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One-pot-synthesis of α-linked deoxy sugar trisaccharides

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Abstract

Various α-linked 2,6-dideoxy-*ribo*-trisaccharides, models for part of the antibiotic kijanimicin, were synthesised by the *N*-iodosuccinimide method employing different pathways. The efficiency of a sequential synthesis suffered from side reactions of the axial HO-3, which are typical of digitoxosides. These problems did not arise in a straightforward polymerisation, performed as a one-pot-procedure. It afforded the trisaccharide directly from the monosaccharide precursor in 30% yield. A combination of the oligomerisation pathway and the sequential synthesis led to trisaccharides with different protecting group patterns. In these reactions different glycal and alcohol components were used and allowed to define the optimal partners in a sequential synthesis: the two components should ideally be of comparable reactivity.

1. Introduction

2-Deoxyglycosides with interglycosidic α linkages are dominant structural features in a variety of biologically active compounds. As examples, the antibiotic kijanimicin (**1**) [1] and the structurally related tetrocarcins [2] and antlerimicin [3] contain oligosaccharides with 2,6-dideoxy-L-*ribo*-hexose (L-digitoxose) units in α-(1 → 3) linkages. Oligosaccharides of this configuration exhibit a 1,3-diaxial interaction at the glycosidic linkage positions and are rarely found in natural compounds. The biological activity of these antibiotics covers an interesting range [4], which is correlated to the number of α-linked deoxy sugars present in the antibiotic [5].

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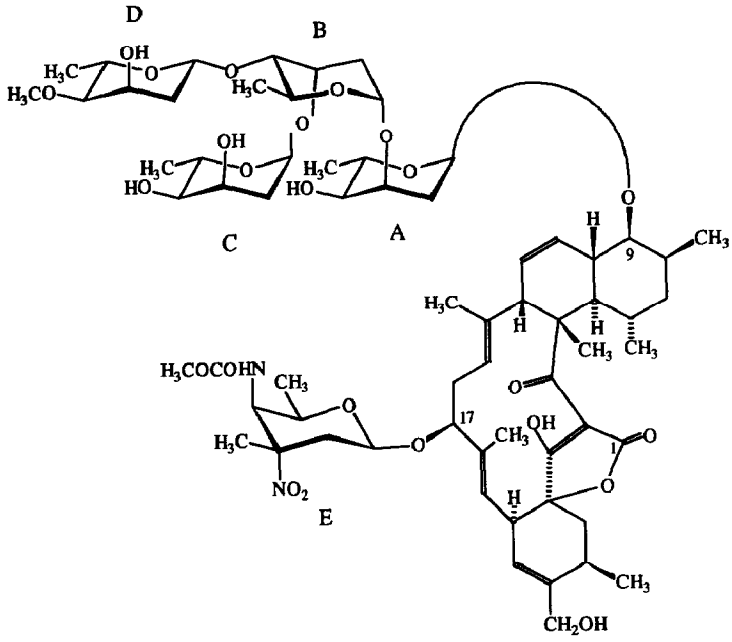


Scheme 1.

A number of synthetic approaches has previously been directed towards the synthesis of these molecules. The stereochemically complex macrolide aglycon of kijanimicin (**1**) has been partly synthesised [6–9] and recently the total synthesis of tetronolide, the aglycon of the tetrocarcins, was accomplished [10]. The monosaccharide component of kijanimicin, the novel nitro-amino sugar D-kijanose (E in **1**), has been synthesised by different approaches [11–13]. The tetrasaccharide block consists entirely of L-digitoxose residues. The L enantiomer of digitoxose has so far been found exclusively in antibiotics; shortly after the isolation and structural elucidation of **1** the synthesis of L-digitoxose was described from nonchiral precursors [14], as well as from the carbohydrate pool [15]. The assembly of the complete oligosaccharide moiety by sequential synthesis was published recently [16].

As part of studies towards this branched moiety, a synthesis of the α-linked trisaccharide backbone of the kijanimicin oligosaccharide had to be developed, and is described in this contribution. The synthesised trisaccharides served as synthetic models for the ABC part of the kijanimicin oligosaccharide and were further used in the conformational analysis of the crucial α-(1 → 3) linkage in digitoxosides [17].

2. Results and discussion

Sequential synthesis.—A straightforward sequential synthesis of a trisaccharide implies several protection–deprotection steps and requires monomers with differ-

