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Reactions of per-*O*-acetylglucosyl isothiocyanate with carbon bases. A new method for the stereocontrolled syntheses of nucleosides and glucosylaminothiophenes

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Abstract

Reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **5** with diethyl malonate in a basic medium gave the corresponding glucopyranosyl thioamide without significant deacetylation. This thioamide in solution presents *Z-anti* as the sole configuration. Reactions of **5** with carbanions which have an ethoxycarbonyl group are a way to prepare anomerically pure *N*-nucleoside derivatives of pyrrole and tetrahydropyridine. Reactions of **5** with carbanions stabilized by one cyano group are used to prepare glucosylamino thiophenes with only the β-configuration. Some other stereochemical aspects of the prepared compounds are discussed.

1. Introduction

Sugar isothiocyanates are versatile starting materials in the syntheses of several types of glycoconjugates of biological interest.[1] Of the sugar isothiocyanates, the glycosyl ones are the most useful, which has prompted the development of both preparation procedures[1–5] and synthetic applications.[1,6–9] At the same time, the nucleosides and aminothiophenes are interesting chemotherapeutic tools in the treatment of various infectious diseases,[10] which has originated an increasing demand for new compounds, and considerable effort is being directed towards the syntheses of nucleoside analogues. In the framework of a program aimed at the development of sugar isothiocyanate chemistry, in this paper we report on the reactions of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate,[11] as an example of easily available glycosyl isothiocyanate, and different carbon bases. We also explore the use of the corresponding adducts in the preparation of pyrrole and pyridine nucleoside derivatives and of glycosylaminothiophenes. Many reactions of sugar isothiocyanates with N-, O- and S-nucleophiles have been studied;[1,12] however, the data on reactions with carbon bases are very scarce and limited to enamines as nucleophiles.[7,12]

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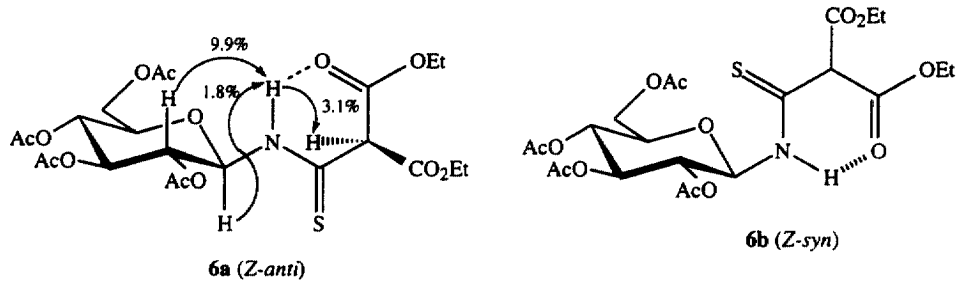
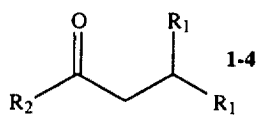


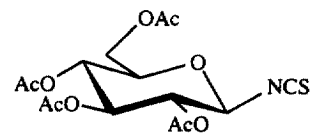
Fig. 1. Conformational stereoisomers by rotation around the C1′–N bond of **6**

2. Results and discussion

Commercially available diethyl malonate, ethyl cyanoacetate, phenylthioacetonitrile, cyanoacetamide and malonodinitrile, and the newly synthesized phenacyl and acetonyl derivatives of diethyl malonate **1–3** and of malonodinitrile **4** were used to generate carbanions to study their reactions with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **5**. Compounds **1–4** were prepared by alkylation of diethyl malonate or malonodinitrile with the corresponding α-haloketone in the presence of sodium hydride under a nitrogen atmosphere. The structures **1–4** were supported by IR, ^{1}H- and ^{13}C-NMR, and mass spectroscopic data (see Experimental).



1-4



5

	1	2	3	4
R_1	CO_2Et	CO_2Et	CO_2Et	CN
R_2	Ph	*p*-Cl-C_6H_4	Me	Ph

2.1. Reactions of the glucosyl isothiocyanate 5 with carbanions having two ester groups

Reaction of the isothiocyanate **5** with diethyl malonate in a basic medium produced the *N*-glucosylthioamide **6** (Fig. 1), whose analytical and spectroscopic (Table 1 and Experimental) data were in agreement with the proposed structure. The hydrogen bond between the NH and an ethoxycarbonyl group, shown in Fig. 1, was evident from the chemical shift of NH (9.55 ppm, close to that for other strongly chelated amino groups[6]), and from the existence of two different resonances in the ^{13}C-NMR spectrum at 165 (CO chelated) and 164 ppm (CO free) for the ethoxycarbonyl groups.

The sugar amides and thioamides can exist in four configurational and conformational stereoisomers (Fig. 2), and because of the important biological role of many glycoconjugates with an amido function, such as glycopeptides, glycolipids, calicheamicins,[13] and istamycins,[14] it is very interesting to know the exact stereochemistry of any amidosugar. This can be a way to rationalize the role of these compounds in molecular recognition or enzyme inhibition phenomena. The aforementioned equilibrium has been evaluated for several types of amidosugar derivative[15] and the *Z-anti* as sole conformer or mixtures of *Z-anti* and *Z-syn* conformers have been described as predominant stereoisomers. The recent observation[16] that the value (9–11 Hz) for the $^{3}J_{H,H}$ between the NH and the vicinal CH sugar proton (H-1 or H-2) is compatible with both the antiperiplanar and synperiplanar arrangements of NH and CH has demonstrated

Table 1
Selected NMR data (δ, ppm; *J*, Hz) for compounds **6–14**, **18–22**, and **25,26** in $CDCl_3$

Comp.	δ_{NH}	$\delta_{H\text{-}1'}$	$J_{1',NH}$	$J_{1',2'}$	$\delta_{C\text{-}1'}$	$\delta_{C=S}$
6	9.55d	5.75dd	8.1	9.5	81.7	193.7
7	11.21d	5.83t	8.2	8.2	81.9	196.5
8	11.15d	5.82t	8.2	8.2	81.9	195.4
9	10.80d	5.78dd	7.7	9.5	81.9	196.5
10[a]	-	6.46d	-	9.6	81.3	193.8
	-	6.40bd	-	9.6	81.2	193.7
11	-	4.77d	-	8.6	92.0	166.3
12[b]	-	4.77d	-	8.4	91.3	164.7
13	-	6.60d	-	9.6	83.1	196.7
14[a]	-	4.88d	-	8.7	89.2	165.4
	-	4.71d	-	8.7	90.5	166.7
18	10.32d	5.59dd	7.8	9.4	82.8	-
19	7.10d	5.42dd	8.3	9.4	83.3	-
20	6.54d	4.65t	9.5	9.5	84.9	-
21	8.66d	4.66t	9.5	9.5	84.5	-
22	6.77d	4.77t	9.5	9.5	84.4	-
25	-	4.88d	-	9.5	89.2	-
26	-	4.71d	-	9.5	90.5	-

[a]As a pair of diastereomers. At room temperature. [b]In $(CD_3)_2SO$.

a possible controversy in the published results, and new experiments have been carried out on both 2-amido-2-deoxy sugars[16] and glycosylamides.[17] In the case of the thioamido derivative **6**, the presence of a sole stereoisomer was evident from the ^{1}H- and ^{13}C-NMR spectra which showed only one signal set. The above-discussed hydrogen bond is compatible with the *Z-anti* **6a** and *Z-syn* **6b** stereoisomers (Fig. 1) and rules out the *E-anti* and *E-syn* configurations. To distinguish between **6a** and **6b** the indicated NOE experiments were carried out. From these, the 1,3-*syn*-axial disposition between N*H* and C2′–*H* was evident, and consequently the *Z-anti* stereoisomer is the only possible one.

Treatment of the glucosyl isothiocyanate **5** with the diethyl phenacyl (acetonyl) malonates **1–3** and sodium hydride gave the glucosyl thioamide derivatives **7–9** respectively. The NMR spectra of compounds **7** and **8** had single sets of signals, the data being very close to those for **6**, and supporting the same structure and stereochemistry. In these two cases, the chemical shift for the NH resonance was ≈11.2 ppm, corroborating the presence of a strong hydrogen bond. Compounds **7** and **8** were stable in solution in chloroform even after 10 days, and no formation of cyclic structures in the aglycon moiety were observed. This is probably due to the conjugation between the carbonyl and phenyl groups of the phenacyl radical. In the case of the reaction **5+3**, the ^{1}H-NMR data of the final product demonstrated the structure **9**; however the ^{1}H- and ^{13}C-NMR spectra showed the existence of an equilibrium between **9** and the two (5*R*,5*S*) hemiaminalic structures **10**. The ratio of **9**:**10** at room temperature was 1.1:10 and did not change over time. The two diastereomers **10** were in a 1:1 ratio, which is consistent with the nonstereogenic character of C-2 and C-3 in the aglycon moiety of **9**. With increasing temperature, the proportion of **9** in the equilibrium increased, the ratio of **9**:**10** reaching 1:4 at 50°C. Selected spectroscopic data of **10** are included in Table 1.

