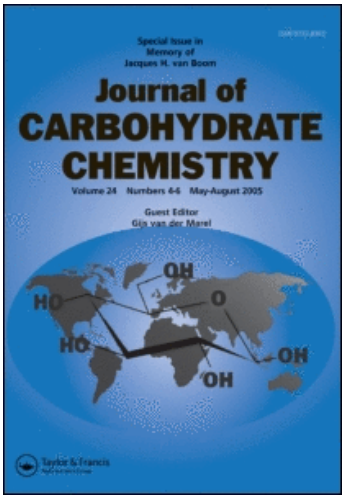

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COMMUNICATION

UNUSUAL FORMATION OF A β-LINKED DISACCHARIDE IN A NIS GLYCOSYLATION

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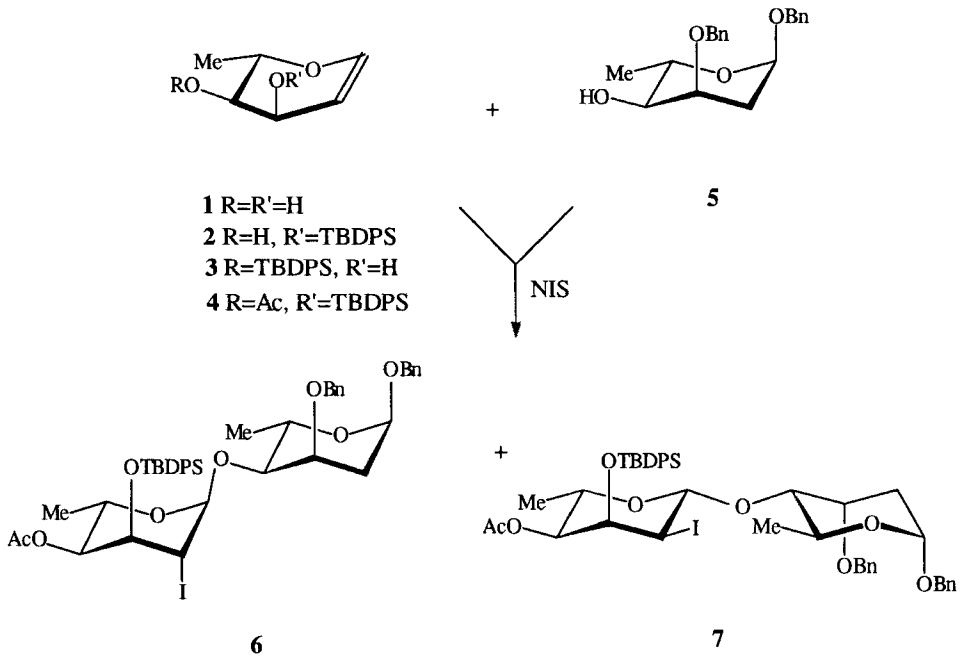
The *N*-halosuccinimide glycosylation is a highly selective reaction that leads to *trans*-configured 1-alkoxy-2-halo-glycosides (halo = bromo, iodo).[2,3] As an exception to the generally observed exclusive formation of α-linked glycosides in such reactions,[2] we obtained a 3 / 1 mixture of α- and β-disaccharide **6** and **7**, when we treated the silylated glycal **4** with NIS (*N*-iodosuccinimide) and the glycoside **5**.[4] The similarly protected *arabino* glycal **9**, on the other hand, gave exclusively the expected α-linked saccharide **11**, when treated with NIS and the alcohol component **10**.[5] Silylated glycals **4** and **9** were obtained from L-digitoxal **1**[6] and L-rhamnal **8**[7] by treatment with *tert*-butyldiphenylchlorosilane[8] and *tert*-butyldimethylchlorosilane,[9] respectively. In both cases the 3-*O*-silylated derivatives formed in high yields. Only in case of the *ribo*-configuration minor amounts of a 4-*O*-silylated product **3** were identified.

