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Synthesis of N-acylated 7-amino-2,6,7-trideoxy-D-erythrohepto-pyranosides from methyl α-D-mannoside

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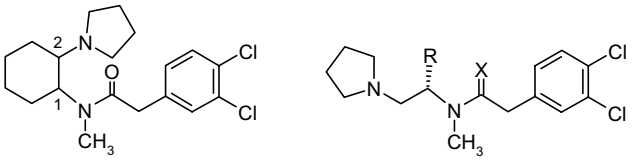
Abstract—Hexopyranoside methyl α-D-mannoside (**8**) was homologated to yield 7-(acylamino)-2,6,7-trideoxy-heptopyranosides **19**–**26**. A crucial reaction step is the radical cleavage of benzylidene derivative **10** to obtain bromide **11**. Since nucleophilic substitution of **11** with KCN provided the bicyclic nitrile **13** instead of nitrile **14**, ketone **11** was protected as the dimethyl acetal **15**. Nucleophilic substitution of **15** with KCN, subsequent hydrogenation with H_2/Raney Ni and acylation with various carboxylic acid derivatives yielded 7-(acylamino)heptopyranosides **19**–**22**.

Keywords: Mannose; 7-(Acylamino)heptopyranosides; Radical cleavage of benzylidene acetal; Nucleophilic substitution; Dioxabicyclo[3.2.1]octane

1. Introduction

The three-dimensional arrangement of pharmacophoric elements is crucial for the interaction of drugs with their targets (enzymes, receptors, DNA, etc.). Monosaccharides represent excellent scaffolds for the introduction of pharmacophoric elements in a defined spatial arrangement, since all positions of a pyranoside ring system are substituted with functional groups. These substituents allow the stereoselective introduction of the desired pharmacophoric groups with defined three-dimensional orientation.

We are interested in the development of novel κ receptor agonists and σ receptor ligands. Several of the described high affinity κ receptor agonists and σ receptor ligands comprise (3,4-dichlorophenyl)acetamide substructure as the pharmacophoric element. In Figure 1 the prototypical κ receptor agonist, U-50488 (**1a**), with (3,4-dichlorophenyl)acetamide substructure is shown.[1] Changing the stereochemistry from the *trans*-(1*S*,2*S*)-configuration (**1a**) into the *cis*-(1*R*,2*S*)-configuration (**1b**) leads to a highly active σ receptor ligand.[1] (3,4-Dichlorophenyl)acetamide **2a** is also a very potent κ receptor agonist with analgesic activity.[2] Formal reduction of amide **2a** affords tertiary amine **2b** with high affinity toward σ receptors.[3]



1a: (1*S*,2*S*) κ-agonist
1b: (1*R*,2*S*) σ-ligand
2a: X = O, R = 2-Pr κ-agonist
2b: X = H_2, R = H σ-ligand

Figure 1. Lead compounds with κ and σ affinity.

The focus of this manuscript is the synthesis of a carbohydrate-based scaffold for drug design. In particular, we are interested in pyranosides bearing an aminoethyl moiety in position 5 (compare compound **3** in Figure 2). It should be possible to introduce amino substituents (e.g., pyrrolidin-1-yl) in position 3 and/or 4 (compound **4**) to mimic κ and σ ligands **1** and **2**. Moreover, it is planned to connect aminoethyl side chain of **3** to the

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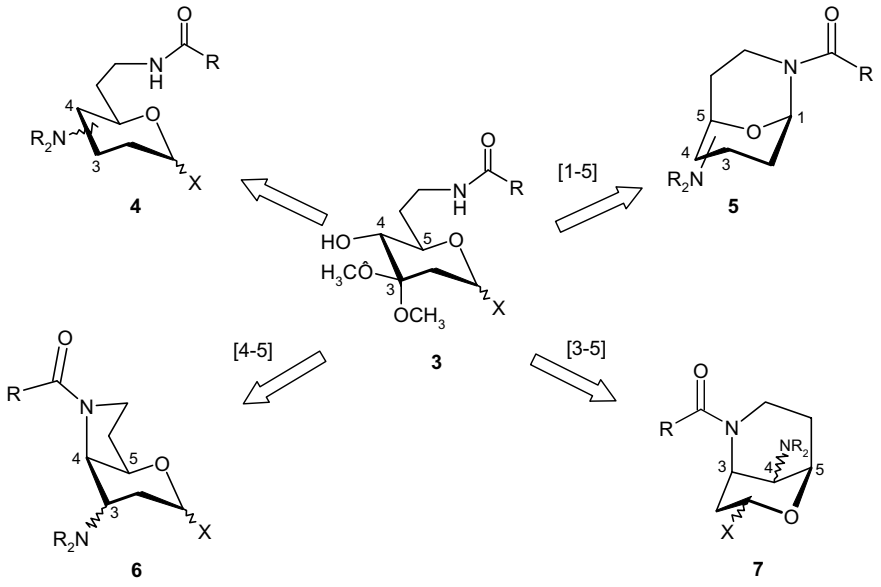


Figure 2. Projected pharmacologically active compounds from 7-acylamino-substituted heptopyranoses.

position 1, 3, or 4 to obtain bicyclic systems **5**–**7**. After introduction of amino substituents (e.g., pyrrolidin-1-yl) the bicyclic systems **5**–**7** represent conformationally constrained analogues of the lead compounds **1** and **2**. Herein, we describe our studies directed to homologization of the monosaccharide D-mannose to provide 7-acylamino-substituted heptopyranose derivatives substituted with functional groups in pyran ring. These substituents will be used for the regio- and stereoselective introduction of further pharmacophoric elements (see Fig. 2).

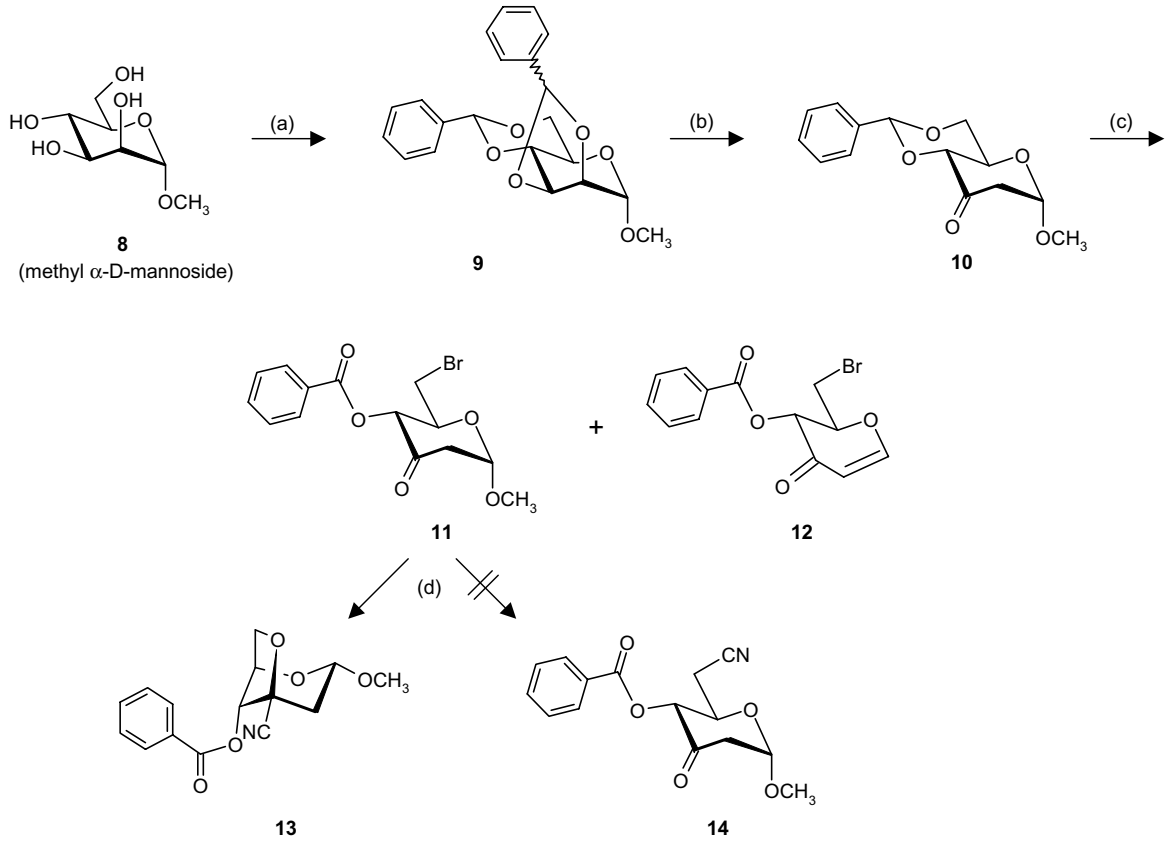
2. Results and discussion

The synthesis started with methyl α-D-mannopyranoside (**8**), which was reacted with 2 equiv of benzaldehyde dimethyl acetal in DMF.[5] Instead of the procedure of Evans, who used a special apparatus to remove DMF and methanol under reduced pressure at 60 °C,[5] the acetalization of **8** was performed in a rotary evaporator at a water bath temperature of 60–70 °C under reduced pressure (about 300 mbar). However, the purification of acetal product **9** turned out to be difficult. In particular, the careful removal of DMF and water was crucial for the further transformation with *n*-butyllithium. Only recrystallization of the crude product from 2-propanol yielded 51% of the pure product **9**. In order to improve the yield of **9**,various solvents were investigated to replace DMF. Finally, the reaction of **8** with benzaldehyde dimethyl acetal was performed using acetonitrile as solvent at a temperature of 60 °C and at a reduced pressure of 600 mbar in a rotary evaporator to afford the acetal product **9** (mixture of diastereomers) in very high yield (97%). Employing this product in the next reaction with *n*-butyllithium at −40 °C afforded ketone **10** in 71% yield (Scheme 1).

