Tetrahedron Vol. 48, No. 29, pp. 6123-6134, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

New Convenient Synthesis of Tunicamine

Jan Ramza and Aleksander Zamojski *

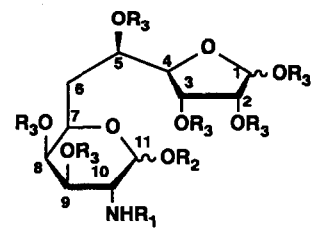
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

(*Received in UK* 27 *May* 1992)

Abstract: *A synthesis of tunicamine, the eleven-carbon atom sugar component of tunicamycin antibiotics, was described. The synthesis started from a derivative of 2-azido-2-deoxy-D-galactose (11) which was condensed with a furfuryl alcohol moiety. Achmatowicz-type transformation of this moiety to* allo*furanose system yielded a derivative of tunicamine. The synthesis required 11 steps and yielded 27 in 5.4% yield (from 11) and with good stereoselectivity.*

INTRODUCTION:

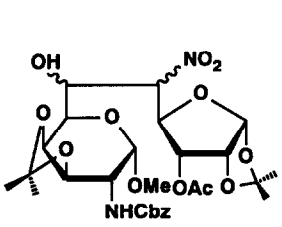
Tunicamine **1** (R_1=R_2=R_3=H), an eleven-carbon atom amino sugar, is the main component of numerous antibiotics belonging to tunicamycin[1], streptovirudin[2], and corynetoxin[3] families.



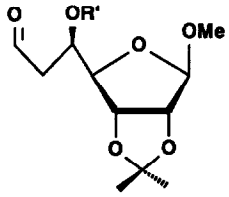
R_1=R_2=R_3=H **1**

The eleven-carbon atom chain of **1** can be viewed as 6-5 linked two sugars units: 2-amino-2-deoxy-D-*galacto*pyranose and D-*allo*pentofuranose. This structure presents an exciting target in higher sugar synthesis and was previously an object of interesting synthetic studies.

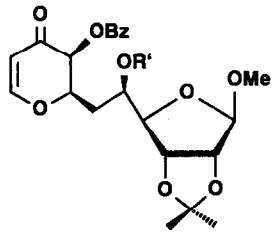
First synthesis of tunicamine **1**, reported by Suami and coworkers,[4] was based on Henry's nitroaldol condensation between suitably blocked derivatives of 5-nitro-5-deoxy-D-*ribo*furanose and 2-amino-2-deoxy-D-*galacto*hexodialdo-1,5-pyranose, catalysed by potassium fluoride. Conversion of the obtained product **2** into peracetylated **1** (R_1= Cbz, R_2= Me R_3=Ac) required seven steps. One of these steps: generation of 5-OH group of R configuration was not stereoselective.



2



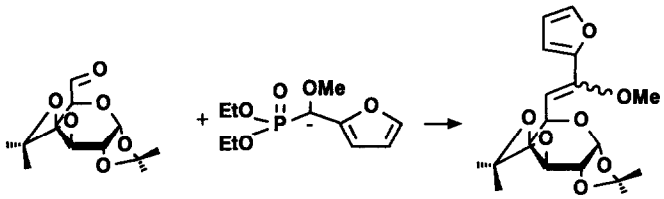
3



4

The second synthesis of **1**, performed by Danishefsky and Barbachyn[5] (see also Ref. 6) , consisted of two stages . In the first stage, a seven-carbon-atom aldehyde **3** was prepared from methyl 2,3-O-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside in three steps. In the second stage, aldehyde **3** was condensed with 1-benzoyloxy-2-t-butyldimethylsilyloxy-4-methoxy-buta-1,3-diene in the presence of $Ce(OAc)_3$-BF_3.OEt_2, and the cycloadduct **4** obtained was stereoselectively converted (in 11 steps) into peracetylated **1** (R_1= R_2= R_3= Ac).

In contrast to Suami's and Danishefsky's approaches we decided to synthesize tunicamine starting from "the galactosamine side" of the carbohydrate chain and to build the "ribo" part from a non-carbohydrate precursor. In our model studies [7] we found that the eleven-carbon atom framework **7** of tunicamine **1** could be readily assembled by one-step elongation of an appropriate six-carbon atom aldehyde eg. **5** by the Horner-type condensation with diethyl (2-furyl)-methoxymethyl phosphonate **6** [7].



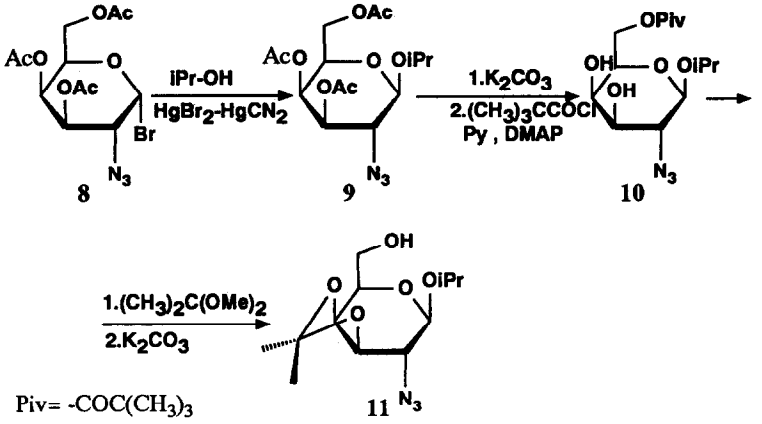
5 6 7

RESULTS:

As the most convenient six-carbon atom substrate we chose isopropyl 2-azido-2-deoxy-3,4-O--isopropylidene-β-D-*galacto*pyranoside (**11**). The isopropylidene grouping was proved to be safe as a protective group in our model studies [7], and the azido group seemed to be more stable under the planned reaction conditions than a protected amino group [8], and readily convertible into the free NH_2-group when needed.

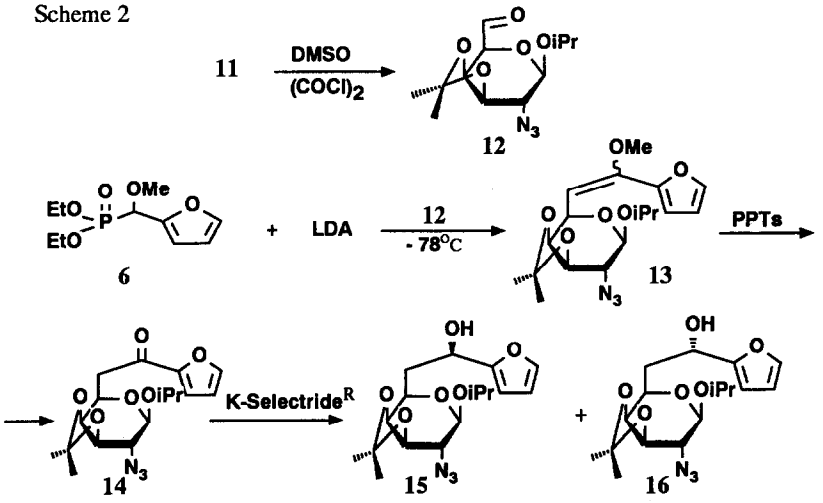
Galactoside **11** was obtained from 3,4,6-tri-O-acetyl-2-azido-2-deoxy-α-D-*galacto*pyranosyl bromide (**8**) [9] by: i. glycosylation with isopropyl alcohol in the presence of mercuric bromide-mercuric cyanide catalyst followed by separation of anomers to give 67% of the β-anomer **9**, ii. deacetylation in methanolic potassium hydrogencarbonate, iii. pivaloylation at O-6 to give **10**, iv. isopropylidenation, and, v. de-pivaloylation to yield **11** in 40% yield from **8** (Scheme 1).

