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Formation of orthoester-linked D-arabinofuranose oligosaccharides and their isomerization into the corresponding glycosides

Polina I. Abronina [a], Sergey L. Sedinkin [a], Nikita M. Podvalnyy [a], Ksenia G. Fedina [a,b], Alexander I. Zinin [a], Vladimir I. Torgov [a], Leonid O. Kononov [a,*]

[a] N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Leninsky Prosp., 47, Moscow 119991, Russian Federation
[b] The Higher Chemical College of the Russian Academy of Sciences, Miyuskaya pl. 9, Moscow 125047, Russian Federation

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ABSTRACT

Orthoester-linked D-arabinofuranose oligosaccharides were isolated in high yield for the first time via glycosylations with 2-*O*-chloroacetyl-substituted D-arabinofuranose thioglycosides promoted by NIS–AgOTf in the presence of 4 Å molecular sieves in CH_2Cl_2. These orthoesters can be rearranged into the isomeric glycosidically-linked oligosaccharides by treatment with TMSOTf in CH_2Cl_2, or in situ by extension of the reaction time.

There has been growing interest in the construction of D-arabinofuranose oligosaccharides related to the mycobacterial cell wall components, arabinogalactan, lipoarabinomannan, and arabinomannan from *Mycobacterium tuberculosis*, over recent years[1] due to the necessity of creating means for diagnostics, prevention, and treatment of human tuberculosis,[2] a major worldwide health problem. Although various strategies have been reported for the preparation of arabinofuranose oligosaccharides,[1] the development of novel approaches to stereoselective oligosaccharide synthesis remains an important task.

We have attempted to develop a synthesis of oligosaccharide fragments of mycobacterial arabinans by making use of a strategy that has never been used for the assembly of oligoarabinofuranosides and relies on the extensive use of the combination of 'permanent' *O*-benzoyl and 'temporary' *O*-chloroacetyl protecting groups. During this work, we needed tri- and tetrasaccharides **6** and **7**, selectively protected with chloroacetyl (CA) groups at O-2 of the terminal arabinofuranose residues (Scheme 1). After selective cleavage of the *O*-chloroacetyl groups, the corresponding diols could be used as glycosyl acceptors for the subsequent introduction of two β-(1→2)-arabinofuranosyl linkages to give access to a hexasaccharide epitope[3,4] (and its pentasaccharide fragment) found at the non-reducing end of these mycobacterial arabinans. The presence of a chloroethyl aglycon in the derived oligosaccharides would enable the preparation of neoglycoconjugates.[5]

The obvious way to prepare oligosaccharides **6** and **7** would involve bis-glycosylation of the corresponding mono- and disaccharide 3,5-diols **2**[6] and **3**[7] with ethyl (or phenyl) 3,5-di-*O*-benzoyl-2-*O*-chloroacetyl-1-thio-α-D-arabinofuranosides (**1a**,**b**)[7] (Scheme 1). Similar thioglycoside glycosyl donors with a 2-*O*-chloroacetyl participating protecting group, such as tolyl (or ethyl) 3,5-di-*O*-benzyl-2-*O*-chloroacetyl-1-thio-α-D-arabinofuranosides,[1f,k] have been successfully used for the preparation of α-linked-arabinofuranose oligosaccharides.

However, we were surprised to find that coupling of disaccharide diol **3** with thioglycoside **1a** under commonly used glycosylation conditions [CH_2Cl_2, 4 Å molecular sieves (MS), NIS–AgOTf (added at −40 °C),−20 °C to +10 °C (over 1 h)][1a] resulted in clean formation of tetrasaccharide bis-orthoester **5**[8,9] as a single isomer, isolated by silica gel chromatography in 90% yield, rather than the expected tetrasaccharide **7**. Prolonged treatment at −20 °C to +10 °C (up to 2 h) resulted in the formation of bis-orthoester **5** as a mixture of isomers at the two orthoester quaternary centers, the exact ratio being dependent on the reaction time. Similarly, the reaction of monosaccharide diol **2** with thioglycoside **1b** at −20 °C to +10 °C (over 2 h) gave only the trisaccharide bis-orthoester **4**[8,9] as a mixture of isomers in 57% yield.

