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Preparation, structural elucidation and reactions of benzyl 2-deoxy-3,5-di-*O*-methyl-1,4-dithio-L-*threo*-pentofuranoside and synthesis of the corresponding 2′-deoxy-4′-thionucleosides [1,2]

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Abstract

Benzyl 2-deoxy-3,5-di-*O*-methyl-1,4-dithio-L-*threo*-pentofuranoside (**5**) is synthesized in five steps starting with 2-deoxy-D-ribose. The anomers **5**α and **5**β are separated and their configuration is unequivocally assigned by use of NOE measurements. 2-Deoxy-3,5-di-*O*-methyl-4-thio-L-*threo*-pentofuranose is obtained from **5** and mercuric 4-nitrobenzoate. The corresponding nucleosides are prepared from **5** and bis-(trimethylsilyl)uracil or bis-(trimethylsilyl)thymine in the presence of *N*-iodosuccinimide.

Keywords: 2-Deoxy-1,4-dithio-L-*threo*-pentofuranosides; 2-Deoxy-4′-thio-L-*threo*-nucleosides; Configuration absolute; NOE-measurements

1. Introduction

In continuation of our studies on semicyclic thioacetals we became interested in the synthesis and reactions of this type of compounds which are derived from chiral natural products [1] and, in particular, 1,4-dithiofuranosides [2]. These should not only exhibit an interesting chemical behaviour but also open up a route to the corresponding 4′-thionucleosides which have found widespread interest in the last decade with respect to their remarkable physiological properties, i.e., antiviral [3,4] and antitumor [5,6] activities.

2. Results and discussion

*Derivatives of 2-deoxy-4-thio-*L-threo*-pentofuranose.*—Following a literature procedure [7] we obtained methyl 2-deoxy-D-*erythro*-pentofuranoside (**1**) from 2-deoxy-D-ribose as a 1:1 mixture of α and β anomers in quantitative yield. The unprotected hydroxyl groups of **1** were deprotonated with sodium hydride in dimethylformamide and alkylated with

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[1] Thiosugars, Part 1.

[2] Dedicated to Professor Hans Paulsen on the occasion of his 75th birthday.

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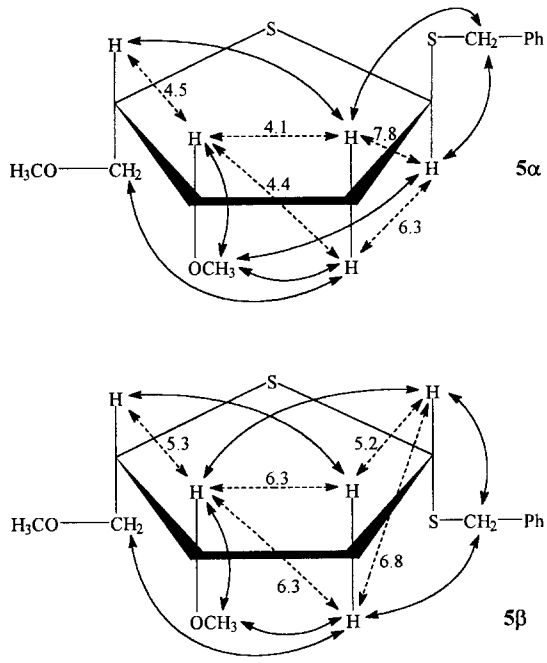
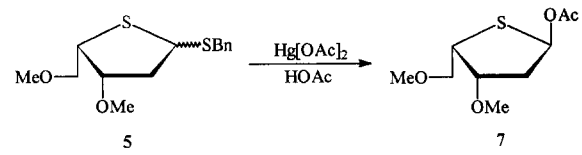


Fig. 1. Demonstration of $^{1}H,^{1}H$–^{3}J-couplings (---) and NOEs (↔) of **5**α and **5**β.

iodomethane to give 59% of the methoxy derivative **2**. Acid-catalyzed reaction of **2** with phenylmethanethiol gave a yield of 84% of the open chain thioacetal **3**, which was then tosylated in the 4-position. The tosylate **4** needed not to be isolated but could be converted into the desired benzyl 2-deoxy-1,4-dithio-L-*threo*-pentofuranoside (**5**) without intermediate purification by boiling under reflux with barium carbonate and sodium iodide in acetone (Scheme 1).

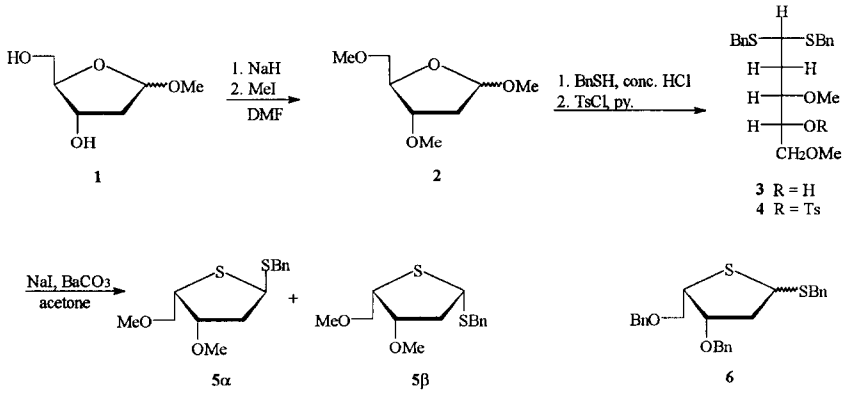
The yield of this latter step was only moderate (35%) and the two anomers **5**α and **5**β were formed as a 10:1 mixture. Column chromatography on silica gel afforded **5**α as a pure isomer whereas **5**β could only be enriched.



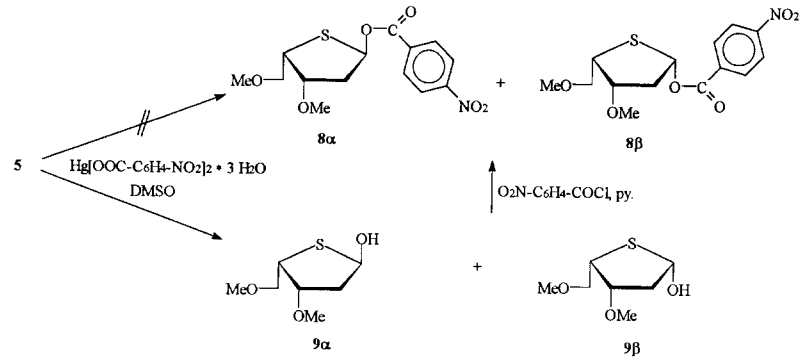
Scheme 2.