Scheme 1



Swern oxidation[10] of **11** gave the aldehyde **12** which was next condensed with the anion generated from phosphonate **6**. The E-Z mixture of enol ethers **13**, obtained in 60% yield, was immediately hydrolysed with pyridynium p-toluene sulfonate (PPTS)[11] in acetone-water to ketone **14**. The crucial point was now the generation of the proper configuration (R) of the secondary alcohol at C-5 by reduction of the ketone grouping. After several attempts it was found that K-Selectride^R furnished diastereoisomeric alcohols **15** and **16** in 3.3:1 proportion and 75% overall yield. The alcohols were separated by chromatography (Scheme 2).

Scheme 2



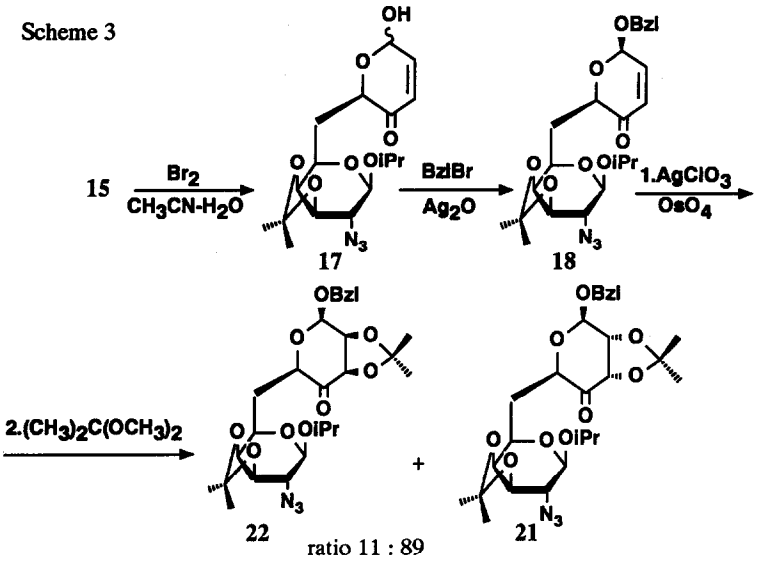
The absolute configuration of alcohol centers at C-5 in both products was determined using the CD-method, which we had earlier developed for benzoates of various furfuryl alcohols[12]. CD-Spectrum of the benzoate of major product **15** exhibited positive absorption maximum at 216 nm and a negative at 230 nm. These data are characteristic for R absolute configuration[12]. CD-Spectrum of the benzoate of the other reduction product **16** exhibited opposite absorption: a negative maximum at 216 nm and a positive at 230 nm - characteristic for S absolute configuration.

The minor product **16** could be converted into the epimer **15** by Swern oxidation and repetated reduction with K-Selectride. These operations increased the yield of the required alcohol **15** to 67%.

For the conversion of the furfuryl alcohol grouping in **15** into the "ribose" system, Achmatowicz's[13,14] approach was employed. Furfuryl alcohol **15** was reacted with bromine in acetonitrile-water solution[15] to yield the unstable 2,3-dideoxy-2-enopyranos-4-ulose derivative **17**. Compound **17** was immediately protected at C-1 as benzyl glycoside. Reaction of **17** with benzyl bromide in the presence of silver oxide yielded the -anomer **18** as the single reaction product. β-Configuration of the glycoside bond in **18** was evident from the $J_{1,2}$ and $J_{1,3}$ coupling constants corresponding to 1.9 and 1.6 Hz, respectively[14,16]. This configuration was necessary to secure stereocontrol of the next step: introduction of hydroxyl groups at C-2 and C-3 opposite to the C-1 substituent.

cis-Hydroxylation of the double bond in **18** using the Braun's method[14,17](silver chlorate and catalytic amount of osmium tetraoxide) was not fully stereoselective and led to two products **19** and **20** in 8:1 proportion. Both products were protected as isopropylidene derivatives **21** and **22** and separated by chromatography. Overall yield of both products was 54% (Scheme 3).

Scheme 3

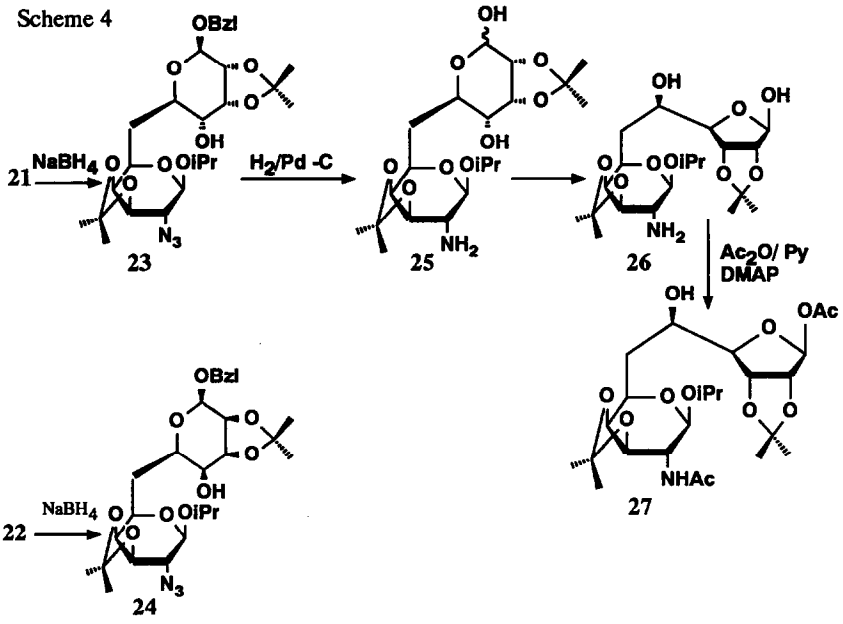


Determination of configuration of the new secondary alcohol centers at C-2 and C-3 was not easy at this stage because of insignificant differences in ^{1}H NMR spectra of both products **21** and **22** caused by deformation of the pyranose ring by the 2,3-isopropylidene protective grouping.

