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Synthesis of LD-Hep*p* and KDO containing di- and tetrasaccharide derivatives of *Neisseria meningitidis* inner-core region *via* iodonium ion promoted glycosidations

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ABSTRACT: The synthesis of methyl(ethyl) 2-thio-KDO (*i.e.* **1**, **2**, **5**, **7** and **10**) and ethyl 1-thio-LD-Hep*p* (*i.e.* **26** and **43**) derivatives will be described. The latter derivatives proved to be suitable donors in iodonium ion (NIS/TfOH) promoted glycosidation reactions. The usefulness of the glycosidation approach was illustrated by the successful conclusion of a spacer containing dimer L-α-D-Hep*p*-(1→5)-α-KDO-2-*O*-$(CH_2)_3NH_2$ (**37**) and tetramer ß-D-Gal*p*-(1→4)-ß-D-Glc*p*-(1→4)-L-α-D-Hep*p*-(1→5)-α-KDO-2-*O*-$(CH_2)_3NH_2$ (**47**).

Infection diseases by the Gram-negative bacteria *Neisseria meningitidis* may cause a serious form of bacteremia and meningitidis[1]. At present, a tetravalent capsular polysaccharide (CPS) meningococcal vaccine, which offers protection against diseases caused by meningococci serogroups A, C, Y and W-134, is available[2]. However, the development of a CPS vaccine against serogroup B meningococci is hampered by the fact that its CPS is not immunogenic in humans. To protect humans against serogroup B meningococcal diseases, efforts are at present directed toward the application of lipopolysaccharides[3,4] (LPS) as vaccine components.

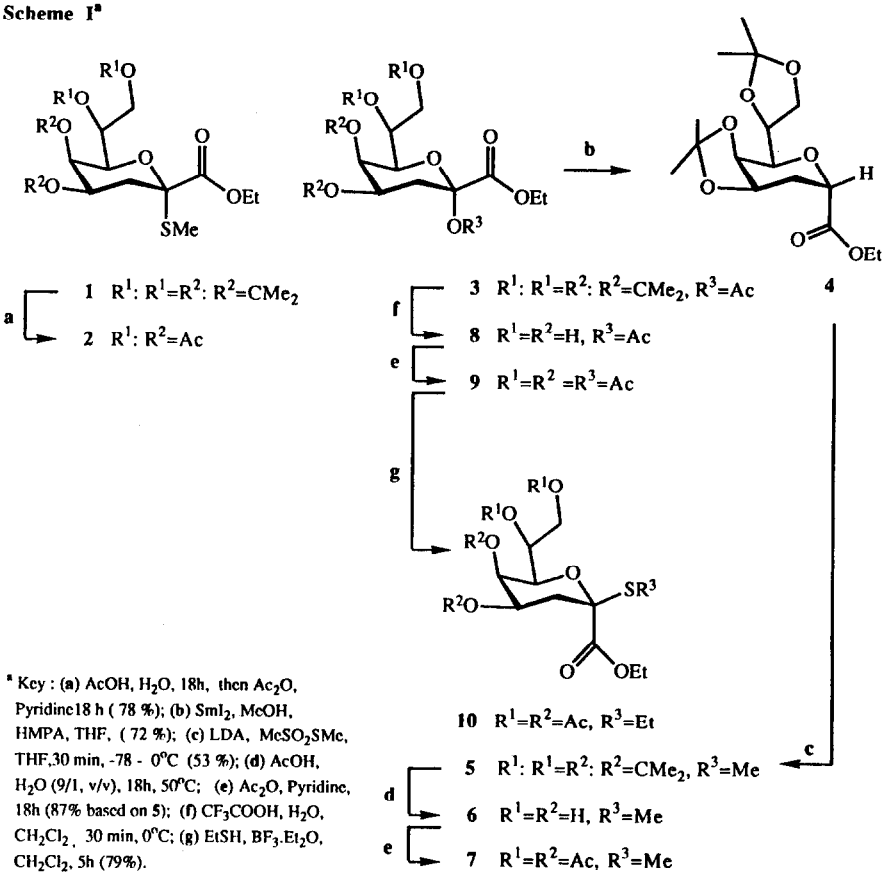
Recently, the structures of the oligosaccharides (core region) of most LPS immunotypes (L1-L7 and L-9) of *Neisseria meningitidis*, which are associated with group B and C meningococcal organisms (L1-L9), have been elucidated[3]. The outcome of this study revealed that the core consists of a structurally invariant outer-core lacto-N-neotetraose region and an inner-core showing micro-heterogenicity. In addition, it was concluded[4], that the epitopes responsible for LPS immunotype specificity and cross reactivity reside largely in the L-*glycero*-D-*manno*-heptose (LD-Hep*p*) and 2-keto-3-deoxy-D-*manno*-octulosonic acid (KDO) containing inner-core region.

As part of a program[5,6] directed toward the development of a broadly protective synthetic vaccine against *Neisseria meningitidis*, we now report the synthesis of the dimer L-α-D-Hep*p*-(1→5)-α-KDO-2-*O*-$(CH_2)_3NH_2$ (**37**) and tetramer ß-D-Gal*p*-(1→4)-ß-D-Glc*p*-(1→4)-L-α-D-Hep*p*-(1→5)-α-KDO-2-*O*-$(CH_2)_3NH_2$ (**47**), containing an α-linked spacer suitable for conjugation with macromolecular carriers.

The synthetic strategy to the target di- and tetrasacchararide **37** and **47**, respectively, entails the following distinct phases. The first one deals with the transformation of KDO derivatives into methyl(ethyl) 2-thio-KDO donors (*i.e.*

1,2,5 and 7 in Scheme I), and a study of the stereochemical outcome of iodionium ion mediated condensations of these donors with the artificial spacer 3-(benzyloxycarbonyl-amino)-1-propanol[7] (*i.e.* **11**). The next phase implies the preparation (Scheme II) of the acceptor α-KDO-*O*-$CH_2CH_2CH_2NHZ$ (*i.e.* **23**), which is a key precursor for the introduction of the requisite KDO-unit at the reducing end of dimer **37** and tetramer **47**. In the third one, readily accessible L-D-Hep*p* derivatives will be converted (Scheme III) *via* protection-deprotection-techniques into the ethyl

Scheme I[a]



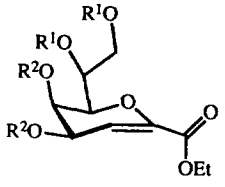
[a] Key : (a) AcOH, H_2O, 18h, then Ac_2O, Pyridine18 h (78 %); (b) SmI_2, MeOH, HMPA, THF, (72 %); (c) LDA, $MeSO_2SMe$, THF,30 min, -78 - 0°C (53 %); (d) AcOH, H_2O (9/1, v/v), 18h, 50°C; (e) Ac_2O, Pyridine, 18h (87% based on 5); (f) CF_3COOH, H_2O, CH_2Cl_2, 30 min, 0°C; (g) EtSH, $BF_3.Et_2O$, CH_2Cl_2, 5h (79%).

2-thio-L-D-Hep*p* donor **26** and acceptor **33**. Finally, the condensation of the appropriate L-D-Hep*p* and KDO building units to give dimer **37** (Scheme IV) and tetramer **47** (Scheme V) will be elaborated in the last two phases.

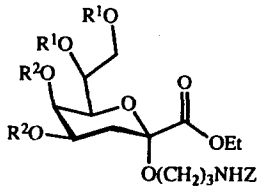
The preparation of the anomerically pure α and β methyl 2-thio-KDO donors **1**, **2** and **5**, **7**, respectively, which will be used to explore iodonium ion promoted glycosylations[8,9] of spacer **11** is presented in Scheme I. Thus, deacetonation of the readily accessible donor methyl 4:5,7:8-di-O-isopropylidene-2-thio-α-D-*manno* octulopyranosonate[10] (**1**) gave, after acetylation, KDO-donor **2** in an excellent yield. The synthesis of the β-anomers **5** and **7** could be realized as follows. Deacetoxylation of the known[6a] KDO-derivative **3** *via* a SmI_2-induced electron transfer process, as reported recently by Kuseda *et al.*[11], gave predominantly **4** as evidenced by the fact that its spectral data (optical rotation and ^{13}C-NMR) were in complete accordance with those of the same epimer prepared earlier by Claesson[12]. On the other hand, the spectral data (^1H- and ^{13}C-NMR) of the epimer of **4** were in excellent

agreement with those of the product obtained by Norbeck *et al.*[13] *via* hydrogenation of the KDO-glycal **12**. In the next step, the lithium enolate from **4** and its epimer generated by treatment with lithium diisopropylamide (LDA) was quenched with methylthiomethane-sulfonate[14] to give, after separation of the anomeric mixture by silica gel chromatography, homogeneous β-isomer **5**. Deacetonation (→ **6**) and acetylation afforded the anomerically pure KDO-donor **7** in 33% overall yield (based on **3**).

Having the anomerically pure 2-thio-KDO donors in hand, we next explored the stereochemical outcome of iodonium ion assisted glycosidations of these donors with acceptor **11**. Recently, we reported[9] that alkyl 1-thio-glycosides having a non participating C-2 ether function (*i.e.* armed donor) could be coupled chemoselectively in the presence of iodonium *sym.*-dicollidine perchlorate (IDCP) with alkyl 1-thio-glycosides bearing a C-2 participating ester

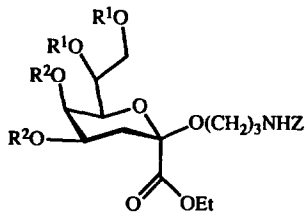


12 $R^1{:}R^1 = R^2{:}R^2 = CMe_2$



13 $R^1{:}R^1{=}R^2{:}R^2{=}CMe_2$

14 $R^1{=}R^2{=}Ac$



15 $R^1{:}R^1{=}R^2{:}R^2{=}CMe_2$

16 $R^1{=}R^2{=}Ac$

$HO(CH_2)_2NHZ$

11

(*i.e.* disarmed acceptor) to give predominantly 1,2-*cis* glycosides. It was also established[9] that a disarmed alkyl 1-thio-glycoside could be coupled with an appropriate acceptor, under the agency of the more thiophilic promoter N-iodosuccinimide (NIS) and catalytic triflic acid (TfOH),to yield exclusively 1,2-*trans* glycosides. On the basis of this knowledge it was to be expected that the methyl 2-thio function present in the KDO-donors **1**, **2**, **5**, and **7** would be virtually inactive, due to the presence of the electron withdrawing ester function at C-2, to the mild thiophilic promoter IDCP. Indeed, IDCP assisted condensation of KDO-donors **2** and **7** with spacer **11** did not give any trace of the respective glycosides **14** and **16**. Similarly, no glycosidation product could be detected in the glycosidation of the diacetonide-2-thio-α-KDO **1** with **11**, however, nearly quantitative formation of the known KDO-glycal **12** was observed. Interestingly, in the case of the corresponding β-KDO donor **5** a low yield (28%) of the glycosides **13** and **15** (α:β = 2:1) and glycal **12** (48%) was obtained.

The results on the NIS/TfOH cat. mediated glycosidations of the anomerically pure 2-thio-KDO donors **1**,**2**,**5** and **7** with spacer **11** are summarized in Table 1. It is evident that the iodonium ion-promoted condensations of the diacetonide KDO donors **1** and **5** with aglycon **11** (entries **1-4**) proceed less effectively than the fully acetylated donors **2** and **7** (entries **5-6**). The relatively low yield obtained with donors **1** and **5** is mainly due to the concomitant generation of glycal **12**. The formation of the latter elimination product may be attributed to the conformational restraint induced by the 4,5-acetonide function[15] in **1** and **5**. In addition, the solvent acetonitrile exerts a rather low effect[16] on the stereochemical outcome of the acetals **1** and **5** (entries **3-4**).

Finally, it is noteworthy that condensation of acceptor **11** with the torsional-free donor **7** proceeded, in contrast with

Table I. Data on the NIS/TfOH promoted glycosylation of acceptor **11** by the KDO donors **1**,**2**,**5**,**7** and **20**.

