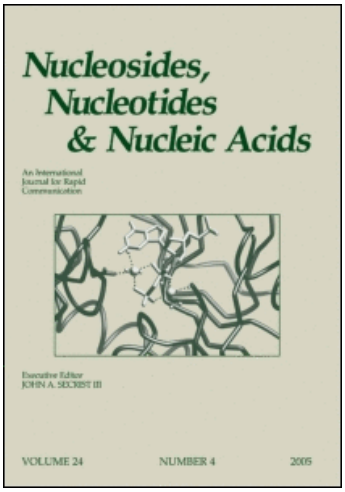


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Efficient Syntheses of (*E*)-5-(2-Bromovinyl)-2'-deoxy-4-thiouridine; A Nucleoside Analogue with Potent Biological Activity

I. Basnak[a]; G. P. Otter[a]; R. J. Duncombe[a]; N. B. Westwood[a]; M. Pietrarelli[a]; G. W. Hardy[b]; G. Mills[b]; S. G. Rahim[b]; R. T. Walker[a]
[a] School of Chemistry, The University of Birmingham, Birmingham, UK [b] Glaxo Wellcome Research and Development, UK

To cite this Article Basnak, I. , Otter, G. P. , Duncombe, R. J. , Westwood, N. B. , Pietrarelli, M. , Hardy, G. W. , Mills, G. , Rahim, S. G. and Walker, R. T.(1998) 'Efficient Syntheses of (*E*)-5-(2-Bromovinyl)-2'-deoxy-4-thiouridine; A Nucleoside Analogue with Potent Biological Activity', Nucleosides, Nucleotides and Nucleic Acids, 17: 1, 29 — 38
To link to this Article: DOI: 10.1080/07328319808005155
URL: http://dx.doi.org/10.1080/07328319808005155

NUCLEOSIDES & NUCLEOTIDES, 17(1-3), 29-38 (1998)

EFFICIENT SYNTHESES OF (*E*)-5-(2-BROMOVINYL)-2′-DEOXY-4′-THIOURIDINE; A NUCLEOSIDE ANALOGUE WITH POTENT BIOLOGICAL ACTIVITY

I. Basnak, G.P. Otter, R.J. Duncombe, N.B. Westwood, M. Pietrarelli, G.W. Hardy[†], G. Mills[†], S.G Rahim[†] and R.T. Walker*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

[†]Glaxo Wellcome Research and Development, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, UK

ABSTRACT: (*E*)-5-(2-Bromovinyl)-2′-deoxy-4′-thiouridine (S-BVDU) is a potent antiherpesvirus agent and its use in gene therapy as an anticancer agent has recently been described. We here outline 2 efficient methods for the synthesis of S-BVDU. The decision as to which method is to be used depends upon the starting materials available but starting from BVU, an overall yield of β-nucleoside of 35% can be expected. From 5-ethyl-2′-deoxy-4′-thiouridine, radical bromination using bromine will give a quantitative conversion to S-BVDU if unreacted starting material is recycled (50%) or using *N*-bromosuccinimide, a one step yield in excess of 80% can be obtained.

INTRODUCTION

The antiherpesvirus agent, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (I, BVDU), first synthesized nearly two decades ago,[1] is still among the most potent and selective antiherpesvirus compounds known, with particularly good activity against varicella-zoster virus (VZV).[2] It was, however, quickly realized that many 5-substituted pyrimidine 2′-deoxynucleosides are very susceptible to nucleoside phosphorylase.[3]

This paper is dedicated to the memory of Professor Tsujiaki Hata

Phone: 44-(0)-121-414-4454
Fax: 44-(0)-121-414-4403

Levels of this enzyme differ from cell line to cell line and were almost certainly responsible for the varying efficacy levels quoted for BVDU. Of more concern is the effect of phosphorylase *in vivo*, where serum levels of BVDU are low and transitory, giving a very low area under the curve in pharmacological experiments.[4] Despite this reduced efficacy, BVDU still appears to have potential as a clinical antiviral compound.