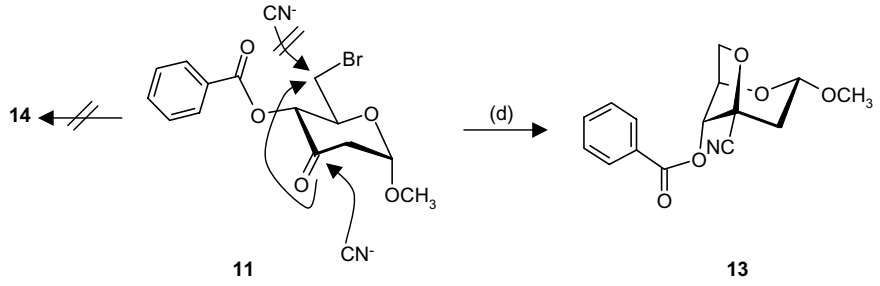
It was planned to transform hexopyranoside **10** into a heptopyranoside system. For this purpose a leaving group should be introduced in position 6 of hexopyranoside system allowing the nucleophilic substitution with cyanide to incorporate the additional carbon atom. Hence, benzylidene derivative **10** was reacted with *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN)[7,8] in a free-radical substitution reaction to provide bromobenzoate **11** in 54% yield. The desired methyl α-D-glycoside **11** was accompanied by small amounts (8%) of the elimination product **12**, which was separated by flash chromatography.

The reaction of bromoketone **11** with KCN in DMSO resulted in a novel product without bromo substituent. Surprisingly, instead of the expected substitution product **14**, the bicyclic compound **13** had been formed. The structure of **13** was unambiguously proven by NMR, IR spectroscopy, and MS. The formation of **13** may be explained by nucleophilic attack of NC^- at carbonyl moiety to yield a cyano-alcoholate, which reacted intramolecularily with bromomethyl group to yield the bicyclic cyanoether **13** instead of the simple substitution product **14** (see Scheme 2).

In order to avoid the cyclization of bromoketone **11**, the carbonyl moiety of **11** was transformed into a dimethyl acetal (→**15**) with methanol and trimethyl orthoformate. This transformation was catalyzed by *p*-toluenesulfonic acid and therefore, led to epimerization of the anomeric center. The α and β anomers **15**α and **15**β were formed in a ratio of 1:1 (total yield 88%) and could be separated by flash chromatography. In a sepa-



Scheme 1. Reagents and conditions: (a) $PhCH(OCH_3)_2$, TosOH, CH_3CN, 60 °C, 600 mbar, 97%. (b) *n*-BuLi, THF, −40 °C, 71%. (c) NBS, AIBN, $BaCO_3$, CCl_4, reflux, 54%; yield of **12** 8%. (d) KCN, DMF, 80 °C, 26%.

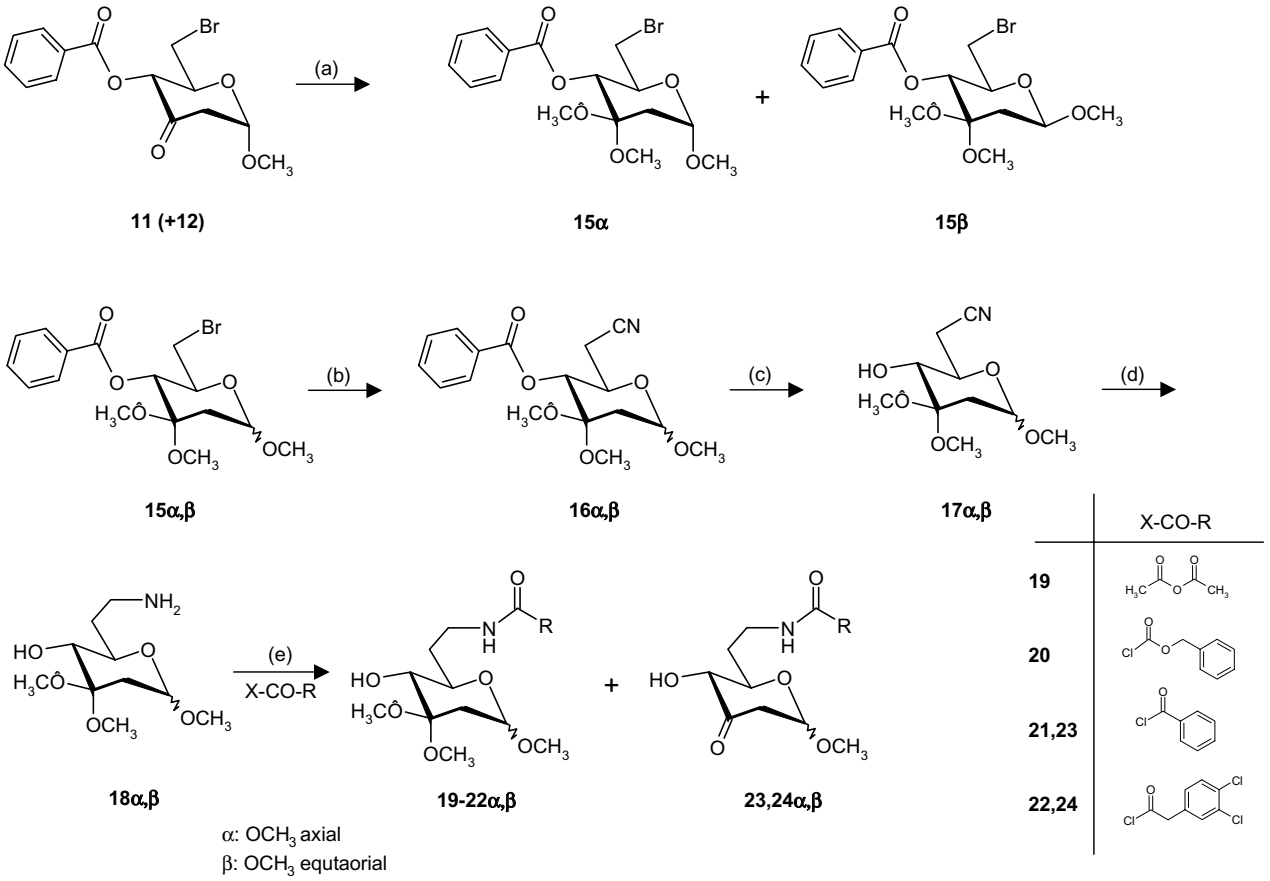


Scheme 2.

rate experiment, it was shown that α,β-unsaturated ketone **12**, the side product during the radical bromination of the benzylidene compound **10**, also reacted with methanol and trimethyl orthoformate to give dimethyl acetals **15**α and **15**β. Therefore, a mixture of **11** and **12** could be used for the synthesis of dimethyl acetals **15**α and **15**β (Scheme 3).

The nucleophilic substitution of the separated anomeric bromo acetals **15**α and **15**β with KCN proceeded to afford the anomeric cyano acetals **16**α and **16**β, respectively. The cleavage of benzoates **16**α and **16**β was performed with NaOH in methanol to obtain anomeric hydroxynitriles **17**α and **17**β, respectively. However, the ^1H NMR spectra of both hydrolysis products **17**α and **17**β showed significant amounts of the corresponding anomer. Obviously anomerization takes place during saponification of ester moiety. Therefore, the synthesis of substantial amounts of hydroxynitriles **17**α and **17**β was usually performed with anomeric mixtures.

