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A Novel Method for Deuteration of 2′-Deoxy-4′-thionucleosides

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Abstract: Oxidation of 2′-deoxy-5-ethyl-4′-thiouridine with sodium *meta*-periodate yielded a separable mixture of (*R*) and(*S*)-sulfoxides. The structure of the (*R*)-sulfoxide was confirmed by X-ray analysis. When treated with sodium deuteroxide, the H-4′ proton was exchanged for deuterium with epimerisation at C-4′. Treatment of the deuteriated sulfoxide nucleoside with TFA/TMSBr furnished the starting material with H-4′ replaced by deuterium.

INTRODUCTION

Tritium labelling of nucleosides and their analogues is often a tedious business and can result in low yields of randomly labelled material of low specific activity. Because of the scale of synthesis possible, it is usually advantageous to incorporate the isotope at as late a stage as possible in the synthesis. Also there is an advantage in labelling at a specific position rather than random labelling. Many nucleoside analogues can be labelled with ^{14}C in the heterocycle moiety and occasionally ^{3}H, particularly in the side chain of C-5 in the pyrimidines[1]. It is often very difficult to put an isotopic label into a specific position in the sugar moiety of a nucleoside analogue, particularly where the chemical modification of the analogue has been in the sugar moiety.

Recently we[2,3] and others[4] have reported the synthesis of a novel series of nucleoside analogues, the 2′-deoxy-4′-thionucleosides. Some of these analogues have potent antiviral activity[5] and have also been investigated for their use in structural studies[6] and in antisense[7] and antigene therapy[8]. However it is far from clear as to how these analogues, particularly the very toxic 4′-thiothymidine, exert their biological effects and it is necessary to have access to labelled material. As the sugar is modified, it is preferable to have a label in that moiety, if possible accompanied by a separate isotopic labelling in the heterocyclic base.

We here describe the facile and efficient synthesis of the antiviral agent 2′-deoxy-5-ethyl-4′-thiouridine labelled at the 4′-H with deuterium by a method easily applicable to the incorporation of tritium. Condensation of ^{14}C- containing bases with thiosugar followed by tritiation would allow a single nucleoside analogue to have two different isotopic labels in the two distinct regions of the nucleoside.

This paper is dedicated to the memory of Professor Wang Yu
† Deceased

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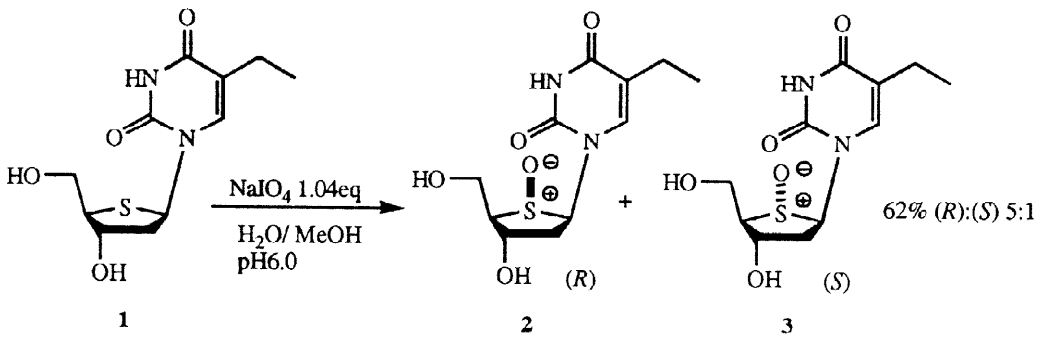
RESULTS AND DISCUSSION

The starting point for our synthesis was the potent antiherpesvirus agent 2′-deoxy-5-ethyl-4′-thiouridine **1**, which had been synthesised as described[2,3]. The 4′-thionucleoside was oxidised in a methanol/water solution using pH6.0 aqueous 0.05M sodium *meta*-periodate over 18 h at 0°C, to give a diastereoisomeric mixture of sulfoxides (**Scheme 1**). Separation by column chromatography yielded the two sulfoxide products **2** and **3** (ratio 5:1). Crystallisation of the faster eluting, major isomer and subsequent analysis by X-ray crystallography confirmed that it is the (*R*)-sulfoxide **2** (**Figure 1**).



