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Disaccharide Blocks for Analogs of OSW-1

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Abstract—The acetalization of phenyl 1-thio-α-L-arabinopyranoside with 2,3-butanedione in the medium of MeOH–$CH(OMe)_3$–CSA proceeded with the prevailing formation of the corresponding 3,4-bisacetal that further was converted in compounds, which were regio- and stereoisomers of disaccharide block of OSW-1.

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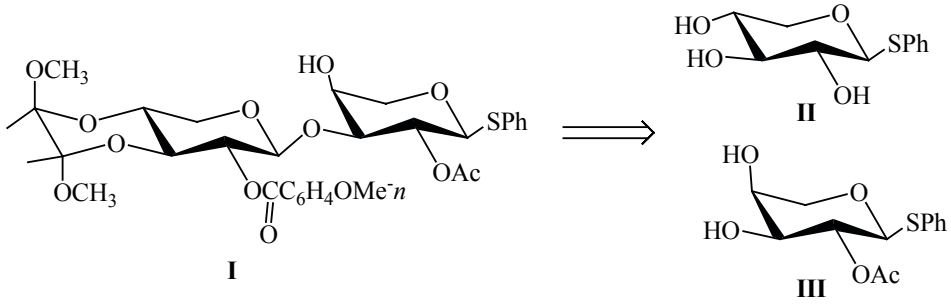
In the sugar chemistry the necessity to work with awkward polyol systems makes the protective groups extremely important [1]. In the course of the planned synthesis of disaccharide block **I** for anticancer steroid OSW-1 based on the known components, glycoside-donor **II** and acceptor **III** [2, 3] (Scheme 1) we tested 2,3-butanedione in conditions described in [4] for the selective protection of the 3,4-diol moiety of triol **II** in the form of butane 2,3-bisacetal. The butane 2,3-bisacetal and the other similar protective groups introduced into the synthetic practice by Liu group [5] are known to provide a selective blocking in cycles of *trans*-vicinal diols, impart the products a crystalline structure, desired conformational rigidity, etc. [6].

As seen from the structure of triol **II** all its hydroxy groups are located in the *trans*-equatorial reciprocal position, and here the possibility of the regiocontrolled acetalization depends mainly on the steric factors. In the experimental test of triol **II** acetalization by heating with excess 2,3-butanedione in the medium of MeOH–$CH(OMe)_3$–camphorsulfonic acid (CSA) (catalyst) we obtained two expected acetals **IV** and **V** in the ratio ~3 : 1 and in the overall yield 80%. The main bisacetal **IV** is a crystalline substance easily isolated from compound **V** by chromatography on SiO_2. Minor bisacetal **V** is oily substance containing ~10% of unidentified isomeric compound. The assignment of the structure of regioisomeric acetals **IV** and **V** was carried out applying spectral data. Their ^{1}H NMR spectra contain a characteristic signal C^{1}H which in the spectrum of 2,3-acetal **V** is located downfield (doublet, δ 4.77 ppm, *J* 9.6 Hz) with respect to the corresponding signal in the spectrum of compound **IV** (δ 4.47 ppm, d, *J* 9.35 Hz) because of the electron-withdrawing inductive effect of the closely