Catalytic hydrogenation (4.1 bar) of nitriles **17**α/**17**β using Raney nickel as catalyst[9,10] provided the primary amines **18**α/**18**β. Since hydrogenation of nitriles **17**α/**17**β with Raney nickel requires basic reaction conditions (4:1 methanol:NaOH (5 M)), the one-pot transformation of cyanobenzoates **16**α/**16**β into the primary amines **18**α/**18**β was also investigated and yielded 97% of the



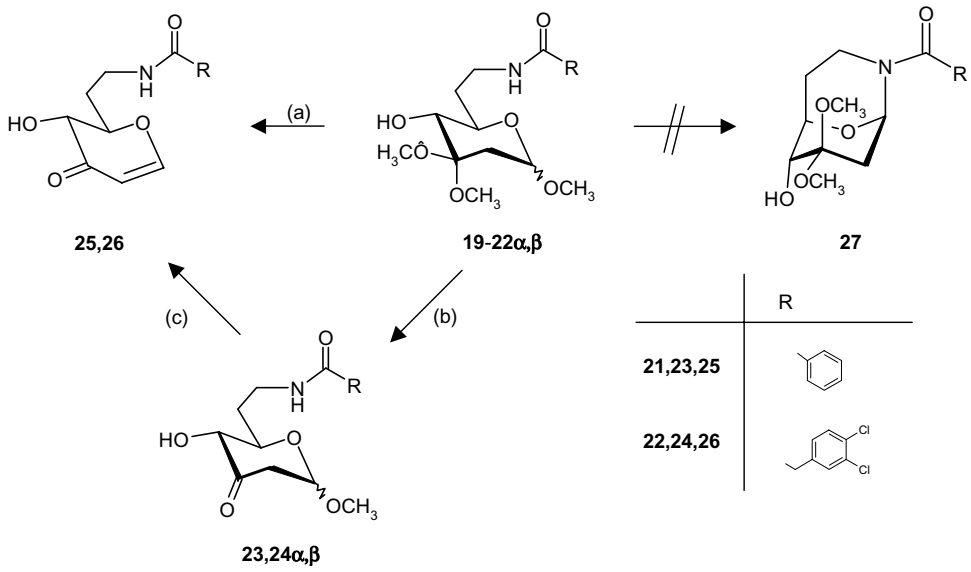
Scheme 3. Reagents and conditions: (a) CH_3OH, $CH(OCH_3)_3$, TosOH, reflux, 88%. (b) KCN, DMSO, 70 °C, **16**α 94%, **16**β 67%. (c) NaOH, CH_3OH, 20 °C, **17**α 76%, **17**β 80%. (d) H_2, Raney Ni, NaOH, CH_3OH, 20 °C, 97% (anomeric mixture). (e) R–COX, NEt_3, CH_2Cl_2, 20 °C (**19**–**21**, **23**); RCO_2H, CDI, CH_2Cl_2, 20 °C, (**22**); yields **19**: 44%; **20**: 60%; **21**: –; **22**: 52%; **23**: 25%.

primary amines **18**α/**18**β over two reaction steps. Because of the high degree of purity, the primary amines **18**α/**18**β were used for the next reaction steps without further purification.

In the next step, the primary amines **18**α/**18**β were acylated with various acylating reagents to yield amides and carbamates **19**–**24** consisting of anomeric mixtures. Interestingly, after acylation of the primary amines **18**α/**18**β with benzoyl chloride and triethylamine, ketone **23**, resulting from additional hydrolysis of acetal moiety, was isolated. The corresponding acetal **21** was only detected by ^1H NMR spectroscopy. With respect to developing novel κ receptor agonists and σ receptor ligands, the introduction of (3,4-dichlorophenyl)acetyl residue was of particular interest. Reaction of the primary amines **18**α/**18**β with (3,4-dichlorophenyl)acetyl chloride in a two-phase system (NaOH, methanol, dichloromethane) provided amides **22**α/**22**β. However, the yield did not exceed 41% since the acylation was accompanied by substantial hydrolysis of the acetal moiety to afford the corresponding ketones **24**α/**24**β. In an alternative synthesis the primary amines **18**α/**18**β were acylated with (3,4-dichlorophenyl)acetic acid in the presence of 1,1′-carbonyldiimidazole to obtain amides **24**α/**24**β in 50% yield calculated over three steps starting with cyanobenzoates **16**α/**16**β. Hydrolysis of dimethyl acetal substructure was not observed with these reaction conditions (Scheme 3).

All attempts to synthesize morphan analogues **27** by intramolecular N/O-acetal formation of amides and carbamate **19**–**22**α/β displaying various nucleophilicity of their nitrogen atoms failed. After heating of (dichlorophenyl)acetamides **22**α/β with *p*-toluenesulfonic acid in 1,2-dichloroethane, the α/β-unsaturated ketone **26** was isolated in 53% yield. During this transformation, the intermediate ketones **24**α/β were detected by thin-layer chromatography. Performing the same reaction at 0 °C for 4 h led to selective hydrolysis of ketone acetal (→**24**α/β), elimination of methanol did not take place. Heating of ketone acetals **22**α/β as well as ketones **24**α/β with $BF_3{\cdot}OEt_2$ or HCl as catalysts also led to the α/β-unsaturated ketone **26** (Scheme 4).

The same reactivity was observed for benzamides **21**α/β, which provided ketones **23**α/β and the α/β-unsaturated ketone **25**, depending on the reaction conditions.



Scheme 4. Reagents and conditions: (a) TosOH, 1,2-dichloroethane, reflux, **26** 53%. (b) TosOH, CH_2Cl_2, 0 °C, **24**α/β 80%. (c) TosOH, CH_2Cl_2, reflux, **25** 34%.

3. Conclusions

Starting from methyl α-D-mannopyranoside (**8**) the anomeric nitriles **16**α/β were prepared in five steps and 22–31% overall yields. Reduction of the cyano moiety and acylation of the resulting primary amines **17**α/β with various carboxylic acid derivatives led to 7-(acylamino)heptopyranosides **19**–**26**. Now, the development of the (acylaminoethyl) substituted pyranosides **19**–**26** into novel κ and σ receptor ligands requires bridging of the pyran system and introduction of amino moieties.

4. Experimental

4.1. Chemistry, general

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Thin-layer chromatography (TLC) was carried out on Silica Gel 60 F_{254} plates (E. Merck). Flash chromatography (FC) was performed with Silica Gel 60, 40–63 μm (E. Merck).[11] Parentheses include the following: (1) diameter of the column (cm), (2) eluent, (3) fraction size (mL), and (4) R_f. Melting points (mp) were determined on an SMP2 (Stuart Scientific) melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer polarimeter model 241 using a 1.0-dm tube with a solute concentration c (g/100 mL) at a temperature of 20 °C. Elemental analyses (CHN) were determined on a VarioEL (Elementaranalysensysteme GmbH) and a Perkin–Elmer Elemental Analyzer model 240. Mass spectra were recorded on MAT 44S, MAT 312, MAT 8200, and TSQ 7000 instruments (Finnigan) in either the electron-impact (EI), chemical ionization (CI), electrospray ionization (LC ESI/ESI direct) or atmospheric pressure chemical ionization (APCI/FIA APCI/LC APCI) mode. IR spectra were recorded on a Perkin–Elmer FTIR spectrophotometer 1605 using the Universal ATR Sampling Accessory (ATR FTIR spectra). ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were determined on a Varian Unity 300 FT NMR spectrometer (Varian); δ values (in ppm) are given relative to the internal standard tetramethylsilane; the coupling constants J (in Hz) are given with 0.5-Hz resolution.

4.2. Preparation of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (9)[4]

To a solution of methyl α-D-mannopyranoside (**8**, 5.0 g, 25.7 mmol) in acetonitrile (30 mL) *p*-toluenesulfonic acid (0.11 g, 0.6 mmol) and benzaldehyde dimethyl acetal (9.1 mL, 60.4 mmol) were added. The reaction was carried out in a rotary evaporator at 60 °C water bath temperature and a reduced pressure of 600 mbar. After 6 h, the residual mixture was concentrated in vacuo until a colorless solid started to precipitate. For complete precipitation of the product, the mixture was added to $NaHCO_3$-containing ice water (3.1 g in 100 mL) under stirring. After filtration of the solvent–water mixture, the colorless solid was dried in vacuo at 60 °C for 24 h. Recrystallization from 2-propanol gave colorless, spicular crystals of **9**: Colorless spicules (2-propanol): mp 179 °C [Ref. 4 178 °C]/176–177 °C (after recrystallization); yield 9.3 g (97%)/4.9 g (51%, after recrystallization); IR (neat): $\tilde{\nu}$ 1082 (νC–O), 736, 696 cm^{-1} (γCH_{oop}, arom.); ^{1}H NMR ($CDCl_3$): δ 3.42 (s, 3 × 0.5H, OCH_3),

3.44 (s, 3 × 0.5H, OCH_3), 3.72–3.94 (m, 3H, 4-H, 5-H, 6-H), 4.15 (d, *J* 5.8 Hz, 0.5H, 2-H), 4.30 (d, *J* 6.4 Hz, 0.5H, 2-H), 4.38–4.30 (m, 1H, 6-H), 4.48 (t, *J* 6.7 Hz, 0.5H, 3-H), 4.64 (dd, *J* 7.6/5.5 Hz, 0.5H, 3-H), 5.03 (s, 0.5H, 1-H), 5.09 (s, 0.5H, 1-H), 5.55 (s, 0.5H, PhCHO$_2$), 5.65 (s, 0.5H, PhCHO$_2$), 5.98 (s, 0.5H, PhCHO$_2$), 6.30 (s, 0.5H, PhCHO$_2$), 7.35–7.57 (m, 10H, arom. H).

