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A novel and expeditious approach to the stereoselective synthesis of 2-*S*-ethyl(phenyl)-2-deoxy-β-glycosides, ready precursors to 2-deoxy-β-glycosides

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Abstract

1,2-Migration and concurrent glycosidation of ethyl(phenyl) 2,3-orthoester-1-thio-α-L-rhamnopyranosides under the action of TMSOTf readily afforded the corresponding 2-*S*-ethyl(phenyl)-2-deoxy-β-glycosides, ready precursors to 2-deoxy-β-glycosides.

2-Deoxy-β-glycosides exist as important structural components in many natural products, such as macrolides, anthracyclines, cardiac glycosides, aureolic acids, and enediynes.[1] However, the synthesis of the 2-deoxy-β-glycosidic linkage has been found to be one of the most challenging tasks in glycosylation reactions.[2] The most extensively developed strategy for the synthesis of 2-deoxy-β-glycosides utilizes donors with equatorial C-2 heteroatom substituents (e.g., -Br, -I, -SR, -SePh, -NHCHO, and -OAc),[2,3] which act as directing groups and are removed after the glycosylation event. The preparation of these donors often requires specialized methods. We report herein an expeditious approach to the stereoselective synthesis of 2-*S*-ethyl(phenyl)-2-deoxy-β-glycosides, ready precursors to 2-deoxy-β-glycosides.

The results surprised us when we attempted to glycosylate thioglycoside acceptor **1** with glycosyl trichloroacetimidate donor **2**: the corresponding coupling product was produced in 64% yield under the promotion of $BF_3 \cdot OEt_2$ (0.1 equiv.) at low temperature (−78°C);[4] however, the main product isolated was found to be **3** (70% yield) when TMSOTf (0.15 equiv.) was used as the promoter and at a higher temperature (−10°C) (Scheme 1).[5] We envisaged that the production of **3** should involve the glycosylation of **1** with 1,2-episulphonium ion C, which resulted from the oxycarbenium ion B, and

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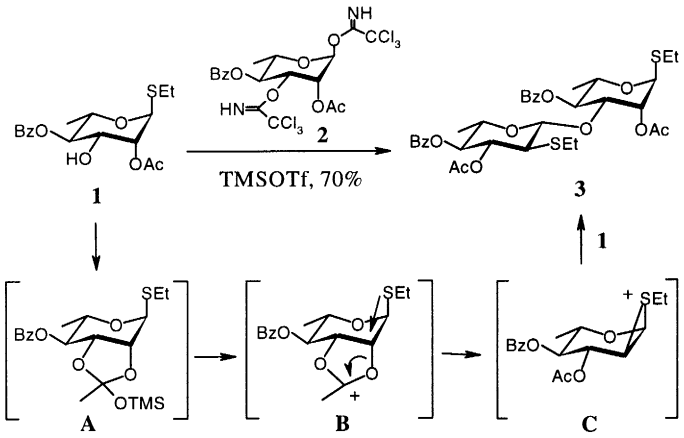
B from orthoester A (Scheme 1). Bundle and Auzanneau have reported that treatment of ethyl 2,3-orthoester-1-thio-α-L-rhamnopyranoside with *p*-TsOH resulted in the 1,2-ethylthio group migration.[6] Nicolaou et al. have demonstrated the preparation of 2-*S*-phenylglycosyl fluoride from phenyl 2-hydroxyl-1-thioglycoside through 1,2-migration under the action of DAST.[7] 1,2-Migration was also directly utilized to prepare 2-*S*-ethyl(phenyl)glycosides employing ethyl(phenyl) thioglycosides with a phenoxythiocarbonyl ester on C-2 as donor and NIS/TfOH as promoter.[8] Recognizing that the present disclosure might provide an expeditious and convenient alternative to the synthesis of 2-deoxy-β-glycosides, we sought to extend the scope of this reaction. Some preliminary results are listed in Table 1.