While this reaction sequence seems straightforward and, in fact, works quite well, the mechanism of the last step, i.e. the ring closure of **4** to **5**, is complicated and not unequivocally clear. The type of cyclization is well known and has, for instance, been applied for the preparation of the benzyloxy compound **6** [8]. However, one cannot without consideration be sure that inversion of configuration occurs once and only once during the cyclization. Instead of a single intramolecular S_N2-reaction with tosylate as the leaving group, a two-step reaction could take place consisting of, first a substitution of tosylate by iodide (S_N2) and subsequently the intramolecular cyclization (S_N2) which would result in a D-*erythro* configuration of the product. Sodium iodide is in fact an essential constituent. The reaction does not take place in its absence as we have shown in a counter-experiment.

We have, therefore, very carefully studied the stereochemistry of **5**, a substance which, unfortunately, does not crystallize. One-dimensional ^{1}H and ^{13}C NMR spectra even if recorded at high resolution (500/125 MHz) do not allow to discriminate between the L-*threo* and the D-*erythro* configuration. This also holds for compound **6** the configuration of which has been arbitrarily, though correctly, assigned without convincing reasoning about its ^{1}H NMR spectrum [8]. Applying 2D-NMR techniques we were able to prove unequivocally the proposed configuration of **5** and, moreover, to assign the anomeric



Scheme 1.



Scheme 3.

structures of **5**α and **5**β. Fig. 1 illustrates the NOE interactions which we observed for the two anomers.

They are in agreement only with the structures shown and definitely demonstrate the configuration at C-1 and C-4 of **5**α and **5**β. Especially the long-range interaction between H-2 and H-4 does only exist in the L-*threo* but not in the D-*erythro* series. On the basis of established configurations of **5**α and **5**β all ^3J couplings that occur in the molecules could also be interpreted in a consistent way (see Section 3) which was *per se* not possible because of the flexibility of the thiolane ring present in the 4-thiofuranoses.

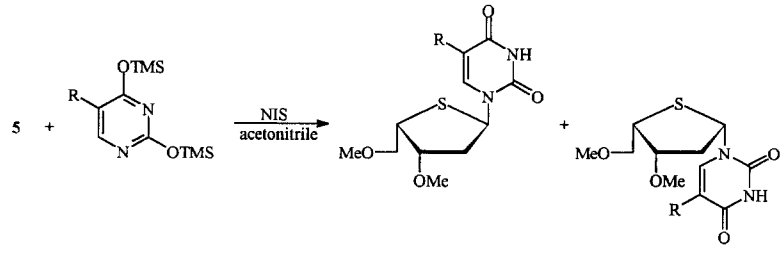
The mixture of benzyl thioglycosides **5** was transformed into the acetate **7** by means of mercuric acetate. Although only one anomer was formed no crystals could be obtained. In the case of **7** no NOE was detected. The coupling constants of H-1, H-2, and H-3 are however indicative of the α-anomeric structure (Scheme 2).

Reaction of **5** with mercuric 4-nitrobenzoate did not yield the 4-nitrobenzoyl aldose **8** (Scheme 3). Instead the free 4-thiofuranose **9** was obtained with 44% yield in an anomeric ratio of **9**α:**9**β = 1:6. The formation of **9** can be explained by the presence of three molecules of hydrate water in the mercuric 4-nitrobenzoate (see Section 3). In order to obtain a higher yield of **9** we performed a reaction of **5** with mercuric chloride plus mercuric oxide under the Seebach conditions [9]. However, only decomposition products were formed.

Acylation of **9** with 4-nitrobenzoyl chloride finally afforded 49% of **8**. In the case of **8** we were able to observe at 500 MHz the NOE between the protons H-2 and H-4 and corroborate the L-*threo* configuration of **8**, **9** and **5**. Again all ^3J coupling constants were in agreement with the structure of **8** and allowed the assignment of the two anomers **8**α and **8**β.

Formation of nucleosides.—The coupling of 4′-thiofuranosides has been known for 30 years. Reist et al. [10] described, for instance, the synthesis of 4′-thioadenosine and 4′-thio-L-adenosine in 1964. However, the numerous number of steps which are needed to achieve the required 4-thiofuranoside and correspondingly, the low yields, are disadvantageous. From the preparative point of view the 1,4-dithiofuranosides are more valuable as starting compounds since they can be prepared in considerably shorter reaction sequences and accordingly, higher overall yields.

The key step for the preparation of 4′-thiopyrimidine nucleosides from 1,4-dithiofuranosides consists in the coupling of the sugar moiety with a trimethylsilyl-protected pyrimidine base. According to the lit-



Scheme 4.

erature the cleavage of the exocyclic carbon–sulfur bond and the subsequent connection of the pyrimidine base can be performed with mercuric bromide [3], mercuric acetate plus trimethylsilyl triflate [11], *N*-iodosuccinimide (NIS) [4,12,13], or with bromine [3].

Starting with benzyl 2-deoxy-3,5-di-*O*-methyl-1,4-dithio-L-*threo*-pentofuranoside (**5**) we have prepared the 2′-deoxy-4′-thio-L-*threo*-nucleosides **12** and **13**. Coupling of **5** with 2,4-bis-*O*-(trimethylsilyl)uracil (**10**) in the presence of mercuric bromide and cadmium carbonate according to Dyson et al. [3] was not successful. We obtained, however, the methylated 2′-deoxy-4′-thio-L-*threo*-uridine (**12**) in 54% yield from **5** and **10** in the presence of NIS in dry acetonitrile. The 1:1 mixture could be completely separated into the two pure anomers **12**α and **12**β by column chromatography. In the same way 2′-deoxy-4′-thio-L-*threo*-thymidine (**13**) was obtained from 2,4-bis-*O*-(trimethylsilyl)thymine (**11**) in 71% yield. In this case a complete separation of the anomers (**13**α:**13**β = 3:2) was not possible. We did not succeed in the preparation of 2′-deoxy-4′-thio-L-*threo*-cytidine in an analogous reaction but recovered the starting material (Scheme 4).