Many attempts have been made to increase the resistance of BVDU to phosphorolysis and these culminated in the reported synthesis of (*E*)-5-(2-bromovinyl)-2′-deoxy-4′-thiouridine (II, S-BVDU) in 1991.[5] *In vitro*, this analogue has an essentially identical antiherpesvirus profile to BVDU but *in vivo*, the compound was shown to be stable to nucleoside phosphorylase, achieved very high serum levels in animals which were maintained for many hours and could achieve arrest of herpesvirus infections at much lower doses than were required for BVDU.[6]

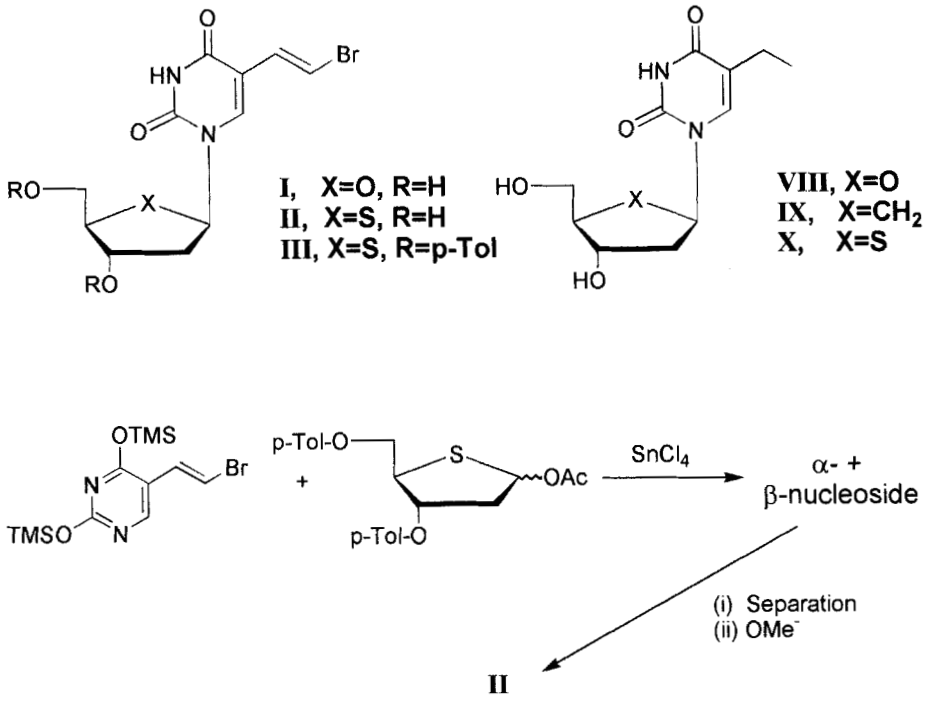
Recently,[7] attempts have been made to use BVDU in combined gene/chemotherapy by transfecting murine mammary carcinoma cells with the HSV-1 thymidine kinase (TK) gene, the product of which would phosphorylate BVDU within the cancer cells. The 5′-monophosphate so produced is a thymidylate synthase inhibitor and so is toxic to the cells. However, once again the efficacy is limited by the susceptibility of the nucleoside to phosphorolysis.

More recently, attention has been focussed on the use of VZV TK as a candidate for such a suicide gene in cancer cells because BVDU and analogues are 5 to 80-fold more potent inhibitors of VZV than of HSV-1 *in vitro*.[8] Results using S-BVDU, which is stable to phosphorolysis, have shown the analogue to be particularly toxic to osteosarcoma cells containing the VZV TK gene, with an IC_{50} value of 40 nM. Thus the compound is a promising candidate for the treatment of VZV TK gene-transfected tumours *in vivo*.

There is thus now a need for a facile and efficient synthesis of S-BVDU, as methods previously reported[5,9] are not particularly reliable, nor are the yields high. We here report methods suitable for the synthesis of S-BVDU in reasonable yield. The first method starts from (*E*)-5-(2-bromovinyl)uracil (BVU) which is then condensed with a suitably protected sugar (SCHEME 1). The other method depends upon the attack of bromine radicals in very reproducible and high yielding reactions on the corresponding 5-ethyl-substituted nucleoside.[11]

RESULTS AND DISCUSSION

Three syntheses of S-BVDU are documented in the literature.[5,6,9] All involve condensation of the base, BVU, with a sugar derivative. The original method[5] gave only a



SCHEME 1

6% isolated yield of the protected nucleoside which was improved to 14% upon replacing the benzyl ether protecting groups by *p*-toluoyl ester protection. The leaving group at the anomeric position in both these preparations was bromide, generated *in situ* from the corresponding thioglycoside. Subsequently, replacement of the thioglycoside with an acetyl functionality and the use of Lewis acid-catalysed condensation conditions (TMSOTf), resulted in a more reproducible reaction, from which a yield of ~ 20% of the deprotected β-nucleoside could be obtained[6] but no details have ever been published.

