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A New Strategy for the Synthesis of the Nephritogenoside Trisaccharide Unit Using Phenylsulfenyl Donors

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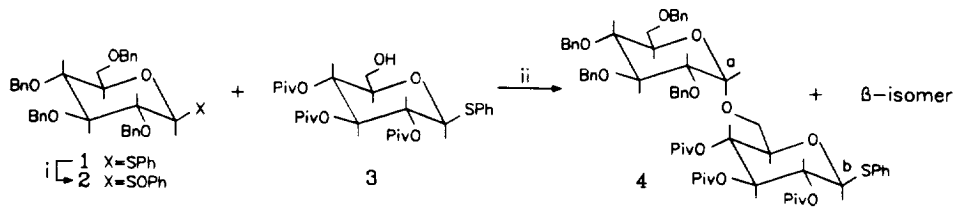
Abstract: An efficient and stereocontrolled synthesis of the nephritogenoside trisaccharide unit using the glycosyl sulfoxide method is reported. This new glycosylation procedure enables complex oligosaccharides to be prepared in a highly convenient and stereoselective manner.

The efficient synthesis of oligosaccharides is still one of the major challenges in the field of carbohydrate synthesis. Many strategies have been developed for the preparation of O-glycosides.[1] The glycosyl donors most widely used in the synthesis of glycosides are glycosyl halides,[1,2] but the conversion of an intermediate oligosaccharide into such a derivative may be difficult. O-glycosylimidates,[3] pent-4-enyl glycosides,[4] isopropenyl glycosides,[5] phosphorus derivatives,[6] temporary silicon connections,[7] fluoride donors,[2] as well as glycal derivatives [8] are also currently used for practical, selective syntheses of complex oligosaccharides and glycoconjugates. Thioglycosides [9] which are stable under a wide range of reaction conditions have been used as glycosyl donors in recent synthetic work. In spite of these developments, the application of phenylsulfenyl glycosyl donors recently gained a new impetus,[10] as rather inactive nucleophiles can be effectively glycosylated in the presence of triflic anhydride. More recently, it was revealed by us [11] and other groups [12] that the glycosylation of a phenyl thioglycoside with a phenyl sulfenyl glycoside occurs selectively and offers some remarkable advantages for polysaccharide synthesis. Here we report the application of this new strategy for the construction of the O-glycosidic bonds in the nephritogenoside trisaccharide unit to widen the scope of this method for oligosaccharide synthesis.

Nephritogenoside, isolated from the basement membrane of rats, was found to be active for the induction of glomerulonephritis in homologous animals.[13] The structure, α-Glc-(1→6)-β-Glc-(1→6)-α-Glc-(1→Asn-peptide, was determined by S. Shibata et al. in 1988 as a glycopeptide in which the trisaccharide, composed of three glucose moieties, is α-N-glycosidically linked to the peptide chain through the amido nitrogen of an asparagine residue at the N-terminus.[14] This glycopeptide has attracted a great deal of attention from synthetic chemists because of its unusual structure and its significant biological properties. Several syntheses leading to the trisaccharide part were described.[15] Here, an efficient and stereocontrolled synthesis of the nephritogenoside core structure using phenyl thioglycoside sulfoxides as new glycosyl donors is presented.

Phenyl 2,3,4,6-tetra-O-benzyl-1-thio-ß-D-glucopyranoside sulfoxide (**2**) was readily obtained in 96 % yield by oxidation of the corresponding sulfide (**1**) with m-chloroperbenzoic acid (mCPBA). Phenyl 2,3,4-tri-

O-pivaloyl-1-thio-ß-D-glucopyranoside (**3**) was prepared by treatment of phenyl 1-thio-glucopyranoside with trityl chloride in pyridine, followed by reaction with pivaloyl chloride and subsequent detritylation. Glycosidation of **2** and **3** was carried out using triflic anhydride (Tf_2O) and 2,6-di-tert-butylpyridine (DtBP) to give **4**[16] in 68 % yield and its β-isomer in 17 % yield respectively (Scheme 1.).

