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Synthesis of novel σ-receptor ligands from methyl α-D-mannopyranoside

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Abstract—For the first time a monosaccharide (methyl α-D-mannopyranoside) has been used as starting material for the synthesis of novel σ-receptor ligands. The hept-3-ulopyranoside dimethyl ketals **14** and **15** were obtained from the nitrile **7** via two synthetic routes. After selective hydrolysis of the ketone dimethyl acetal, various amino substituents were introduced into position 3. High σ_1-receptor affinity and selectivity was attained with equatorially arranged amino substituents in position 3 and a dichlorophenylacetamide moiety in position 7. The anomeric mixture of dimethylamines **26α/β** displayed the highest σ_1-receptor affinity ($K_i = 21$ nM) within this small series of test compounds.

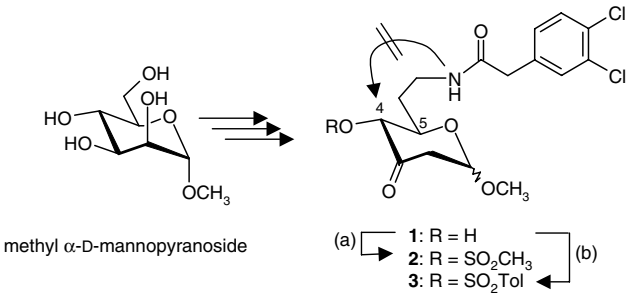
Keywords: Mannose; 3-Amino-1,5-heptopyranosides; σ_1-Receptor ligands; Barton–McCombie deoxygenation

1. Introduction

σ Receptors are involved in several physiological and pathophysiological events.[1] In particular, ligands interacting with σ receptors possess a potential as antipsychotics,[2] antidepressants,[3] anticocaine agents,[4] and antitumor agents.[5] In order to find novel σ-receptor ligands, we planned to exploit the synthetic potential of monosaccharides.

Recently, we have described the synthesis of methyl hept-3-uloyranosides **1** from methyl α-D-mannopyranoside.[6] Further transformations of **1**, in particular introduction of amino moieties into positions 3 or 4, turned out to be difficult because of the instability of the α-hydroxyketone substructure. For example, the α-hydroxyketone **1** with the 3,4-dichlorophenylacetyl moiety was transformed into the sulfonates **2** and **3**. However, all attempts to further react the sulfonates **2** and **3** failed to yield the desired products (intermolecular substitution with NaN_3 or Bu_4NN_3, intramolecular substitution by the amide moiety to yield bicyclic systems, and reductive removal of the tosyloxy group with hydrazine/Br_2[7]). In all cases very rapid decomposition was observed (Scheme 1).

Therefore, we decided to remove the hydroxy group in position 4 of the mannose-derived building block **1** and subsequently transform the carbonyl moiety in position 3 into amino substituents. In particular, removal of the 4-OH moiety should lead to the central intermediate **4**, which should give access to amino-substituted oxamorphanes **5**[8] and monocyclic amines **6** (Scheme 2).



Scheme 1. Reagents and conditions: (a) H_3CSO_2Cl, NEt_3, CH_2Cl_2, rt, 70%; (b) TsCl, NEt_3, DMAP, CH_2Cl_2, rt, 77%.

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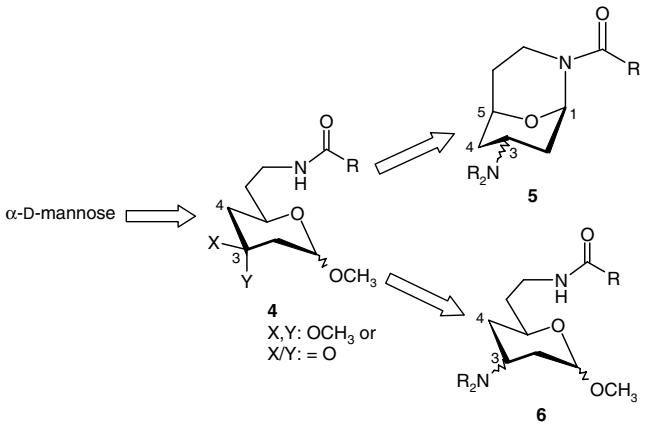