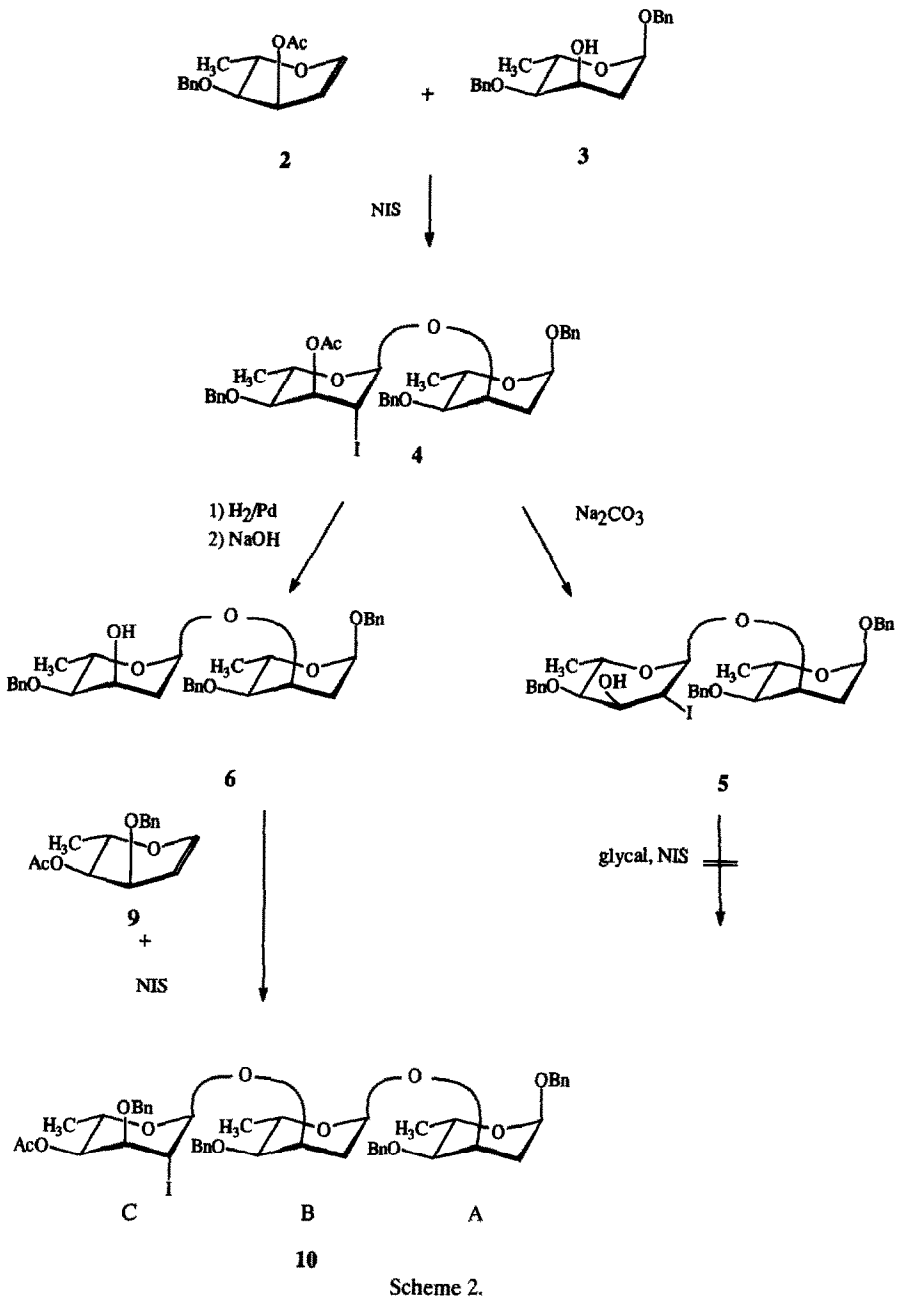
ent protecting groups at positions 3 and 4. Such selectively protected sugars are available as L-digitoxosides or as L-digitoxals, and since the linkages of our target trisaccharide are exclusively α, both these building blocks should ideally be linked using the *N*-iodosuccinimide (NIS) procedure [18].

Treatment of the glycal **2** [19] with the alcohol component **3** [20] and NIS gave selectively the α-linked iodo disaccharide **4** in 48% yield. Further condensation of the third sugar was first attempted by use of the *O*-deacetylated disaccharide **5**, which was obtained by basic deacetylation of compound **4**. No reaction occurred when **5** was used as the alcohol component in a NIS glycosylation. The disaccharide **5**, moreover, proved to be stable to reductive cleavage of the halide by hydrogenolysis and it did not liberate any iodine, when kept in a solution with chloroform or ethyl acetate as solvent for several weeks. A liberation of iodine is generally observed with 2-deoxy-2-iodo saccharides. ^{1}H NMR spectroscopy revealed that the nonreducing ring of **5** adopts a half chair conformation. A similar combination of conformational change with nonreactivity has previously been observed in an analogous disaccharide bearing a methoxybenzyl group [16] instead of the benzyl ether at position 3'.

In addition to the conformational change, the stabilising effect in **5** might be due to the substitution by iodine. Therefore, we first removed the iodine in **4** by catalytic hydrogenation and, without isolation, the 2'-deoxy product was *O*-deacetylated immediately to obtain **6**. In order to achieve this deacetylation, drastic conditions had to be applied. Neither catalytic deesterification using NaOMe nor reductive deacetylation employing LAH were successful. Only by treatment with 20% sodium hydroxide in methanol for 10 days was disaccharide **6** finally obtained in a yield of 60% from **4**. As a side product of this two-step reaction, the elimination product **7** formed in 18% yield by trans diaxial elimination [21] under the basic conditions of hydrogenolysis. Basic conditions had to be applied in the hydrogenolysis in order to prevent a reductive cleavage of the benzyl groups. Under the conditions applied the unsaturated disaccharide **7** was partly hydrogenated to **8**.

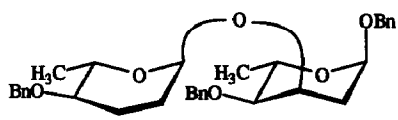
In the final step of the sequential synthesis the disaccharide **6** was condensed with the glycal **9** [19] to give the trisaccharide **10** in a yield of 38%. As both the glycal and the alcohol component are not very reactive compounds, the reaction was performed without solvent in a syrup, following a method which had previously been developed for D-digitoxosides [22].

The α-(1 $\rightarrow$ 3) linked trisaccharide chain was thus prepared by following sequential synthesis. The yields obtained in this approach, however, were not satisfying. One reason for this is the low reactivity of the individual components. Another reason originates from specific characteristics of the 3-O-axial position in digitoxosides. Depending on the substitution pattern at position 3, digitoxosides easily undergo conformational changes as in **5** (and in other examples [16]). Position 3 in digitoxosides also tends to undergo eliminations, giving 2,3-unsaturated products such as **7**. Similar elimination reactions were also observed in Koenigs–Knorr type glycosylations [16,23] and in NIS reactions [24] of digitoxosides.



Scheme 2.