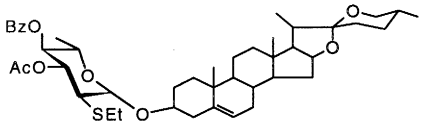
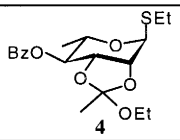
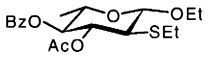
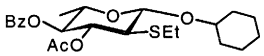
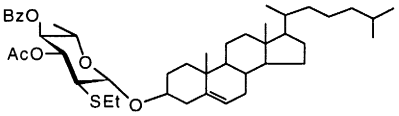
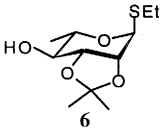
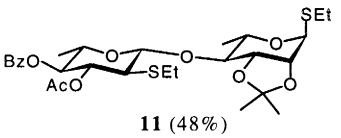
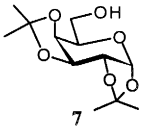
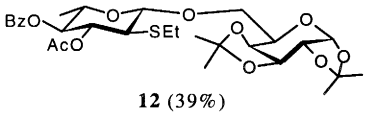
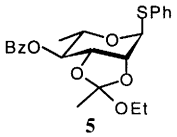
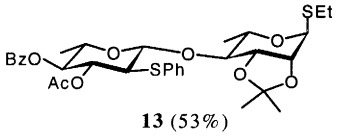
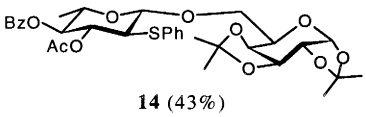


Scheme 1.

As expected on mechanistic grounds (Scheme 1), in the absence of the trichloroacetimidate **2**, the 1,2-migrated self-coupled product **3** was still produced in a comparable yield (64%) (entry 1). When an alcohol acceptor (diosgenin, 1.5 equiv.) was added to the reaction, the glycosidation product of diosgenin (**8**) was isolated in 19% yield, whereas the self-coupling product **3** turned out to be the major 'byproduct' (entry 2). Therefore, the readily accessible 2,3-orthoester **4** was prepared[9] and used instead as the donor in the reaction. Treatment of **4** with diosgenin, cyclohexanol, cholesterol, as well as with sugar alcohols **6** and **7** (0.15 equiv. TMSOTf, rt) produced the expected 2-*S*-ethyl-β-glycosides (**8**–**12**) in moderate to good yields (39–68%); the corresponding α-anomers were not detected (entries 3–7).[10,11] The anomeric ethylthio ether on acceptor **6** was unaffected (entry 6). However, the resulting -OEt from the 2,3-orthoester of donor **4** competed considerably with the alcohol acceptors for the glycosidation reactions, producing the corresponding ethyl 3-*O*-acetyl-4-*O*-benzoyl-2,6-deoxy-2-*S*-ethyl-β-L-glucopyranoside (**15**) in 20–53% yields. It is known that Raney nickel mediated desulfurization of the SEt derivative is less facile than that of the corresponding SPh derivative.[3c,8] Therefore, phenyl 2,3-orthoester-1-thio-α-L-rhamnopyranoside **5** was prepared[9] and used as a donor (entries 8 and 9). The reactions of phenyl 1-thioglycoside **5** with sugar alcohols **6** and **7** (0.2 equiv. TMSOTf, room temperature, 0.5 h) provided the corresponding 2-*S*-phenyl-2-deoxyglycoside **13** and **14** in 53 and 43% yields, with the OEt transfer product **16** in 32 and 38% yields, respectively.

Although the expected 2-*S*-ethyl(phenyl)glycosides were produced in only moderate to good yields due to the OEt transfer side reaction in this protocol, it should be noted that the yields for the expected glycosides (**8**–**14**) were calculated based on the 2,3-orthoester donors (**4** and **5**) added (1.2 equiv.). The

Table 1
Expeditious synthesis of 2-*S*-ethyl(phenyl)-β-glycosides[10,11]

Entry	**Donor** (1.2 equiv)	**Acceptor** (1.0 equiv)	**Products** (yields, based on Donors)	
1	**1**	**1**	**3** (64%)	
2	**1**	diosgenin	 **8** (19%)	**3** (major)
3	 **4**	diosgenin	**8** (54%)	 **15** (20%)
4	**4**	cyclo-hexanol	 **9** (44%)	**15** (20%)
5	**4**	cholesterol	 **10** (68%)	**15** (25%)
6	**4**	 **6**	 **11** (48%)	**15** (45%)
7	**4**	 **7**	 **12** (39%)	**15** (53%)
8	 **5**	**6**	 **13** (53%)	 **16** (32%)
9	**5**	**7**	 **14** (43%)	**16** (38%)

yields would be excellent if they were calculated on the consumed acceptors and the latter calculation would be reasonable in the synthesis of 2-deoxy-β-glycoside containing natural products in which the aglycone is precious (e.g., antibiotics) and the preparation of the orthoester donors (**4** and **5**) is very convenient.[9] Improvement of this novel protocol and its application to other sugar donors and to the synthesis of biologically important 2-deoxy-glycosides are in progress and will be reported in due course.