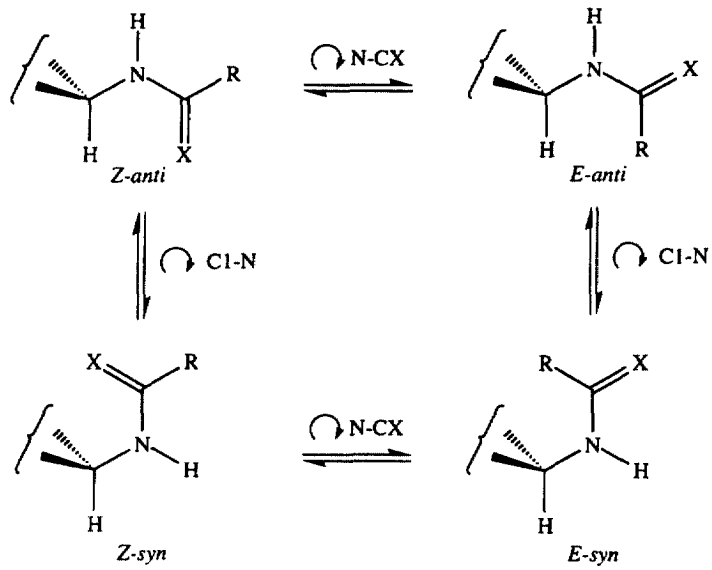
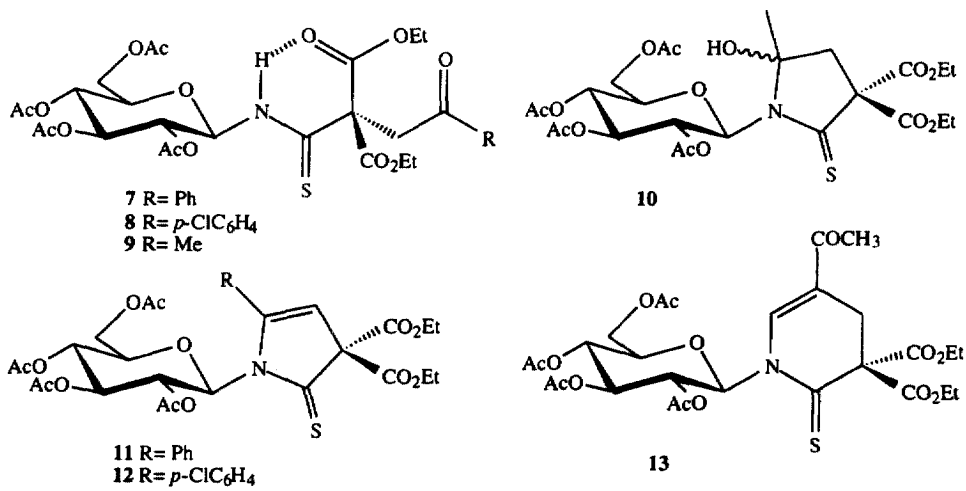


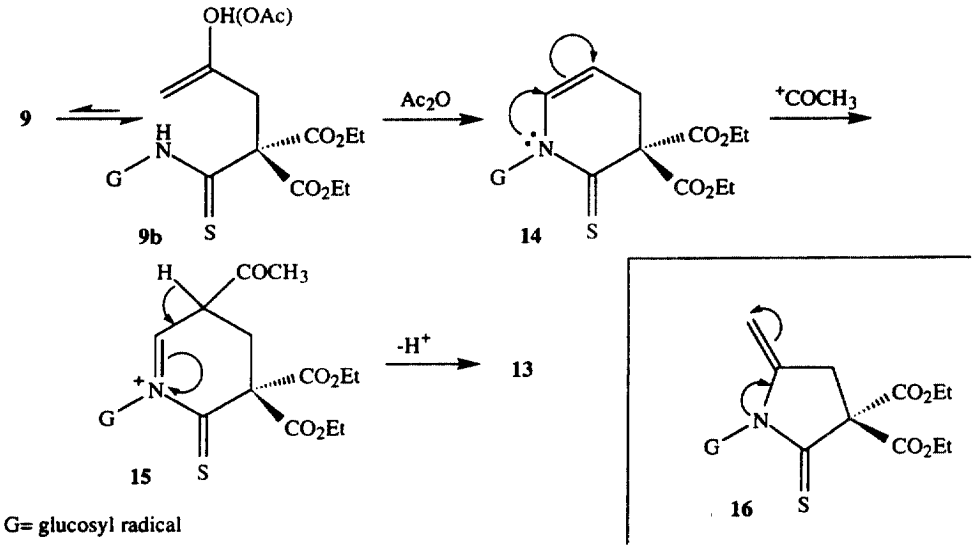
Fig. 2. Stereochemical equilibrium for the amide moiety of sugar amides (X=O) and thioamides (X=S)



Cyclodehydration of **7** and **8** with acetic anhydride and phosphoric acid gave the *N*-nucleoside derivatives of pyrroline-5-thione **11** and **12**. The resonance of the C=S group of **11** and **12** appeared at ≈165 ppm, a value very different to that for the starting materials, and close to that reported for related azolinethiones.[18] The ^{13}C resonances at ≈141 (C-2) and 116 (C-3) ppm and the ^{1}H resonance at 6.22 ppm supported the presence of the double bond in the aglycon moiety.

When the same treatment with acetic anhydride and phosphoric acid was carried out on **9**, the *N*-glucosyl pyridine derivative **13** was obtained in 65% yield after purification. The ^{1}H- and ^{13}C-NMR spectra of **13** showed a sole signal set, and no signals attributable to the other diasteromeric structure were observed. In contrast to **11** and **12**, the C=S group of **13** resonated at 196.7 ppm; the signals for the C=CH group appeared at 152.9 (C-5), 105.1 (C-6) and 6.49 (=CH) ppm. This latter resonance was a double doublet showing allylic couplings (2.2 and 1.7 Hz) with the protons on C-4. The resonance of the ketone C=O was observed at 199.6 and there was no signal for NH. A possible mechanism to explain the formation of the *N*-nucleoside analogue **13** is depicted in Scheme 1. The enolic form **9b**,

which can be acetylated, undergoes internal addition, followed by dehydration (if acetylated elimination of AcOH) to give **14**. This intermediate is an enamine analogue with strong nucleophilic character at the β-carbon (C-5). Consequently it can react at this position with an acetyl cation to give **13**, after loss of a proton. A possible structure **16** for the intermediate was considered, but the spectroscopic data and the existence of only one stereoisomer for **13** ruled out this formula. Related six-membered cyclizations of γ-oxothioureas have been described.[19]



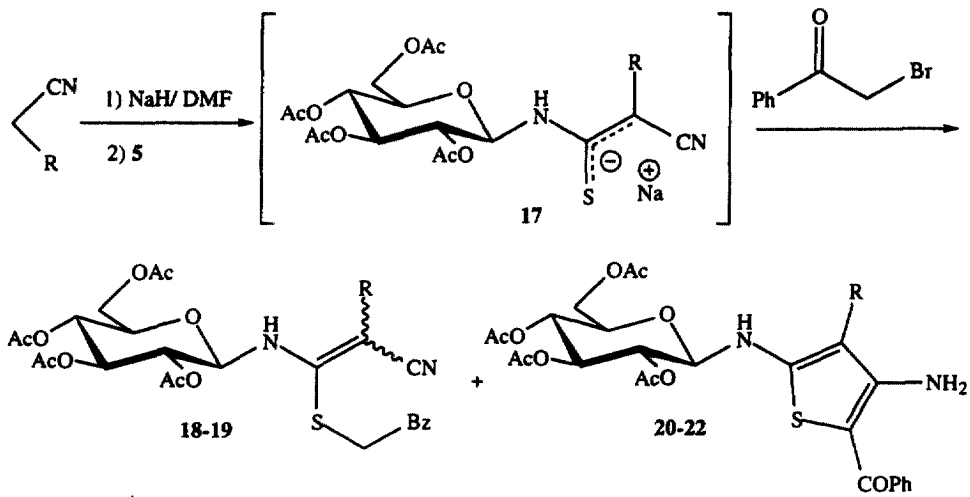
Scheme 1. Possible mechanism for the formation of **13**

2.2. *Reactions of the isothiocyanate 5 with carbanions having one cyano group*

When the carbanion from ethyl cyanoacetate reacted with the glucosyl isothiocyanate **5**, a non-isolatable salt (**17**) was formed (Scheme 2); which by reaction with phenacyl bromide gave the *S*-phenacyl derivative **18** in high yield, and no cyclization to a thiophene derivative was observed. The phenacyl group of **18** was evident from the IR band at 1684 cm^{-1} (C=O) and from the ^1H resonances at 4.96 and 4.63 ppm (AB system for CH_2, J_{AB} 17.1 Hz) and ^{13}C resonances at 191.8 (C=O) and 42.7 ppm (CH_2).[20] The cyano group resonated at 117.3 ppm and its IR C≡N bond appeared at 2212 cm^{-1}; there were no signals for a C=S group. The chemical shift for the resonance of the NH (10.32 ppm) demonstrated a strong hydrogen bond between this proton and the carbonyl of the ester group. The existence of this H-bond supported the *E* configuration assigned to the C=C double bond.