From these experiments we learn that BVU often does not condense to give high yields of nucleoside and there are problems associated with benzyl ether protecting groups as the sugar moiety then tends to give the products of elimination reactions. Indeed, BVDU itself has never been made on any reasonable scale by condensation of BVU with a 2-deoxyribose derivative and was always made by exemplification of a pre-formed β-nucleoside (usually 2′-deoxy 5-iodouridine).[12] In the 4′-thio series, this type of reaction is not suitable as 2′-deoxy-5-iodo-4′-thiouridine is not readily available. Thus we require a synthesis in which BVU can be condensed under Lewis acid-catalysed conditions with a 4-

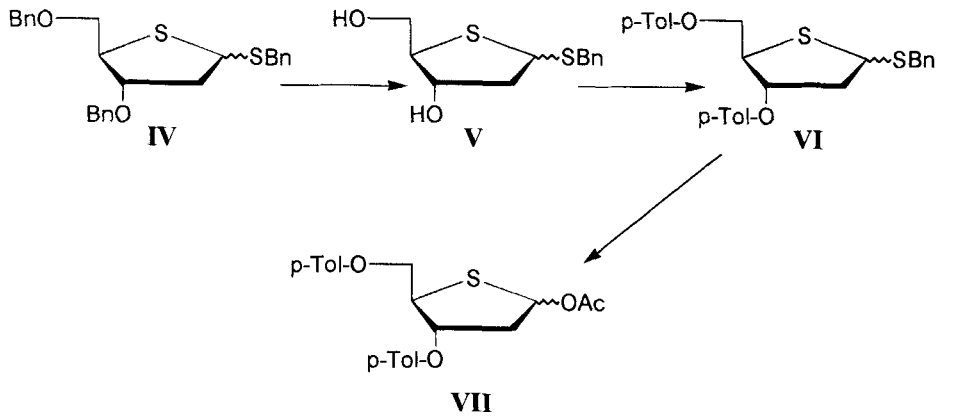
thio sugar where the anomeric leaving group is acetyl and the sugar hydroxyl protecting groups are acyl groups.

Such a synthesis has previously been described by Secrist *et al.*,[13] but the 4-thio sugar (VII) used came from the tedious preparation described by Bobek.[14] The currently preferred 4-thio sugar synthesis yields the dibenzyl-protected thioglycoside (IV) and we here describe the optimum method for its conversion into the desired compound (VII, SCHEME 2). The removal of *O*-benzyl groups and subsequent reprotection by *p*-toluoylation has previously been described by Secrist (using BBr_3),[15] Dyson *et al.*, (using BCl_3),[9] and by Rahim *et al.*, (using BCl_3).[6] Only Dyson *et al.*,[9] provide any experimental details and claim a 53% isolated yield of the di-*O*-*p*-toluoylated species (VI). However, it is known that the deprotected thio sugar (V) is extremely unstable, BCl_3 is very expensive and it is also difficult to control the temperature required (-90 °C) on anything other than a small scale. $TiCl_4$ has been used for the large scale debenzylation of 2′-deoxy-4′-thionucleosides[11] and its use for deprotection of the thio sugar has been mentioned in passing but no details have been given.[16] The advantage of using $TiCl_4$ is that the reaction can easily be controlled at -20°, is relatively cheap and hence can be used on a large scale. This is necessary if multi-gram quantities of nucleoside are required because the α:β ratio produced in the condensation process means that no more than 100 mg of deprotected β-nucleoside per gram of protected sugar can be expected.[17]

The procedure described here is reproducible and due to the instability of the deprotected material (V), the crude product is normally immediately subjected to *p*-toluoylation. This latter reaction is straightforward and is performed as previously described.[11] The subsequent replacement of the benzyl-thiol group by acetyl is also straightforward. This has been described previously[6,15] but on neither occasion was any experimental detail provided. Although compound VII is obtained in crystalline form, the compound is an α/β (1.4:1) mixture. Further recrystallization results in the isolation of the pure α-anomer (m.p. 91-93 °C). The structure of this compound as determined by X-ray analysis has been published.[17]

The sugar derivative (VII) is now a good substrate for the Lewis acid-catalysed (actually >1 equivalent of 'catalyst') condensation with BVU to give a high overall yield of nucleoside with an acceptable (1:1) α:β ratio. The two anomers can readily be separated and deprotected to give an overall isolated yield of β-nucleoside of 35% (from BVU, SCHEME 1).

