Pergamon

Tetrahedron Letters 41 (2000) 10099–10105

TETRAHEDRON LETTERS

A novel synthesis of 4′-thionucleosides and a potential stereospecific route to pyrimidine nucleosides

J. Allen Miller,*,† Ashley W. Pugh, G. Mustafa Ullah and Clare Gutteridge

Department of Medicinal Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, UK

Received 25 August 2000; accepted 11 October 2000

Abstract

Starting with the L-ascorbate derived epoxide **1**, a di-*t*-butyl dithioacetal cyclisation route to 2′-deoxy-4′-thionucleosides has been developed. Based on an intermediate in this route, a novel and stereospecific route to α- or β-pyrimidine nucleosides has been conceived, but its implementation failed at a key ring-closure step.

Keywords: 2′-deoxy-4′-thionucleoside synthesis; di-*t*-butyl dithioacetal cyclisation; epoxide opening.

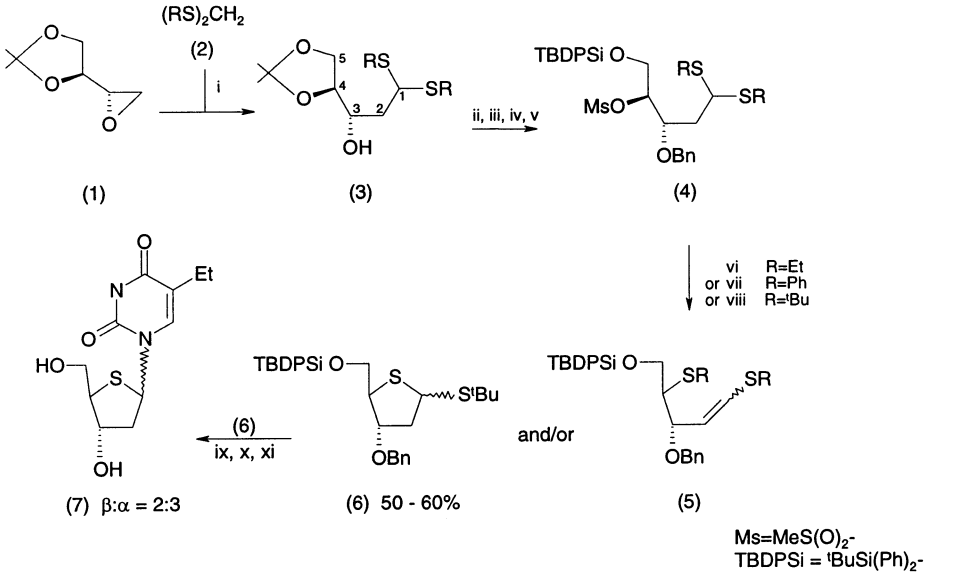
4′-Thionucleosides have had something of a renaissance over the last decade or so, largely due to their apparent promise as anti-viral[1] and anti-tumour agents,[2] although none as yet appear to have reached the marketplace as therapeutics. In keeping with this interest, a great deal of ingenuity has recently gone into novel syntheses of 4′-thionucleosides and their sugar precursors,[3] and considerable progress has been made since the pioneering, but long and difficult, routes used by Whistler, Reist and Bobek and their collaborators in the 1960s and 1970s.[4]

These early routes involved forming the S to C-4 bond of the thiosugar early in the synthesis, but more recent syntheses, some of which work on a multi-gram scale, have depended upon formation of the S to C-1 bond first, followed by ring-closure of the sulphur at C-4. This has now become established as the preferred approach in the 2-deoxypentose series, largely due to the efforts of Walker et al.[1b,5] and this route and its variants have been followed by several other groups.[6] Nevertheless, there are drawbacks associated with 2-deoxypentose starting material availability, with the conditions used in the cyclisation step (benzyl iodide is a stoichiometric product!) and with the difficult separation of the roughly equal amounts of the α- and β-nucleosides formed after the base coupling step. In this paper, we show how the readily

* Corresponding author. Tel: +0044 (0)1625 500555; fax: +0044 (0)1625 500666; e-mail: allen.miller@protherics.com
† Present address: Protherics PLC, Beechfield House, Lyme Green Business Park, Macclesfield, Cheshire SK11 0JL, UK.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01796-2