In the case of the reaction of **5** with phenylthioacetonitrile, and afterwards with phenacyl chloride, the *S*-phenacyl derivative **19** and the glucosylamino thiophene **20** were obtained after chromatography. The structural data of **19** closely resembled those of **18** (see Table 1 and Experimental), except the resonance for NH, which appeared at 7.10 ppm and corresponds to a weakly chelated amino proton. This fact is indicative of *Z* configuration of the C=C double bond, with a hydrogen bond between the *cis* NH and C≡N groups. Dilution studies confirmed the intramolecular chelated structure. Compound **20** (see structure discussion together with **21** and **22**) with a thiophene structure arises from the nucleophilic addition of the methylene of the phenacyl group onto the cyano group of the *E* stereoisomer of **19**.

When cyanoacetamide and malonodinitrile were used to generate the carbanions, the glucosylamino-thiophenes **21** and **22** were isolated. The IR spectra of **20–22** revealed the presence of the NH_2 stretching



	18	19	20	21	22
R=	CO_2Et	SPh	SPh	$CONH_2$	CN
Conf. C=C	*E*	*Z*	-	-	-

Scheme 2. Reaction of compound **5** with cyanoderivatives

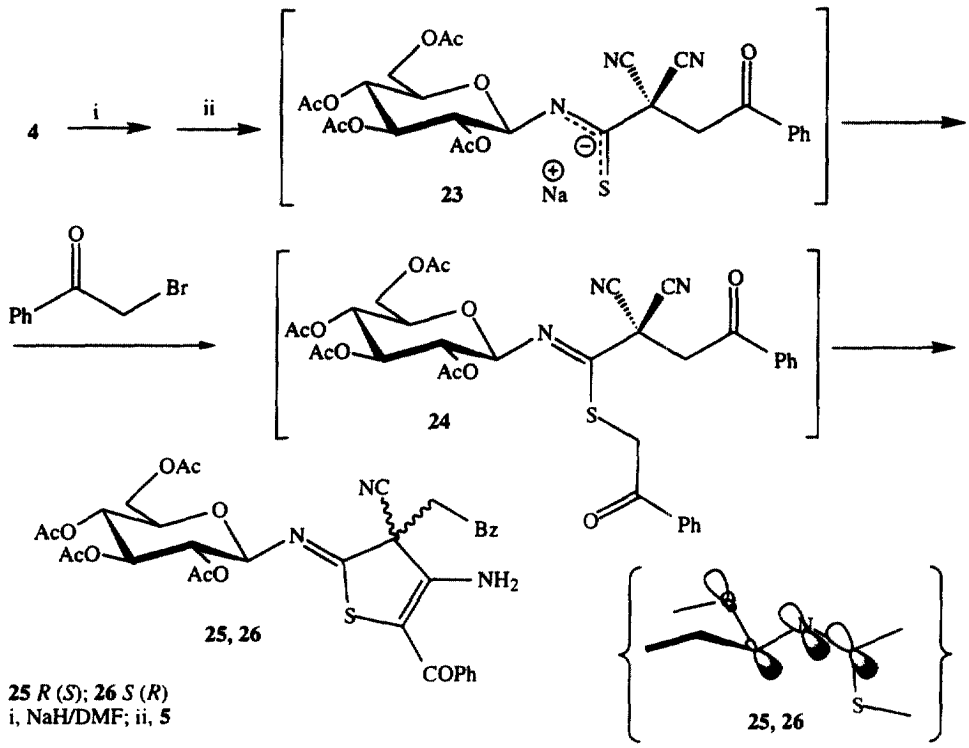
band at 3424–3322 cm^{-1} and, in the case of **22**, a C≡N absorption at 2212 cm^{-1}. The ^{1}H-NMR spectra showed broad signals for the NH_2 groups and a doublet for the NH at 6.54 ppm for **20** (nonchelated structure), 8.66 ppm for **21** (hydrogen bond between NH and CO groups) and 6.77 ppm (weak hydrogen bond between NH and C≡N). In contrast with what happened with **18** and **19**, in the three cases **20–22**, the H-1 of the sugar ring resonated at higher field than H-2, H-3 and H-4. No signals for a C=S group were observed.

Some reactions between benzoyl isothiocyanate and methylene active reagents have been studied[21] and a structure related to **17** has been proposed as an intermediate.

The reaction of **5** with a dicyano derivative has also been studied. Thus, when **5** was added on the carbanion proceeding from phenacylmalonodinitrile **4**, and the resulting salt **23** was *S*-alkylated with phenacyl bromide, the diasteromeric mixture (C-3 epimers) of glucosyliminothiophenes **25** and **26** was obtained. This mixture could be resolved chromatographically, and **25** (major) and **26** (minor) were isolated as pure products, although the configuration of C-3 could not be assigned. Compounds **25** and **26** are formed (Scheme 3) by nucleophilic addition of the methylene of the *S*-alkyl group of **24** on each one of the cyano groups. The ^{1}H-NMR spectra (Table 1 and Experimental) of **25** and **26** had no signals for NH, and H-1 of the sugar ring resonated as a doublet. The chemical shifts for the resonances of C-1 of the sugar ring and C=N (C-2 of the thiophene ring) were close to those described for related glucosylimino derivatives.[22] The resonances for the C–CH_2 group appeared at ≈42.5 ppm and the chemical shifts for the resonances of the NH_2 were ≈8.4 ppm, a value at a remarkably lower field than those for the same protons in **20–22**; this suggests a possible seven-membered ring hydrogen bond with the carbonyl of phenacyl group.

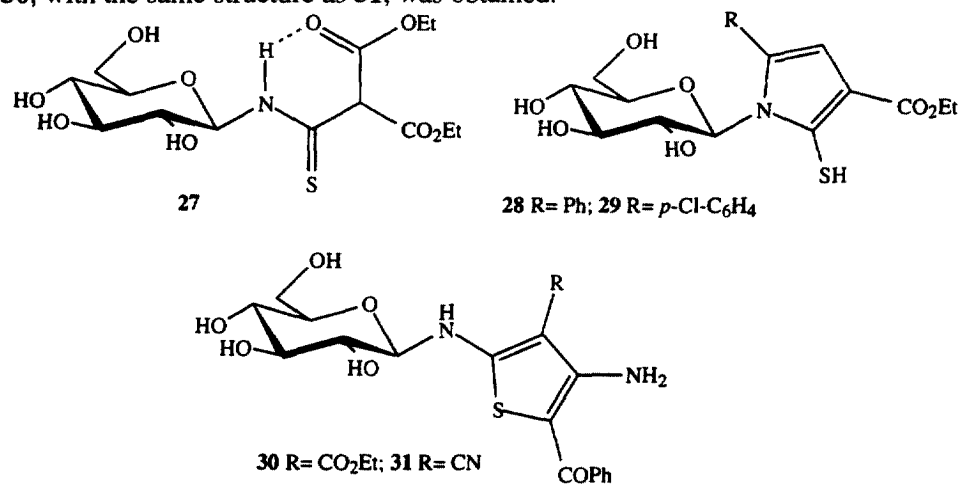
As with other aldimines,[22] the glucosylimines **25** and **26** probably prefer the conformation indicated in the Scheme 3, because this is stabilized by a $\pi \rightarrow \sigma^*$ delocalization of the π electrons of the C=N bond in the σ^* orbital of the C1–O bond in the pyranosyl ring.

Conventional deacetylation of compounds **6**, **11**, **12**, **18** and **22** gave the glucosyl thioamide **27**, the *N*-nucleosides **28** and **29**, and the glucosylaminothiophenes **30–31**. The deacetylation of the phenylthio- and



Scheme 3. Reaction of compound **5** with phenacyl malonodinitrile

carbamoylderivatives **19–21** was also tried but in these three cases decomposition took place, and it was not possible to isolate the corresponding deacetylated derivative. Compounds **27–31** were characterized by their NMR data (see Experimental). Compound **27** showed a strongly chelated structure (δ_{NH} 10.6 ppm). During the treatment with sodium methoxide of the *N*-nucleosides **11** and **12**, saponification of an ethoxycarbonyl group and then decarboxylation took place, and in this way **28** and **29** had only one ethoxycarbonyl group. Compound **29** was isolated whereas **28** was only spectroscopically detected. In the case of compound **18**, under deacylation conditions, the cyclization took place and the aminothiophene derivative **30**, with the same structure as **31**, was obtained.