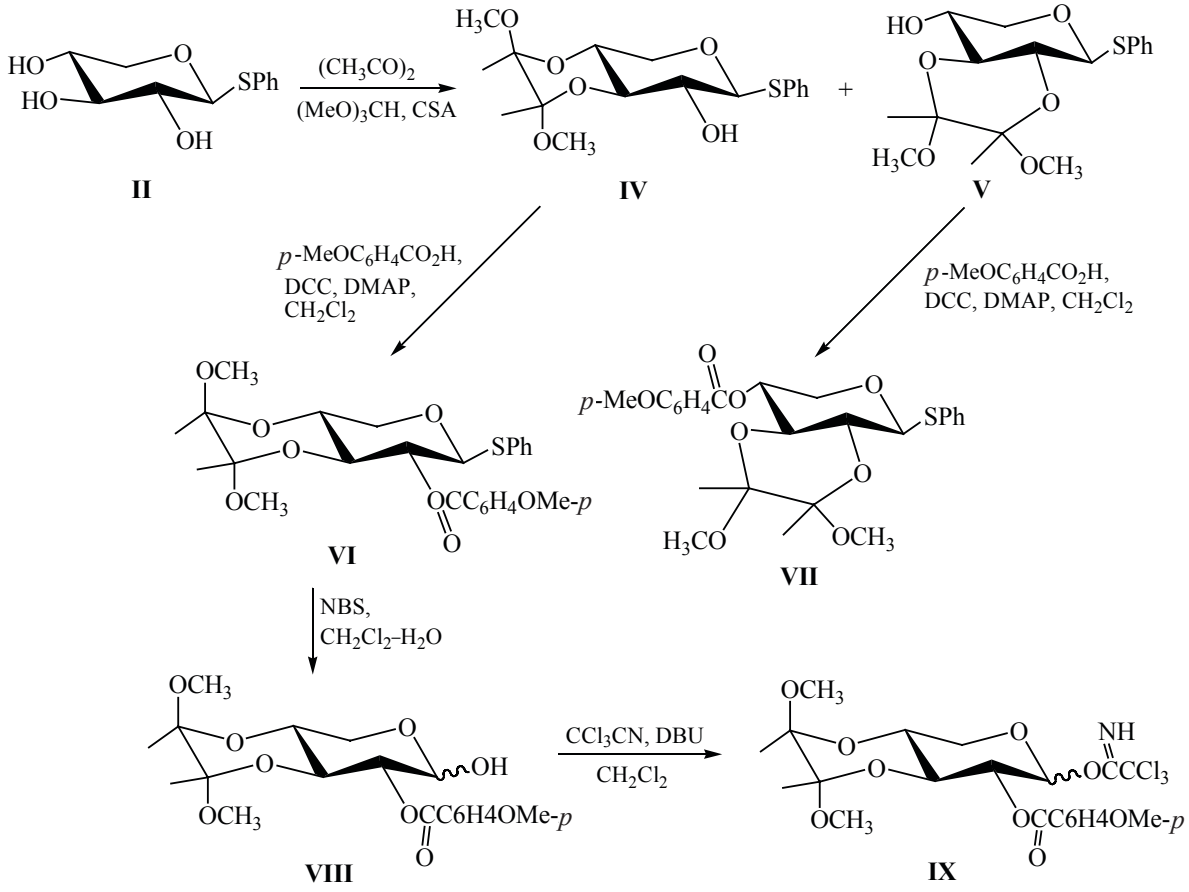
Scheme 1.