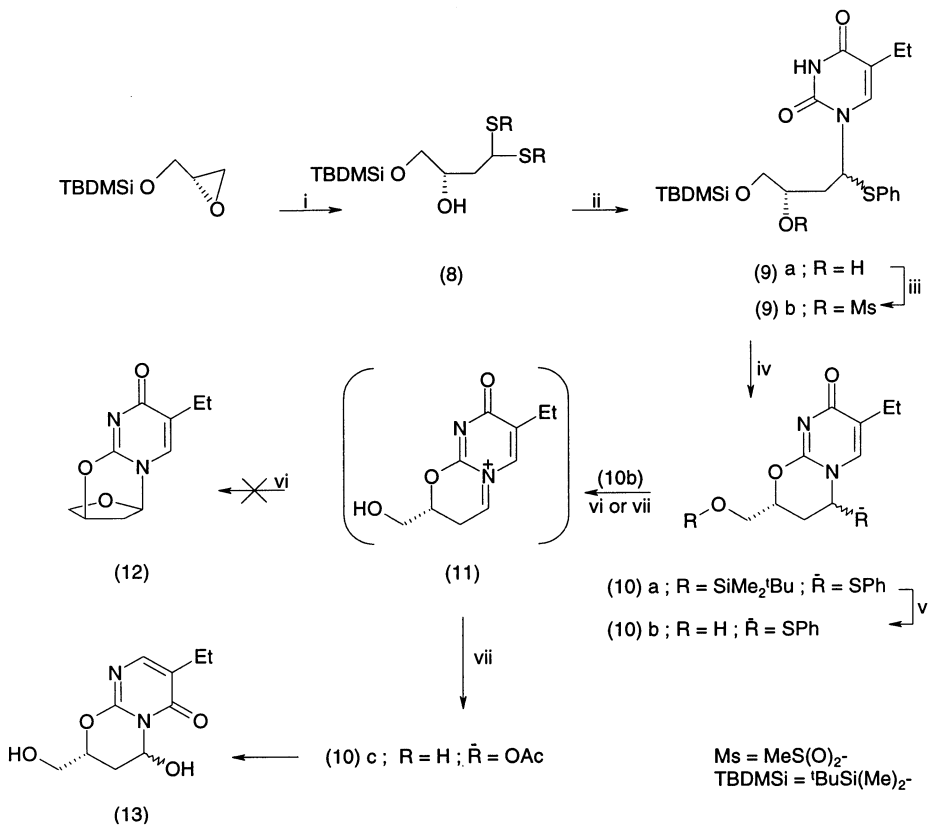
available epoxide **1** can be used as starting material for a 2′-deoxy-4′-thionucleoside synthesis based on a novel di-*t*-butyl dithioacetal cyclisation (Scheme 1), and we also outline a potentially general, albeit unfulfilled, strategy for the stereospecific synthesis of α- or β-nucleosides in the pyrimidine series (Scheme 2).



Scheme 1. Reagents: (i) *n*-BuLi (R = Et 95%; R = Ph 90%; R = ^{t}Bu 97%); (ii) NaH, BnBr, DMF (88%); (iii) HCl, MeOH (96%); (iv) ^{t}BuSi(Ph)$_2$Cl, DMAP, pyridine (96%); (v) $MeSO_2Cl$, DMAP, pyridine (91%); (vi) Δ, NaI, Et_3N, butan-2-one; (vii) Δ, Et_3N, butan-2-one; (viii) Δ, DBU (4 equiv.); (ix) 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine, NBS, MeCN (82%); (x) Bu_4NF (92%); (xi) BBr_3, CH_2Cl_2 at −30°C (70%)

Our starting point is the epoxide **1**, which can be prepared conveniently from L-ascorbic acid[7] and one of the attractions of our approach is that the other three stereoisomers of **1** are also cheap and readily available.[7,8] Following earlier work of Trost et al.,[9] and that of Kamikawa et al.,[10] epoxide **1** was opened exclusively at the terminal carbon by a range of anions derived by metalation of the formaldehyde dithioacetals **2**, to give the hydroxydithioacetals **3**,[11] as shown in Scheme 1. Fairly standard protection–deprotection steps led to the mesylates **4**, ready for ring-closure. However, under a range of conditions the mesylates **4** (R = Ph or Et) did not cyclise, but yielded a mixture of the *E*- and *Z*-vinyl sulphides **5**, the result of 1,4-*SR* shifts reflecting the prior experiences of Hughes et al., Holzapfel et al. and Blomberg et al.,[12] on whose work Walker's route[5] was based.