Radical bromination of 2′-deoxy-5-ethyluridine (VIII) was initially described many years ago although the products were initially misidentified.[18] Yields were very variable when the reaction was initiated by UV light although this method of preparation of BVDU



SCHEME 2

has been used for many years on a large scale.[19] Recently, AIBN has been used as a radical initiator for the synthesis of carbocyclic BVDU (IX) from the corresponding 5-ethyl derivative.[20] We report here that this method of radical initiation with bromine or *N*-bromosuccinimide is suitable for the conversion of 2′-deoxy-5-ethyl-4′-thiouridine (X) into S-BVDU (II). Compound (X) is a particularly suitable starting material for further exemplification in the 4′-thio series of analogues as it is easily synthesized by condensation of the base and appropriate sugar derivative to give an α/β mixture from which the β-anomer can be readily isolated by recrystallization following deprotection of the mixture.[11]

Using bromine as the source of bromine radical, the reaction is clean and the product easily isolated from unchanged starting material if only 2 equivalents of bromine are used. The yield is only moderate (~50%) but unchanged starting material can be recycled and attempts to increase the yield, by increasing the quantity of bromine available, result in complete disappearance of starting material, a lower yield of product and the presence of other unidentified compounds. When NBS is used, much higher yields can be obtained (~85%), no starting material remains and it is only necessary to remove the resulting succinimide from the product.

Thus, depending upon the availability of starting materials, it is now possible to select the most appropriate method, from the two described above, for the synthesis of S-BVDU in reasonable and reproducible yields.

EXPERIMENTAL

Thin layer chromatography was performed on precoated aluminium-backed TLC plates (Silica gel 60 F_{254}) supplied by E. Merck A.G. Glass chromatography columns were slurry

packed with 70-250 mesh Silica gel and eluted under pressure. NMR spectra were recorded on a Bruker AC300 (300 MHz) spectrometer, mass spectra were recorded on a Kratos MS80 mass spectrometer where electron impact or chemical ionization were used as necessary. Fast Atom Bomarbardment MS were obtained from a VG Zabspec mass spectrometer with m-nitrobenzyl alcohol, spectra were obtained in the positive-ion mode at a scan speed of 10 s per decade. For accurate mass measurement, narrow voltage scanning at a resolution of 5000 was employed and polyethylene glycol was used as a reference.

All chemical reactions were performed under scrupulously dry conditions unless otherwise stated and all evaporation of solvents were carried out under reduced pressure.

Benzyl 3,5-di-*O*-*p*-toluoyl-2-deoxy-1,4-dithio-α/β-D-*erythro*-pentofuranoside (VI). A reaction vessel, containing benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside (IV, 9.37 g, 21.45 mmol)[21] dissolved in dry dichloromethane (DCM, 78 ml), was cooled to -24 °C in a cryostat. Deprotection was carried out by the dropwise addition of $TiCl_4$ (7.1 ml, 65 mmol) in dry DCM from a pressure equalizing funnel cooled to -78 °C with CO_2/acetone. The reaction was maintained below -20 °C throughout the addition of $TiCl_4$ (70 minutes) by which time, the reaction had gone to completion (TLC). 2-Butanone (methyl ethyl ketone, MEK, 77.5 ml) was added dropwise over a period of 15 minutes followed by an ice-cold solution of citric acid (12.35 g) in water (69 ml) which was added accompanied by vigorous stirring. The reaction mixture was then left to warm up to room temperature whereupon it was transferred to a separating funnel, the organic layer separated and the residual aqueous layer extracted with DCM (3 × 50 ml). The combined organic extracts were washed with sodium bicarbonate solution (5%, 2 × 50 ml), dried ($MgSO_4$) and taken to dryness to yield a dark coloured syrup (10.2 g).

