Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1871-1874, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00139-6

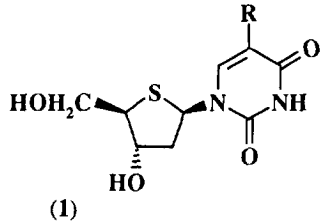
New Synthesis of both D- and L-3-*O*-Carbamoyl-2-deoxy-4-thioribosides, Substrates for β-Selective Glycosylations.

Sue Shaw-Ponter, Peter Rider, and Robert J. Young*.

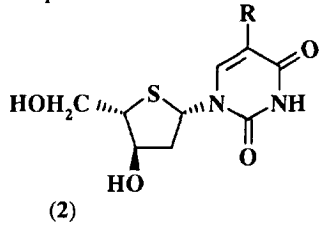
Department of Medicinal Chemistry, The Wellcome Foundation Limited,
Beckenham, Kent, BR3 3BS, U.K.
(Current Address: GlaxoWellcome Medicines Research Centre, Stevenage, Hertfordshire, SG1 2NY, U.K.)

Abstract: A new route to intermediates for the synthesis of 2'-deoxy-4'-thionucleosides is described. By utilising enantiomeric *erythro*-dibenzyldithioacetals, both D- and L-3-*O*-(*N*-acyl)carbamoyl thiosugars, which give β-selective glycosylations, are readily produced.

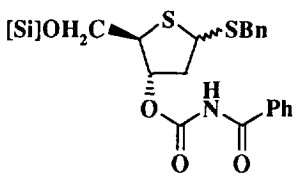
In the accompanying paper,[1] we described the utility of 3-*O*-(*N*-acyl)carbamoyl directing groups in the anomer-selective synthesis of the potent anti-herpes virus agent, 2'-deoxy-5-ethyl-4'-thio-D-uridine (**1**, R = Et). Interestingly, the antiviral actions of (**1** R = Et) and the cytotoxicity of the thymidine analogue (**1**, R = Me)[2], appear to be unique to the natural, or D-series: amongst the few reported examples, the L-5-ethyluridine analogue (**2**, R = Et) is inactive[3] and the corresponding thymidine (**2**, R = Me) is >10,000-fold less toxic.[4] These results are part of the considerable interest and therapeutic potential in unnaturally configured nucleosides, where potency and selectivity often differ in enantiomeric forms: indeed some of our recent research has produced 4'-thiocytidine analogues where the activity resides only in the L-series.[5] We report here on a new chiral-pool based synthesis applicable to the production of the enantiomeric glycosidation intermediates (**3**) and (**4**) which can be converted to D- or L-2'-deoxy-4'-thionucleosides respectively, with substantial anomeric control and the utilisation of more amenable deprotection conditions.



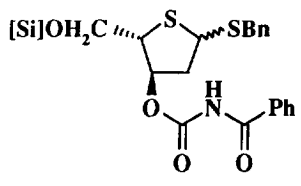
(**1**)



(**2**)

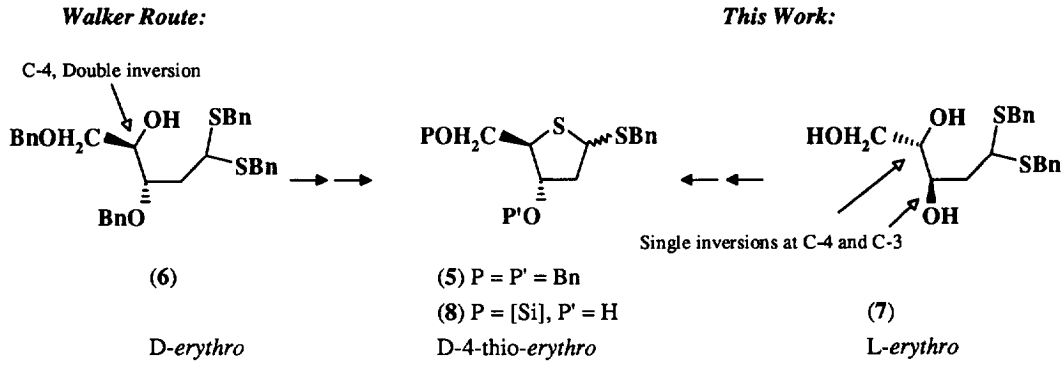


(**3**)