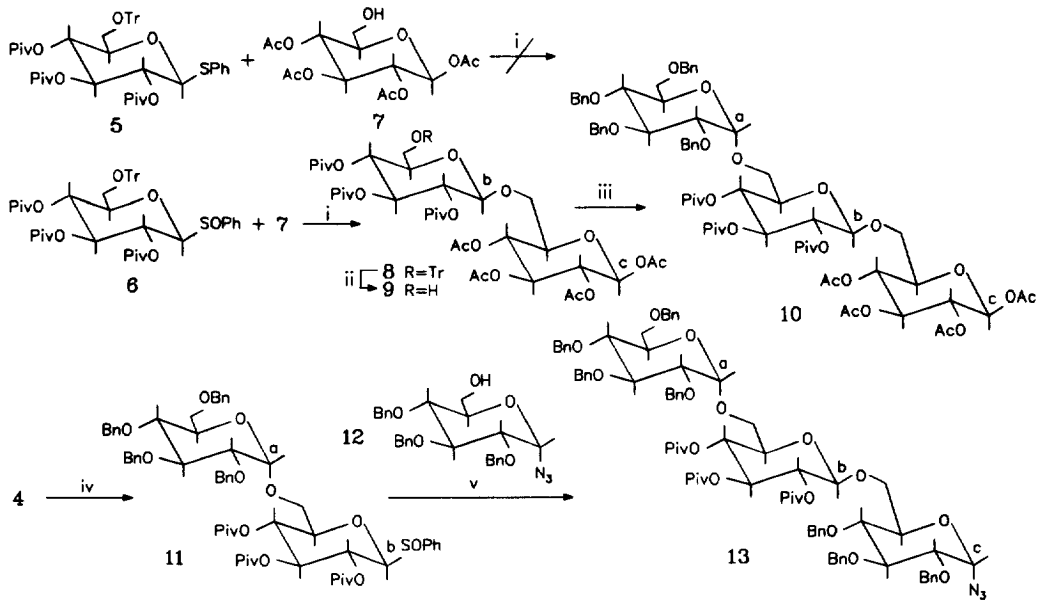


Scheme 1. i) mCPBA, CH_2Cl_2, -78 to 10 °C; ii) Tf_2O, DtBP, CH_2Cl_2/ether (1:4), -78 to 0 °C.

The high yield of the glycosidation reaction suggests that the anomeric phenyl thioglycosides are stable under the conditions used for the activation. Further proof for the selective activation of phenyl thioglycoside sulfoxides over the phenyl thioglycosides was obtained from the following reaction (Scheme 2.): Phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-ß-D-glucopyranoside (**5**) and phenyl 2,3,4-tri-O-pivaloyl-6-O-trityl-1-thio-ß-D-glucopyranoside sulfoxide (**6**) were treated seperately with the acceptor 1,2,3,4-tetra-O-acetyl-ß-D-glucopyranose (**7**) in the presence of 2 equivalents of DtBP and one equivalent of triflic anhydride. As expected, **6** and **7** yielded stereoselectively 81 % of the protected disaccharide **8** [16] and no coupling was observed between **5** and **7**. It is worthwhile mentioning that the trityl group was not removed under these neutral glycosidation conditions. Therefore, other similar acid labile protecting groups can also be used for these glycosylation reactions. It should also be noted that in the presence of one equivalent of DtBP removal of the trityl group was observed and a complex mixture of products was obtained. Treatment of **8** with 15 % trifloroacetic acid in dichloromethane at 0 °C yielded the disaccharide derivative **9**, which after glycosylation with **2** gave **10** in high yield and good selectivity. In the armed/disarmed concept [4] changing C-substituents from O-acyl to O-alkyl would be required in order to activate the disaccharide derivative for further coupling. However, the high yield for **8** resulting from the reaction of **6** and **7** demonstrates that glycosyl sulfoxides can be activated for glycosylation at low temperature even in the presence of pivaloyl disarmed substituents. Therefore we were able to directly use neighboring group participation of **4** to obtain the β-linkage of the trisaccharide **13**. As seen from scheme 2, the phenylthio group of **4** could easily be converted with mCPBA into the corresponding phenyl thioglycoside sulfoxide **11** as a new glycosyl donor, which coupled to **12** in the presence of triflic anhydride and DtBP in CH_2Cl_2 at -78°C to yield (78 %) the trisaccharide **13** [16] under complete stereocontrol.

Finally we would like to stress several of the advantages of the described procedure: Firstly, compared to the armed/disarmed concept no change of protecting groups is required, if the synthons are O-acyl-protected. Secondly, stereospecific synthesis of both, α- and ß- glycosidic linkages, can be achieved in high yield. Thirdly, the extremely mild reaction conditions allow to use acid-sensitive protecting groups, e.g. trityl, for temporary protection of the carbohydrate moieties. Lastly, the fact, that phenyl thioglycosides are glycosyl acceptors during the coupling reaction and can be easily converted to phenyl thioglycoside sulfoxides

which function as glycosyl donors, enabled us to prepare oligosaccharides in a highly convergent manner. This strategy for sure will be of advantageous use for the synthesis of complex oligosaccharides in future time.