It is likely that the success of Walker[5] and others[6,12] with analogues of **4**, (R = Bn) is a consequence of the relative ease of nucleophilic attack (by iodide ion) on the benzylic carbon in the presumed sulphonium intermediate, leading to *S*-debenzylation. We have now found that an alternative way of achieving cyclisation via a sulphonium salt is to use a di-*t*-butyl dithioacetal, e.g. **4**, (R = ^{t}Bu), and a strong base such as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). It is presumed that DBU facilitates de-*t*-butylation via loss of isobutylene, such that the kinetics of ring-closure to **6** can compete with the 1,4-shift of a ^{t}BuS group to give **5**. This method allows the protected thiosugar **6** to be obtained as mixed α- and β isomers in 50–60% yields, which compares reasonably with the 35–40% yields found by others in the 2-deoxy series when R = Bn and the iodide ion is used as a debenzylating agent.[5,6] Finally, the known 4′-thionucleosides **7**,



Scheme 2. Reagents: (i) $(RS)_2CH_2$, *n*-BuLi, THF (62–90%); (ii) 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine, NBS, MeCN (79%); (iii) $MeSO_2Cl$, pyridine; (iv) Δ, $^iPr_2NH$, *n*-propanol (97%, two steps); (v) Bu_4NF (92%); (vi) NBS, MeCN, 0–20°C; (vii) $Hg(OAc)_2$, MeCN

of prime interest because of the powerful anti-herpes activity of the β isomer,[13] were obtained from **6** using standard deprotection procedures, thus confirming the configurational assignments in **6**.

The above synthesis of **7** shares a common feature with those of other 2′-deoxy-4′-thionucleosides—unfavourable β:α ratios. Separation of the anomers can be difficult and laborious, but is often essential because biological activity is resident only, or largely, in one isomer. In the last few years, a number of groups, notably that led by Liotta,[14,15] have successfully addressed the anomer problem.[16] Several of these approaches rely upon differential facial additions to double bonds, an iminium bond in the first case[14b] and a 1,2-glycal in other cases.[17] We regarded chemistry derived from the acetal **3** and its analogues as an opportunity to explore a general α- or β-specific approach to pyrimidine nucleosides based on stereospecific addition to an iminium intermediate—see Scheme 2.

The proposed sequence can start from the acetals **3**, or the simpler analogues **8**,[18] and the detailed sequence for the latter is set out in Scheme 2. The desired outcome was the anhydronucleoside-like compound **12**, which lacks the usual 4′-hydroxymethyl group of a pentose-derived anhydronucleoside. With acetals **3** as starting material, it was anticipated that a 'normal' 2,3′-anhydronucleoside would be produced, and subsequently would bring with it the usual valued synthetic options[19] associated with regiospecific ring-opening of these compounds.

Clearly, the configuration at C-4 in **3**, or its isomers (see Scheme 1 for numbering), will determine the D- or L-assignment to the 2,3′-anhydronucleoside. Moreover, the relative configuration at C-3 and C-4 will determine whether the outcome is an α- or a β-nucleoside, e.g. epoxide **1** should yield **3** with a 3*S*,4*S*-configuration, and this in turn should produce an α,L-2,3′-anhydronucleoside.

This proposed chemistry was initially investigated with the dithioacetal **8**, (R = Ph), available from TBDMS-protected R-glycidol in 90% yield, but it was extended subsequently to the acetals **3**. From **8**, mono-exchange[20] with 5-ethyluracil was achieved in good yield using *N*-bromosuccinimide (NBS) to give diastereoisomers **9a** (ratio varies from 3:2 to 1:1), which were then converted into the separable methanesulphonates **9b**,[21] as in Scheme 2. Base-catalysed, quantitative displacement of the methanesulphonates gave **10a**, deprotection of which then gave **10b**,[22] ready, in principle, for the formation of the 'sugar ring' by addition of the hydroxy group to the iminium ion **11**. However, using NBS, the key ring-closure to give the anhydronucleoside **12** was not successful. The lability of the PhS group in **10b** was confirmed by mercuric acetate induced exchange to give acetates **10c**, presumably via the iminium species **11**. Under these conditions, the N-3 linked bicyclic aminol **13**[23] was also formed as a minor product.

The result with mercuric acetate suggests that an intramolecular exchange at C-1′ may be achievable, but the circumstances in our laboratory at that time did not permit a proper evaluation of this prospect. As far as we are aware, this approach to homochiral nucleosides remains novel and, we believe, worthy of further scrutiny.