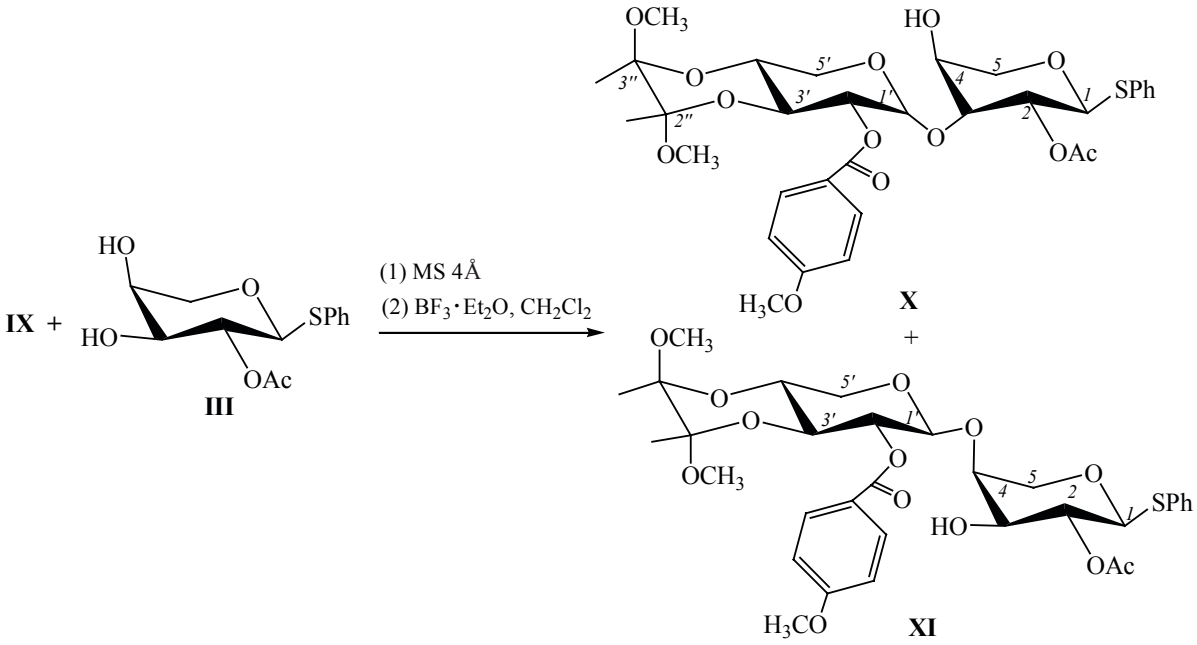
located acetal function. And in contrast, in the ^{13}C NMR spectra the signal of C^1 of 2,3-bisacetal **V** appears upfield (δ 85.86 ppm) due to the stronger than in 3,4-bisacetal **IV** (δ 89.24 ppm) sterical shielding by the SPh group and the bisacetal fragment. Besides, in the ^1H NMR spectra of para-methoxybenzoates **VI** and **VII** obtained from alcohols **IV** and **V** characteristic downfield signals are observed belonging to the proton attached to the same carbon atom as the benzoate group: 5.20 t (H^2, J 9.4 Hz) (**VI**) and 5.18 d.d.d (H^4, J 5.5, 8.7 and 9.3 Hz) (**VII**).

Taking into account that compound **VI** as a possible glycoside-donor is weakened by the presence of electron-acceptor benzoate and acetal groups its direct application in the stage of coupling with diol **III** by the known methods [7] is undesirable. Therefore compound **VI** was subjected to hydration with aqueous NBS to convert it into lactol **VIII** and further into trichloroacetimidate **IX**, an activated glycoside-donor (Scheme 2). The latter is an α,β-anomeric mixture of imidates (3 : 1). By repeated chromatography we succeeded to isolate and characterize α-anomer **IX** (δ 6.32, d, J 3.6 Hz), for the β-anomer δ 6.0, d, J 6.9 Hz (cf. [2]). Bringing into the coupling with diol **III** this α,β-anomeric mixture of imidates **IX** resulted in a complex mixture of compounds. Therefore in the stage of glycosilation we used α-anomer **IX** and as the glycoside-acceptor, arabinose derivative **III**, aiming at the estimation of the possibility of a regioselective glycosilation. The coupling of blocks **IX** and **III** was promoted with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at –30°C. As a result we observed sufficiently fast (TLC monitoring) formation of three coupling products that were separated by column chromatography on silica gel. In keeping with the spectral data two more polar on silica gel compounds than imidate **IX** were regarded as regioisomeric disaccharides **X** and **XI** (Scheme 3). Therewith the overall yield of the coupling products was 60%, the ratio **X**–**XI** was ~1 : 1. The structure of the low polar coupling product was not established. In the ^1H NMR spectra of regioisomeric

Scheme 2.



Scheme 3.



disaccharides **X** and **XI** a significant difference was observed in the chemical shifts of H^{2} signals. The doublets of H^{1} and H$^{1'}$ serve as reference signals. In the spectrum of regioisomer **X** the separate doublet of doublets appears from H^{2} at 5.3 ppm and a triplet from H$^{2'}$ at 5.14 ppm, whereas in compound **XI** they coalesce and are observed as a multiplet at 5.15 ppm.