In conclusion, a glycosyl isothiocyanate, the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **5**, can react with methylene active compounds, in a basic medium, without significant deacylation. These reactions open ways to prepare glycosylthioamides, nucleoside analogues of different heterocycles, and glycosylamino heterocycles. In all cases, the anomeric configuration is fixed by the C-1′ configuration of the glucosyl isothiocyanate. In cases of the glucosylamino derivatives, the anomerization described for other free and *O*-protected glycosyl amines did not take place.[23,24]

3. Experimental

3.1. General

Melting points are uncorrected. Optical rotations were measured for solutions in dichloromethane. FTIR spectra were recorded for KBr discs or thin films. ^{1}H-NMR (500 and 300 MHz) and ^{13}C-NMR (125.7 and 75.4 MHz) spectra were obtained for solutions in $CDCl_3$, $(CD_3)_2SO$ or MeOH-d_4. Assignments were confirmed by homonuclear 2D COSY and heteronuclear 2D correlated experiments. FAB-mass spectra were recorded with a Kratos MS-80RFA instrument with a resolution of 1000 (10% valley definition). Ions were produced by a beam of xenon atoms (6–7 kV) using a matrix consisting of thioglycerol or 3-nitrobenzyl alcohol and NaI as salt. HREIMS (70 eV), HRCIMS (150 eV) and HRDCIMS (150 eV) experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10 000 (5% valley definition). Isobutane was used as the reactive gas (500 mA, 8 kV). TLC was performed on silica gel HF_{254}, with detection by UV light or charring with H_2SO_4. Silica gel 60 (Merck, 230–400 mesh) was used for preparative chromatography.

3.2. General procedure for the preparation of 1–4

To a stirred solution of diethyl malonate (6.59 mmol) for **1–3** or malononitrile for **4** (6.59 mmol) in *v* mL of dry DMF over molecular sieves and under nitrogen, 9.88 mmol of NaH (as a suspension in mineral oil) are added. After 5 min, the corresponding α-haloketone (6.59 mmol) was added dropwise as a solution in 1.5 mL of dry DMF over molecular sieves and under nitrogen (for **1–3**) or added directly as a solid (in the case of **4**) onto the carbanion. The corresponding mixture was stirred at 30°C for 30 min, then diluted with ether (for **1–3**) or dichloromethane (for **4**), washed with water, dried ($MgSO_4$), filtered and evaporated to dryness.

3.2.1. Diethyl phenacylmalonate 1

v=1 mL. Column chromatography (ether:hexane=1:4) of the residue gave an oil (1.08 g, 59%); IR ν_{max} 3063, 2984, 2934, 1732, 1690, 1451, 1368, 1267, 1155 and 1031 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.01–7.27 (m, 5H, Ph), 4.29–4.20 (m, 2H, C*H*$_2$CH$_3$), 4.06 (t, 1H, J_{HC,CH_2}=7.1, HC), 3.64 (d, 2H, C*H*$_2$COPh), 1.30 (t, 6H, $^3J_{H,H}$=7.1, 2CH$_2$C*H*$_3$) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 196.5 (*C*OPh), 169.0 (2C, 2*C*O$_2$Et), 136.4–128.1 (6C, Ph), 61.7 (2C, 2*C*H$_2$CH$_3$), 47.1 (HC), 37.7 (*C*H$_2$COPh), 13.9 (2C, 2CH$_2$*C*H$_3$) ppm; HREIMS *m/z* obsd 278.1152, calcd for $C_{15}H_{18}O_5$ 278.1154.

3.2.2. Diethyl p-chlorophenacylmalonate 2

v=2 mL. Column chromatography (ether:hexane=1:4) of the residue gave an oil (1.65 g, 80%); IR ν_{max} 3094, 2984, 2936, 1738, 1690, 1454, 1368, 1275, 1179 and 1032 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96–7.42 (m, 4H, Ph), 4.27, 4.26 (each q, each 2H, $^3J_{H,H}$=7.1, 2C*H*$_2$CH$_3$), 4.07 (t, 1H, J_{HC,CH_2}=7.1,

HC), 3.61 (d, 2H, CH_2COPh), 1.31 (t, 6H, $2CH_2CH_3$) ppm; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 195.3 (*C*OPh), 168.8 (2C, $2CO_2$Et), 140.3–128.9 (6C, Ph), 61.7 (2C, $2CH_2CH_3$), 47.0 (HC), 36.7 (CH_2COPh), 13.9 (2C, $2CH_2CH_3$) ppm; HREIMS *m/z* obsd 312.0780, calcd for $C_{15}H_{17}O_5Cl$ 312.0765.

3.2.3. Diethyl acetonylmalonate 3

v=1 mL. Column chromatography (ether:hexane=1:4) of the residue gave an oil (0.60 g, 42%); IR ν_{max} 2986, 2940, 1738, 1458, 1366, 1271, 1159 and 1024 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.20 (q, 4H, $^3J_{H,H}$=7.1, $2CH_2CH_3$), 3.85 (t, 1H, J_{HC,CH_2}=7.1, HC), 3.06 (d, 2H, CH_2COCH_3), 2.21 (s, 3H, CH_2COCH_3), 1.27 (t, 6H, $2CH_2CH_3$) ppm; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 204.8 ($COCH_3$), 168.7 (2C, $2CO_2$Et), 61.6 (2C, $2CH_2CH_3$), 46.8 (HC), 41.9 (CH_2COPh), 29.6 ($COCH_3$), 13.9 (2C, $2CH_2CH_3$) ppm; HREIMS *m/z* obsd 216.1004, calcd for $C_{10}H_{16}O_5$ 216.0998.

3.2.4. Phenacyl malonodinitrile 4

v=2 mL. Column chromatography (dichloromethane) of the residue gave a white solid (0.79 g, 65%) which gradually becomes brown at room temperature. This brown impurity could be removed by further column chromatography (ether:hexane=1:1); IR ν_{max} 3054, 2907, 1732, 2255, 1682, 1589, 1447, 1358 and 1217 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.03–7.56 (m, 5H, Ph), 4.48 (t, 1H, J_{HC,CH_2}=6.8, HC), 3.84 (d, 2H, CH_2) ppm; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 192.2 (*C*OPh), 134.7–128.0 (6C, Ph), 112.3 (2C, 2CN), 39.4 (CH_2COPh), 17.6 (HC) ppm; HREIMS *m/z* obsd 184.0635, calcd for $C_{11}H_8ON_2$ 184.0637.

3.3. Diethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-aminothiocarbonyl malonate 6

To a stirred solution of **5**[11] (0.50 mg, 1.28 mmol) in dry DMF (4 mL) under argon at 40°C, diethyl malonate (0.19 mL, 1.28 mmol) and KOH (1.28 mmol) were added. The mixture was stirred for 1 h at 40°C, then diluted with dichloromethane, washed with water, dried ($MgSO_4$), filtered and evaporated to dryness. The resulting product was purified by recrystallization (ether:hexane). **6** was obtained as a crystalline solid (0.43 mg, 61%) which had mp 101–102°C (ether:hexane); [α] +52 (*c* 1.0); IR ν_{max} 3308, 2982, 2942, 1750, 1537, 1420, 1370, 1225 and 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.55 (d, 1H, $J_{NH,1}$=8.1, NH), 5.75 (dd, 1H, $J_{1,2}$=9.5, H-1), 5.35 (t, 1H, $J_{2,3}$=$J_{3,4}$=9.5, H-3), 5.21 (t, 1H, H-2), 5.12 (t, 1H, $J_{4,5}$=9.5, H-4), 4.97 (s, 1H, CH), 4.31–4.21 (m, 5H, H-6a and $2CH_2CH_3$), 4.11 (dd, 1H, $J_{5,6b}$=2.1, $J_{6a,6b}$=12.5, H-6b), 3.86 (ddd, 1H, $J_{5,6a}$=4.5, H-5), 2.09, 2.08, 2.04, 2.03 (each s, each 3H, 4Ac), 1.31, 1.28 (each t, each 3H, $^3J_{H,H}$=7.1, $2CH_2CH_3$) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 193.7 (C=S), 170.5, 170.4, 169.7, 169.3 ($4COCH_3$), 165.0, 164.0 ($2CO_2$Et), 81.7 (C-1), 73.7 (C-5), 72.4 (C-3), 69.8 (C-2), 68.0 (C-4), 66.2 (CH), 62.8, 62.7 ($2CH_2CH_3$), 61.4 (C-6), 20.5, 20.2 ($2COCH_3$), 20.4 (2C, $2COCH_3$), 13.8 and 13.6 ($2CH_2CH_3$) ppm; FABMS *m/z* 572 (100, $[M+Na]^+$). Anal. calcd for $C_{22}H_{31}O_{13}NS$: C, 48.08; H, 5.69; N, 2.55; S, 5.83. Found: C, 47.94; H, 5.60; N, 2.66; S, 5.66.

3.4. General procedure for the preparation of 7–10

To a stirred solution of 0.26 mmol **1** for **7**, **2** for **8**, or **3** for **9** and **10** in *v* mL of dry DMF over molecular sieves and under nitrogen, 0.31 mmol of NaH (as a suspension in mineral oil) was added. After 5 min, 0.26 mmol of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate **5** was added dropwise as a solution in 0.75 mL of dry DMF over molecular sieves and under nitrogen onto the carbanion. The mixture was stirred at 30°C for *t* min, then diluted with ether, washed with water, dried ($MgSO_4$), filtered and evaporated to dryness.