Entry	Donor	Solvent	Glycoside	Yield%	α/β Ratio
1	**1**[c]	DCE/Ether[a]	**13**α + **15**β	52[b]	2:1
2	**5**[c]	DCE/Ether[a]	**13**α + **15**β	57[b]	2:1
3	**1**[c]	MeCN	**13**α + **15**β	53[b]	1:1
4	**5**[c]	MeCN	**13**α + **15**β	57[b]	1:1
5	**2**[c]	DCE/Ether[a]	**14**α + **16**β	77	1:1
6	**7**[c]	DCE/Ether[a]	**16**β	78	
7	**20**[d]	DCE/Ether[a]	**21**α + **22**β	81	1:2.5
8	**20**[d]	MeCN	**21**α + **22**β	79	3:1

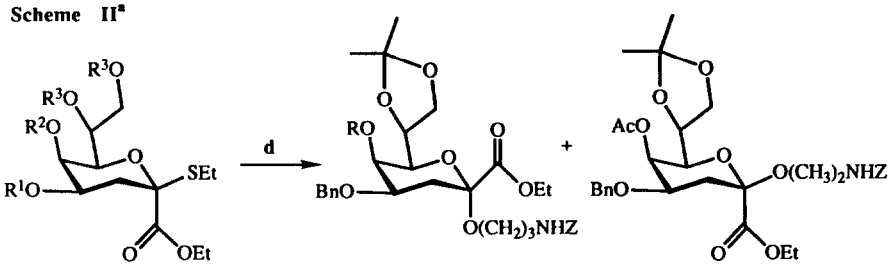
[a] Ratio 1:1, v/v (DCE = 1,2-dichloroethane). [b] Glycosylation was accompanied by the formation of the glycal **12**. [c] Glycosylation was executed at -25°C or (d) at 0°C.

the corresponding donor **2** (entry **5**), with retention of configuration.

We now, after having gained some insight into the factors which may influence the stereochemical outcome and yield of an iodonium ion-promoted glycosidation of the KDO donors **1**, **2**, **5** and **7** by the rather reactive acceptor **11**, turned our attention to the synthesis of the KDO-synthon **20**. To this end, the diacetonide **3** (Scheme I) was transformed by acidic hydrolysis and acetylation of **8** followed by treatment of fully acetylated **9** with ethanethiol, under the agency of boron trifluoride etherate, into the anomerically pure ethyl 2-thio-β-KDO derivative **10**. Zemplén deacetylation of **10** gave **17** which was transformed, as presented in Scheme II, into **20**. Thus kinetically controlled acetonation[17] of **17** and subsequent stannylidene-assisted regioselective benzylation[18] of **17** gave, after acetylation of the axially orientated hydroxyl group at C-4, key donor **20** in 30% yield (based on **17**). Iodonium ion-mediated glycosidation of **20** by **11** resulted mainly in the formation of the non-required β-glycoside **22** (entry **7** in Table 1). Fortunately, the use of the solvent acetonitrile had a beneficial effect on the formation of the requisite α-glycoside **21**, the deacetylation of which afforded key KDO-acceptor **23**.

The preparation of the two ethyl 1-thio-α-LD-Hep*p* donors **26** and **33** starting from the corresponding known chloride[5a] and bromide[5c] derivatives **24** and **27**, respectively, is outlined in Scheme III. Thus, *in situ* conversion of **24** with ethanethiol and potassium *t*-butoxide gave, after benzoylation, the homogeneous donor **26**. In this respect, it is of interest to note that the anchimeric assistance of a benzoyl instead of an acetyl group in donor **26** exerts, as reported earlier[19], a beneficial effect on the yield of an iodonium ion-promoted 1,2-*trans* glycosylation. On the other hand, donor **33** was obtained by the following protecting group manipulations. In the first place, bromide **27** was

Scheme II[a]



a ⟶ **17** $R^1=R^2=R^3=H$
a ⟶ **18** $R^1=R^2=H$, R^3: $R^3=CMe_2$
b ⟶ **19** $R^1=Bn$, $R^2=H$, R^3: $R^3=CMe_2$
c ⟶ **20** $R^1=Bn$, $R^2=Ac$, R^3: $R^3=CMe_2$

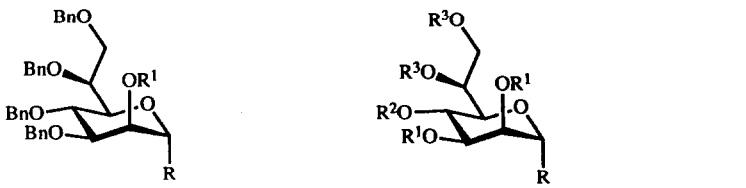
e ⟶ **21** R=Ac
e ⟶ **23** R=H

22

[a] Key: (a) $H_2C=C(OMe)CH_3$, PTSOH, DMF, 0°C, 1h, (57 %); (b) Bu_2SnO, Toluene, 2h reflux , then BnBr, CsF, DMF, 18 h, (81%); (c) Ac_2O, DMAP, Pyridine, CH_2Cl_2 ,18h (79%); (d) **11** , NIS, TfOH (cat.), MeCN, 0°C, 5 min (81%), (e) EtOH, KO*t*Bu, 45 min (77 %).

converted into the ethyl 1-thio-α-LD-Hepp derivative **28** under the same conditions mentioned above for **24** → **25**. Deacetonation (→ **29**) followed by the introduction of the 4-methoxybenzyl (MBn) group (→ **30**), and selective acidic hydrolysis of the 6,7-O-isopropylidene function, afforded intermediate **31**. Finally, benzylation (→ **32**) and subsequent removal of the MBn group with DDQ[20] gave the key synthon **33** in 20% yield for the six steps.

Scheme III[a]

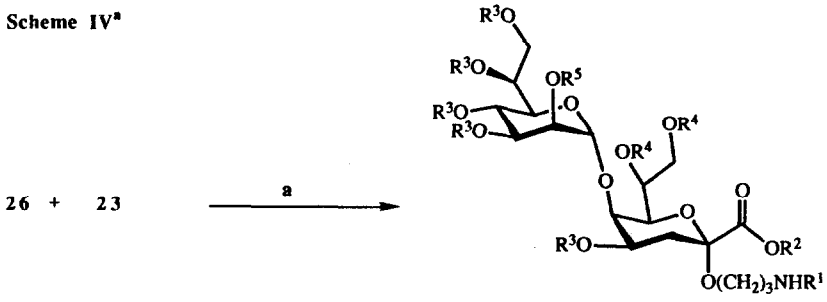


a ⟶ **24** R=Cl, R^1=Ac
a ⟶ **25** R=SEt, R^1=H
b ⟶ **26** R=SEt, R^1=Bz

a ⟶ **27** R=Br, $R^1=R^2=R^3$=Ac
a ⟶ **28** R=SEt, $R^1=R^2=R^3=H$
c ⟶ **29** R=SEt, R^1: $R^1=R^3$: $R^3=CMe_2$, $R^2=H$
d ⟶ **30** R=SEt, R^1: $R^1=R^3$: $R^3=CMe_2$, R^2=MBn
e ⟶ **31** R=SEt, R^1: $R^1=CMe_2$, R^2=MBn, $R^3=H$
f ⟶ **32** R=SEt, R^1: $R^1=CMe_2$, R^2=MBn, R^3=Bn
g ⟶ **33** R=SEt, $R^1=CMe_2$, $R^2=H$, R^3=Bn

[a] Key: (a)EtSH, KO*t*Bu, ethyl acetate, MeOH, 15 min; (b)BzCl, pyridine, 16h (68% based on 24); (c) $(MeO)_2CMe_2$, acetone, PTSOH, 18h (58% based on 27); (d) MBnCl, NaH, $(n\text{-}Bu)_4NI$, DMF, 0° → 20°C (73%); (e) AcOH, H_2O (7/3, v/v), 5h (65%); (f) BnBr, NaH, DMF, 0° → 20°C, 3h (89%); (g) DDQ, CH_2Cl_2, H_2O (9/1, v/v), 45 min (81%).

Scheme IV[a]



[a] Key: (a) NIS, TfOH (cat.), CH_2Cl_2/ Et_2O (1/1, v/v),5 min, 0°C (87%); (b) AcOH/H_2O (4/1, v/v), 2h, 50° (96%); (c) Dioxane McOH/4N NaOH (29/9/2, v/v), 3h (95%), (d) H_2 , Pd/C/H_2' *iso*-propanol, AcOH, 48 h (60%).

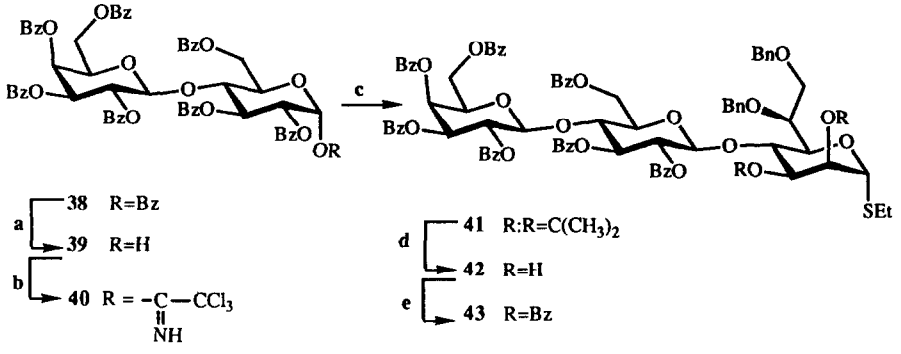
b → **34** R^1=Z, R^2=Et, R^3=Bn, R^4:R^4=$C(CH_3)_2$, R^5=Bz

b → **35** R^1=Z, R^2=Et, R^3=Bn, R^4=H, R^5=Bz

c → **36** R^1=Z, R^2 =R^5 =H, R^3=Bn

d → **37** R^1=R^2=R^3=R^4=R^5=H

Scheme V[a]



a → **38** R=Bz

a → **39** R=H

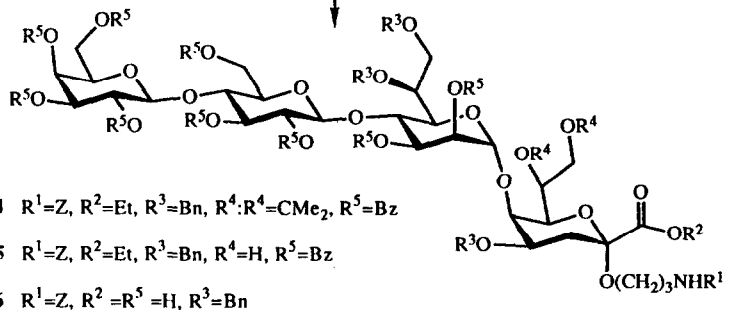
b → **40** R = $-C(=NH)-CCl_3$

d → **41** R:R=$C(CH_3)_2$

d → **42** R=H

e → **43** R=Bz

f



g → **44** R^1=Z, R^2=Et, R^3=Bn, R^4:R^4=CMe_2, R^5=Bz

g → **45** R^1=Z, R^2=Et, R^3=Bn, R^4=H, R^5=Bz

h → **46** R^1=Z, R^2 =R^5 =H, R^3=Bn

i → **47** R^1=R^2=R^3=R^4=R^5=H

[a] Key: (a) Me_2NH, MeCN, 18h (90%); (b) CCl_3CN, NaH, CH_2Cl_2, 30 min, 0°C (72%); (c) 33,TMSOTf, CH_2Cl_2, 30 min, 10°C (76%); (d) AcOH, H_2O (4/1, v/v), 8h, 50°; (e) BzCl, pyridine, 18h (91% based on 41); (f) 23, NIS, TfOH (cat.), CH_2Cl_2/Et_2O (1/1, v/v), 5 min, 0°C (55%); (g) AcOH/H_2O (9/1, v/v), 8h, 50°C (82%); (h) Dioxane, MeOH, 4N NAOH (29/9/2, v/v/v), 3h; (i) Pd/C/H_2, *iso*-propanol, AcOH, 48h (20%).

The iodonium ion (NIS/TfOH cat.) promoted 1,2-*trans* glycosidation of the LD-Hepp donor **26** by the KDO acceptor **23** (see Scheme IV) gave, as expected the fully protected disaccharide **34**, which was completely deprotected by the following three-step procedure. Thus, deacetonation (**34**→**35**), debenzoylation (→**36**) and catalytic hydrogenolysis of the benzyloxycarbonyl and benzyl groups gave, after purification by Sephadex-S100 column chromatography, the homogeneous disaccharide **37**. The identity of dimer **37** was, as gauged by ^{1}H- and ^{13}C-NMR as well as FAB mass spectroscopy, in excellent agreement with the proposed structure.

