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D-Ribofuranosylenamine: a versatile starting material for preparing azasugar thioglycosides and building blocks for thioureylene-di-nucleosides

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Abstract—Six-membered azasugar thioglycosides (piperidines) are prepared from a β-D-ribofuranosylenamine, with a 1,5-anhydro derivative being the key intermediate. The α-anomer of the same D-ribofuranosylenamine is transformed into a 5-deoxy-5-isothiocyanato derivative, useful for preparing D-ribosylamino derivatives with a non-ionic thiourea bridge, isosteric of the phosphate bridge. The prepared thioureas are potential building blocks for the synthesis of thioureylene-di-nucleosides.

1. Introduction

Over the last few decades, azasugars, due to their biological interest have become an important subject of research in the field of organic and pharmaceutical chemistry.[1,2] Thioglycosides, that is 1-thio analogues of glycosides, have been widely used as glycosyl donors in glycosylation reactions, to prepare oligosaccharides.[3–6] Thioglycosides have also been used to prepare monosaccharide derivatives *O*-protected in every position except the anomeric hydroxyl group, as thioalkyl and thiophenyl groups can be selectively removed from per-*O*-protected sugars with different *O*-protecting groups.[7,8] From a biological point of view, the thioglycosides have been tested as antithrombotic agents.

Five-[9] and seven-membered[10] iminocyclitols have been prepared from hexopyranosylenamines; the key chiral intermediate of these syntheses being anhydroazasugar derivatives. The same type of chiral intermediate has been used to prepare thiofuranosides of 5-aminosugars[11] and ethylthioglycosides of pyrrolizine-derived azasugars.[12]

At the same time, nucleosides and nucleotides are compounds of pharmaceutical interest, due to the successful use of the former in the treatment of many infectious diseases,[13] in particular for the therapy of AIDS,[14] and the therapeutic activity of the latter as inhibitors of protein biosynthesis.[15] The synthesis of analogues of natural oligonucleotides (antisense oligonucleotides) has been a growing research topic over the last few years, and several nucleotide analogues changing the negatively charged phosphodiester linkage by non-ionic isosteric spacers,[16] such as guanidino,[17] (*S*)-methylthioureido,[18] amide,[19] carbamate[20] and phosphoramidate[21] have been synthetized. We have reported the preparation of thioureylene-di-*C*-nucleosides (tetrofuranosides) by reaction of aminonucleosides and isothiocyanato erythrosides.[22]

In an earlier paper[23] we have described the preparation of *N*-2,2-diethoxycarbonylvinyl-2,3-*O*-isopropylidene-β **1** and α-ribofuranosylamines **9** from D-ribosylamine, and recently we have communicated[24] our preliminary results on the preparation of azasugar thioglycosides. Herein we report that the β-anomer **1** is a suitable starting material for preparing alkyl and aryl thioglycosides of six-membered iminocyclitols, and α-anomer **9** can be easily transformed, through the preparation of a 5-isothiocyanato derivative **13** into the thiourea **16** with *C*-nucleoside and glycosylenamine moieties. The

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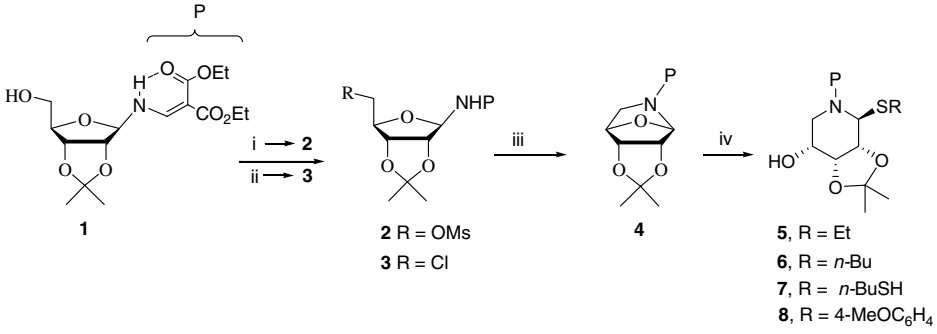
enamino group is potentially transformable into different heterocycles.[25–27]

2. Results and discussion

The reaction of 2,3-*O*-isopropylidene-β-D-ribofuranosylamine *p*-toluenesulfonate[28] with diethyl ethoxymethylenemalonate gives[23] the separable mixture of *N*-2,2-diethoxycarbonylvinyl-2,3-*O*-isopropylidene-β **1** and α-D-ribofuranosylamines **9**. Treatment of **1** with mesyl chloride in pyridine, under argon for 15 h gives the 5-*O*-mesyl derivative **2** in 70% yield (Scheme 1). Longer treatment (72 h) and more-concentrated solution (see Experimental) produce the substitution of the mesyloxy group by chloro, giving 5-chloro-5-deoxy-β-D-ribofuranosylenamine **3**. The chemical shifts for the resonances of H-5a and H-5b in **2** and **3** (Table 1) were indicative of the introduction of the mesyl group and the chlorine atom, respectively.

Intramolecular substitution, induced by sodium methoxide in DMF,[10] of the mesyloxy group in **2**, or of the chloro in **3**, gives in high yield the anhydroazasugar derivative **4**, whose ^{1}H NMR data showed no signal for NH; the resonance of *H*C═ was a singlet. The chemical shifts of the signals of H-5a, H-5b, C-1, C-5 and ═CH showed, with respect to the same signals for **2** and **3**, the described changes[10] by the formation of the aza-bridge.

