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Note

# Regioselective synthesis of novel 3-alkoxy (phenyl) thiophosphorylamido-2-(per-*O*-acetylglycosyl-1′-imino)thiazolidine-4-one derivatives from *O*-alkyl $N^4$-glycosyl(thiosemicarbazido)phosphonothioates

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ABSTRACT

A series of 3-alkoxy(phenyl)thiophosphorylamido-2-(per-*O*-acetylglycosyl-1′-imino)thiazolidine-4-one derivatives were prepared by the reaction of 1-alkoxy(phenyl)thiophosphoryl-4-(per-*O*-acetylglycosyl) thiosemicarbazides with ethyl bromoacetate. $^1H/^{13}C$ HMBC measurements corroborated by X-ray crystallographic results revealed the exclusive regioselectivity of these ring closures toward the N-2 position of the thiosemicarbazide moiety. The bioactivity data of **3a–k** suggest that the thiazolidine-4-one ring is critical for the herbicidal and fungicidal activities.

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Thiazolidine-4-one compounds have been shown to display antimicrobial,[1] antimycobacterial,[2] anticonvulsant,[3] anti-inflammatory,[4] anti-HIV-1,[5] analgesic,[6] antituberculosis,[7] immunosuppressant,[8] and antimalarial[9] activities. Recently, it was reported that thiazolidinones displayed antidegenerative activity on human chondrocyte cultures.[10] Previously, we have described the synthesis of bioactive 2-arylsulfonylhydrazono-3-(per-*O*-acetylglycosyl)thiazolidine-4-ones using 1-arylsulfonyl-4-(per-*O*-acetylglycosyl)thiosemicarbazides as precursor.[11] Since organo phosphorus compounds are known as highly effective agrochemicals,[12] we planned to prepare a series of 2-alkoxy(phenyl) thiophosphorylhydrazono-3-(per-*O*-acetylglycosyl)thiazolidine-4-one derivatives.

We started from 1-alkoxy(phenyl)thiophosphoryl-4-(per-*O*-acetylglycosyl) thiosemicarbazides **2a–k**, obtained from the reaction of glycosyl isothiocyanates[13,14] and thiophosphoryl hydrazines.[15] Reaction of **2a–k** with ethyl bromoacetate was investigated (Scheme 1). We first tried to use chloroform as the reaction medium. Unfortunately, we failed to obtain any cyclization product. However, we successfully separated a moderately stable S-alkylated intermediate in the presence of sodium acetate. FABMS (*m/z* 948 $[M+H]^+$ for **2k** with ethyl bromoacetate) indicates that it is an uncyclized product. It is likely that this S-alkylated intermediate was unstable when the reaction was refluxed in chloroform. Finally, we obtained cyclization products when we used dichloromethane as solvent. A reaction time of 12 h at reflux in dichloromethane was maintained since a longer reaction time did not improve the yield.

Several reports regarding the condensation of thiosemicarbazides with alkyl halides have pointed out that main products are of type **3′a**,[16,17] resulting from cyclization at N-4. 2-(Dimethylhydrazono)-3-phenylthiazol-4-one was obtained by reflux of thiosemicarbazide with ethyl bromoacetate for 7 days in dichloromethane.[18] In the presence of a weak base, Saleh et al. cyclized substituted thioureas with chloroacetic acid, giving thiazolidine-4-one compounds substituted at N-4.[19] Conversely, the cyclization at N-2 has been more scarcely reported. Moghaddam and Hojabri[20] and Rajanarendar et al.[21] have reported cyclizations at N-2 position. A detailed study of the condensation of thiosemicarbazides with ethyl bromoacetate to give N-2 isomers as major products has been reported.[22]

It is of interest that the cyclization of thiosemicarbazides **2a–k**, which includes a relatively bulky substituent, with ethyl bromoacetate leads to the formation of N-2 isomers **3a–k**. When these reactions were monitored by TLC, we found that the polarity of **3a–k** was smaller than that of **2a–k** and the polarity of previously reported 2-arylsulfonylhydrazono-3-(per-*O*-acetylglycosyl)thiazolidine-4-ones was higher than that of 1-arylsulfonyl-4-(per-*O*-acetylglycosyl)thiosemicarbazides. $^1H$ and $^{13}C$ NMR spectra of final products (after work-up) suggest absence of any trace of the isomers, indicating that the final products are isomerically pure.

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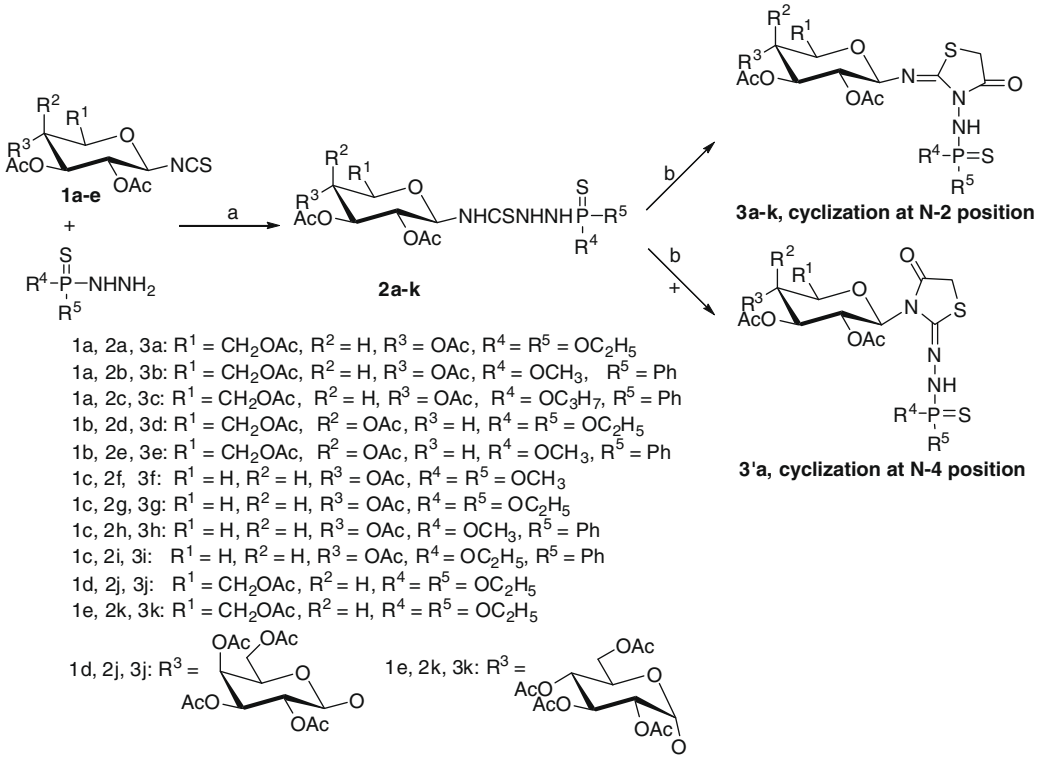