The assembly of the tetrasaccharide **47** is outlined in Scheme V and commences with the removal of the benzoyl group at the anomeric centre of the fully benzoylated lactose **38** and conversion of **39** into the α-trichloroacetimidate **40** *via* a well-established procedure[21]. Glycosylation of the LD-Hepp acceptor **33** by **40** in the presence of the promotor trimethylsilyl triflate[22] gave, after work-up and purification, the fully protected trimer **41**. Deacetonation (→**42**) followed by benzoylation furnished trimer **43** , the ethyl 1-thio function and neighbouring benzoyl group of which will secure the formation of the second 1,2-*trans* glycosidic linkage. Indeed, NIS/TfOH cat. promoted condensation of **43** with KDO acceptor **23** gave, after purification, by Sephadex LH-20 column chromatography , the ß-linked tetramer **44** in an acceptable yield. Deacetonation (→**45**) and deesterification (→**46**) followed by catalytic hydrogenation gave after purification, homogeneous tetramer **47**, the structure of which was unambiguously ascertained by ^{1}H- and ^{13}C-NMR as well as FAB mass spectroscopy.

In conclusion, the results presented in this paper indicate that the stable and readily accessible methyl(ethyl) 2-thio-KDO (*i.e.* **1**, **2**, **5**, **7** and **10**) and ethyl 1-thio-LD-Hepp (*i.e.* **26** and **43**) derivatives are suitable donors in iodonium ion (NIS/TfOH cat.) promoted glycosylation reactions. The latter aspect is *inter alia* nicely illustrated by the successful introduction of the α(1→5) interglycosidic linkage in dimer **37** and tetramer **47**. Further, the above referenced KDO derivatives may present an attractive alternative for the thus far used halogen-KDO donors (*i.e.* fluorides[23] or bromides[24]).

Experimental

General methods. - Acetonitrile and pyridine were dried by refluxing with CaH_2 (5 g/l) and then distilled. Dichloromethane and toluene were distilled from P_2O_5. Acetonitrile, pyridine and dichloromethane were stored over molecular sieves 4Å (Aldrich) and toluene over sodium wire. Reactions were performed at ambient temperature unless noted otherwise. Silica gel 60 (Merck 70-230 mesh) was used for column chromatography. TLC was conducted on DC Fertigfolien (Schleicher & Schüll F 1500 LS 254). Compounds were detected by charring with 20% sulfuric acid in methanol or by spraying with a solution of potassium permanganate (1%, w/v) in aqueous sodium carbonate (2% w/v). Optical rotations were determined with a Perkin-Elmer Model 242 polarimeter. NMR spectra were recorded with a Jeol JNM-FX 200 (^{13}C, 50.1 MHz, internal Me_4Si) and a Brucker WM-300 spectrometer equipped with an Aspect-2000 computer (^{1}H, 300 MHz Me_4Si).

Ethyl [methyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-2-thio-α-D-*manno*-octulopyranosid]onate (2) - A solution of compound **1** (0.38 g, 1.0 mmol) in acetic acid/water (9/1, v/v, 10 mL) was stirred for 18 h at 50°C. TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) showed complete conversion of the starting material into a more hydrophillic product. The reaction mixture was diluted with toluene (10 mL) and the solvents were evaporated under reduced pressure. The oily residue was dissolved in toluene and concentrated (4x 10 mL). The crude product was dissolved in CH_2Cl_2 (10 mL) and treated with pyridine (5 mL) and acetic anhydride (5 mL) and a catalytic amount of 4-dimethylaminopyridine. After stirring for 18 h, the reaction mixture was diluted with toluene (10 mL) and the solution

was concentrated *in vacuo*. The resulting syrup was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous sodium bicarbonate (10 mL, 10%), water (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was purified by silica gel (5 g) column chromatography. Elution of the column was effected with CH_2Cl_2. Concentration of the appropriate fractions gave **2** as an oil. Yield 0.40 g (87 %), R_f 0.8 (acetone/CH_2Cl_2, 3/97, v/v), $[\alpha]_D$ (c , $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ 170.2, 170.1, 169.6. 169.4 (C=O, Ac), 168.4 (C-1), 84.6 (C-2), 68.1, 67.2, 66.8, 64.1 (C-4, C-5, C-6, C-7), 61.9, 61.7 (C-8, CH_2, OEt), 31.4 (C-3), 20.5, 20.4 (CH_3, Ac), 13.7, 11.3 (CH_3, OEt, CH_3S).

Ethyl 2,6 anhydro-3-deoxy-4,5:7,8-di-isopropylidene-D-*glycero*-D-*talo*-octonate (4) - A solution of SmI_2 in THF (0.1 mM, 45 mL) was added dropwise during 30 min, under a blacket of nitrogen, to a stirred solution of compound **3** (0.63 g, 1.6 mmol) in THF (15 mL), methanol (0.1 mL) and HMPA (2.4 mL). After an additional 30 min, TLC analysis showed complete conversion of **3** into **4**. The mixture was exposed to air to quench excess SmI_2. The mixture was diluted was CH_2Cl_2 (100 mL) and washed with water. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The syrup was applied onto a column of silica gel (15 g) and elution was effected with CH_2Cl_2 followed by CH_2Cl_2/acetone (1/99, v/v) to afford **4**. Yield 0.52 g (72 %), R_f 0.8 (acetone/CH_2Cl_2, 3/97, v/v). ^1H NMR ($CDCl_3$): δ 4.59 (dt, 1H, H-4, $J_{3a,4}$ $J_{3b,4}$ 3.1 Hz, $J_{4,5}$ 8.0 Hz), 4.53 (dd, 1H, H-2, $J_{2,3a}$ 6.0 Hz, $J_{2,3b}$ 11.4 Hz, 4.34 (dd, 1H, H-5, $J_{5,6}$ 1.7 Hz), 4.24 - 4.10 (m, 5H, H-7, H-8a,b, CH_2, OEt), 3.51 (dd, 1H, H-6), 2.32 (ddd, $J_{3a,3b}$ 15.0 Hz), 1.86 (ddd, 1H, H-3b), 1.29 (t, 3H, CH_3, OEt); ^{13}C NMR ($CDCl_3$): δ 168.4 (C-1), 109.2, 109.1 (Cq, isoprop), 73.5, 72.6, 72.1, 69.6, 68.2 (C-2, C-4, C-5, C-6, C-7), 67.0 (C-8), 60.8 (CH_2, OEt), 30.5 (C-3), 26.9, 26.0, 24.9, 24.8 (CH_3, isoprop), 14.1 (CH_3, OEt).

Ethyl [methyl 3-deoxy-4,5:7,8-di-*O*-isopropylidene-2-thio-ß-D-*manno*-octulopyranosid]onate (5) - Compound **4** (1.0 g, 3.0 mmol) was dissolved in THF (20 mL) and placed under a blanket of N_2. To the cooled solution (-78°C) was added dropwise a solution of lithium diisopropylamide (LDA) in cyclohexane (2.1 mL, 1.6 M). The temperature was allowed to rise to -20°C in 20 min. Subsequently, the reaction mixture was cooled to -78°C and treated with $MeSO_2SMe$ (3.9 mmol) in THF (1 mL). After the resulting mixture was warmed up to 20°C, it was poured into aqueous NH_4Cl (10 mL, 20%, w/v) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was applied onto a column of silica gel (15 g) and elution was effected with CH_2Cl_2 followed by CH_2Cl_2/acetone (1/99, v/v). Concentration of the appropriate fractions afforded **5** as an oil. Yield 0.60 g (53 %), R_f 0.45 (light petroleum/ether, 1/1, v/v). ^1H NMR data ($CDCl_3$): δ 4.22 (m, H-4, H-5, H-7, H-8a,b, CH_2, OEt), 3.45 (dd, 1H, H-6, $J_{5,6}$ 2.3 Hz, $J_{6,7}$ 8.4 Hz), 2.53 (dd, 1H, H-3a, $J_{3a,3b}$ 14.1, $J_{3a,4}$ 5.7 Hz), 2.16 (s, 3H, CH_3, SEt), 1.98 (dd, 1H, H-3b, $J_{3b,4}$ 6.7 Hz), 1.63, 154, 1.41, 1.37 (4x CH_3, isoprop); ^{13}C NMR data ($CDCl_3$): δ 168.7 (C-1), 109.1, 109.1 (2x Cq, isoprop), 81.6 (C-2), 74.1, 73.6, 70.4, 70.0 (C-4, C-5, C-6, C-7), 66.7 (C-8), 61.5 (CH_2, OEt), 34.3 (C-3), 27.4, 26.8, 25.9, 25.0, (4x CH_3, isoprop), 13.9 (CH_3, OEt), 11.7 (SCH_3). Further elution of the column gave **1**. R_f 0.40 (light petroleum/ether, 1/1, v/v). Yield 0.32 g (28 %), R_f 0.40 (light petroleum/ether, 1/1, v/v), $[\alpha]_D$ +125.0 (c 1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 4.52 (ddd, 1H, H-4), 4.35 (m, 2H, H-5, H-7), 4.28 (m, 2H, CH_2, OEt), 4.16 (m, 1H, H-8a, 3.95 (dd, 1H, H-8b, $J_{8a,8b}$ 8.5 Hz, $J_{7,8b}$ 4.5 Hz), 3.62 (dd, 1H, H-6, $J_{5,6}$ 1.8 Hz, $J_{6,7}$ 8.0 Hz), 3.00 (dd, 1H, H-3a, $J_{3a,3b}$ 15.2 Hz , $J_{3a,4}$ 3.8 Hz), 2.06 (s, 3H, SCH_3), 1.83 (dd, 1H, H-3b, $J_{3b,4}$ 2.6 Hz), 1.42 (t, 3H, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 168.9 (C-1), 109.5, 109.0 (2x Cq, isoprop), 82.9 (C-2), 73.3, 72.3, 71.2, 70.2 (C-4, C-5, C-6, C-7), 66.9 (C-8), 61.3 (CH_2, OEt), 32.2 (C-3), 26.7, 25.5, 25.0, 24,9, (4x CH_3, isoprop), 14.0 (CH_3, OEt), 10.9 (SMe).

Ethyl [methyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-2-thio-ß-D-*manno*-octulopyranosid]onate (7) - A solution of compound **5** (0.38 g, 1.0 mmol) in acetic acid/water (9/1, v/v, 10 mL) was stirred for 18 h at 50°C. TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) showed complete conversion of starting material into a more hydrophilic product. The reaction mixture was diluted with toluene (10 mL) and concentrated. The residue was dissolved in toluene and evaporated to dryness (4 x 10 mL). Crude **6** was dissolved in CH_2Cl_2 (10 mL) and treated with pyridine (5 mL), acetic anhydride (5 mL) and a catalytic amount of 4-dimethylaminopyridine. After the reaction mixture was stirred for 18 h at 20°C, it was diluted with toluene (10 mL) and the solution was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (50 mL), washed with aqueous sodium bicarbonate (10 mL, 10%), water (10 mL) and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was purified by silica gel (5 g) column chromatography. Elution of the column was effected with CH_2Cl_2 and concentration of appropriate fractions gave **7** as an oil. Yield 0.40 g (87 %), R_f 0.8 (acetone/CH_2Cl_2, 3/97, v/v), $[\alpha]_D$ +19.0 (c 2, $CHCl_3$). ^{13}C NMR data ($CDCl_3$): δ 170.2, 170.0, 169.4 169.2 (4x C=O, Ac), 167.1 (C-1), 82.8 (C-2), 71.6, 67.5, 66.9, 63.7 (C-4, C-5, C-6, C-7), 61.9, 61.8 (C-8, CH_2, OEt), 31.9 (C-3), 20.3 (CH_3, Ac), 13.8 (CH_3, OEt), 11.3 (CH_3S).
Anal. Calcd. for $C_{19}H_{28}O_{11}S$: C 49.13, H 6.08; found: C 48.56, H 5.91%.