Reaction of **4** with ethanethiol, 1-butanethiol, 1,4-butanedithiol, and 4-methoxythiophenol in the presence of PTSA, in DMF (S_N2 conditions) yielded the corresponding alkyls **5**–**7** or 4-methoxyphenyl **8** azasugar thioglycoside as only the β(2*S*) anomer. In the case of 1,4-butanedithiol the monopiperidinyl derivative **7** was the only product isolated. The chemical shift for the resonances of H-2 and C-2 in **5**–**8** (Table 1) was in agreement with the presence of the sulfur atom. The resonance of C-2 undergoes an upfield shift of roughly 23 ppm with respect to that for the same atom (C-1) in **4**. The piperidine structure was also evident from the chemical shifts for the resonances of H-6a, H-6b and C-6, indicative of an N–CH_2 group, and from the strong changes in the $^3J_{H,H}$ values (see Experimental) of the piperidine ring with respect to those for the furanoid ring. Double-pulsed field gradient spin-echo (DPFGSE) NOE[29] experiments were used to assess the configuration of C-2 on **5** and **8**. The NOEs observed for the C-6 methylene protons of both compounds allowed the assignment of such diastereotopic hydrogens (H-6a



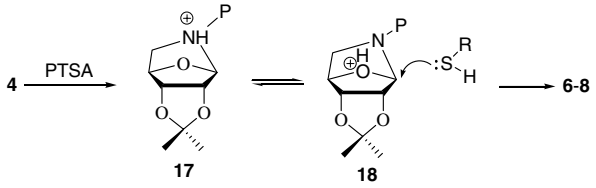
Scheme 1. Reagents and conditions. (i) ClMs/Py, 15 min (70%); (ii) ClMs/Py, 72 h (70%); (iii) NaMeO/DMF, rt, 20 mmHg, 15 h 91% (from **2**), 91% (from **3**); (iv) RSH/DMF, PTSA.

Table 1. Selected NMR spectroscopic data (δ, ppm; *J* Hz) for compounds **2**–**8** and **10**–**13** at 500 (^{1}H) and 125 (^{13}C) MHz

	Sugar ring					Enamino moiety				C═S
	δH-1	δH-5a	δH-5b	δC-1	δC-5	δNH	δ = C*H*	$J_{NH,=CH}$	δ = *C*H	
2	5.14	4.46	4.20	96.7	69.1	9.51	7.99	13.3	157.6	—
3	5.15	3.66	3.61	95.1	44.8	9.48	8.04	13.3	157.4	—
4	5.22	3.03	2.89	92.4	48.0	—	7.60	—	146.8	—
	δH-2	δH-6a	δH-6b	δC-2	δC-6					
5[a]	4.62	3.49	3.05	68.9	46.2	—	7.48	—	150.0	—
6[a]	4.63	3.50	3.08	68.9	46.1	—	7.44	—	149.7	—
7[a]	4.62	3.51	3.06	69.0	46.1	—	7.43	—	149.7	—
8[a]	4.69	3.49	3.13	73.9	45.9	—	7.41	—	149.6	—
	δH-1	δH-5a	δH-5b	δC-1	δC-5					
10	5.39	3.64	3.64	90.3	45.6	9.48	8.04	13.1	157.2	—
11	5.39	3.60	3.49	89.7	53.3	9.51	8.07	13.1	157.2	—
12	5.30	2.89	2.78	88.6	43.1	9.50	8.07	13.1	157.1	—
13	5.33	3.80	3.70	89.6	47.6	9.54	8.07	13.2	157.2	135.2

[a] The data for the same atom are maintained in each column although in compounds **5**–**8**, the numbering changes.

pro-R and H-6b *pro-S*). Particularly important was the presence of a long-range NOE effect between H-6b and the *endo* methyl group of the isopropylidene moiety, not observed for H-6a. With the stereospecific assignment of these prochiral protons already done, the NOE interaction between H-6a and the protons at vicinal positions to the sulfur atom in the aglycon (CH_2 for **5** and aromatics for **8**), absent in the case of H-6b, clearly supports (*S*)-configuration for C-2. The formation of **5**–**7** is stereoselective, and only the β-anomers were isolated after purification in medium-to-high yield. Protonation of **4** by PTSA produces the cations **17** and **18**, which are in equilibrium (Scheme 2). The aprotic solvent favours the S_N2 attack of the RSH on C-1 (D-ribose numbering) with cleavage of the C1–O bond, as the OH is a better leaving group than NH, and inversion of the configuration. This behaviour is different to that observed for related compounds,[11] which under S_N1 conditions, produce thioglycosides of 5-aminosugars, with cleavage of the C1–N bond.

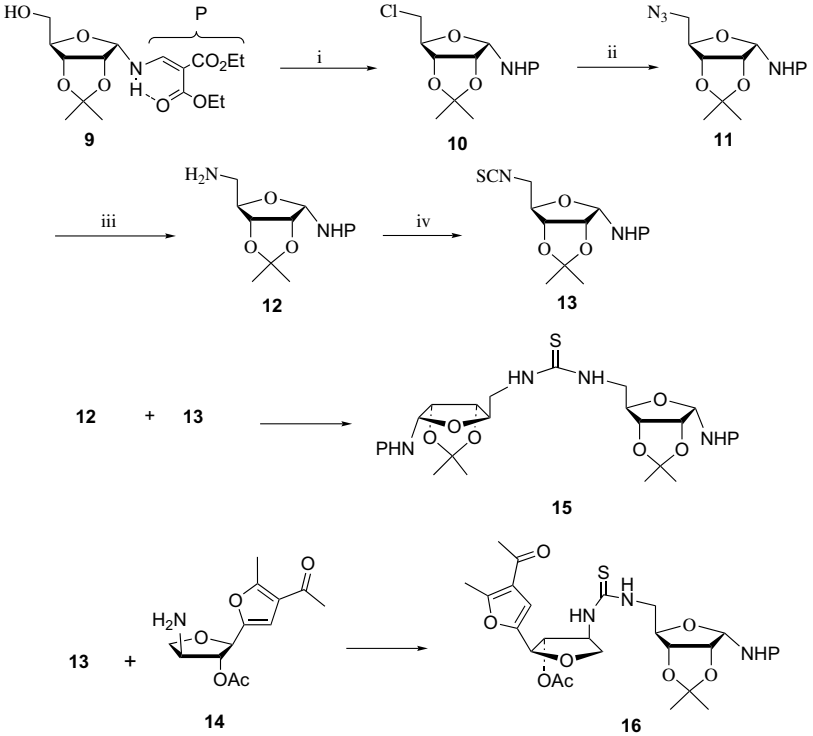


Scheme 2. Mechanism of the formation of **6**–**8**.