**Scheme 1.** Reagents and conditions: (a) MeCN, rt and (b) $CH_2Cl_2$, $BrCH_2CO_2Et$, reflux.

Due to the presence of the imino group, the chemical shift value of H-1′ for **3f** (4.76 ppm) is smaller than that of H-1′ (5.42 ppm), as we previously reported in the case of 2-phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one, and the chemical shift value of C-1′ for **3f** (88.90 ppm) is larger than that of C-1′ (81.63 ppm).[11] These differences in chemical shifts may indicate different types of ring closures. Formation of the N-4 vs N-2 type closure for the sulfonylhydrazono versus glycosylimino derivatives has now been proven by HMBC experiments. Figure 1 shows the HMBC spectra of 2-phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one[11] (Fig. 1A), **3a** (Fig. 1C) and **3f** (Fig. 1E). Based on the HMBC correlations in Figure 1, we can unambiguously assign all chemical shift values of carbon and proton atoms in the sugar ring. On the other hand, the three-bond connectivity of H-1′ at δ 5.42 ppm with C-2 at $\delta$ 164 ppm and with C-4 at $\delta$ 172 ppm in the HMBC spectrum confirmed the cyclization of 1-arylsulfonyl-4-(per-*O*-acetylglycosyl)thiosemicarbazides with ethyl bromoacetate at N-4 (Figure 1B); the three-bond connectivity of H-1′ at $\delta$ 4.76 ppm with C-2 at $\delta$ 155 ppm in the HMBC spectrum proved the cyclization of 1-alkoxy(phenyl)thiophosphoryl-4-(per-*O*-acetyl glycosyl)thiosemicarbazides with ethyl bromoacetate at N-2 (Fig. 1F). This type of ring closure was confirmed by X-ray crystallography.[23]

Compounds **2a–k** and **3a–k** were tested in soil treatment against several herbs such as *Brassica campestris, Echinochloa crus-galli, Amaranthus retroflexus L., and Digitaria sanguinalis(L.)Scop* at 1.5 kg/ha.[24] The bioassay results showed that **3a–k** have a rather moderate herbicidal activity. The inhibitory rate of **3b** against *Brassica campestris* was 62.7%. Compounds **2a–k** and **3a–k** were also tested for their growth inhibition and fungicidal activity in vitro against *Gibberella zeae*, *Alternaria solani, Cercospora arachidicola, Physalospora piricola*, *Phoma asparagi* at 50 ppm. The inhibitory rates of **3a–k** against *Physalospora piricola*, *Phoma asparagi* were between 40% and 50%. Higher inhibitory rate of **3a–k** compared to that of **2a–k** indicates that the thiazolidine-4-one ring is critical for the herbicidal and fungicidal activities.

## 1. Experimental

### 1.1. General methods

Melting points were obtained on a Yanaco MP-500 micro-melting point apparatus. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-400 instrument using $CDCl_3$ as solvent and $Me_4Si$ as internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyzer. Mass spectra were recorded with a VG ZAB-HS instrument using the FAB ionization mode.

### 1.2. 1-Alkoxy(phenyl)thiophosphoryl-4-(per-*O*-acetylglycosyl)-thiosemicarbazide derivatives (2a–k), general method

To a soln of **1a–e** (4 mmol) in MeCN (20 mL), the corresponding thiophosphoryl hydrazine (6 mmol) was added with stirring. The mixture was heated at reflux for 2 h and the solvent was removed under diminished pressure. Concentration resulted in a crude product which was purified on a silica gel column (1:2 EtOAc–petroleum ether).

#### 1.2.1. 1-Diethoxythiophosphoryl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (2a)

From 1.56 g (4 mmol) of **1a** (1.97 g, 87%); white crystals from EtOAc–petroleum ether; mp 164–165 °C. $^1$H NMR ($CDCl_3$, ppm): $\delta$ 7.64 (d, *J* 8.4 Hz, 1H, NH), 7.60 (br s, 1H, NH), 5.78 (t, 1H, H-1′), 5.37 (m, 2H, H-2′, H-3′), 5.06 (m, 2H, H-4′, H-6′), 4.31 (dd, $J_1$ 4.2 Hz, $J_2$ 3.6 Hz, 1H, H-5′), 4.13 (m, 5H, H-6′, 2 × $POCH_2$), 3.86 (d, *J* 8.4 Hz, 1H, NH), 2.10, 2.06, 2.04, 2.02 (4s, 12H, 4 × OAc), 1.32 (t, 6H, 2 × $POCH_2CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): $\delta$ 183.67 (C=S), 171.20, 170.83, 169.99, 169.74 (4C, 4 × CO), 82.28 (C-6′), 73.59 (C-3′), 72.91 (C-2′), 68.30 (C-1′), 64.66, 63.89 (2C, 2 × $POCH_2$), 63.50 (C-5′), 61.82 (C-4′), 20.82, 20.75, 20.70, 20.67 (4C, 4 × OAc),