4.3. Preparation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-3-ulopyranoside (10)[6]

The bisacetal **9** (5.1 g, 19.3 mmol) was dissolved in THF (100 mL). At −40 °C *n*-butyllithium (2.4 M in *n*-hexane, 20 mL, 48.0 mmol), was added and the solution was stirred at −40 °C for 3.5 h. The color of the solution changed from yellow to red. The mixture was added to NH_4Cl-containing ice water (12 g in 100 mL). Then, THF was evaporated at 30 °C water bath temperature without separation of the layers. The aq solution was cooled to 0 °C, and the yellow crystalline product was filtered off. Recrystallization from EtOH gave **10** as colorless crystals. Colorless, crystalline solid, mp 171–172 °C [Ref. 6 170–171 °C]; yield after recrystallization 2.6 g (71%); IR (neat): $\tilde{\nu}$ 1743 (νC=O), 1129 (νC–O), 908, 736, 650 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 2.66 (d, 1H, *J* 14.7 Hz, 2-H$_{eq}$), 2.82 (dd, *J* 14.7/4.9 Hz 1H, 2-H$_{ax}$), 3.37 (s, 3H, OCH_3), 3.90 (t, *J* 10.1 Hz, 1H, 6-H$_{ax}$), 4.14 (td, *J* 9.8/4.9 Hz, 1H, 5-H), 4.29 (d, *J* 9.8 Hz, 1H, 4-H), 4.37 (dd, *J* 10.1/4.9 Hz, 1H, 6-H$_{eq}$), 5.13 (d, *J* 4.6 Hz, 1H, 1-H), 5.57 (s, 1H, PhCHO$_2$), 7.33–7.35 (m, 3H, arom. H), 7.48–7.51 (m, 2H, arom. H).

4.4. Methyl 4-*O*-benzoyl-6-bromo-2,6-didedoxy-α-D-*erythro*-hex-3-ulopyranoside (11) and 1,5-anhydro-4-*O*-benzoyl-6-bromo-2,6-dideoxy-D-*erythro*-hex-1-en-3-ulose (12)

Ketone **10** (8.1 g, 30.4 mmol) was dissolved in CCl_4 (360 mL) and *N*-bromosuccinimide (8.5 g, 47.8 mmol), barium carbonate (13.8 g, 69.9 mmol) and AIBN (0.44 g, 2.7 mmol) were added. At first the mixture was carefully heated until the reaction started, then it was heated to reflux for 3.5 h. After cooling down the mixture was washed with satd aq $NaHSO_3$ (150 mL) and satd aq NaCl (150 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (8 cm, 80:20 petroleum ether–EtAOc, fractions 50 mL).

4.4.1. Data for 11. R_f 0.31; colorless solid, mp 92 °C, yield 5.3 g (54%); IR (neat): $\tilde{\nu}$ 1728 (νC=O), 1599, 1492, 1451 (νC=C, arom.), 1247 (νO=*C*–*O*), 1109 (νC–O), 733, 706 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 2.71 (dd, *J* 14.0/0.9 Hz, 1H, 2-H$_{eq}$), 2.93 (ddd, *J* 14.0/4.6/0.9 Hz, 1H, 2-H$_{ax}$), 3.44 (s, 3H, OCH_3), 3.61 (dd, *J* 11.3/6.1 Hz, 1H, CH_2Br), 3.71 (dd, *J* 11.3/2.4 Hz, 1H, CH_2Br), 4.36 (dddd, *J* 9.8/6.1/2.4/0.6 Hz, 1H, 5-H), 5.21 (d, *J* 4.3 Hz, 1H, 1-H$_{eq}$), 5.47 (dd, *J* 10.1/0.9 Hz, 1H, 4-H), 7.35 (td, *J* 7.3/1.3 Hz, 2H, arom. H, *m*-pos.), 7.59 (tt, *J* 7.3/1.3 Hz, 1H, arom. H, *p*-pos.), 8.04–8.08 (m, 2H, arom. H, *o*-pos.); ^{13}C NMR ($CDCl_3$): δ 32.5 (1C, C-6), 46.0 (1C, C-2), 55.3 (1C, OCH$_3$), 70.4 (1C, C-4), 75.8 (1C, C-5), 99.6 (1C, C-1), 128.5 (2C, arom. C), 128.8 (1C, arom. C), 130.0 (2C, arom. C), 133.6 (1C, arom. C), 164.8 (1C, PhCOO), 196.9 (1C, CHCOCH$_2$); EIMS: *m*/*z* [%] 105 [PhCO$^+$, 100], 77 [Ph$^+$, 24]; CIMS (NH_3): *m*/*z* [%] 360/362 [M + NH$_4^+$, 79/78], 343/345 [MH$^+$, 32/32], 328/330 [MH$^+$−CH$_3$, 100/95], 311/313 [MH$^+$− OCH$_3$, 30/28], 105 [PhCO$^+$, 25]; Anal. Calcd for $C_{14}H_{15}BrO_5$ (343.2): C, 48.99; H, 4.41. Found: C, 48.97; H, 4.37.

4.4.2. Data for 12. R_f 0.17; colorless oil; yield 0.70 g (8%); IR (met): $\tilde{\nu}$ 1730 (νO=*C*–O), 1690 (νC=O), 1655 (νC=C), 1597, 1491, 1451 (νC=C, arom.), 1245 (νO=*C*–*O*), 1109, 1040 (νC–O), 702, 690 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 3.69 (dd, *J* 11.9/4.9 Hz, 1H, CH_2Br), 3.79 (dd, *J* 11.9/2.7 Hz, 1H, CH_2Br), 4.79 (ddd, *J* 12.8/5.2/2.7 Hz, 1H, 2-H), 5.56 (d, *J* 5.8 Hz, 1H, 5-H), 5.81 (d, *J* 12.8 Hz, 1H, 3-H), 7.44 (d, *J* 6.1 Hz, 1H, 6-H), 7.45–7.51 (m, 2H, arom. H, *m*-pos.), 7.62 (tt, *J* 7.3/1.5 Hz, 1H, arom. H, *p*-pos.), 8.07–8.10 (m, 2H, arom. H, *o*-pos.); CIMS (isobutane): *m*/*z* [%] 311/313 [MH$^+$, 100/95], 189/191 [M−PhCOO, 4/4], 105 [PhCO$^+$, 7]; Anal. Calcd for $C_{13}H_{11}BrO_4$ (311.1): C, 50.19; H, 4.56. Found: C, 50.08; H, 4.20.

4.5. [(1*R*,3*S*,5*S*,8*R*)-5-Cyano-3-methoxy-2,6-dioxabicyclo[3.2.1]octane-8-yl] benzoate (13)

Bromide **11** (120 mg, 0.35 mmol) was dissolved in DMF (5 mL), and KCN (70 mg, 1.05 mmol) was added. After stirring at 80 °C for 1.5 h, H_2O (5 mL) was added, and the mixture was extracted with petroleum ether (10 mL). Then, the aq layer was extracted with 95:5 petroleum ether–EtOAc (3 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (1 cm, 8:2 petroleum ether–EtOAc, fractions 2 mL, R_f 0.22). Colorless solid: mp 80 °C; yield 30 mg (26%); $[\alpha]_{589}$ −62.5 (*c* 0.048, MeOH); IR (neat): $\tilde{\nu}$ 2255 (νC≡N), 1734 (νO=*C*–O), 1269 (O=*C*–*O*), 1100 (νC–O), 909, 734 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 2.39 (dd, *J* 13.7/4.9 Hz, 1H, 4-H$_{eq}$), 2.45 (dd, *J* 13.7/7.6 Hz, 1H, 4-H$_{ax}$), 3.50 (s, 3H, OCH_3), 4.27 (dd, *J* 10.7/2.7 Hz, 1H, 7-H), 4.32 (d, *J* 10.7 Hz 1H, 7-H), 4.81 (t, *J* 2.7 Hz, 1H, 1-H), 4.99 (dd, *J* 7.3/5.2 Hz, 1H, 3-H), 5.30 (d, *J* 3.0 Hz, 1H, 8-H), 7.50 (t, *J* 7.3 Hz, 2H, arom. H, *m*-pos.), 7.63 (tt, *J* 7.3/1.7 Hz, 1H, arom. H, *p*-pos.), 8.08–8.12 (m, 2H, arom. H, *o*-pos.); EIMS: *m*/*z* [%] 289 [M$^+$, 1], 184 [M−PhCO, 3], 105 [PhCO$^+$, 100], 77 [Ph$^+$, 15]; CIMS

(NH_3): *m*/z [%] 307 [$M+NH_4^+$, 100], 105 [$PhCO^+$, 17]; HREIMS: calcd for $C_{15}H_{15}NO_5$: 289.0950. Found: 289.0950.

4.6. Methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (15α) and methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-β-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (15β)

p-Toluenesulfonic acid (0.13 g, 0.68 mmol) and trimethyl orthoformate (17 mL, 155 mmol) were added to a solution of ketone **11** (4.1 g, 11.9 mmol) in MeOH (40 mL), and the mixture was heated to reflux for 24 h. After completion of the reaction, a saturated solution of $NaHCO_3$ (60 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (5.5 cm, 8:2 petroleum ether–EtOAc, fractions 20 mL).