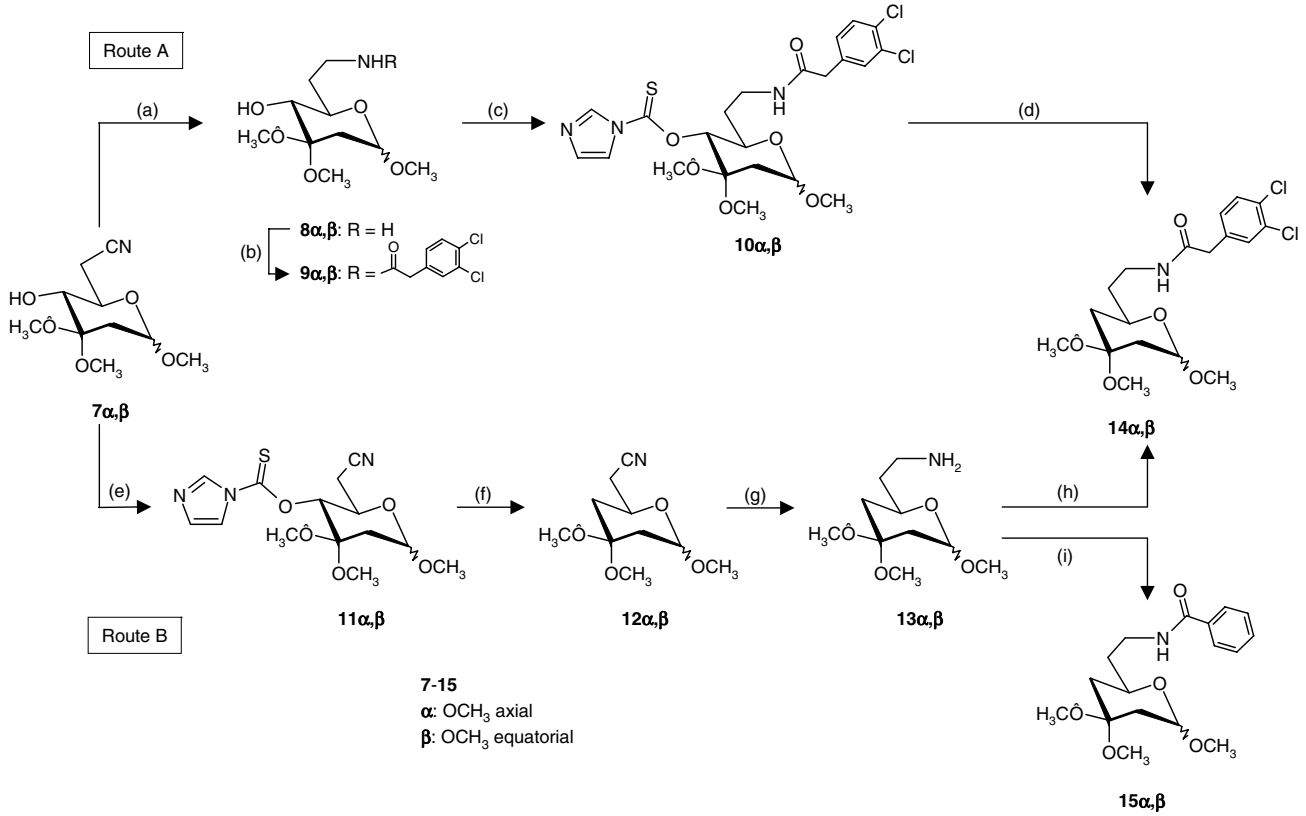
Scheme 2.