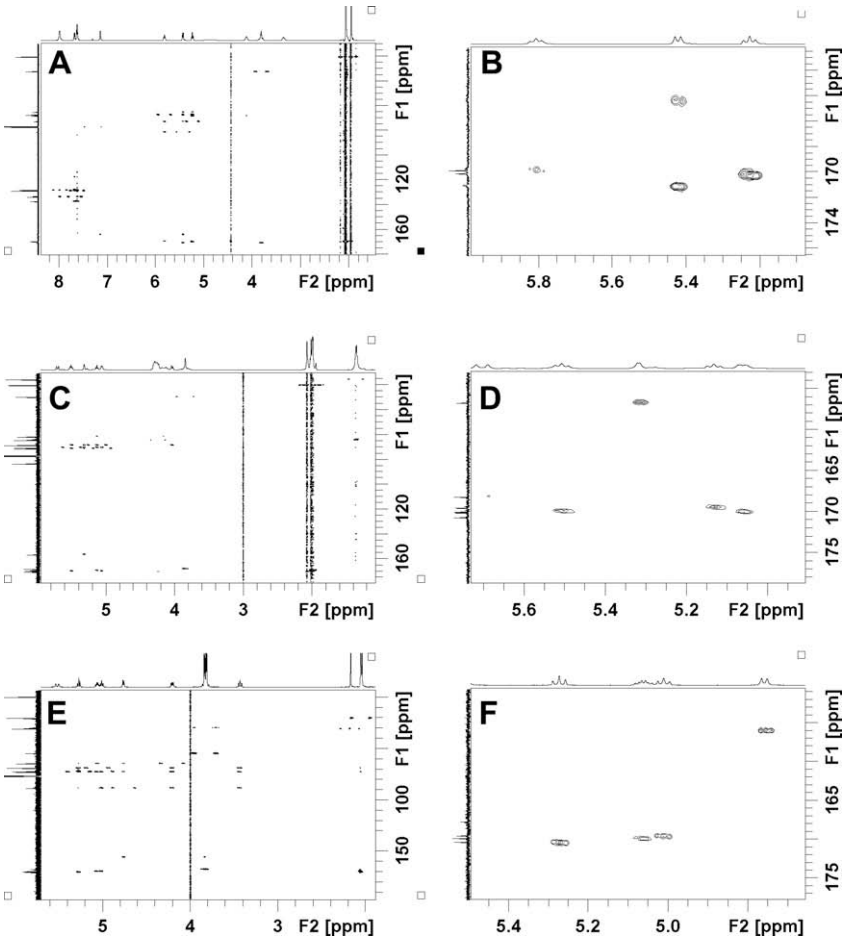


**Figure 1.** (A) $^{1}H-^{13}C$ HMBC spectra of 2-phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one[11]; (B) $^{1}H-^{13}C$ HMBC spectra of H-1′/C-2,C-4 in 2-phenylsulfonylhydrazono-3-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)thiazolidine-4-one; (C) $^{1}H-^{13}C$ HMBC spectra **3a**; (D) $^{1}H-^{13}C$ HMBC spectra of H-1′ with C-2 in **3a**; (E) $^{1}H-^{13}C$ HMBC spectra **3f**; and (F) $^{1}H-^{13}C$ HMBC spectra of H-1′ with C-2 in **3f**.

15.83 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 79.16. Anal. Calcd for $C_{19}H_{32}N_3O_{11}PS_2$: C, 41.78; H, 5.32; N, 5.04. Found: C, 41.58; H, 5.61; N, 4.98.

### 1.2.2. 1-Methoxy(phenyl)thiophosphoryl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (2b)

From 1.56 g (4 mmol) of **1a** (1.80 g, 76%); white crystals from EtOAc–petroleum ether; mp 169–171 °C. $^{1}H$ NMR ($CDCl_3$, ppm): δ 7.83 (m, 2H, Ar-H), 7.70 (d, *J* 9.2 Hz, 1H, NH), 7.54–7.46 (m, 4H, Ar-H, NH), 5.89 (br s, 1H, NH), 5.71–3.69 (m, 10H, $OCH_3$, H-1′, H-2′, H-3′, H-4′, H-5′, H-6′), 2.08, 2.01, 1.98, 1.96, 1.98, (4s, 12H, 4 × OAc); $^{13}C$ NMR ($CDCl_3$, ppm): δ 183.65 (C=S), 171.02, 170.89, 170.04, 169.75, 170.04, 170.89, 171.02 (4C, 4 × CO), 133.34, 131.94, 131.86, 131.74, 129.12, 128.98 (6C, Ar-C), 82.35, 73.74, 73.00, 70.78, 68.18, 61.75 (6C, C-1′, C-2′, C-3′, C-4′, C-5′, C-6′) 53.36 ($OCH_3$), 21.01, 20.81 (4C, 4 × OAc); $^{31}P$ NMR ($CDCl_3$, ppm): δ 81.94, 81.76. Anal. Calcd for $C_{22}H_{30}N_3O_{10}PS_2$: C, 44.67; H, 5.11; N, 7.10. Found: C, 44.38; H, 5.24; N, 7.01.

### 1.2.3. 1-Phenyl(propoxy)thiophosphoryl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (2c)

From 1.56 g (4 mmol) of **1a** (1.70 g, 69%); white crystals from EtOAc–petroleum ether; mp 166–167 °C. $^{1}H$ NMR ($CDCl_3$, ppm): δ 7.91 (br s, 1H, NH), 7.79–7.41 (m, 6H, Ar-H, NH), 5.89 (br s, 1H, NH), 5.68–3.75 (m, 9H, $OCH_2$, H-1′, H-2′, H-3′, H-4′, H-5′, H-6′), 2.09, 2.03, 1.97, 1.93 (4s, 12H, 4×OAc), 1.29 (m, 2H, $POCH_2CH_2$), 0.91 (t, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$): δ 184.08 (C=S), 170.33, 170.13, 170.04, 169.84 (4C, 4 × CO), 140.33, 132.65, 131.87, 131.29, 129.43, 138.96 (6H, Ar-C), 82.89, 73.79, 69.34, 63.85, 63.52, 63.43, 61.45 (7C, C-1′, C-2′, C-3′, C-4′, C-5′, C-6′, $OCH_2$), 33.68 ($POCH_2CH_2$), 20.81, 20.54, 20.36, 20.12 (4C, 4 × OAc), 16.29 ($CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 79.27, 79.01. Anal. Calcd for $C_{24}H_{34}N3O_{10}PS_2$: C, 46.52; H, 5.53; N, 6.78. Found: C, 46.23; H, 5.60; N, 6.95.