Ethyl [2,4,5,7,8-penta-*O*-acetyl-3-deoxy-ß-D-*manno*-octulopyranos]onate (9) - Compound **3** (0.93 g, 2.4 mmol) was dissolved in a cooled (0°C) mixture of CH_2Cl_2 (9 mL) and aqueous trifluoroacetic acid (95%, 1 mL). The solution was stirred for 30 min at 0°C and then diluted with toluene (10 mL) and concentrated under reduced pressure. The resulting oil was redissolved in toluene (4x 10 mL) and concentrated. Crude **8**, thus obtained, was acetylated with pyridine (2 mL) and acetic anhydride (2 mL) for 18 h at room temperature. The reaction mixture was diluted with toluene (5 mL) and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (20 mL), washed with aqueous sodium bicarbonate (5 mL, 10%) and water (5 mL). The dried ($MgSO_4$) organic phase was concentrated to an oil which was purified by silica gel column chromatography (10 g). Elution of the column was effected with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, 1/49, v/v). The appropriate fractions were concentrated *in vacuo* to give **9** as an oil. Yield 0.81 g, (73%), R_f 0.5 (acetone/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.8, 168.7, 168.3, 168.0, 164.6 (C=O, Ac), 166.6 (C-1), 96.0 (C-2), 68.3, 66.0. 64.6, 62.7 (C-4, C-5, C-6, C-7), 62.8, 62.7 (C-8, CH_2, OEt), 29.6 (C-3), 19.1 (CH_3, Ac), 12.6 (CH_3, OEt).

Ethyl [ethyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-2-thio-ß-D-*manno*-octulopyranosid]onate (10) To a solution of **9** (1.2 g, 2.6 mmol) and ethanethiol (0.22 mL, 3.0 mmol) in CH_2Cl_2 (10 mL) was added boron trifluoride etherate (0.21 mL, 2.9 mmol). After stirring for 5 h, TLC analysis showed (acetone/CH_2Cl_2, 3/97, v/v) complete conversion of the starting material (R_f 0.6) into a more lipophilic product (R_f 0.8). The reaction mixture was neutralized with pyridine, diluted with CH_2Cl_2 (20 mL) and washed with aqueous sodium bicarbonate (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The oil thus obtained was applied onto a column of silica gel (15 g) and eluted with CH_2Cl_2. Concentration of the appropriate fractions afforded **10** as an oil. Yield 0.95 g (79 %), R_f 0.8 (acetone/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.8, 168.7, 168.3, 168.0 (C=O, Ac), 166.6 (C-1), 82.8 (C-2), 71.9, 67.7, 67.1, 63.9 (C-4, C-5, C-6, C-7), 62.8, 62.7 (C-8, CH_2, OEt), 29.6 (C-3), 20.0 (CH_3, Ac), 14.2, 14.1 (CH_3, OEt, CH_3S).
Anal. Calcd. for $C_{20}H_{30}O_{11}S$: C 50.20, H 6.32; found: C 50.57, H 6.06%.

***General procedures for iodonium ion mediated glycosylation reactions*:**

Method A: A mixture of methyl thioglycoside (0.32 mmol) and acceptor **11** (84 mg, 0.4 mmol) in 1:5 1,2 dichloroethane-diethylether (2.5 mL) was stirred with powdered molecular sieves (0.5 g, 4Å) for 30 min. IDCP (0.35 mmol) was added while stiring was continued for 2h. The reaction mixture was filtered, diluted with CH_2Cl_2 (25 mL) and extracted with aqueous $Na_2S_2O_3$ (1M, 2x 10 mL) and water. The organic phase was dried, concentrated under reduced pressure, and purified by silica gel (1 g) chromatography.

Method B: To a solution of alcohol **11** (84 mg, 0.40 mmol) and methyl(ethyl) 2-thioglycoside (0.32 mmol) in 1,2 dichloroethane/diethylether (1/1, v/v, 1 mL) was added activated molecular sieves (0.5 g, 4Å). The mixture was stirred at ambient temperature under an atmosphere of nitrogen and then cooled to (0°C or -25°C). A freshly prepared solution of *N*-iodosuccinimide (54 mg, 0.38 mmol) and trifluoromethanesulfonic acid (0.05 mmol) in 1,2 dichloroethane/ether (1/1, v/v, 4 mL) was added. After stirring for 5 min, the mixture was treated with pyridine (one drop) and filtered. The filtrate was diluted with CH_2Cl_2 (15 mL) and washed successively with aqueous sodium thiosulfate (5 mL, 20%), aqueous sodium bicarbonate (5 mL) and water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1 g).

Method C: A mixture of alcohol **11** (84 mg, 0.40 mmol), methyl 2-thioglycoside (0.32 mmol) and activated molecular sieves (0.5 g, 4Å) in acetonitrile (2 mL) was stirred at ambient temperature under an atmosphere of nitrogen. To the cooled (-25°C) solution was added *N*-iodosuccinimide (85.5 mg, 0.38 mmol) and trifluoromethanesulfonic acid (0.05 mmol). After stirring for 2 min at -25°C, TLC analysis revealed complete disappearance of **5**. The reaction was quenched by the addition of pyridine and filtrated. The filtrate was diluted with CH_2Cl_2 (15 mL) and washed successively with aqueous sodium thiosulfate (5 mL, 20%), aqueous sodium bicarbonate (5 mL) and water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1 g).

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 3-deoxy-4,5:7,8-di-*O*-isopropylidene-α/ß-D-*manno*-octulopyranosid]onate (13 and 15).

Analytical data of compound **13**: R_f 0.35 (acetone/CH_2Cl_2, 3/97, v/v), $[\alpha]_D$ +21.4 (c 2, $CHCl_3$.) ^1H NMR data ($CDCl_3$): 7.12-7.35 (5H, H-arom), 5.27 (bs, 1H, NH, spacer), 5.09 (s, 2H, CH_2, Z), 4.47 (m, 1H, H-4), 4.35 (q, 1H, H-7, $J_{6,7}$ $J_{7,8a}$ $J_{7,8b}$ 5.9 Hz), 4.24 (m, 3H, H-5, CH_2, OEt), 4.10 (m, 2H, H-8a,b), 3.75, 3.25 (2x m, 2H, CH_2O, spacer), 3.62 (dd, 1H, H-6, $J_{5,6}$ 1.9), 3.28 (m, 2H, CH2N, spacer), 2.77 (dd, 1H, H-3a, $J_{3a,3b}$ 15.4 Hz, $J_{3a,4}$ 3.9 Hz), 1.81 (dd, 1H, H-3b, $J_{3b,4}$ 1.0 Hz), 1.72 (m, 2H, CH_2, spacer), 1.42, 1.40, 1.29 (12H, CH_3, isoprop), 1.28 (t, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 168.9 (C-1), 165.5 (C=O, Z), 128.4, 128.1, 128.0 (CH, arom), 74.2, 72.0, 71.0, 70.1 (C-4, C-5, C-6, C-7), 66.5 (C-8), 61.6, 60.5 (CH_2, OEt, CH_2, Z), 38.8 (CH_2N), 32.9 (C-3), 25.2 (CH_2, spacer), 26.6, 25.5, 25.9, 25.4 (4x, CH_3, isoprop).

Anal. Calcd. for $C_{27}H_{39}O_{10}N$: C 60.32, H 7.31; found: C 59.44, H 6.88%.

Analytical data of compound **15**: R_f 0.40 (acetone/CH_2Cl_2, 3/97, v/v), $[\alpha]_D$ -1.0 (c 1, $CHCl_3$.) ^1H NMR data ($CDCl_3$): δ 7.32 (5H, H-arom), 5.62 (t, 1H, NH, spacer, $J_{NH,CH2}$ 5.9 Hz), 5.08 (AB, 2H, CH_2, Z), 4.55 (ddd, 1H, H-4), 4.31-4.00 (m, 5H, H-5, H-8a,b, CH_2, OEt), 3.79 (m, 1H, H-7), 3.48 (dd, H-6, $J_{5,6}$ 2.0 Hz, $J_{6,7}$ 8.0 Hz), 3.67 (m, OCH_2, spacer), 3.36 (m, 2H, NCH_2, spacer), 2.32 (dd, 1H, H-3a, $J_{3a,3b}$ 15.5 Hz, $J_{3a,4}$ 3.6 Hz), 1.89 (dd, 1H, H-3b, $J_{3b,4}$ 3.8 Hz), 1.71 (m, CH_2, spacer), 1.47, 1.41, 1.34, 1.29 (4x s, 4x CH_3, isoprop), 1.26 (t, 3H, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 168.9 (C-1), 165.5 (C=O, Z), 128.3, 128.2, 127.9 (CH, arom), 98.3 (C-2), 73.7, 71,3, 69.9, (C-4, C-5, C-6, C-7), 66.8 (C-8), 62.6, 60.4 (CH_2, OEt, CH_2, Z), 32.8 (C-3), 29.1 (CH_2, spacer), 27.0, 26.4, 25.1, 24.7 (4x, CH_3, isoprop), 14.2 (CH_3, OEt).

Anal. Calcd. for $C_{27}H_{39}O_{10}N$: C 60.32, H 7.31; found: C 59.67, H 6.90%.

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 4,5,7,8-tetra-*O*-acetyl-3-deoxy-α/ß-D-*manno*-octulopyranosid]onate (14 and 16)

Analytical data of compound **16**: R_f 0.35 (acetone/CH_2Cl_2, 1/19, v/v), $[\alpha]_D$ +25.6 (c 1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 7.31 (5H, H-arom), 5.28 (t, 1H, H-5), 5.16 (m, 1H, H-7), 5.10 (s, 2H, CH_2, Z), 4.89 (ddd, 1H, H-4), 4.34 (dAB, 1H, H-8), 4.19 (dd, 1H, H-6), 3.82, 3.42 (2x m, 2H, OCH_2, spacer), 3.62 (m, 2H, CH_2, OEt), 3.35 (m, 2H, CH_2N), 2.34 (dd, 1H, H-3a), 2.11 (dd, 1H, H-3b), 1.71 (m, CH_2, spacer), 1.29 (t, 3H, OEt); ^{13}C NMR data ($CDCl_3$): δ 170.6, 170.3, 169.7, 169.6 (4x C=O, Ac), 167.5 (C-1), 156.3 (C=O, Z), 128.3-127.8 (CH arom), 99.1 (C-2), 70.6, 67.9, 66.9, 63.9 (C-8, CH_2, OEt, CH_2, spacer, CH_2, Z), 38.4 (CH_2N, spacer), 32.1 (C-3), 29.2 (CH_2, spacer), 20.6, 20.5 (CH_3, Ac), 14.0 (CH_3, OEt).

Analytical data of compound **14**: R_f 0.30 (acetone/CH_2Cl_2, 1/19, v/v), $[\alpha]_D$ +17.5 (c 1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 5.36 (dd, 1H, H-5, $J_{4,5}$ 1.8 Hz), 5.30 (m, 1H, H-4), 5.22 (m, 1H, H-7), 5.09 (s, CH_2, Z), 4.59 (dd, 1H, H-6, $J_{6,7}$ 12.3 Hz), 4.08 (m, 2H, H-8a,b), 4.25 (q, 2H, OEt), 3.55-3.38 (m, 4H, CH_2O, CH_2N, spacer), 2.08, 2.04, 1.98, 1.97 (4x s, 12H, CH_3, Ac), 2.12 (m, 2H, H-3a,b), 1.75 (m, 2H, CH_2, spacer), 1.29 (t, 3H, CH_3, OEt).

Ethyl [methyl 3-deoxy-7,8-*O*-isopropylidene-2-thio-ß-D-*manno*-octulopyranosid]onate (18) - To a cooled (0°C) solution of compound **17** (5.0 mmol) in DMF was added 2-methoxypropene (0.5 mL, 5.2 mmol) and a catalytic amount of *p*-toluenesulfonic acid (50 mg). After the reaction mixture was stirred for 0.5 h, an extra amount of 2-methoxypropene (0.2 mL, 2.1 mmol) was added and stirring was contineud for an other 0.5 h. The solution was neutralized by the addition of Na_2CO_3 (0.2 g), and the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was applied onto a column of silica gel (10 g) and elution was effected with CH_2Cl_2 followed by methanol/CH_2Cl_2 (1/99, 1/49, 3/97, v/v). Concentration of the appropriate fractions gave **18** as an oil. Yield 0.99 g (57 %), R_f 0.3 (methanol/CH_2Cl_2, 1/19, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.1 (C-1), 108.6 (Cq, isoprop), 82.2 (C-2), 76.8, 72.3, 66.5, 65.4 (C-4, C-5, C-6, C-7), 66.4 (C-8), 61.0 (CH_2, OEt), 34.2 (C-3), 26.2, 24.6 (2x CH_3, isoprop), 13.5 (CH_3, OEt), 10.8 (CH_3S).