The downfield shift of H^{2} signal in disaccharide **X** we ascribe to the electron-withdrawing effect of the xylose fragment at C^{3}. The small value of $J_{1',2'}$ (3.6 Hz) in compound **X** indicates the α-configuration of the anomeric center.

Hence in this study we developed new disaccharide blocks **X** and **XI** for the analogs of OSW-1 modified in the glycoside part.

EXPERIMENTAL

IR spectra were obtained on spectrometers Specord M-80 and Shimadzu IR Prestige-21 from thin films or mulls in mineral oil. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 (300.13 and 75.47 MHz respectively) in $CDCl_3$ or acetone-d_6, internal reference TMS. Rotation angles were measured on a polarimeter Perkin Elmer-341. Mass spectrum was measured on an instrument Thermo Finnigan MAT 95XP, ionizing voltage 70 V. The reaction progress was monitored by TLC on Sorbfil plates, spots visualized by acidified solution of anisaldehyde in ethanol. The reaction products were isolated by column chromatography on silica gel (30–60 g of adsorbent per 1 g of substance), eluents were freshly distilled solvents.

Reaction of phenyl-1-thio-D-xylopyranoside with 2,3-butanedione. To a solution of 0.50 g (0.002 mol) of triol **II** in 7 ml of methanol was added 0.22 ml (2.4 mmol) of 2,3-butanedione, 0.68 ml (0.006 mol) of trimethyl orthoformate, and 3 mg of CSA as catalyst, the reaction mixture was stirred at heating over ~24 h till complete consumption of initial triol (TLC monitoring). The reaction mixture was evaporated, the reaction product was purified by column chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 1:1). We obtained 0.43 g (59%) of compound **IV** and 0.18 g (25%) of compound **V**.

Phenyl-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1*S*-thio-D-xylopyranoside (IV). Colorless crystals, mp 163–165°C, $[\alpha]_D^{20}$ +132.0° (*C* 0.525, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 s (3H), 1.32 s (3H, CH_3), 2.69 d (1H, OH, *J* 2.2 Hz), 3.23 s (3H, OCH_3), 3.29 s (3H, OCH_3), 3.40–3.50 m (2H, OCH), 3.60–3.70 m (2H, OCH), 3.96 d.d (1H, H^{5}, *J* 4.45, 11.0 Hz), 4.47 d (1H, H^{1}, *J* 9.35 Hz), 7.27–7.30 m (3H), 7.51–7.55 m (2H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.45, 17.61 (2 CH_3), 47.87 (2 OCH_3), 65.43 (C^{3}), 67.82 (C^{5}), 69.13 (C^{2}), 73.91 (C^{4}), 89.24 (C^{1}), 99.37, 99.79 (C$^{2',3'}$),

128.22, 128.91, 131.21, 133.22 (Ar). Found, %: C 56.98; H 7.10; S 8.96. $C_{17}H_{24}O_6S$. Calculated, %: C 57.28; H 6.79; S 9.00.

Phenyl-2,3-O-(2',3'-dimethoxybutane-2',3'-diyl)-1*S*-thio-D-xylopyranoside (V). Light-yellow needle crystals, mp 136–138°C, $[\alpha]_D^{20}$ –113.8° (*C* 2.15, $CHCl_3$). ^1H ($CDCl_3$), δ, ppm: 1.34 s (3H, CH_3), 1.35 s (3H, CH_3), 2.55 br.s (1H, OH), 3.23 s (3H, OCH_3), 3.30 s (3H, OCH_3), 3.61 t (1H, H^3, *J* 9.6 Hz), 3.70 t (1H, H^2, *J* 9.6 Hz), 3.82–3.91 m (1H, OCH_2), 4.10 m (2H, H^4, OCH_2), 4.77 d (1H, H^1, *J* 9.6 Hz), 7.25–7.33 m (3H), 7.51–7.58 m (2H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.55 (2 CH_3), 47.87, 48.08 (2 OCH_3), 67.08 (C^3), 67.91 (C^2), 69.68 (C^5), 74.83 (C^4), 85.86 (C^1), 99.54, 100.14 ($C^{2',3'}$), 127.37, 128.79, 131.66, 133.21 (Ar).