### 1.2.4. 1-Diethoxythiophosphoryl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazide (2d)

From 1.56 g (4 mmol) of **1b** (1.56 g, 68%); white crystals from EtOAc–petroleum ether; mp 167–168 °C. $^{1}H$ NMR ($CDCl_3$, ppm): δ 7.59 (m, 2H, NHNH), 5.71 (t, 1H, H-1′), 5.43 (m, 2H, H-2′, H-3′), 5.17 (m, 2H, H-4′, H-6′), 4.01 (m, 7H, H-5′, H-6′, 2 × $POCH_2$, NH), 2.14, 2.04, 2.01, 1.97 (4s, 12H, 4 × OAc), 1.31 (t, 6H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): δ 183.76 (C=S), 171.41, 170.60, 170.26, 169.95 (4C, 4 × CO), 82.96 (C-6′), 72.63 (C-3′), 71.01 (C-2′), 68.79 (C-1′), 67.38 (C-5′), 65.09, 64.92 (2C, 2 × $POCH_2$), 61.24 (C-4′), 21.08, 20.83, 20.73, 20.56 (4C, 4 × OAc), 16.10, 16.04 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 79.16. Anal. Calcd for $C_{19}H_{32}N_3O_{11}PS_2$: C, 41.78; H, 5.32; N, 5.04. Found: C, 41.35; H, 5.11; N, 4.98.

#### 1.2.5. 1-Methoxy(phenyl)thiophosphoryl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazide (2e)

From 1.56 g (4 mmol) of **1b** (1.7 g, 72%); white crystals from EtOAc–petroleum ether; mp 178–179 °C. $^1$H NMR ($CDCl_3$, ppm): δ 8.10 (br s, 1H, NH), 7.87 (m, 6H, Ar-H, NH), 5.84 (d, *J* 8.4 Hz, 1H, NH), 5.78–3.57 (m, 10H, H-1′, H-2′, H-3′, H-4′, H-5′, H-6′, $OCH_3$), 2.15, 2.04, 1.98, 1.96 (4s, 12H, 4 × OAc); $^{13}$C NMR ($CDCl_3$, ppm): δ 184.98 (C=S), 171.32, 171.03, 170.27, 169.67 (4C, 4 × CO), 139.76, 134.02, 133.10, 132.68, 130.64, 128.96 (6C, Ar-C), 81.98, 73.85, 72.69, 71.78, 67.56, 61.71, 61.55 (7C, C-1′, C-2′, C-3′, C-4′, C-5′, C-6′, $CH_3O$), 21.00, 20.89, 20.81, 20.79 (4C, 4 × OAc); $^{31}$P NMR ($CDCl_3$, ppm): δ 79.86, 79.65. Anal. Calcd for $C_{22}H_{30}N_3O_{10}PS_2$: C, 44.67; H, 5.11; N, 7.10. Found: C, 44.34; H, 4.89; N, 7.28.

#### 1.2.6. 1-Dimethoxythiophosphoryl-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiosemicarbazide (2f)

From 1.26 g (4 mmol) of **1c** (1.48 g, 78%); white crystals from EtOAc–petroleum ether; mp 181–182 °C. $^1$H NMR ($CDCl_3$, ppm): δ 8.02 (br s, 1H, NH), 7.84 (d, *J* 8.4 Hz, 1H, NH), 5.63 (br s, 1H, NH), 5.57–3.54 (m, 12H, H-1′, H-2′, H-3′, H-4′, H-5′, 2×$OCH_3$), 2.04, 2.03, 1.89 (3s, 9H, 3×OAc); $^{13}$C NMR ($CDCl_3$, ppm): δ 185.13 (C=S), 170.56, 170.03, 169.84 (3C, 3 × CO), 80.97, 72.36, 68.72, 67.88, 64.66, 66.68, 59.89 (7C, C-1′, C-2′, C-3′, C-4′, C-5′, 2×$OCH_3$), 20.98, 20.24, 20.02 (3C, 3 × OAc); $^{31}$P NMR ($CDCl_3$, ppm): δ 69.63. Anal. Calcd for $C_{14}H_{24}N_3O_9PS_2$: C, 35.52; H, 5.11; N, 8.88. Found: C, 35.50; H, 5.21; N, 8.39.

#### 1.2.7. 1-Diethoxythiophosphoryl-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiosemicarbazide (2g)

From 1.26 g (4 mmol) of **1c** (1.38 g, 69%); white crystals from EtOAc–petroleum ether; mp 179–181 °C. $^1$H NMR ($CDCl_3$, ppm): δ 8.01 (br s, 1H, NH), 7.72 (d, *J* 8.4 Hz, 1H, NH), 5.68 (br s, 1H, NH), 5.58–3.44 (m, 10H, H-1′, H-2′, H-3′, H-4′, H-5′, 2×$OCH_2$), 2.01, 2.00, 1.98 (3s, 9H, 3 × OAc), 1.25 (t, 6H, 2 × $POCH_2CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): δ 184.56 (C=S), 171.25, 170.32, 169.98 (3C, 3 × CO), 81.32, 71.67, 68.77, 67.82, 64.65, 63.25, 61.04 (7C, C-1′, C-2′, C-3′, C-4′, C-5′, 2 × $OCH_2$), 21.33, 20.72, 20.54 (3C, 3×OAc), 16.16, 16.11 (2C, 2 × $POCH_2CH_3$); $^{31}$P NMR ($CDCl_3$, ppm): δ 69.74, 69.61. Anal. Calcd for $C_{16}H_{28}N_3O_9PS_2$: C, 38.33; H, 5.63; N, 8.38. Found: C, 38.78; H, 5.38; N, 7.98.