2. Results and Discussion

2.1. Chemistry

Starting with nitrile **7**, the synthesis of deoxygenated pyranosides **14** comprises modification of the cyano moiety and removal of the hydroxy group in position 4. According to route A (upper reactions) reduction of **7** with H_2 and Raney nickel provided the primary amine **8**, which was acylated with (3,4-dichlorophenyl)acetic acid and 1,1′-carbonyldiimidazole (CDI)[9] to yield the amide **9** with the σ-pharmacophoric (3,4-dichlorophenyl)acetyl residue.[10] Deoxygenation of the hydroxyacetal **9** was performed according to the method of Barton and McCombie.[11] Thus, acylation of **9** with 1,1′-thiocarbonyldiimidazole led to the thionocarbamate **10**, which was reduced by Bu_3SnH in a radical chain reaction to afford the deoxygenated pyranoside **14**. During this sequence (**7**→**8**→**9**→**10**→**14**), the ratio of α to β anomers was about 1:1 (Scheme 3).

In order to improve the yield of **14** and to gain flexibility, that is, introduction of various acyl residues at a late stage of the synthesis, the reaction sequence was changed. At first the Barton–McCombie free-radical deoxygenation[11] was performed by reacting the hydroxynitrile **7** with 1,1′-thiocarbonyldiimidazole to obtain the thionocarbamate **11**. Radical reduction of the thionocarbamate **11** with Bu_3SnH afforded a mixture of products, containing the desired deoxygenated nitrile **12** and the starting hydroxynitrile **7**. In the ^1H NMR spectra of both products, signals indicating Bu_3Sn impurities were observed. Therefore, instead of Bu_3SnH, the reducing agent $(Me_3Si)_3SiH$[12] was used for the



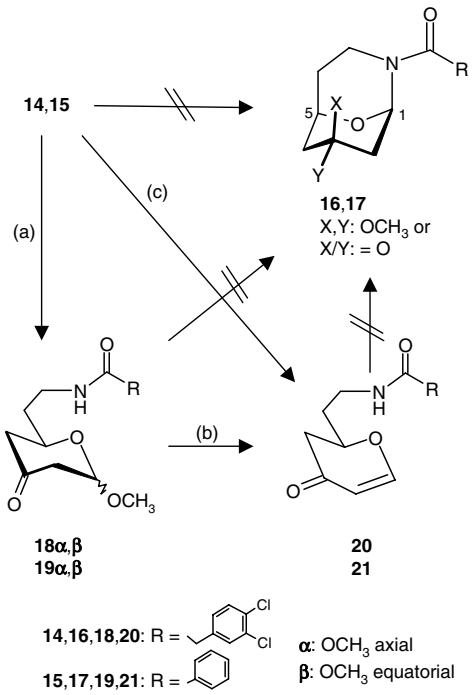
Scheme 3. Reagents and conditions: (a) H_2, Raney nickel, 4.1 bar, MeOH, rt; (b) (dichlorophenyl)acetic acid, CDI, CH_2Cl_2, rt, 52% (from **7**); (c) $S{=}C(Im)_2$, toluene, 110 °C, 60%; (d) Bu_3SnH, AIBN, toluene 110 °C, 70%; (e) $S{=}C(Im)_2$, toluene, 110 °C, 90%; (f) $(Me_3Si)_3SiH$, AIBN, toluene, 110 °C, 89%; (g) H_2, Raney nickel, 4 bar, MeOH, rt, 81%; (h) (dichlorophenyl)acetic acid, CDI, CH_2Cl_2, rt, 79% (from **12**); (i) PhCOCl, NEt_3, CH_2Cl_2, rt, 73% (from **12**).

radical deoxygenation of the thionocarbamate **11**. This reagent led to a clean transformation of **11**, and the deoxygenated nitrile **12** was isolated in 89% yield. Hydrogenation of the nitrile **12** with H_2 and Raney nickel provided the primary amine **13**, which was acylated with (3,4-dichlorophenyl)acetic acid and CDI[9] to give the deoxygenated (3,4-dichlorophenyl)acetamide **14** in 79% yield over two steps. In this reaction sequence the ratio of α and β anomers was about 1:1. Comparison of the synthesis of amide **14** from the hydroxynitrile **7** via route A (upper reactions) and route B (lower reactions) clearly indicates route B giving higher overall yield (64%) than route A (21%). Moreover, route B increases the possibilities for generating chemical diversity, since the acyl residue is introduced in the last reaction step. This is demonstrated by acylation of the primary amine **13** with benzoyl chloride to afford the benzamide **15**.