Phenyl-2-O-(4-methoxybenzoyl)-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-1*S*-thio-D-xylopyranoside (VI). To a solution of 0.32 g (0.89 mmol) of compound **IV** in 10 ml of anhydrous CH_2Cl_2 was added 0.16 g (1.07 mmol) of anise acid and 0.065 g (0.5 mmol) of DMAP, the reaction mixture was cooled to 0°C and a solution of 0.218 g (1.07 mmol) of DCC in 3 ml CH_2Cl_2 was added dropwise. The reaction mixture was stirred at room temperature over 12 h, then it was washed in succession with 10% solution of HCl and with a saturated solution of $NaHCO_3$. The organic layer was washed with brine, dried with $MgSO_4$, evaporated, the residue was subjected to column chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 1 : 1). Yield 0.43 g (95%), colorless crystals, mp 65–67°C, $[\alpha]_D^{20}$ +146.0° (*C* 0.285, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 s (3H, CH_3), 1.27 s (3H, CH_3), 3.17 s (3H, OCH_3), 3.25 s (3H, OCH_3), 3.49 m (1H, OCH), 3.87 s (3H, OCH_3), 3.83–3.93 m (2H), 4.05 d.d (1H, OCH, OCH_2, *J* 4.3, 11.5 Hz), 4.75 d (1H, H^1, *J* 9.6 Hz), 5.20 t (1H, H^2, *J* 9.4 Hz), 6.94 d (2H, *J* 8.5 Hz), 8.03 d (2H, C_6H_4, *J* 8.8 Hz), 7.26–7.28 m (3H), 7.44–7.46 m (2H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.39, 17.51 (CH_3), 47.53, 47.82 (OCH_3), 55.32 (OCH_3), 65.66 (C^3), 67.65 (C^5), 69.48 (C^2), 72.32 (C^4), 87.51 (C^1), 99.41, 99.83 ($C^{2',3'}$), 113.58, 122.09, 127.81, 128.77, 131.68, 132.51, 132.57, 163.43 (Ar), 164.48 (C=O). Found, %: C 60.95; H 5.85; S 6.69. $C_{12}H_{18}O_2S$. Calculated, %: C 61.21; H 6.16; S 6.54.

Phenyl-4-O-(4-methoxybenzoyl)-2,3-O-(2',3'-dimethoxybutane-2',3'-diyl)-1*S*-thio-D-xylopyranoside (VII) was obtained analogously. Yield 93%, colorless crystals, mp 119–120°C, $[\alpha]_D^{20}$ –150.9° (*C* 0.555, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (3H, CH_3), 1.35 s (3H, CH_3), 3.23 s (3H, OCH_3), 3.32 s (3H, OCH_3), 3.40 d.d (1H, H^5, *J* 8.8, 10.8 Hz), 3.75 t (1H, H^3, *J* 9.7 Hz), 3.86 s (3H, OCH_3), 4.08 t (1H, H^2, *J* 9.5 Hz), 4.35 d.d (1H, H^5, *J* 5.3, 11.57 Hz), 4.85 d (1H, H^1, *J* 9.5 Hz), 5.18 d.d.d (1H, H^4, *J* 5.5, 8.7, 9.3 Hz), 6.91 d (2H, *J* 7.96 Hz), 7.95 d (2H, C_6H_4, *J* 7.96 Hz), 7.25–7.31 m (3H) and 7.52–7.55 m (2H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.35 (2 CH_3), 47.55, 47.89 (OCH_3), 55.19 (OCH_3), 66.88 (C^3), 67.95 (C^5), 68.73 (C^2), 71.27, (C^4), 85.69 (C^1), 99.44, 99.98 ($C^{2',3'}$), 113.52, 121.69, 127.27, 128.67, 131.53, 131.72, 132.99, 163.37 (Ar), 164.95 (C=O).