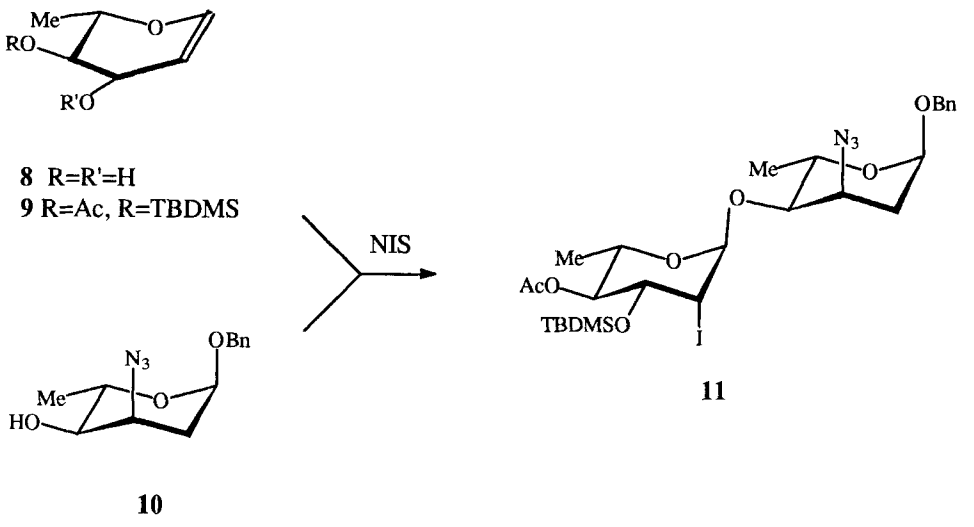
We believe that formation of the β-glycoside **7** is due to steric hindrance of the bulky *tert*-butyldiphenylsilyl group. Similar steric effects on the stereochemical outcome of NIS reactions were observed in the synthesis of glycopeptides at slightly elevated temperatures.[10] During the NIS reaction of **4**, equilibrating iodonium ions with *allo*- and



altro-configuration are formed, but due to steric hindrance of the protecting group in a pseudo axial orientation of position 3, opening of the *allo*-ion is encouraged and leads to the β-product **7**. This is in accord with the fact that only α-products are obtained from *arabino* glycal **9**. The pseudo equatorially oriented silyl group in this derivative cannot exert a similar steric effect.

Previous exceptions to the exclusive formation of α-glycosides in NIS reactions were reported for glycals with *lyxo*-configuration[11] and for glucuronic acid derivatives.[12] In both cases the reaction with NIS was slowed down and yields were not as high as usual. Also, in both cases the formation of the β–glycoside was shown to be due to conformational effects either in the glycals or the intermediately formed iodonium ions. None of these phenomena was observed in this particular case. Coupling constants in the ^{1}H NMR spectra of **4** clearly show that the ring adopts a pure $^4H_5$(L)-conformation, as would be expected. A conformational change in the intermediately formed iodonium ion cannot be ruled out, of course, but has never been observed in NIS reactions. The reaction was not slowed down and yields were quite normal.

Therefore, a controlled steric induction in NIS glycosylations might be attractive. We did not undertake further studies but expect an even more bulky group or a double substitution with *tert*-butyldiphenylsilyl groups to lead to a higher percentage of the valuable 2-deoxy β–glycosides.



EXPERIMENTAL

General methods. Reactions were followed by TLC on DC-Alufolien Kieselgel GF_{254} (Merck), detection was by UV and / or staining with 10 % ethanolic sulfuric acid and charring. Preparative thin layer chromatography (PLC) was performed on Kieselgel Fertigplatten 60 F_{254} (Merck). For column chromatography Kieselgel 60 (70-230 mesh, Merck) was used. Optical rotations were determined with a Perkin-Elmer polarimeter 241. NMR spectra were recorded on a Bruker WM 300. Chemical shifts are given downfield to tetramethylsilane as internal standard. For NIS reactions recrystallized *N*-iodosuccinimide (from CCl_4) was used; and the reactions were carried out under a nitrogen cover and with protection from light.