The structural elucidation and assignment of **12**α and **12**β as well as of **13**α and **13**β was achieved by NMR spectroscopy, in particular by virtue of the observed NOEs. The anomers **12**β and **13**β clearly exhibited NOEs between H-6 of the nucleobase and the protons of the 3′-OCH_3, 5′-OCH_3, and 5′-CH_2 groups, and one of the two 2′-CH_2 protons. These interactions are only possible if **12**β and **13**β represent the β anomers. NOEs between H-6 of the nucleobase and H-3′, H-4′, and the other H-2′ of the sugar moiety are indicative of the α anomers **12**α and **13**α, respectively (Fig. 2).

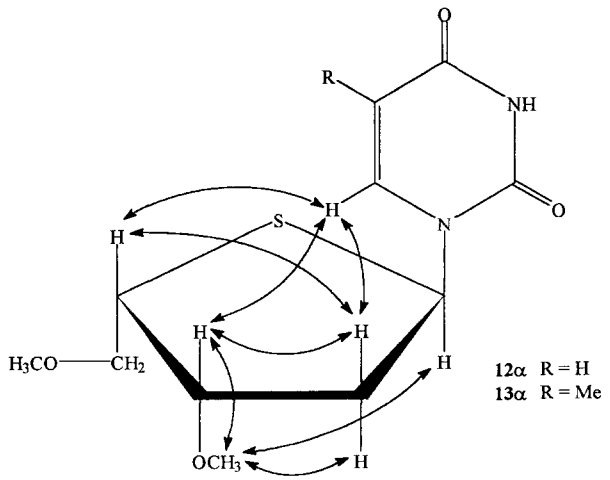


Fig. 2. NOEs (↔) of **12**α and **13**β.

3. Experimental

General Procedures.—Melting points were determined by the use of an Electrothermal apparatus (values are corrected). Boiling points were determined during distillation (values are corrected). IR spectra were measured with an ATI Mattson Genesis spectrometer. NMR spectra were recorded with Bruker AMX 400 and DRX 500 spectrometers. Chemical shifts (ppm) are related to Me_4Si (^1H) and $CDCl_3$ (^{13}C, δ 77.05). Standard correlation techniques were used for assignments. Mass spectra were measured on Varian CH 7 and VG Analytical 70–250 S (HRMS) spectrometers. TLC was carried out on Merck PF_{254} foils (detection: UV light, iodine vapour, or EtOH/H_2SO_4 spray/200 °C), and column chromatography on Merck Kieselgel 60 (70–230 mesh). Solvents were purified and dried according to standard laboratory procedures [14].

Methyl 2-deoxy-D-erythro-*pentofuranoside* (*1*) *[7].* —Acetyl chloride (0.33 mL) was added to 415 mL dry MeOH under nitrogen and the solution was stirred for 1 h at room temperature. Then 2-deoxy-D-ribose (Merck, 11.88 g, 88 mmol) was added and the mixture was stirred for 15 min at room temperature. The acidic solution was neutralized by stirring for another 40 min with Na_2CO_3 (13.20 g). After filtration and evaporation, the residue was extracted several times with EtOAc. Evaporation of the extracts in vacuo gave a quantitative yield (13.00 g) of **1**, isolated as a light yellow syrup (1:1 mixture of anomers). IR: ν 3390, 2929, 1447, 1370, 1209, 1093, 950, 863 cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6): **1**α: δ 1.64 (ddd, 1 H, $J_{2a,1}$ 2.4, $J_{2a,3}$ 5.0, $J_{2a,2b}$ 13.7 Hz, H-2_a), 2.26 (ddd, 1 H, $J_{2b,1}$ 5.8, $J_{2b,3}$ 8.2 Hz, H-2_b), 3.24 (s, 3 H, OCH_3), 3.35–3.42 (m, 1 H, H-5_a), 3.50 (ddd, 1 H, $J_{5b,4}$ 3.5, $J_{5b,OH}$ 5.6, $J_{5b,5a}$ 11.8 Hz, H-5_b), 3.66–3.72 (m, 1 H, H-4), 3.92 (dddd, 1 H, $J_{3,4}$ 5.2, $J_{3,OH}$ 5.2 Hz, H-3), 4.59 (dd, 1 H, $J_{OH,5a}$ 5.7 Hz, HO-5), 4.83 (d, 1 H, HO-3), 4.90 (dd, 1 H, H-1); **1**β: δ 1.88 (ddd, 1 H, $J_{2a,1}$ 5.5, $J_{2a,3}$ 5.4, $J_{2a,2b}$ 13.3 Hz, H-2_a), 1.98 (ddd, 1 H, $J_{2b,1}$ 2.5, $J_{2b,3}$ 6.6 Hz, H-2_b), 3.20 (s, 3 H, OCH_3), 3.35–3.42 (m, 2 H, H-5_a,5_b), 3.66–3.72 (m, 1 H, H-4), 4.10 (dddd, 1 H, $J_{3,4}$ 5.3, $J_{3,OH}$ 4.4 Hz, H-3), 4.62 (dd, 1 H, $J_{OH,5a}$ 5.4, $J_{OH,5b}$ 6.1 Hz, HO-5), 4.95 (d, 1 H, HO-3), 4.98 (dd, 1 H, H-1); ^{13}C NMR (100 MHz, Me_2SO-d_6): **1**α: δ 41.68 (C-2), 55.12 (OCH_3), 66.22 (C-5), 70.92 (C-3), 85.80

(C-4), 104.96 (C-1); **1**β: δ 41.93 (C-2), 55.08 (OCH_3), 64.01 (C-5), 71.68 (C-3), 87.82 (C-4), 105.41 (C-1).