Identification of sugar-sugar orthoesters **4** and **5** was carried out by a combination of chemical and spectrometric methods. The orthoesters were easily detected on TLC by their ready decomposition under acidic conditions [treatment with 90% TFA (aq)–$CHCl_3$

* Corresponding author. Tel.: +7 495 943 2946, fax: +7 499 135 5328.
E-mail addresses: kononov@ioc.ac.ru, leonid.kononov@gmail.com (L.O. Kononov).

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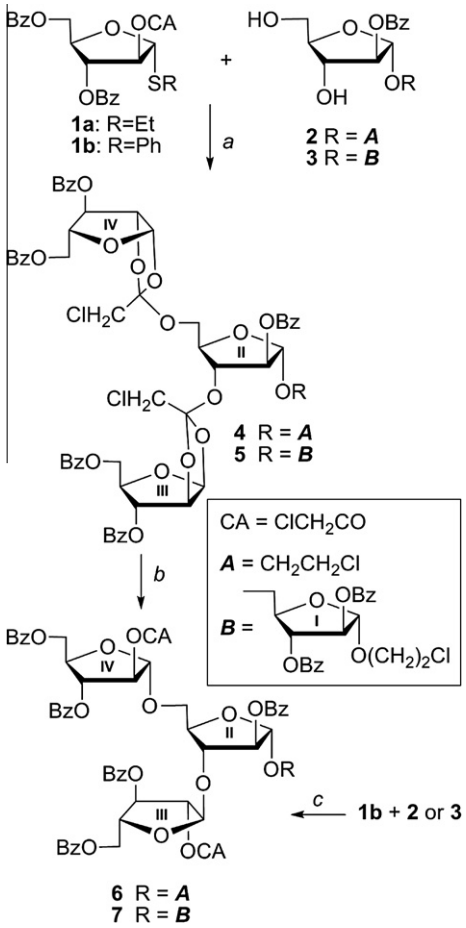

Scheme 1. Reagents and conditions: (a) **1a** + **3**: CH_2Cl_2, 4 Å MS, NIS–AgOTf (added at −40 °C), −20 °C to +10 °C (over 1 h) (90% of **5**); **1b** + **2**: CH_2Cl_2, 4 Å MS, NIS–AgOTf (added at −40 °C), −20 °C to +10 °C (over 2 h) (57% of **4**); (b) **4** or **5**, CH_2Cl_2, 4 Å MS, TMSOTf (added at −40 °C), 20 °C, 2 h (71% of **6**, 80% of **7**); (c) **1b** + **3**, **1b** + **2**: CH_2Cl_2, 4 Å MS, NIS–AgOTf (added at −40 °C), −17 °C to +4 °C (over 4 h) (97 % of **6**, 84% of **7**).

(1:99, v/v) before elution]. Additional evidence for the orthoester structure of **5** came from the low-field position of the respective anomeric protons and relatively large vicinal coupling constants [δ_H 6.06 (1 H, d, J = 3.9 Hz, H-1^{III}) and 6.15 (1 H, d, J = 3.8 Hz, H-1^{IV})], the latter being indicative of the 1,2-*cis*-arrangement expected in such orthoesters. The presence of 1,3-intersaccharide linkages between Ara^{III} and Ara^{II} residues followed from the observation of a H-3^{II}/C-1^{III} correlation in the HMBC and the following H/H correlations in the ROESY spectrum of **5**: H-1^{III}/H-3^{II}, H-2^{III}/H-3^{II}, H-3^{III}/CCH$_2$Cl^{III}, H-2^{II}/CCH$_2$Cl^{III}. The observation of H-1^{IV}/H-5^{II}, H-2^{IV}/H-5^{II} correlations in the ROESY spectrum of **5** suggested that Ara^{IV} and Ara^{II} were (1-5)-linked. The ^{13}C NMR spectra of both **4** and **5** clearly showed signals of the orthoester quaternary carbons at δ_C 121–123.

The formation of orthoester-linked oligosaccharides during glycosylation with glycosyl donors possessing participating acyl groups at O-2 is well known in the pyranose series,[10,11] and to a lesser extent in the furanose series[12] (intersaccharidic orthoacetates were only reported for oligosaccharides containing ribo- or galactofuranose residues). These acid-labile orthoesters are usually formed when insufficient acid is present in the reaction mixture (e.g., in the presence of a base) and are believed to be intermediates on the way to their more stable glycosidically-linked isomers, the final products of the glycosylation reaction. No reports describing the formation of similar oligosaccharide orthoesters comprising arabinofuranose residues have been published, to the best of our knowledge. Moreover, the orthoesters **4** and **5** are the first examples of oligosaccharides with an orthochloroacetyl bridge between the furanose residues. Similar derivatives of pyranoses with orthochloroacetyl bridges have been described.[11]

It is important to stress that no base (except for molecular sieves) was added to the reaction mixture in our case. Formation of intersaccharidic orthoesters is highly unusual considering the high anomeric reactivity of arabinofuranose derivatives.[1] We believe it is the presence of both 2-*O*-chloroacetyl and *O*-benzoyl electron-withdrawing groups that makes the orthoesters **4** and **5** so stable that their isolation by silica gel column chromatography becomes possible.