The D-ribofuranosylenamine α-anomer **9** was treated with mesyl chloride (Scheme 3), under the same conditions described above for **3**, to obtain **10**, whose NMR data confirmed the structure and α-anomeric configuration. The described[23] differences in the resonances of C-1 and H-1 in the parent compounds **1** and **9** were observed in the anomers **3** and **10**.

Reaction of **10** with sodium azide (→**11**), followed by hydrogenation on palladium/carbon (→**12**), and reaction with thiocarbonyldiimidazole afforded the 5-isothiocyanato ribofuranosylenamine derivative **13** in an overall quantitative yield from **10**. Compound **11** had the IR absorption for the azido group at 2110 cm^{-1}, and the δ values for the resonances of H-5a, H-5b and C-5 were very close to those described for other azido derivatives of sugars in a primary position.[30] Signals of resonance of H-5a, H-5b and C-5 in **12** were upfield shifted with respect to the same signal for **11** as corresponds to the substitution of the azido by the amino group. The isothiocyanato group of **13** was supported[22] on the basis of the IR absorption at 2112 cm^{-1} and the ^{13}C resonance at 135.2 ppm. The introduction of the NCS group in C-5 position produced an increase in the δ values for H-5a, H-5b and C-5 with respect to the same signals in the amino precursor **12**. When the resonance of C-5 in **13** is compared with the same signal for the azido derivative,[11] the described[22] shielding of ~5.0 ppm was observed (Table 1).

With the aim of having building blocks to prepare dinucleoside analogues having a thiourea bridge, we have prepared (Scheme 3) the symmetric **15** and non-symmetric **16** thioureyleneglycosylenamines. Thus the reaction of amino derivative **12** with isothiocyanate **13** in DMF, under anhydrous conditions, produced thiourea



Scheme 3. Reagents and conditions. (i) MsCl/Py, 72 h; (ii) NaN_3/DMF, 70 °C; (iii) H_2/Pd–C/MeOH; (iv) Im_2CS/CH_2Cl_2, 0 °C.

15 in high yield. In the same way, the reaction of **13** with 3′-aminothreofuranoside **14**[22] gave compound **16** having glycosylamine and nucleoside moieties. The enamino groups of **15** and **16** are potentially useful for preparing different heterocycles.[25–27] The C=S of the thiourea spacer of **15** and **16** resonated at 183.3 ppm, as in related di-*C*-nucleosides[22] and di- and tri-saccharides[31] with a thioureylene group. Broad NMR signals for resonances of the CH_2–NH groups of **15** and **16** and for H-3 and C-3 (L-threofuranose ring) of **16** also supported the presence of the thiourea group.

3. Conclusion

The nucleophilic opening of *N*-diethoxycarbonylvinyl-anhydroazasugar derivatives is a stereoselective method for preparing six-membered azasugar thioglycosides; particularly starting from β-D-ribose derivatives, 2-thioalcoxy (thioaroxy) piperidines are obtained. The reaction of 5-isothiocyanato-5-deoxy-α-D-ribofuranosyl-enamines with amino compounds gives access to different thioureylene derivatives, potentially useful as building blocks to prepare di-nucleosides with a non-ionic thiourea bridge.

4. Experimental

4.1. General methods

Melting points were determined with a Gallenkamp apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter, 1 cm tubes, and solutions in CH_2Cl_2, at 589 nm, were used for measurement of specific rotations. IR spectra were recorded for KBr discs on a Bomen Michelson MB-120 FTIR spectrophotometer. Mass spectra (EI, CI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 60,000 (10% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (6–7 keV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and NaI as salt. TLC was performed on Silica Gel HF_{254}, with detection by UV light or charring with H_2SO_4. Silica Gel 60 (Merck, 70–230 and 230–400 mesh) was used for preparative chromatography.

NMR experiments were recorded on a Bruker Avance 500 spectrometer (500.13 MHz for ^1H and 125.75 MHz for ^{13}C). Sample concentrations were typically in the range 10–15 mg per 0.6 mL of $CDCl_3$. Chemical shifts are given in ppm, using the residual protonated solvent signal as reference. ^1H and ^{13}C assignments were confirmed by 2D conventional COSY and HSQC experiments. 1D NOESY experiments were carried out on a 5 mm inverse detection probe operating at 303 K, by using the double-pulsed field gradient spin-echo technique (DPFGSE-NOE).[29] A mixing time of 400 ms, a recycle delay of 2 s, and 1024 transients per spectrum, were used in all cases. Selective inversions were performed by using Gaussian-shaped soft pulses (50 ms).

4.2. Preparation of compounds 2, 3 and 10

To a cooled (0 °C) stirred solution of the 2,3-*O*-isopropylidene-*N*-(2,2-diethoxycarbonylvinyl)-β-D-ribofuranosylamine **1** or 2,3-*O*-isopropylidene-*N*-(2,2-diethoxycarbonylvinyl)-α-D-ribofuranosylamine **9** (0.278 mmol) in pyridine (*y* mL) under argon, a solution of mesyl chloride (0.975 mmol) was dropped. The mixture was stirred at rt for *t* h. The solution was poured into ice water and extracted with CH_2Cl_2, the organic layer was washed with 1 M sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (ether/hexane 2:1).