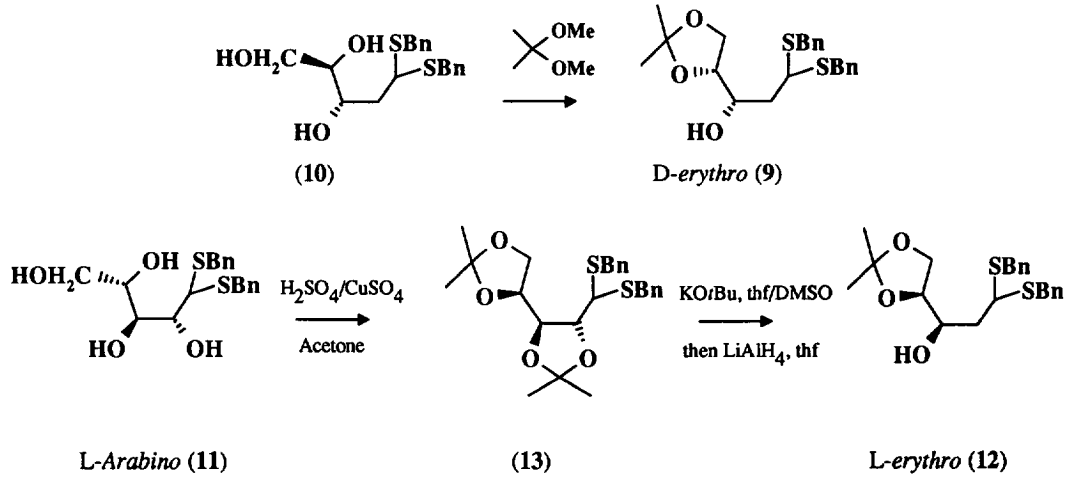


(**4**)

The Walker synthesis[6] of tribenzyl 2-deoxy-1,4-thio-D-*erythro*-pentofuranoside (**5**) was based on the double inversion of a D-*erythro* precursor (**6**). The sequence necessitated the use of benzyl protecting groups, notably to survive the harsh conditions required to form a dibenzyl dithioacetal. Ultimately, removal of these benzyl groups is incompatible with efficient large scale synthesis, compounding the problems of poor coupling ratios. Our new route was based on the formation of the dibenzyl dithioacetal as the first step, thus allowing the introduction of more tractable protection on the 3'/5' hydroxyls. Using this strategy, we proposed to convert L-*erythro* (**7**), to D-4-thio-*erythro* (**8**) [or D-(**9**) to L-4-thio] by single inversions at C-3 and C-4.

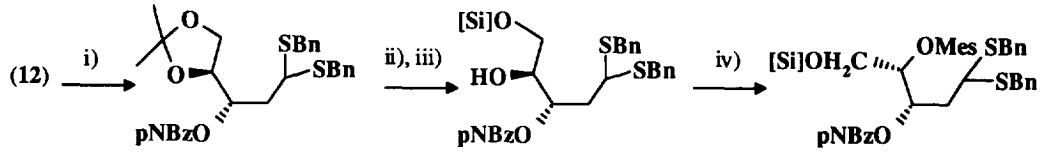


The key D-*erythro* chiron (**9**) was prepared from 2-deoxy-D-ribose dibenzyldithioacetal (**10**),[7] by treatment with HCl in 2,2-dimethoxypropane, which exclusively formed the 4,5-*O*-regioisomer in 78% yield.[8] The prohibitive cost of 2-deoxy-L-ribose prompted the use of a cheap and more readily available L-*erythro* sugar. Thus L-arabinose dibenzyl dithioacetal (**11**) was converted to the L-*erythro* (**12**) by elimination of acetone from the diacetonide (**13**) and reduction of the ketenedithioacetal with lithium aluminium hydride, by an adaptation of a published procedure,[9] in 79% overall yield.