General procedure for preparation of hydroxy-dithioacetals. Compound **3**; (R = ^{t}Bu): Di-(*t*-butylthio)methane (422 mg, 2.2 mmol) was dissolved in dry THF (15 ml) under argon. After cooling to −78°C, *n*-BuLi (1.6 M in hexane, 1.5 ml, 2.4 mmol) was added. After stirring the solution for 30 min, epoxide **1** (288 mg, 2.0 mmol) was added dropwise as a solution in dry THF (5 ml). The solution was slowly allowed to warm to 0°C and stirring continued until TLC indicated complete consumption of the epoxide **1**. Then ammonium chloride solution was added to the mixture, and this was washed with ethyl acetate (3×15 ml). The combined extracts were washed with water and then brine, and dried over magnesium sulphate. After filtration, the solvent was evaporated and the resulting yellow oil was chromatographed (silica gel, 18:1 petrol:ether) to yield the hydroxy-di-*t*-butylthio acetal **3** (R = ^{t}Bu) as a pure (TLC), colourless oil (652 mg, 97%).

Ring-closure of di-t-butyl dithioacetal **4**; (R = ^{t}Bu). Compound **6**: Dithioacetal **4** (R = ^{t}Bu) (703 mg, 1.0 mmol) was added to a solution of DBU (0.61 ml, 4 mmol) in butan-2-one and the solution refluxed overnight under nitrogen, by which time all of the dithioacetal had been consumed (TLC in 9:1 petrol:ether). The solvent was removed and the resulting oil was dissolved in dichloromethane (20 ml) and the solution washed with water (×3), then dilute HCl (20 ml, 0.05 M). The organic phase was dried, and the solvent evaporated to leave an oily product which was carefully columned on silica gel using 100:3 petrol:ether. The major product (330 mg, 60%) was the thiosugar **6**. The *E*- and *Z*-vinyl sulphides **5**, (R = ^{t}Bu) (15–25% and <10%, respectively) were identified by their characteristic ^{1}H NMR features (*E*-: δ 6.3 (d, J = 15 Hz, 1H, =C*H*S–^{t}Bu) and 5.85 (dd, J = 15 Hz, 7 Hz, 1H, *H*C=CHS-^{t}Bu); *Z*-: δ 6.15 (d, J = 11 Hz, 1H, =C*H*S–^{t}Bu) and 5.66 (dd, J = 11 Hz, 11 Hz, 1H, *H*C=CHS–^{t}Bu).

Procedure for mono-exchange of dithioacetals. Compound **9a**: Bis-2,4-trimethylsilyloxy-5-ethylpyrimidine was freshly prepared from 5-ethyluracil (308 mg, 2.2 mmol) using hexamethyldisilazane and chlorotrimethylsilane in dry acetonitrile (20 ml) under nitrogen at room temperature.[13] Diphenyl dithioacetal **8** (842 mg, 2.0 mmol) in dry acetonitrile (10 ml) was added

to the stirred mixture. *N*-Bromosuccinimide (390 mg, 2.2 mmol) was then added, and the mixture stirred until TLC showed consumption of all of the dithioacetal **8**. The reaction was quenched by adding a solution of sodium thiosulphate and conventional extractive work-up led to a slightly yellow oil which was purified using flash chromatography. The mixture of diastereoisomers **9a** (710 mg, 79%) solidified upon standing overnight.

*Procedure for ring-closure of the hydroxy thioaminals **9a***. Compound **10a**: Methanesulphonyl chloride (230 mg, 2.0 mmol) in pyridine (5 ml) was added to a solution of the hydroxy thioaminal **9a** (676 mg, 1.5 mmol) in dichloromethane, stirred at 0°C. The temperature of the solution was gradually allowed to rise to 20°C. After mesylation was complete (TLC), further dichloromethane was added and conventional acid, then base, extractions yielded the crude methanesulphonates **9b**, which were then heated at reflux in a mixture of di-isopropylamine (1 ml) and *n*-propanol (10 ml). The methanesulphonates were consumed after 2–3 h (TLC) and volatile materials were then removed on a rotary evaporator. The residual oil was dissolved in dichloromethane (10 ml) and underwent acid and then base washes, prior to flash chromatography, which yielded compound **10a** (630 mg, 97%).