4.2.1. *N*-(2,2-Diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-5-*O*-mesyl-β-D-ribofuranosylamine, 2. $y = 83.0$ mL; $t = 15$ h. Amorphous solid. Yield 70%; $[\alpha]^{24} = -88$ (*c* 1.2, CH_2Cl_2); FABMS *m/z* 460 [(M+Na)$^+$]; IR 3306, 2986, 2928, 1690, 1607, 1452, 1360, 1280, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (dd, 1H, $J_{NH,1} = 9.6$, $J_{NH,HC=} = 13.3$, NH), 7.99 (d, 1H, HC=), 5.14 (dd, 1H, $J_{1,2} = 2.1$, H-1), 4.83 (d, 1H, $J_{2,3} = 6.1$, H-3), 4.68 (dd, 1H, H-2), 4.46 (dd, 1H, $J_{4,5a} = 3.0$, $J_{5a,5b} = 12.8$, H-5a), 4.45 (m, 1H, H-4), 4.23–4.15 (m, 5H, H-5b, 2CH_2CH$_3$), 3.17 (s, 3H, Ms), 1.52, 1.33 (each s, each 3H, 2(CH$_3$)$_2$C), 1.31, 1.26 (each t, each 3H, $J_{H,H} = 7.1$, CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.9, 165.3 (2C=O), 157.6 (CH=), 114.0 (*C*(CH$_3$)$_2$), 96.7 (C-1), 92.8 (C=), 85.7 (C-2), 83.2 (C-4), 81.5 (C-3), 69.1 (C-5), 60.1, 59.9 (2*C*$_2$CH$_3$), 37.6 (OMs), 26.7, 24,9 [(*C*H$_3$)$_2$C], 14.3, 14.2 (2CH$_2$C$_3$); Anal. Calcd for $C_{17}H_{27}NO_{10}S$: C, 46.68; H, 6.22; N, 3.20. Found: C, 47.04; H, 6.15; N, 3.01.

4.2.2. 5-Chloro-5-deoxy-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-β-D-ribofuranosylamine, 3. $y = 1.0$ mL; $t = 72$ h. Amorphous solid. Yield 70%; $[\alpha]^{23} = -7.5$ (*c* 1.0, CH_2Cl_2); FABMS *m/z* 400 [(M+Na)$^+$]; IR, 3257, 2991, 2948, 1697, 1652, 1611, 1451, 1402, 1381, 1225, 1098, 1022, 870, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (dd, 1H, $J_{NH,1} = 8.9$, $J_{NH,HC=} = 13.3$, NH), 8.04 (d, 1H, HC=), 5.15 (dd, 1H, $J_{1,2} = 2.6$, H-1), 4.78 (dd, 1H, $J_{2,3} = 6.3$, $J_{3,4} = 2.1$, H-3), 4.69 (dd, 1H, H-2), 4.45 (m, 1H, H-4), 4.25, 4.19 (each q, each 2H, $J_{H,H} = 7.1$, 2CH_2CH$_3$), 3.66 (dd, 1H, $J_{4,5a} = 3.8$, $J_{5a,5b} = 11.8$, H-5a), 3.61 (dd, 1H, $J_{4,5b} = 5.4$, H-5b), 1.62, 1.39 (each s, each 3H, 2(CH$_3$)$_2$C), 1.32, 1.21 (each t, each 3H, 2CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.6, 165.3 (2C=O), 157.4 (CH=), 114.2 (*C*(CH$_3$)$_2$), 95.5 (C-1), 93.2 (C=), 85.4 (C-2), 84.5 (C-4), 82.3 (C-3), 60.1, 59.8 (2*C*H$_2$CH$_3$), 44.8 (C-5), 26.7, 25.0 ((*C*H$_3$)$_2$C), 14.3, 14.2 (2CH$_2$*C*H$_3$); Anal. Calcd for $C_{16}H_{24}NO_7Cl$: C, 50.87; H, 6.38; N, 3.71. Found: C, 51.25; H, 6.61; N, 3.57.

4.2.3. 5-Chloro-5-deoxy-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-α-D-ribofuranosylamine, 10. 1.0 mL; $t = 72$ h. Amorphous solid. Yield 60%; $[\alpha]^{24} = -53$ (*c* 0.7, CH_2Cl_2); FABMS *m/z* 400 [(M+Na)$^+$]; IR 3347, 3032, 2984, 1658, 1601, 1472, 1433, 1370, 1280, 1248, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (dd, 1H, $J_{NH,1} = 9.3$, $J_{NH,HC=} = 13.1$, NH), 8.04 (d,

1H, HC=), 5.39 (dd, 1H, $J_{1,2}$ = 4.2, H-1), 4.83 (dd, 1H, $J_{2,3}$ = 6.3, $J_{3,4}$ = 1.4, H-3), 4.81 (dd, 1H, H-2), 4.41 (m, 1H, H-4), 4.24, 4.17 (each q, each 2H, $J_{H,H}$ = 7.1, $2CH_2CH_3$), 3.64 (m, 2H, H-5a, H-5b), 1.62, 1.38 (each s, each 3H, $2(CH_3)_2CO_2$), 1.31, 1.27 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.9, 165.6 (2C=O), 157.2 (CH=), 114.4 [$(CH_3)_2CO_2$], 93.7 (C=), 90.3 (C-1), 82.7 (C-3), 81.5 (C-4), 79.5 (C-2), 60.0, 59.8 ($2CH_2CH_3$), 45.6 (C-5), 26.0, 24.4 [$(CH_3)_2CO_2$], 14.3 ($2CH_2CH_3$); Anal. Calcd for $C_{16}H_{24}NO_7Cl$: C, 50.87; H, 6.38; N, 3.71. Found: C, 51.26; H, 6.37; N, 3.78.