Scheme 1: Oxidation of 2′-deoxy-4′-thionucleosides with sodium *meta*-periodate

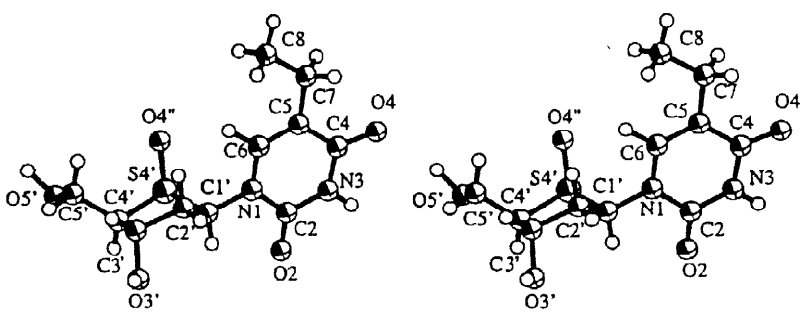
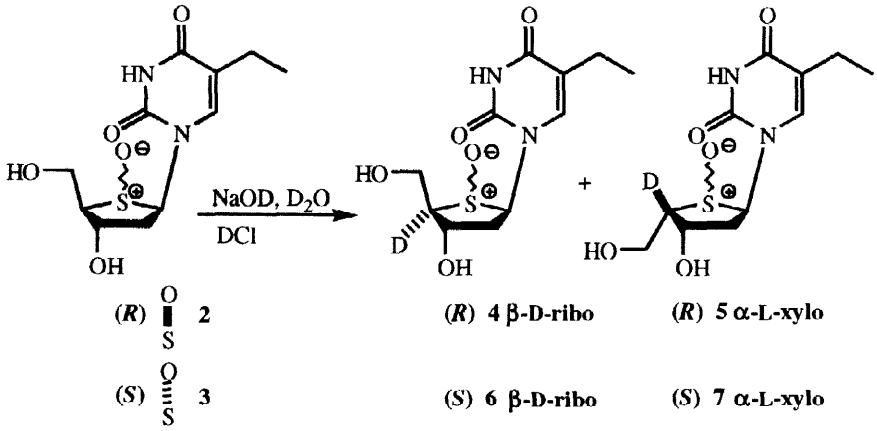


Figure 1: Stereoview of the X-ray crystal structure of the (*R*)-sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine

The (*R*)-sulfoxide nucleoside **2** is in an envelope conformation with the C-1′ atom being twisted away from the plane of the other sugar atoms. Also the glycosic torsion angle S-4′-C-1′-N-1-C-6, at 78.48°, is markedly different to those reported for other 4′-thionucleosides (33-59°)[9,10]. The only similar torsion angle reported is that of the sulfone of 4′-thiothymidine at 85.5°.[11] Most crystal structures of nucleosides have been found to contain the sugar in one of 2 conformations, either C-2′ *exo*, C-3′ *endo* or C-2′ *endo*, C-3′ *exo*. It has been suggested,[12] that the antiviral sugar conformation is probably due to crystallisation forces induced with the co-

crystallisation with a water molecule (omitted for clarity), but coupling constants from NMR spectroscopic data suggest that in solution the nucleoside adopts a structure similar to natural thymidine.