1,5-Anhydro-3-*O*-(*tert*-butyldiphenylsilyl)-2,6-dideoxy-L-*ribo*-hex-1-enitol (2) and **1,5-Anhydro-4-*O*-(*tert*-butyldiphenylsilyl)-2,6-dideoxy-L-*ribo*-hex-1-enitol (3)**. Glycal **1**[3] (134 mg, 1.0 mmol) and imidazole (188 mg, 2.76 mmol) in dimethylformamide (8 mL) were stirred with molecular sieve for 30 min. Then *tert*-butyldiphenylchlorosilane (0.42 mL, 1.84 mmol) was added. Stirring was continued for 4 d, with repeated addition of imidazole (80 mg, 1.2 mmol) and *tert*-butyldiphenylchlorosilane (0.26 mL, 1.0 mmol) after 3 d. The solvent was removed *in vacuo*, the remaining syrup dissolved in dichloromethane, washed with water, dried and purified by chromatography (ethyl acetate / toluene, 1:20) giving 216 mg (62 %) of **2**: $[\alpha]_D^{20}$ = -156.2° (*c* 1.3, dichloromethane); ^{1}H NMR ($CDCl_3$) δ 7.70 and 7.37 (mc, 10 H, aryl-H), 6.22 (d, $J_{1,2}$ = 5.9 Hz, H-1), 4.38 (dd, $J_{2,3}$ = 5.3 Hz, H-2), 4.18 (dd, $J_{3,4}$ = 4.2 Hz, H-3), 3.98 (dq,

$J_{4,5}$ = 9.7 Hz, H-5), 3.38 (ddd, $J_{4,4\text{-OH}}$ = 9.8 Hz, H-4), 2.70 (d, 4-OH), 1.35 (d, 3H, $J_{5,6}$ = 6.4 Hz, CH_3-6), 1.06 (s, 9 H , Si-C-CH_3).

Anal. Calcd for $C_{22}H_{28}O_3Si$ (340.5): C, 77.61; H, 8.29. Found: C, 77.65; H, 8.31.

Additionally, 288 mg of a mixture of **2** and **3** in the ratio of 10:1 was isolated. Glycal **3** was only characterised by ^1H NMR spectroscopy: ($CDCl_3$) δ 7.70 and 7.37 (mc, 10 H, aryl-H), 6.30 (d, $J_{1,2}$ = 5.9 Hz, H-1), 4.76 (dd, $J_{2,3}$ = 5.9 Hz, H-2), 3.84 (ddd, $J_{3,3\text{-OH}}$ = 2.6 Hz, H-3), 3.67 (dd, $J_{3,4}$ = 3.8 Hz, H-4), 3.29 (dq, $J_{4,5}$ = 9.1 Hz, H-5), 2.55 (d, 3-OH), 1.13 (d, $J_{5,6}$ = 6.3 Hz, 3 H, CH_3-6), 1.09 (s, 9 H, Si-C-CH_3).

4-*O*-Acetyl-1,5-anhydro-3-*O*-(*tert*-butyldiphenylsilyl)-2,6-dideoxy-L-*ribo*-hex-1-enitol (4). Glycal **2** (102 mg, 2. 1 mmol) in pyridine (3 mL) was treated with acetic anhydride (0.24 mL, 2.4 mmol) for 12 h at 4 °C. It was diluted with toluene, the solvent evaporated and three times co-evaporated with toluene. Purification by chromatography (toluene) yielded 83 mg (69 %) of **4**: $[\alpha]_D^{20}$ = -150.7° (*c* 0.9, chloroform); ^1H NMR ($CDCl_3$) δ = 7.67 and 7.33 (mc, 10 H, aryl-H), 6.26 (dd, $J_{1,2}$ = 5.9 Hz, H-1), 4.66 (dd, $J_{4,5}$ = 9.8 Hz, H-4), 4.53 (dd, $J_{2,3}$ = 5.9 Hz, H-2), 4.40 (dq, $J_{5,6}$ = 6.3 Hz, H-5), 4.31 (dd, $J_{3,4}$ = 3.6 Hz, H-3), 1.99 (s, 3 H, $OCOCH_3$), 1.28 (d, 3 H, CH_3-6), 1.07 (s, 9 H, Si-C-CH_3).

Anal. Calcd for $C_{24}H_{30}O_4Si$ (410.6): C, 70.21; H, 7.36. Found: C, 70.10; H, 7.30.