The next step - reduction of carbonyl grouping at C-4 was performed for both compounds **21** and **22** separately. As expected, reduction with sodium borohydride occurred exclusively *trans* to the bulky dioxolane grouping and gave single products **23** and **24** respectively, in a yield of 75% in both cases.

At this stage differences in ^{1}H NMR spectra of both products **23** and **24** were significant enough to permit the determination of configuration. Because the corresponding detailed ^{1}H NMR data were not available from literature, we performed the synthesis of appropriate model compounds: methyl 2,3:4,6-di-O-isopropylidene-β-D-*allo*pyranoside **(28)** and methyl 2,3:4,6-di-O-isopropylidene-β-D--*talo*pyranoside **(29)** starting from the parent hexoses and using Gelas and Horton's isopropylidenation

Scheme 4



method[18,19]. Comparison of ^{1}H NMR data of compounds **23** and **24** with the figures obtained for model compounds (Table 1) showed that the major product **23** was the required benzyl 5-C-2,3-O-isopropylidene-β-D-*allo*pentopyranoside derivative in which absolute configuration of all centers of chirality were the same as in tunicamine. Similar figures have been also noted by Achmatowicz and Grynkiewicz for 2,3-O-isopropylidene-β-DL-*ribo*pyranose derivatives in their ribose synthesis[14].

Table 1

No	H-1	H-2	H-3	H-4	H-5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
23	4.65	4.18	5.52	3.74	3.82	5.1	6.1	3.9	9.9
28	4.90	4.07	4.48	3.99	3.79	5.9	5.35	3.4	9.7
24	4.77	4.25	4.23	3.63	3.59	2.58	6.45	5.1	1.7
29	5.76	4.05	4.32	4.15	3.62	4.19	7.08	4.75	2.2

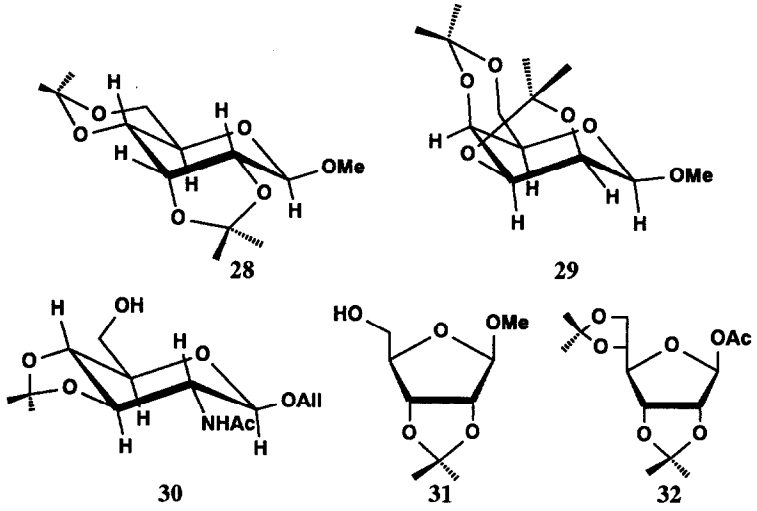
The last step of the synthesis consisted in transformation of the D-allopyranose system in compound **23** into isomeric furanose form. Isomerisation occurred spontaneously [14,19] after deprotection of the anomeric center at C-1 by catalytic hydrogenation. The single reaction product was the furanose ring containing derivative **26**. Simultaneously the azido group at position C-10 was reduced to the amino group. The product was separated as diacetyl derivative and was fully characterized as 11-isopropyl 10-N-acetyl-1-O-β-acetyl-2,3:8,9-di-O-isopropylidene-β-tunicaminide (**27**). ^{1}H NMR data of **27** were fully compatible with the values recorded for a similarly protected methyl β-D-galactosaminide **30** [20](Table 2), ribofuranose **31** [21], and 1-O-acetyl 2,3:5,6-di-O-isopropylidene-β-D-allofuranoside (**32**)[18,19](Table 3).

Table 2

No	H-11	H-10	H-9	H-8	H-7	$J_{11,10}$	$J_{10,9}$	$J_{9,8}$	$J_{8,7}$
27	5.14	2.92	4.80	4.04	4.15	8.6	8.3	5.5	2.04
30	5.04	3.1	4.76	4.18	4.02	8.6	8.2	5.3	2.1

Table 3

No	H-1	H-2	H-3	H-4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
27	6.25	4.69	4.93	4.22	0	6.0	1.0
32	6.15	4.68	4.88	4.11	0	5.97	0.5
33	4.98	4.60	4.85	4.44	0	5.94	0.5



Scarse amount of **27** available did not permit to perform a direct comparison with a derivative of original tunicamine, nevertheless the evidence presented above leaves no doubt about the identity of the compound synthesized.

The synthetic route to tunicamine presented here demonstrated clearly the convenience of the furfuryl alcohol system as a substrate for higher sugar synthesis. Tunicamine was obtained with a good stereoselectivity in a good total yield 5.4% (from **11**) in a form suitable for tunicamycin and other related antibiotics synthesis. Diastereoisomers of tunicamine can also be obtained via modification of the route employed.

EXPERIMENTAL:

Optical rotations were measured with JASCO DIP 360 DIGITAL POLARIMETER. IR spectra were measured with BECKMAN IR 4240 spectrometer in chloroform solutions. ^{1}H NMR spectra were measured with BRUKER AM-500 (500 MHz) and VARIAN AC-200 (200 MHz) spectrometers in $CDCl_3$ solutions with TMS as internal standard. CD-spectra were measured with JASCO J-120 spectrometer in acetonitrile solution. High resolution mass spectra (HR-MS) were measured with AMD-604 mass-spectrometer. Reactions were controlled using TLC on MERCK's ALU-PLATES (0,2 mm). All reagents and solvents were purified and dried according to common methods[22]. Organic solutions were dried with anhydrous magnesium sulfate. Reaction products were purified by flash chromatography[23], using MERCK's Kieselgel 60 (230-400 mesh).

Isopropyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-β-D-*galacto*pyranoside (9): To a solution of **8** [10](5.25 g, 13.3 mM) in dichloromethane (50 mL), molecular sieves 3A (1 g) were added at room temperature. After one hour of stirring the mixture was cooled to -5 °C and mercuric cyanide (3.36 g ,13.3 mM) and mercuric bromide (4.79 g, 13,3 mM) were added. After 15' at -5 °C anhydrous isopropanol (0.8 mL) was dropwise added. The mixture was stirred 2 hours at -5°C and after this period was filtered, washed with water, dried and concentrated under reduced pressure. Chromatography (hexane-ethyl acetate, 4:1) of the crude product gave first α-anomer (430 mg, 10.2%) as colorless syrup, $[\alpha]_D$ 62° (c 1.2, chloroform); ν_{max}: 2980, 2120, 1750, 1230 cm^{-1}; ^{1}H NMR δ: 5.32 (dd, $J_{4,5}$1.7 Hz, 1H, H-4), 5.28 (dd, 1H, H-3), 5.13 (d, $J_{1,2}$3.5 Hz, 1H, H-1), 4.21 (m, 1H, H-5), 4.20 (m, 1H, H-2), 4.08 (m, 2H, H-6, H-6'), 3.88 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 2.13, 2.04, 1.89 (3s 3x$COCH_3$), 1.21, 1.15 (2s 2xCH_3); and as the second product β-anomer **9** (3.32 g, 67%) as colorless syrup, $[\alpha]_D$ 3.6° (c 0.6, chloroform); ν_{max}: 2995, 2120, 1765, 1250 cm^{-1}; ^{1}H NMR δ: 5.32 (dd, $J_{4,5}$1.0 Hz, 1H, H-4), 4.76 (dd, $J_{3,4}$3.3 Hz, 1H, H-3), 4.44 (d, $J_{1,2}$8.1 Hz, 1H, H-1), 4.18 (dd, $J_{6,6'}$11.1 Hz, 1H, H-6), 4.11 (dd, $J_{5,6'}$6.7 Hz, 1H, H-6'), 4.04 (sep, J_{iPr}6.1 Hz, 1H, $CHMe_2$), 3.84 (dd, $J_{5,6}$6.8 Hz, 1H, H-5), 3.67 (dd, $J_{2,3}$11.0 Hz, 1H, H-2), 2.15, 2.05, 2.04 (3s, 9H, 3x$COCH_3$), 1.31, 1.27 (2d,6H, $CHMe_2$); HR-MS:found: 314.0969, calc for $C_{12}H_{16}N_3O_7$: 314.0988.

Isopropyl 2-azido-2-deoxy-6-O-pivaloyl-β-D-*galacto*pyranoside (10): To a solution of **9** (4.85 g, 13 mM) in methanol (50 mL) potassium hydrogencarbonate (500 mg) was added at room temperature. After 6 h of stirring the mixture was filtered, and concentrated under reduced pressure. The residue was dissolved in pyridine (10 mL) and dichloromethane (40 mL) and cooled to -5°C. Pivaloyl chloride (1.97 g, 16 mM) was added and the mixture was stirred 8 h at -5°C. The mixture was poured into saturated ammonium chloride solution, extracted with chloroform, dried and concentrated under diminished pressure. Chromatography (hexane-acetone, 3:1) of the crude product gave **10** (3.41 g, 79%) as colorless syrup, $[\alpha]_D$ 70.8° (c 3.4, chloroform); ν_{max}: 3420, 2995, 2120, 1740, 1116 cm^{-1}; ^{1}H NMR δ: 4.37 (dd, $J_{6,6'}$11.5 Hz, 1H, H-6), 4.35 (d, $J_{1,2}$7.5 Hz, 1H, H-1), 4.27 (dd, $J_{5,6'}$6.9 Hz, 1H, H-6'), 4.0 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.82 (dd, $J_{4,5}$1.0 Hz, 1H, H-4), 3.64 (ddd, $J_{5,6}$6.3 Hz, 1H, H-5), 3.54 (dd, $J_{2,3}$10.2 Hz, 1H, H-2), 3.44 (dd, $J_{3,4}$3.15 Hz, 1H, H-3), 1.28, 1.25 (2d, 6H, $CHMe_2$), 1.20 (s, 9H, $C(CH_3)_3$); HR-MS: found:272.1247, calc for $C_{11}H_{28}N_3O_5$: 272.1246.

Isopropyl 2-azido-2-deoxy-3,4-O-isopropylidene-β-D-*galacto*pyranoside (11): To a solution of **10** (3 g, 9.1 mM) in acetone (50 mL) 2,2-dimethoxypropane (2 mL), p-toluenesulfonic acid (20 mg) and copper sulfate were added at room temperature. After 12 h of stirring the mixture was neutralised with triethylamine, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol (25 mL) and potassium hydrogencarbonate (250 mg) was added and the mixture was stirred 2 h at room temperature. The mixture was filtered and concentrated under reduced pressure. Chromatography (hexane-acetone, 4:1) of the crude product gave **11** (1.77 g, 75.1%) as colorless syrup, $[\alpha]_D$ 79° (c 1.35, chloroform); ν_{max}: 3450, 2980, 2110, 1390 cm^{-1}; ^{1}H NMR δ: 4.33 (d, $J_{1,2}$8.5 Hz, 1H, H-1), 4.10 (dd, $J_{4,5}$2.0

Hz, 1H, H-4), 4.0 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.92 (dd, $J_{3,4}$5.3 Hz, 1H, H-3), 3.82 (m, 3H, H-5, H-6, H-6'), 3.39 (dd, $J_{2,3}$8.0 Hz, 1H, H-2), 1.54, 1.34 (2s, 6H, CMe_2),1.28, 1.25 (2d, 6H, $CHMe_2$); Anal. found: C, 49.80; H, 7.70; N, 14.69; calc for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63.

Isopropyl 2-azido-2,6-dideoxy-7-C-(2-furyl)-3,4-O-isopropylidene-β-D-*galacto*hept-7-ulopyranoside (14): To a solution of diisopropylamine (0.36 g, 3.55 mM) in oxolane (25 mL) at -78°C under argon atmosphere n-butyllithium (2.2 mL of 1.6 M solution in oxolane) was added and after 15 min phosphonate **6** [7](0.95 g, 3.85 mM) was added. After 1.5 h of stirring at -78°C the aldehyde **12** obtained by Swern oxidation[10] of **11** (0.861 g, 3 mM) was added in oxolane solution. The mixture was stirred for additional 2 h at -78°C and was poured into saturated ammonium chloride solution, extracted with ether, dried and concentrated under reduced pressure. Chromatography (hexane-ether, 9:1) of the crude product gave **13** (650 mg, 59%) as a mixture of two unstable compounds, **13a** and **13b**; $\tilde{\nu}_{max}$: 3000, 2120, 1210, 890 cm^{-1};^{1}H NMR for **13a** δ: 7.44 (dd, $J_{1,2}$1.8 Hz, 1H, H-1), 6.60 (dd, $J_{1,3}$0.8 Hz, 1H, H-3), 6.46 (dd, $J_{2,3}$3.4 Hz, 1H, H-2), 5.16 (d, 1H, H-6), 4.89 (dd, $J_{6,7}$9.0 Hz, 1H, H-7), 4.40 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.08 (dd, $J_{7,8}$2.2 Hz, 1H, H-8), 4.02 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.90 (dd, $J_{8,9}$5.2 Hz, 1H, H-9), 3.42 (dd, $J_{9,10}$7.9 Hz, 1H, H-10), 3.74 (s, 3H, OCH_3), 1.58, 1.35 (2s, 6H, CMe_2), 1.24, 1.23 (2d, 6H, $CHMe_2$); ^{1}H NMR for **13b** δ: 7.42 (dd, $J_{1,2}$1.8 Hz, 1H, H-1), 6.49 (dd, $J_{1,3}$0.8 Hz, 1H, H-3), 6.44 (dd, $J_{2,3}$3.4 Hz, 1H, H-2), 5.40 (d, 1H, H-6), 4.82 (dd, $J_{6,7}$8.8 Hz, 1H, H-7), 4.40 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.05 (dd, $J_{7,8}$2.1 Hz, 1H, H-8), 4.01 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.89 (dd, $J_{8,9}$5.3 Hz, 1H, H-9), 3.40 (dd, $J_{9,10}$7.9 Hz, 1H, H-10), 3.73 (s, 3H, OCH_3), 1.56, 1.36 (2s, 6H, CMe_2), 1.24, 1.23 (2d, 6H, $CHMe_2$); Anal. found: C, 56.87; H, 6.63; N, 10.85; calc for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08. The mixture **13** was dissolved in oxolane (25 mL) and water (5 mL) and pyridinium p-toluenesulfonate (200 mg) were added and the solution was refluxed 3 h. After cooling, the mixture was extracted with ether, dried and concentrated under reduced pressure. Chromatography (hexane-ether, 4: 1) of the residue gave **14** (489 mg, 78%), as colorless oil; $[\alpha]_D$35° (c 1.6, chloroform); $\tilde{\nu}_{max}$: 3000, 2120, 1690, 1210, 890 cm^{-1}; ^{1}H NMR δ: 7.62 (dd, $J_{1,2}$1.7 Hz, 1H, H-1), 7.28 (dd, $J_{1,3}$0.8 Hz, 1H, H-3), 6.55 (dd, $J_{2,3}$3.6 Hz, 1H, H-2), 4.39 (ddd, $J_{6,7}$7.9 Hz, 1H, H-7), 4.32 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.12 (dd, $J_{7,8}$2.2 Hz, 1H, H-8), 3.93 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.92 (dd, $J_{8,9}$5.5 Hz, 1H, H-9), 3.50 (dd, $J_{6,6'}$17.0 Hz, 1H, H-6), 3.38 (dd, $J_{9,10}$8.0 Hz, 1H, H-10), 3.10 (dd, $J_{6',7}$5.0 Hz, 1H, H-6'), 1.56, 1.33 (2s, 6H, CMe_2), 1.21, 1.16 (2d, 6H, $CHMe_2$); Anal. found: C, 55.69; H, 6.58; N, 11.22; calc for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50.