Ethyl [methyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-2-thio-ß-D-*manno*-octulopyranosid]onate (19) -A mixture of compound **18** (0.99 g, 2.8 mmol), dibutyltin oxide (0.85 g, 3.4 mmol) and molecular sieves (0.5 g, 4 Å) in toluene (20 mL) was heated under reflux for 2 h. The cooled mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (10 mL) and benzyl bromide (0.40 mL, 3.4 mmol) and CsF (0.64 g, 4.2 mmol) were added. After the reaction mixture was stirred for 18 h at room temperature, TLC (methanol/CH_2Cl_2, 3/97, v/v) analysis showed almost complete conversion of the starting product into **19** (R_f 0.7). The reaction mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The oil thus obtained was applied onto a column of silica gel (10 g) and elution was effected with CH_2Cl_2 followed by methanol/CH_2Cl_2 (1/99, 1/49, v/v). Concentration of the appropriate fractions afforded **19** as an oil. Yield 1.01 g (81 %), R_f 0.7 (methanol/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.8 (C-1), 137.3 (Cq, arom), 128.3-127.6 (CH, arom), 109.2 (Cq, isoprop), 83.6 (C-2), 77.1, 73.4, 72.6, 63.6 (C-4, C-5, C-6, C-7), 67.2 (C-8), 61.6 (CH_2, OEt), 32.3 (C-3), 26.6, 24.9 (2x CH_3, isoprop), 14.1 (CH_3, OEt), 11.5 (CH_3S).

Ethyl [methyl 5-*O*-acetyl-4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-2-thio-ß-D-*manno*-octulopyranosid]onate (20) - A mixture of compound **19** (1.01 g 2.3 mmol), 4-dimethylaminopyridine, acetic anhydride (1.1 mL) and pyridine (0.8 mL) in CH_2Cl_2 (10 mL) was stirred for 18 h at room temperature. The reaction mixture was diluted with toluene (10 mL) and the solvents were evaporated. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with aqueous sodium bicarbonate (10 mL) and water (10 mL). The organic phase was concentrated and the oil thus obtained was applied onto a column of silica gel (10 g). Elution of the column was effected with CH_2Cl_2. Concentration of the appropriate fractions afforded **20** as an oil. Yield 0.87 g (79 %), R_f 0.8 (acetone/CH_2Cl_2 1/19, v/v). ^{1}H NMR data ($CDCl_3$): δ 7.34-7.26 (5H, H-arom), 5.57 (d, 1H, H-5, $J_{4,5}$ 2.7 Hz), 5.77-4.43 (AB, 2H, CH_2, Bn), 4.20 (m, 2H, CH_2, OEt), 4.16 and 3.42 (2x m, 5H, H-4, H-6, H-7, H-8a,b), 2.61 (dd, 1H, H-3a), 2.16 (s, 3H, CH_3, Ac), 2.14 (t, 1H, H-3b), 1.39, 1.32 (2x s, 6H, CH_3, isoprop), 1.25 (m, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 169.7 (C=O, Ac), 168.1 (C-1), 137.5 (Cq, arom), 128.1-127.4 (CH, arom), 109.3 (Cq, isoprop), 82.9 (C-2), 76.1, 72.6, 72.4, 64.2 (C-4, C-5, C-6, C-7), 66.8 (C-8), 61.6 (CH_2, OEt), 33.5 (C-3), 26.6, 24.9 (2x CH_3, isoprop), 20.7 (CH_3, Ac), 14.1 (CH_3, OEt), 11.5 (CH_3S).

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 5-*O*-acetyl-4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α/ß-D-*manno*-octulopyranosid]onate (21 and 22) - Condensation of methyl 2-thioglycoside **7** (0.24 g, 0.5 mmol), with alcohol **11** (0.13 g, 0.6 mmol) was executed as described above. After work-up the crude product was purified by silica gel (5 g) column chromatography, (eluent: light petroleum/CH_2Cl_2 (1/1 → 1/9) followed by acetone/CH_2Cl_2 (1/99) to give **22**. Yield 0.072 g; R_f 0.45 (acetone/CH_2Cl_2, 3/97, v/v). ^{1}H NMR data ($CDCl_3$): δ 7.21-7.42 (10 H, H-arom), 5.55 (d, 1H, H-5, $J_{4,5}$ 2.3 Hz), 5.39 (t, 1H, NH, spacer), 5.09 (s, 1H, CH_2, Z), 4.76-4.45 (dd, 2H, CH_2, Bn), 4.23 (m, 2H, CH_2, OEt), 3.59 (ddd, 1H, H-4), 4.19-3.68 (m, 4H, H-6, H-7, H-8a,b), 3.32, 3.54 (2x m, 2H, CH_2O, spacer), 3.26 (m, 2H, CH_2N, spacer), 2.41 (dd, 1H, H-3a), 2.02 (dd, 1H, H-3b), 1.73 (m, 2H, CH_2, spacer), 1.26 (t, 3H, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 169.7 (C=O, Ac), 166.9 (C-1), 156.2 (C=O, Z), 137.5 (Cq, arom), 128.2-127.6 (CH, arom), 109.4 (Cq, isoprop), 99.2 (C-2), 74.8, 73.0, 72.4, 64.2 (C-4, C-5, C-6, C-7), 70.4 (CH_2, Bn), 66.8 (C-8), 66.4 (CH_2, Z), 61.7 (CH_2O, spacer), 61.3 (CH_2, OEt), 38.2 (CH_2N, spacer), 33.2 (C-3), 29.0 (CH_2, spacer), 26.7, 25.0 (CH_3, isoprop), 20.7 (CH_3, Ac), 13.9 (CH_3, OEt). Further elution of the column gave **21**. Yield 0.182 g; R_f 0.40 (acetone/CH_2Cl_2, 3/97, v/v). ^{1}H NMR data ($CDCl_3$): δ 7.21-7.42 (10 H, H-arom), 5.59 (d, 1H, H-5, $J_{4,5}$ 2.4 Hz), 5.38 (t, 1H, NH, spacer), 5.09 (s, 1H, CH_2, Z), 4.73 (d, 2H, CH_2, Bn), 4.23 (m, 2H, CH_2, OEt), 3.93 (ddd, 1H, H-4), 4.19-3.68 (m, 4H, H-6, H-7, H-8a,b), 3.27 (m, 2H, CH_2N, spacer), 3.37, 3.56 (2x m, 2H, CH_2O, spacer), 2.21 (dd, 1H, H-3a), 1.98 (dd, 1H, H-3b), 1.79 (m, 2H, CH_2, spacer), 1.28 (t, 3H, CH_3, OEt); ^{13}C NMR data ($CDCl_3$): δ 170.0 (C=O, Ac), 167.8 (C-1), 156.4 (C=O, Z), 137.7 (Cq, arom), 128.4-127.6 (CH, arom), 109.4 (Cq, isoprop), 98.9 (C-2), 73.9, 71.9, 71.6, 64.9 (C-4, C-5, C-6, C-7), 70.8 (CH_2, Bn), 66.5 (C-8), 66.0 (CH_2, Z), 61.8 (CH_2, spacer), 61.3 (CH_2, OEt), 38.2 (CH_2N, spacer), 33.6 (C-3), 29.3 (CH_2, spacer), 26.6, 25.4 (CH_3, isoprop), 20.9 (CH_3, Ac), 14.1 (CH_3, OEt).

Anal. Calcd. for $C_{33}H_{43}O_{11}N$: C 62.95, H 6.88; found: C 63.24, H 7.01%.

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-octulopyranosid]onate (23) - Compound **21** (0.18 g, 0.29 mmol) was dissolved in a dry ethanol (4 mL) and potassium *tert*-butoxide (36 mg, 0.3 mmol) was added. After the reaction mixture was stirred for 45 min at room temperature, TLC analysis (acetone/CH_2Cl_2, 1/19, v/v) indicated complete conversion of **21** (R_f 0.4) into **23** (R_f 0.2). The solution was neutralized with Dowex (50 W, H^+ form) resin and filtrated. The filtrate was concentrated under

reduced pressure and the resulting oil was applied onto a column of silica gel (2 g). The column was eluted with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, v/v). Concentration of the appropriate fractions afforded **23** as an oil. Yield 0.13 g (77 %), R_f 0.2 (acetone/CH_2Cl_2, 1/19, v/v). ^{13}C NMR data ($CDCl_3$): δ 167.7 (C-1), 156.3 (C=*O*, Z), 137.6 (Cq, Bn), 128.4-127.5 (CH, arom), 109.0 (Cq, isoprop), 98.8 (C-2), 74.1, 73.0, 72.3, 64.1 (C-4, C-5, C-6, C-7), 70.2 (CH_2, Bn), 66.4 (C-8, CH_2, Z), 61.7, 61.0 (CH_2, spacer, CH_2, OEt), 38.1 (CH_2N, spacer), 32.0 (C-3), 29.2 (CH_2, spacer), 26.5, 25.3 (CH_3, isoprop), 20.2 (CH_3, Ac), 14.0 (CH_3, OEt).

Ethyl 2-*O*-benzoyl-3,4,6,7-tetra-*O*-benzyl-1-thio-L-*glycero*-D-*manno*-heptopyranoside (26) -To a mixture of potassium *tert*-butoxide (0.14 g) and ethanethiol (0.09 mL) in methanol (5 mL) was added dropwise a solution of chloride **24** (1 mmol) in ethyl acetate (5 mL). After stirring the reaction mixture for 15 min at room temperature, TLC analysis (acetone/CH_2Cl_2, 1/99, v/v) indicated complete conversion of **24** (R_f 0.8) into **25** (R_f 0.4). The reaction mixture was neutralized with Dowex (50 W, H^+-form) resin and filtered over a pad of celite. The filtrate was concentrated under reduced pressure. The residual oil was dissolved in toluene (3x 10 mL) and concentrated under reduced pressure. Crude **25** was dissolved in pyridine (5 mL) and benzoyl chloride (1.5 mmol) was added. After stirring the reaction mixture for 16 h, TLC analysis (acetone/CH_2Cl_2, 1/99, v/v) showed the presence of a more lipophilic product (R_f 0.6). The reaction was quenched by the addition of water (0.1 mL). After stirring for 30 min the solution was diluted with toluene (10 mL) and concentrated *in vacuo*. The oily product was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with aqueous sodium bicarbonate (10 mL) and water (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The oil thus obtained was applied onto a column of silica gel (5 g) and elution was effected with light petroleum/CH_2Cl_2 (1/1 → 0/1). Concentration of the appropriate fraction afforded **26** as an oil. Yield 0.49 g (68 %), R_f 0.6 (acetone/CH_2Cl_2, 1/99, v/v), $[\alpha]_D$ +27.1° (c 1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 8.12-7.15 (25H, H-arom), 5.70 (dd, 1H, H-2, $J_{1,2}$ 1.7 Hz, $J_{2,3}$ 2.9 Hz), 5.44 (d, 1H, H-1), 4.93-4.17 (10H, CH_2, Bn), 4.31 (t, 1H, H-4), 4.01 (dd, 1H, H-3), 3.86 (dd, 1H, H-7a, $J_{7a,7b}$ 9.8Hz, $J_{6,7a}$ 7.0Hz), 3.73 (dd, 1H, H-7b, $J_{6,7b}$ 6.8 Hz), 2.58 (m, 2H, CH_2, SEt), 1.23 (t, 3H, CH_3, SEt); ^{13}C NMR data ($CDCl_3$): δ 165.1 (C=O, Bz), 137.9, 137.7 (Cq, arom), 129.7 - 126.7 (CH, arom), 81.6 (C-1), 78.3, 74.5, 73.1, 71.2, 69.8 (C-2, C-3, C-4, C-5, C-6, 74.1, 72.7, 72.4, 70.7 (CH_2, Bn), 69.9 (C-7), 24.5 (CH_2, SEt), 13.9 (CH_3, SEt).
Anal. Calcd. for $C_{44}H_{46}O_7S$: C 73.51, H 6.45; found: C 73.05, H 6.18%.