3.4.1. N-*(2′,3′,4′,6′-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,2-diethoxycarbonyl-4-phenyl-4-oxo-thiobutanamide 7*

Column chromatography (ether:hexane=1:1 and 3:1) of the residue gave a white amorphous solid (69 mg, 40%) which had [α] +39 (*c* 1.0); IR ν_{max} 3214, 3030, 2980, 2942, 1751, 1688, 1537, 1452, 1370, 1225 and 1042 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.21 (d, 1H, $J_{NH,1'}$=8.2, NH), 7.98–7.27 (m, 5H, Ph), 5.83 (t, 1H, $J_{1',2'}$=8.2, H-1′), 5.37–5.30 (m, 2H, H-2′, 3′), 5.15 (m, 1H, H-4′), 4.70 (d, 1H, $J_{3a,3b}$=18.6, C-3a), 4.33–4.20 (m, 5H, H-6′a and 2CH_2CH$_3$), 4.29 (d, 1H, C-3b), 4.09 (dd, 1H, $J_{5',6'b}$=2.3, $J_{6'a,6'b}$=12.4, H-6′b), 3.83 (ddd, 1H, $J_{4,5}$=10.0, $J_{5',6'a}$=4.6, H-5), 2.09, 2.06 (each s, each 3H, 2Ac), 2.03 (s, 6H, 2Ac), 1.22, 1.19 (each t, each 3H, $^3J_{H,H}$=7.1, 2CH$_2$CH_3) ppm; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 199.9 (C-4), 196.5 (C-1), 170.6, 170.0, 169.9, 169.4 (4*C*OCH$_3$), 168.0, 166.2 (2*C*O$_2$Et), 135.9–128.1 (6C, Ph), 81.9 (C-1′), 73.9 (C-5′), 73.0, 69.9 (C-2′, 3′), 68.3 (C-4′), 65.4 (C-2), 63.0, 62.9 (2*C*H$_2$CH$_3$), 61.6 (C-6′), 47.1 (C-3), 20.6, 20.4 (2CO*C*H$_3$), 20.5 (2C, 2CO*C*H$_3$), 13.6, 13.5 (2CH$_2$*C*H$_3$) ppm; FABMS *m/z* 690 (100, [M+Na]$^{+\cdot}$). Anal. calcd for $C_{30}H_{37}O_{14}NS$: C, 53.97; H, 5.59; N, 2.10; S, 4.80. Found: C, 53.97; H, 5.51; N, 2.21; S, 5.18.

3.4.2. N-*(2′,3′,4′,6′-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-4-(4-chlorophenyl)-2,2-diethoxycarbonyl-4-oxo-2-thiobutanamide 8*

Column chromatography (ether:hexane=1:1 and 3:1) of the residue gave a white amorphous solid (108 mg, 59%) which had [α] +45 (*c* 1.0); IR ν_{max} 3206, 3041, 2984, 2942, 1755, 1684, 1539, 1368, 1225 and 1038 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.15 (d, 1H, $J_{NH,1'}$=8.2, NH), 7.93–7.40 (m, 4H, Ar), 5.82 (t, 1H, $J_{1',2'}$=8.2, H-1′), 5.37–5.27 (m, 2H, H-2′, 3′), 5.15 (t, 1H, $J_{3',4'}$=$J_{4',5'}$=10.0, H-4′), 4.66, 4.25 (each d, each 1H, $J_{3a,3b}$=18.6, H-3a, 3b), 4.24 (dd, 1H, $J_{5',6'a}$=4.6, $J_{6'a,6'b}$=12.4, H-6′a), 4.24 (q, 4H, $^3J_{H,H}$=7.1, 2CH_2CH$_3$), 4.09 (dd, 1H, $J_{5',6'b}$=2.3, H-6′b), 3.83 (ddd, 1H, H-5′), 2.09, 2.07 (each s, each 3H, 2Ac), 2.04 (s, 6H, 2Ac), 1.23, 1.20 (each t, each 3H, 2CH$_2$CH_3) ppm; ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 199.6 (C-4), 195.4 (C-1), 170.5, 169.4 (2*C*OCH$_3$), 169.9 (2C, 2*C*OCH$_3$), 167.8, 166.0 (2*C*O$_2$Et), 140.0–128.9 (6C, Ar), 81.9 (C-1′), 73.8 (C-5′), 72.9, 70.4 (C-2′, 3′), 68.2 (C-4′), 65.3 (C-2), 63.0, 62.9 (2*C*H$_2$CH$_3$), 61.6 (C-6′), 46.9 (C-3), 20.6, 20.4 (2CO*C*H$_3$), 20.5 (2C, 2CO*C*H$_3$), 13.5 and 13.4 (2CH$_2$*C*H$_3$) ppm; FABMS *m/z* 724 (100, [M+Na]$^{+\cdot}$). Anal. calcd for $C_{30}H_{36}O_{14}NSCl$: C, 51.32; H, 5.17; N, 1.99; S, 4.57. Found: C, 51.21; H, 4.99; N, 2.05; S, 4.58.

3.4.3. N-*(2′,3′,4′,6′-Tetra*-O-*acetyl-β*-D-*glucopyranosyl)-2,2-diethoxycarbonyl-4-oxothiopentanamide (9) and 2(*R,S*)-4,4-diethoxycarbonyl-2-hydroxy-2-methyl-1-(2′,3′,4′,6′-tetra*-O-*acetyl-β*-D-*glucopyranosyl)-5-thioxopyrrolidine 10*

Column chromatography (ether:hexane=3:1) of the residue gave a white amorphous solid **9**+**10** (58 mg, 37%).

Compound **9**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 10.80 (d, 1H, $J_{NH,1'}$=7.7, NH), 5.78 (dd, 1H, $J_{1',2'}$=9.5, H-1′), 5.39 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.5, H-3′), 5.24 (t, 1H, H-2′), 5.12 (t, 1H, $J_{4',5'}$=9.5, H-4′), 4.30–4.18 (m, 4H, H-6′a, 6′b and CH_2CH$_3$), 3.86–3.83 (m, 1H, H-5′), 2.95–2.75 (m, 2H, H-3a, 3b), 2.09, 2.06, 2.02, 1.92 (each s, each 3H, 4Ac), 1.73 (s, 1H, CH_3COCH$_2$), 1.26 (t, 6H, $^3J_{H,H}$=7.1, 2CH$_2$CH_3) ppm.

Compound **10**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.38 (d, 1H, $J_{1',2'}$=9.5, H-1′), 5.35, 5.33 (each t, each 1H, $J_{2',3'}$=$J_{3',4'}$=9.5, H-2′, 3′), 5.15 (t, 1H, $J_{4',5'}$=9.5, H-4′), 4.30–4.18 (m, 4H, H-6′a, 6′b and CH_2CH$_3$), 3.81 (dt, 1H, $J_{5',6'a}$=$J_{5',6'b}$=3.3, H-5′), 2.81–2.76 (m, 2H, H-3a, 3b), 2.07, 2.04, 2.01, 1.98 (each s, each 3H, 4Ac), 1.62 (s, 1H, CH_3COCH$_2$), 1.29 (t, 6H, $^3J_{H,H}$=7.1, 2CH$_2$CH_3) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ 199.7, 195.8 (2CS), 171.9–166.0 (12C, 4*C*O$_2$Et and 8*C*OCH$_3$), 84.2, 83.7 (2C-1′), 75.6, 74.9 (2C-5′), 73.0, 71.9 (2C-2′), 72.3, 70.4 (2C-3′), 67.9, 67.6 (2C-4′), 96.7, 95.2 (2C-2), 70.9, 70.2 (2C-4), 63.0–60.9 (2C-6′ and 4*C*H$_2$CH$_3$), 46.7, 44.9 (2C-3), 27.3, 25.0 (2CH$_3$), 20.7–20.2 (8C, 8CO*C*H$_3$), 13.8,

13.7 (4C, $4CH_2CH_3$) ppm; FABMS *m/z* 628 (100, $[M+Na]^{+\cdot}$). HRFABMS *m/z* obsd 628.1665, calcd for $C_{25}H_{35}O_{14}NSNa$ 628.1676. Anal. calcd for $C_{25}H_{35}O_{14}NS$: C, 49.58; H, 5.83; N, 2.31; S, 5.29. Found: C, 48.91; H, 5.47; N, 2.45; S, 5.25.

3.5. General procedure for the preparation of 11–13

The starting material (**7** for **11**, **8** for **12** or **9** for **13**, 0.34 mmol) was dissolved in 3.4 mL of acetic anhydride and 0.17 mL of melted anhydrous H_3PO_4. The mixture was stirred at r.t. for *t* hours and then poured into ice–water, extracted with ether, washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was taken up in 96% ethanol and treated with basic resin Amberlist IR-45(OH), filtered and evaporated. The residue was purified by column chromatography (ether:hexane=3:1).