For characterization purposes, the product (compound V) can be purified at this stage by silica gel chromatography (hexane-ethyl acetate 1:9) and the appropriate fractions combined and taken to dryness to yield benzyl 2-deoxy-1,4-dithio-α,β-D-*erythro*-pentofuranoside (V) (1.64 g 30%) as a clear syrup. FABMS *m/z* 256 (M^+), 279 ($M+Na^+$). ^{1}H-NMR δ ($CDCl_3$) 7.4-7.2 (5H, m, benzyl), 4.60-4.55 (m, H-1α), 4.45-4.30 (m, H-1β, H-3), 3.90-3.85 (2H, m, $PhCH_2S$), 3.80-3.65 (1H, m, H-4), 3.60-3.40 (2H, m, H-5, H-5′), 2.45-2.15 (2H, m, H-2, H-2′), 2.10-1.80 (2H, bs, 3′-OH, 5′-OH). ^{13}C-NMR δ ($CDCl_3$) 128.8 (phenyl), 78.1 (C-1), 64.2 ($PhCH_2S$), 57.5 (C-4), 48.6 (C-3), 44.0 (C-5), 37.4 (C-2).

This intermediate (compound V) is very unstable and its isolation is accompanied by a drastic reduction in yield and so normally the crude product is further reacted before any attempt at purification is made.

Thus, the crude syrup isolated above (10.2 g) was dissolved in dry pyridine (50 ml) and cooled in ice to 0 °C. To this solution was added a solution of *p*-toluoyl chloride (10.55 ml, 79.8 mmol) in dry pyridine (50 ml) over a period of 45 minutes. After a further 1 hour, the reaction was complete (TLC) and the solution was taken to dryness and co-evaporated with toluene and methanol to remove the last traces of pyridine. The dark coloured syrup that remained was dissolved in chloroform (100 ml), washed with HCl (2M, 2 × 50 ml), sodium bicarbonate solution (5%, 2 × 50 ml), dried ($MgSO_4$) and the solvent removed. The resulting coloured syrup was purified on a column of silica (hexane, with a gradient of ethyl acetate from 0-10%) and the appropriate fractions combined to give compound VI (4.01 g, 38%). FABMS *m/z* 515 $(M+Na)^+$. ^{1}H-NMR δ ($CDCl_3$) 8.00-7.78 (4H, m, toluoyl), 7.38-7.28 (4H, m, toluoyl), 7.29-7.08 (5H, m, benzyl), 5.77 (m, H-1α), 5.60 (m, H-1β), 4.74-4.52 (1H, m, H-3), 4.52-4.38 (2H, m, H-5, H-5'), 4.17 (1H, m, H-4), 3.88 (2H, m, Ph CH_2S), 2.94-2.47 (2H, m, H-2, H-2'), 2.45-2.30 (6H, 4×s, CH_3-Ar). ^{13}C-NMR δ ($CDCl_3$) 129.8 (phenyl), 78.5 (C-1), 66.3 (PhCH_2S), 50.7 (C-4), 45.8 (C-3), 43.5 (C-3), 36.9 (C-2), 21.7 (CH_3).

1-*O*-Acetyl-3,5-di-*O*-*p*-toluoyl-4-thio-2-deoxy-α/β-D-ribofuranose (VII). To compound VI (1.0 g, 2.03 mmol), dissolved in glacial acetic acid (5.6 ml), was added mercuric acetate (0.72 g, 2.26 mmol) to give a pale yellow-coloured solution which was left to stir at room temperature overnight. The reaction was then judged to be complete (TLC) and to it was added chloroform (100 ml) and water (100 ml). The organic phase was separated, the aqueous phase was extracted with chloroform (2 × 50 ml), the organic layers combined, washed with water (50 ml), dried ($MgSO_4$) and taken to dryness to give a solid white residue. This was purified on a silica column with hexane-ethyl acetate (8:2) as eluent, the appropriate fractions combined, taken to dryness and the residue recrystallized from methanol to give the title compound (α:β ~ 1.4:1, 0.67 g, 77%). FABMS *m/z* 451 $(M+Na)^+$. ^{1}H-NMR δ ($CDCl_3$) 7.93-7.80 (4H, m, toluoyl), 7.37-7.24 (4H, m, toluoyl), 6.17 (m, H-1α), 6.07 (m, H-1β), 5.74-5.55 (1H, m, H-3), 4.45-4.26 (2H, m, H-5,H-5'), 4.05-3.91 (1H, m, H-4), 2.73-2.64 (2H, m, H-2), 2.36 (6H, 4×s, CH_3-Ar), 2.02 (3H, 2×s, CH_3CO). ^{13}C-NMR δ ($CDCl_3$) 170.4 (CH_3CO). 166.2 (CO toluoyl), 144.2, 143.8 (qC- toluoyl), 129.8, 129.1 (CH- toluoyl), 126.8, 126.7 (qC- toluoyl), 79.1(C-3), 65.9(C-5), 59.4(C-1), 50.3(C-4), 40.6(C-2), 21.7 (CH_3- toluoyl), 21.1(CH_3-toluoyl).