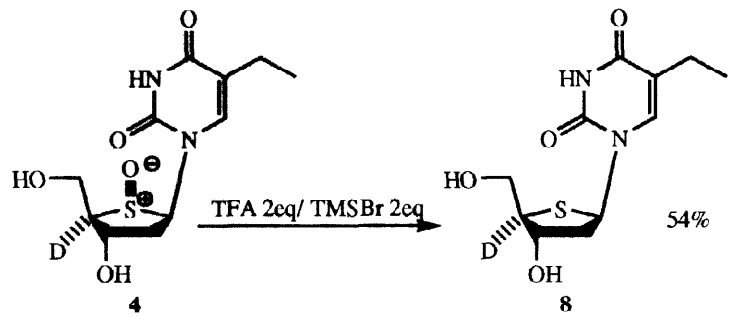
The hydrogen substituents on carbon atoms at positions α- to the oxidised sulfur atom of the 4′-thionucleoside sulfoxides were expected to have increased acidity and to be susceptible to replacement under basic conditions. The (*R*)-sulfoxide **2** was dissolved in deuterium oxide and sodium deuteroxide added and the rate of reaction followed by NMR spectroscopy. This showed a slow doubling of many of the proton signals, along with the disappearance of the H-4′ proton signal. After 18 h the H-4′ proton signal had completely disappeared and the reaction mixture was neutralised with DCl and the products isolated by column chromatography. The ratio of the deuteriated sulfoxide products **4**:**5** was found to be 2.1:1 β-D-/α-L-*xylo*-. Separation of the 2 products as their sulfoxides was found to be fairly demanding. It would be more convenient to reduce the nucleosides and then separate them. Repeating the isotope exchange reaction on the (*S*)-sulfoxide diastereoisomer proceeded as planned, yielding the β-D-/ α-L-*xylo*- deutero products **6**:**7** in the ratio 1.3:1.



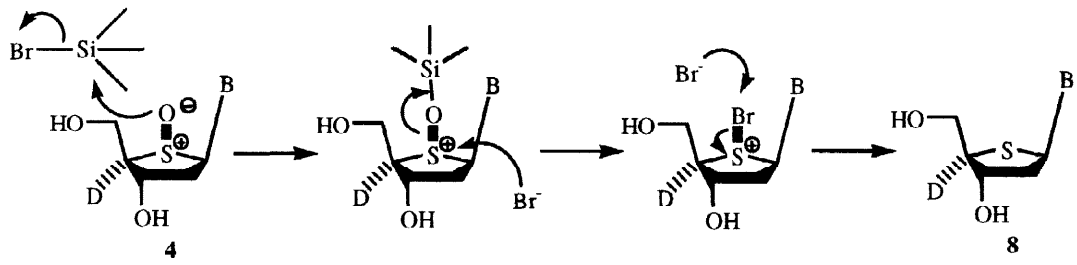
Scheme 2: Reaction of 2′-deoxy-4′-thionucleosides with sodium deuteroxide

The mechanism of deuterium incorporation is believed to involve the proton being removed from C-4′ resulting in a planar carbanion intermediate. A deuterium ion can then attack from either face, resulting in racemisation of the C-4′ position. The carbanion is not thought to be stabilised by a double bond between the C-4′ and sulfur atom as this would also result in racemisation of the chiral sulfoxide, which does not occur.

There are various reported methods for reducing sulfoxides to sulfides but most of these are not applicable to nucleoside analogues.[13,14] However it has been reported that conditions developed for removing benzyl ether protecting groups from peptides also reduce a methionine sulfoxide residue to a sulfide. The conditions involved treating the peptide with trifluoroacetic acid (TFA)/ trimethylsilyl bromide (TMSBr) (20eq/ 20eq) in the presence of thioanisole.[15] Earlier Olah and co-workers used trimethylsilyl bromide to reduce diphenyl sulfoxide back to diphenyl sulfide.[16] Investigation of the conditions required resulted in the amount of TFA/ TMSBr being reduced to 2eq and the thioanisole being omitted. Using the optimised conditions a sample of the deuterated sulfoxide **4** could be reduced to yield the deuterated sulfide **8** in 54% isolated yield.



The reduction reaction proceeds with either diastereoisomer. The suggested mechanism of reduction is outline below (**Scheme 3**) with the intermediate bromosulfonium ion being attacked by a bromide ion to produce the reduced sulfide and bromine.



B = 5-Ethyluracil

Scheme 3: Mechanism for the reduction of the sulfoxides of 2′-deoxy-4′-thionucleosides

EXPERIMENTAL

General: NMR spectra were recorded using a Bruker AC300 spectrometer. ^{13}C NMR spectra were run as ^{13}C PENDANT NMR spectra[17]. Mass spectra were obtained using a VG ZabSpec mass spectrometer. Chromatography was performed on Kieselgel 60, 70-250 mesh ASTM, supplied by E. Merck AG.