Isopropyl 2-azido-2,6-dideoxy-7-C-(2-furyl)-3,4-O-isopropylidene-L-and-D-*glycero*-β-D-*galacto*heptopyranoside (15) and (16): To a solution of **14** (365 mg, 1 mM) in oxolane (25 mL) at -78°C potassium tri-sec-butyl-borohydride (1.2 mL of 1M solution in oxolane) was added. After 2 h of stirring at -78°C the mixture was poured into saturated ammonium chloride solution, extracted with ether, dried and concentrated under reduced pressure. Chromatography (hexane-ether, 9:1) of the crude product gave first **16** (65 mg, 17.7%), colorless oil; $[\alpha]_D$ 56° (c 1.55, chloroform); $\tilde{\nu}_{max}$: 3610, 2985, 2110, 1385, 830 cm^{-1}; ^{1}H NMR δ: 7.44 (dd, $J_{1,2}$1.8 Hz ,1H, H-1), 6.28 (dd, $J_{1,3}$0.8 Hz, 1H, H-3), 6.35 (dd, $J_{2,3}$3.4 Hz, 1H, H-2), 4.96 (dd, $J_{5,6}$8.1 Hz, 1H, H-5), 4.26 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.03 (dd, $J_{7,8}$2.1 Hz, 1H, H-8), 3.98 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.85 (dd, $J_{8,9}$5.2 Hz, 1H, H-9), 3.79 (ddd, $J_{6,7}$8.8 Hz, 1H, H-7), 3.38 (dd, $J_{9,10}$8.0 Hz, 1H, H-10), 2.49 (ddd, $J_{6,6'}$14.3 Hz, 1H, H-6), 2.46 (bs, 1H, OH), 2.25 (ddd, $J_{5,6'}$5.6 Hz, $J_{6',7}$4.8 Hz, 1H, H-6'), 1.56, 1.35 (2s, 6H, CMe_2), 1.29, 1.24 (2d, 6H, $CHMe_2$); HR-MS: found: 352.1514; calc for $C_{16}H_{22}N_3O_6$: 352.1508; and as the second product, compound **15** (208 mg, 57%), as a colorless oil; $[\alpha]_D$ 67° (c 0.45, chloroform); $\tilde{\nu}_{max}$: 3600, 2980, 2110, 1385, 830 cm^{-1}; ^{1}H NMR δ: 7.38 (dd, $J_{1,2}$1.7 Hz, 1H, H-1), 6.27 (dd, $J_{1,3}$0.8 Hz, 1H, H-3), 6.34 (dd, $J_{2,3}$3.2 Hz, 1H, H-2), 4.98 (dd, $J_{5,6}$2.8 Hz, 1H, H-5), 4.32 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.0 (dd, 1H, H-8), 4.0 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 4.0 (ddd, $J_{6,7}$10.1 Hz, 1H, H-7), 3.88 (dd, $J_{8,9}$5.3 Hz, 1H, H-9), 3.38 (dd, $J_{9,10}$8.0 Hz, 1H, H-10), 2.41 (ddd, $J_{6,6'}$14.6 Hz, 1H, H-6), 2.28 (bs, 1H, OH), 2.13 (ddd, $J_{5,6'}$9.8 Hz, $J_{6',7}$3.0 Hz, 1H, H-6'), 1.55, 1.35 (2s, 6H, CMe_2), 1.31, 1.27 (2d, 6H, $CHMe_2$); HR-MS: found: 352.1505; calc for $C_{16}H_{22}N_3O_6$: 352.1508. Compounds **15** and **16** were converted

into benzoates under standard conditions. CD-spectrum of benzoate of **15**: λ_{max}215 nm; λ_{min}230, 260 nm (conc. 0.1 mg/mL). CD-spectrum of benzoate of **16**: λ_{max}230, 259 nm; λ_{min}216 nm (conc. 0.13 mg/mL).