One-pot condensation.—Since the target trisaccharide chain in kijanimicin is uniformly composed of α-linkages, it should be available by oligomerisation of a suitable monomer. We considered the benzylated glycal **11** [19] to be an appropri-



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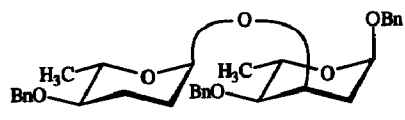

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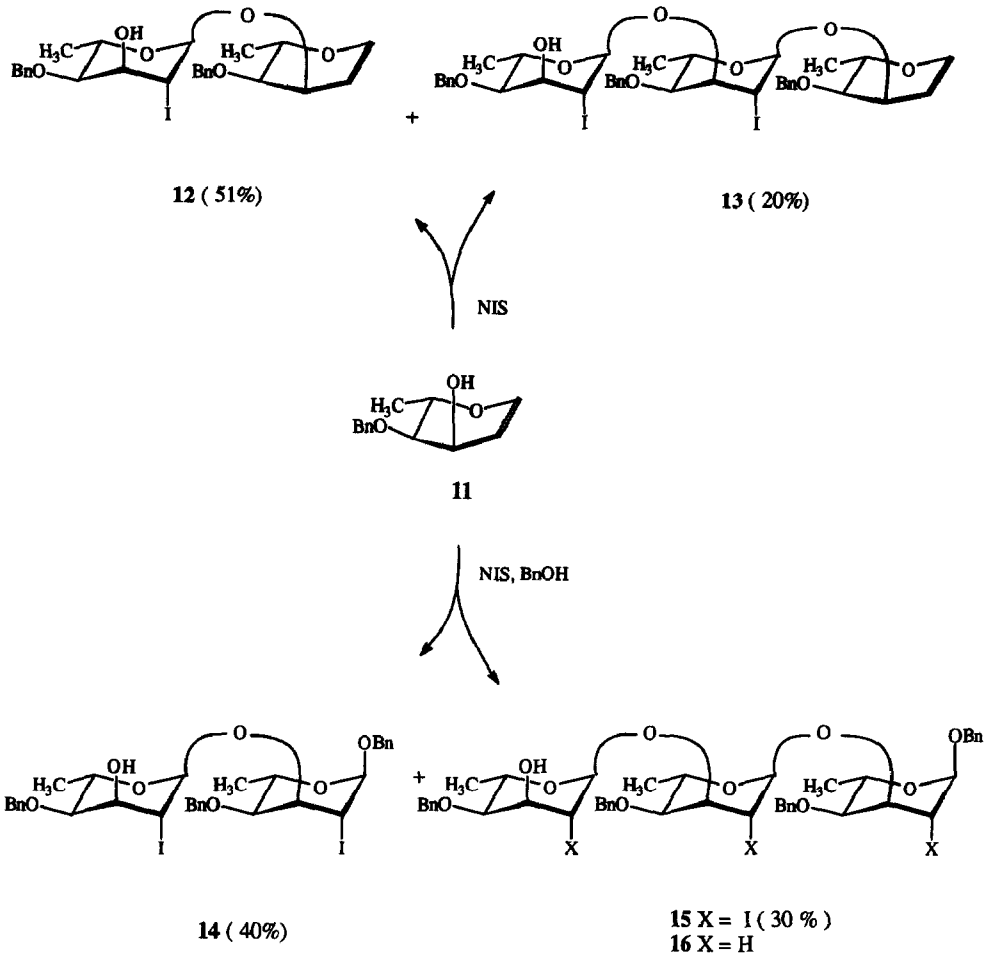
Scheme 3.

ate synthon for this reaction; it should be reactive enough for self condensation in an NIS reaction. Glycal **11** was treated dropwise with NIS under TLC control, in order to circumvent uncontrolled oligomerisation. This procedure afforded a mixture of the trisaccharide glycal **13** (21%) and disaccharide glycal **12** (51%). Both these products are still reactive compounds. Therefore, a final glycosylation with benzyl alcohol was included in the one-pot procedure. By thorough supervision of the reaction and careful addition of the components, the yield of the trisaccharide could, thus, be increased. Trisaccharide **15** was obtained in a three-step-one-pot-reaction in 30% yield starting from the monomer. A final routine hydrogenation yielded the fully deoxygenated trisaccharide **16**.

Disaccharides **12** and **14** were formed as major components in the oligomerisation reactions. They are ideal models for a study of different concepts in NIS-glycosylations. Yields of NIS reactions are very sensitive to the reactivity of the individual components. The 3-hydroxyl group in digitoxosides is only slightly nucleophilic. In planning the synthesis of a trisaccharide by condensation of a disaccharide with a monosaccharide, it is, therefore, not obvious which component should ideally be the alcohol component and which the glycal component. Glycosylation of a reactive monosaccharide glycal with the insignificantly nucleophilic 3′-OH group of a disaccharide, or, alternatively, treatment of a less reactive disaccharide glycal with the slightly more nucleophilic hydroxyl group of a monosaccharide could be considered.

We carried out a condensation of disaccharide glycal **12** with the monosaccharide **3** and NIS in a syrupy mixture and obtained the trisaccharide **18** in a yield of 49%. The difference in reactivity of the free hydroxyl group of monosaccharide **3** and disaccharide **12** was large enough to prevent any self condensation of the glycal. A less satisfactory yield of 39% was obtained when the monosaccharide glycal **9** was similarly treated with disaccharide **14** and NIS. The unreacted, precious disaccharide could be recovered in this reaction, whereas the disaccharide component was consumed by the NIS in the treatment of the disaccharide glycal. Final dehalogenation of **19** afforded the trisaccharide **20**, which is composed of dideoxy sugar units.

