H)^+$, 338 $(M + Na)^+$. Anal. $C_{11}H_{17}N_5O_4S$ requires C 41.85%, H 5.42%, N 22.18%, found C 42.05%, H 5.54%, N 22.18%.

2'-Deoxy-4'-thio-1'-[4,5-bis(*N*-ethyloxycarbamoyl)-1,2,3-triazole]-β-D-erythro-pentofuranoside (**7**). A solution of **4β** (46.3mg, 0.146mmol) in ethylamine (2M solution in methanol, 15ml) was stirred at room temperature under nitrogen for 3 hours then concentrated under reduced pressure and purified by column chromatography (chloroform) to give **7** as a white solid. Yield: 48mg (96%). T.l.c. system : chloroform-methanol 90:10 v/v, R_F : 0.47. ^{1}H n.m.r. (CD_3OD) δ 7.13 (dd, J = 5.2, 8.8Hz, 1, H-1'), 4.36 (dd, J = 6.1, 12.2Hz, 1, H-3'), 3.85 (dd, J = 4.5, 10.3Hz, 1, H-4'), 3.65 (m, 2, H-5'), 3.41 (m, 4, 2 x CH_2), 3.06 (ddd, J = 5.3, 6.5, 11.9Hz, 1, H-2'a), 2.99 (ddd, J = 6.0, 7.9, 13.9Hz, 1, H-2'b), 1.26 (m, 6, 2 x CH_3); ^{13}C n.m.r. (CD_3OD) δ 161.61 and 157.48 (2 x C=O), 139.77 and 131.162 (2 x C), 76.00 (CH, C-3'), 64.25 (CH, C-1'), 63.58 (CH_2, C-5'), 58.57 (CH, C-4'), 41.51 (CH_2, C-2'), 34.49, 34.42 and 34.35 (CH_2, ethyl), 13.80, 13.71 and 13.39 (CH_3, ethyl). MS (FAB), *m/z* : 344 $(M + H)^+$, 366 $(M+ Na)^+$. Anal. $C_{13}H_{21}N_5O_4S$ requires C 45.61%, H 6.28%, N 20.33%, found C 45.46%, H 6.16%, N 20.39%.

2'-Deoxy-4'-thio-1'-[4,5-bis(*N*-propyloxycarbamoyl)-1,2,3-triazole]-β-D-erythro-pentofuranoside (**8**). To a solution of **4β** (48.3mg, 0.151mmol) in dry methanol (10ml) was added propylamine (10ml) and the reaction stirred at room temperature under nitrogen for 3 hours. The reaction was concentrated under reduced pressure and purified by column chromatography (chloroform) to give **8** as a white solid. Yield: 50.4mg (89.5%). T.l.c. system: chloroform-methanol 90:10 v/v, R_F : 0.36. ^{1}H n.m.r. (CD_3OD) δ 7.14 (dd, J = 5.7, 7.9Hz, 1, H-1'), 4.36 (dd,J = 6.1, 12.1Hz, 1, H-3'), 3.85 (dd, J = 4.5, 10.3Hz, 1, H-4'), 3.65 (ddd, J = 6.7, 12.5, 16.9Hz, 2, H-5'), 3.36 (m, 4, 2 x CH_2 Pr), 3.06 (ddd, J = 5.3, 6.4, 11.8Hz, 1, H-2'a), 2.88 (ddd, J = 6.0, 7.9, 13.9Hz, 1, H-2'b), 1.66 (dt, J = 7.3, 14.4, 4, 2 x CH_2 Pr), 1.01 (dd, J = 7.4, 15.7Hz, 6, 2 x CH_3 Pr); ^{13}C n.m.r. (CD_3OD) δ 161.80 and 157.63 (2 x C=O), 139.79 and 131.14 (2 x C), 75.74 (CH, C-3'), 64.42 (CH, C-1'), 63.58 (CH_2, C-5'), 58.55 (CH, C-4'), 41.48, 41.38 and 41.24 (CH_2, C-2' and 2 x CH_2 Pr), 22.61 and 22.26 (CH_2, Pr), 10.87 and 10.67 (CH_3, Pr).

