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STEREOSPECIFIC 1,2-ETHYL(PHENYL)THIO GROUP MIGRATION IN SUGARS: STEREOCONTROLLED SYNTHESIS OF PRECURSORS TO α- AND ß-2-DEOXYGLYCOSIDES

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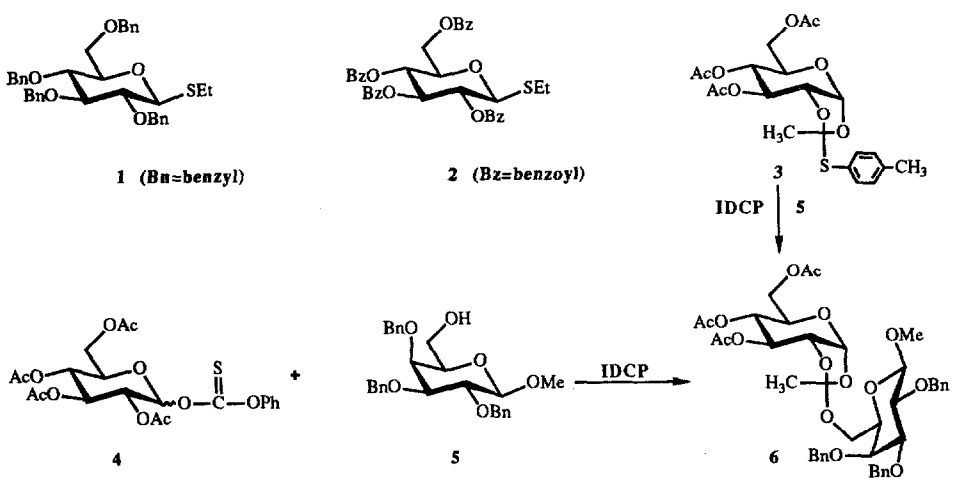
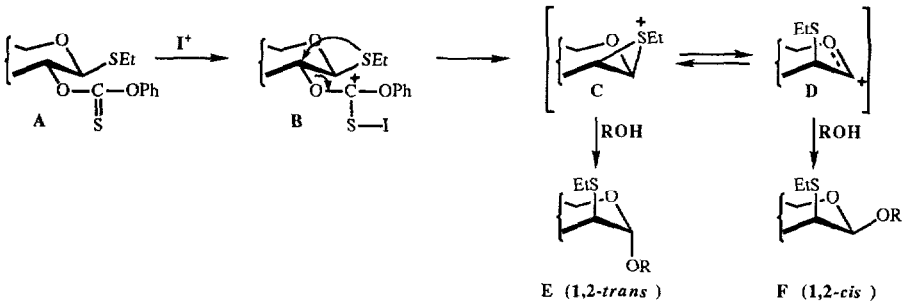
Abstract: Iodonium ion (NIS/TfOH, *cat.*) assisted glycosylation of a sugar acceptor with properly protected ethyl(phenyl)-2-*O*-phenoxythiocarbonyl 1-thio-ß-D-gluco- or 1-thio-α-D-mannopyranoside donors gives the respective 1,2-*trans* linked 2'-ethyl(phenyl)thio-2'-deoxy-α-D-manno- or ß-D-glucopyranosides.

Earlier studies from this laboratory revealed[1] that the benzoylated ethyl 1-thioglycoside donor **2** was, in contrast with the corresponding benzylated donor **1**, completely inert towards the thiophilic promoter iodonium dicollidine perchlorate (IDCP). On the other hand, glycosylation with **2** could be executed smoothly[2] with *N*-iodosuccinimide and catalytic trifluoromethanesulfonic acid (NIS/TfOH, *cat.*). The difference in reactivity between the ethyl 1-thioglycoside **1** (armed donor) and **2** (disarmed donor) showed to be of great promise[3] for the synthesis of biologically interesting oligosaccharides. Apart from this, it was also reported[4] that IDCP-mediated glycosylation of acceptor **5** by the fully acetylated 1,2-thio-orthoester **3** giving the orthoester derivative **6** was a fast and high-yielding process.