The results show that a combination of a disaccharide glycal of low reactivity with a hydroxyl group of the average nucleophilicity of digitoxose is favourable over the combination of quite unequal partners, as performed in the reaction of a reactive benzylated glycal and a disaccharide alcohol component of low nucleophilicity. Hence, the rules that apply for Koenigs–Knorr glycosylations [25] are also

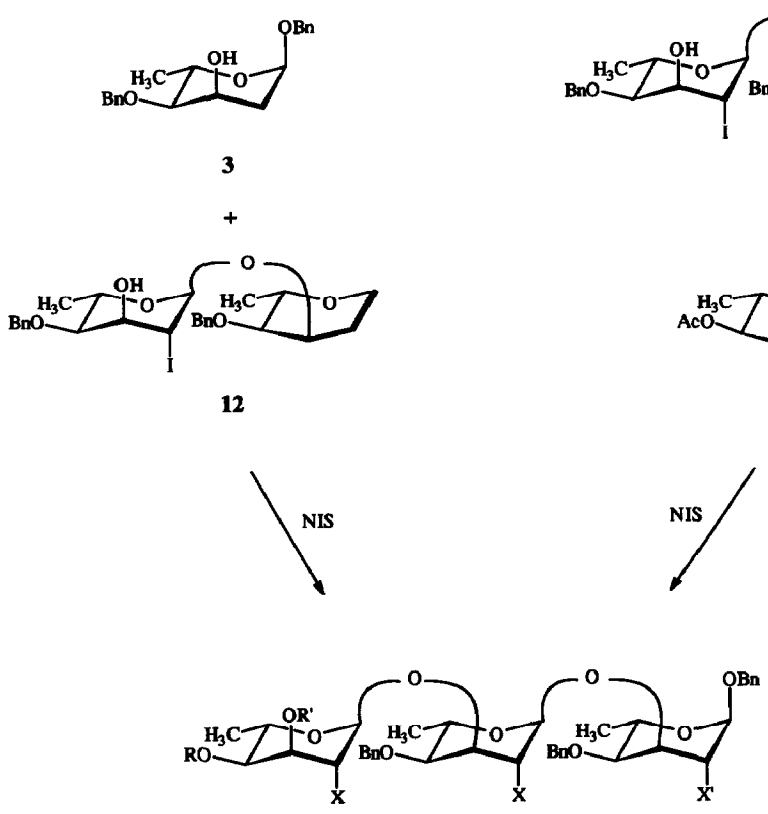


Scheme 4.

valid in NIS reactions: it is favourable to combine partners of comparable reactivity.

The three different pathways for preparation of trisaccharides afforded the tridigitoxosides in an overall yield of 11%, when the sequential procedure was applied. A combination of the one-pot and sequential pathway yielded **19** in 15% and **18** in 24%, and the oligomerisation gave a 30% overall yield of trisaccharide **15**. Therefore, the one-pot-oligomerisation procedure is advantageous, not only with respect to time and work consumed, but also to the yields produced. A similar approach should be generally applicable for the synthesis of deoxy sugar oligosaccharides.

All glycosides prepared were characterised by ^{1}H NMR spectroscopy. The individual sugar units in the saccharides have identical multiplicity and coupling constants. Therefore, a complete assignment of the signals could only be achieved



18 R=Bn, R'=H, X = I, X'=H
19 R=Ac, R'=Bn, X=X'=I
20 R=Ac, R'=Bn, X=X'=H

Scheme 5.

by two-dimensional spectroscopy. The NMR data are as expected for digitoxosides. Only the shift differences for the geminal 2-deoxy protons show an unusually high mean value of 0.5 ppm. This is mainly due to an upfield shift of the 2-axial protons, which show chemical shifts around δ 1.5 ($CDCl_3$). The "normal" value for 2,6-dideoxyhexoses and especially digitoxosides is δ 1.9. This unusual high-field resonance was observed in all di- and tri-saccharides synthesised here and elsewhere [16], and seems to be characteristic for the orientation of the α-(1 → 3) linkage in digitoxosides.

3. Experimental

General methods.—Reactions were followed by TLC on DC-Alufolien Kieselgel GF_{254} (Merck), detection was effected by examination with UV light and/or staining with 10% ethanolic H_2SO_4 and charring. Preparative thin layer chro-

Table 1
Selected ^1H NMR parameters of disaccharides in $CDCl_3$

Atom (coupling constant)		Chemical shifts (δ) and coupling constants (Hz) of individual compounds						
		4	**5**	**6**	**7**	**8**	**12**	**14**
Ring A								
	($J_{1,2a}$)	(4.1)	(4.0)	(4.5)	(4.0)	(4.2)		
H-1	($J_{1,2e}$)	4.80 (1.0)	4.86 (1.4)	4.81 (1.0)	4.84 (1.0)	4.84 (1.3) [b]	6.44 (6.0)	5.08 (0.8)
H-2*a*	($J_{2a,2e}$)	1.6 (15.2)	1.67 (14.9)	1.62 (15.0)	1.67 (15.0)	1.67 (4.9)		
H-2*e*	($J_{2a,3}$)	2.21 (2.8)	2.30 (2.9)	2.23 (2.8)	2.32 (3.1)	2.32 (3.0)	4.83	4.38
H-3	($J_{2e,3}$)	4.24 (3.4)	4.33 (3.6)	4.18 (3.0)	4.40 (3.4)	4.25 (3.5)	4.18 (5.6)	4.20 (3.0)
H-4	($J_{3,4}$)	3.10 (2.7)	3.18 (3.0)	4.70 (2.9)	3.17 (3.0)	3.17 (3.0)	3.33 (3.4)	3.86 (2.9)
H-5	($J_{4,5}$)	4.21 (9.1)	4.39 (9.0)	4.21 (9.4)	(9.0)	4.29 (9.0)	4.10 (10.2)	4.18 (9.4)
CH_3-6	($J_{5,6}$)	1.22 (6.4)	1.24 (6.3)	1.18 (6.4)	1.24 (6.2) [a]	1.18 (6.2) [a]	1.31 (6.3)	1.19 (6.2) [a]
Ring B								
	($J_{1,2a}$)			(3.4)	(1.2)	(3.3)		
H-1	($J_{1,2e}$)	5.23 (0.6)	5.15 (3.0)	5.12 (1.0)	5.20 ($J_{1,3}$ 2.5)	4.98 (1.0) [b]	6.36 (1.2)	5.22 (0.8)
H-2*a*	($J_{2a,2e}$)			1.71 (14.3)	($J_{1,4}$ 1.4)	1.67		
H-2*e*	($J_{2a,3}$)	4.30	3.28	2.06 (3.0)	5.90 (10.1)	1.86	4.34	4.21
H-3	($J_{2e,3}$)	5.31 (2.8)	3.36 (4.0)	4.18 (3.4)	5.61 ($J_{2,4}$ 1.6)	($J_{3a,4}$ 10.0)	4.21 (3.4)	4.14 (3.0)
H-4	($J_{3,4}$)	3.89 (2.9)	3.40 (1.2)	3.00 (2.6)	3.67 (2.0)	3.04 ($J_{3e,4}$ 4.3)	3.87 (3.0)	3.83 (2.9)
H-5	($J_{4,5}$)	4.38 (9.4)	4.05 (9.0)	4.16 (9.7)	4.00 (9.0)	4.01 (9.0)	4.09 (9.4)	4.04 (9.4)
CH_3-6	($J_{5,6}$)	1.21 (6.1)	1.14 (6.3)	1.20 (6.4)	1.23 (6.2) [a]	1.21 (6.2) [a]	1.21 (6.2)	1.20 (6.2) [a]