2-O-(4-Methoxybenzoyl)-3,4-O-(2',3'-dimethoxybutane-2',3'-diyl)-D-xylopyranosyltrichloro-acetimidate (IX). To a stirred solution of 2.0 g (5.60 mmol) of compound **VI** in 10 ml of a mixture CH_2Cl_2–H_2O, 8 : 1, was added at room temperature 0.6 g (3.40 mmol) of NBS. The reaction mixture was stirred at this temperature till complete consumption of the initial compound (TLC monitoring), then saturated solution of Na_2SO_3 was added. The reaction product was extracted into CH_2Cl_2 (3 × 10 ml), combined organic solutions were washed with brine,dried with $MgSO_4$, and evaporated. The residue was purified by flash-chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 3:1), and the obtained lactol **VIII** [0.94 g (82%), anomers mixture] was at once brought into the next stage of imidation.

To a solution of 0.86 g (2.0 mmol) of compound **VIII** in 7 ml of anhydrous CH_2Cl_2 was added 1 ml (10.0 mmol) of CCl_3CN and several drops of DBU, the reaction mixture was stirred at room temperature for 4 h, then it was evaporated in a vacuum. The residue was purified by flash-chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 1 : 1, containing 1% of Et_3N). Yield of anomeric mixture 0.54 g (57%). The repeated chromatography of the anomers mixture on a column packed with SiO_2 furnished an analytically pure sample of α-anomer **IX**. Oily substance, $[\alpha]_D^{20}$ +143.3° (*C* 2.038, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (3H, CH_3), 1.32 s (3H, CH_3), 3.29 s (3H, OCH_3), 3.31 s (3H, OCH_3), 3.83 s (3H, OCH_3), 3.80–4.05 m (3H, H^4, OCH_2), 4.35 t (1H, H^3, *J* 10.4 Hz), 5.27 d.d (1H, H^2, *J* 3.6, 10.6 Hz), 6.62 d (1H, H^1, *J* 3.6 Hz), 6.89 d (2H, *J* 8.8 Hz) and 7.96 d (2H, C_6H_4, *J* 8.80 Hz), 8.46 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.56, 17.70 (CH_3), 47.70, 48.09 (OCH_3), 55.44 (OCH_3), 62.26 (C^5), 65.77 (C^3), 67.53 (C^2), 69.79 (C^4), 90.98 (CCl_3), 94.10 (C^1), 99.70, 100.0 ($C^{2',3'}$), 113.66, 121.72, 131.78, 163.62

(Ar), 160.81 (C=NH), 165.15 (C=O).

β-Anomer. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.00 d (1H, H^1, *J* 6.9 Hz), 8.67 s (1H, NH). ^{13}C NMR spectrum $CDCl_3$), δ, ppm: 17.32, 17.56 (CH_3), 48.09 (OCH_3), 55.44 (OCH_3), 62.11 (C^5), 66.30 (C^3), 67.71 (C^2), 70.52 (C^4), 90.98 (CCl_3), 94.15 (C^1), 99.70 and 100.0 (C$^{2',3'}$), 113.66, 121.72, 131.78, 163.62 (Ar), 161.07 (C=NH), 165.20 (C=O).

To a mixture of 0.2 g (0.36 mmol) of α-anomer of imidate **IX** and 0.08 g (0.28 mmol) of compound **III** in anhydrous CH_2Cl_2 was added 0.25 g of finely ground freshly calcined molecular sieves 4 Å. The mixture was stirred at room temperature for 40 miin, cooled to –60°C, and 0.26 ml of 0.1 M solution of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 was added dropwise, and the stirring at –30°C was continued for 2 h. The reaction was stopped by adding triethylamine, the mixture was filtered, the filtrate was evaporated, the residue was purified by column chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 2 : 1) to furnish 0.050 g (27%) of compound **X** and 0.048 g (26%) of compound **XI**.