(*R*)/(*S*)-Sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine (2/3)

To a stirred solution of 2′-deoxy-5-ethyl-4′-thiouridine (498mg, 1.83mmol)) in distilled water (20ml) and methanol (20ml) at 0 °C, was added an 0.05M aqueous solution of sodium *meta*-periodate (38ml, 1.90mmol). The reaction mixture was then left to warm to room temperature overnight before the product was purified by column chromatography (SiO_2, dichloromethane/methanol, 6/1, v/v) to yield the separate (*R*)- and (*S*)-sulfoxide diastereoisomers **(2)** and **(3)**. [(*R*)-Sulfoxide (271mg, 51.3%), (*S*)-sulfoxide (57mg, 10.7%)].

(*R*)-Sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine (2)

δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.35 (1H, s, H-6), 5.96-5.88 (1H, dd, ^3J=8.0Hz, 10.0Hz, H-1′), 5.50-5.47 (1H, d, ^3J=5.0Hz, 3′-OH), 5.14-5.09 (1H, t, ^3J=4.5Hz, 5′-OH), 4.32-4.23 (1H, m, H-3′), 3.82-3.68 (2H, m, H-5′), 3.20-3.13 (1H, m, H-4′), 2.76-2.66, 2.33-2.25 (2H, m, H-2′), 2.27-2.18 (2H, q, ^3J=8.0Hz, $\underline{CH_2}CH_3$), 1.04-0.98 (3H, t, ^3J=8.0Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.16 (C-4), 150.82 (C-2), 137.60 (C-6), 114.16 (C-5),

71.01 (C-3′), 70.86 (C-1′), 68.25 (C-4′), 55.88 (C-5′), 35.94 (C-2′), 19.93 ($\underline{C}H_2CH_3$), 13.42 ($CH_2\underline{C}H_3$). Mass Spectra ((+ve) FAB) m/z 311 (100%, $[M+Na]^+$), 289 (25%, $[M+H]^+$). Elemental analysis $C_{11}H_{16}N_2O_5S$ requires C 45.8, H 5.6, N 9.7, S 11.1; found C 45.6, H 5.8, N 9.7, S 11.0%.

(*S*)-Sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine (3)

δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.64-7.59 (1H, s, H-6), 5.75-5.67 (1H, dd, ^3J=8.0Hz, 11.0Hz, H-1′), 5.63-5.56 (1H, d, ^3J=4.0Hz, 3′-OH), 5.42-5.38 (1H, t, ^3J=5.0Hz, 5′-OH), 4.33-4.27 (1H, m, H-3′), 3.89-3.69 (2H, m, H-5′), 3.09-3.01 (1H, m, H-4′), 2.54-2.43,2.36-2.25 (2H, m, H-2′), 2.27-2.18 (2H, q, ^3J=8.0Hz, $\underline{CH_2}CH_3$), 1.07-1.01 (3H, t, ^3J=8.0Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.32 (C-4), 150.53 (C-2), 138.2 (C-6), 115.9 (C-5), 82.59 (C-3′), 78.23 (C-1′), 70.66 (C-4′), 58.44 (C-5′), 37.00 (C-2′), 19.64 ($\underline{C}H_2CH_3$), 13.10 ($CH_2\underline{C}H_3$). Mass spectrum ((+ve) FAB) m/z 311 (100%, $[M+Na]^+$), 289 (20%, $[M+H]^+$). Elemental analysis $C_{11}H_{16}N_2O_5S$ requires C 45.8, H 5.6, N 9.7; found C 45.6, H 5.5, N 9.5%.

Reaction of the sulfoxides of 2′-deoxy-5-ethyl-4′-thiouridine with sodium deuteroxide

To a stirred solution of the (*R*)-sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine **(10)** (200mg, 0.69mmol) in deuterium oxide (5ml) was added sodium deuterioxide (40% solution) (200μl). After 18 h the reaction mixture was neutralised with DCl, concentrated *in vacuo*, and purified by column chromatography (SiO_2, dichloromethane/methanol, 9/1, v/v) to yield 2 deuterated products, the (*R*)-sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-uridine **(4)** (64mg, 32%), and the (*R*)-sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-α-L-xylo-uridine **(5)** (30mg, 15%).