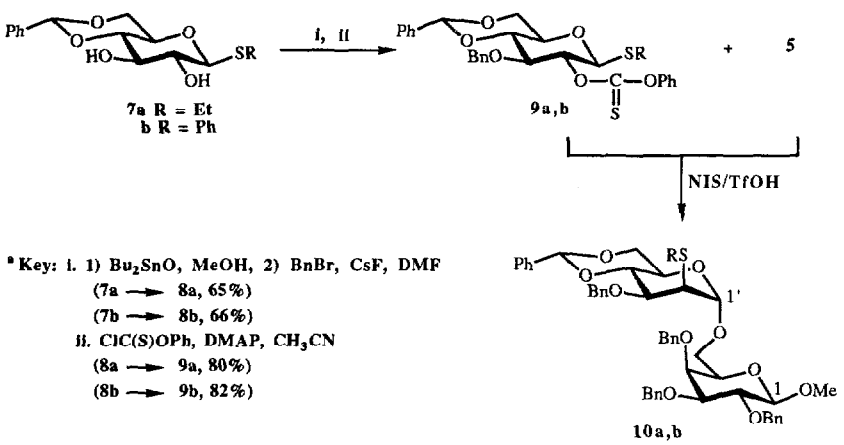
As part of a continuous program[5] to study in detail the chemo- and stereoselective glycosidation of alkyl(aryl) 1-thioglycosides, we report here that NIS/TfOH (*cat.*)-assisted glycosidation of alkyl(aryl) 1-thioglycosides having a phenoxythiocarbonyl (PTC) ester group at C-2 opens the way to the stereospecific synthesis of 2-deoxyoligosaccharide precursors.

Scheme 1



The rapid IDCP-mediated glycosylation of **5** with **3** urged us to examine the glycosidation properties of 1-*O*-phenoxythiocarbonyl 2,3,4,6-tetra-*O*-acetyl-α/ß-D-glucopyranose (**4**), which was easily accessible by thioacylation of 2,3,4,6-tetra-*O*-acetyl-α/ß-D-glucopyranose[6] with the commercially available reagent phenyl chlorothionocarbonate[7] (PTC-Cl). Interestingly, condensation of **4** (1.3 mmol) with **5** (1.0 mmol) under the influence of IDCP (2 equiv) resulted in the rapid (5 min) formation of the earlier obtained orthoester **6** (65% yield). The latter finding goaded us to investigate whether a phenoxythiocarbonyl (PTC) ester at C-2 of a sugar derivative could be activated chemoselectively with I^+-ions in the presence of an ethylthio group at the anomeric centre. If so, it was conceivable that I^+-ion activation of such a sugar derivative in the presence of an aglycon (ROH) would follow the pathway illustrated in Scheme 1. Thus, activation of the D-glucopyranoside derivative **A** with I^+-ions affords intermediate **B**. Intramolecular nucleophilic substitution of the activated PTC-function by the ethylthio group gives *via* a push-pull mechanism the episulfonium ion **C**. The latter ion will be opened subsequently from the α-face by the aglycon (ROH) to yield the 1,2-*trans* α-D-mannopyranoside **E**. On the other hand, it is not excluded that ion **C** is in equilibrium with the oxonium ion **D** which, in turn, reacts with ROH giving both **E** and the 1,2-*cis* ß-D-mannoside **F**.