Methyl 2-deoxy-3,5-di-O-methyl-D-erythro-pentofuranoside (**2**).—NaH (Merck, 9.30 g, 388 mmol) was stirred for 2 h at room temperature in 180 mL dry dimethylformamide. A solution of **1** (13.00 g, 88 mmol) in 80 mL dry dimethylformamide was dropped into the suspension at 0 °C and the brown reaction mixture was stirred for 1 h at room temperature. After cooling to 0 °C, methyl iodide (25 mL, 400 mmol) was added dropwise. MeOH (100 mL) was added 4 h later. The solvents were distilled off in vacuo and the residue extracted with 10:1 petroleum ether–EtOAc. The extract was concentrated and the product distilled in vacuo to yield **2**, isolated as a colourless liquid (9.10 g, 59%), bp 36 °C/0.02 Torr. IR: ν 2927, 2829, 1450, 1376, 1247, 1110, 1045, 980, 927, 864, 817, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): **2**β: δ 2.00 (ddd, 1 H, $J_{2a,1}$ 1.0, $J_{2a,3}$ 2.2, $J_{2a,2b}$ 14.7 Hz, H-2), 2.19 (ddd, 1 H, $J_{2b,1}$ 5.6, $J_{2b,3}$ 6.8 Hz, H-2), 3.35 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.48–3.54 (m, 2 H, H-5), 3.77 (ddd, 1 H, $J_{3,4}$ 4.4 Hz, H-3), 4.17 (ddd, 1 H, $J_{4,5a} = J_{4,5b} = 4.6$ Hz, H-4), 5.07 (dd, 1 H, H-1); **2**α: δ 2.06 (ddd, 1 H, $J_{2a,1}$ 5.7, $J_{2a,3}$ 5.7, $J_{2a,2b}$ 13.8 Hz, H-2), 2.33 (ddd, 1 H, $J_{2b,1}$ 2.0, $J_{2b,3}$ 6.8 Hz, H-2), 3.32 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.43–3.47 (m, 2 H, H-5), 3.91 (ddd, 1 H, $J_{3,4}$ 3.8 Hz, H-3), 4.12 (ddd, 1 H, $J_{4,5a}$ 6.3, $J_{4,5b}$ 6.4 Hz, H-4), 5.06–5.09 (m, 1 H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): **2**β: δ 38.44 (C-2), 55.22 (OCH_3), 57.49 (OCH_3), 59.40 (OCH_3), 73.21 (C-5), 81.41 (C-3), 82.01 (C-4), 105.29 (C-1); **2**α: δ 38.95 (C-2), 55.49 (OCH_3), 57.18 (OCH_3), 59.21 (OCH_3), 74.77 (C-5), 81.97 (C-3), 82.40 (C-4), 105.45 (C-1); MS (70 eV): *m/z* (%) 175 (0.1) [M^+–H], 145 (5), 131 (37), 113 (5), 101 (15), 99 (47), 87 (9), 81 (7), 75 (10), 73 (19), 72 (13), 71 (100), 59 (29), 58 (12), 53 (5).

2-Deoxy-3,5-di-O-methyl-D-erythro-pentose dibenzyl dithioacetal (**3**).—A solution of **2** (16.82 g, 95 mmol), 50 mL phenylmethanethiol, and 31 mL concentrated aqueous HCl was stirred for 48 h at room temperature. Water (250 mL) was added and the mixture extracted several times with $CHCl_3$. The combined extracts were washed with saturated $NaHCO_3$ and water, dried, and concentrated. Column chromatography of the residue ($CHCl_3$, R_f 0.05) yielded **3**, isolated as a yellow syrup (31.32 g, 84%); $[\alpha]_D^{20}$ −96.3° (*c* 1.0, $CHCl_3$); IR: ν 3452, 3062, 3028, 2920, 2826, 1602, 1496, 1455, 1326, 1196, 1102, 992, 966, 914, 880, 763, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.80 (ddd, 1 H, $J_{2a,1}$ 10.3, $J_{2a,3}$ 2.8, $J_{2a,2b}$ 14.7 Hz, H-2), 2.03 (ddd, 1 H, $J_{2b,1}$ 4.2, $J_{2b,3}$ 9.9 Hz, H-2), 3.06 (s, 3 H, OCH_3), 3.28–3.30 (m, 3 H, H-3, 2x H-5), 3.33–3.37 (m, 1 H, H-4), 3.35 (s, 3 H, OCH_3), 3.73 (dd, 1 H, H-1), 3.72/3.83 (AB-system, 2 H, J_{AB} 13.2 Hz, SCH_2Ph), 3.77/3.81 (AB-system, 2 H, SCH_2Ph), 7.14–7.33 (m, 10 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.33 (SCH_2Ph), 37.04 (C-2), 46.79 (C-1), 58.22 (OCH_3), 59.10 (OCH_3), 71.02 (C-4), 73.14 (C-5), 78.99 (C-1), 126.89, 126.99, 128.47, 128.54, 129.11, and 129.21 ($C_{Ar}H$), 138.29 and 138.40 (C_q); MS (70 eV): *m/z* (%) 392 (0.8) [M^+], 301 (0.6) [M^+–C_7H_7], 269 (0.7) [M^+–SCH_2Ph], 268 (0.8) [M^+–$HSCH_2Ph$], 146 (5), 145 (64), 119 (9), 113 (22), 92 (9), 91 (100) [$C_7H_7^+$], 89 (13), 87 (24), 71 (6), 65 (9), 59 (15), 45 (58). Anal. Calcd for $C_{21}H_{28}O_3S_2$ (392.58): C, 64.25; H, 7.19; S, 16.34. Found: C, 63.45; H, 7.30; S, 16.15.

2-Deoxy-3,5-di-O-methyl-4-O-tosyl-D-erythro-pentose dibenzyl dithioacetal (**4**).—Thioacetal **3** (26.38 g, 67 mmol) was dissolved in 150 mL dry pyridine under nitrogen. Tosyl chloride (32.13 g, 169 mmol) was added on cooling and the mixture stirred for 48 h at room temperature. Water (200 mL) was added and the stirring was continued for 1 h. The solution was extracted with $CHCl_3$, the combined extracts were washed with dilute HCl and saturated $NaHCO_3$, dried, and evaporated in vacuo. Yield: 33.80 g (92%) **4**, isolated as a red syrup. ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (ddd, 1 H, $J_{2a,1}$ 11.0, $J_{2a,3}$ 2.7, $J_{2a,2b}$ 14.6 Hz, H-2), 1.91 (ddd, 1 H, $J_{2b,1}$ 3.7, $J_{2b,3}$ 10.6 Hz, H-2), 2.40 (s, 3 H, CH_3), 2.92 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $J_{5a,4}$ 4.9, $J_{5a,5b}$ 10.9 Hz, H-5), 3.44 (dd, 1 H, $J_{5b,4}$ 5.8 Hz, H-5), 3.52 (ddd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 3.61 (dd, 1 H, H-1), 3.62–3.78 (m, 4 H, SCH_2Ph), 4.61 (ddd, 1 H, H-4), 7.07–7.80 (m, 14 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.62 (CH_3), 34.22 (SCH_2Ph), 35.11 (SCH_2Ph), 37.19 (C-2), 46.34 (C-1), 58.35 (OCH_3), 59.02 (OCH_3), 70.57 (C-5), 77.46 (C-3), 81.05 (C-4), 126.90, 127.00, 128.47, 128.53, 129.06, 129.20, and 129.53 ($C_{Ar}H$), 134.28, 138.09, 138.16, and 144.53 (C_q).