[a,b] Assignment may be inverted.

Table 2
Selected ^{1}H NMR parameters of trisaccharides in $CDCl_3$

Atom (coupling constant)		Chemical shifts (δ) and coupling constants (Hz) of individual compounds						
		10	**13**	**15**	**16**	**18**	**19**	**20**[b]
Ring A								
	($J_{1,2a}$)	(4.2)			(3.0)	(4.0)		(4.1)
H-1	($J_{1,2e}$)	4.79 (1.0)	6.37 (5.9)	5.03 (0.7)	4.77 (1.0)	4.79 (0.8)	5.02 (1.2)	4.62 (0.8)
H-2*a*	($J_{2a,3}$)	1.51 (3.1)			1.54 (2.6)	1.51 (2.5)		1.09 (3.0)
H-2*e*	($J_{2a,2e}$)	2.26 (15.0)	4.82	4.39	2.17 (14.6)	2.20 (15.4)	4.41	1.89 (14.4)
H-3	($J_{2e,3}$)	4.25 (3.0)	4.21 (5.6)	4.21 (2.8)	4.20 (2.8)	4.17 (3.0)	4.24 (2.6)	4.12 (3.0)
H-4	($J_{3,4}$)	3.12 (3.0)	4.13 (3.2)	4.20 (2.6)	3.06 (2.9)	3.09 (2.6)	4.33 (2.8)	2.96 (2.8)
H-5	($J_{4,5}$)	4.51 (9.4)	3.30 (10.0)	3.86 (9.4)	4.14 (9.2)[a]	4.18 (9.4)	3.81 (8.9)	4.37 (9.0)
CH_3-6	($J_{5,6}$)	1.36 (6.2)[a]	1.40 (6.3)	1.33 (6.2)	1.17 (6.4)	1.34 (6.4)	1.33 (6.4)	1.42 (6.2)
Ring B								
	($J_{1,2a}$)	(4.2)			(0.8)			(0.8)
H-1	($J_{1,2e}$)	4.98 (1.0)	5.19 (0.6)	5.04 (0.7)	4.93 (4.2)	5.14 (0.8)	5.18 (0.8)	4.87 (4.0)
H-2*a*	($J_{2a,3}$)	1.47 (3.1)			1.50 (3.0)			1.30 (3.0)
H-2*e*	($J_{2a,2e}$)	2.15 (14.8)	4.37	4.07	2.16 (14.6)	4.03	4.34	2.30 (14.8)
H-3	($J_{2e,3}$)	4.18 (3.2)	4.18 (2.8)	3.99 (2.7)	4.10 (2.8)	4.03	4.24 (2.7)	4.28 (3.1)
H-4	($J_{3,4}$)	3.10 (2.9)	3.88 (2.8)	3.79 (2.8)	2.94 (2.7)	3.81 (2.2)	3.82 (2.7)	3.09 (2.7)
H-5	($J_{4,5}$)	4.51 (9.0)	4.31 (9.4)	4.25 (9.5)	4.06 (9.6)[a]	4.26 (9.5)	4.41 (9.2)	4.66 (9.9)
CH_3-6	($J_{5,6}$)	1.24 (6.1)	1.21 (6.3)	1.06 (6.4)	1.20 (6.2)	1.12 (6.4)	1.06 (6.3)[a]	1.42 (6.2)
Ring C								
	($J_{1,2a}$)				3.2			(4.0)
H-1	($J_{1,2e}$)	5.39 (0.8)	5.23 (0.6)	5.11 (0.8)	5.12 (1.0)	5.13 (0.8)	5.17 (1.0)	5.17 (1.1)
H-2*a*	($J_{2a,3}$)				1.57 (2.9)			1.58 (3.0)
H-2*e*	($J_{2a,2}$)	4.66	4.64	4.53	2.25 (14.0)	4.63	4.56	2.46 (14.2)
H-3	($J_{2e,3}$)	4.06 (2.8)	4.00 (2.6)	4.12 (2.8)	4.11 (3.0)	4.08 (2.8)	4.03 (3.0)	4.03 (3.6)
H-4	($J_{3,4}$)	5.25 (3.0)	3.80 (2.8)	3.81 (2.8)	3.05 (2.8)	3.80 (2.5)	5.15 (3.0)	4.87 (2.9)
H-5	($J_{4,5}$)	4.51 (9.4)	3.99 (9.7)	3.88 (9.9)	4.29 (9.4)[a]	3.89 (9.6)	4.36 (9.5)	4.75 (9.0)
CH_3-6	($J_{5,6}$)	1.13 (6.3)[a]	1.21 (6.2)	1.19 (5.9)	1.05 (6.4)	1.20 (6.0)	1.22 (6.4)[a]	1.29 (6.2)

[a] Assignment may be inverted. [b] In benzene-d_6.