3.5.1. 4,4-Diethoxycarbonyl-2-phenyl-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-5-thioxo-2-pyrroline 11

White and amorphous solid (168 mg, 76%); *t*=12 h; [α] −7 (*c* 0.9); IR ν_{max} 3067, 2980, 1750, 1653, 1447, 1371, 1225 and 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.52–7.39 (m, 5H, Ph), 6.22 (s, 1H, H-3), 5.32 (t, 1H, $J_{2',3'}=J_{3',4'}$=8.9, H-3′), 5.23 (dd, 1H, $J_{1',2'}$=8.6, H-2′), 5.20 (t, 1H, $J_{4',5'}$=8.9, H-4′), 4.77 (d, 1H, H-1′), 4.32–4.24 (m, 5H, H-6′a and $2CH_2CH_3$), 4.20 (dd, 1H, $J_{5',6'b}$=2.2, $J_{6'a,6'b}$=12.3, H-6′b), 3.86 (ddd, 1H, $J_{5',6'a}$=5.1, H-5′), 2.09, 2.05, 2.01, 1.97 (each s, each 3H, 4Ac), 1.29, 1.28 (each t, each 3H, $^3J_{H,H}$=7.0, $2CH_2CH_3$) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 170.7, 170.3, 169.3, 168.9 ($4COCH_3$), 166.3 (C-5), 165.3, 165.2 ($2CO_2Et$), 142.4 (C-2), 132.1–126.4 (6C, Ph), 115.0 (C-3), 92.0 (C-1′), 76.9 (C-4), 73.7 (C-5′), 73.5 (C-3′), 71.4 (C-2′), 68.4 (C-4′), 62.9, 62.8 ($2CH_2CH_3$), 62.1 (C-6′), 20.7 ($COCH_3$), 20.5 (3C, $3COCH_3$), 13.9 and 13.8 ($2CH_2CH_3$) ppm; FABMS *m/z* 672 (100, $[M+Na]^{+\cdot}$). Anal. calcd for $C_{30}H_{35}O_{13}NS$: C, 55.46; H, 5.43; N, 2.16; S, 4.94. Found: C, 55.43; H, 5.20; N, 2.17; S, 5.08.

3.5.2. 2-(4-Chlorophenyl)-4,4-diethoxycarbonyl-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-5-thioxo-2-pyrroline 12

White and amorphous solid (156 mg, 67%); *t*=10 h; [α] +54 (*c* 0.7); IR ν_{max} 3075, 2980, 1753, 1655, 1437, 1371, 1225 and 1040 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42–7.40 (m, 4H, Ar), 6.22 (s, 1H, H-3), 5.32 (t, 1H, $J_{2',3'}=J_{3',4'}$=9.3, H-3′), 5.22 (dd, 1H, $J_{1',2'}$=8.4, H-2′), 5.19 (t, 1H, $J_{4',5'}$=9.3, H-4′), 4.77 (d, 1H, H-1′), 4.32–4.24 (m, 4H, H-6′a), 4.29 (q, 4H, $^3J_{H,H}$=7.1, $2CH_2CH_3$), 4.20 (dd, 1H, $J_{5',6'b}$=2.4, $J_{6'a,6'b}$=12.4, H-6′b), 3.86 (ddd, 1H, $J_{5',6'a}$=4.6, H-5′), 2.09, 2.05, 2.01, 1.97 (each s, each 3H, 4Ac), 1.29, 1.28 (each t, each 3H, $2CH_2CH_3$) ppm; ^{13}C-NMR (125.7 MHz, DMSO-d_6): δ 170.0, 169.6, 169.3, 168.6 ($4COCH_3$), 164.8, 164.8 ($2CO_2Et$), 164.7 (C-5), 140.3 (C-2), 134.5–128.1 (6C, Ar), 116.4 (C-3), 91.3 (C-1′), 76.7 (C-4), 72.5 (C-5′), 72.3 (C-3′), 71.2 (C-2′), 68.0 (C-4′), 62.5, 62.4 ($2CH_2CH_3$), 61.8 (C-6′), 20.5, 20.4 ($2COCH_3$), 20.3 (2C, $2COCH_3$), 13.7, 13.6 ($2CH_2CH_3$) ppm; FABMS *m/z* 706 (100, $[M+Na]^{+\cdot}$). Anal. calcd for $C_{30}H_{34}O_{13}NSCl$: C, 52.67; H, 5.01; N, 2.05; S, 4.69. Found: C, 52.49; H, 4.94; N, 2.40; S, 4.59.

3.5.3. 5-Acetyl-3,3-diethoxycarbonyl-1,2,3,4-tetrahydro-1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxopyridine 13

Amorphous solid (139 mg, 65%); *t*=7 h; [α] −20 (*c* 0.4); IR ν_{max} 2978, 1753, 1690, 1605, 1439, 1371, 1223, 1098 and 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.60 (d, 1H, $J_{1',2'}$=9.6, H-1′), 6.49 (dd, 1H, H-6), 5.66 (t, 1H, $J_{2',3'}$=9.6, H-2′), 5.42 (t, 1H, $J_{3',4'}$=9.6, H-3′), 5.25 (t, 1H, $J_{4',5'}$=9.6, H-

4′), 4.39 (dd, $J_{5',6'a}$=3.7, $J_{6'a,6'b}$=12.7, H-6′a), 4.33–4.21 (m, 4H, 2CH_2CH$_3$), 4.17 (dd, 1H, $J_{5',6'b}$=2.0, H-6′b), 3.93 (ddd, 1H, H-5′), 4.03 (dd, 1H, $J_{4a,4b}$=19.1, $J_{4a,6}$=1.7, H-4a), 3.75 (dd, 1H, $J_{4b,6}$=2.2, H-4b), 2.33 (s, 3H, =CCOCH$_3$), 2.13, 2.08, 2.04, 1.94 (each s, each 3H, 4Ac), 1.30, 1.29 (each t, each 3H, $^3J_{H,H}$=7.1, 2CH$_2$CH_3) ppm; ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 199.6 (=C*C*OCH$_3$), 196.7 (C-2), 170.1, 169.6 (2*C*OCH$_3$), 169.3 (2C, 2*C*OCH$_3$), 166.4, 165.8 (2*C*O$_2$Et), 152.9 (C-5), 105.1 (C-6), 83.1 (C-1′), 74.8 (C-5′), 72.8 (C-3′), 69.9 (C-3), 67.2 (C-2′), 66.9 (C-4′), 62.8, 62.7 (2*C*H$_2$CH$_3$), 61.1 (C-6′), 36.6 (C-4), 32.1 (=CCO*C*H$_3$), 20.4, 20.0 (2CO*C*H$_3$), 20.3 (2C, 2CO*C*H$_3$), 13.7, 13.6 (2CH$_2$*C*H$_3$) ppm; FABMS *m/z* 652 (100, [M+Na]$^{+\cdot}$). Anal. calcd for $C_{27}H_{35}O_{14}NS$: C, 51.50; H, 5.60; N, 2.22; S, 5.09. Found: C, 50.29; H, 5.71; N, 2.64; S, 5.47.

*3.6. General procedure for the reaction of **5** with cyanocarbanions*

To a stirred solution of 0.26 mmol of ethyl cyanoacetate for **18**, phenylthioacetonitrile for **19** and **20**, cyanoacetamide for **21**, malononitrile for **22**, or **4** for **25** and **26** in 0.75 mL of dry DMF at 30°C and under nitrogen, 0.33 mmol of NaH (as a suspension in mineral oil) was added. After 5 min, **5** (0.26 mmol) was dropped, as a solution in 0.75 mL of dry DMF under nitrogen onto the carbanion. The mixture was stirred at 30°C for t_1 min, then 0.26 mmol of phenacyl bromide was added and stirred for t_2 min. The mixture was poured into saturated aqueous NH_4Cl, extracted with ether (except for the case of **21**, which was extracted with dichloromethane), washed with water, dried ($MgSO_4$), filtered and evaporated to dryness.

*3.6.1. (E)-Ethyl 2-cyano-3-phenacylthio-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylamino) acrylate **18***

t_1=t_2=10 min. Column chromatography (ether:hexane=3:1) of the residue gave an amorphous solid (150 mg, 93%); [α] +15 (*c* 1.0); IR ν_{max} 3192, 3063, 2982, 2212, (CN), 1770, 1684 (CO of phenacyl), 1582, 1439, 1370, 1260, 1084 and 1032 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 10.32 (d, 1H, $J_{NH,1'}$=7.8, NH), 7.98–7.50 (m, 5H, Ph), 5.59 (dd, 1H, $J_{1',2'}$=9.4, H-1′), 5.35 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.4, H-3′), 5.21 (t, 1H, H-2′), 5.09 (t, 1H, $J_{4',5'}$=9.4, H-4′), 4.96, 4.63 (each d, each 1H, $^2J_{H,H}$=17.1, CH$_2$COPh), 4.23 (dd, 1H, $J_{5',6'a}$=4.8, $J_{6'a,6'b}$=12.4, H-6′a), 4.23 (q, 2H, $^3J_{H,H}$=7.1, CH_2CH$_3$), 4.08 (dd, 1H, $J_{5',6'b}$=2.2, H-6′b), 3.85 (ddd, 1H, H-5′), 2.09, 2.06 (each s, each 3H, 2Ac), 2.04 (s, 6H, 2Ac), 1.30 (t, 3H, CH$_2$CH_3) ppm; ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 191.8 (*C*OPh), 170.5, 169.9, 169.8, 169.7, 169.3, 166.3 (4*C*OCH$_3$, *C*O$_2$Et and C-3), 134.8–128.4 (6C, Ph), 117.3 (CN), 82.8 (C-1′), 81.5 (C-2), 73.3 (C-5′), 72.7 (C-3′), 69.9 (C-2′), 68.1 (C-4′), 61.5 (2C, C-6′ and *C*H$_2$CH$_3$), 42.7 (*C*H$_2$COPh), 20.6, 20.4 (2CO*C*H$_3$), 20.5 (2C, 2CO*C*H$_3$), 14.1 (CH$_2$*C*H$_3$) ppm; FABMS *m/z* 643 (100, [M+Na]$^{+\cdot}$). Anal. calcd for $C_{28}H_{32}O_{12}N_2S$: C, 54.19; H, 5.20; N, 4.51. Found: C, 54.63; H, 5.79; N, 4.47.