Benzyl 2-deoxy-3,5-di-O-methyl-1,4-dithio-L-threo-pentofuranoside (**5**).—A solution of tosylate **4** (6.56 g, 12 mmol), sodium iodide (19.90 g, 133 mmol), and barium carbonate (9.60 g, 49 mmol) in dry acetone (160 mL) was heated to reflux under nitrogen for 48 h. The white precipitate was filtered, the acetone distilled off, and the residue dissolved in water (70 mL). The aqueous solution was extracted

with $CHCl_3$ several times. After evaporation, the residue was chromatographed (20:1 $CHCl_3$–EtOAc, R_f 0.35 [**5**α], R_f 0.29 [**5**β]), yielding **5**, isolated as a yellow syrup (1.20 g, 35%; **5**α:**5**β = 10:1). IR: ν 3061, 3028, 2826, 1601, 1495, 1445, 1353, 1194, 1103, 1030, 979, 912, 769, 703, 486 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): **5**α: δ 1.92 (ddd, 1 H, $J_{2a,1}$ 7.8, $J_{2a,3}$ 4.1, $J_{2a,2b}$ 13.4 Hz, H-2), 2.46 (ddd, 1 H, $J_{2b,1}$ 6.3, $J_{2b,3}$ 4.4 Hz, H-2), 3.33 (s, 3 H, 3-OCH_3), 3.36 (s, 3 H, 5-OCH_3), 3.43 (dd, 1 H, $J_{5a,4}$ 7.0, $J_{5a,5b}$ 9.6 Hz, H-5), 3.71 (dd, 1 H, $J_{5b,4}$ 6.7 Hz, H-5), 3.81 (ddd, 1 H, $J_{4,3}$ 4.5 Hz, H-4), 3.85 (s, 2 H, SCH_2Ph), 4.08 (ddd, 1 H, H-3), 4.44 (dd, 1 H, H-1), 7.22–7.34 (m, 5 H, ArH); **5**β: δ 2.20 (ddd, 1 H, $J_{2a,1}$ 5.9, $J_{2a,3}$ 6.4, $J_{2a,2b}$ 13.6 Hz, H-2), 2.32 (ddd, 1 H, $J_{2b,1}$ 7.4, $J_{2b,3}$ 4.9 Hz, H-2), 3.36 (s, 3 H, 3-OCH_3), 3.39 (s, 3 H, 5-OCH_3), 3.54 (dd, 1 H, $J_{5a,4}$ 7.6, $J_{5a,5b}$ 9.5 Hz, H-5), 3.65 (ddd, 1 H, $J_{4,3}$ 5.3, $J_{4,5b}$ 5.5 Hz, H-4), 3.79–3.82 (m, 1 H, H-5), 3.83 (s, 2 H, SCH_2Ph), 3.98 (ddd, 1 H, H-3), 4.28 (dd, 1 H, H-1), 7.22–7.34 (m, 5 H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$): **5**α: δ 36.70 (SCH_2Ph), 40.61 (C-2), 48.26 (C-1), 50.77 (C-4), 56.98 (3-OCH_3), 58.59 (5-OCH_3), 71.36 (C-5), 82.61 (C-3), 126.68, 128.17, and 128.48 ($C_{Ar}H$), 137.36 (C_q); **5**β: δ 36.87 (SCH_2Ph), 39.41 (C-2), 47.26 (C-1), 50.45 (C-4), 57.01 (3-OCH_3), 58.69 (5-OCH_3), 72.21 (C-5), 82.91 (C-3), 126.63, 128.11, and 128.56 ($C_{Ar}H$), 137.29 (C_q); MS (70 eV): *m/z* (%) 284 (3) [M^+], 193 (3) [M^+–C_7H_7], 161 (14) [M^+–$PhCH_2S$], 160 (3) [M^+–$PhCH_2SH$], 129 (24), 115 (5), 97 (24), 91 (24) [$C_7H_7^+$], 85 (4), 71 (5), 45 (100); HRMS Calcd for $C_{14}H_{20}O_2S_2$: 284.0905; $C_7H_{13}O_2S_2$: 193.0357; $C_7H_{13}O_2S$: 161.0636. Found: 284.0907; 193.0428; 161.0626.

*1-O-Acetyl-2-deoxy-3,5-di-O-methyl-4-thio-α-*L-threo-*pentofuranose* (**7**).—Compound **1** (1.20 g, 4.2 mmol) and mercuric acetate (2.86 g, 9.0 mmol) were dissolved in glacial HOAc (38 mL) and the solution was stirred for 24 h at 50 °C [11,15,16]. The precipitate was removed by filtration through Celite, and the filtrate was extracted several times with $CHCl_3$. The combined extracts were washed with water, saturated aqueous $NaHCO_3$, 5% aqueous potassium cyanide (pH 7), and water. After drying, $CHCl_3$ was distilled off in vacuo and the residue was chromatographed (20:1 toluene–MeOH, R_f 0.2), yielding **7**, isolated as a yellow syrup (0.312 g, 34%); $[\alpha]_D^{20}$ −229.6° (*c* 1.0, $CHCl_3$); IR: ν 2982, 2935, 2890, 2828, 1742 (C=O), 1671, 1455, 1373, 1292, 1233, 1114, 1018, 985, 957, 854, 745, 644, 483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.05 (s, 3 H, $COCH_3$), 2.26 (ddd, 1 H, $J_{2a,1}$ 2.8, $J_{2a,3}$ 5.2, $J_{2a,2b}$ 13.5 Hz, H-2), 2.39 (ddd, 1 H, $J_{2b,1}$ 5.6, $J_{2b,3}$ 8.7 Hz, H-2), 3.37 (s, 3 H, OCH_3), 3.37–3.41 (m, 1 H, H-5), 3.42 (s, 3 H, OCH_3), 3.66–3.68 (m, 1 H, H-5), 3.69–3.73 (m, 1 H, H-4), 4.21 (ddd, 1 H, $J_{3,4}$ 5.4 Hz, H-3), 6.05 (dd, 1 H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.17 ($COCH_3$), 39.13 (C-2), 47.85 (C-4), 58.15 (OCH_3), 59.20 (OCH_3), 72.20 (C-5), 78.00 (C-1), 82.48 (C-3), 170.38 (CO); MS (70 eV): *m/z* (%) 220 (2) [M^+], 161 (2), [M^+–CH_3CO_2], 160 (16) [M^+–CH_3CO_2H], 145 (5), 129 (7), 128 (21), 127 (9), 116 (8), 115 (58), 104 (7), 102 (10), 101 (22), 97 (14), 87 (24), 86 (5), 85 (18), 84 (13), 75 (7), 71 (19), 60 (9), 59 (26), 45 (100). HRMS Calcd for $C_9H_{16}O_4S$: 220.0769. Found: 220.0755.