matography (PLC) was performed on Kieselgel Fertigplatten 60 F_{254} (Merck). For column chromatography on silica gel Kieselgel 60 (70–230 mesh, Merck) was used. Permeation chromatography was performed on Bio-beads S-X2 (Bio-Rad Laboratories) with toluene as eluent and a flow rate of 7–12 drops/min. For HPLC separations, LiChrosorb Si 60 (7 μm Knauer) was used with 8 × 500 mm columns and flow rates of 2.0 to 2.5 mL/min. Optical rotations were determined with Perkin–Elmer 241 polarimeter. NMR spectra were recorded on a Bruker WM 300 instrument; chemical shifts are given downfield to Me_4Si as internal standard. All signals were unequivocally assigned, partly using 2D-COSY spectroscopy under standard conditions. For NIS glycosylations, NIS recrystallised from CCl_4 was used, and the reactions were carried out with protection from light and under N_2.

Workup of N-*iodosuccinimide glycosylations (general procedure, GP I).*—The mixture was evaporated to dryness in vacuo, the remaining material dissolved in CH_2Cl_2 and the solution washed with aq $Na_2S_2O_3$. The washings were reextracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo.

*Benzyl 3-*O*-(3-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-4-*O*-benzyl-2,6-dideoxy-α-*L*-ribo-hexopyranoside* (**4**).—A solution of glycal **2** [19] (111 mg, 0.42 mmol) and digitoxoside **3** [20] (125 mg, 0.38 mmol) in anhyd MeCN (3 mL) was stirred for 30 min with molecular sieves. *N*-Iodosuccinimide (115 mg, 0.51 mmol) was added and stirring was continued for 1 day. Workup following GP I and separation on silica gel (1:4 EtOAc–hexane) yielded **4** (131 mg, 48%) as a colourless syrup; $[\alpha]_D^{29} - 146.6°$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 1.91 (s, 3 H, $OCOCH_3$), 4.36, 4.41, 4.44, 4.58, 4.67, and 4.68 (6 d, 6 H, *J* 11.4, 11.6, and 11.8 Hz, aryl-CH_2), 7.29 (m, 15 H, aryl-H). Anal. Calcd for $C_{35}H_{42}IO_8$ (717.62): C, 58.58; H, 5.90. Found: C, 58.54; H, 5.79.

*Benzyl 4-*O*-benzyl-3-O-(4-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-2,6-dideoxy-α-*L*-ribo-hexopranoside* (**5**).—A solution of **4** (27 mg, 0.038 mmol) in anhyd MeOH (5 mL) was stirred with Na_2CO_3 for 4 days, filtered, neutralised with ion exchange resin (Amberlite IR 120, H^+), again filtered, and concentrated in vacuo. Separation on silica gel (1:3 EtOAc–hexane) yielded **5** (15.9 mg, 63%) as a colourless syrup; $[\alpha]_D^{25} - 120.8°$ (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 4.33, 4.48, 4.46, 4.68, 4.72, and 4.76 (6 d, 6 H, *J* 11.9, 12.0, and 12.0 Hz, aryl-CH_2), 7.36 (m, 15 H, aryl-H). Anal. Calcd for $C_{33}H_{39}IO_7$ (674.6): C, 58.76; H, 5.83. Found: C, 58.64; H, 5.79.

*Benzyl(4-*O*-benzyl-O-*O*-(4-*O*-benzyl-2,6-dideoxy-α-*L*-ribo-hexopyranosyl-2,6-dideoxy-α-*L*-ribo-hexopyranoside* (**6**).—A solution of **4** (83 mg, 0.12 mmol) and 2 drops of Et_3N in 1,2-dimethoxyethane (2.5 mL) was stirred for 24 h with Pd–C (10%, 15 mg) under H_2. The catalyst was removed by filtration through Celite. Following concentration the remaining syrup was dissolved in NaOH solution (20% in MeOH, 1 mL) and kept at ambient temperature for 10 days (TLC control of the reaction was not possible since starting material and product show identical R_f values in all solvent systems tested). The solution was treated with ion exchange resin (Amberlite IR 120, H^+), filtered, the solvent evaporated, and the residue separated on silica gel (1:3 EtOAc–hexane) to give **6** (37.6 mg, 60%) as a

colourless syrup; $[\alpha]_D^{20} - 195.1°$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 4.36, 4.49, 4.50, 4.70, 4.71, and 4.75 (6 d, 6 H, *J* 11.9, 12.0, and 12.1 Hz, aryl-CH_2), 7.31 (m, 15 H, aryl-H). Anal. Calcd for $C_{33}H_{40}O_7$ (548.7): C, 72.24; H, 7.35. Found: C, 72.34; H, 7.33.

Additionally a 2.3 : 1.0 mixture of benzyl 4-*O*-benzyl-3-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hexopyranosyl)-2,6-dideoxy-α-L-*ribo*-hexopyranoside (**8**) and benzyl 3-*O*-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl)-4-*O*-benzyl-2,6-dideoxy-L-*ribo*-hexopyranoside (**7**) (11 mg, 18%) was eluted and characterised by NMR spectroscopy. For **7**: ^1H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 4.36 and 4.74 (2 d, each 1 H, *J* 11.6, aryl-CH_2), 4.48, 4.49, 4.62, and 4.74 (4 d, each 1 H, *J* 12.0 Hz, aryl-CH_2), 7.29 (m, 15 H, aryl-H). **8**: δ 4.36, 4.47, 4.74, and 4.74 (4 d, each 1 H, *J* 11.4, and 11.6 Hz, aryl-CH_2), 4.44 and 4.62, (2 d, 2 H, *J* 12.0 Hz, aryl-CH_2), 7.29 (m, 15 H, aryl-H).