The deoxygenated amides **14** and **15** were thought to be suitable precursors for the synthesis of bicyclic morphan analogues **16** and **17**. However, all attempts to form the bicyclic *N*/*O*-acetals **16** and **17** by reacting **14** and **15** with acids failed. Reaction of the benzamide **15** with *p*-toluenesulfonic acid at 0 °C led to the ketone **19** by cleavage of the dimethyl acetal. Performing the same reaction at 20 °C instead of 0 °C provided a mixture of the ketone **19** and the α,β-unsaturated ketone **21**. Heating of the benzamide **15** or the ketone **19** with $BF_3{\cdot}Et_2O$ in THF also did not yield the bicyclic compound **17**, but the α,β-unsaturated ketone **21** instead. The same observations were made with the analogous phenylacetamide **14**. Treatment of **14** with *p*-toluenesulfonic acid at 0 °C predominantly led to the ketone **18**, while at room temperature a mixture of ketone **18** and α,β-unsaturated ketone **20** was formed, and heating with $BF_3{\cdot}Et_2O$ exclusively yielded the α,β-unsaturated ketone **20**. In no case was the bicyclic product **16** detected. Attempts to deprotonate the secondary amide **20** with KHMDS and initiate an intramolecular Michael addition also failed to give the bicyclic product **16** (Scheme 4).

The ketones **18** and **19** were used for the introduction of amino moieties in position 3. At first the phenylacetamide **18** was treated with benzylamine and $NaBH_3CN$ in MeOH at pH 6.0.[13] Purification of the product by flash chromatography yielded small amounts of diastereomerically pure benzylamine **22β** and a mixture of the diastereomers **22α**, **22β**, and **23α**. Reductive amination of the ketone **18** with methylamine and $NaBH_3CN$ led to a mixture of anomers **24α/β** and diastereomerically pure methylamine **25β**. With dimethylamine and $NaBH_3CN$, the ketone **18** was transformed into the anomeric mixture **26α/β** bearing the amino moiety in an equatorial position (Scheme 5).

The reductive amination of benzamido ketone **19** gave very similar results. Reaction with benzylamine and



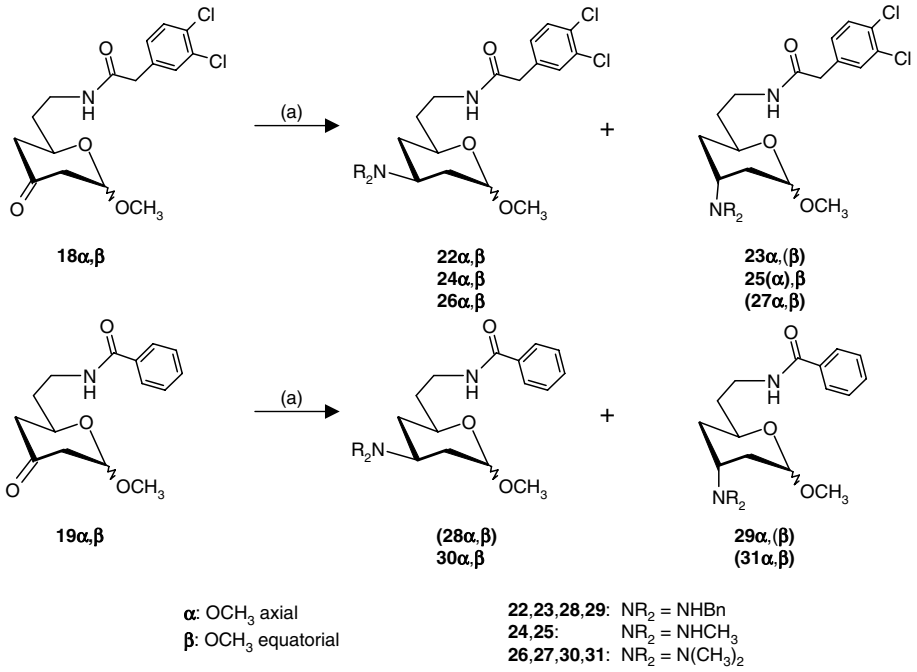
Scheme 4. Reagents and conditions: (a) TsOH, CH_2Cl_2, 0 °C, **18**: 63%, **19**: 91%; (b) $BF_3{\cdot}OEt_3$, THF, 65 °C, **21**: 64%; (c) $BF_3{\cdot}OEt_2$, THF, 65 °C, **20**: 86%.