Mercuric 4-nitrobenzoate.—NaOH (0.95 g, 24 mmol) was dissolved in water (100 mL) and neutralized with 4-nitrobenzoic acid (4.55 g, 27 mmol). Excess acid was filtered off and a solution of mercuric acetate (5.21 g, 16 mmol) in water (100 mL) was added. The white precipitate was filtered with suction, washed with cold aqueous 80% EtOH and recrystallized from boiling water. Yield: 6.91 g (95%), white solid, mp 246 °C. IR: ν 3426, 1619, 1585 (NO_2), 1509, 1392, 1351 (NO_2), 1322, 1106, 881, 831, 800, 726, 511 cm^{-1}; ^1H NMR (400 MHz, Me_2SO-d_6): δ 3.32 (s, water), 8.21/8.32 (AB-system, 4 H, J_{AB} 8.7 Hz, ArH); ^{13}C NMR (62 MHz, Me_2SO-d_6): δ 135.52 (C-3,5), 131.07 (C-2,6), 139.12 (C-1), 149.39 (C-4), 167.52 (Ar–CO_2); MS (70 eV): *m/z* (%) 534 (0.15), 533 (0.15), 532 (0.15) [M^+]; 420 (7), 418 (56), 417 (8), 416 (40), 340 (6), 339 (7), 338 (42), 291 (10), 290 (35), 275 (11), 247 (6), 204 (4) [$^{204}Hg^+$]; 202 (15) [$^{202}Hg^+$]; 201 (22) [$^{201}Hg^+$]; 200 (17) [$^{200}Hg^+$]; 199 (8) [$^{199}Hg^+$]; 198 (3) [$^{198}Hg^+$]; 168 (13), 167 (48), 154 (13), 150 (8), 122 (26) [$C_6H_4NO_2^+$]; 121 (35), 109 (17), 98 (10), 92 (9), 81 (12), 76 (22), 75 (27), 65 (100), 52 (22), 51 (60), 50 (18). Anal. Calcd for $C_{14}H_8HgN_2O_8 \cdot 3H_2O$ (586.86): C, 28.65; H, 2.40; Hg, 34.18; N, 4.77. Found: C, 28.12; H, 1.84; Hg, 42.20; N, 5.04 (obviously the mercuric 4-nitrobenzoate was contaminated with an inorganic mercury compound).

*2-Deoxy-3,5-di-*O*-methyl-4-thio-*L*-threo-pentofuranose* (**9**).—Compound **1** (0.38 g, 1.3 mmol) and mercuric 4-nitrobenzoate (1.33 g, 2.5 mmol) were dissolved in Me_2SO (60 mL), and the solution was stirred for 24 h at 50 °C. The precipitate was filtered with suction through Celite and the filtrate was extracted with $CHCl_3$. The combined extracts were washed with water, saturated aqueous $NaHCO_3$, aqueous 5% potassium cyanide (pH 7), and water. After drying, $CHCl_3$ was distilled off in vacuo and

the residue was chromatographed (20:1 toluene–MeOH), yielding **9**, isolated as a yellow syrup (0.105 g, 44%; $\alpha:\beta$ = 1:6). IR: ν 3417, 2930, 2828, 1456, 1385, 1311, 1195, 1102, 980, 959, 896, 828, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): **9**α: δ 2.18 (ddd, 1 H, $J_{2a,1}$ 3.4, $J_{2a,3}$ 4.7, $J_{2a,2b}$ 13.3 Hz, H-2), 2.37 (ddd, 1 H, $J_{2b,1}$ 5.3, $J_{2b,3}$ 8.0 Hz, H-2), 3.37 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.70 (d, 1 H, $J_{OH,1}$ 9.7 Hz, OH), 4.24 (ddd, 1 H, $J_{3,4}$ 5.2 Hz, H-3), 5.50–5.54 (m, 1 H, H-1); the H-4 and H-5 signals are superimposed by the stronger signals of **9**β. **9**β: δ 1.99 (ddd, 1 H, $J_{2a,1}$ 5.1, $J_{2a,3}$ 3.4, $J_{2a,2b}$ 13.9 Hz, H-2), 2.57 (ddd, 1 H, $J_{2b,1}$ 1.1, $J_{2b,3}$ 2.1 Hz, H-2), 3.40 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.59–3.63 (m, 2 H, H-4,5), 3.69 (d, 1 H, $J_{OH,1}$ 12.2 Hz, OH), 3.85 (dd, 1 H, $J_{5a,4}$ 9.7, $J_{5a,5b}$ 11.3 Hz, H-5), 4.10–4.13 (m, 1 H, H-3), 5.54 (ddd, 1 H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): **9**β: δ 43.76 (C-2), 52.49 (C-4), 57.97 (OCH_3), 58.99 (OCH_3), 71.82 (C-5), 82.39 (C-1), 83.98 (C-3); MS (70 eV): *m/z* (%) 178 (10), [M^+], 161 (1), 160 (11) [$M^+ - H_2O$], 146 (12), 129 (2), 128 (13), 118 (7), 115 (6), 114 (6), 113 (7), 102 (30), 101 (20), 97 (18), 89 (7), 88 (8), 87 (59), 86 (15), 85 (15), 84 (22), 82 (5), 81 (5), 75 (7), 73 (25), 71 (26), 61 (7), 60 (13), 59 (44), 58 (8), 57 (7), 56 (5), 55 (7), 54 (6), 53 (11), 51 (10), 45 (100); HRMS Calcd for $C_7H_{14}O_3S$: 178.0664. Found: 178.0647.