*Benzyl 3-*O*-[3-*O*-(4-*O*-acetyl-3-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-4-*O*-benzyl-2,6-dideoxy-α-*L*-ribo-hexopyranosyl]-4-*O*-benzyl-2,6-dideoxy-α-*L*-ribo-hexopyranoside* (**10**).—A solution of **6** (22 mg, 0.04 mmol), **9** [19] (27 mg, 0.10 mmol), and *N*-iodosuccinimide (28 mg, 0.12 mmol) in anhyd MeCN (1.5 mL) was concentrated in vacuo. The remaining syrup was kept under N_2 for 36 h and worked up following GP I. By chromatography on Bio-beads **6** (10.9 mg, 50%) was recovered and **10** 14.3 mg, 38%) obtained as a colourless syrup; $[\alpha]_D^{20} - 141.1°$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2): δ 2.00 (s, 3 H, $OCOCH_3$), 4.06, 4.37, 4.41, 4.40, 4.53, 4.57, 4.61, and 4.79 (4 d, 8 H, *J* 11.8, 11.9, 12.0, and 12.0 Hz, aryl-CH_2), 7.25 (m, 20 H, aryl-H). Anal. Calcd for $C_{53}H_{58}I_2O_{11}$ (1124.9): C, 56.59; H, 5.20. Found: C, 55.96; H, 5.16.

*1,5-Anhydro-4-*O*-benzyl-3-*O*-(4-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-2,6-dideoxy-*L*-ribo-hex-1-enitol* (**12**) *and 1,5-anhydro-4-*O*-benzyl-3-*O*-[4-*O*-benzyl-3-*O*-(4-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl]-2,6-dideoxy-α-*L*-ribo-hex-1-enitol* (**13**).—Following stirring with molecular sieve for 1 h, *N*-iodosuccinimide (62 mg, 0.27 mmol) in anhyd MeCN (1.5 mL) was added dropwise over a period of 2 h to a solution of **11** [19] (89 mg, 0.4 mmol) in anhyd MeCN (3.5 mL) and kept overnight. The work-up was performed according to GP I, followed by chromatography on Bio-beads, and final purification by HPLC (1:1 EtOAc–hexane). First, **13** (24.2 mg, 20%) was obtained as a colourless syrup; $[\alpha]_D^{20} - 205.8°$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2): δ 3.71 (d, $J_{3'',3''\text{-OH}}$ 11.0, 3″-OH), 4.43, 4.53, 4.62, and 4.80 (4 d, 4 H, *J* 11.9 and 12.0 Hz, aryl-CH_2), 4.49 and 4.65 (2d, each 1 H, *J* 11.6 Hz, aryl-CH_2), 7.30 (m, 15 H, aryl-H). Anal. Calcd for $C_{39}H_{46}I_2O_9$ (912.6): C, 51.33; H, 5.08. Found: C, 51.15; H, 5.04.

Obtained second was **12** (48.3 mg, 51%) of **12**; $[\alpha]_D^{20} - 248.0°$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 3.78 (d, $J_{3',3'\text{-OH}}$ 10.6 Hz, 3′-OH), 4.49 and 4.53 (2 d, 2 H, *J* 11.6 Hz, aryl-CH_2), 4.70 (AB, 2 H, aryl-CH_2), 7.29 (m, 10 H, aryl-H). Anal. Calcd for $C_{26}H_{31}IO_6$ (566.4): C, 55.13; H, 5.52. Found: C, 55.54; H, 5.65.

*Benzyl 4-*O*-benzyl-3-*O*-(4-*O*-benzyl-2,6-dideoxy-2-iodo-α-*L*-altropyranosyl)-2,6-dideoxy-2-iodo-α-*L*-altropyranoside* (**14**) *and benzyl4-*O*-benzyl-3-*O*-[4-*O*-benzyl-3-*O*-*

(4-O-benzyl-2,6-dideoxy-2-iodo-α-L-altropyranosyl)-2,6-dideoxy-2-iodo-α-L-altropyranosyl]-2,6-dideoxy-2-iodo-α-L-altropyranoside (**15**).—A solution of glycal **11** [19] (91 mg, 0.41 mmol) in anhyd MeCN (3.5 mL) was stirred for 1 h with molecular sieves. *N*-Iodosuccinimide (56 mg, 0.24 mmol) in MeCN (1 mL) was added dropwise over a period of 50 min. TLC control (1:3 EtOAc–hexane) revealed that the disaccharide glycal **12** was formed predominantly besides smaller amounts of the trisaccharide glycal **13**. The mixture was cooled to 0°C, *N*-iodosuccinimide (50 mg, 0.22 mmol) was added and additional glycal **11** (45 mg, 0.20 mmol) in anhyd MeCN (1.5 mL) was added dropwise over 20 min. The relative proportion of trisaccharide glycal **13** increased and the mixture was allowed to warm to ambient temperature and stirred for an additional 20 min. Then *N*-iodosuccinimide (60 mg, 0.26 mmol) and benzyl alcohol (50 μL) were added and the solution was kept overnight. Work-up according to GP I followed by chromatography on Bio-beads and final purification by HPLC (1:3 EtOAc–hexane) of the individual fractions yielded **15** (70.1 mg, 30%); $[\alpha]_D^{20} - 123.0°$ (*c* 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2): 3.78 (δ, $J_{3'',3''\text{-OH}}$ 10.9, 3''-OH), 4.38, 4.46, 4.48, 4.48, 4.56, 4.64, 4.68, and 4.70 (4 d, *J* 11.8, 11.8, 11.9, and 12.0 Hz, aryl-CH_2), 7.31 (m, 20 H, aryl-H). Anal. Calcd for $C_{46}H_{53}I_3O_{10}$ (1146.6): C, 48.18; H, 4.66. Found: C, 47.95; H, 4.59.