Phenyl 2-O-(4-methoxybenzoyl)-3,4-O,O-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranosyl(1→3)-2-O-acetyl-1*S*-thio-α-L-arabinopyranoside (X). $[\alpha]_D^{20}$ +37.6° (*C* 1.68, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 s (3H) and 1.28 s (3H, CH_3), 1.91 s (3H, OAc), 2.88 d (1H, OH, *J* 6.2 Hz), 3.19 s, 3.27 s (6H, OCH_3), 3.51–3.58 m (2H, OCH), 3.61 d (1H, OCH, *J* 2.9 Hz), 3.84 s (3H, OCH_3), 3.86–4.01 m (4H, OCH_2), 4.72 d (1H, H^1, *J* 7.8 Hz), 4.93 d (1H, H$^{1'}$, *J* 3.6 Hz), 5.14 t (1H, H$^{2'}$, *J* 3.9, 4.4 Hz), 5.32 d.d (1H, H^2, *J* 7.8 Hz), 6.91 d (2H, *J* 8.8 Hz), 8.04 d (2H, C_6H_4, *J* 8.8 Hz), 7.06–7.16 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.40, 17.52 (CH_3), 20.64 (CH_3), 47.58, 47.87 (OCH_3), 55.34 (OCH_3), 64.31 (C$^{5,5'}$), 64.76, 65.63, 70.33, 70.70 (C$^{2,2',3,4',3',4}$), 85.16 (C^1), 99.48, 99.72 (C$^{2'',3''}$), 101.94 (C$^{1'}$), 113.56, 122.54, 126.83, 128.48, 130.69, 131.79, 135.48, 163.31 (Ph), 164.45 (C=O), 169.36 (OAC). MaCC-Cпeqtp, *m/z* ($I_{OtH.}$, %): 633 [M – OCH_3]$^+$ (0.5), 555 [M – SPh]$^+$ (3), 524 [M – OCH_3 – SPh]$^+$ (8), 523 [M – H – OCH_3 – SPh]$^+$ (24), 381 [M – $COC_6H_4OCH_3$ – OCMe(OMe)CMe(OMe)O]$^+$ (12), 249 (6), 233 (22), 157 (12), 135 [$COC_6H_4OCH_3$]$^+$ (100), 109 [SPh]$^+$ (1).

Phenyl 2-O-(4-methoxybenzoyl)-3,4-O,O-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-xylopyranozyl-(1→4)-2-O-acetyl-1*S*-thio-α-L-arabinopyranoside (XI). $[\alpha]_D^{20}$ +40.3° (*C* 1.30, $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (3H) and 1.30 s (3H, CH_3), 2.07 s (3H, OAc), 2.83 d (1H, OH, *J* 6.2 Hz), 3.26 s, 3.33 s (6H, OCH_3), 3.52 m (1H, OCH), 3.62 d.d (1H, OCH_2, *J* 3.1, 12.0 Hz), 3.74 m (1H, OCH), 3.87 s (3H, OCH_3), 3.92–3.98 m (3H, OCH, OCH_2), 4.29 d.d (1H, OCH_2, *J* 6.5, 12.2 Hz), 4.71 d (1H, H^1, *J* 6.7 Hz), 4.90 d (1H, H$^{1'}$, *J* 5.4 Hz), 5.13–5.15 m (2H, H$^{2,2'}$), 6.93 d (2H, *J* 8.8 Hz) and 7.99 d (2H, C_6H_4, *J* 8.8 Hz), 7.26–7.30 m (3H) and 7.45–7.48 (2H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.53 (CH_3), 20.91 (CH_3), 47.67, 47.95 (OCH_3), 55.37 (OCH_3), 63.89 (C$^{5,5'}$), 65.11, 69.46, 69.88, 71.93, 75.24 (C$^{2,2',3,4',3',4}$), 85.85 (C^1), 99.42, 99.69 (C$^{2'',3''}$), 102.92 (C$^{1'}$), 113.72, 121.67, 127.22, 128.77, 131.31, 131.71, 135.00, 163.60 (Ph), 165.28 (C=O), 169.57 (OAC). Found, %: C 57.36; H 6.53; S 4.79. $C_{32}H_{40}O_{13}S$. Calculated, %: C 57.82; H 6.07; S 4.82.

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