#### 1.2.8. 1-Methoxy(phenyl)thiophosphoryl-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiosemicarbazide (2h)

From 1.26 g (4 mmol) of **1c** (1.48 g, 72%); white crystals from EtOAc–petroleum ether; mp 163–164 °C. $^1$H NMR ($CDCl_3$, ppm): δ 7.86 (m, 7H, NHNH, Ar-H), 5.71–3.52 (m, 10H, H-1′, H-2′, H-3′, H-4′, H-5′, $OCH_3$, NH), 2.09, 2.04, 1.98 (3s, 9H, 3 × OAc); $^{13}$C NMR ($CDCl_3$, ppm): δ 183.89 (C=S), 171.22, 170.96, 170.38 (3C, 3 × CO), 140.82, 133.22, 131.97, 130.65, 128.39, 127.56 (6H, Ar-C), 82.80, 72.19, 69.17, 64.12, 63.03, 61.25 (6C, C-1′, C-2′, C-3′, C-4′, C-5′, $OCH_3$), 20.86, 20.43, 19.87 (3C, 3 × OAc). Anal. Calcd for $C_{19}H_{26}N_3O_8PS_2$: C, 43.93; H, 5.04; N, 8.09. Found: C, 43.60; H, 4.69; N, 7.93.

#### 1.2.9. 1-Ethoxy(phenyl)thiophosphoryl-4-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)thiosemicarbazide (2i)

From 1.26 g (4 mmol) of **1c** (1.56 g, 73%); white crystals from EtOAc–petroleum ether; mp 163–164 °C. $^1$H NMR ($CDCl_3$, ppm): δ 8.02 (br s, 1H, NH), 7.45 (d, *J* 8.4 Hz, 1H, NH), 7.86–3.49 (m, 14H, H-1′, H-2′, H-3′, H-4′, H-5′, $OCH_2$, NH, Ar-H), 2.11, 2.03, 2.00 (3s, 9H, 3 × OAc), 1.56 (t, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): δ 183.66 (C=S), 170.82, 170.49, 170.36 (3C, 3 × CO), 149.87, 132.65, 131.87, 131.39, 128.34, 126.97 (6C, Ar-C), 83.60, 82.55, 72.16, 69.46, 65.64, 63.56, 63.01 (6C, C-1′, C-2′, C-3′, C-4′, C-5′, $OCH_2$), 20.96, 20.89, 20.43 (3C, 3×OAc), 16.33 ($POCH_2CH_3$). Anal. Calcd for $C_{20}H_{28}N_3O_8PS_2$: C, 45.02; H, 5.29; N, 7.88. Found: C, 44.73; H, 5.00; N, 7.66.

#### 1.2.10. 1-Diethoxythiophosphoryl-4-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl] thiosemicarbazide (2j)

From 2.7 g (4 mmol) of **1d** (2.3 g, 67%); white crystals from EtOAc–petroleum ether; mp 140–141 °C. $^1$H NMR ($CDCl_3$, ppm): δ 7.88 (br s, 1H, NH), 7.43 (br s, 1H, NH), 5.76–3.56 (m, 18H, 2 × $POCH_2$, sugar ring), 2.04, 2.01, 1.98, 1.97, 1.95, 1.92, 1.91 (7s, 21H, 7 × OAc), 1.26 (t, 6H, 2C, 2 × $POCH_2CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): δ 184.86 (C=S), 170.96, 170.48, 170.26, 170.12, 169.81, 169.38, 169.27 (7C, 7 × CO), 89.37, 79.69, 76.33, 74.39, 72.93, 71.76, 70.73, 68.28, 67.83, 62.96, 62.34, 61.97, 61.36, 58.12 (14C, sugar ring, 2 × P × $POCH_2$), 21.32, 21.13, 21.09, 21.03, 21.01, 20.99, 20.94, 20.88 (7C, 7 × OAc), 15.97, 15.88 (2C, 2 × $POCH_2CH_3$); $^{31}$P NMR ($CDCl_3$, ppm): δ 79.82. Anal. Calcd for $C_{31}H_{48}N_3O_{19}PS_2$: C, 43.20; H, 5.61; N, 4.88. Found: C, 42.90; H, 5.60; N, 5.12.

#### 1.2.11. 1-Diethoxythiophosphoryl-4-[2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-thiosemicarbazide (2k)

From 2.7 g (4 mmol) of **1e** (1.58 g, 75%); white crystals from EtOAc–petroleum ether; mp 160–163 °C. $^1$H NMR ($CDCl_3$, ppm): δ 7.59 (br s, 1H, NH), 7.48 (d, *J* 8.8 Hz, 1H, NH), 5.75 (t, 1H, H-1′), 5.38–3.81 (m, 18H, 2 × $POCH_2$, sugar ring), 2.10, 2.06, 2.03, 2.01, 1.99, 1.98, 1.96 (7s, 21H, 7×OAc), 1.29 (t, 6H, 2C, 2 × $POCH_2CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): δ 183.84 (C=S), 171.19, 170.85, 170.72, 170.58, 170.00, 169.87, 169.66 (7C, 7 × CO), 95.78, 82.18, 75.17, 74.20, 72.88, 71.61, 70.23, 68.72, 68.48, 68.15, 65.11, 64.98, 62.79, 61.16 (14C, sugar ring, 2 × $POCH_2$), 21.06, 20.96, 20.81 (7C, 7 × OAc), 16.14, 16.02 (2C, 2 × $POCH_2CH_3$); $^{31}$P NMR ($CDCl_3$, ppm): δ 69.47. Anal. Calcd for $C_{31}H_{48}N_3O_{19}PS_2$: C, 43.20; H, 5.61; N, 4.88. Found: C, 43.18; H, 5.78; N, 4.67.