Obtained second was **14** (98.2 mg, 40%) as a colourless syrup; $[\alpha]_D^{20} - 118.0°$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 1): δ 3.65 (d, $J_{3',3'\text{-OH}}$ 11.0 Hz, 3'-OH), 4.37, 4.43, 4.58, and 4.64 (4 d, 4 H, *J* 11.8, and 11.9 Hz, aryl-CH_2), 4.49 and 4.62 (2 d, each 1 H, *J* 11.6 Hz, aryl-CH_2), 7.29 (m, 15 H, aryl-H). Anal. Calcd for $C_{33}H_{38}I_2O_7$ (800.5): C, 49.52; H, 4.78. Found: C, 49.12; H, 4.74.

Benzyl 4-O-benzyl-3-O-[4-O-benzyl-3-O-(4-O-benzyl-2,6-dideoxy-α-L-ribo-hexopyranosyl)-2,6-dideoxy-α-L-ribo-hexopyranosyl]-2,6-dideoxy-α-L-ribo-hexopyranoside (**16**).—A mixture of **15** (32 mg, 0.028 mmol), one drop of Et_3N Pd–C (10%, 10 mg) in 1,2-dimethoxyethane (1 mL) was stirred under H_2 for 3 days. The mixture was filtered over Celite, washed with CH_2Cl_2, evaporated and separated on silica (1:4 EtOAc–toluene) to yield **16** (15 mg, 70%) as a colourless syrup; [α]u20$_D$ − 221.0° (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2): δ 4.01 (d, $J_{3'',3''\text{-OH}}$ 10.0, 3''-OH), 4.37, 4.44, 4.46, 4.49, 4.63, 4.68, 4.74, and 4.76 (8 d, *J* 11.9, 12.0, 12.1, and 12.2 Hz, 8 H, aryl-CH_2), 7.28 (m, 20 H, aryl-H). Anal. Calcd for $C_{46}H_{56}O_{10}$ (768.9): C, 71.84; H, 7.35; Found: C, 71.57; H, 7.31.

Benzyl 4-O-benzyl-3-O-[4-O-benzyl-3-O-(4-O-benzyl-2,6-dideoxy-2-iodo-α-L-altropyranosyl)-2,6-dideoxy-2-iodo-α-L-altropyranosyl]-2,6-dideoxy-α-L-ribo-hexopyranoside (**18**).—A solution of glycal **12** (24 mg, 0.08 mmol), digitoxoside **3** [20] (28 mg, 0.08 mmol) and *N*-iodosuccinimide (12.4 mg, 0.05 mmol) in MeCN (0.5 mL) was kept for 24 h at ambient temperature. The reaction was worked up as in GP I and chromatography on Bio-beads yielded **18** (20.5 mg, 47%); $[\alpha]_D^{20} - 150.6°$ (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2) 3.81 (δ, $J_{3'',3''\text{-OH}}$ 11.0, 3''-OH), 4.33, 4.46, 4.48, 4.58, 4.67, and 4.70 (6 d, each 1 H, *J* 11.9, 11.9, and 12.0 Hz, aryl-CH_2), 4.44 and 4.69 (2 d, each 1 H, *J* 11.2 Hz, aryl-CH_2), 7.31 (m, 20 H, aryl-H). Anal. Calcd for $C_{46}H_{54}I_2O_{10}$ (1020.7): C, 54.13; H, 5.33. Found: C, 53.97; H, 5.31.

Benzyl 3-O-[3-O-(4-O-acetyl-3-O-benzyl-2,6-dideoxy-2-iodo-α-L-altropyranosyl)-4-O-benzyl-2,6-dideoxy-2-iodo-α-L-altropyranosyl]-4-O-benzyl-2,6-dideoxy-2-iodo-α-L-altropyranoside (**19**).—A solution of disaccharide **14** (52 mg, 0.065 mmol), glycal **17** [19] (34 mg, 0.13 mmol), and *N*-iodosuccinimide (30 mg, 0.13 mmol) in anhyd benzene (2 mL) was evaporated in vacuo. The partly crystalline mixture was treated with anhyd MeCN (1 mL) under N_2 and kept at ambient temperature for 2 days. By work-up according to GP I and chromatography on Bio-beads **14** (21 mg, 42%) was recovered, and **19** (30.2, 39%) was obtained as a syrup; $[\alpha]_D^{20}$ − 131.0° (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$, sugar ring protons see Table 2): δ 1.96 (s, 3 H, $OCOCH_3$), 4.18, 4.40, 4.43, 4.44, 4.62, and 4.80 (6 d, each 1 H, *J* 11.8, 11.9, and 12.0 Hz, aryl-CH_2), 4.33 and 4.58 (2 d, each 1 H, *J* 11.6 Hz, aryl-CH_2), 7.25 (m, 20H, aryl-H). Anal. Calcd for $C_{48}H_{55}I_3O_{11}$ (1188.7): C, 48.50; H, 4.66. Found: C, 48.10; H, 4.67.

Benzyl 3-O-[3-O-(4-O-acetyl-3-O-benzyl-2,6-dideoxy-α-L-ribo-hexopyranosyl)-4-O-benzyl-2,6-dideoxy-α-L-ribo-hexopyranosyl]-4-O-benzyl-2,6-dideoxy-α-L-ribo-hexopyranoside (**20**).—A solution of **19** (28 mg, 0.023 mmol) in 1,2-dimethoxyethane (1 mL) was treated as described for **16** and worked up. PLC (1:3 EtOAc–toluene) yielded **20** (15.4 mg, 81%); $[\alpha]_D^{20}$ −179.7° (*c* 0.8, $CHCl_3$). ^1H NMR (C_6D_6, sugar ring protons see Table 2): δ 1.65 (s, 3 H, $OCOCH_3$), 4.19, 4.32, 4.40, and 4.66 (4 d, each 1 H, *J* 12.0 Hz, aryl-CH_2), 4.20, 4.26, 4.62, and 4.89 (4 d, each 1 H, *J* 11.2 and 11.4 Hz, aryl-CH_2), 7.18 (m, 20 H, aryl-H). Anal. Calcd for $C_{48}H_{58}O_{11}$ (811.0): C, 71.09; H, 7.21. Found: C, 70.98; H, 7.18.

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