Ethyl 2,3:6,7 di-*O*-isopropylidene-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (29) - A solution of crude bromide **27** (10 mmol) in ethyl acetate was added dropwise to a mixture of potassium *tert*-butoxide (1.35 g, 12 mmol) and ethanethiol (0.9 mL, 12 mmol) in methanol (50 mL). After the reaction mixture was stirred for 45 min at room temperature, TLC analysis (methanol/CH_2Cl_2, 1/4, v/v) revealed the conversion of **27** into **28** (R_f 0.3). The reaction mixture was neutralized Dowex (50 W, H^+ form) resin, filtered over a pad of celite and the filtrate was concentrated *in vacuo*. The oil thus obtained was dissolved in toluene (3x 50 mL) and concentrated. The residu was dissolved in a mixture of acetone (85 mL) and dimethoxypropane (7.4 mL) and the solution was acidified (pH 4) with camphorsulfonic acid. After the reaction mixture was stirred for 18 h at room temperature, TLC analysis (methanol/CH_2Cl_2, 3/97, v/v) showed the conversion of **28** into **29** (R_f 0.5). The reaction mixture was neutralized with $PbCO_3$-$Pb(OH)_2$ and filtered over a pad of celite. The solvents were evaporated *in vacuo* and the resulting oil was applied onto a column of silica gel (40 g). Elution of the column was effected with CH_2Cl_2 followed by methanol/CH_2Cl_2 (1/99, 2/49/ 3/97, v/v). The appropriate fractions were concentrated to give **29** as an oil. Yield 1.9 g (58 %), R_f 0.5 (methanol/CH_2Cl_2, 3/97, v/v), $[\alpha]_D$ + 32.5° (c 1, $CHCl_3$). ^1H NMR data ($CDCl_3$): δ 5.56 (s, 1H, H-

1), 4.39 (dt, 1H, H-6, $J_{5,6}$ 7.0 Hz, $J_{6,7a,b}$ 7.3 Hz), 4.18 (dd, 1H, H-2, $J_{2,3}$ 6.7 Hz), 4.12-4.05 (m, H-3, H-7a), 3.98-3.88 (m, 2H, H-7b, H-5), 3.82-3.76 (m 1H, H-4), 3.10 (s, 1H, OH), 2.78-2.52 (m, CH_2, SEt), 1.54-1.35 4x s, 12H, 4x CH_3, isoprop), 1.31 (t, 3H, CH_3, SEt); ^{13}C NMR data ($CDCl_3$): δ 109.1, 108.6 (2x Cq, isoprop), 79.4, 78.3, 76.0. 74.5, 69.8, 69.3 (C-1, C-2, C-3, C-4, C-5, C-6), 65.4 (C-7), 27.6, 25.8, 25.7, 25.2 (CH_3, isoprop), 23.7 (CH_2, SEt), 14.0 (CH_3, SEt).

Ethyl 2,3:6,7-di-*O*-isopropylidene-4-*O*-(4-methoxy)benzyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (30) - *n*-Tetrabutylammonium iodide (0.10 g), sodium hydride (0.094 g, 3.8 mmol) and 4-methoxybenzyl chloride (0.44 mL, 3.1 mmol) were added to a cooled (0°C) solution of **29** (0.85 g, 2.55 mmol) in DMF (10 mL). After stirring for 1.5 h at room temperature, TLC analysis (acetone/CH_2Cl_2, 1/99, v/v) showed complete conversion of **29** into **30** (R_f 0.5). The reaction was quenched with methanol (1 mL) and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (50 mL) and water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated to an oil, which was applied onto a column of silica gel (10 g). Elution of the column was effected with light petroleum followed by light petroleum/CH_2Cl_2 (9/1→1/9, v/v). Concentration of the appropriate fractions gave **30** as an oil. Yield 0.84 g (73 %). R_f 0.5 (acetone/CH_2Cl_2, 1/99, v/v). ^{13}C NMR data ($CDCl_3$): δ 158.9, 129.9 (Cq, MBn), 128.4, 113.4 (CH, MBn), 109.0, 108.5 (2x Cq, isoprop), 79.6, 78.4, 76.8. 76.3, 74.8, 68.7 (C-1, C-2, C-3, C-4, C-5, C-6), 72.5 (CH_2, MBn), 65.7 (C-7), 54.8 (OCH_3), 26.6, 26.0, 25.9, 25.5 (CH_3, isoprop), 23.7 (CH_2, SEt), 14.2 (CH_3, SEt).

Ethyl 2,3-*O*-isopropylidene-4-*O*-(4-methoxy)benzyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (31) - Compound **30** (0.70 g, 1.55 mmol) was dissolved in a mixture of acetic acid/water (7/3, v/v). After stirred for 5 h at room temperature, the reaction mixture was diluted with toluene and concentrated *in vacuo* (3x 50 mL). The oily product was purified by silica gel (10 g) column chromatography. Elution of the column was effected with CH_2Cl_2 to give the starting compound **30** in a yield of 12 %. Further elution with a mixture of methanol/CH_2Cl_2 (1/99 → 4/96) gave, after concentration of the appropriate fractions, **31** as an oil. Yield 0.41 g (65 %), R_f 0.3 (methanol/CH_2Cl_2, 3/97, v/v). ^1H NMR data ($CDCl_3$): δ 5.56, (s, 1H, H-1), 4.85 - 4.39 (AB, 2H, CH_2, MBn), 4.30 (m, 2H, H-5, H-6), 4.18 (dd, 1H, H-2, $J_{1,2}$ 0.7 Hz, $J_{2,3}$ 5.8 Hz), 3.97 (dd, 1H, H-3, $J_{3,4}$ 8.2 Hz), 3.88 (m, 2H, H-7a,b), 3.80 (s, 3H, OCH_3), 3.64 (dd, 1H, H-4, $J_{4,5}$ 9.9 Hz), 2.62 (m, 2H, CH_2, SEt), 1.29 (t, 3H, CH_3, SEt); ^{13}C NMR data ($CDCl_3$): δ 158.9, 129.1 (Cq, MBn), 128.4, 113.4 (CH, MBn), 109.1 (Cq, isoprop), 79.6, 78.2, 76.1. 75.1, 69.4, 69.0 (C-1, C-2, C-3, C-4, C-5, C-6), 72.7 (CH_2, MBn), 64.3 (C-7), 54.9 (OCH_3), 27.7, 26.2 (CH_3, isoprop), 24.0 (CH_2, SEt), 14.1 (CH_3, SEt).

Ethyl 6,7-*O*-di-*O*-benzyl-2,3-*O*-isopropylidene-4-*O*-(4-methoxy)benzyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (32) - To a cooled (0°) solution of compound **31** (0.4 g, 0.95 mmol) in DMF was added sodium hydride (0.074 g, 3 mmol). After stirring the suspension for 30 min, benzyl bromide (0.26 mL, 2.2 mmol) was added and the reaction mixture was stirred for an additional 3 h at room temperature. TLC analysis (acetone/CH_2Cl_2, 1/99, v/v) indicated the reaction to be complete. Methanol (1 mL) was added and after stirring for 30 min, the solvents were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The oil thus obtained was applied onto a column of silica gel (10 g) and elution was effected with light petroleum followed by light petroleum/CH_2Cl_2 (1/1 → 0/1). Concentration of the appropriate fractions gave **32** as an oil. Yield 0.50 g (89 %), R_f 0.7 (acetone/CH_2Cl_2, 1/99, v/v). ^{13}C NMR data ($CDCl_3$): δ 158.9, 129.1 (Cq, MBn), 130.3, 129.3 (Cq, Bn), 128.4, 113.4 (CH, MBn), 127.8 -127.2 (CH, Bn), 109.0

(Cq, isoprop), 79.6, 78.6, 76.2, 75.1, 74.6, 68.9 (C-1, C-2, C-3, C-4, C-5, C-6), 73.2, 73.0, 71.5 (CH_2, MBn, Bn), 70.2 (C-7), 54.7 (OCH_3), 27.6, 26.1 (CH_3, isoprop), 23.7 (CH_2, SEt), 14.0 (CH_3, SEt).

Ethyl 6,7-*O*-di-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (33) - A mixture of **32** (0.32 g, 0.54 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.16 g, 0.7 mmol) in CH_2Cl_2 (13.5 mL) and water (1.5 mL) was stirred for 45 min at 20°C in the dark and and filtered over a pad of celite. The filtrate was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$ (10 mL, 10%), water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The oil thus obtained was applied onto a column of silica gel (5 g) and eluted with CH_2Cl_2 followed by CH_2Cl_2/MeOH (1/99, v/v). Concentration of the appropriate fractions afforded **33** as an oil. Yield 0.21 g (81 %), R_f 0.5 (acetone/CH_2Cl_2, 3/97, v/v). ^1H NMR data ($CDCl_3$): δ 5.57 (s, 1H, H-1), 4.83 - 4.58 (AB, 2H, CH_2, Bn), 4.53 (s, 1H, CH_2, Bn), 4.14 (dd, 1H, H-2, $J_{1,2}$ 1.1 Hz, $J_{2,3}$ 5.6 Hz), 4.02 (m, 1H, H-4), 3.97 - 3.92 (m 2H, H-5, H-6), 3.70 (AB, H-7a,b), 2.51 (m, 2H, CH_2, SEt), 1.50, 1.31 (2x s, 6H, CH_3, isoprop), 1.21 (t, 3H, CH_3, SEt); ^{13}C NMR data ($CDCl_3$): δ 138.1, 137.8 (Cq, Bn), 128.2-127.4 (CH, Bn), 109.4 (Cq, isoprop), 79.6, 78.3, 76.2, 74.6, 69.5, 69.2 (C-1. C-2, C-3, C-4, C-5, C-6), 63.2 (CH_2, Bn), 69.7 (C-7), 24.0 (CH_2, SEt), 14.2 (CH_3, SEt).

Anal. Calcd. for $C_{26}H_{34}O_6S$: C 65.80, H 7.22; found: C 66.34, H 7.78%.

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 5-*O*-(2-*O*-benzoyl-3,4,6,7-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*--heptopyranosyl)-4-O-benzyl-3-deoxy-7,8-isopropylidene-α-D-*manno*-octulopyranosid]onate (34) - A mixture of donor **26** (0.106 g, 0.15 mmol) and acceptor **23** (0.070 g, 0.12 mmol) and activated molecular sieves (0.2 g, 4Å) in 1,2 dichloroethane/ diethylether (1/1, v/v, 1.5 mL) was stirred for 30 min at ambient temperature under an atmosphere of nitrogen. To the cooled mixture (0°C) was added a freshly prepared solution of *N*-iodosuccinimide (0.038 g, 0.17 mmol) and trifluoromethanesulfonic acid (2.7 uL) in ether/1,2 dichloroethane (1/1, v/v, 1.7 mL). After stirring the reaction mixture for 5 min at 0°C, TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) revealed almost complete disappearance of **23** (R_f 0.8) and **26** (R_f 0.1) and the presence of the coupling product **34** (R_f 0.35). The mixture was treated with pyridine (one drop), diluted with CH_2Cl_2 and filtrated. The filtrate was washed successively with aqueous sodium thiosulfate (5 mL, 20%), aqueous sodium bicarbonate (5 mL) and water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was applied onto a column of silica gel (2 g) and elution was effected with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, 1/49, v/v). The dimer containing fractions were further purified by Sephadex LH-20 column chromatography (eluent: CH_2Cl_2/methanol) to give, after concentration of the appropriate fractions, pure **34**. Yield 0.13 g (0.87 %), R_f 0.35 (acetone/CH_2Cl_2, 3/97, v/v). ^1H NMR data ($CDCl_3$): δ 8.08-7.05 (35H, H-arom), 5.67 (dd, 1H, H-2', $J_{1,2}$ 1.9 Hz, $J_{2,3}$ 2.6 Hz), 5.37 (t, 1H, NH, spacer), 5.24 (s, 2H, CH_2, Z), 5.09-4.32 (10, CH_2, Bn), 4.18 (dd, 1H, H-3'), 4.25 (m, 2H, CH_2, OEt), 4.10-3.25 (11H, H-4, H-5, H-6, H-7, H-8a,b, H-4', H-5', H-6', H-7'a,b), 3.32-3.23 (m, 2H, CH_2O, spacer), 3.30 (m, 2H, CH_2N, spacer), 2.21 (dd, 1H, H-3a, $J_{3a,3b}$ 12.3 Hz, $J_{3a,4}$ 5.9 Hz), 1.98 (t, 1H, H-3b, $J_{3b,4}$ 12.5 Hz), 1.72 (m, CH_2, spacer), 1.28 (t, CH_3, OEt), 1.33, 1.26 (2x s, CH_3, isprop); ^{13}C NMR data ($CDCl_3$): δ 168.0 (C-1), 165.6 (C=O, Bz), 156.3 (C=O, Z), 139.2-127.1 (Cq, arom), 138.2-127.1 (CH, arom), 99.0 (C-1), 97.7 (C-1'), 78.2, 76.1, 74.7, 74.1, 72.7, 72.2, 72.0, 71.9, 68.6 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6'), 74.9, 73.4, 72.9 (CH_2, Bn), 71.3 (C-7'), 69.9, 67.7, 66.4, 61.7 (C-8, CH_2, Z, CH_2, OEt, CH_2O, spacer), 38.2 (CH_2N, spacer), 33.2 (C-3), 29.0 (CH_2, spacer), 26.7, 24.6 (CH_3, isoprop), 14.1 (CH_3, OEt).