### 1.3. 3-Alkoxy(phenyl)thiophosphorylamido-2-(per-*O*-acetylglycosyl-1′-imino)thiazolidine-4-one derivatives (3a–k), general method

To a soln of **2a–k** (2 mmol) in $CH_2Cl_2$ (20 mL), ethyl bromoacetate (0.5 g, 3 mmol) was added dropwise with stirring. The mixture was heated at reflux for 12 h and the solvent was removed under diminished pressure. Concentration resulted in a crude product which was purified on a silica gel column (1:2 EtOAc–petroleum ether).

#### 1.3.1. 3-Diethoxythiophosphorylamido-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1′-imino)thiazolidine-4-one (3a)

From 1.14 g of **2a** (0.59 g, 48%); white crystals from EtOAc–petroleum ether; mp 140–141 °C; $^1$H NMR ($CDCl_3$, ppm): δ 5.71 (d, *J* 8.74 Hz, 1H, NH), 5.50 (m, 1H, H-2′), 5.32 (d, 1H, *J* 3.6 Hz, H-1′), 5.13 (m, 1H, H-3′), 5.06 (t, 1H, H-4′), 4.28 (m, 7H, H-5′, H-6′, 2 × $POCH_2$), 3.84 (s, 2H, H-5), 2.06, 2.02, 1.99, 1.98 (4s, 12H, 4×OAc), 1.28 (t, 6H, 2 × $POCH_2CH_3$); $^{13}$C NMR ($CDCl_3$, ppm): δ 170.71, 170.11, 170.01, 169.53 (4C, 4 × CO), 168.18 (C-4), 156.70 (C-2), 83.41 (C-6′), 71.33 (C-3′), 70.68 (C-2′), 68.69 (C-1′), 64.59, 64.56(2C, 2 × $POCH_2$), 63.75 (C-5′), 61.89(C-4′), 29.93 (C-5), 20.84, 20.77, 20.68, 20.59 (4C, 4 × OAc), 15.90, 15.85 (2C, 2 × $POCH_2CH_3$); $^{31}$P NMR ($CDCl_3$, ppm): δ 71.17. FABMS: *m/z* 613 $[M+H]^+$. Anal. Calcd for $C_{21}H_{32}N_3O_{12}PS_2$: C, 41.11; H, 5.26; N, 6.85. Found: C, 41.24; H, 5.27; N, 6.76.

#### 1.3.2. 3-Methoxy(phenyl)thiophosphorylamido-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1′-imino)thiazolidine-4-one (3b)

From 1.18 g of **2b** (0.79 g, 64%); white crystals from EtOAc–petroleum ether; mp 87–89 °C; $^1$H NMR ($CDCl_3$, ppm): δ 8.07–7.36 (m, 5H, Ar-H), 5.70 (d, *J* 8.4 Hz, 1H, NH), 5.48 (t, 1H, H-2′), 5.27 (d, *J* 4.4 Hz, 1H, H-1′), 5.22 (t, 1H, H-3′), 5.11 (t, 1H, H-4′),

5.02 (m, 2H, H-6′, H-5′), 3.90 (s, 3H, $CH_3O$), 3.72 (m, 3H, H-6′, H-5), 2.06, 2.02, 2.00, 1.96 (4s, 12H, 4 × OAc); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.93, 170.81, 170.30, 169.73 (4C, 4 × CO), 168.68 (C-4), 157.40 (C-2), 132.74, 131.83, 131.69, 131.57, 128.86, 128.71 (6C, Ar-C), 88.30 ($CH_3O$), 83.73 (C-6′), 71.52 (C-3′), 70.87 (C-2′), 68.92 (C-1′), 62.01 (C-5′), 53.23 (C-4′), 29.98 (C-5), 21.15, 20.99, 20.94, 20.86 (4C, 4 × OAc); $^{31}P$ NMR ($CDCl_3$, ppm): δ 81.75, 81.69. FABMS: *m/z* 631 $[M+H]^+$. Anal. Calcd for $C_{24}H_{30}N_3O_{11}PS_2$: C, 45.64; H, 4.79; N, 6.65. Found: C, 45.91; H, 4.96; N, 6.92.

### 1.3.3. 3-Phenyl(propoxy)thiophosphorylamido-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl-1′-imino)thiazolidine-4-one (3c)

From 1.2 g of **2c** (0.55 g, 42%); white crystals from EtOAc–petroleum ether; mp 107–108 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 7.79–7.41 (m, 5H, Ar-H), 5.68 (d, *J* 8.4 Hz, 1H, NH), 5.50 (t, 1H, H-2′), 5.22 (d, *J* 4.4 Hz, 1H, H-1′), 5.11 (t, 1H, H-3′), 5.09 (m, 3H, H-4′, H-5′, H-6′), 3.94 (m, 2H, $CH_2O$), 3.75(m, 3H, H-6′, H-5), 2.06, 1.98, 1.97, 1.95 (4s, 12H, 4 × OAc), 1.28 (t, 2H, $CH_2$), 0.93 (t, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm) δ 170.27, 169.94, 169.58, 169.20 (4C, 4 × CO), 168.88 (C-4), 154.92 (C-2), 132.34, 131.65, 131.54, 128.69, 128.54, 128.38 (6C, Ar-C), 86.74, 74.71, 73.66, 68.23, 67.34, 62.79, 62.43 (7C, C-1′, C-2′, C-3′, C-4′, C-5′, C-6, $POCH_2$), 32.81 (C-5), 23.67 ($POCH_2CH_2$), 20.92, 20.79, 20.55 (4C, 4×OAc), 10.45 ($POCH_2CH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 82.37, 82.26. FABMS: *m/z* 659 $[M+H]^+$. Anal. Calcd for $C_{26}H_{34}N_3O_{11}PS_2$: C, 47.34; H, 5.20; N, 6.37. Found: C, 47.58; H, 5.39, N, 5.53.