Benzyl 4-*O*-[4-*O*-Acetyl-2,6-dideoxy-2-iodo-3-*O*-(*tert*-butyldiphenylsilyl)-α-L-altro (6) and β-L-allo (7) pyranosyl]-3-*O*-benzyl-2,6-dideoxy-α-L-*ribo*-hexopyranoside. A solution of the glycal **4** (32 mg, 0.08 mmol) and the alcohol component **5** (36 mg, 0.10 mmol) in acetonitrile (1 mL) was stirred with molecular sieve for 30 min. Then *N*-iodosuccinimide (20 mg, 0.09 mmol) was added and stirring continued for 24 h. The solution was concentrated *in vacuo*, dissolved in dichloromethane and washed with a solution of sodium thiosulfate and water, dried and concentrated to dryness. The mixture was purified by PLC (ethyl acetate / toluene, 1:12), yielding 22 mg (32%) of **6**: $[\alpha]_D^{20}$ = -103.2° (*c* 0.8, chloroform); ^1H NMR ($CDCl_3$) δ 7.70, 7.62 and 7.28 (each mc, 30 H, aryl-H), 5.19 (d, $J_{1',2'}$ = 0.8 Hz, H-1'), 5.13 (dd, $J_{4',5'}$ = 9.5 Hz, H-4'), 4.90 (dd, $J_{1,2a}$ =4.6 Hz, H-1), 4,79, 4,72, 4.49 and 4.47 (2 x d, 4 H, J_{AB} = 11.9 and 12.0 Hz, aryl-CH_2), 4.36 (dq, $J_{5,6}$ = 6.3 Hz, H-5), 4.51 (dq, $J_{5',6}$ = 6.3 Hz, H-5'), 4.35 (dd, $J_{2',3'}$ = 3.0 Hz, H-2'), 4.21 (dd, $J_{3',4'}$ = 2.7 Hz, H-3'), 3.88 (ddd, $J_{3,4}$ = 3.3 Hz, H-3), 3.53(dd, $J_{4,5}$ = 9.0 Hz, H-4), 2.35 (ddd, $J_{2e,3}$ = 4.7 Hz, H-2e), 1.85 (s, 3 H, $OCOCH_3$), 1.75 (ddd, $J_{2a,2e}$ = 14.5 Hz, $J_{2a,3}$ = 3.4 Hz, H-2a), 1.28 (d, 3 H, CH_3-6), 1.15 (d, 3 H, CH_3 -6'), 1.07 (s, 9 H, Si-C-CH_3).

Anal. Calcd for $C_{44}H_{53}IO_8Si$ (864.9): C, 61.10; H, 618. Found: C, 61.35; H, 6.24.

And 7.4 mg (11%) of **7**: $[\alpha]_D^{20}$ = -55° (*c* 0.3, chloroform); ^1H NMR ($CDCl_3$) δ 7.67 and 7.30 (mc, 20 H,aryl-H), 5.06 (d, $J_{1',2'}$ =8.7 Hz, H-1'), 4.88 (dd, $J_{1,2a}$ = 4.5 Hz, $J_{1,2e}$ = 0.8 Hz, H-1), 4.79 and 4.43 (each d, 2 H, aryl-CH_2), 4.51 (dd, $J_{4',5'}$ = 0.6 Hz, H-4'), 4.37 (dq, $J_{5',6'}$ = 6.3 Hz, H-5' [a]),4.34 (dq, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.3 Hz, H-5 [a]), 4.14 (dd, $J_{2',3'}$ = 2.0 Hz, $J_{3',4'}$ =2.2 Hz, H-3'), 4.06 (dd, H-2'), 4.04 (ddd, $J_{2a,3}$ = 3.4 Hz, $J_{2e,3}$ = 3.2 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 3.38 (dd, H-4), 2.25 (ddd, $J_{2a,2e}$ = 14.4 Hz, H-2e), 2.15 (s, 3 H, $OCOCH_3$) 1.81 (ddd, H-2a), 1.40 (d, CH_3-6 [b]), 1.13 (s, 9 H, Si-C-CH_3), 1.08 (d, 3 H, CH_3-6' [b]), [a], [b] may be inverted.

Anal. Calcd for $C_{44}H_{53}IO_8Si$ (864.9): C, 61.10; H, 6.18. Found: C, 59.93; H, 6.14.