4.3. 1,5-Anhydro-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-β-D-ribofuranosylamine, 4

To a stirred solution of the corresponding 5-chloro, **3**, or 5-*O*-mesylated compound **2**, (2.119 mmol) in DMF (14.0 mL) at 40 °C and 20 mmHg, sodium methoxide (114 mg, 2.119 mmol) was added. The reaction controlled by TLC (ether/hexane 4:1). After 15 min, the mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography (AcOEt/toluene 1:7) to give an amorphous solid. Yield 91% (from **2**), 92% (from **3**); $[\alpha]^{23} = 0$ (*c* 1.0, CH_2Cl_2); FABMS *m/z* 364 [(M+Na)$^+$]; IR 3308, 2965, 2930, 1696, 1524, 1456, 1370, 1261, 802 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s 1H, HC=), 5.22 (br s, 1H, H-1), 4.65 (d, 1H, $J_{4,5a}$ = 4.6, H-4), 4.41 (d, 1H, $J_{2,3}$ = 5.4, H-2), 4.34 (d, 1H, H-3), 4.17, 4.11 (each q, each 2H, $J_{H,\ H}$ = 7.1, $2CH_2CH_3$), 3.03 (dd, 1H, $J_{5a,5bb}$ = 10.3, H-5a), 2.89 (d, 1H, H-5b), 1.39, 1.23 (each s, each 3H, $2(CH_3)_2C$), 1.25, 1.20 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.6, 166.4 (2C=O), 146.8 (CH=), 112.9 ($C(CH_3)_2$), 96.3 (C=), 92.4 (C-1), 81.3 (C-2), 80.2 (C-3), 79.3 (C-4), 60.7, 60.2 ($2CH_2CH_3$), 48.0 (C-5), 25.7, 25.1 ($(CH_3)_2CO_2$), 14.2, 14.1 ($2CH_2CH_3$); Anal. Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 55.92; H, 6.71; N, 4.29.

4.4. Preparation of compounds 5–8

To a stirred solution of the 1,4-anhydro compound **4** (0.293 mmol) in DMF (2.0 mL) over 4 Å molecular sieves at rt, the corresponding 1-ethanethiol for **5**, 1-butanethiol for **6**, 1,4-butanedithiol for **7**, and 4-methoxythiophenol for **8** (7.325 mmol) and PTSA (0.439 mmol) were added. The reaction mixture was stirred for 15 min, monitored by TLC (ether/hexane 4:1), and then neutralized with satd aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water, and dried over $MgSO_4$, filtered and concentrated to dryness. In all cases, the residue was purified by column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH 100:1).

4.4.1. (2*S*,3*R*,4*R*,5*R*)-*N*-(2,2-Diethoxycarbonylvinyl)-2-ethylthio-5-hydroxy-3,4-*O*-isopropylidenepiperidine, 5. Amorphous solid. Yield 83%; $[\alpha]_D^{28} = -46$ (*c* 0.9, CH_2Cl_2); FABMS *m/z* 426 [(M+Na)$^+$]; IR 3368, 2978, 2922, 1701, 1672, 1589, 1454, 1370, 1200, 885 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H, HC=), 4.62 (m, 2H, H-2, H-5), 4.49 (dd, 1H, $J_{3,4}$ = 7.7, $J_{4,5}$ = 3.0, H-4), 4.38 (dd, 1H, $J_{2,3}$ = 1.7, H-3), 4.24, 4.14 (each q, each 2H, $J_{H,H}$ = 7.0, $2CH_2CH_3$), 3.49 (dd, 1H, $J_{5,6a}$ = 6.2, $J_{6a,6b}$ = 11.9, H-6a), 3.05 (dd, 1H, $J_{5,6b}$ = 11.0, H-6b), 2.59 (m, 2H, SCH_2), 2.21 (d, 1H, $J_{5,OH}$ = 9.9, OH-5), 1.43, 1.33 (each s, each 3H, $2(CH_3)_2C$), 1.30, 1.25 (each t, each 3H, $2CH_2CH_3$); 1.22 (m, 3H, SCH_2CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.4, 167.0 (2C=O), 150.0 (CH=), 110.6 ($C(CH_3)_2$), 96.2 (C=), 76.2 (C-3), 72.9 (C-4), 68.9 (C-2), 63.4 (C-5), 61.1, 60.3 ($2CH_2CH_3$), 46.2 (C-6), 26.3, 24.6 [$(CH_3)_2C$], 25.7 (SCH_2), 14.5, 14.4 ($2CH_2CH_3$), 14.2 (SCH_2CH_3); HRCIMS *m/z* obsd. 403.1666 calcd. for $C_{18}H_{29}NO_7S$ 403.1665.

4.4.2. (2*S*,3*R*,4*R*,5*R*)-2-Butylthio-*N*-(2,2-diethoxycarbonylvinyl)-5-hydroxy-3,4-*O*-isopropylidenepiperidine, 6. Amorphous solid. Yield 84%; $[\alpha]_D^{24} = -56$ (*c* 0.9, CH_2Cl_2); FABMS *m/z* 454 [(M+Na)$^+$]; IR 3396, 2986, 2932, 2872, 1706, 1677, 1588, 1459, 1365, 1283, 880 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H, HC=), 4.63 (m, 2H, H-2, H-5), 4.51 (dd, 1H, $J_{3,4}$ = 7.7, $J_{4,5}$ = 3.1, H-4), 4.40 (dd, 1H, $J_{2,3}$ = 1.7, H-3), 4.26, 4.17 (each q, each 2H, $J_{H,H}$ = 7.0, $2CH_2CH_3$), 3.50 (dd, 1H, $J_{5,6a}$ = 6.2, $J_{6a,6b}$ = 11.9, H-6a), 3.08 (dd, 1H, $J_{5,6b}$ = 10.2, H-6b), 2.59 (m, 2H, SCH_2), 2.07 (d, 1H, $J_{5,OH}$ = 9.9, OH-5), 1.59 (m, 2H, SCH_2CH_2), 1.45, 1.35 (each s, each 3H, 2[$(CH_3)_2C$]), 1.40 (qd, 2H, $J_{CH2,CH3}$ = 7.4, $J_{CH2,CH2}$ = 2.5, $SCH_2CH_2CH_2CH_3$), 1.33, 1.25 (each t, each 3H, $2CH_2CH_3$), 0.91 (t, 3H, $SCH_2CH_2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.3, 166.8 (2C=O), 149.7 (CH=), 110.5 [$C(CH_3)_2$], 96.1 (C=), 76.1 (C-3), 72.7 (C-4), 68.9 (C-2), 63.3 (C-5), 60.9, 60.1 ($2CH_2CH_3$), 46.1 (C-6), 31.2 (SCH_2CH_2), 31.1 (SCH_2), 26.2, 24.5 [$(CH_3)_2C$], 21.8 ($SCH_2CH_2CH_2$), 14.3, 14.1 ($2CH_2CH_3$), 13.4 ($SCH_2CH_2CH_2CH_3$); Anal. Calcd for $C_{20}H_{33}NO_7S$: C, 55.66; H, 7.71; N, 3.25; S, 7.44. Found: C, 55.36; H, 7.68; N, 3.37; S, 7.51.