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl 5-*O*-(2-*O*-benzoyl-3,4,6,7-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranossyl)-4-*O*-benzyl-3-deoxy-α-D-*manno*-octulopyranosid]onate (35) - After stirring a solution of compound **34** (0.078 g, 0.063 mmol) in acetic acid/water (4/1, 2 mL) at 50 °C for 2 h, TLC analysis (methanol/CH_2Cl_2, 3/97, v/v) indicated complete conversion of **34** (R_f 0.9) into **35** (R_f 0.3). The mixture was diluted with toluene and the solvents were evaporated under reduced pressure. The residue was dissolved in toluene (3x 10 mL) and concentrated. The oil thus obtained was applied onto a column of silica gel (1 g) and elution was effected with CH_2Cl_2 followed by methanol/CH_2Cl_2 (1/99, 1/49, v/v). Concentration of the appropriate fractions afforded **35** as oil. Yield 0.076 g (96 %), R_f 0.3 (methanol/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.2 (C-1), 165.5 (C=O, Bz), 156.4 (C=O, Z), 139.2-127.1 (Cq, arom), 138.2-127.1 (CH, arom), 98.7 (C-1), 98.6 (C-1'), 78.1 - 61.4 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6'), 74.9, 73.4, 72.9 (CH_2, Bn), 71.9 (C-7'), 69.9 - 61.6 (C-8, CH_2, Z, CH_2, OEt, CH_2O, spacer), 38.2 (CH_2N, spacer), 33.2 (C-3), 29.0 (CH_2, spacer), 14.1 (CH_3, OEt).

Triethylamine [*N*-benzyloxycarbonyl-3-amino-propyl 5-*O*-(3,4,6,7-tetra-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-4-*O*-benzyl-3-deoxy-α-D-*manno*-octulopyranosid]onate (36) - A solution of dimer **35** in a mixture of dioxane, methanol and 4N aqueous NaOH (29/9/2, v/v, 2 mL) was stirred for 3 h at room temperature. TLC analysis (methanol/CH_2Cl_2, 8/92, v/v) showed complete conversion of **35** into **36** (R_f 0.7). The reaction mixture was diluted with methanol (10 mL) and neutralized by the addition of Dowex (50 W H^+ form) resin. After filtration, triethylamine (1 mL) was added to the filtrate and the solution was concentrated *in vacuo*. The residue was purified by Sephadex LH-20 column chromatography (eluent: methanol/CH_2Cl_2, 1/1, v/v). Concentration of the appropriate fractions gave **36**. Yield 0.071 g (95 %), R_f 0.7 (methanol/CH_2Cl_2, 8/92, v/v). ^{13}C NMR data ($CDCl_3$): δ 171.8 (C-1), 152.3 (C=O, Z), 138.4-137.8 (Cq, arom), 129.5-127.0 (CH, arom), 99.6 (C-1'), 99.1 (C-2), 79.3, 75.7, 73.5, 72.7, 72.4, 72.1, 68.4, 67.6 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6'), 74.0, 73.2, 72.9, 72.6 (CH_2, Bn), 69.5 (C-7'), 66.1 (CH_2, Z), 63.7, 63.0, 61.8 (C-8, CH_2, OEt, CH_2O, spacer), 37.5 (CH_2N, spacer), 32.0 (C-3), 28.8 (CH_2, spacer).

Sodium [3-amino-propyl 3-deoxy-5-*O*-(L-*glycero*-α-D-*manno*-heptopyranosyl)-α-D-*manno*-octulopyranosid]onate (37) - A mixture of compound **36** and palladium on active carbon (10 %) in isopropanol, water and acetic acid (4/1/0.3, v/v/v, 2 mL) was stirred under an atmosphere of H_2 for 48 h. The catalyst was removed by filtration and washed with water. The combined filtrates were concentrated under reduced pressure and the residue was purified by Hiload Sephacryl S100 HR 26/60 column chromatography (eluent, 2M TEAB). The appropriate fractions were concentrated *in vacuo*. The TEAB salts were removed by dissolving the residue in water (10x 1 mL) followed by concentration under reduced pressure to give pure **37**. Yield 0.017 g (60 %), R_f 0.1 (methanol/ethyl acetate/water, 3/5/2, v/v/v). ^1H NMR data ($CDCl_3$): δ 5.08 (d, 1H, H-1', $J_{1,2}$ 1.8 Hz), 4.16 (ddd, 1H, H-4, J3,4a 4.8 Hz, $J_{3,4b}$ 9.0 Hz, $J_{4,5}$ 2.8 Hz), 4.10 (d, H-5), 4.08 (dd, 1H, H-2', $J_{2,3}$ 2.3 Hz), 4.01 (dt, 1H, H-6', $J_{5,6}$ 0.7 Hz, $J_{6,7a,b}$ 6.7 Hz), 3.94 (dd, 1H, H-3'), 3.88 (t, 2H, H7a,b), 3.91 - 3.82 (m, 3H, H-5', H-4', H-8a), 3.76 -3.63 (m, 2H, H-8b, H-6), 3.60, 3.32 (2x m, 2H, CH_2O, spacer), 3.22 - 3.01 (m, 2H, CH_2N, spacer), 1.90 (m, 4H, H-3a,b, CH_2, spacer): ^{13}C NMR data ($CDCl_3$): δ 176.4 (C-1), 102.4 (C-1'), 101.2 (C-2), 76.0 (C-5), 72.7 (C-5'), 72.0 (C-4'), 71.2 (C-3'), 71.1 (C-2'), 69.7 (C-7'), 69.6 (C-6'), 66.9 (C-4'), 66.3 (C-4), 63.9 (H-7'), 63.7 (H-8), 62.6 (CH_2O, spacer), 39.2 (CH_2N, spacer), 35.6 (C-3), 26.9 (CH_2, spacer).

2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-ß-D-galactopyranosyl)-α/ß-D-glucopyranose (39) - To a solution

of compound **38** (4.6 g , 3.9 mmol) in acetonitrile (5 mL) was added a solution of dimethylamine (8.0 mmol) in acetonitrile (20 mL). After the reaction mixture was stirred for 18 h at room temperature, TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) indicated conversion of **38** (R_f 0.8) into **39** (R_f 0.5, 0.45). The reaction mixture was diluted with toluene (10 mL) and the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and the solution was washed with aqueous sodium bicarbonate (10 mL) and water (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The oily product was applied onto a column of silica gel (10 g) and elution was effected with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, 1/49, 3/97, v/v). Concentration of the appropriate fractions gave **39** (α/ß mixture) as an oil. Yield 3.8 g (90 %), R_f 0.5 and 0.45 (acetone/CH_2Cl_2, 3/97, v/v).

Trichloroacetimidate 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-α/ß-D-galactopyranosyl)-α/ß-D--glucopyranoside (40) - A mixture of compound **39** (0.38 g, 0.36 mmol), trichloroacetonitrile (0.24 mL) and molecular sieves (4 Å, 0.25 g) in CH_2Cl_2 (5 mL) was stirred for 1 h at room temperature. The mixture was cooled (0°) and sodium hydride (8.6 mg) was added. After stirring for 4 h at 0 °C, TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) showed the conversion of **39** into **40** (R_f 0.71 and 0.76). The mixture was diluted with toluene (10 mL), filtered over a pad of celite and the filtrate was concentrated *in vacuo*. The residual oil was applied onto a column of silica gel (5 g) and elution was effected with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, 1/49, v/v). Concentration of the appropriate fraction afforded **40** (α/ß mixture) as an oil. yield 0.31 g (72 %), R_f 0.71 and 0.76 (acetone/CH_2Cl_2, 3/97, v/v).

Ethyl (2,3,4,6-tetra-*O*-benzoyl-ß-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-ß-D-glucopyranosyl)-(1→4)--6,7-di-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (41) - A mixture of compound **33** (0.095 g, 0.2 mmol) and **40** (0.29 g , 0.24 mmol) and molecular sieves (0.5 g, 4 Å) in CH_2Cl_2 (4 mL) was stirred for 30 min under an atmosphere of nitrogen. To the cooled mixture (10 °C) was added dropwise 1.0 mL of a stock solution of trimethylsilyl triflate (80 µL) in CH_2Cl_2 (5 mL). After the reaction mixture was stirred for 30 min at 10°C, TLC analysis (acetone/CH_2CL_2, 3/97, v/v) showed the disappearance of **33** and **40** and the formation of the coupling product **41** (R_f 0.8). The reaction mixture was neutralized with pyridine (1 dr) and filtered. The filtrate was diluted with CH_2Cl_2 (20 mL) and washed with aqueous sodium bicarbonate (5 mL) and water (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was applied onto a column of silica gel (1 g) and eluted with light petroleum/CH_2Cl_2 (1/1 → 0/1). Concentration of the appropriate fractions gave **41** as an oil. Yield 0.23 g (76 %), R_f 0.8 (acetone/CH_2Cl_2, 3/97, v/v). ^1H NMR ($CDCl_3$): δ 8.13 - 7.02 (45H, H-arom), 5.74 -5.68 (m, 2H, H-2", H-4"), 5.55 (t, 1H, H-3', $J_{2,3}$ $J_{3,4}$ 6.0 Hz), 5.47 (s, 1H, H-1), 5.46 (dd, 1H, H-2'), 5.33 (dd, 1H, H-3", $J_{2,3}$ 10.4 Hz, $J_{3,4}$ 3.5 Hz), 4.86-4.38 (AB, 2H, CH_2, Bn), 4.79 (d, 1H, H-1"), 4.56 (d, 1H, H-1'), 4.30 (s, 2H, CH_2, Bn), 4.32 (d, 1H, H-2), 4.09 (t, 1H, H-4'), 4.22 - 3.41 (other protons), 2.52 - 2.28 (m, 2H, CH_2, SEt), 1.28, 1.15 (2x s, 6H, CH_3, isoprop), 1.12 (t, CH_3, SEt); ^{13}C NMR data ($CDCl_3$): δ 165.6 - 164.5 (C=O, Bz), 138.6, 137.7 (Cq, Bn), 133.2 - 127.0 (CH, arom), 108.9 (Cq, isoprop), 100.6, 99.7 (C-1', C-1"), 79.9 (C-1), 76.2, 76.1, 75.8, 75.5, 72.3, 72.2, 71.5, 71.2, 69.9, 69.2, 67.4 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-2", C-3", C-4", C-5"), 72.8, 72.6 (CH_2, Bn), 70.4 (C-7), 61.2, 60.8 (C-6', C-6"), 27.6, 26.0 (CH_3, isoprop), 23.9 (CH_2, SEt), 14.0 (CH_3, SEt).