(*E*)-5-(2-Bromovinyl)-2'-deoxy-4'-thiouridine (II) Method 1. To a solution of *N,O*-bis (trimethylsilyl) acetamide (2 g, 9.8 mmol) in dry acetonitrile (30 ml), was added (*E*)-5-(2-bromovinyl)uracil[10] (1 g, 4.58 mmol) and the mixture was stirred at room temperature

under a stream of dry N_2 until complete solution had been achieved. To this solution was then added compound VII (1.9 g, 4.43 mmol) in dry acetonitrile, to be immediately followed by $SnCl_4$ (0.8 ml, 6.9 mmol) and the mixture was stirred at room temperature for 1 hour by which time the reaction was judged to be complete (TLC). The reaction was quenched by the slow addition of ethanol (35 ml) and upon standing at 4 °C a white solid, which proved to be an anomeric mixture of two nucleosides, precipitated and could be removed by filtration. The anomers (α:β ~ 1:1) could be separated by silica gel chromatography using an increasing gradient of acetone (1-10%) in DCM. The appropriate fractions were combined to give the title compound III (0.9 g, 35% yield) which could be deprotected to give the title compound **II** in 92% yield as previously described.[9]. The ^{1}H-NMR, MS and m.p. corresponded to that reported in the literature.[9]

(*E*)-5-(2-Bromovinyl)-2′-deoxy-4′-thiouridine (II). Method 2. To a solution of 3′,5′-di-*O*-acetyl-2′-deoxy-5-ethyl-4′-thiouridine (1.20 g, 3.36 mmol)[22] in carbon tetrachloride (50 ml) was added *N*-bromosuccinimide (1.49 g, 8.4 mmol) and AIBN (0.080 g, 0.028 mmol) and the solution was heated under reflux in an atmosphere of N_2 for 2 hours and then allowed to cool. Triethylamine (1.20 ml, 8.40 mmol) was added over a period while maintaining the temperature below 50 °C. DCM (35 ml) and sodium bicarbonate solution (5%, 35 ml) were added, the organic layer was separated, the aqueous layer back-extracted with carbon tetrachloride (3 × 50 ml), the organic layers combined, washed with HCl (2 M, 25 ml) and water (25 ml), dried ($MgSO_4$) and the solvent removed to afford an orange oil which contained only one compound by TLC (1.22 g, 84%) which could be deacylated in the usual way in almost quantitative yield to give the title compound which was indistinguishable from a sample of the authentic material.[9]

An alternative method involes the use of molecular bromine as follows: a solution of 3′,5′-di-*O*-acetyl-2′-deoxy-5-ethyl-4′-thiouridine (0.4 g, 1.12 mmol)[22] in chloroform (10 ml) heated under reflux in an atmosphere of N_2, was added a solution of bromine (0.114 ml, 1.12 mmol) and AIBN (0.04 g, 0.028 mmol) in chloroform (10 ml) at a rate which maintained a pale orange solution. When the addition had been completed, the reaction was heated for a further 2 hours and then cooled. Triethylamine (0.40 ml, 2.8 mmol) was added over a period while maintaining the temperature below 50 °C. DCM (35 ml) and water (35 ml) were then added, the organic layer separated, the aqueous layer back-extracted with DCM (3 × 50 ml), the organic layers combined, washed with HCl (2M, 25 ml) and water (25 ml), dried ($MgSO_4$) and the solvent removed to afford an orange oil. Analysis by TLC showed that the isolated material was a mixture of starting material and the acylated title compound in a ratio of ~ 1:1. These compounds could be separated on a silica column (hexane-ethylacetate, 1:1) to yield 3′,5′-di-*O*-acetyl-(*E*)-5-(2-bromovinyl)-

2′-deoxy-4′-thiouridine (0.24 g, 50%) which could be deacylated in the usual way in almost quantitative yield to give the title compound which was indistinguishable from a sample of the authentic material.[9]

Acknowledgements

The authors wish to thank Glaxo Wellcome for funding part of this project (to IB and NBW [CASE]) and the EPSRC (to NBW and RJD) and BBSRC (to GPO) for research studentships. We would also like to acknowledge the help and advice given by Mr. M.S. Robertson.