*3.6.2. (Z)-3-Phenacylthio-2-phenylthio-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylamino) acrylonitrile **19** and 3-amino-2-benzoyl-4-phenylthio-5-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl-amino)thiophene **20***

t_1=t_2=30 min. Column chromatography (ether:hexane=2:1) of the residue gave **19** (56 mg, 33%) and **20** (29 mg, 17%).

19: [α] −4 (*c* 0.3); IR ν_{max} 3312, 3059, 2953, 2195 (CN), 1746, 1709 (CO of phenacyl), 1549, 1452, 1371, 1227 and 1036 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 8.04–7.08 (m, 11H, NH and 2Ph), 5.42 (dd, 1H, $J_{NH,1'}$=8.3, $J_{1',2'}$=9.4, H-1′), 5.32 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.4, H-3′), 5.04, 5.00 (each t, each 1H, $J_{4',5'}$=9.4, H-2′, 4′), 4.96, 4.48 (each d, each 1H, $^2J_{H,H}$=16.9, CH$_2$COPh), 4.22 (dd, 1H, $J_{5',6'a}$=4.8, $J_{6'a,6'b}$=12.4, H-6′a), 4.04 (dd, 1H, $J_{5',6'b}$=2.2, H-6′b), 3.79 (ddd, 1H, H-5′), 2.04, 2.02, 2.01, 1.78 (each s, each 3H, 4Ac) ppm; ^{13}C-NMR (125.7 MHz, CDCl$_3$): δ 192.3 (*C*OPh), 170.7, 170.6, 170.4, 169.7,

169.3 (C-3 and 4*C*OCH$_3$), 134.8–125.7 (12C, 2Ph), 119.2 (CN), 83.3 (C-1′), 79.2 (C-2), 73.0 (C-5′), 72.4 (C-3′), 69.9 (C-2′), 68.2 (C-4′), 61.5 (C-6′), 42.0 (*C*H$_2$COPh), 20.5, 20.4, 20.0, 19.9 (4CO*C*H$_3$) ppm; FABMS *m/z* 679 (100, [M+Na]$^+$). Anal. calcd for $C_{31}H_{33}O_{10}N_2S_2$: C, 56.61; H, 5.06; N, 4.26; S, 9.75. Found: C, 56.30; H, 5.02; N, 4.20; S, 9.40.

20: [α] −11 (*c* 0.7); IR ν_{max} 3322 (NH), 3057, 2918, 2851, 1748, 1460, 1371, 1227 and 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.76–7.06 (m, 10H, 2Ph), 6.54 (d, 1H, $J_{NH,1'}$=9.5, NH), 5.29 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.5, H-3′), 5.01 (t, 1H, $J_{4',5'}$=9.5, H-4′), 4.99 (t, 1H, $J_{1',2'}$=9.5, H-2′), 4.65 (t, 1H, H-1′), 4.21 (dd, 1H, $J_{5',6'a}$=5.5, $J_{6'a,6'b}$=12.4, H-6′a), 4.08 (dd, 1H, $J_{5',6'b}$=2.3, H-6′b), 3.79 (ddd, 1H, H-5′), 2.02, 2.00, 1.88, 1.68 (each s, each 3H, 4Ac) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 186.1 (*C*OPh), 170.8, 170.5, 169.8, 169.4 (4*C*OCH$_3$), 162.7, 157.8 (2C, thiophene ring), 140.1–125.7 (12C, 2Ph), 97.8, 95.1 (2C, thiophene ring), 84.9 (C-1′), 73.1 (C-5′), 72.1 (C-3′), 70.4 (C-2′), 68.3 (C-4′), 61.6 (C-6′), 20.4 (2C, 2CO*C*H$_3$), 20.3, 19.9 (2CO*C*H$_3$) ppm; HREIMS *m/z* obsd 656.1510, calcd for $C_{31}H_{32}O_{10}N_2S_2$ 656.1498.

*3.6.3. 3-Amino-2-benzoyl-4-carbamoyl-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosylamino) thiophene 21*

t_1=15 min, t_2=30 min. Column chromatography (dichloromethane:methanol=40:1) of the residue gave **21** (71 mg, 46%) as an amorphous solid which had [α] −58 (*c* 0.7); IR ν_{max} 3443 (NH), 3287, 3061, 2951, 1753, 1657, 1466, 1371, 1225 and 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.66 (d, 1H, $J_{NH,1'}$=9.5, NH), 7.69–7.45 (m, 5H, Ph), 5.75 (s, 2H, NH_2), 5.33 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.5, H-3′), 5.12 (t, 1H, $J_{1',2'}$=9.5, H-2′), 5.05 (t, 1H, $J_{4',5'}$=9.5, H-4′), 4.66 (t, 1H, H-1′), 4.19 (dd, 1H, $J_{5',6'a}$=5.4, $J_{6'a,6'b}$=12.4, H-6′a), 4.09 (dd, 1H, $J_{5',6'b}$=2.2, H-6′b), 3.78 (ddd, 1H, H-5′), 2.07, 2.04, 2.03, 1.87 (each s, each 3H, 4Ac) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 187.1 (*C*OPh), 170.4, 170.2, 169.9, 169.3 (4*C*OCH$_3$), 164.9, 155.9 (2C, thiophene ring), 141.2–127.2 (6C, Ph), 103.2, 98.8 (2C, thiophene ring), 84.5 (C-1′), 73.2 (C-5′), 72.4 (C-3′), 70.6 (C-2′), 68.2 (C-4′), 61.6 (C-6′), 20.5, 20.3 (2CO*C*H$_3$), 20.4 (2C, 2CO*C*H$_3$) ppm; FABMS *m/z* 614 (100, [M+Na]$^+$). Anal. calcd for $C_{26}H_{29}O_{11}N_3S$: C, 52.79; H, 4.94; N, 7.10; S, 5.42. Found: C, 52.64; H, 5.10; N, 6.96; S, 5.84.

*3.6.4. 3-Amino-2-benzoyl-4-cyano-5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosylamino)thiophene 22*

t_1=15 min, t_2=10 min. Column chromatography (ether:hexane=6:1) of the residue gave **22** (136 mg, 91%) as an amorphous solid which had [α] −103 (*c* 0.5); IR ν_{max} 3424 (NH), 3302, 3055, 2951, 2212 (CN), 1753, 1597, 1478, 1371, 1221 and 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.70–7.43 (m, 5H, Ph), 7.10–6.85 (bs, 2H, NH_2), 6.77 (d, 1H, $J_{NH,1}$=9.5, NH), 5.34 (t, 1H, $J_{2',3'}$=$J_{3',4'}$=9.5, H-3′), 5.07 (t, 1H, $J_{4',5'}$=9.5, H-4′), 5.03 (t, 1H, $J_{1',2'}$=9.5, H-2′), 4.77 (t, 1H, H-1′), 4.24 (dd, 1H, $J_{5',6'a}$=5.2, $J_{6'a,6'b}$=12.5, H-6′a), 4.12 (dd, 1H, $J_{5',6'b}$=2.1, H-6′b), 3.84 (ddd, 1H, H-5′), 2.11, 2.04, 2.03, 1.91 (each s, each 3H, 4Ac) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 186.5 (*C*OPh), 171.4, 170.4, 169.8, 169.3 (4*C*OCH$_3$), 164.5, 157.8 (2C, thiophene ring), 140.1–127.1 (6C, Ph), 112.6 (CN), 97.0 (1C, thiophene ring), 84.4 (C-1′), 82.2 (1C, thiophene ring), 73.0 (C-5′), 72.1 (C-3′), 70.9 (C-2′), 67.9 (C-4′), 61.5 (C-6′), 20.6, 20.4 (2CO*C*H$_3$), 20.5 (2C, 2CO*C*H$_3$) ppm; FABMS *m/z* 596 (100, [M+Na]$^+$). Anal. calcd for $C_{26}H_{27}O_{10}N_3S$: C, 54.44; H, 4.74; N, 7.33; S, 5.59. Found: C, 54.04; H, 4.95; N, 7.29.