4.6.1. Data for 15α. R_f 0.35; colorless oil; yield 1.50 g (32%); $[\alpha]_{589}$ +55.0 (*c* 0.166, MeOH); IR (neat): $\tilde{\nu}$ 1721 (ν*O*=*C*–O), 1263 (νO=*C*–*O*), 1110, 1048 (νC–O), 708 cm^{-1} (γCH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 2.08 (ddd, *J* 14.3/3.9/0.9 Hz, 1H, 2-H_{eq}), 2.23 (dd, *J* 14.3/4.5 Hz, 1H, 2-H_{ax}), 3.25 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.53–3.57 (m, 2H, CH_2Br), 4.33 (td, *J* 6.7/5.2 Hz, 1H, 5-H), 4.80 (t, *J* 4.3 Hz, 1H, 1-H_{eq}), 5.23 (dd, *J* 6.7/0.9 Hz, 1H, 4-H), 7.46 (td, *J* 7.3/1.5 Hz, 2H, arom. H, *m*-pos.), 7.59 (tt, *J* 7.3/1.5 Hz, 1H, arom. H, *p*-pos.), 8.06–8.10 (m, 2H, arom. H, *o*-pos.); ^{13}C NMR ($CDCl_3$): δ 31.5 (1C, C-6), 35.6 (1C, C-2), 48.9 (1C, O*C*H_3), 49.5 (1C, O*C*H_3), 56.0 (1C, O*C*H_3), 73.3 (1C, C-4), 74.1 (1C, C-5), 97.2 (1C, C-1), 100.1 (1C, C-3), 128.5 (2C, arom. C, *m*-pos.), 128.6 (1C, quart., arom. C), 133.5 (2C, arom. C, *o*-pos.), 133.5 (1C, arom. C, *p*-pos.), 165.4 (1C, Ph*C*OO); EIMS: *m*/*z* [%] 357/359 [M−OCH_3, 6/6]; CIMS (NH_3): *m*/*z* [%] 406/408 [$M+NH_4^+$, 4.5/4.5], 357/359 [M−OCH_3, 100/97]; Anal. Calcd for $C_{16}H_{21}BrO_6$ (389.2): C, 49.37; H, 5.44. Found: C, 49.53; H, 5.43.

4.6.2. Data for 15β. R_f 0.41; colorless solid; mp 73 °C, yield 0.61 g (13%)]; $[\alpha]_{589}$ −22.0 (*c* 0.216, MeOH); ^1H NMR ($CDCl_3$): δ 1.87 (dd, *J* 13.4/7.3 Hz, 1H, 2-H_{ax}), 2.31 (dd, *J* 13.4/2.7 Hz, 1H, 2-H_{eq}), 3.24 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.52 (dd, *J* 11.0/7.3 Hz, 1H, CH_2Br), 3.54 (s, 3H, OCH_3), 3.58 (dd, *J* 11.0/4.0 Hz, 1H, CH_2Br), 4.07 (td, *J* 7.8/3.9 Hz, 1H, 5-H), 4.74 (dd, *J* 7.6/2.7 Hz, 1H, 1-H_{ax}), 5.27 (d, *J* 7.9 Hz, 1H, 4-H), 7.47 (t, *J* 7.6 Hz, 2H, arom. H, *m*-pos.), 7.59 (tt, *J* 7.5/1.5 Hz, 1H, arom. H, *p*-pos.), 8.04–8.08 (m, 2H, arom. H, *o*-pos.); ^{13}C NMR ($CDCl_3$): 32.4 (1C, C-6), 37.5 (1C, C-2), 49.1 (1C, O*C*H_3), 49.7 (1C, O*C*H_3), 56.7 (1C, O*C*H_3), 71.9 (1C, C-4), 72.1 (1C, C-5), 97.5 (1C, C-3), 98.4 (1C, C-1), 128.6 (2C, arom. C, *m*-pos.), 129.4 (1C, quart., arom. C), 130.0 (2C, arom. C, *o*-pos.), 133.5 (1C, arom. C, *p*-pos.), 165.3 (1C, Ph*C*OO); Anal. Calcd for $C_{16}H_{21}BrO_6$ (389.2): C, 49.37; H, 5.44. Found: C, 49.11; H, 5.23.

In addition to the pure samples **15**α and **15**β, a mixture of **15**α/**15**β, was isolated as a colorless: oil, yield 2.0 g (43%); total yield 88%.

4.7. Methyl 4-*O*-benzoyl-6-cyano-2,6-dideoxy-α-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (16α)

A solution of **15**α (1.5 g, 3.8 mmol) and KCN (1.5 g, 23.7 mmol) in DMSO (20 mL) was stirred at 70 °C for 2.5 h. After cooling to room temperature, water (25 mL) was added, and the aq layer was extracted with 95:5 petroleum ether–EtOAc (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (4 cm, 8:2 EtOAc–petroleum ether, fractions 10 mL, R_f 0.39). Colorless oil: yield 1.2 g (94%); $[\alpha]_{589}$ +59.0 (c 0.473, MeOH); IR (neat): $\tilde{\nu}$ 1720 (ν*O*=*C*–O), 1266 (νO=*C*–*O*), 1105, 1049 (νC–O), 711 cm^{-1} (γCH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 2.05 (dd, *J* 14.6/3.9 Hz, 1H, 2-H_{ax}), 2.27 (dd, *J* 14.6/3.9 Hz, 1H, 2-H_{eq}), 2.62 (dd, 1H, *J* 16.8/4.3 Hz, CH_2CN), 2.76 (dd, 1H, *J* 16.8/9.3 Hz, CH_2CN), 3.24 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 4.38 (ddd, *J* 8.9/7.3/4.3 Hz, 1H, 5-H), 4.80 (t, *J* 3.9 Hz, 1H, 1-H_{eq}), 5.11 (d, *J* 7.3 Hz, 1H, 4-H), 7.46 (t, *J* 7.6 Hz, 2H, arom. H, *m*-pos.), 7.60 (tt, *J* 7.5/1.5 Hz, 1H, arom. H, *p*-pos.), 8.06–8.09 (m, 2H, arom. H, *o*-pos.); ^{13}C NMR ($CDCl_3$): δ 20.7 (1C, C-6), 35.6 (1C, C-2), 49.0 (1C, O*C*H_3), 49.6 (1C, O*C*H_3), 55.9 (1C, O*C*H_3), 67.4 (1C, C-5 *o*.C-4), 73.1 (1C, C-4 *o*.C-5), 97.4 (1C, C-1 *o*.C-3), 97.9 (1C, C-3 *o*.C-1), 116.8 (1C, *C*N), 128.5 (2C, arom. C), 129.0 (1C, arom. C), 130.0 (2C, arom. C), 133.7 (1C, arom. C), 165.6 (1C, Ph*C*OO); EIMS: *m*/*z* [%] 304 [M−OCH_3, 10], 272 [M−$HOCH_3$−OCH_3, 8], 105 [$PhCO^+$, 100], 77 [Ph^+, 24]; CIMS (NH_3): *m*/*z* [%] 353 [$M+NH_4^+$, 100], 304 [M−OCH_3, 99]; Anal. Calcd for $C_{17}H_{21}NO_6$ (335.4): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.84; H, 6.46; N, 4.15.

4.8. Methyl 4-*O*-benzoyl-6-cyano-2,6-dideoxy-β-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (16β)

A solution of **15**β (810 mg, 2.1 mmol) and KCN (843 mg, 12.9 mmol) in DMSO (25 mL) was stirred at 70 °C for 2.5 h. After cooling to room temperature, water (25 mL) was added, and the aq layer was extracted with 95:5 petroleum ether–EtOAc (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (3 cm, 8:2 EtOAc–petroleum ether, fractions 10 mL, R_f 0.43). Colorless solid: mp 112 °C; yield 465 mg (67%); $[\alpha]_{589}$ −6.0 (*c* 0.360, MeOH); ^1H NMR ($CDCl_3$): δ 1.85 (dd,

J 13.7/7.6 Hz, 1H, 2-H_{ax}), 2.33 (dd, *J* 13.7/2.7 Hz, 1H, 2-H_{eq}), 2.63 (dd, 1H, *J* 16.8/4.3 Hz, CH_2CN), 2.79 (dd, *J* 16.8/8.9 Hz, 1H, CH_2CN), 3.24 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 4.13 (ddd, *J* 8.9/7.9/4.3 Hz, 1H, 5-H), 4.76 (dd, *J* 7.6/2.7 Hz, 1H, 1-H_{ax}), 5.15 (d, *J* 7.9 Hz, 1H, 4-H), 7.48 (t, *J* 7.5 Hz, 2H, arom. H, *m*-pos.), 7.61 (tt, *J* 7.5/1.5 Hz, 1H, arom. H, *p*-pos.), 8.04–8.07 (m, 2H, arom. H, *o*-pos.); ^{13}C NMR ($CDCl_3$): δ 21.6 (1C, C-6), 37.4 (1C, C-2), 49.1 (1C, OCH_3), 49.7 (1C, OCH_3), 56.8 (1C, OCH_3), 70.0 (1C, C-5 *o*.C-4), 73.9 (1C, C-4 *o*.C-5), 97.2 (1C, C-1 *o*.C-3), 100.3 (1C, C-3 *o*.C-1), 117.0 (1C, *C*N), 128.6 (2C, arom. C), 129.0 (1C, arom. C), 129.9 (2C, arom. C), 133.7 (1C, arom. C), 165.4 (1C, Ph*C*OO); Anal. Calcd for $C_{17}H_{21}NO_6$ (335.4): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.55; H, 6.29; N, 4.05.