Benzyl 2,3-di-deoxy-5-C-(Isopropyl-2-azido-2,6-dideoxy-3,4-O-isopropylidene-β-D- *galacto*-pyranoside-6-yl)-β-D-*glycero*-hex-2-eno-pyranos-4-uloside (18): To a solution of **15** (102 mg, 0.28 mM) in acetonitrile (5 mL) and water (1 mL) at -10°C bromine (46 mg, 0.29 mM) was added. After 10 min minutes of stirring the mixture was poured into ice water, extracted with chloroform, dried and concentrated under reduced pressure (bath temperature below 20°C). The crude product **17** (95 mg, 85%) ν_{max}: 3400, 2990, 2120, 1705, 1640, 1075 cm^{-1}; ^1H NMR δ: 6.94 (dd, $J_{2,3}$10.3 Hz, 1H, H-2), 6.15 (dd, $J_{1,3}$0.5 Hz, 1H, H-3), 5.67 (dd, $J_{1,2}$3.4 Hz, 1H, H-1), 4.80 (m, 1H, H-5), 4.28 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.0 (m, 3H, H-8, H-7, $CHMe_2$), 3.84 (dd, $J_{8,9}$6.0 Hz, 1H, H-9), 3.38 (dd, $J_{9,10}$8.2 Hz, 1H, H-10), 3.0 (bs, 1H, OH), 2.40 (m, 1H, H-6), 2.0 (m, 1H, H-6'), 1.54, 1.34 (2s, 6H, CMe_2), 1.24, 1.20 (2d, 6H, $CHMe_2$) was dissolved in dichloromethane. Silver oxide (380 mg) and benzyl bromide (240 mg) were added and the mixture was stirred 3 h in darkness at room temperature. The mixture was then filtered and evaporated under reduced pressure. Chromatography (hexane-ether, 9:1) of the residue gave compound **18** (72 mg, 63.5%), as a colorless oil; $[\alpha]_D$ 75.° (c 0.4, chloroform); ν_{max}: 2990, 2120, 1705, 1640,1390, 1075 cm^{-1}; ^1H NMR δ: 6.93 (dd, $J_{2,3}$10.3 Hz1H, H-2), 6.19 (dd, $J_{1,3}$1.6 Hz, 1H, H-3), 5.43 (dd, $J_{1,2}$1.9 Hz, 1H, H-1), 4.82 (ABq, J_{AB}12.0 Hz, 2H, CH_2Ph), 4.36 (dd, $J_{5,6}$3.1 Hz, 1H, H-5), 4.25 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 3.97 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.86 (ddd, $J_{6,7}$10.9 Hz, 1H, H-7), 3.80 (dd, $J_{7,8}$2.0 Hz, 1H, H-8), 3.8 (dd, 1H, H-9), 3.36 (dd, $J_{9,10}$7.4 Hz, 1H, H-10), 2.59 (ddd, $J_{6,6'}$14.9 Hz, 1H, H-6), 2.01 (ddd, $J_{5,6'}$11.0 Hz, $J_{6',7}$2.8 Hz, 1H, H-6'), 1.53, 1.29 (2s, 6H, CMe_2), 1.27, 1.24(2d, 6H, $CHMe_2$); HR-MS: found: 458.1930; calc for $C_{23}H_{28}N_3O_7$: 458.1927.

Benzyl 5-C-(isopropyl-2-azido-2,6-dideoxy-3,4-O-isopropylidene-β-D-*galacto*pyrano side-6-yl)—2,3-O-isopropylidene-β-D-*lyxo*-and-*ribo*pentopyranos-4-uloside (22) and (21): To a solution of **18** (90 mg, 0.19 mM) in oxolane (10 mL) and water (2 mL), at room temperature, silver chlorate (61 mg) and osmium tetraoxide (2 mg) were added. The mixture was stirred 24 hours in darkness at room temperature, then was filtered, and distilled water (25 mL) was added. The mixture was extracted with chloroform, and the extract was dried and concentrated under reduced pressure. The crude products **19** and **20** were dissolved in anhydrous acetone. 2,2-Dimethoxypropane (1 mL) and p-toluenesulfonic acid (5 mg) were added and the mixture was stirred 12 hours at room temperature. The mixture was neutralized with triethylamine, filtered and evaporated under reduced pressure. Chromatography (hexane-ether, 4:1) of the residue gave first compound **21** (50 mg, 48%), colorless oil; $[\alpha]_D$ 87° (c 0.4 chloroform); ν_{max}: 3000, 2120, 1760, 1395, 1080 cm^{-1}; ^1H NMR δ: 4.80 (d, $J_{1,2}$4.1 Hz, 1H, H-1), 4.72 (ABq, J_{AB}11.8 Hz, 2H, CH_2Ph), 4.60 (dd, $J_{2,3}$8.0 Hz, 1H, H-2), 4.54 (d, 1H, H-3), 4.54 (dd, $J_{5,6}$3.1 Hz, 1H, H-5), 4.26 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 3.96 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.92 (ddd, $J_{6,7}$10.5 Hz, 1H, H-7), 3.91 (dd, $J_{7,8}$2.0 Hz, 1H, H-8), 3.87 (dd, $J_{8,9}$5.3 Hz, 1H, H-9), 3.37 (dd, $J_{9,10}$7.8 Hz, 1H, H-10), 2.48 (ddd, $J_{6,6'}$14.7 Hz, 1H, H-6), 1.83 (ddd, $J_{5,6'}$11.2 Hz, $J_{6',7}$2.8 Hz, 1H, H-6'), 1.53, 1.50, 1.37, 1.32 (4s, 12H, 2xCMe_2), 1.27, 1.24 (2d, 6H, $CHMe_2$); HR-MS: found: 532.2291; calc for $C_{26}H_{34}N_3O_9$: 532.2295; and as the second product, compound **22** (6 mg, 6%) as a colorless oil; $[\alpha]_D$ 52° (c 1.1, chloroform); ν_{max}: 3000, 2120, 1755, 1390, 1080 cm^{-1}; ^1H NMR δ: 4.99 (d, $J_{1,2}$2.2 Hz, 1H, H-1), 4.80 (ABq, J_{AB}12.6 Hz, 2H, CH_2Ph), 4.66 (dd, $J_{2,3}$7.4 Hz, 1H, H-2), 4.51 (d, 1H, H-3), 4.23 (dd, $J_{5,6}$2.7 Hz, 1H, H-5), 4.26 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 3.95 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.92 (ddd, $J_{6,7}$10.7 Hz, 1H, H-7), 3.92, (dd, 1H, H-8), 3.87 (dd, $J_{8,9}$5.1 Hz, 1H, H-9), 3.35 (dd, $J_{9,10}$7.8 Hz, 1H, H-10), 2.55 (ddd, $J_{6,6'}$15.0 Hz, 1H, H-6), 1.89 (ddd, $J_{5,6'}$10.7 Hz, $J_{6',7}$2.7 Hz, 1H, H-6'), 1.54, 1.53, 1.41, 1.32 (4s, 12H, 2xCMe_2), 1.26, 1.24 (2d, 6H, $CHMe_2$); HR-MS: found: 532.2296; calc for $C_{26}H_{34}N_3O_9$: 532.2295.