Anal. $C_{15}H_{25}N_5O_4S$ requires C 48.67%, H 6.98%, N 18.72%, found C 48.50%, H 6.78%, N 18.85%.

2'-Deoxy-4'-thio-1'-[4,5-bis(*N*-butyloxycarbamoyl)-1,2,3-triazole]-β-D-erythro-pentofuranoside (9). To a solution of **4β** (44.4mg, 0.14 mmol) in dry methanol (10ml) was added butylamine (10ml) and the reaction stirred at room temperature under nitrogen for 3 hours. The reaction was concentrated under reduced pressure and purified by column chromatography (chloroform) to give **9** as a white solid. Yield : 55.6mg (99.5%). T.l.c. system: chloroform-methanol 90:10 v/v, R_F : 0.37. ^{1}H n.m.r. (CD_3OD) δ 7.14 (dd, J = 5.2, 7.9Hz, 1, H-1'), 4.36 (dd, J = 6.0, 12.0Hz, 1, H-3'), 3.85 (dd, J = 4.5, 10.3Hz, 1, H-4'), 3.65 (ddd, J = 6.7, 12.6, 16.9Hz, 2, H-5'), 3.38 (m, 4, 2 x CH_2 Bu), 3.07 (ddd, J = 5.2, 6.5, 11.8Hz, 1, H-2'a), 2.88 (ddd, J = 6.0, 7.9, 13.9Hz, 1, H-2'b), 1.65 (m, 4, 2 x CH_2 Bu), 1.45 (m, 4, 2 x CH_2 Bu), 0.98 (t, J = 7.4, 14.5Hz, 6, 2 x CH_3 Bu); ^{13}C n.m.r. (CD_3OD) δ 161.76 and 157.58 (2 x C=O), 139.81 and 131.12 (2 x C), 75.73 (CH, C-3'), 64.41 (CH, C-1'), 63.57 (CH_2, C-5'), 58.54 (CH, C-4'), 41.47 (CH_2, C-2'), 39.31 and 39.26 (CH_2, 2 x CH_2 Bu), 20.19 and 20.11 (CH_2, CH_2 Bu), 13.10 and 13.05 (CH_3, CH_3 Bu). HRMS (CI) Calcd for $C_{17}H_{29}N_5O_4S$; 399.5132 M^+. Found: 400.2016 (error 0.23ppm).

2'-Deoxy-4'-thio-1'-[4,5-bis(*N*-cyclopropyloxycarbamoyl)-1,2,3-triazole]-β-D-erythro-pentofuranoside (10). To a solution of **4β** (48.9mg, 0.15mmol) in dry methanol (10ml) was added cyclopropylamine (5ml) and the reaction stirred at room temperature under nitrogen for 16 hours. The reaction was concentrated under reduced pressure and purified by column chromatography (chloroform) to give **10** as a white solid. Yield : 54mg (95%). Tl.c. system : chloroform-methanol 90:10 v/v, R_F : 0.21. ^{1}H n.m.r. (CD_3OD) δ 7.10 (dd, J = 5.2, 7.9Hz, 1, H-1'), 4.35 (dd, J = 6.1, 12.2Hz, 1, H-3'), 3.85 (dd, J = 4.1, 10.0Hz, 1, H-4'), 3.65 (ddd, J = 6.8, 11.5, 12.7Hz, 2, H-5'), 3.33 (m, 1, CH cyclopr), 3.06 (ddd, J = 5.3, 6.6, 12.0Hz, 1, H-2'a), 2.90 (m, 2, H-2'b and CH cyclopr), 0.83 (m, 4, CH_2 cyclopr), 0.71 (m, 4, CH_2 cyclopr); ^{13}C n.m.r. (CD_3OD) δ 163.41 and 159.10 (2 x C=O), 139.57 and 131.02 (2 x C), 75.69 (CH, C-3'), 64.38 (CH, C-1'), 63.55 (CH_2, C-5'), 58.52 (CH, C-4'), 41.48 (CH_2, C-2'), 22.69 and 22.53 (2 x CH, cyclopr), 5.55 (CH_2, 4 x CH_2 cyclopr). Anal. $C_{15}H_{21}N_5O_4S$ requires C 49.03%, H 5.76%, N 19.06%, found C 48.97%, H 5.90%, N 18.87%.

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