(*R*)-Sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-uridine (4)

δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.34-7.32 (1H, s, H-6), 5.94-5.87 (1H, dd, ^3J=7.6Hz, 9.9Hz, *H*-1′), 5.47-5.42 (1H, d, ^3J=5.0Hz, 3′-OH), 5.12-5.09 (1H, t, ^3J=4.5Hz, 5′-OH), 4.32-4.23 (1H, m, H-3′), 3.82-3.68 (2H, m, H-5′), 2.76-2.66, 2.33-2.25 (2H, m, H-2′), 2.27-2.18 (2H, q, ^3J=8.0Hz, $\underline{CH_2}CH_3$), 1.04-0.98 (3H, t, ^3J=8.0Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 167.12 (C-4), 153.47 (C-2), 136.56 (C-6), 114.26 (C-5), 70.34 (C-3′), 68.64 (C-1′), 55.75 (C-5′), 50.23 (C-4′), 35.77 (C-2′), 20.20 ($\underline{C}H_2CH_3$), 13.38 ($CH_2\underline{C}H_3$). Mass spectrum ((+ve) FAB) m/z 334 (15%, $[M+2Na]^+$), 312 (100%, $[M+Na]^+$). Elemental analysis $C_{11}H_{15}N_2O_5SD$ requires C 45.7, H 5.9, N 9.7, S 11.1; found C 45.4, H 5.8, N 9.5, S 10.9%.

(*R*)-Sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-α-L-xylo-uridine (5)

δ_H (DMSO-d_6) 11.56-11.52 (1H, s, NH), 7.51-7.49 (1H, s, H-6), 5.82-5.73 (1H, dd, ^3J=6.4Hz, 12Hz, H-1′), 5.55-5.48 (1H, d, ^3J=3.8Hz, 3′-OH), 5.26-5.21 (1H, t, ^3J=5.0Hz, 5′-OH), 4.59-4.53 (1H, m, H-3′), 3.94-3.82 (2H, m, H-5′), 2.88-2.76, 2.47-2.39 (2H, m, H-2′), 2.25-2.20 (2H, q, ^3J=7.4Hz, $\underline{CH_2}CH_3$), 1.06-0.98 (3H, t, ^3J=7.4Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.13 (C-4), 151.00 (C-2), 138.42 (C-6), 113.52 (C-5), 78.95 (C-3′), 67.95 (C-1′), 67.28 (C-4′), 57.37 (C-5′), 36.71 (C-2′), 19.76 ($\underline{C}H_2CH_3$), 13.30 ($CH_2\underline{C}H_3$). Mass spectrum

((+ve) FAB) m/z 312 (15%, $[M+Na]^+$), 290 (100%, $[M+H]^+$). Elemental analysis $C_{11}H_{15}N_2O_5SD$ requires C 45.7, H 5.9, N 9.7, S 11.1; found C 45.4, H 5.9, N 9.5, S 10.9%.

Using the method outlined above the (*S*)-sulfoxide of 2′-deoxy-5-ethyl-4′-thiouridine **(3)** (130mg, 0.45mmol) was dissolved in deuterium oxide (5ml) and reacted with sodium deuteroxide (40% solution) (200µl). Purification of the reaction mixture by column chromatography (SiO_2, dichloromethane/methanol, 8/1, v/v) yielded 2 deuteriated products as white powders, the (*S*)-sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-uridine **(6)** (34mg, 26%), and the (*S*)-sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-α-L-xylo-uridine **(7)** (26mg, 20%).