4.9. Methyl 6-cyano-2,6-dideoxy-α-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (17α)

A mixture of **16**α (0.76 g, 2.3 mmol), MeOH (40 mL), and 3 N NaOH (10 mL) was stirred at room temperature for 9 h. After addition of H_2O (10 mL), it was extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (3 cm, 7:3 petroleum ether–EtOAc, fractions 10 mL, R_f 0.31). Colorless crystals: mp 83 °C; yield 0.4 g (76%); $[\alpha]_{589}$ +66.2 (*c* 0.303, MeOH); IR (neat): $\tilde{\nu}$ 2945 (νC–H), 2279 (νCN), 1127, 1046 cm^{-1} (νC–O); ^{1}H NMR ($CDCl_3$): δ 1.74 (dd, *J* 15.0/4.5 Hz, 1H, 2-H_{ax}), 2.31 (dd, *J* 15.2/1.2 Hz, 1H, 2-H_{eq}), 2.60 (dd, *J* 16.9/7.8 Hz, 1H, CH_2CN), 2.85 (dd, *J* 16.5/3.5 Hz, 1H, CH_2CN), 3.45 (t, *J* 9.9 Hz, 1H, 4-H), 3.33 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.82 (ddd, *J* 9.5/7.7/3.1 Hz, 1H, 5-H), 4.73 (dd, *J* 4.5/1.2 Hz, 1H, 1-H_{eq}), a signal for the OH-proton was not observed; ^{13}C NMR ($CDCl_3$): δ 20.8 (1C, C-6), 34.8 (1C, C-2), 49.1 (1C, OCH_3), 51.0 (1C, OCH_3), 55.4 (1C, OCH_3), 67.5 (1C, C-5), 74.3 (1C, C-4), 96.5 (1C, C-1 *o*.C-3), 97.8 (1C, C-3 *o*.C-1), 117.5 (1C, *C*N); EIMS: *m*/*z* [%] 231 [M^+, 1], 200 [M−OCH_3, 7], 168 [M−$HOCH_3$−OCH_3, 25], 88 [–$C(OCH_3)_2$–CH_2^+, 100]; CIMS (NH_3): *m*/*z* [%] 249 [M + NH_4^+, 74]; CIMS (isobutane): *m*/*z* [%] 288 [M + $C_4H_9^+$, 13], 232 [MH^+, 28], 168 [M−$HOCH_3$−OCH_3, 47]; Anal. Calcd for $C_{10}H_{17}NO_5$ (231.3): C, 51.94; H, 7.41; N, 6.06. Found: C, 52.13; H, 7.54; N, 5.82.

4.10. Methyl 6-cyano-2,6-dideoxy-β-D-*erythro*-hex-3-ulopyranoside dimethyl ketal (17β)

A mixture of **16**β (316 mg, 0.9 mmol), MeOH (15 mL), and 3 N NaOH (6 mL) was stirred at room temperature for 9 h. After addition of H_2O (5 mL), the mixture was extracted with CH_2Cl_2 (25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (3 cm, 7:3 petroleum ether–EtOAc, fractions 10 mL, R_f 0.32). Colorless solid: mp 82 °C; yield 174 mg (80%); $[\alpha]_{589}$ −35.0 (*c* 0.195, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.59 (dd, *J* 14.0/9.5 Hz, 1H, 2-H_{ax}), 2.29 (dd, *J* 14.0/2.1 Hz, 1H, 2-H_{eq}), 2.64 (dd, *J* 16.8/7.9 Hz, 1H, CH_2CN), 2.47 (s, broad, 1H, OH), 2.89 (dd, *J* 16.8/3.4 Hz, 1H, CH_2CN), 3.41–3.47 (m, 1H, 4-H), 3.34 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.58 (ddd, *J* 9.3/7.8/3.6 Hz, 1H, 5-H), 4.47 (dd, *J* 9.5/2.1 Hz, 1H, 1-H_{ax}); ^{13}C NMR ($CDCl_3$): δ 21.2 (1C, C-6), 37.0 (1C, C-2), 48.9 (1C, OCH_3), 50.8 (1C, OCH_3), 56.5 (1C, OCH_3), 71.7 (1C, C-5), 74.4 (1C, C-4), 97.3 (1C, C-1 *o*.C-3), 99.7 (1C, C-3 *o*.C-1), 117.3 (1C, *C*N); Anal. Calcd for $C_{10}H_{17}NO_5$ (231.3): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.64; H, 7.36; N, 5.95.

4.11. Methyl 7-amino-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside dimethyl ketal (18α and 18β)

A solution of **16** (anomeric mixture, 1.0 g, 3.1 mmol) in MeOH (60 mL) and 5 N NaOH (15 mL) was stirred at room temperature for 2 h. After completion of the reaction, Raney nickel was added to the resulting hydrolysis product (**17**, anomeric mixture), and the mixture was shaken under an H_2 atmosphere (4.1 bar) at room temperature for 24 h. Raney Ni was removed by filtration through Celite® AFA. The solution was concentrated to a volume of about 20 mL. After addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a yellow oil (yield 0.70 g, 97%), which was pure enough for further reactions. In order to characterize the primary amine **18**, a sample (103 mg) of the residue was purified by FC [2 cm, 8:2 ethanol–acetone, 2% *N*-ethyl-*N,N*-dimethylamine, fractions 5 mL, R_f 0.11, yield 17 mg (<10%)]; IR (neat): $\tilde{\nu}$ 2945 (νC–H), 1128, 1053 cm^{-1} (νC–O); ^{1}H NMR ($CDCl_3$): δ 1.47 (dd, *J* 13.7/9.8 Hz, 0.45H, 2-H_{ax}, β-is.), 1.69 (dd, *J* 14.9/4.6 Hz, 0.55H, 2-H_{ax}, α-is.), 1.70–1.86 (m, 1H, CH_2CH_2NH_2, α+β-is.), 1.92–2.03 (m, 1H, CH_2CH_2NH_2, α+β-is.), 2.21 (dd, *J* 12.8/2.1 Hz, 0.45H, 2-H_{eq}, β-is.), 2.23 (dd, *J* 14.0/2.0 Hz, 0.55H, 2-H_{eq}, α-is.), 2.94–3.07 (m, 1H, $CH_2CH_2NH_2$, α+β-is.), 2.80–2.91 (m, 1H, $CH_2CH_2NH_2$, α+β-is.), 3.29–3.53 (m, 0.45H, 5-H, β-is./1H, 4-H, α+β-is./2H, NH_2, α+β-is.), 3.28 (s, 3 × 0.55H, OCH_3, α-is.), 3.30 (s, 3 × 0.55H, OCH_3, α-is.), 3.31 (s, 3 × 0.45H, OCH_3, β-is.), 3.34 (s, 3 × 0.55H, OCH_3, α-is.), 3.37 (s, 3 × 0.45H, OCH_3, β-is.), 3.42 (s, 3 × 0.45H, OCH_3, β-is.) 3.67 (td, *J* 8.6/4.0 Hz, 0.55H, 5-H, α-is.), 4.39 (dd, *J* 9.8/1.8 Hz, 0.45H, 1-H_{ax}, β-is.), 4.63 (dd, *J* 4.4/2.1 Hz, 0.55H, 1-H_{eq}, α-is.), a signal for the OH-proton was not found; the ratio of α- and β-anomers was 55:45; EIMS: *m*/*z* [%] 204 [M−OCH_3, 7], 173 [M−2 × OCH_3,

3], 88 [$C(OCH_3)_2$–CH_2^+–, 100]; CIMS (NH_3): *m/z* [%] 236 [MH^+, 17], 204 [M−OCH_3, 100]; HREIMS: calcd for $C_9H_{18}NO_5$: 220.1185. Found: 220.1185.

4.12. Methyl 7-(acetylamino)-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside dimethyl ketal (19α and 19β)

Under N_2 atmosphere, Et_3N (0.4 mL, 2.9 mmol) and Ac_2O (0.2 mL, 2.1 mmol) were added to a solution of crude primary amine **18** (anomeric mixture, 101 mg, 0.37 mmol) in CH_2Cl_2 (10 mL). After stirring the mixture at room temperature for 2.5 h, the mixture was concentrated in vacuo, and the residue was purified by FC (2 cm, 9:1 EtOAc–MeOH, fractions 5 mL, R_f 0.31). Yellow oil: yield 47 mg (44% referring to nitrile **16**); IR (neat): $\tilde{\nu}$ 3299 (νN–H), 2943 (νC–H), 1650 (ν*O*=*C*–NH, amide I), 1553 (δN–H, amide II), 1129, 1047 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.52 (dd, *J* 14.0/9.8 Hz, 0.45H, 2-H_{ax}, β-is.), 1.61–1.76 (m, 1H, C$H_2$$CH_2$NH, α+β-is.), 1.73 (dd, *J* 14.9/4.3 Hz, 0.55H, 2-H_{ax}, α-is.), 1.96 (s, 3H, NHCOCH_3, α+β-is.), 2.00–2.19 (m, 1H, C$H_2$$CH_2$NH, α+β-is.), 2.25 (dd, *J* 14.9/1.8 Hz, 0.55H, 2-H_{eq}, α-is.), 2.30 (dd, *J* 14.0/1.8 Hz, 0.45H, 2-H_{eq}, β-is.), 2.42 (d, *J* 7.6 Hz, 0.45H, OH, β-is.), 2.53 (d, *J* 9.5 Hz, 0.55H, OH, α-is.), 3.24–3.59 (m, 1H, 4-H, α+β-is./2H, CH_2CH_2NH, α+β-is.), 3.32 (s, 3 × 0.55H, OCH_3, α-is.), 3.33 (s, 3 × 0.55H, OCH_3, α-is.), 3.34 (s, 3 × 0.45H, OCH_3, β-is.), 3.36 (s, 3 × 0.55H, OCH_3, α-is.), 3.38 (s, 3 × 0.45H, OCH_3, β-is.), 3.49 (s, 3 × 0.45H, OCH_3, β-is.), 3.64 (td, *J* 9.2/2.7 Hz, 1H, 5-H, α+β-is.), 4.69 (dd, *J* 4.5/2.0 Hz, 0.55H, 1-H_{eq}, α-is.), 4.40 (dd, *J* 9.8/2.1 Hz, 0.45H, 1-H_{ax}, β-is.), 6.00 (s, broad, 1H, NH, α+β-is.); the ratio of α- and β-anomers was 55:45; EIMS: *m/z* [%] 246 [M−OCH_3, 2], 215 [M−2 × OCH_3, 2]; ESIMS: *m/z* [%] 300 [M+Na^+, 100], 214 [M−$HOCH_3$−OCH_3, 31]; CIMS (NH_3): *m/z* [%] 295 [$M + NH_4^+$, 3], 278 [MH^+, 13], 246 [M−OCH_3, 100], 214 [M−$HOCH_3$−OCH_3, 83]. HREIMS: calcd for $C_{11}H_{20}NO_5$: 246.1342. Found: 246.1338.