Ethyl (2,3,4,6-tetra-*O*-benzoyl-ß-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-ß-D-glucopyranosyl)-(1→4)-2,3-

-di-*O*-benzoyl-6,7-di-*O*-benzyl-1-thio-L-*glycero*-α-D-*manno*-heptopyranoside (43) - Compound **41** (0.23 g) was dissolved in a mixture of acetic acid (4 mL) and water (1 mL) and after stirring for 8 h at 50°C, TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) indicated complete conversion of **41** into **42** (R_f 0.2). The mixture was diluted with toluene (10 mL) and concentrated under reduced pressure. The oily residue was dissolved in toluene (3x 10 mL) and concentrated. Crude **42** was dissolved in pyridine (1 mL) and benzoyl chloride (45 uL, 0.4 mmol) was added. After the reaction mixture was stirred for 18 h, TLC analysis (acetone/CH_2Cl_2, 3/97, v/v) revealed the presence of a more lipophilic product (R_f 0.7). The reaction was quenched by the addition of water (0.1 mL), diluted with toluene and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with aqueous sodium bicarbonate (5 mL) and water (5 mL). The dried organic layer was concentrated under reduced pressure and the oily residue was applied onto a column of silica gel (5 g). Elution of the column was effected by light petroleum/CH_2Cl_2 (2/1, 0/1). Concentration of the appropriate fraction afforded **43** as an oil. Yield 0.22 g (91 %), R_f 0.7 (acetone/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 165.4 - 164.5 (C=O, Bz), 138.9, 137.7 (Cq, Bn), 133.3 -126.9 (CH, arom), 100.7, 100.0 (C-1', C-1"), 82.7 (C-1), 77.5, 75.3, 74.5, 72.8, 71.2, 71.1, 70.8, 69.7 (C-2, C-3, C-4, C-5, C-6, C-2', C-3', C-4', C-5', C-2", C-3", C-4", C-5"), 72.6, 72.4 (CH_2, Bn), 70.4 (C-7), 61.3, 60.9 (C-6', C-6"), 24.2 (CH_2, SEt), 14.0 (CH_3, SEt).

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl (2,3,4,6-tetra-*O*-benzoyl-ß-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzoyl-ß-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-benzoyl-6,7-*O*-benzyl-l-*glycero*-α-d-*manno*-heptopyranosyl)-(1→5)-4-*O*-benzyl-3-deoxy-7,8-*O*-isopropylidene-α-D-*manno*-octulopyranosid]onate (44) -To a solution of acceptor **23** (0.059 g, 0.083 mmol) and donor **43** (0.169 g, 0.1 mmol) in 1,2 dichloroethane/diethylether (1/1, v/v, 1.5 mL) was added activated molecular sieves (0.5 g, 4Å) and the mixture was stirred for 1 h at ambient temperature under an atmosphere of nitrogen. To the cooled (0°C) mixture was added a freshly prepared solution of *N*-iodosuccinimide (0.025 g, 0.11 mmol) and trifluoromethanesulfonic acid (2 uL) in 1,2 dichloroethane/ether (1/1, v/v, 1.1 mL). After stirring the reaction mixture for 5 min at 0°C, TLC analysis (acetone/CH_2Cl_2, 1/19, v/v) revealed complete disappearance of **23** and **43** and the formation of the coupling product **44** (R_f 0.6). The reaction mixture was treated with pyridine (1 dr) and filtered. The filtrate was diluted with CH_2Cl_2 (15 mL) and washed successively with aqueous sodium thiosulfate (5 mL, 20%), aqueous sodium bicarbonate (5 mL) and water (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was applied onto a column of silica gel (1 g) and elution was effected with CH_2Cl_2 followed by acetone/CH_2Cl_2 (1/99, 2/49, 3/97, v/v). The tetramer containing fractions were further purified by LH-20 Sephadex column chromatography. (eluent: methanol/CH_2Cl_2, 1/1, v/v). Concentration of the appropriate fraction afforded **44** as an oil. Yield 0.123 g (55 %), R_f 0.6 (acetone/CH_2Cl_2, 1/19, v/v). ^1H NMR data ($CDCl_3$): δ 8.11 - 6.82 (65H, H-arom), 5.74 (dd, 1H, H-3', $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 9.9 Hz), 5.64 - 5.57 (m, 3H, H-2', H-3", H-4"'), 5.42 (t, 1H, H-3", $J_{2,3}$ $J_{3,4}$ 10.0 Hz), 5.40 - 5.32 (m, 2H, H-2", H-1'), 5.12 (dd, 1H, H-3"', $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 3,5 Hz), 5.26 - 4.78 (AB, 2H, CH_2, Bn), 4.56 (t, 1H, H-4', $J_{4,5}$ 9.8 Hz), 4.32 (d, 1H, H-1"', $J_{1,2}$ 8.0 Hz), 4.32 (d, 1H, $J_{1,2}$ 7.9 Hz), 4.24 (m, CH_2, OEt), 3.93 (1H, H-4"), 3.73 (m, 1H, H-4), 4.23 (m, 1H, H-5'), 3.38 (m, 2H, CH_2O, spacer), 3.23 (m, 2H, CH_2N, spacer), 2.02 (m, 2H, H-3a,b), 1.68 (m, 2H CH_2, spacer), 1.27 (t, 3H, CH_3, OEt), 1.28, 1.22 (2x s, 6H, CH_3, isoprop); ^{13}C NMR data ($CDCl_3$): δ 168.1 (C-1), 165.5 - 164.5 (C=O, Bz), 156.3 (C=O, Z), 139.8, 138.5, 137.7 (Cq, Bn), 133.4 - 126.8 (CH, arom), 109.5 (Cq, ioprop), 100.4, 100.1, 100.0 (C-1', C-1", C-1"'), 98.9 (C-2), 74.7, 73.4, 72.7, 72.5, 72.0, 71.9, 71.7, 71.4, 71.0, 70.9, 69.5, 69.0, 67.3 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5", C-2"', C-3"', C-4"', C-5"'), 73.9, 73.0, 72.4 (CH_2, Bn), 68.6, 67.7, 66.9, 66.3, 62.0, 61.1 (C-8, C-7', C-6", C-6"', CH_2, OEt, CH_2O, spacer, CH_2, Z), 37.9 (CH_2N, spacer), 31.7 (C-3), 29.1 (CH_2, spacer), 26.6,

24.5 (CH_3, isoprop), 13.9 (CH_3, OEt).

Ethyl [*N*-benzyloxycarbonyl-3-amino-propyl (2,3,4,6-tetra-*O*-benzoyl-ß-D-galactopyranosyl)-(1→4)-(2,3,6-tri--*O*-benzoyl-ß-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-benzoyl-6,7-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→5)--4-*O*-benzyl-3-deoxy-α-D-*manno*-octulopyranosid]onate (45) - A solution of compound **44** (0.082 g, 0.037 mmol) in acetic acid/water (9/1, v/v, 2.5 mL) was stirred for 8 h at 50°C. TLC analysis (methanol/CH_2Cl_2, 3/97, v/v) showed complete conversion of the starting material into a more hydrophilic product. The reaction mixture was diluted with toluene (4x 10 mL) and concentrated under reduced pressure. The oil thus obtained was applied onto a column of silica gel (0.2 g) and elution was effected with CH_2Cl_2 followed by methanol/CH_2Cl_2 (1/99, 2/49, v/v). Concentration of the appropriate fractions gave pure **45**. Yield 0.066 g (82 %), R_f 0.4 (methanol/CH_2Cl_2, 3/97, v/v). ^{13}C NMR data ($CDCl_3$): δ 168.1 (C-1), 165.9 -164.6 (C=O, Bz), 156.5 (C=O, Z), 139.7, 138.4, 137.9 (Cq, Bn), 133.4 - 125.2 (CH, arom), 100.3, 97.8 (C-1', C-1", C-1"'), 98.9 (C-2), 76.0, 74.6, 72.8, 72.5, 72.1, 71.8, 71.4, 71.1, 70.7, 69.7, 69.6, 68.4, 67.3 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5", C-2"', C-3"', C-4"', C-5"'), 73.2, 73.0 (CH_2, Bn), 69.3, 66.3, 61.7, 60.8 (C-8, C-7', C-6", C-6"', CH_2, OEt, CH_2O, spacer, CH_2, Z), 37.8 (CH_2N, spacer), 31.7 (C-3), 29.2 (CH_2, spacer), 14.0 (CH_3, OEt).

Triethylamine [*N*-benzyloxycarbonyl-3-aminopropyl 4-*O*-benzyl-3-deoxy-(ß-D-galactopyranosyl)-(1→4)-(ß-D--glucopyranosyl)-(1→4)-(6,7-di-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranosyl)-(1→5)-α-D-*manno*-octulopyranosid]onate (46) - Tetramer **45** (66 mg, 0.03 mmol) was dissolved in a mixture of dioxane, methanol and 4N aqueous NaOH (29/9/2, v/v, 2 mL). After stirring the reaction mixture for 3 h at room temperature, TLC analysis (isopropanol/ethyl acetate/water, 3/5/2, v/v/v) indicated the reaction to be complete. The reaction mixture was diluted with methanol (10 mL) and neutralized by the addition of Dowex (50 W H^+ form) resin. After filtration, the filtrate was treated with triethylamine and the solution was concentrated *in vacuo*. The residue was purified by sephadex LH-20 column chromatography (eluent: methanol/water, 15/85, v/v). Concentration of the tetramer containing fractions gave **46** (27 mg), containing a small amount of benzoate salts. ^{13}C NMR data (MeOD): δ 175.7 (C-1), 158.5 (C=O, Z), 139.7, 138.4, 137.9 (Cq, Bn), 129.7 - 128.0 (CH, arom), 104.3, 103.1, 101.8 (C-1', C-1", C-1"'), 101.2 (C-2), 79.6, 78.2, 76.8, 76.6, 76.0, 75.5, 74.0, 73.2, 72.7, 72.1, 70.9, 70.4, 68.8 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5", C-2"', C-3"', C-4"', C-5"'), 73.7, 73.5, 72.9 (CH_2, Bn), 70.4, 67.4, 63.7, 62.1 (C-8, C-7', C-6", C-6"', CH_2O, spacer, CH_2, Z), 39.7 (CH_2N, spacer), 31.7 (C-3), 29.8 (CH_2, spacer).

Sodium [3-amino-propyl 3-deoxy-(ß-D-galactopyranosyl)-(1→4)-(ß-D-glucopyranosyl)-(1→4)-(L-*glycero*-α-D--*manno*-heptopyranosyl)-(1→5)-α-D-*manno*-octulopyranosid]onate (47) - A mixture of compound **46** (27 mg) and palladium on active carbon (10 %, 30 mg) in isopropanol, water and acetic acid (4/1/0.3, v/v/v, 2 mL) was stirred under an atmosphere of H_2 for 48 h. The catalyst was removed by filtration and washed with water. The combined filtrates were concentrated under reduces pressure and the residue was purified by hiload Sephadex S100 HR 26/60 column chromatography (eluent, 2M TEAB). The appropriate fractions were concentrated. The residue was dissolved in water (10x 1 mL) and concentrated to remove the TEAB salts, to give pure **47**. Yield 3.3 mg (20 %), R_f 0.05 (methanol/ethyl acetate/water, 3/5/2, v/v/v). ^1H NMR data ($CDCl_3$): δ 5.13 (d, 1H, H-1', $J_{1,2}$ 1.8 Hz), 4.62 (d, 1H, $J_{1,2}$ 8.0 Hz), 4.49 (d, 1H, H-1"', $J_{1,2}$ 8.0 Hz), 4.03 (dd, 1H, H-5", $J_{5,6}$ 2.0 Hz, $J_{4,5}$ 11Hz), 3.88 (m, 1H, H-4"), 3.71 (m, 2H, H-3", H-3"'), 3.59 (t, 1H, H-2"'), 3.41 (t, 1H, H-2", $J_{2,3}$ 8.0 Hz), 3.65, 3.37 (2x m, 2H, CH_2O, spacer), 3.25 - 2.99 (m, 2H, CH_2N spacer), 2.05 (dd, 1H, H-3a, $J_{3a,3b}$ 11 Hz, $J_{3a,4}$ 5.0 Hz), 1.99 (m, 2H, CH_2, spacer), 1.89 (t, 1H,

H-3b, $J_{3b,4}$ 11Hz); ^{13}C NMR data ($CDCl_3$): δ 176.3 (C-1), 103,7 (C-1'"), 103.2 (C-1"), 101.9 (C-1'), 101.2 (C-2), 78.9, 769, 76.1, 75.9, 75.6, 74.8, 73.6, 73.2, 72.0, 71.7, 71.4, 70.6, 69.7, 69.6, 69.3, 69.0, 66.8, 66.3 (C-4, C-5, C-6, C-7, C-2', C-3', C-4', C-5', C-6', C-2", C-3", C-4", C-5", C-2"', C-3"', C-4"', C-5"') 62.6 (CH_2O, spacer), 63.7, 63.6, 61.8, 60.7 (C-8, C-7', C-6", C-6"'), 39.2 (CH_2N, spacer), 35.5 (C-3), 30.9 (CH_2, spacer).

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