Scheme 2. i) 1 equiv. of Tf_2O, 2 equiv. of DtBP, CH_2Cl_2, -78 to 0 °C; ii) 15 % TFA, CH_2Cl_2, 0 °C; iii) Tf_2O, DtBP, CH_2Cl_2/ether (1:4), -78 to 0 °C; iv) mCPBA, CH_2Cl_2, -78 to 10 °C; v) Tf_2O, DtBP, CH_2Cl_2, -78 to 0 °C.

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16. Physical data for compounds **4, 8** and **13**: Phenyl 2,3,4-tri-*O*-pivaloyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside **4**: -FD-MS: 1047 [M^+]. $[\alpha]_D^{20}$ = + 7.2 (c = 2.5, chloroform). -^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.4-7.0 (m, 25H, 5 Ph), 5.23-3.25 (m, 22H, Ha-1--Ha-6, Hb-1--Hb-6, 4 CH_2Ph), 1.14, 1.09, 1.03 [3s, 27H, 3 C(CH_3)$_3$]. -^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 175.6, 175.0, 174.9 (3C, 3 *C*OCMe$_3$), 137.5, 137.0 136.7 136.5 (4C, Cq, arom.), 131.6-123.6 (m, arom.), 95.8(Ca-1), 85.7(Cb-1), 80.6, 78.6, 76.3, 75.2, 74.2, 73.4, 72.1, 71.9, 71.8, 68.7, 68.2, 67.1, 67.0, 65.7 (14C, Ca-2--Ca-6, Cb-2--Cb-6, 4 *C*H$_2$Ph), 37.3 (3C, 3 *C*Me$_3$), 25.7-25.6 [9C, 3 C(*C*H$_3$)$_3$]. 1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4-tri-*O*-pivaloyl-6-*O*-trityl-ß-D-glucopyranosyl)-β-D-glucopyranose **8:** -FD-MS: 1005 [M^+]. -^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.06 (m, 15H, 3 Ph), 5.64 (d, J = 8.3, 1H, Hc-1), 5.20-4.83 (m, 6H), 4.55 (d, J = 8.1, 1H, Hb-1), 4.0-3.55 (m, 6H), 1.93, 1.91, 1.90, 1.87 (4s, 12H, 4 CH_3), 1.06, 0.96, 0.73 [3s, 27H, 3 C(CH_3)$_3$]. -^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.3, 176.7, 176.4 (3C, 3 *C*OCMe$_3$), 170.2, 169.8, 169.5, 168.7 (4C, 4 *C*OMe), 143.8 (Cq, arom.), 128.9-127.2 (m, arom.), 100.5 (Cb-1), 91.8 (Cc-1), 91.6 (CPh$_3$), 86.8-60.5 (10C, Cb-2--Cb-6, Cc-2--Cc-6), 38.9-38.6 (3C, 3 *C*Me$_3$), 27.4-27.0 [9C, 3 C(*C*H$_3$)$_3$], 21.2-20.5 (4C, 4 CO*C*H$_3$). 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-pivaloyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranosyl)-α-D-glucopyranosyl azide **13**: -FD-MS: 1413 [M^+]. $[\alpha]_D^{20}$ = + 38.9 (c = 3.5, chloroform). -^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25-7.02 (m, 35H, 7 Ph), 5.05 (d, J = 4.0, 1H, Hc-1), 1.07, 1.06, 1.03 (3s, 27H, 3 C(CH_3)$_3$]. -^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 176.8, 176.6 (3C, 3 *C*OCMe$_3$), 139.1, 138.9, 138.7, 138.5, 138.3, 138.2, 137.8 (7C, Cq, arom.), 128.9-127.8 (m, arom.), 100.4 (Cb-1), 97.3 (Ca-1), 87.9 (Cc-1), 82.2-68.8 (22C, Ca-2--Ca-6, Cb-2--Cb-6, Cc-2--Cc-6, 7 *C*H$_2$Ph), 39.0 (3C, 3 *C*Me$_3$), 27.4 [9C, 3 C(*C*H$_3$)$_3$].

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