$NaBH_3CN$ resulted in a mixture of products, from which the α anomer **29α** with an axially oriented benzylamino group was isolated in 27% yield. After reductive amination with dimethylamine and $NaBH_3CN$, an anomeric mixture of tertiary amines **30α/β** bearing an equatorially oriented amino moiety was isolated.

2.2. Receptor-binding studies

The affinities of the mannose-derived amines **22β**, **24α/β**, **25β**, **26α/β**, **29α**, and **30α/β** toward σ_1 and σ_2 receptors were determined in receptor-binding studies using radioligands with high affinity and selectivity to the corresponding receptors. In the σ_1 assay the radioligand [^{3}H]-(+)-pentazocine was used. Since a selective radioligand for labeling of σ_2 receptors is not commercially available, the nonselective radioligand, [^{3}H]-ditolylguanidine, was employed in the presence of nontritiated (+)-pentazocine to mask the σ_1 receptors. Membrane preparations from guinea pig brains were used in the σ_1 assay, and rat liver preparations served as receptor material in the σ_2 assay.[14] In addition to the σ_1 and σ_2 receptor affinity, the receptor selectivity of some compounds was investigated by determination of the affinity to the phencyclidine binding site of the NMDA receptor ([^{3}H]-(+)-MK-801]),[15] to κ-opioid ([^{3}H]-U-69593), and μ-opioid receptors ([^{3}H]-DAMGO)[16] with receptor-binding studies.

In Table 1 the results of the receptor-binding studies toward σ_1 and σ_2 receptors are summarized. Three of



Scheme 5. Reagents and conditions: (a) $BnNH_2$ or CH_3NH_2 or $(H_3C)_2NH$, MeOH, 3 Å MS, $NaBH_3CN$, rt.

Table 1. σ-Receptor affinity

Compound	σ_1 $K_i \pm$ SEM (nM) $n = 3$	σ_2 $K_i \pm$ SEM (nM) $n = 3$
22β	83 ± 32	2520 ± 960
24α/β	69 ± 5	IC_{50} >10 μM[b]
25β	1420 ± 281	IC_{50} >10 μM[b]
26α/β	21 ± 1	IC_{50} >10 μM[b]
29α	250 ± 115	6120 ± 2760
30α/β	—[a]	IC_{50} >10 μM[b]
(±)-Pentazocine	3.58 ± 0.20	n.d.[c]
Haloperidol	2.20 ± 0.31	34.2 ± 2.3
Ditolylguanidine	n.d.[c]	63.9 ± 10.8

[a] At a test concentration of 100 nM, binding of the radioligand was not significantly reduced (IC_{50} >100 nM).
[b] At a test concentration of 10 μM, binding of the radioligand was not significantly reduced (IC_{50} >10 μM).
[c] n.d. = not determined.

the investigated compounds (**22β**, **24α/β**, **26α/β**) reveal high affinity to σ_1 receptors, and the corresponding K_i values are below 100 nM. These high-affinity ligands are substituted with equatorially oriented amino moieties. Analogues with axially arranged amino substituents, for example, **25β**, display considerably lower affinity. The data clearly indicate that the dichlorophenylacetyl residue is crucial for high σ_1-receptor affinity, since the corresponding benzamide derivatives **29α** and **30α/β** display significantly lower affinities.