Benzyl 5-C-(isopropyl 2-azido-2,6-dideoxy-3,4-O-isopropylidene-β-D-*galacto*pyranosid-6-yl)--2,3-O-isopropylidene-β-D-*allo*pentopyranoside (23): To a solution of **21** (15 mg, 0.027 mM) in oxolane

(5 mL) at -78°C, sodium borohydride (1.3 mg, 0.035 mM) was added. The mixture was stirred 2 h at the same temperature, than was poured into saturated ammonium solution. The mixture was extracted with ether, and the extract was dried and concentrated under reduced pressure. Chromatography (hexane-ether, 9:1) of the residue gave compound **23** (12 mg, 80.7%), as a colorless oil; $[\alpha]_D$ 64° (c 0.25, chloroform); ν_{max}: 3460, 3000, 2120, 1640, 1395, cm^{-1}; ^1H NMR δ: 4.65 (d, $J_{1,2}$5.1 Hz, 1H, H-1), 4.63 (ABq, J_{AB}12.4 Hz, 2H, CH_2Ph), 4.52 (dd, $J_{3,4}$3.9 Hz, 1H, H-3), 4.24 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 4.18 (dd, $J_{2,3}$6.2 Hz, 1H, H-2), 3.94 (dd, $J_{7,8}$2.2 Hz, 1H, H-8), 3.91 (ddd, $J_{6,7}$10.7 Hz, 1H, H-7), 3.90 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 3.87 (dd, $J_{8,9}$5.3 Hz, 1H, H-9), 3.83 (ddd, $J_{5,6}$2.15 Hz, 1H, H-5), 3.74 (dd, $J_{4,5}$9.9 Hz, 1H, H-4), 3.36 (dd, $J_{9,10}$8.1 Hz, 1H, H-10), 2.52 (ddd, $J_{6,6'}$14.6 Hz, 1H, H-6), 2.1 (bs, 1H, OH), 1.63 (ddd, $J_{5,6'}$10.6 Hz, $J_{6',7}$2.6 Hz, 1H, H-6'), 1.53, 1.42, 1.37, 1.33 (4s, 12H, 2xCMe_2), 1.24, 1.21 (2d, 6H, $CHMe_2$); HR-MS: found: 534.2432; calc for $C_{26}H_{36}N_3O_9$: 534.2451.

Benzyl 5-C-(isopropyl 2-azido-2,6-dideoxy-3,4-O-isopropylidene-β-D-*galacto*-pyranoside-6-yl)-2,3-O-isopropylidene-β-D-*talo*pentopyranoside (24): Compound **22** (15 mg, 0.027 mM) was reduced under the same conditions as compound **21**. Chromatography (hexane-ether, 9:1) gave compound **24** (11 mg, 76%), as a colorless oil; $[\alpha]_D$ 41° (c 0.25, chloroform); ν_{max}: 3500, 3000, 2120, 1640, 1395, cm^{-1}; ^1H NMR δ: 4.87 (ABq, J_{AB}12.7 Hz, 2H, CH_2Ph), 4.77 (d, $J_{1,2}$2.6 Hz, 1H, H-1), 4.26 (dd, $J_{3,4}$5.1 Hz, 1H, H-3), 4.23 (dd, $J_{2,3}$6.4 Hz, 1H, H-2), 4.21 (d, $J_{10,11}$8.5 Hz, 1H, H-11), 3.95 (sep, J_{iPr}6.6 Hz, 1H, $CHMe_2$), 3.94 (dd, $J_{7,8}$2.1 Hz, 1H, H-8), 3.88 (dd, $J_{8,9}$5.3 Hz, 1H, H-9), 3.85 (ddd, $J_{6,7}$11.0 Hz, 1H, H-7), 3.64 (dd, $J_{4,5}$1.5 Hz, 1H, H-4), 3.60 (ddd, $J_{5,6}$2.0 Hz, 1H, H-5), 3.34 (dd, $J_{9,10}$7.8 Hz, 1H, H-10), 2.75 (bs, 1H, OH), 2.26 (ddd, $J_{6,6'}$14.9 Hz, 1H, H-6), 2.06 (ddd, $J_{5,6'}$11.2 Hz, $J_{6',7}$2.0 Hz, 1H, H-6'), 1.63, 1.43, 1.34, 1.25 (4s, 12H, 2xCMe_2), 1.21, 1.12 (2d, 6H, $CHMe_2$); HR-MS: found: 534.2458; calc for $C_{26}H_{36}N_3O_9$: 534.2451.

Acetyl 5-C-(isopropyl 2-acetamido-2,6-dideoxy-3,4-O-isopropylidene-β-D-*galacto*-pyranosid-6-yl)-2,3-O-isopropylidene-β-D-*allo*pentofuranoside (27): To a solution of **23** (10 mg, 0.018 mM) in ethanol (10 mL) at room temperature, 5% Pd/C catalyst (10 mg) was added. The mixture was stirred 12 h under the hydrogen atmosphere. The catalyst was filtered off and washed with ethanol. The filtrate was concentrated and dried under reduced pressure. The residue was dissolved in dichloromethane (5 mL). Triethylamine (0.03 mL) and acetic anhydride were added and the mixture was stirred 12 h at room temperature. Toluene (5 mL) was added and the mixture was evaporated under reduced pressure. Chromatography (hexane-ether-methanol, 10:10:1) of the residue gave compound **27** (8 mg, 86%), as a colorless oil; $[\alpha]_D$ 5° (c 0.3 chloroform); ν_{max}: 3600, 3000, 2120, 1750, 1640, 1390, 1200 cm^{-1}; ^1H NMR δ: 6.25 (s, $J_{1,2}$<0.2 Hz, 1H, H-1), 5.86 (bd, $J_{10,NH}$8.5 Hz, 1H, NH), 5.11 (d, $J_{10,11}$8.6 Hz, 1H, H-11), 4.93 (dd, $J_{3,4}$1.0 Hz, 1H, H-3), 4.80 (dd, $J_{8,9}$5,5 Hz, 1H, H-9), 4.69 (d, $J_{2,3}$6.0 Hz, 1H, H-2), 4.22 (dd, $J_{4,5}$5.5 Hz, 1H, H-4), 4.15 (ddd, $J_{6,7}$10.8 Hz, 1H, H-7), 4.04 (dd, $J_{7,8}$2.0 Hz, 1H, H-8), 3.95 (ddd, $J_{5,6}$2.3 Hz, 1H, H-5), 3.91 (sep, J_{iPr}6.2 Hz, 1H, $CHMe_2$), 2.92 (ddd, $J_{9,10}$8.3 Hz, 1H, H-10), 2.20 (ddd, $J_{6,6'}$14.6 Hz, 1H, H-6), 2.1, 1.98 (2s, 6H, 2x$COCH_3$), 1.73 (ddd, $J_{6',5}$9.1 Hz, $J_{6',7}$2.5 Hz, 1H, H-6'), 1.51, 1.50, 1.34, 1.33 (4s, 12H, 2xCMe_2), 1.22, 1.12 (2d, 6H, $CHMe_2$); HR-MS: found: 502.2289; calc for $C_{23}H_{36}NO_{11}$: 502.2288.