4.4.3. (2*S*,3*R*,4*R*,5*R*)-*N*-(2,2-Diethoxycarbonylvinyl)-5-hydroxy-3,4-*O*-isopropylidene-2-mercaptobutylthiopiperidine, 7. Amorphous solid. Yield 77% $[\alpha]_D^{24} = -48$ (*c* 0.7, CH_2Cl_2); FABMS *m/z* 486 [(M+Na)$^+$]; IR 3302, 2984, 2932, 1695, 1592, 1425, 1373, 1282, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H, HC=), 4.62 (m, 2H, H-2, H-5), 4.51 (dd, 1H, $J_{3,4}$ = 7.5, $J_{4,5}$ = 3.0, H-4), 4.39 (dd, 1H, $J_{2,3}$ = 1.5, H-3), 4.26, 4.16 (each q, each 2H, $J_{H,\ H}$ = 7.5, $2CH_2CH_3$), 3.51 (dd, 1H, $J_{5,6a}$ = 6.0, $J_{6a,6b}$ = 12.0, H-6a), 3.06 (dd, 1H, $J_{5,6b}$ = 11.0, H-6b), 2.61 [m, 2H, $SCH_2(CH_2)_3SH$], 2.53 (m, 2H, CH_2SH), 2.11 (d, 1H, $J_{5,OH}$ = 9.5, OH-5), 1.74–1.68 (m, 4H, $SCH_2CH_2CH_2CH_2SH$), 1.45, 1.35 [each s, each 3H, $2(CH_3)_2C$], 1.36 (s, 1H, SH), 1.32, 1.25 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.2, 166.7 (2C=O), 149.7 (CH=), 110.5 [$C(CH_3)_2$], 96.3 (C=), 76.1 (C-3), 72.8 (C-4), 69.0 (C-2), 63.2 (C-5), 61.0, 60.2 ($2CH_2CH_3$), 46.1 (C-6), 32.8 (SCH_2CH_2), 30.9 (SCH_2), 27.8 ($SCH_2CH_2CH_2CH_2SH$), 26.1, 24.5 [$(CH_3)_2C$], 23.9 (CH_2SH), 14.3, 14.1 ($2CH_2CH_3$); HRCIMS *m/z* obsd. 463.1701 calcd. for $C_{20}H_{33}NO_7S_2$ 463.1698.

4.4.4. (2*S*,3*R*,4*R*,5*R*)-*N*-(2,2-Diethoxycarbonylvinyl)-5-hydroxy-3,4-*O*-isopropylidene-2-(4-methoxyphenyl)thiopiperidine, 8. Amorphous solid. Yield 46%; $[\alpha]_D^{24} = -141$ (*c* 1.1 CH_2Cl_2); FABMS *m/z* 504 [(M+Na)$^+$]; IR 3453, 2983, 2932, 1700, 1593, 1505, 1381, 1250, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (br s, 1H, HC=), 6.94–6.84 (m, 4H, Ar), 4.69 (m, 2H, H-2, H-5), 4.58 (dd, 1H, $J_{3,4} = 7.7$, $J_{4,5} = 2.8$, H-4), 4.54 (dd, 1H, $J_{2,3} = 1.0$, H-3), 4.25, 4.08 (each q, each 2H, $J_{H,H} = 7.1$, $2CH_2CH_3$), 3.79 (s, 3H, OCH_3), 3.49 (dd, 1H, $J_{5,6a} = 6.0$, $J_{6a,6b} = 11.7$, H-6a), 3.13 (dd, 1H, $J_{5,6b} = 11.2$, H-6b), 2.17 (d, 1H, $J_{5,OH} = 10.0$, OH-5), 1.42, 1.35 [each s, each 3H, $2(CH_3)_2C$], 1.31, 1.19 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.6, 166.7 (2C=O), 161.9–121.4 (Ar), 149.6 (CH=), 110.7 [$C(CH_3)_2$], 96.5 (C=), 75.7 (C-3), 73.9 (C-2), 72.7 (C-4), 63.8 (C-5), 61.2, 60.2 ($2CH_2CH_3$), 55.6 (OCH_3), 45.9 (C-6), 26.4, 24.8 [$(CH_3)_2C$], 14.5, 14.4 ($2CH_2CH_3$); HRCIMS *m/z* obsd. 481.1763 calcd. for $C_{23}H_{31}NO_8S$ 481.1770.