4.13. Methyl 7-(benzyloxycarbonylamino)-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside dimethyl ketal (20α and 20β)

Under N_2 atmosphere, Et_3N (0.4 mL, 2.9 mmol) and benzyl chloroformate (0.4 mL, 2.8 mmol) were added to a solution of crude primary amine **18** (anomeric mixture, 180 mg, 0.77 mmol) in CH_2Cl_2 (15 mL). After stirring the reaction mixture at room temperature for 5 h, it was concentrated in vacuo. The residue was purified by FC (2 cm, 6:4 petroleum ether–EtOAc, fractions 5 mL, R_f 0.22). Colorless oil: yield 177 mg (60%, referring to nitrile **16**); IR (neat): $\tilde{\nu}$ 3347 (νN–H), 1702 (ν*O*=*C*–NH, amide I), 1525 (δN–H, amide II), 1250, 1128, 1051 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 50 (dd, *J* 14.0/9.8 Hz, 0.5H, 2-H_{ax}, β-is.), 1.61–1.72 (m, 1H, C$H_2$$CH_2$NH, α+β-is.), 1.69 (dd, *J* 14.9/4.6 Hz, 0.5H, 2-H_{ax}, α-is.), 2.04–2.18 (m, 1H, m, 1H, C$H_2$$CH_2$NH, α+β-is.), 2.23 (dd, *J* 14.0/2.1 Hz, 0.5H, 2-H_{eq}, β-is.), 2.27 (dd, *J* 14.0/1.8 Hz, 0.5H, 2-H_{eq}, α-is.), 2.28 (d, *J* 8.5 Hz, 0.5H, OH, β-is.), 2.44 (d, *J* 9.8 Hz, 0.5H, OH, α-is.), 3.25–3.48 (m, 1H, 4-H, α+β-is./2H, CH_2CH_2NH, α+β-is.), 3.28 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.29 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.31 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.33 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.35 (s, 6 × 0.5H, OCH_3, α/β-is.), 3.59 (td, *J* 9.2/2.4 Hz, 1H, 5-H, α+β-is.), 4.35 (dd, *J* 9.8/2.1 Hz, 0.5H, 1-H_{ax}, β-is.), 4.65 (dd, *J* 4.3/1.8 Hz, 0.5H, 1-H_{eq}, α-is.), 5.07 (s, 2H, OCH_2Ph, α+β-is.), 5.13 (s, broad, 1H, NH, α+β-is.), 7.26–7.38 (m, 5H, arom. H, α+β-is.); the ratio of α- and β-anomers was 1:1; EIMS: *m/z* [%] 91 [CH_2Ph^+, 100]. ESIMS: *m/z* [%] 392 [M+Na^+, 100]. CIMS (NH_3): *m/z* [%] 287 [$M + NH_4^+$, 3], 338 [M−OCH_3, 16], 306 [M^+−$HOCH_3$−OCH_3, 100]. HREIMS: calcd for $C_{17}H_{24}NO_6$: 338.1604. Found: 338.1611.

4.14. Methyl 7-[2-(3,4-dichlorophenyl)acetylamino]-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside dimethyl ketal (22α and 22β)

Under N_2 atmosphere, a solution of (3,4-dichlorophenyl)acetic acid (540 mg, 2.6 mmol) and 1,1′-carbonyldiimidazole (420 mg, 2.6 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 1 h. Then, the unpurified primary amine **18** (anomeric mixture, 498 mg, 2.1 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to the mixture under ice cooling. The mixture was stirred at room temperature for 6 h. After completion of the transformation the solvent was removed in vacuo, and the residue was purified by FC (3 cm, 95:5 EtOAc–acetone, fractions 10 mL, R_f 0.31). Pale-yellow oil: yield 468 mg (52%, referring to nitrile **16**); IR (neat): $\tilde{\nu}$ 3301 (νN–H), 2942 (νC–H), 1647 (ν*O*=*C*–NH, amide I), 1552 (δN–H, amide II), 1129, 1048 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.49 (dd, *J* 14.0/9.8 Hz, 0.5H, 2-H_{ax}, β-is.), 1.59–1.75 (m, 1H, C$H_2$$CH_2$NH, α+β-is.), 1.64 (dd, *J* 14.9/4.3 Hz, 0.5H, 2-H_{ax}, α-is.), 2.00–2.14 (m, 1H, C$H_2$$CH_2$NH, α+β-is.), 2.24 (dd, *J* 14.9/1.5 Hz, 0.5H, 2-H_{eq}, α-is.), 2.28 (dd, *J* 14.0/1.8 Hz, 0.5H, 2-H_{eq}, β-is.), 2.36 (d, *J* 8.6 Hz, 0.5H, OH, β-is.), 2.46 (d, *J* 10.1 Hz, 0.5H, OH, α-is.), 3.21–3.62 (m, 1H, 4-H, α+β-is./1H, 5-H, α+β-is./2H, CH_2CH_2NH, α+β-is.), 3.17 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.30 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.33 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.34 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.36 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.42 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.47 (s, 2 × 0.5H, COCH_2Ph, α/β-is.), 3.50 (s, 2 × 0.5H, COCH_2Ph, α/β-is.), 4.33 (dd, *J* 9.5/2.0 Hz, 0.5H, 1-H_{ax}, β-is.), 4.45 (dd, *J* 4.3/1.5 Hz, 0.5H, 1-H_{eq}, α-is.), 6.00 (s, broad, 0.5H, NH, α/β-is.), 6.13 (s, broad, 0.5H, NH, α/β-is.), 7.12 (dd, *J* 8.2/2.1 Hz, 0.5H, arom.

H, 6′H, α/β-is.), 7.13 (dd, *J* 8.2/2.1 Hz, 0.5H, arom. H, 6′-H, α/β-is.), 7.37 (d, *J* 2.4 Hz, 0.5H, arom. H, 2′-H, α/β-is.), 7.38 (d, *J* 2.4 Hz, 0.5H, arom. H, 2′-H, α/β-is.), 7.39 (d, *J* 8.2 Hz, 0.5H, arom. H, 5′-H, α/β-is.), 7.42 (d, *J* 8.2 Hz, 0.5H, arom. H, 5′-H, α/β-is.); the ratio of α- and β-anomers was 1:1; EIMS: *m/z* [%] 358/360/362 [$M^+-HOCH_3-OCH_3$, 7.7/5.3/0.9]; CIMS (NH_3): *m/z* [%] 438/440/442 [$M+NH_3$, 4.1/2.7/0.5], 422/424/426 [MH^+, 17/11/2], 358/360/362 [$M-HOCH_3-OCH_3$, 100/65/12]; Anal. Calcd for $C_{18}H_{25}Cl_2NO_6$ (422.3): C, 51.19; H, 5.97; N, 3.32. Found: C, 50.98; H, 6.11; N, 3.47.