2-Deoxy-3,5-di-O-*methyl-1*-O-*(4-nitrobenzoyl)-4-thio*-L-threo-*pentofuranose* (**8**).—A solution of **9** (57 mg, 0.32 mmol) and 4-nitrobenzoyl chloride (225 mg, 1.21 mmol) in dry pyridine (5 mL) was stirred for 24 h at room temperature [17]. Then water (5 mL) was added and stirring was continued for another 30 min. Subsequently water (100 mL) was added and the solution extracted several times with $CHCl_3$. The combined extracts were washed twice, each time with 1.5 M H_2SO_4 (100 mL), water (100 mL), and aqueous $NaHCO_3$ (100 mL), and after drying $CHCl_3$ was distilled off. The residue was chromatographed (20:1 $CHCl_3$–EtOAc, R_f 0.35), affording **8**, isolated as a yellow syrup (51 mg, 49%; $\alpha:\beta$ = 1:1). IR: ν 3111, 3080, 3053, 2983, 2930, 2981, 2829, 1726 (CO), 1607, 1529 (NO_2), 1459, 1347 (NO_2), 1271, 1197, 1100, 1013, 984, 875, 785, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): **8**α: δ 2.43 (ddd, 1 H, $J_{2a,1}$ 2.9, $J_{2a,3}$ 5.2, $J_{2a,2b}$ 13.8 Hz, H-2), 2.57 (ddd, 1 H, $J_{2b,1}$ 5.7, $J_{2b,3}$ 8.5 Hz, H-2), 3.39 (s, 3 H, 5-OCH_3), 3.47 (s, 3 H, 3-OCH_3), 3.45–3.49 (m, 1 H, H-5), 3.72 (dd, 1 H, $J_{5b,4}$ 5.5, $J_{5b,5a}$ 9.6 Hz, H-5), 3.79 (ddd, 1 H, $J_{4,3}$ 5.6, $J_{4,5a}$ 7.2 Hz, H-4), 4.32 (ddd, 1 H, H-3), 6.34 (dd, 1 H, H-1), 8.18–8.28 (m, 2 H, ArH), 8.27–8.31 (m, 2 H, ArH); **8**β: δ 2.29 (ddd, 1 H, $J_{2a,1}$ 6.0, $J_{2a,3}$ 4.3, $J_{2a,2b}$ 14.6 Hz, H-2), 2.78 (ddd, 1 H, $J_{2b,1}$ 1.8, $J_{2b,3}$ 3.4 Hz, H-2), 3.38 (s, 3 H, 5-OCH_3), 3.46 (s, 3 H, 3-OCH_3), 3.58 (dd, 1 H, $J_{5a,4}$ 7.1, $J_{5a,5b}$ 9.5 Hz, H-5), 3.72 (ddd, 1 H, $J_{4,3}$ 4.5, $J_{4,5b}$ 6.7 Hz, H-4), 3.90 (dd, 1 H, H-5), 4.17 (ddd, 1 H, H-3), 6.40 (dd, 1 H, H-1), 8.18–8.21 (m, 2 H, ArH), 8.27–8.31 (m, 2 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): **8**α: δ 39.45 (C-2), 48.27 (C-4), 57.08 (3-OCH_3), 59.21 (5-OCH_3), 72.06 (C-5), 80.07 (C-1), 82.58 (C-3), 123.57 and 130.82 ($C_{Ar}H$), 135.16 and 150.71 (C_q), 164.10 (Ar–CO_2); **8**β: δ 39.34 (C-2), 52.52 (C-4), 58.23 (3-OCH_3); 59.12 (5-OCH_3); 71.87 (C-5), 82.05 (C-1), 82.31 (C-3), 123.54 and 130.83 ($C_{Ar}H$); 135.55 and 150.64 (C_q); 164.29 (Ar–CO_2); MS (70 eV): *m/z* (%) 327 (0.3) [M^+]; 167 (32), 160 (35), 151 (7), 150 (32), 145 (4), 142 (6), 129 (12), 128 (59), 127 (29), 121 (23), 116 (9), 115 (54), 113 (7), 108 (6), 104 (14), 103 (5), 102 (12), 101 (15), 99 (7), 98 (10), 97 (100) [$C_5H_5S^+$]; 95 (5), 87 (14), 85 (25), 84 (54), 81 (7), 76 (10), 75 (17), 70 (16), 68 (16), 65 (44), 59 (15), 58 (9), 55 (7), 53 (16), 51 (10), 50 (8), 45 (43).

1-(2-Deoxy-3,5-di-O-*methyl-4-thio*-L-threo-*pentofuranosyl)uracil* (**12**).—Benzyl 2-deoxy-3,5-di-*O*-methyl-1,4-dithio-L-*threo*-pentofuranoside (102 mg, 0.36 mmol) (**5**), 2,4-bis-*O*-(trimethylsilyl)uracil (120 mg) (**10**) [4,12,13] and molecular sieves (20 mg) were added to dry acetonitrile (5 mL), and the solution was stirred at room temperature for 10 min. After both educts were dissolved, *N*-iodosuccinimide (96 mg, 0.43 mmol) was added and stirring was continued for 2 h. Then aqueous 10% sodium thiosulfate (30 mL) was added and the solution was extracted twice with methylene chloride. The combined organic phases were dried over Na_2SO_4 and concentrated. The resulting crude product (anomeric ratio: 1:1) was purified and the anomers were separated by column chromatography (EtOAc). Yields: **12**α: 21 mg (21%), R_f 0.25, isolated as colourless crystals, mp 156 °C; $[\alpha]_D^{20}$ +45.9° (*c* 1.0, $CHCl_3$). **12**β: 24 mg (25%), R_f 0.17, isolated as colourless syrup; $[\alpha]_D^{20}$ 42.5° (*c* 1.0, $CHCl_3$); plus 8 mg (8%) of the anomeric mixture. IR: ν 3463, 3148, 3096, 3013, 2930, 2815, 1705, 1673, 1465, 1422, 1410, 1388, 1366, 1282, 1250, 1171, 1141, 1121, 1108, 1084, 975, 938, 895, 768, 625, 554, 502. **12**α: ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (ddd, 1 H, $J_{2a',1'}$ 9.1, $J_{2a',3'}$ 3.7, $J_{2a',2b'}$ 13.7 Hz, H-2a'), 2.77 (ddd, 1 H, $J_{2b',1'}$ 6.8, $J_{2b',3'}$ 3.5 Hz, H-2b'), 3.39 (s, 6 H, OCH_3), 3.52 (dd, 1 H, $J_{5a',4'}$ 7.2, $J_{5a',5b'}$ 9.6 Hz, H-5a'), 3.77 (dd, 1 H, $J_{5b',4'}$ 6.3 Hz, H-5b'), 3.98 (ddd, 1 H, $J_{4',3'}$ 3.8 Hz, H-4'), 4.09 (ddd, 1 H, H-3'), 5.81 (dd, 1 H, $J_{5,6}$ 8.2, $J_{5,NH}$ 1.8 Hz, H-5), 6.41 (dd, 1 H, H-1'),