4.5. 5-Azido-5-deoxy-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-α-D-ribofuranosylamine, 11

To a stirred solution of compound **10** (0.514 mmol) in DMF (20 mL), sodium azide (2.569 mmol) was added. The mixture was kept for 6 h at 70 °C, then poured into ice water and extracted with AcOEt. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (CH_2Cl_2) and gave an amorphous solid in quantitative yield. $[\alpha]_D^{23} = -74$ (*c* 1.0, CH_2Cl_2); FABMS *m/z* 407 [(M+Na)$^+$]; IR 3290, 3030, 2989, 2110, 1694, 1662, 1605, 1516, 1454, 1427, 1373, 1284, 1226, 1163, 1109, 1073, 986, 875, 752, 625 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (dd, 1H, $J_{NH,1} = 9.2$, $J_{NH,HC=} = 13.1$, NH), 8.07 (d, 1H, HC=), 5.30 (dd, 1H, $J_{1,2} = 4.5$, H-1), 4.81 (t, 1H, $J_{2,3} = 6.2$, H-2), 4.73 (dd, 1H, $J_{3,4} = 1.7$, H-3), 4.24, 4.17 (each q, each 2H, $J_{H,H} = 7.1$, $2CH_2CH_3$), 4.24 (m, 1H, H-4), 3.60 (dd, 1H, $J_{4,5a} = 3.6$, $J_{5a,5b} = 13.0$, H-5a), 3.49 (dd, 1H, $J_{4,5b} = 3.7$, H-5b), 1.64, 1.39 (each s, each 3H, 2 $(CH_3)_2CO_2$), 1.32, 1.31 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.9, 165.4 (2C=O), 157.2 (CH=), 114.5 [$(CH_3)_2CO_2$], 93.6 (C=), 89.7 (C-1), 82.2 (C-4), 80.5 (C-3), 79.4 (C-2), 60.0, 59.8 ($2CH_2CH_3$), 53.3 (C-5), 26.1, 24,8 [$(CH_3)_2CO_2$], 14.3 ($2CH_2CH_3$); HRCIMS *m/z* obsd. 384.1645 calcd. for $C_{16}H_{24}N_4O_7$ 384.1645.

4.6. 5-Amino-5-deoxy-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-α-D-ribofuranosylamine, 12

A mixture of azide **11** (0.487 mmol) and Pd–C (18.7 mg) in MeOH (14 mL) was hydrogenated under a slightly positive pressure of hydrogen (balloon) at rt for 3 h. The suspension was diluted with MeOH, filtered through Celite and concentrated to dryness. The residue, purified by column chromatography (CH_2Cl_2, MeOH 15:1) gave an amorphous solid in quantitative yield. $[\alpha]_D^{24} = -77$ (*c* 1.0, CH_2Cl_2); FABMS *m/z* 381 [(M+Na)$^+$]; IR 3742, 3619, 3300, 2984, 2933, 1700, 1653, 1615, 1539, 1523, 1456, 1376, 1227, 1163, 1120, 1075, 995, 870, 747, 683 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (dd, 1H, $J_{NH,1} = 8.9$, $J_{NH,HC=} = 13.1$, NH), 8.07 (d, 1H, HC=), 5.20 (dd, 1H, $J_{1,2} = 4.6$, H-1), 4.77 (t, 1H, $J_{2,3} = 6.5$, H-2), 4.67 (dd, 1H, $J_{3,4} = 2.2$, H-3), 4.26 (each q, each 2H, $J_{H,H} = 7.1$, $2CH_2CH_3$), 4.08 (m, 1H, H-4), 2.89 (dd, 1H, $J_{4,5a} = 4.4$, $J_{5a,5b} = 13.4$, H-5a), 2.78 (dd, 1H, $J_{4,5b} = 6.3$, H-5b), 2.16 (s, 2H, NH_2), 1.64, 1.39 (each s, each 3H, $2(CH_3)_2CO_2$), 1.31, 1.30 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.7, 165.6 (2C=O), 157.1 (CH=), 114.3 [$(CH_3)_2CO_2$], 93.1 (C=), 88.6 (C-1), 83.3 (C-4), 82.2 (C-3), 79.3 (C-2), 59.8, 59.6 ($2CH_2CH_3$), 43.1 (C-5), 25.9, 24,6 [$(CH_3)_2CO_2$], 14.1 ($2CH_2CH_3$); HRCIMS *m/z* obsd. 358.1739 calcd. for $C_{16}H_{26}N_2O_7$ 358.1740.

4.7. 5-Deoxy-*N*-(2,2-diethoxycarbonylvinyl)-2,3-*O*-isopropylidene-5-isothiocianato-α-D-ribofuranosylamine, 13

To a solution of the amino compound **12** (0.274 mmol) in dichloromethane (9 mL) at 0 °C, *N*,*N*′-thiocarbonyldiimidazole (49 mg, 0.274 mmol) was added. When monitoring of the reaction by TLC (CH_2Cl_2/MeOH, 50:1) indicated that all starting material had been consumed (1 h), the solvent was evaporated to dryness. The residue was purified by column chromatography to give an amorphous solid in quantitative yield $[\alpha]_D^{23} = -14$ (*c* 0.9, CH_2Cl_2); FABMS *m/z* 423 [(M+Na)$^+$]; IR 3387, 3385, 2982, 2934, 2112, 1706, 1665, 1601, 1442, 1382, 1215, 960, 797 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (dd, 1H, $J_{NH,1} = 9.0$, $J_{NH,HC=} = 13.2$, NH), 8.07 (d, 1H, HC=), 5.33 (dd, 1H, $J_{1,2} = 4.6$, H-1), 4.88 (t, 1H, $J_{2,3} = 6.3$, H-2), 4.79 (dd, 1H, $J_{3,4} = 2.2$, H-3), 4.25, 4.18 (each q, each 2H, $J_{H,H} = 7.1$, $2CH_2CH_3$), 4.23 (m, 1H, H-4), 3.80 (dd, 1H, $J_{4,5a} = 4.1$, $J_{5a,5b} = 14.7$, H-5a), 3.70 (dd, 1H, $J_{4,5b} = 3.7$, H-5b), 1.65, 1.41 (each s, each 3H, $2(CH_3)_2CO_2$), 1.34, 1.30 (each t, each 3H, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.0, 165.6 (2C=O), 157.2 (CH=), 135.2 (C=S), 115.1 [$(CH_3)_2CO_2$], 94.0 (C=), 89.6 (C-1), 82.2 (C-4), 80.0 (C-3), 79.3 (C-2), 60.1, 60.0 ($2CH_2CH_3$), 47.6 (C-5), 26.1, 24.8 [$(CH_3)_2CO_2$], 14.4, 14.3 ($2CH_2CH_3$); Anal. Calcd for $C_{17}H_{24}N_2O_7S$: C, 50.99; H, 6.04; N, 6.99; S, 8.01. Found: C, 50.80; H, 6.03; N, 6.89; S, 7.76.