4.15. Methyl 7-(benzoylamino)-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside (23α and 23β)

Under N_2 atmosphere, benzoyl chloride (0.33 mL, 2.8 mmol) and Et_3N (0.54 mL, 3.9 mmol) were added to a solution of the unpurified primary amine **18** (anomeric mixture, 468 mg, 2.1 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 22 h. The mixture was concentrated in vacuo, and the residue was purified by FC (2 cm, EtOAc, fractions 5 mL, R_f 0.39). Pale-yellow solid: mp 154 °C; yield 180 mg (25%, referring to nitrile **16**); IR (neat): $\tilde{\nu}$ 3340 (νN–H), 2943 (νC–H), 1712 (νC=O), (1638 (ν*O*=*C*–NH, amide I), 1536 (δN–H, amide II), 1051 (νC–O), 711, 693 cm^{-1} (γCH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 1.99–2.13 (m, 1H, CH_2CH$_2$NH, α+β-is.), 2.22–2.35 (m, 1H, CH_2CH$_2$NH, α+β-is.), 2.71 (dd, *J* 14.0/1.2 Hz, 0.6H, 2-H_{eq}, α-is.), 2.70 (ddd, *J* 14.3/9.2/1.5 Hz, 0.4H, 2-H_{ax}, β-is.), 2.83 (ddd, *J* 14.0/4.6/1.2 Hz, 0.6H, 2-H_{ax}, α-is.), 2.87 (dd, *J* 14.3/2.7 Hz, 0.4H, 2-H_{eq}, β-is.), 3.23 (s, 3 × 0.6H, OCH_3, α-is.), 3.52 (s, 3 × 0.4H, OCH_3, β-is.), 3.36–3.91 (m, 2H, CH$_2$CH_2NH, α+β-is./1H, OH, α+β-is./1H, 5-H, α+β-is.), 3.95 (dd, *J* 10.1/1.5 Hz, 0.4H, 4-H, β-is.), 3.97 (dd, *J* 9.8/1.2 Hz, 0.6H, 4-H, α-is.), 4.58 (dd, *J* 9.2/2.4 Hz, 0.4H, 1-H_{ax}, β-is.), 5.14 (d, *J* 4.0 Hz, 0.6H, 1-H_{eq}, α-is.), 6.76 (s, broad, 1H, NH, α+β-is.), 7.39–7.53 (m, 3H, arom. H, α+β-is.), 7.75–7.79 (m, 2H, arom. H, α+β-is.); the ratio of α- and β-anomers was 3:2; EIMS: *m/z* [%] 243 [$M-HOCH_3-H_2O$, 9], 105 [$PhCO^+$, 100]; CIMS (isobutane): *m/z* [%] 294 [MH^+, 100], 262 [$M-OCH_3$,85]; Anal. Calcd for $C_{15}H_{19}NO_5$ (293.3): C, 61.42; H, 6.52; N, 4.78. Found: C, 61.71; H, 6.54; N, 4.69.

4.16. Methyl 7-[2-(3,4-dichlorophenyl)acetylamino]-2,6,7-trideoxy-α- and β-D-*erythro*-hept-3-ulo-1,5-pyranoside (24α and 24β)

A solution of acetal **22** (anomeric mixture, 178 mg, 0.42 mmol) and *p*-toluenesulfonic acid monohydrate (53 mg, 0.28 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 4 h. After completion of the transformation, the mixture was washed with satd aq $NaHCO_3$ (2 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (2 cm, 95:5 EtOAc–acetone, fractions 5 mL, $R_f = 0.23$). Colorless solid, mp 147 °C, yield 127 mg (80%); IR (neat): $\tilde{\nu}$ 3423 (νN–H), 3287 (νO-H), 2968 (νC–H), 1627 (ν*O*=*C*–NH, amide I), 1566 (δN–H, amide II), 1118 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.79–1.96 (m, 1H, CH_2CH$_2$NH, α+β-is.), 2.05–2.18 (m, 1H, CH_2CH$_2$NH, α+β-is.), 2.65 (dd, *J* 14.0/9.2 Hz, 0.45H, 2-H_{ax}, β-is.), 2.66 (d, *J* 14.0 Hz, 0.55H, 2-H_{eq}, α-is.), 2.74 (dd, *J* 14.0/4.3 Hz, 0.55H, 2-H_{ax}, α-is.), 2.85 (dd, *J* 14.3/2.7 Hz, 0.45H, 2-H_{eq}, β-is.), 3.20 (s, 2H, COCH_2Ph, α+β-is.), 3.26–3.68 (m, 1H, 5-H, α+β-is./1H, OH, α+β-is./2H, CH$_2$CH_2NH, α+β-is.), 3.48 (s, 3 × 0.45H, OCH_3, β-is.), 3.51 (s, 3 × 0.55H, OCH_3, α-is.), 3.84 (d, *J* 9.8 Hz, 1H, 4-H, α+β-is.), 4.49 (dd, *J* 9.2/2.4 Hz, 0.45H, 1-H_{ax}, β-is.), 4.90 (d, *J* 4.3 Hz, 0.55H, 1-H_{eq}, α-is.), 5.81 (s, broad, 0.45H, NH, β-is.), 5.94 (s, broad, 0.55H, NH, α-is.), 7.11 (dd, *J* 8.2/2.1 Hz, 0.45H, arom. H, 6′, β-is.), 7.12 (dd, *J* 8.2/2.4 Hz, 0.55H, arom. H, 6′-H, α-is.), 7.37 (d, *J* 2.1 Hz, 0.55H, arom. H, 2′-H, α-is.), 7.38 (d, *J* 1.8 Hz, 0.45H, arom. H, 2′-H, β-is.), 7.41 (d, *J* 8.2 Hz, 0.45H, arom. H, 5′-H, β-is.), 7.42 (d, *J* 8.2 Hz, 0.55H, arom. H, 5′-H, α-is.); the ratio of α- and β-anomers was 55:45; EIMS: *m/z* [%] 343/345/347 [$M-HOCH_3$, 16/11/2], 159/161/163 [$-CH_2PhCl_2^+$, 100/66/11]; CIMS (NH_3): *m/z* [%] 393/395 [$M+NH_4^+$, 10/7], 376/378/380 [MH^+, 100/63/15], 344/346/348 [$M-HOCH_3$, 95/60/11]; Anal. Calcd for $C_{16}H_{19}Cl_2NO_5$ (376.3): C, 51.08; H, 5.09; N, 3.72. Found: C, 51.84; H, 5.58; N, 3.72.

4.17. 1,5-Anhydro-7-(benzoylamino)-2,6,7-trideoxy-D-*erythro*-hept-1- en-3-ulose (25)

A solution of ketone **23** (anomeric mixture, 97 mg, 0.29 mmol) and *p*-toluenesulfonic acid monohydrate (62 mg, 0.32 mmol) in CH_2Cl_2 (15 mL) was heated to reflux for 30 min. Then, the mixture was washed with satd aq $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by FC (2 cm, EtOAc, fractions 2 mL, $R_f = 0.42$). Colorless oil: yield 25 mg (34%); IR (neat): $\tilde{\nu}$ 3346 (νN–H), 2934 (νC–H), 1721 (νC=O), 1622 (ν*O*=*C*–NH, amide I), 1598 (νC=C), 1537 (δN–H, amide II), 1256, 1113 (νC–O), 698 cm^{-1} (γCH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 2.15–2.27 (m, 1H, CH_2CH$_2$NH), 2.30–2.40 (m, 1H, CH_2CH$_2$NH), 3.68–3.85 (m, 2H, CH$_2$CH_2NH), 4.13 (d, *J* 13.1 Hz, 1H, 4-H), 4.23 (ddd, *J* 13.4/7.0/3.8 Hz, 1H, 5-H), 5.49 (d, *J* 5.8 Hz, 1H, 2-H), 6.62 (s, broad, 1H, NH), 7.52–7.38 (m, 3H, arom. H), 7.48 (d, *J* 5.5 Hz, 1H, 1-H), 7.75–7.79 (m, 2H, arom. H), a signal for the OH-proton was not observed in the spectrum; $C_{14}H_{15}NO_4$ (261.3). CIMS (isobutane): *m/z* [%] 262 (MH^+, 100).

4.18. 1,5-Anhydro-7-[2-(3,4-dichlorophenyl)acetylamino]-2,6,7-trideoxy-D-*erythro*-hept-1-en-3-ulose (26)

A solution of acetal **22** (anomeric mixture, 152 mg, 0.36 mmol) and *p*-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol) in CH_2Cl_2 (15 mL) was heated to reflux for 45 min. Then, the mixture was washed with satd aq $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by FC (2 cm, 95:5 EtOAc–acetone, fractions 2 mL, R_f 0.23). Pale-yellow solid: mp 142 °C; yield 65 mg (53%); IR (neat): $\tilde{\nu}$ 3286 (νN–H), 1670 (ν*O*═*C*–NH, amide I), 1620 (νC═C), 1592 (δN–H, amide II), 1114, 1032 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 2.03 (dt, *J* 13.4/6.7 Hz, 1H, CH_2CH$_2$NH), 2.14–2.24 (m, 1H, CH_2CH$_2$NH), 3.46–3.59 (m, 2H, CH$_2$CH_2NH), 3.50 (s, 2H, COCH_2), 4.00 (d, *J* 13.1 Hz, 1H, 4-H), 4.09 (ddd, *J* 13.1/6.7/3.4 Hz, 1H, 5-H), 5.47 (d, *J* 5.8 Hz, 1H, 2-H), 5.78 (s, broad, 1H, NH), 7.12 (dd, *J* 8.2/2.1 Hz, 1H, arom. H, 6′-H), 7.29 (d, *J* 5.8 Hz, 1H, 1-H), 7.38 (d, *J* 1.8 Hz, 1H, arom. H, 2′-H), 7.42 (d, *J* 8.2 Hz, 1H, arom. H, 5′-H), a signal for the OH-proton was not observed; EIMS: *m*/*z* [%] 343/345/347 [M^+, 5.8/3.4/0.8], 159/161/163 [–$CH_2PhCl_2^+$, 94/60/12]; CIMS (isobutane): *m*/*z* [%] 344/346/348 [MH^+, 100/65/13], 310/312 [MH^+-Cl, 67/24], 274 [$M-2\times Cl$, 35]; Anal. Calcd for $C_{15}H_{15}Cl_2NO_4$ (344.2): C, 52.34; H, 4.39; N, 4.07. Found: C, 52.17; H, 4.68; N, 4.02.

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