Scheme 2 [a]

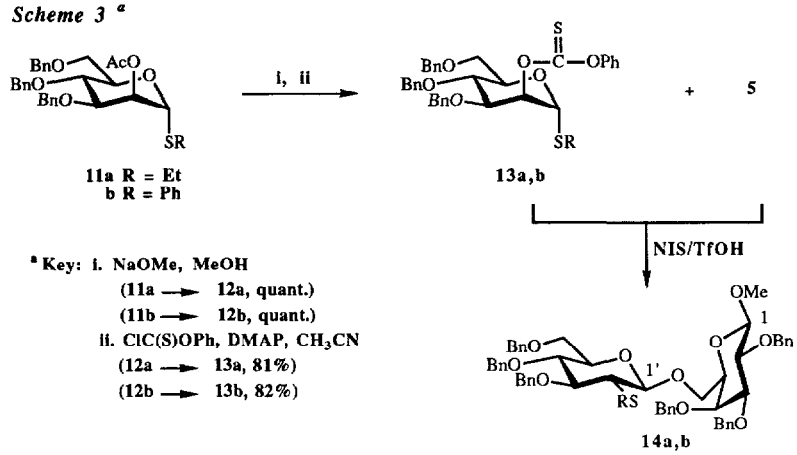


[a] Key: I. 1) Bu_2SnO, MeOH, 2) BnBr, CsF, DMF
(7a → 8a, 65%)
(7b → 8b, 66%)
II. ClC(S)OPh, DMAP, CH_3CN
(8a → 9a, 80%)
(8b → 9b, 82%)

The pathway proposed in Scheme 1 was substantiated by executing first the glycosylation (Scheme 2) of acceptor **5** (1.0 mmol) in 1,2-dichloroethane/diethylether (1/1, v/v, 10 mL) with the ethyl 2-*O*-PTC-1-

thio-ß-D-glucopyranoside **9a**[8] (1.2 mmol), obtained by regioselective benzylation[9] of **7a**[10] followed by reaction of **8a** with PTC-Cl, in the presence of IDCP. However, it was established that glycosidation was extremely slow. Fortunately, fast disappearance of **9a** (1.2 mmol) and **5** (1.0 mmol) was observed (TLC-analysis) by performing the glycosylation in the presence of NIS (1.2 mmol) and TfOH (0.12 mmol). Work up, after 10 min at 20°C, and purification gave a homogeneous product (85% yield based on **5**), the ^{1}H- and ^{13}C-NMR data of which were in accordance with the 1,2-*trans* linked α-D-*manno* disaccharide **10a**[8] ($J_{C\text{-}1',H\text{-}1'}$ = 173 Hz). In addition, TLC analysis of the crude reaction mixture showed the absence of the corresponding 1,2-*cis* linked disaccharide. It may therefore be concluded that the formation of **10a** is in agreement with the pathway[11] proposed in Scheme 1 and that the condensation is a stereospecific process (*i.e.* acceptor **5** reacts exclusively with the episulfonium ion **C**). It was also established that the glycosylation of **5** with the corresponding phenyl 2-*O*-PTC-1-thio-ß-D-glucopyranoside **9b**[8,10] afforded solely the 1,2-*trans* linked dimer **10b**[8] (71% based on **5**). In this respect, it is of interest to note that the glycosidation proceeded rather sluggishly (*i.e.* reaction was complete after 1h at 20°C). The latter is probably due to the relatively lower nucleophilicity of the phenylthio group, which will result in a decreased rate of formation of the episulfonium ion **C**.

Scheme 3 [a]



[a] Key: i. NaOMe, MeOH
(11a → 12a, quant.)
(11b → 12b, quant.)
ii. ClC(S)OPh, DMAP, CH_3CN
(12a → 13a, 81%)
(12b → 13b, 82%)

The scope of the new glycosylation procedure was further illustrated (Scheme 3) by the synthesis of the 1,2-*trans* linked ß-D-*gluco* dimer **14a**. Thus, NIS/TfOH (*cat.*)-mediated coupling of **5** with the ethyl 2-*O*-PTC-1-thio-D-mannopyranoside **13a**[8], prepared by Zemplén deacetylation of **11a**[12] and subsequent reaction with PTC-Cl, proceeded rapidly (within 10 min) to give, as evidenced by ^{1}H- and ^{13}C-NMR spectroscopy, dimer **14a**[8] ($J_{C\text{-}1',H\text{-}1'}$ = 157 Hz) in 85% yield (based on **5**). In a similar fashion (see Scheme 3), the corresponding dimer **14b**[8] was obtained in a good yield (75%) by glycosylation of **5** with the thiophenyl donor **13b**[8].