Oligosaccharides with intersaccharidic orthoacetyl[10] or orthochloroacetyl[11a,11b] linkages between the pyranose residues of various sugars are known to rearrange under acid catalysis into the corresponding isomeric glycosidically-linked oligosaccharides with a 2-*O*-acetyl or 2-*O*-chloroacetyl group, respectively (however, this is not always possible to perform[10,11c,d]). We were pleased to find that application of a similar approach [CH_2Cl_2, 4 Å MS, TMSOTf (addition at −40 °C), +20 °C, 2 h][13] to arabinofuranose orthoesters **4** and **5** afforded the target glycosidically-linked tri- and tetrasaccharides **6** and **7** in good yields (71% and 80%, respectively). This process can be monitored conveniently by ^{13}C NMR spectroscopy since the resonances of the chloromethyl groups in orthoesters **4** and **5** (δ_C ~45), and in glycosides **6** and **7** with 2-*O*-chloroacetyl groups (δ_C ~40) are clearly distinguishable from each other and from the signals of the CH_2Cl groups in the aglycon (δ_C ~42). It is important that isomerization proceeded stereoselectively[10a] and no cleavage or anomerization of the acid-sensitive arabinofuranose glycosidic bonds in tri- and tetrasaccharides **6** and **7** occurred under the conditions used.

To simplify the glycosylation process and enable large scale preparation, we developed one-pot conditions in which the initially formed orthoesters would rearrange in situ to the required glycosides. It is known,[10] that orthoesters can be transformed into the corresponding glycosides in situ by the addition of an extra catalyst or by extension of the reaction time. In our case, the best results were obtained by gradually increasing the reaction temperature from −17 °C to +4 °C over 4 h.[14] Under these conditions the yields of glycosidically-linked tri- and tetrasaccharides **6** and **7** were 97% and 84%, respectively.

The results obtained in this study clearly indicate that formation of oligosaccharides by glycosylation of the corresponding glycosyl acceptors with a 2-*O*-chloroacetyl-substituted D-arabinofuranose thioglycoside proceeds through the formation of intersaccharidic orthoesters. In some cases, these orthoesters can be isolated and the orthoester moiety used as a protecting group orthogonal to *O*-acyl groups. The latter could be removed at this stage under basic conditions without affecting the orthoester moiety, as was demonstrated in the pyranose series.[11c,d]

This finding is very important from a practical point of view since it creates a basis for reliable glycosylation with arabinofuranose glycosyl donors possessing a 2-*O*-chloroacetyl protecting group. Thus, if a complex mixture results from a glycosylation reaction, it may be indicative of orthoester formation. Such a mixture must first be analyzed by ^{13}C NMR spectroscopy, and if signals characteristic of orthoesters are found, it can then be subjected to TMSOTf-catalyzed isomerization. Only after this should any attempts at product isolation be undertaken.

In summary, for the first time, orthoester-linked D-arabinofuranose oligosaccharides **4** and **5** were isolated and characterized. It was demonstrated that these orthoesters serve as intermediates in efficient one-pot, two-stage bis-glycosylation of the corresponding glycosyl acceptors with ethyl (or phenyl) 3,5-di-*O*-benzoyl-2-*O*-chloroacetyl-1-thio-α-D-arabinofuranosides **1a**,**b**, promoted by NIS–AgOTf, leading to formation of protected α-D-linked tri- and

tetraarabinofuranosides **6** and **7**, which are useful building blocks for the synthesis of larger oligosaccharides related to mycobacterial cell wall components.