### 1.3.4. 3-Diethoxythiophosphorylamido-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl-1′-imino)thiazolidine-4-one (3d)

From 1.14 g of **2d** (0.34 g, 24%); syrup; $^1H$ NMR ($CDCl_3$, ppm): δ 5.65 (d, *J* 8.4 Hz, 1H, NH), 5.41 (t, 1H, H-2′), 5.22 (t, 1H, H-3′), 5.10 (t, 1H, H-4′), 4.70 (d, *J* 8.8 Hz, 1H, H-1′), 4.22–4.10 (m, 6H, H-6′, H-5′, 2 × $POCH_2$), 3.60 (m, 3H, H-6′, H-5), 2.13, 2.07, 2.02, 1.98 (4s, 12H, 4 × OAc), 1.30 (t, 6H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.61, 170.41, 170.17, 168.54 (4C, 4 × CO), 167.80 (C-4), 156.46 (C-2), 84.23 (C-1′), 72.01 (C-5′), 67.79 (C-3′), 66.69 (C-2′), 64.74 (C-4′), 64.01, 63.77 (2C, 2 × $POCH_2$), 61.56(C-6′), 33.47 (C-5), 21.16, 20.92, 20.84, 20.77 (4C, 4 × OAc), 16.17, 16.09 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 71.74. FABMS: *m/z* 613 $[M+H]^+$. Anal. Calcd for $C_{21}H_{32}N_3O_{12}PS_2$: C, 41.11; H, 5.26; N, 6.85. Found: C, 41.00; H, 5.43; N, 6.78.

### 1.3.5. 3-Methoxy(phenyl)thiophosphorylamido-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl-1′-imino)thiazolidine-4-one (3e)

From 1.18 g of **2e** (0.77 g, 61%); white crystals from EtOAc–petroleum ether; mp 98–100 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 7.93–7.37 (m, 5H, Ar-H), δ 5.70 (d, *J* 8.4 Hz, 1H, NH), 5.44 (t, 1H, H-5′), 5.25 (t, 1H, H-3′), 5.16 (t, 1H, H-2′), 4.82 (d, *J* 8.8 Hz, 1H, H-1′), 4.33–4.19 (m, 5H, H-6′, H-4′, $POCH_3$), 3.73 (m, 3H, H-6′, H-5), 2.05, 2.03, 1.98, 1.95 (4s, 12H, 4 × OAc); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.69, 170.59, 170.32, 170.10 (4C, 4 × CO), 169.55 (C-4), 156.75 (C-2), 132.56, 131.75, 131.65, 131.52, 128.52, 128.37 (6C, Ar-C), 95.88 (C-1′), 76.37 (C-5′), 76.14 (C-3′), 70.18 (C-2′), 69.49 (C-4′), 68.73 ($POCH_3$), 68.22 (C-6′), 30.07 (C-5), 30.07, 21.04, 20.84, 20.75 (4C, 4 × OAc); $^{31}P$ NMR ($CDCl_3$, ppm): δ 83.87, 83.62. FABMS: *m/z* 631 $[M+H]^+$. Anal. Calcd for $C_{24}H_{30}N_3O_{11}PS_2$: C, 47.59; H, 5.18; N, 4.50. Found: C, 47.44; H, 5.58; N, 4.70.

### 1.3.6. 3-Dimethoxythiophosphorylamido-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl-1′-imino)thiazolidine-4-one (3f)

From 0.84 g of **2f** (0.44 g, 43%); white crystals from EtOAc–petroleum ether; mp 146–148 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 5.53 (br s, 1H, NH), 5.27 (m, 1H, H-3′), 5.06 (m, 1H, H-4′), 5.01 (m, 1H, H-2′), 4.76 (d, *J* 8.4 Hz, 1H, H-1′), 4.20 (m, 1H, H-5′), 3.83 (m, 8H, 2 × $CH_3O$, 2 × H-5), 3.43 (m, 1H, H-5′), 2.07, 2.06, 2.05 (3s, 9H, 3 × OAc); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.30, 169.8, 169.5 (3C, 3 × CO), 167.76 (C-4), 155.8 (C-2), 89.73 (C-1′), 81.67 (C-5′), 72.8 (C-3′), 72.43 (C-2′), 68.97 (C-4′), 54.97, 54.76 (2C, 2 × $POCH_3$), 29.98 (C-5), 21.00, 20.95, 20.84 (3C, 3 × OAc); $^{31}P$ NMR ($CDCl_3$, ppm): δ 70.65. FABMS: *m/z* 514.2 $[M+H]^+$. Anal. Calcd for $C_{16}H_{24}N_3O_{10}PS_2$: C, 37.43; H, 4.71; N, 8.18. Found: C, 37.35; H, 5.02; N, 8.32.

### 1.3.7. 3-Diethoxythiophosphorylamido-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl-1′-imino)thiazolidine-4-one (3g)

From 1.02 g of **2g** (0.60 g, 58%); white crystals from EtOAc–petroleum ether; mp 101–103 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 7.96–7.52 (m, 5H, Ar-H), 5.54 (br s, 1H, NH), 5.30 (m, 2H, H-3′), 5.01 (m, 1H, H-4′), 4.92 (m, 1H, H-2′), 4.39 (d, *J* 8.4 Hz, 1H, H-1′), 4.03 (s, 2H, H-5′), 3.92 (m, 6H, 2 × $POCH_2$, 2 × H-5), 3.70 (m, 1H, H-5′), 2.06, 2.05, 2.03 (3s, 9H, 3 × OAc), 1.40 (t, 6H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.87, 170.33, 169.42 (3C, 3 × CO), 168.70 (C-4), 157.11 (C-2), 89.84 (C-1′), 82.37 (C-5′), 71.99 (C-2′), 71.01, 67.45, 60.29, 54.96 (4C, C-3′, C-4′, 2 × $POCH_2$), 30.47 (C-5), 21.01, 20.68, 20.43 (3C, 3 × OAc), 16.23, 16.17 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 70.66. FABMS: *m/z* 541 $[M+H]^+$. Anal. Calcd for $C_{18}H_{28}N_3O_{10}PS_2$: C, 39.92; H, 5.21; N, 7.76. Found: C, 39.74; H, 5.30; N, 7.88.