In conclusion, the NIS/TfOH (*cat.*)-mediated stereospecific glycosidation of ethyl(phenyl) 2-*O*-PTC-1-thioglycosides gives access to valuable 1,2-*trans* linked oligosaccharides. For example, desulfurization of **10b** or **14b** with Raney nickel[13] will afford the respective 2-deoxy-α- or ß-linked dimers.

Acknowledgment

We wish to thank Mr. A.W.M. Lefeber for recording the ^{1}H NMR spectra.

References and notes

1. Veeneman, G.H.; Van Boom, J.H. *Tetrahedron Lett.*, **1990**, *31*, 275.
2. Veeneman, G.H.; Van Leeuwen, S.H.; Van Boom, J.H. *Tetrahedron Lett.*, **1990**, *31*, 1331.
3. Veeneman, G.H.; Van Leeuwen, S.H.; Zuurmond, H.M.; Van Boom, J.H. *J. Carbohydr. Chem.*, **1990**, *9*, 783. Zuurmond, H.M.; Van der Klein, P.A.M.; Veeneman, G.H.; Van Boom, J.H. *Recl. Trav. Chim. Pays-Bas*, **1990**, *109*, 437. Smid, P.; De Ruiter, G.A.; Van der Marel, G.A.; Rombouts, F.M.; Van Boom, J.H. *J. Carbohydr. Chem.*, **1991**, *10*, 833.
4. Zuurmond, H.M.; Van der Marel, G.A.; Van Boom, J.H. *Recl. Trav. Chim. Pays-Bas*, **1990**, *109*, 437.
5. Zuurmond, H.M.; Van der Laan, S.C.; Van der Marel, G.A.; Van Boom, J.H. *Carbohydrate Res.*, **1991**, *215*, C1-C3.
6. Helferich, B.; Portz, W. *Chem. Ber*, **1953**, *86*, 604.
7. Robins, M.J.; Wilson, J.S. *J. Am. Chem. Soc.*, **1981**, *103*, 932.
8. All new compounds were characterized by ^{1}H- and ^{13}C-NMR as well as combustion analysis. Relevant ^{1}H NMR data (δ values) of compounds **10a,b** and **14a,b**: **10a**; 1.25 (t, 3H, SCH_2CH_3, J = 7.4 Hz), 2.70 (m, 2H, SCH_2CH_3), 3.07 (dd, 1H, H-2', $J_{1',2'}$ = 1.4 Hz, $J_{2',3'}$ = 3.7 Hz), 4.26 (d, 1H, H-1, $J_{1,2}$ = 7.7 Hz), 4.78 (d, 1H, H-1', $J_{1',2'}$ = 1.4 Hz). **10b**; 3.58 (dd, 1H, H-2', $J_{1',2'}$ = 1.3 Hz, $J_{2',3'}$ = 4.8 Hz), 4.23 (d, 1H, H-1, $J_{1,2}$ = 7.7 Hz), 4.83 (d, 1H, H-1', $J_{1',2'}$ = 1.3 Hz). **14a**; 1.22 (t, 3H, SCH_2CH_3, J = 7.4 Hz), 2.62-2.79 (m, 3H, SCH_2CH_3, H-2'), 4.29 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 4.40 (d, 1H, H-1', $J_{1',2'}$ = 8.8 Hz). **14b**; 3.24 (dd, 1H, H-2', $J_{1',2'}$ = 8.9 Hz, $J_{2',3'}$ = 10.9 Hz), 4.24 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 4.47 (d, 1H, H-1', $J_{1',2'}$ = 8.9 Hz). Relevant ^{13}C NMR data (δ values) of compounds **9a,b**, **10a,b**, **13a,b** and **14a,b**: **9a**; 14.7 (SCH_2CH_3), 24.8 (SCH_2CH_3), 