Acknowledgments

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8. Reactions sensitive to air and/or moisture were performed under an argon atmosphere with the use of anhydrous solvents purified according to standard procedures, and commercial reagents (Aldrich and Fluka). All compounds were fully characterized by 1D-(^{1}H, ^{13}C, APT) and 2D-NMR (COSY, HSQC, HMBC, HMQC-TOCSY, ROESY) spectroscopy as solutions in $CDCl_3$ [the ^{1}H NMR chemical shifts are referred to the residual signal of $CHCl_3$ (δ_H 7.27), and the ^{13}C NMR chemical shifts to the $CDCl_3$ signal (δ_C 77.0)].
Trisaccharide bis-orthoester **4** (mixture of isomers): R_f 0.25 (toluene–EtOAc 10:1). ^{1}H NMR (500.13 MHz, selected signals) δ_H 6.05 (1H, d, J = 3.7 Hz), 6.16 (1H, d, J = 4.3 Hz). ^{13}C NMR (125.37 MHz, selected signals) δ_C 42.5, 42.6 (CH_2CH_2Cl), 45.65, 45.68 (ClH_2CC), 104.5, 104.78, 104.99, 105.8, 105.95 (C-1), 122.7, 123.0 (ClH_2CC).
Tetrasaccharide bis-orthoester **5**: R_f 0.52 (toluene–EtOAc 10:1). ESIMS found m/z 1506.3313 [M+NH_4^+]. Calcd for $C_{75}H_{71}Cl_3O_{26}N$ 1506.3324. ^{1}H NMR (500.13 MHz) δ_H 3.68–3.75 (4H, m, OCH_2CH_2Cl, ClH_2CC^{III}), 3.77 (1H, d, J = 3.9 Hz, ClH_2CC^{IV}), 3.84 (1H, dt, J = 10.7 Hz, J = 5.4 Hz, OCH_a), 3.89 (2H, br s, H-5$^{II}{}_a$, H-5$^{II}{}_b$), 3.92 (1H, dd, J = 4.2 Hz, J = 11.2 Hz, H-5$^{I}{}_b$), 4.03 (1H, dt, J = 10.7 Hz, J = 5.4 Hz, OCH_b), 4.16 (1H, dd, J = 4.2 Hz, J = 11.2 Hz, H-5$^{I}{}_b$), 4.40–4.44 (1H, m, H-4^{III}), 4.45–4.51 (3H, m, H-4^{IV}, H-4^{II}, H-3^{II}), 4.52–4.58 (1H, m, H-4^{I}), 4.58–4.62 (4H, m, H-5$^{III}{}_a$, H-5$^{III}{}_b$, H-5$^{IV}{}_a$, H-5$^{IV}{}_b$), 5.04 (1H, d, J = 3.9 Hz, H-2^{IV}), 5.22 (1H, d, J = 3.9 Hz, H-2^{III}), 5.28 (1H, s, H-1^{II}), 5.31 (1H, d, J = 3.9 Hz, H-3^{IV}), 5.32 (1H, s, H-1^{I}), 5.43 (1H, d, J = 4.4 Hz, H-3^{III}), 5.47 (1H, s, H-2^{II}), 5.54 (2H, br s, H-2^{I}), 5.65 (1H, d, J = 4.9 Hz, H-3^{I}), 6.05 (1H, d, J = 3.9 Hz, H-1^{III}), 6.14 (1H, d, J = 3.8 Hz, H-1^{IV}), 7.29–7.65 (20H, m, Ph), 7.90–8.16 (16H, m, Ph). ^{13}C NMR (125.37 MHz) δ_C 42.7 (OCH_2CH_2Cl), 45.3 (ClH_2C^{III}), 45.5 (ClH_2C^{IV}), 60.6 (C-5^{II}), 63.65 (C-5^{III}), 63.75 (C-5^{IV}), 65.7 (C-5^{I}), 67.4 (OCH_2), 75.6 (C-3^{II}), 76.9 (C-3^{I}, C-3^{III}, C-3^{IV}), 81.0 (C-4^{II}), 81.6 (C-4^{III}), 81.9 (C-2^{I},C-4^{I}), 82.2 (C-4^{IV}), 82.8 (C-2^{II}), 86.0 (C-2^{IV}), 86.2 (C-2^{III}), 104.8 (C-1^{III}), 105.1 (C-1^{IV}), 105.5 (C-1^{II}), 105.6 (C-1^{I}), 122.7, 123.1 (ClH_2CC^{III}, ClH_2CC^{IV}), 128.5, 129.8, 130.0, 133.3,133.5, 133.6, 133.7 (Ph), 165.2, 165.6, 165.8, 166.1 (CO).