*3.6.5. 3R(S) and 3S(R)-4-Amino-5-benzoyl-3-cyano-2,3-dihydro-3-phenacyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosylimino)thiophene 25 and 26*

t_1=t_2=20 min. Column chromatography (ether:hexane=2:1 and 4:1) of the residue gave **25** (22 mg, 12%) and **26** (40 mg, 22%).

25: [α] −135 (*c* 0.6); IR ν_{max} 3395 (NH), 3283, 3063, 2955, 2208 (CN), 1751, 1684, 1613, 1481, 1371, 1227 and 1040 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.41 (bs, 2H, NH_2), 8.06–7.26 (m, 10H, 2Ph), 5.32 (t, 1H, $J_{2',3'}=J_{3',4'}=9.5$, H-3′), 5.15 (t, 1H, $J_{1',2'}=9.5$, H-2′), 5.08 (t, 1H, $J_{4',5'}=9.5$, H-4′), 4.88 (d, 1H, H-1′), 4.20 (dd, 1H, $J_{5',6'a}=5.7$, $J_{6'a,6'b}=12.3$, H-6′a), 4.18 (d, 1H, $^2J_{H,H}=18.6$, C*H*HCOPh), 4.10 (dd, 1H, $J_{5',6'b}=2.2$, H-6′b), 3.88 (d, 1H, CH*H*COPh), 3.82 (ddd, 1H, H-5′), 2.04 (s, 6H, 2Ac), 2.03, 1.79 (each s, each 3H, 2Ac) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 195.5 (CH_2*C*OPh), 189.3 (*C*OPh), 170.5, 170.1, 170.0, 169.5 (4*C*OCH_3), 165.4, 162.6, 153.5 (3C, thiophene ring), 140.0–127.0 (12C, 2Ph), 115.5 (CN), 97.3 (1C, thiophene ring), 89.2 (C-1′), 74.1 (C-5′), 72.8 (C-3′), 71.2 (C-2′), 68.5 (C-4′), 62.1 (C-6′), 48.5 (CH_2Ph), 20.8, 20.6, 20.5, 20.4 (4CO*C*H_3) ppm; HREIMS *m/z* obsd 691.1857, calcd for $C_{34}H_{33}O_{11}N_3S$ 691.1836.

26: [α] +89.2 (*c* 0.7); IR ν_{max} 3368 (NH), 3298, 3059, 2957, 2185 (CN), 1759, 1694, 1620, 1481, 1371, 1229 and 1036 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.36 (bs, 2H, NH_2), 8.04–7.26 (m, 10H, 2Ph), 5.31 (t, 1H, $J_{2',3'}=J_{3',4'}=9.5$, H-3′), 5.20 (t, 1H, $J_{1',2'}=9.5$, H-2′), 5.12 (t, 1H, $J_{4',5'}=9.5$, H-4′), 4.71 (d, 1H, H-1′), 4.25 (dd, 1H, $J_{5',6'a}=5.1$, $J_{6'a,6'b}=12.6$, H-6′a), 4.24 (d, 1H, $^2J_{H,H}=18.4$, C*H*HCOPh), 4.15 (dd, 1H, $J_{5',6'b}=2.2$, H-6′b), 3.82 (ddd, 1H, H-5′), 3.81 (d, 1H, CH*H*COPh), 2.03, 2.01, 2.00, 1.99 (each s, each 3H, 4Ac) ppm; ^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 194.4 (CH_2*C*OPh), 189.0 (*C*OPh), 170.8, 170.2, 169.5, 169.4 (4*C*OCH_3), 166.7, 162.6, 153.6 (3C, thiophene ring), 139.8–126.9 (12C, 2Ph), 115.0 (CN), 95.5 (1C, thiophene ring), 90.5 (C-1′), 73.7 (C-5′), 73.0 (C-3′), 71.7 (C-2′), 68.2 (C-4′), 61.9 (C-6′), 48.1 (CH_2Ph), 20.9, 20.7 (2CO*C*H_3), 20.6 (2C, 2CO*C*H_3) ppm; HREIMS *m/z* obsd 691.1872, calcd for $C_{34}H_{33}O_{11}N_3S$ 691.1836.

3.7. General deacetylation method

The acetylated product (0.48 mmol) was dissolved in 6 mL of anhydrous methanol at r.t. and 1.0 mmol of NaOMe was added with stirring to the solution. The process was controlled by TLC (ether:hexane=6:1 and dichloromethane:methanol=4:1) until total deacylation of the starting material. After *t* min, the reaction mixture was neutralized with acid resin Amberlite IR-120(H), filtered and the solvent evaporated under reduced pressure. The following products were prepared in this manner.

3.7.1. Diethyl β-D-glucopyranosylaminothiocarbonyl malonate 27

t=15 min. In this case, the ratio NaOMe/**6**, was three times that of the general method. ^{13}C-NMR (75.4 MHz, DMSO-d_6): δ 194.3 (CS), 164.9 (2C, 2*C*O_2Et), 83.6 (C-1′), 79.0 (C-5′), 77.5 (C-3′), 72.4 (C-2′), 69.7 (C-4′), 64.8 (CH), 61.6 (2C, 2CH_2), 60.5 (C-6′) ppm; FABMS *m/z* 404 (100, $[M+Na]^{+\cdot}$). HRCIMS *m/z* obsd 381.1060, calcd for $C_{14}H_{23}O_9NS$+H 381.1094.

3.7.2. 4-Ethoxycarbonyl-1-(β-D-glucopyranosyl-2-phenyl-5-mercapto-2-pyrrole 28

t=15 min. This compound was not isolated pure. ^{13}C-NMR (125.7 MHz, MeOH-d_4): δ 166.6–162.4 (C-5, *C*O_2Et), 135.4–126.7 (6C, Ph), 122.2 (C-4), 109.2 (C-2), 89.0 (C-1′), 85.4 (C-3), 79.3 (C-5′), 78.9 (C-3′), 74.8 (C-2′), 71.6 (C-4′), 62.7 (C-6′), 61.1 (CO*C*H_2CH_3), 14.8 (COCH$_2$*C*H_3) ppm; FABMS *m/z* 432 (100, $[M+Na]^{+\cdot}$). HRDCIMS *m/z* obsd 410.1292, calcd for $C_{19}H_{23}O_7NS$+H 410.1273.

3.7.3. 2-Chlorophenyl-4-ethoxycarbonyl-1-(β-D-glucopyranosyl)-5-mercapto-pyrrole 29

t=20 min. ^{13}C-NMR (125.7 MHz, MeOH-d_4): δ 166.5, 164.0 (C-5, *C*O_2Et), 134.2–126.3 (6C, Ph), 122.5 (C-4), 109.2 (C-2), 88.9 (C-1′), 85.4 (C-3), 79.4, 78.9 (C-3′, 5′), 74.7 (C-2′), 71.5 (C-4′), 62.6, 61.1 (C-6′, CO*C*H_2CH_3), 14.8 (COCH$_2$*C*H_3) ppm; FABMS *m/z* 443 (100, $M^{+\cdot}$). HRDCIMS *m/z* obsd 444.0891, calcd for $C_{19}H_{22}O_7NSCl$+H 444.0884.

3.7.4. 3-Amino-2-benzoyl-4-ethoxycarbonyl-5-(β-D-glucopyranosylamino)thiophene 30

t=10 min. ^{13}C-NMR (75.4 MHz, MeOH-d_4): δ 187.5 (*C*OPh), 171.1 (*C*O_2Et), 166.1, 159.8 (2C, thiophene ring), 142.7–128.1 (6C, Ph), 98.3, 97.0 (2C, thiophene ring), 87.4 (C-1′), 79.4 (C-5′), 78.5 (C-3′), 74.5 (C-2′), 71.1 (C-4′), 62.3 (C-6′), 61.8 (*C*H_2CH$_3$), 14.6 (CH$_2$*C*H$_3$) ppm; FABMS *m/z* 475 (100, [M+Na]$^{+\cdot}$). HRDCIMS *m/z* obsd 453.1340, calcd for $C_{20}H_{23}O_8N_2S$+H 453.1331.

3.7.5. 3-Amino-2-benzoyl-4-cyano-5-(β-D-glucopyranosylamino)thiophene 31

t=15 min. ^{13}C-NMR (75.4 MHz, MeOH-d_4): δ 187.4 (*C*OPh), 166.8, 159.6 (2C, thiophene ring), 142.2–128.1 (6C, Ph), 114.1 (CN), 96.9 (1C, thiophene ring), 87.6 (C-1′), 80.6 (1C, thiophene ring), 79.1, 78.7 (C-3′, 5′), 73.8 (C-2′), 71.0 (C-4′), 62.3 (C-6′) ppm; FABMS *m/z* 428 (100, [M+Na]$^{+\cdot}$). HRDCIMS *m/z* obsd 406.1088, calcd for $C_{18}H_{19}O_6N_3S$+H 406.1073.

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