Acknowledgements

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5. At −78°C, little **1** was consumed. Therefore, the reaction temperature was raised to −10°C; at and above this temperature **3** was produced as the major product.
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8. (a) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1992**, *33*, 2063. (b) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501.
9. 2,3-Orthoester **4** (or **5**) was readily prepared from ethyl (or phenyl) 1-thio-α-L-rhamnopyranoside by two routes. Route 1: (1) $CH_3C(OEt)_3$ (2.5 equiv.), *p*-TsOH (cat.), DMF, rt, 1.5 h; (2) BzCl, Py, rt; ~46% for two steps. Route 2: (1) $CH_3C(OMe)_2CH_3$, *p*-TsOH (0.03 equiv), CH_2Cl_2, rt; (2) BzCl, Py, rt; (3) 80% HOAc, 75°C, 3 h; (4) $CH_3C(OEt)_3$ (1.5 equiv.), *p*-TsOH (cat.), CH_2Cl_2, rt, 1.0 h; ~89% for four steps.
10. A typical procedure was as follows: To a stirred solution of cholesterol (101 mg, 0.313 mmol) in anhydrous CH_2Cl_2 (2 mL) at room temperature under argon was added a solution of TMSOTf in CH_2Cl_2 (0.1 M, 0.39 mmol) followed by the addition of a solution of orthoester **4** (100 mg, 0.26 mmol) in CH_2Cl_2 (0.5 mL). After being stirred for 1 h, the mixture was filtered, concentrated, and applied to a silica gel column (petroleum ether:EtOAc, 8:1) to give **10** (142 mg, 68%) and **15** (28 mg, 25%) as white solids.
11. All new compounds exhibited satisfactory ^{1}H NMR, MS, and elemental analytical data. The indicated stereochemistry at C-1 and C-2 of the 2-*S*-ethyl(phenyl)glycosyl moiety in the products (**3**, **8**–**16**) was expected on mechanistic grounds and determined by ^{1}H NMR data. The ^{1}H NMR signals (300 MHz, $CDCl_3$) for H-1 and H-2 of the corresponding 2-*S*-ethyl(phenyl)-β-gluco- residue were characteristic: Compound **3**: 4.46 (1H, d, *J*=8.7 Hz, H-1), 2.73–2.52 (5H, m, H-2, 2×SC$H_2$$CH_3$). Compound **8**: 4.57 (1H, d, *J*=8.7 Hz, H-1), 2.80–2.63 (3H, m, H-2, SC$H_2$$CH_3$). Compound **9**: 4.54 (1H, d, *J*=8.8 Hz, H-1), 2.79–2.61 (3H, m, H-2, SC$H_2$$CH_3$). Compound **10**: 4.42 (1H, d, *J*=8.9 Hz, H-1), 2.80–2.60 (3H, m, H-2, SC$H_2$$CH_3$). Compound **11**: 4.62 (1H, d, *J*=8.8 Hz, H-1), 2.83–2.48 (5H, m, H-2, 2×SC$H_2$$CH_3$). Compound **12**: 4.45 (1H, d, *J*=8.9 Hz, H-1), 2.80–2.60 (3H, m, H-2, SC$H_2$$CH_3$). Compound **13**: 4.69 (1H, d, *J*=9.1 Hz, H-1), 3.40 (1H, dd, *J*=8.8, 11.3 Hz, H-2). Compound **14**: 4.41 (1H, d, *J*=8.8 Hz, H-1), 3.18 (1H, dd, *J*=8.8, 11.2 Hz, H-2). Compound **15**: 4.50 (1H, d, *J*=8.7 Hz, H-1), 2.80–2.63 (3H, m, H-2, SC$H_2$$CH_3$). Compound **16**: 4.36 (1H, d, *J*=8.8 Hz, H-1), 3.18 (1H, dd, *J*=8.8, 11.3 Hz, H-2).