### 1.3.8. 3-Methoxy(phenyl)thiophosphorylamido-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl-1′-imino)thiazolidine-4-one (3h)

From 1.03 g of **2h** (0.52 g, 47%); white crystals from EtOAc–petroleum ether; mp 95–96 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 8.06–7.51 (m, 5H, Ar-H), 5.56 (br s, 1H, NH), 5.29 (m, 2H, H-3′, H-4′), 5.00 (m, 1H, H-2′), 4.36 (d, *J* 8.4 Hz, 1H, H-1′), 4.02 (m, 1H, H-5′), 3.91 (m, 5H, $CH_3O$, 2 × H-5), 3.79 (m, 1H, H-5′), 2.07, 2.06, 2.05 (3s, 9H, 3×OAc); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.50, 170.46, 169.35 (3C, 3 × CO), 168.76 (C-4), 156.40 (C-2), 132.82, 131.79, 131.67, 131.50, 128.66, 128.45 (6C, Ar-C), 93.74, 83.46, 73.42, 70.46, 68.82, 62.45, 53.43 (6C, C-1′, C-2′, C-3′, C-4′, C-5′, $CH_3O$), 31.54 (C-5), 21.00, 20.89, 20.46 (3C, 3×OAc); $^{31}P$ NMR ($CDCl_3$, ppm): δ 81.70, 81.52. FABMS: *m/z* 559 $[M+H]^+$. Anal. Calcd for $C_{21}H_{26}N_3O_9PS_2$: C, 45.08; H, 4.68; N, 7.51. Found: C, 45.11; H, 4.96; N, 7.22.

### 1.3.9. 3-Ethoxy(phenyl)thiophosphorylamido-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl-1′-imino)thiazolidine-4-one (3i)

From 1.06 g of **2i** (0.71 g, 63%); syrup; $^1H$ NMR ($CDCl_3$, ppm): δ 8.01–7.66 (m, 5H, Ar-H), 5.57 (br s, 1H, NH), 5.31 (m, 2H, H-3′), 5.12 (m, 1H, H-4′), 5.02 (m, 1H, H-2′), 4.33 (d, *J* 8.4 Hz, 1H, H-1′), 3.99 (m, 4H, 2 × H-5, $CH_2O$), 3.83 (m, 1H, H-5′), 2.07, 2.04, 2.03 (3s, 9H, 3 × OAc), 1.36 (t, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.52, 170.12 (3C, 3 × CO), 168.99 (C-4), 159.52 (C-2), 135.29, 134.36, 134.64, 133.58, 130.66, 129.87 (6C, Ar-C), 89.45, 80.21, 73.26, 69.37, 62.55, 53.60 (6C, C-1′, C-2′, C-3′, C-4′, C-5′, $CH_3O$), 30.57 (C-5), 20.94, 20.83, 20.32 (3C, 3×OAc), 16.25 ($POCH_2CH_3$), $^{31}P$ NMR ($CDCl_3$, ppm): δ 81.85, 81.70. FABMS: *m/z* 573 $[M+H]^+$. Anal. Calcd for $C_{22}H_{28}N_3O_9PS_2$: C, 46.07; H, 4.92; N, 7.33. Found: C, 46.39; H, 5.18; N, 7.70.

### 1.3.10. 3-Diethoxythiophosphorylamido-2-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl-1′-imino]thiazolidine-4-one (3j)

From 1.72 g of **2j** (0.6 g, 35%); white crystals from EtOAc–petroleum ether; mp 88–91 °C; $^1H$ NMR ($CDCl_3$, ppm): δ 5.53–3.48 (m, 20H, lactosyl ring, 2 × $POCH_2$, 5-H), 2.14, 2.10, 2.09, 2.04, 2.03, 1.94 (m, 21H, 7 × OAc), 1.27 (t, 6H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): δ 170.55, 170.49, 170.33, 170.27, 169.67 (7C, 7 × CO), 169.22 (C-4), 156.13 (C-2), 91.36, 88.30, 74.22, 72.77, 71.18, 70.92, 69.23, 66.80, 63.76, 62.04, 61.02 (14C, lactosyl ring, 2 × $CH_2O$), 33.69 (C-5), 21.08, 20.97, 20.85, 20.72 (7C, 7 × $COCH_3$), 16.19, 16.11 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): δ 71.05.

FABMS: *m/z* 901 $[M+H]^+$. Anal. Calcd for $C_{33}H_{48}N_3O_{20}PS_2$: C, 43.95; H, 5.36; N, 4.66. Found: C, 44.16; H, 5.54; N, 4.97.

### 1.3.11. 3-Diethoxythiophosphorylamido-2-[2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl-1′-imino] thiazolidine-4-one (3k)

From 0.26 g of **2k** (0.56 g, 33%); syrup; $^1H$ NMR ($CDCl_3$, ppm): $\delta$ 5.58–3.48 (m, 20H, maltosyl ring, 2 × $CH_2O$, 5-H), 2.19, 2.13, 2.10, 2.07, 2.03, 2.00, 1.97 (s, 21H, $COCH_3$), 1.22 (t, 6H, 2 × $POCH_2CH_3$); $^{13}C$ NMR ($CDCl_3$, ppm): $\delta$ 168.17, 168.01, 167.81, 167.56, 167.35, 167.05, 166.40, 165.26 (8C, 7 × CO, C-4), 160.17 (C-2), 93.09, 85.18, 80.83, 76.47, 73.50, 70.48, 70.43, 69.55, 67.65, 67.01, 66.04, 65.67, 60.57, 59.58 (14C, sugar ring, 2 × $CH_2O$), 30.57 (C-5), 18.55, 18.49, 18.30, 18.21 (7C, 7 × $COCH_3$), 14.26, 13.99 (2C, 2 × $POCH_2CH_3$); $^{31}P$ NMR ($CDCl_3$, ppm): $\delta$ 68.99. FABMS: *m/z* 901 $[M+H]^+$. Anal. Calcd for $C_{33}H_{48}N_3O_{20}PS_2$: C, 43.95; H, 5.36; N, 4.66. Found: C, 43.88; H, 5.76; N, 4.38.

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