4.8. General procedure for the preparation of thioureas 15 and 16

A solution of the isothiocyanate **13** (0.144 mmol) and the amino derivative **12** for **15** and **14** for **16** (0.144 mmol) in DMF (1.5 mL) at 40 °C was stirred for 3 h. When monitoring of the reaction by TLC (ether, hexane 4:1 for **15** and CH_2Cl_2, MeOH, 40:1 for **16**) indicated that all starting material had been consumed, the solvent was evaporated to dryness. The residue was purified as described.

4.8.1. 1-Deoxy-(2,2-diethoxycarbonylvinylamino)-*N*,*N*′-bis-(2,3-*O*-isopropylidene-α-D-ribofuranos-5-yl) thiourea, 15. Column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH 60:1) gave an amorphous solid. Yield 88%. $[\alpha]_D^{24} = -69$ (*c* 1.0, CH_2Cl_2); FABMS *m/z* 781 [(M+Na)$^+$]; IR 3326, 2984, 2936, 1722, 1667, 1611,

1445, 1377, 1223, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.21 (dd, 1H, $J_{NH,1}$ = 9.1, $J_{NH,HC=}$ = 13.7, NH–CH=), 8.10 (d, 1H, HC=), 7.72 (br s, 1H, NH–C=S), 5.43 (m, 1H, H-1), 4.76–4.71 (m, 2H, H-2, H-3), 4.14–4.03 (m, 5H, H-4, $2CH_2CH_3$), 3.62 (br s, 1H, H-5a), 3.45 (br s, 1H, H-5b), 1.45, 1.28 (each s, each 3H, $2(CH_3)_2CO_2$), 1.20, 1.19 (each t, each 3H, $J_{H,H}$ = 7.0, $2CH_2CH_3$); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 183.3 (C=S), 167.2, 164.9 (2C=O), 157.5 (CH=), 112.7 [$(CH_3)_2CO_2$], 92.1 (C=), 87.8 (C-1), 81.8 (C-3), 80.0 (C-4), 78.6 (C-2), 59.3, 59.2 ($2CH_2CH_3$), 44.0 (C-5), 26.0, 24.8 [$(CH_3)_2CO_2$], 14.3, 14.2 ($2CH_2CH_3$). HRFABMS *m/z* obsd. 781.292992 calcd for $C_{33}H_{50}N_4O_{14}NaS$ 781.294194.

4.8.2. *N*-[2-*O*-Acetyl-1,3-dideoxy-1-(3″-acetyl-2″-methyl-fur-5″-yl)-α-L-threofuranos-3-yl],*N*′-[1-(2,2-diethoxycarbonylvinylamino-2,3-*O*-isopropylidene)-1-deoxy-α-D-ribofuranos-5-yl] thiourea, 16. Column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH 100:1) gave an amorphous solid. Yield 94%, $[\alpha]_D^{24} = -44$ (*c* 1.1, CH_2Cl_2); FABMS *m/z* 720 [$(M+Na)^+$]; IR, 3321, 2978, 2938, 1723, 1610, 1544, 1459, 1386, 1227, 1075, 1022, 864, 745 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.14 (dd, 1H, $J_{NH',1}$ = 9.0, $J_{NH',H'C=}$ = 13.9, NH′–CH′=), 8.05 (d, 1H, H′=), 7.92 (d, 1H, $J_{NH,3}$ = 6.5, NH), 7.56 (br s, 1H, NH′), 6.62 (s, 1H, H-4″), 5.40 (dd, 1H, $J_{1'2'}$ = 4.0, H-1′), 5.34 (m, 1H, H-2), 4.75–4.70 (m, 4H, H-1, H-3, H-2′ H-3′), 4.19 (q, 2H, $J_{H,H}$ = 7.1, CH_3CH_2''), 4.14–4.04 (m, 6H, H-4a, H-4′ $2CH_3CH_2'$), 3.78 (dd, 1H, $J_{3,4b}$ = 4.0, $J_{4a,4b}$ = 9.6, H-4b), 3.63 (m, 1H, H-5a′), 3.47 (m, 1H, H-5b′), 2.49 (s, 3H, =C—CH_3''), 2.02 (s, 3H, $OCOCH_3$), 1.45, 1.29 (each s, each 3H, $2(CH_3')_2CO_2$), 1.24, 1.20 (each t, each 3H, $J_{H,H}$ = 7.1, $2CH_2CH_3'$); 1.18 (t, 3H, CH_2CH_3); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 183.3 (C=S), 169.4 ($COOCH_3$), 167.0, 164.9 (2O=*C*), 162.7 (O=*C*″), 158.6 (C5″), 157.3 (C′=), 149.4 (C2″), 113.5 (C3″), 112.4 [$(CH_3)_2CO_2$], 108.9 (C4″), 91.9 (C=), 87.5 (C-1′), 81.6 (C-3′), 79.8 (C-2), 79.6 (C-4′), 78.3 (C-1), 77.3 (C-2′), 70.8 (C-4), 59.7 (C3), 59.7 (C_2''), 59.1, 58.9 ($2CH_2'CH_3$), 43.9 (C-5′), 25.7, 24.5 [$(CH_3)_2CO_2$], 20.4 ($COOCH_3$), 14.1, 14.0 ($2CH_2CH_3$), 13.9 (CH_2CH_3), 13.2 (=C—CH_3''). Anal. Calcd for $C_{31}H_{43}N_3O_{13}S$: C, 53.36; H, 6.21; N, 6.02; S, 4.60. Found: C, 53.36; H, 6.07; N, 5.74; S, 4.28.

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