Scheme 1

The utility of these dithioacetals as chiral precursors for nucleoside synthesis is illustrated by the conversion L-(**12**) to D-4-thio (**3**). Required protection and inversion of the free 3-hydroxyl of (**12**) was effected under Mitsunobu conditions[10] with 4-nitrobenzoic acid, to give L-*threo*-(**14**) in 68% yield. The acetonide was cleanly removed with acidic resin in methanol, then primary-selective silylation of the 5-hydroxyl was followed by activation of the 4-hydroxyl *via* mesylation to give (**15**) in 67% overall yield from (**14**).



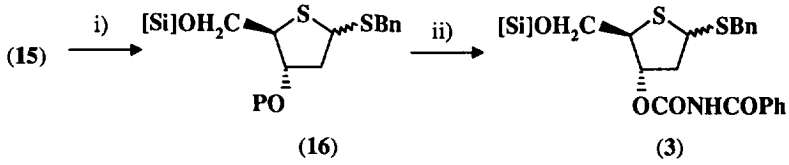
[Si] = *t*BuPh$_2$Si; pNBzO = 4-O$_2$NC$_6$H$_4$CO

i) pNBzOH, DIAD, PPh$_3$, thf; ii) Dowex® H$^+$, MeOH;

iii) [Si]Cl, DMAP, imidazole, DCM; iv) MesCl, DMAP, DCM.

Scheme 2

Ring closure of this intermediate with inversion of configuration at C-4 was achieved by treatment with sodium iodide/triethylamine in 2-butanone in 67% yield. Saponification gave (**16**, P = H), the precursor to the required 3-*O*-carbamoyl intermediate (**3**) which was formed in the usual manner with benzoyl isocyanate in toluene, ultimately furnishing (**1** R = Et),[1] identical to material produced by other routes.[11] Similarly the D-erythro intermediate (**9**) could be converted to the L-erythro (**4**), providing anomer-controlled access to the unnaturally-configured nucleosides.



i) NaI, Et$_3$N, 2-butanone; ii) NaOMe, MeOH, (P = pNBz to P = H); then PhCONCO, toluene.

Scheme 3

Thus we have established a convenient new, enantiospecific, route to anomeric 2-deoxy-4-thioribosides. This can be used to furnish 2'-deoxy-4'-thionucleosides, in either enantiomeric series, with β-selectivity in the glycosylation step. The mild and amenable conditions employed provide the potential to produce significant quantities of these nucleosides.

Acknowledgements.

We thank George Rahim of Medicinal Chemistry and Mark Robertson, John O'Callaghan and Iain Gillies at CDL, Dartford for helpful discussions.

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8. All new compounds gave satisfactory spectroscopic and analytical data, e.g. for enantiomeric dithioacetals (**9**) and (**12**): ^{1}H NMR (200 MHz, $CDCl_3$) δ_H, 1.30 and 1.38 (each 3H, s, Me), 1.83 (2H, m, H-2), 2.36 (1H, d, OH), 3.65 to 3.95 (9H, m, H-1, H-3, H-4, H-5, 2x $\underline{CH_2}Ph$), 7.25 (10H, m, aromatics); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C, 25.18, 28.52 (q, 2x Me), 34.48, 35.10 (t, 2x $\underline{CH_2}Ph$), 38.64 (t, C-2), 47.35 (d, C-3), 65.49 (t, C-5), 69.05 (t, C-4), 78.10 (d, C-1), 109.11 (s, $\underline{C}Me_2$), 127.02, 128.52, 129.01 (d, Ar-CH), 137.91, 138.02 (s, Ar-C); Mass spectrum (m/z) (EI) 404 (M^+, 10%); Microanalysis: Found, C, 65.10; H, 6.83; $C_{22}H_{28}O_3S_2$ requires C, 65.31; H, 6.98%; CD Spectra (MeCN) 248 nm $\Delta\varepsilon_{mol}$ -1.1 (D-*erythro* **9**), +1.1 (L-*erythro* **12**).

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(*Received in UK* 6 *December* 1995; *revised* 18 *January* 1996; *accepted* 26 *January* 1996)