4-*O*-Acetyl-1,5-anhydro-2,6-dideoxy-3-*O*-(*tert*-butyldimethylsilyl)-L-*arabino*-hex-1-enitol (9). A solution of L-rhamnal **8**[5] (1.30 g, 10.0 mmol) and imidazole (1.50 g, 22.0 mmol) in dimethylformamide (20 mL) was cooled to -20 °C and *tert*-butyldimethylchlorosilane (1.80 g, 12.0 mmol) was added with stirring. The mixture was kept at 0 °C until the reaction was complete. The solvent was then evaporated, the remaining syrup dissolved in dichloromethane, the solution washed with water, dried over $MgSO_4$, and concentrated to dryness. The residue dissolved in ether, filtered over silica gel, and concentrated. Acetylation according to the procedure described for the preparation of **4**, followed by chromatography (ethyl acetate / toluene, 1:20) yielded 2.15 g (76 %) of **9**: $[\alpha]_D^{20}$ = +58.3° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 6.32 (dd, $J_{1,2}$ = 6.2 Hz, $J_{1,3}$ = 1.4 Hz, H-1), 4.92 (dd, $J_{4,5}$ = 8.2 Hz, H-4), 4.68 (dd, $J_{2,3}$ = 2.9 Hz, H-2), 4.27 (dddd, $J_{3,4}$ = 6.2 Hz, H-3), 4.03 (ddq, $J_{5,6}$ = 6.6 Hz, H-5), 1.28 (d, 3 H, CH_3-6), 0.04 and 0.05 (2s, 2 x 3 H, Si-CH_3).

Anal. Calcd for $C_{14}H_{26}O_4Si$ (268.4): C, 58.70; H, 9.15. Found: C, 59.10; H, 9.10.

Benzyl 4-*O*-[4-*O*-acetyl-2,6-dideoxy-2-iodo-3-*O*-(*tert*-butyldimethylsilyl)-α-L-mannopyranosyl]-3-azido-2,3,6-trideoxy-α-L-*ribo*-hexopyranoside (11). Glycal **9** (145 mg, 0.51 mmol) and glycosyl acceptor **10**[4] (95 mg, 0.36 mmol) in dichloromethane (2 mL) and acetonitrile (2 mL) were stirred with molecular sieves 4 Å. *N*-iodosuccinimide (135 mg, 0.60 mmol) was added and the mixture kept at room temp for 36 h. It was worked up as described for **6** and **7**, purified by chromatography (ethyl acetate / toluene, 1:15), and crystallised from ether yielding 161 mg (66 %) of **11**: mp 97 °C, $[\alpha]_D^{20}$ = -104.7° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 7.25-7.37 (m, 5H, aryl-CH_2), 5.33 (br s, $J_{1',2'}$ = 1.0 Hz, H-1'), 5.00 (dd, $J_{4',5'}$ = 9.8 Hz, H-4'), 4.83 (dd, $J_{1,2a}$ = 4.3 Hz, $J_{1,2e}$ = 1.3 Hz, H-1), 4.50 and 4.76 (2d, J = 12.4 Hz, 2 H, aryl-CH_2), 4.35

(dd, $J_{2',3'}$ = 4.2 Hz, H-2'), 4.20 (dq, $J_{5,6}$ = 6.5 Hz, H-5), 4.08 (ddd, $J_{3,4}$ = 3.5 Hz, H-3), 3.84 (dq, $J_{5',6'}$ = 6.2 Hz, H-5'), 3.49 (dd, $J_{4,5}$ = 9.0 Hz, H-4), 3.26 (dd, $J_{3',4'}$ = 9.0 Hz, H-3'), 2.18 (ddd, $J_{2e,3}$ = 4.0 Hz, H-2e), 2.06 (s, 3 H, $OCOCH_3$), 1.95 (ddd, $J_{2a,2e}$ = 14.8 Hz, $J_{2a,3}$ = 4.0 Hz, H-2a), 1.23 (d, 3 H, CH_3-6), 1.18 (d, 3 H, CH_3-6'), 0.86 (s, 9 H, C-CH_3), 0.04 and 0.08 (2s, 2 x 3 H, $SiCH_3$).

Anal. Calcd for $C_{27}H_{42}IN_3O_7Si$ (675.6): C, 48.00; H, 6.27; I, 18.78; N, 6.22. Found: C, 48.03; H, 6.27; I, 19.31; N, 6.22.

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