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11. Hydroxy di-*t*-butyl dithioacetal **3**; (R = ^{t}Bu): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.42 (s, 9H, ^{t}BuS), 1.44 (s, 9H, ^{t}BuS), 1.46 (s, 3H, CH_3), 1.68–1.80 (ddd, 1H, 2-C*H*), 2.05–2.25 (ddd, 1H, 2-C*H*), 2.5 (solvent and concentration dependent) (d, J = 5 Hz, *H*O–CH,), 3.70–4.05 (m, 4H), 4.23 (dd, J = 10 Hz, 4 Hz, 1-C*H*). MS (m/z) 336 (M^+). Anal ($C_{16}H_{32}O_3S_2$): C, H.
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18. Hydroxy diphenyl dithioacetal **8**, (R = Ph): ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 6H, Me_2Si), 1.1 (s, 9H, ^{t}BuSi), 1.70–1.86 (ddd, 1H, 2-C*H*), 2.0–2.16 (ddd, 1H, 2-C*H*), 2.7 (solvent and concentration dependent) (d, J = 5 Hz, 1H, 3-CHO*H*), 3.25 (dd, J = 7 Hz, 9 Hz, 1H, 4-C*H*), 3.42 (dd, J = 9 Hz, 4 Hz, 1H, 4-C*H*), 4.07 (m, 1H, 3-C*H*OH), 4.75 (dd, J = 12 Hz, 3.5 Hz, 1H, 1-C*H*), and 7.0–7.5 (m, 10H, PhS×2). MS (m/z) 421 (M^+).
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20. We wish to thank Dr. S. G. Rahim and N. Trivedi for unpublished observations that dithioacetal exchange with trimethylsilylated pyrimidine bases conveniently stops at the mono-exchange stage.

21. Compound **9** was fully characterised as a TLC-pure, higher R_f (10:1 petrol:ether) diastereoisomer of the methanesulphonates **9b**: ^{1}H NMR δ ($CDCl_3$) 0.1 (s, 6H, Me_2Si), 0.83 (s, 9H, ^{t}BuSi), 0.98 (t, $J=7$ Hz, 3H, 5-CH_2CH_3), 2.1–2.4 (m, 4H, overlapped quartet 5-CH_2CH_3 and 2′-CH_2), 2.94 (s, 3H, $S(O)_2CH_3$), 3.73 (dd, $J=13$ Hz, 5 Hz, 2H, 4′-CH_2), 4.7–4.8 (m, 1H, 3′-C*H*), 6.0 (dd, $J=10$ Hz, 10 Hz, 1H, 1′-C*H*), and 7.0–7.4 (bm, 6H, SPh and 6-C*H*). MS (m/z) 529 (M^+). Anal ($C_{23}H_{36}N_2O_6SiS_2$): C, H, N.
22. Compound **10** was characterised as the alcohol **10b** (following de-silylation of **10a** with tetra-*n*-butylammonium fluoride): ^{1}H NMR (CD_3OD), major diastereomer ($\sim$60%), δ 1.19 (t, $J=6$ Hz, 3H, 5-CH_2CH_3), 2.46 (q, $J=6$ Hz, 2H, 5-CH_2CH_3), 2.2–2.75 (m, 2H, 2′-CH_2), 3.7–3.83 (ddd, 2H, 4′-CH_2), 4.4–4.52 (m, 1H, 3′-C*H*), 5.67 (dd, $J=9$ Hz, 5 Hz, 1′-C*H*), 7.4–7.55 (m, 5H, PhS), and 7.81 (s, 1H, 6-C*H*); minor diastereomer ($\sim$40%), δ 0.97 (t, $J=6$ Hz, 3H, 5-CH_2CH_3), 2.23 (q, $J=6$ Hz, 2H, 5-CH_2CH_3), 2.35–2.75 (m, 2H, 2′-CH_2), 3.75–4.00 (ddd, 2H, 4′-CH_2), 4.87–5.00 (m, 1H, 3′-C*H*), 5.74 (bs, 1H, 1′-C*H*) 6.80 (s, 1H, 6-C*H*), and 7.4–7.6 (m, 5H, PhS). Peak assignments were enabled by appropriate spin-decoupling and 2D COSY studies. MS (m/z) 318 (M^+) on diastereomeric mixture.
23. The structure of **13** follows from detailed spin-decoupling and NOE difference spectroscopy. The lack of enhancement between H-6 and H-1′ (as compared with **10b** and **10c** for example), and a significantly different UV spectrum (λ_{max} 280 nm) led to the view that N-3, instead of N-1, was incorporated into the 1,3-oxazine ring of **13**, formed as only one diastereomer. A similar cyclisation via N-3 has been observed by Liotta et al. in their work on the 3′-tether approach to β-nucleosides.[16a] This study also targeted a 2,3′-anhydronucleoside intermediate, but the approach is, in detail, quite different to the work described here.