Trisaccharide **6**: R_f 0.25 (toluene–EtOAc 10:1). $[\alpha]_D^{23}$+49.0 (c 1.0, $CHCl_3$). ESIMS found m/z 1171.1963 [M+Na^+]. Calcd. for $C_{56}H_{51}Cl_3NaO_{20}$ 1171.1937. ^{1}H NMR (500.13 MHz) δ_H 3.63 (2H, t, J = 5.6 Hz, OCH_2CH_2Cl), 3.79 (1H, dt, J = 11.2 Hz, J = 5.7 Hz, OCH_a), 3.87 (1H, dd, J = 11.6 Hz, J = 2.6 Hz, H-5$^{II}{}_a$), 3.90–3.98 (3H, m, OCH_b, ClH_2CC), 4.00 (2H, s, ClH_2CC), 4.03 (1H, dd, J = 11.5 Hz, J = 4.4 Hz, H-5$^{II}{}_b$), 4.37–4.40 (1H, m, H-3^{II}), 4.40–4.44 (1H, m, H-4^{II}), 4.53–4.62 (4H, m, H-4^{III}, H-4^{IV}, H-5$^{III}{}_a$, H-5$^{IV}{}_a$), 4.68 (1H, dd, J = 11.9 Hz, J = 3.5 Hz, H-5$^{III}{}_b$), 4.75 (1H, dd, J = 11.9 Hz, J = 3.5 Hz, H-5$^{IV}{}_b$), 5.24 (2H, s, H-1^{II}, H-1^{IV}), 5.36–5.39 (3H, m, H-2^{II}, H-2^{III}, H-3^{IV}), 5.43 (1H, d, J = 4.0 Hz, H-3^{III}), 5.47 (1H, br s, H-1^{III}), 5.49 (1H, br s, H-2^{III}), 7.12–7.65 (16H, m), 7.90–8.10 (8H, m, Ph). ^{13}C NMR (125.37 MHz) δ_C 40.27, 40.31 (2× $COCH_2Cl$), 42.6 (OCH_2CH_2Cl), 63.2 (2C, C-5^{III}, C-5^{IV}), 65.8 (C-5^{II}), 67.4 (OCH_2CH_2Cl), 77.4 (2C, C-3^{III}, C-3^{IV}), 81.1 (C-4^{II}), 81.3, 81.4 (C-4^{III}, C-4^{IV}), 81.6 (C-3^{II}), 82.5 (2C, C-2^{III}, C-2^{IV}), 82.60 (C-3^{II}), 105.1 (C-1^{IV}), 105.5 (C-1^{II}), 105.8 (C-1^{III}), 128.3, 128.40, 128.45, 128.50, 129.67, 129.73, 129.85, 133.2, 133.46, 133.5, 133.6 (Ph), 165.50, 165.55, 165.90, 165.95, 166.0 (CO).
Tetrasaccharide **7**: R_f 0.52 (toluene–EtOAc 10:1), ESIMS found m/z 1511.2773 [M+Na^+]. Calcd. for $C_{75}H_{67}Cl_3NaO_{26}$ 1511.2878. $[\alpha]_D^{24}$+53.4 (c 1.0, $CHCl_3$). ^{1}H NMR (600.13 MHz) δ_H 3.67–3.74 (2H, m, OCH_2CH_2Cl), 3.82 (1H, dt, J = 11.1 Hz, J = 5.6 Hz, OCH_a), 3.86–3.95 (6H, m, H-5$^{I}{}_a$, H-5$^{II}{}_a$, 2 × ClH_2CC), 3.99 (1H, dt, J = 11.1 Hz, J = 5.6 Hz,OCH_b), 4.05 (1H, dd, J = 11.7, 4.2 Hz, H-5$^{II}{}_b$), 4.11–4.16 (1H, m, H-5$^{I}{}_b$), 4.43 (1H, d, J = 5.8 Hz, H-3^{II}), 4.45–4.49 (1H, m, H-4^{I}), 4.49–4.60 (5H, m, H-5$^{III}{}_a$, H-5$^{IV}{}_a$, H-4^{II}, H-4^{III}, H-4^{IV}), 4.65–4.70 (1H, m, H-5$^{III}{}_b$), 4.73 (1H, dd, J = 12.0 Hz, J = 3.5 Hz, H-5$^{IV}{}_b$), 5.27 (2H, s, H-1^{I}, H-1^{II}), 5.32–5.36 (2H, m, H-2^{IV}, H-3^{III}), 5.36–5.39 (3H, m, H-1^{IV}, H-3^{IV}, H-2^{III}), 5.44 (1H, s, H-1^{III}), 5.47 (2H, s, H-2^{I}, H-2^{II}), 5.64 (1H, d, J = 5.0 Hz, H-3^{I}), 7.30–7.58 (21H, m, Ph), 7.88–7.90 (4H, m, Ph), 7.94–7.98 (4H, m, Ph), 8.01–8.07 (6H, m, Ph). ^{13}C NMR (125.37 MHz) δ_C 40.3 ($OCOCH_2Cl$), 42.8 (OCH_2CH_2Cl), 63.3 (2C, C-5^{III}, C-5^{IV}), 65.6 (2C, C-5^{I}, C-5^{II}), 67.4 (CH_2O), 76.8 (C-3^{I}), 77.3 (C-3^{IV}), 77.5 (C-3^{III}), 80.9 (C-4^{III}), 81.3 (C-4^{IV}), 81.5 (C-3^{II}), 81.7 (C-4^{II}), 81.9C-2^{I}), 82.1 (C-4^{I}), 82.4 (C-2^{IV}), 82.7 (C-2^{II}, C-2^{III}), 105.3 (C-1^{III}), 105.47, 105.51 (C-1^{II}, C-1^{IV}), 105.57 (C-1^{I}), 128.08, 128.11, 128.17, 128.21, 128.35, 128.50, 128.82, 128.86, 129.00, 129.42, 129.4, 129.51, 129.60, 129.64, 132.89, 132.93, 133.16, 133.23, 133.30 (Ph), 165.16, 165.18, 165.24, 165.34, 165.39, 165.55, 165.61, 165.74 (CO).