REFERENCES

1. R.T. Walker, P.J. Barr, E. De Clercq, J. Descamps, A.S. Jones, P. Serafinowski, *Nucleic Acids Res., Special Publ.* **1978**, *4*, s103-s106.
2. E. De Clercq, J. Descamps, P. De Somer, P.J. Barr, A.S. Jones, R.T. Walker, *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 2947-2591.
3. C. Desgranges, G. Razaka, M. Rabaud, H. Bricaud, J. Balzarini, E. De Clercq, *Biochem. Pharmac.* **1983**, *32*, 3583-3590.
4. E. De Clercq, J. Descamps, P.C. Maudgal, L. Missotten, R. Leyten, G. Verhelst, A.S. Jones, R.T. Walker, R. Busson, H. Vanderhaeghe, P. De Somer, *Developments in Antiviral Chemotherapy*, L.H. Collier and J. Oxford, eds, Academic Press, **1980**, 21-42.
5. M.R. Dyson, P.L. Coe, R.T. Walker, *J. Chem. Soc. Chem. Commun.* **1991**, 741-742.
6. S.G. Rahim, E. Littler, K.L. Powell, P. Collins, P.L. Coe, M.R. Dyson, R.T. Walker, *31st ICAAC, Chicago* **1991**, 1232.
7. J. Balzarini, *Nucleosides Nucleotides* **1996**, *15*, 821-831.
8. B. Degrève, G. Andrei, M. Izquierdo, J. Piette, E.E. Knaus, L.I. Wiebe, I. Basnak, R.T. Walker, E. De Clercq, J. Balzarini, Submitted.
9. M.R. Dyson, P.L. Coe, R.T. Walker, *J. Med. Chem.* **1991**, *34*, 2782-2786.
10. I. Basnak, S. Takatori, R.T. Walker, *Tetrahedron Lett. In the press.*
11. S.G. Rahim, N. Trivedi, M.V. Bogunovic-Batchelor, G.W. Hardy, G. Mills, J.W.T. Selway, W. Snowden, E. Littler, P.L. Coe, I. Basnak, R.F. Whale, R.T. Walker, *J. Med. Chem.* **1996**, *39*, 789-795.
12. A.S. Jones, G. Verhelst, R.T. Walker, *Tetrahedron Lett.* **1979**, 4415-4418.
13. J.A. Secrist, K.N. Tiwari, J.M. Riordan, J.A. Montgomery, *J. Med. Chem.* **1991**, *34*, 2361-2366.
14. Y.-L. Fu, M. Bobek, *J. Org. Chem.* **1976**, *41*, 3831-3834.
15. J.A. Secrist, W.B. Parker, K.N. Tiwari, L. Messini, S.C. Shaddix, L.M. Rose, L.L. Bennett, J.A. Montgomery, *Nucleosides Nucleotides* **1995**, *14*, 675-686.
16. S. Shaw-Ponter, G. Mills, M. Robertson, R.D. Bostwick, G.W. Hardy, R.J. Young, *Tetrahedron Lett.* **1996**, *37*, 1867-1871.

17. R.T. Walker, Recent Advances in the Chemistry of Anti-infective Agents, P.H. Bentley and P.J. O'Hanlon, eds., *Royal Society of Chemistry* **1997**, 203-237.

18. D. Bärwolf, P. Langen, *Nucleic Acids Research Special Publ.* **1975**, *1*, s29-s31.

19. D. Bärwolf, German (East) Patent, DD 247,663, 15 Jul 1987, (Chem. Abs. 109, 129605x).

20. P.G. Wyatt, A.S. Anslow, B.A. Coomber, R.P.C. Cousins, D.N. Evans, V.S. Gilbert, D.C. Humber, I.L. Paternoster, S.L. Sollis, D.J. Tapolczay, G.G. Weingarten, *Nucleosides Nucleotides* **1995**, *14*, 2039-2049.

21. M.R. Dyson, P.L. Coe, R.T. Walker, *Carbohydrate Res.* **1991**, *216*, 237-248.

22. E.L. Hancox, R.T. Walker, *Nucleosides Nucleotides* **1996**, *15*, 135-148.