Methyl 2,3:4,6-di-O-isopropylidene-β-D-*allo*pyranoside (28), and **1-O-acetyl 2,3:5,6-di-O-isopropylidene-β-D-*allo*furanoside (32):** To a solution of D-allose (250 mg, 1.38 mM) in dimethylformamide (10 mL) at 0°C, 2-methoxypropene (500 mg, 7 mM) and p-toluenesulfonic acid (10 mg) were added. The mixture was stirred 2 h at the same temperature. After neutralization with triethylamine the mixture was poured into ice water, extracted with chloroform, dried and concentrated under reduced pressure. Chromatography (hexane-acetone, 4:1) of the residue gave first compound **28** (120 mg, 32%), as a colorless oil; $[\alpha]_D$ -38° (c 0.5, chloroform); ν_{max}: 3000, 1395, 1120 cm^{-1}; ^1H NMR δ: 4.92 (d, $J_{1,2}$5.99 Hz, 1H, H-1), 4.47 (dd, $J_{2,3}$5.4 Hz, $J_{3,4}$3.4 Hz, 1H, H-3), 4.06 (dd, 1H, H-2), 3.99 (dd, $J_{4,5}$9.65 Hz, 1H, H-4), 3.92 (dd, $J_{5,6}$4.9 Hz, $J_{6,6'}$9.9 Hz, 1H, H-6), 3.89 (ddd, $J_{5,6'}$10.0 Hz, 1H, H-5), 3.73 (dd, 1H, H-6), 3.27 (s, 3H,

OCH_3), 1.59, 1.51, 1.49, 1.40 (4s, 12H, 2xCMe_2); HR-MS: found: 259.1180; calc for $C_{12}H_{19}O_6$: 259.1182. Second fraction from chromatography was concentrated and dried under reduced pressure and the residue was acetylated under standard conditions. Chromatography (hexane-acetone, 4:1) gave compound **32** (152 mg, 36.5%), as colorless oil; $[\alpha]_D$ -42° (c 1.35, chloroform); ν_{max}: 3000, 1760, 1380, 1080 cm^{-1}; ^1H NMR δ: 6.14 (s, 1H, H-1), 4.88 (dd, $J_{2,3}$5.97 Hz, $J_{3,4}$0.5 Hz, 1H, H-3), 4.68 (d, 1H, H-2), 4.11 (dd, $J_{4,5}$9.6 Hz, 1H, H-4), 4.01 (dd, $J_{5,6}$5.8 Hz, $J_{6,6'}$8.3 Hz, 1H, H-6), 3.95 (ddd, $J_{5,6'}$4.8 Hz, 1H, H-5), 3.90 (dd, 1H, H-6), 2.03 (s, 3H, $COCH_3$), 1.47, 1.41, 1.33, 1.31 (4s, 12H, 2xCMe_2); HR-MS: found: 287.1129; calc for $C_{13}H_{19}O_7$: 287.1131.

Methyl 2,3:4,6-di-O-isopropylidene-β-D-*talo*pyranoside (29): To a solution of D-talose (250 mg, 1.38 mM) in dimethylformamide (10 mL) at 0°C, 2-methoxypropene (500 mg, 7 mM) and p-toluenesulfonic acid (10 mg) were added. The mixture was stirred 2 hours at the same temperature. After neutralization with triethylamine the mixture was poured into ice water, extracted with chloroform, dried and concentrated under reduced pressure. Chromatography (hexane-acetone, 4:1) of the residue gave compound **29** (186 mg, 49%), as a colorless oil; $[\alpha]_D$ 28° (c 1.15, chloroform); ν_{max}: 3000, 1395, 1220, 1080 cm^{-1}; ^1H NMRδ: 5.67 (d, $J_{1,2}$4.2 Hz, 1H, H-1), 4.32 (dd, $J_{2,3}$7.08 Hz, $J_{3,4}$4.75 Hz, 1H, H-3), 4.05 (dd, 1H, H-2), 4.15 (dd, $J_{4,5}$2.2 Hz, 1H, H-4), 4.03 (dd, $J_{5,6}$2.3 Hz, $J_{6,6'}$12.7 Hz, 1H, H-6), 3.92 (dd, $J_{5,6'}$2.1 Hz, 1H, H-6'), 3.62 (ddd, 1H, H-5), 3.27 (s, 3H, OCH_3), 1.53, 1.48, 1.39, 1.36 (4s, 12H, 2xCMe_2); HR-MS: found: 259.1180; calc for $C_{12}H_{19}O_6$: 259.1182.

REFERENCES:

1. Takasuki, A.; Arima, K.; Tamura, G. J. Antibiotics, **1971**, 24, 215-224.
2. Eckhardt, K.; Wetzstein, H.; Trumm, H.; Ihn, W. J. Antibiotics, **1980**, 33, 908-910.
3. Edgar, J. A.; Frahn, J. L.; Cockrum, P. A.; Anderton, N.; Jago, M. V.; Culvenor, C. C. J.; Jones, A. J.; Murray, K.; Shaw, J. K. J. Chem. Soc., Chem. Comm., **1982**, 222-224.
4. Sasai, H.; Matsuno, K.; Suami, T. J. Carbohydr. Chem., **1985**, 4, 99-112.
5. Danishefsky, S. J.; Barbachyn, M. J. Am. Chem. Soc., **1985**, 107, 7761-7762.
6. Danishefsky, S. J.; DeNinno, S. L.; Chen, S.; Boisvert, L.; Barbachyn, M. J. Am. Chem. Soc., **1989**, 111, 5810-5818.
7. Ramza, J.; Zamojski, A. Carbohydr. Res., in the press.
8. Maurer, P. J.; Knudsen, Ch. G.; Palkowitz, A. D.; Rapoport, H. J. Org. Chem., **1985**, 50, 325-332.
9. Lemieux, R. U.; Ratcliffe, R. M. Can. J. Chem., **1979**, 57, 1244-1251.
10. Mancuso, A. J.; Huang, S.-L.; Swern, D. J. Org. Chem., **1978**, 43, 2480-2482.
11. Sterzycki, R. Synthesis, **1979**, 724-725.
12. Gawronski, J.; Radocki, D.; Jurczak, J.; Pakulski, Z.; Raczko, J.; Ramza, J.; Zamojski, A. J. Org. Chem., **1990**, 55, 1118-1120.
13. Achmatowicz, O. *Organic Synthesis Today and Tomorrow*; Trost B. M.; Hutchinson, C. R. Eds.; Pergamon Press, Oxford, New York, **1981**, p. 307.
14. Achmatowicz, O.; Grynkiewicz, G. Carbohydr. Res., **1977**, 54, 193-198.
15. Pikul, S.; Jurczak, J.; Ankner, K. Tetrahedron Let., **1986**, 1711-1714.
16. Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. Tetrahedron, **1971**, 27, 1973-1996.
17. Braun, G. J. Am. Chem. Soc., **1929**, 51, 228-248.
18. Gelas, J.; Horton, D. Carbohydr. Res., **1979**, 71, 103-121.
19. Gelas, J.; Horton, D. Heterocycles, **1981**, 16, 1587-1601.

20. Wong, I. C.; Townsend, R. R.; Lee, Y. Ch. Carbohydr. Res., **1987**, 170, 27-46.
21. Leonard, N. J.; Carraway, K. L. J. Heterocycl. Chem., **1966**, 31, 485-498.
22. Perrin, D. D.; Armarego, W. F. L.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press, 1980.
23. Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923-2925.