7.75 (d, 1 H, H-6), 9.10 (bs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.79 (C-2′), 52.83 (C-4′), 57.52 (OCH_3), 59.21 (OCH_3), 61.02 (C-1′), 71.67 (C-5′), 82.33 (C-3′), 103.21 (C-5), 140.70 (C-6), 150.57 (2-CO), 162.94 (4-CO). **12β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (ddd, 1 H, $J_{2a',1'}$ 7.5, $J_{2a',3'}$ 3.9, $J_{2a',2b'}$ 14.6 Hz, H-2a′), 2.46 (ddd, 1 H, $J_{2b',1'}$ 2.9, $J_{2b',3'}$ 3.5 Hz, H-2b′), 3.25 (s, 3 H, 3′-OCH_3), 3.41 (s, 3 H, 5′-OCH_3), 3.66 (dd, 1 H, $J_{5a',4'}$ 6.2, $J_{5a',5b'}$ 9.2 Hz, H-5a′), 3.74 (ddd, 1 H, $J_{4',3'}$ 4.2, $J_{4',5b'}$ 6.0 Hz, H-4′), 3.83 (dd, 1 H, H-5′), 4.03 (ddd, 1 H, H-3′), 5.72 (dd, 1 H, $J_{5,6}$ 8.3, $J_{5,NH}$ 1.2 Hz, H-5), 6.25 (dd, 1 H, H-1′), 8.23 (d, 1 H, H-6), 9.23 (bs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.74 (C-2′), 53.64 (C-4′), 56.76 (3′-OCH_3), 59.14 (5′-OCH_3), 61.86 (C-1′), 71.37 (C-5′), 82.06 (C-3′), 101.29 (C-5), 142.83 (C-6), 151.10 (2-CO), 16.46 (4-CO). MS (70 eV): *m/z* 160 (4), 129 (9), 128 (24), 117 (5), 115 (14), 113 (5), 112 (7), 97 (19) [$C_5H_5S^+$], 85 (7), 84 (11), 71 (16), 69 (9), 59 (5), 45 (100). Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.47; H, 6.04; N, 9.08; S, 10.94.

*1-(2-Deoxy-3,5-di-O-methyl-4-thio-*L*-threo-pentofuranosyl)thymine* (**13**).—Compounds **13α** and **13β** were prepared from **5** (96 mg, 0.34 mmol), 2,4-bis-*O*-(trimethyl)silylthymine (140 mg, 0.54 mmol) (**11**) [4,12,13] and *N*-iodosuccinimide (99 mg, 0.44 mmol), as described for **12α** and **12β**. The crude product was worked up by column chromatography (EtOAc) and gave **13** (69 mg, 71%; **13α**:**13β** = 3:2). A second column chromatography (EtOAc) step gave 31 mg of pure **13β** (R_f 0.39), isolated as a colourless syrup and 30 mg of pure **13α** (R_f 0.32), isolated as a white solid, mp 140 °C. IR: ν 3204, 3099, 3055, 2925, 2892, 2825, 1704, 1682, 1466, 1386, 1240, 1223, 1197, 1125, 1100, 1014, 896, 795, 629, 538. **13α**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (ddd, 1 H, $J_{2a',1'}$ 8.7, $J_{2a',3'}$ 3.6, $J_{2a',2b'}$ 13.6 Hz, H-2a′), 1.96 (d, 1 H, $J_{CH_3,6}$ 1.2 Hz, CH_3), 2.77 (ddd, 1 H, $J_{2b',1'}$ 6.8, $J_{2b',3'}$ 3.3 Hz, H-2b′), 3.386 (s, 3 H, OCH_3), 3.392 (s, 3 H, OCH_3), 3.53 (dd, 1 H, $J_{5a',4'}$ 7.3, $J_{5a',5b'}$ 9.5 Hz, H-5a′), 3.78 (dd, 1 H, $J_{5b',4'}$ 6.3 Hz, H-5b′), 4.00 (ddd, 1 H, $J_{4',3'}$ 3.7 Hz, H-4′), 4.10 (ddd, 1 H, H-3′), 6.43 (dd, 1 H, H-1′), 7.51 (q, 1 H, H-6), 8.50 (bs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69 (CH_3), 40.61 (C-2′), 53.07 (C-4′), 57.44 (OCH_3), 59.23 (OCH_3), 60.79 (C-1′), 71.74 (C-5′), 82.34 (C-3′), 111.17 (C-5), 136.24 (C-6), 150.49 (2-CO), 163.29 (4-CO). **13β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (d, 1 H, $J_{CH_3,6}$ 1.2 Hz, CH_3), 2.35 (ddd, 1 H, $J_{2a',1'}$ 7.3, $J_{2a',3'}$ 4.3, $J_{2a',2b'}$ 14.2 Hz, H-2a′), 2.40 (ddd, 1 H, $J_{2b',1'}$ 4.4, $J_{2b',3'}$ 4.4 Hz, H-2b′), 3.29 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.68–3.73 (m, 1 H, H-4′), 3.71 (dd, 1 H, $J_{5a',4'}$ 5.7, $J_{5a',5b'}$ 11.7 Hz, H-5a′), 3.80 (dd, 1 H, $J_{5b',4'}$ 8.0 Hz, H-5b′), 4.02 (ddd, 1 H, $J_{3',4'}$ 4.3 Hz, H-3′), 6.29 (dd, 1 H, H-1′), 8.07 (q, 1 H, H-6), 8.85 (bs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.65 (CH_3), 40.30 (C-2′), 52.73 (C-4′), 56.96 (OCH_3), 59.07 (OCH_3), 60.36 (C-1′), 71.42 (C-5′), 82.07 (C-3′), 110.07 (C-5), 138.45 (C-6), 151.03 (2-CO), 163.72 (4-CO). MS (70 eV): *m/z* (%) 161 (3), 129 (12), 128 (12), 126 (9), 115 (10), 97 (24), 85 (6), 84 (8), 71 (9), 45 (100). Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78; S, 11.20. Found: C, 50.81; H, 6.69; N, 8.78; S, 10.22.

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