(*S*)-Sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-xylouridine (6)

δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.58-7.55 (1H, s, H-6), 5.71-5.65 (1H, dd, ^3J=7.7Hz, 9.6Hz, H-1′), 5.61-5.57 (1H, d, ^3J=3.7Hz, 3′-OH), 5.42-5.38 (1H, t, ^3J=4.8Hz, 5′-OH), 4.29-4.23 (1H, m, H-3′), 3.89-3.68 (2H, m, H-5′), 2.54-2.27 (2H, m, H-2′), 2.27-2.18 (2H, q, ^3J=7.3Hz, $\underline{CH_2}CH_3$), 1.04-0.98 (3H, t, ^3J=7.3Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.48 (C-4), 150.54 (C-2), 138.21 (C-6), 115.94 (C-5), 82.64 (C-3′), 70.66 (C-1′), 67.52 (C-4′), 58.34 (C-5′), 37.00 (C-2′), 19.65 ($\underline{C}H_2CH_3$), 13.11 ($CH_2\underline{C}H_3$). Mass spectrum ((+ve) FAB) m/z 334 (15%, $[M+2Na]^+$), 312 (100%, $[M+Na]^+$). Elemental analysis $C_{11}H_{15}N_2O_5SD$ requires C 45.7, H 5.9, N 9.7, S 11.1; found C 45.6, H 5.8, N 9.7, S 11.0%.

(*S*)-Sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-α-L-xylo-uridine (7)

δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.73-7.71 (1H, s, H-6), 5.47-5.40 (1H, dd, ^3J=8.4Hz, 11.0Hz, H-1′), 5.20-5.16 (1H, d, ^3J=4.4Hz, 3′-OH), 4.98-4.94 (1H, t, ^3J=4.0Hz, 5′-OH), 4.62-4.57 (1H, m, H-3′), 3.99-3.72 (2H, m, H-5′), 2.40-2.27 (2H, m, H-2′), 2.27-2.18 (2H, q, ^3J=7.4Hz, $\underline{CH_2}CH_3$), 1.04-0.98 (3H, t, ^3J=7.4Hz, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.31 (C-4), 150.41 (C-2), 138.64 (C-6), 115.52 (C-5), 87.87 (C-3′), 73.93 (C-1′), 54.72 (C-5′), 50.92 (C-4′), 37.00 (C-2′), 19.65 ($\underline{C}H_2CH_3$), 13.11 ($CH_2\underline{C}H_3$). Accurate Mass $C_{11}H_{15}N_2O_5SDNa$ requires 312.0749; found 312.0740.

2′-Deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-uridine (8)

Trifluoroacetic acid (561µl, 4.26mmol) and trimethylsilyl bromide (TMSBr) (328µl, 4.26 mmol) were added to the (*R*)-sulfoxide of 2′-deoxy-4′-deuterio-5-ethyl-4′-thiouridine **(4)** (246mg, 0.85mmol) was added. The reaction mixture showed no starting material after 20 minutes (TLC dichloromethane/methanol, 6/1, v/v). It was then quenched with saturated aqueous sodium bicarbonate solution and concentrated *in vacuo* to dryness to give a white solid which was purified by column chromatography (SiO_2, dichloromethane/methanol, 6/1, v/v) to yield the 2′-deoxy-4′-deuterio-5-ethyl-4′-thio-β-D-uridine **(8)** as a white powder (125mg, 54%).

δ_H (DMSO-d_6) 11.29-11.26 (1H, bs, NH), 7.78-7.75 (1H, s, H-6), 6.27-6.23 (1H, dd, ^3J=6.7Hz , 7.7Hz, H-1′), 5.25-5.22 (1H, d, 3′-OH), 5.20-5.18 (1H, m, 5′-OH), 4.32-4.27 (1H, m, H-3′), 3.58-3.52 (2H, m, H-5′), 2.28-

2.06 (4H, m, H-2′, $\underline{CH_2}CH_3$), 1.02-0.97 (3H, t, $CH_2\underline{CH_3}$). δ_C (DMSO-d_6) 163.5 (C-4), 150.7 (C-2), 138.65 (C-6), 116.72 (C-5), 76.32 (C-3′), 65.20 (C-5′), 63.07 (C-1′), 43.72 (C-2′), 22.11 ($\underline{C}H_2CH_3$), 14.12 ($CH_2\underline{C}H_3$). Mass spectrum ((+ve) FAB) m/z 312 (27%, $[M+K]^+$), 296 (100%, $[M+Na]^+$), 274 (40%, $[M+H]^+$). Elemental Analysis $C_{11}H_{15}N_2O_4SD$ requires C 48.3, H 6.3, N 10.3; found C 48.2, H 6.2, N 10.4%.

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