68.4 (C-6), 74.5 (CH_2, benzyl), 70.5, 80.0, 80.7, 81.1 (C-2, C-3, C-4, C-5), 83.7 (C-1), 101.1 (CH, benzylidene), 121.8-129.4 (CH-arom.), 194.5 (C=S). **9b**; 68.0 (C-6); 74.2 (CH_2, benzyl), 70.0, 79.7, 80.4, 80.5 (C-2, C-3, C-4, C-5), 86.4 (C-1), 100.7 (CH, benzylidene), 121.5-131.9 (CH-arom.), 194.1 (C=S). **10a**; 14.5 (SCH_2CH_3), 27.9 (SCH_2CH_3), 50.4 (C-2'), 56.9 (OCH_3), 65.7, 68.6 (C-6, C-6'), 72.6, 73.2, 74.2, 75.0 (4xCH_2, benzyl), 101.3 (CH, benzylidene, C-1', $J_{C-1',H-1'}$ = 173 Hz), 104.8 (C-1), 125.8-129.3 (CH-arom.). **10b**; 54.4 (C-2'), 56.9 (OCH_3), 65.7, 68.5 (C-6, C-6'), 72.2, 73.1, 74.1, 75.0 (4xCH_2, benzyl), 100.6 (CH, benzylidene), 101.3 (C-1', $J_{C-1',H-1'}$ = 173 Hz), 104.7 (C-1), 125.9-131.9 (CH-arom.). **13a**; 14.6 (SCH_2CH_3), 25.3 (SCH_2CH_3), 68.5 (C-6), 71.7, 72.0, 74.8 (3xCH_2, benzyl), 71.7, 74.4, 78,1, 80.4 (C-2, C-3, C-4, C-5), 80.9 (C-1), 121.4-129.1 (CH-arom.), 194.0 (C=S). **13b**; 68.5 (C-6), 71.9, 73.1, 75.1 (3xCH_2, benzyl), 72.4, 74.5, 78.1, 80.0 (C-2, C-3, C-4, C-5), 84.9 (C-1), 121.6-131.9 (CH-arom.), 194.0 (C=S). **14a**; 15.0 (SCH_2CH_3), 26.0 (SCH_2CH_3), 52.2 (C-2'), 56.9 (OCH_3), 68.4, 72.8 (C-6, C-6'), 73.2, 74.0, 74.7, 74.8, 76.1 (6xCH_2, benzyl), 104.6 (C-1', $J_{C-1',H-1'}$ = 157 Hz), 104.7 (C-1), 127.3-128.1 (CH-arom.). **14b**; 55.9 (C-2'), 57.0 (OCH_3), 67.8, 68.5 (C-6, C-6'), 72.6, 73.4, 74.2, 74.8, 75.0, 76.1 (CH_2, benzyl), 103.8 (C-1', $J_{C-1',H-1'}$ = 157 Hz), 104.7 (C-1), 126.3-130.7 (CH-arom.).
9. Nagashima, N.; Ohno, M. *Chem. Lett.*, **1987**, 141.
10. Nicolaou, K.C.; Randall, J.L.; Furst, G.T. *J. Am. Chem. Soc.*, **1985**, *107*, 5556.
11. A similar pathway was recently proposed by D.R. Bundle *et al.* [*Carbohydr. Res.* **1991**, *212*, 13] to explain the stereospecific 1,2-ethylthio group migration during the synthesis of ethyl 1-thio-α-D-rhamnopyranoside 2,3-orthoesters. Another example of stereospecific 1,2-migration in sugars was reported earlier by Nicolaou *et al.* (see reference 13).
12. Peters, T. *Liebigs Ann. Chem.* **1991**, 135.
13. For instance, K.C. Nicolaou *et al.* showed earlier [see: *J. Am. Chem. Soc.*, **1986**, *108*, 2466] that the deoxygenation of a phenylthiogroup at C-2' of several oligosaccharides (dimers) with Raney nickel in EtOH was a high-yielding process.

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