9. *Preparation of bis-orthoester* **5** *(Typical procedure)*. A mixture of the thioglycoside **1a** (80 mg, 0.167 mmol), diol **3** (46 mg, 0.07 mmol), and freshly activated 4 Å MS (200 mg) in dry CH_2Cl_2 (2.5 mL) was stirred for 2 h at ~20 °C. *N*-Iodosuccinimide (47 mg, 0.21 mmol) and AgOTf (5.4 mg, 0.021 mmol) were added at −40 °C, the reaction mixture was stirred for 15 min at −20 °C, then allowed to reach +10 °C over 1 h, the course of the reaction being monitored by TLC. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.1 mL). The mixture was diluted with CH_2Cl_2 (50 mL), filtered through Celite, and washed with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (gradient toluene to toluene–EtOAc, 10:1) to afford the bis-orthoester **5** (94 mg, 90%).
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13. *Rearrangement of orthoester* **5** *into tetrasaccharide* **7** *(Typical procedure)*. A solution of bis-orthoester **5** (67 mg, 0.05 mmol)) in CH_2Cl_2 (2 mL) was stirred with freshly activated 4 Å MS (0.1 g) for 2 h at ~20 °C. TMSOTf (45 μL, 0.003 mmol) was added to the reaction mixture at −40 °C. After 2 h at 20 °C the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.1 mL). The mixture was diluted with CH_2Cl_2 (50 mL), filtered through Celite, washed with H_2O (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (gradient toluene to toluene–EtOAc, 10:1) to afford tetrasaccharide **7** (24 mg, 80%).
14. *Preparation of tetrasaccharide* **7** *without isolation of orthoester* **5** *(Typical procedure)*. A mixture of the thioglycoside **1b** (381 mg, 0.72 mmol), diol **3** (198 mg, 0.30 mmol), and freshly activated 4 Å MS (0.5 g) in dry CH_2Cl_2 (5 mL) was stirred for 2 h at ~20 °C. *N*-Iodosuccinimide (203 mg, 0.90 mmol) and AgOTf (23 mg, 0.09 mmol) were added at −45 °C, and the reaction mixture was stirred for 1 h at −17 °C, then allowed to reach +4 °C over 3 h, the course of the reaction being monitored by TLC. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.1 mL). The mixture was diluted with CH_2Cl_2 (100 mL), filtered through Celite, and washed with a 1:1 mixture of saturated aqueous $Na_2S_2O_3$–$NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (gradient toluene to toluene–EtOAc, 10:1) to afford tetrasaccharide **7** (377 mg, 84%).