The most σ_1-active compound in this series is the anomeric mixture **26α/β** bearing an equatorially oriented dimethylamino moiety in position 3. The K_i-value of the tertiary amine **26α/β** is 21 nM. The corresponding secondary amine **24α/β** is threefold less active. Exchange of the methyl group for a benzyl moiety leads to the secondary benzyl amine **22β** (only one anomer), which displays almost the same σ_1-receptor affinity as the methylamine **24α/β**.

The σ_2-receptor affinity (Table 1) of all test compounds is very low, indicating high σ_1-receptor selectivity of these ligands. That means that the compounds with high σ_1-receptor affinity (**22β**, **24α/β**, **26α/β**) represent selective σ_1-receptor ligands.

Since ligands for σ_1 receptors are often very similar to ligands for the phencyclidine (PCP) binding site of the NMDA receptor,[17] for κ-opioid receptors,[17,18] and for μ-opioid receptors[17] the affinity of these mannose-derived σ_1-receptor ligands toward these receptor systems was also investigated. At a concentration of 10 μM, all test compounds did not significantly interact with the PCP binding site, with κ-opioid receptors and with μ-opioid receptors, indicating K_i values greater than 10 μM. Obviously the novel high-affinity mannose-derived σ_1-receptor ligands **22β**, **24α/β**, and **26α/β** display high selectivity against σ_2 receptors, κ-opioid receptors, μ-opioid receptors, and the phencyclidine binding site of the NMDA receptor.

3. Conclusions

Starting with the monosaccharide, methyl α-D-mannopyranoside, the synthesis of a small series of 3-amino-

substituted heptopyranosides with an attached σ-pharmacophoric dichlorophenylacetyl residue is described. It was shown that some of the prepared compounds represent highly active σ_1-receptor ligands, the dimethylamine **26α/β** showing the highest σ_1-receptor affinity ($K_i = 21$ nM). Within this small series of amines it was demonstrated that the 3,4-dichlorophenylacetyl residue and the equatorial orientation of the amino moiety in position 3 are crucial for high σ_1-receptor affinity. Compounds with tertiary amines give lower K_i values than analogues with secondary amino groups. The highly active compounds are very selective for σ_1 receptors. In this project it has been shown for the first time that a monosaccharide (methyl α-D-mannopyranoside) can be used as a building block for the synthesis of novel drugs with high σ_1-receptor affinity and selectivity.

4. Experimental

4.1. Chemistry, general

Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. THF was distilled from sodium–benzophenone ketyl prior to use. Petroleum ether used refers to the fraction boiling at 40–60 °C. Thin-layer chromatography (TLC): Silica Gel 60 F_{254} plates (E. Merck). Flash chromatography (FC):[19] Silica Gel 60, 0.040–0.063 mm (E. Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL] and R_f. Melting points (mp's) were determined on a melting-point apparatus SMP2 (Stuart Scientific), and the mp's are uncorrected. Optical rotation: Polarimeter 241 (Perkin–Elmer); 1.0-dm tube; concentration c [g/100 mL]; temperature 20 °C. Elemental analyses: Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); EI, electron impact; CI, chemical ionization. High-resolution MS (HRMS): MAT 8200 (Finnigan). IR: 1605 FTIR spectrometer (Perkin–Elmer), (br, broad; m, medium; s, strong). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian); δ in parts per million relative to tetramethylsilane; coupling constants are given with 0.5-Hz resolution; the assignments of ^{13}C and of ^{1}H NMR signals were supported by 2D NMR techniques.

4.2. Methyl 2,6,7-trideoxy-7-[(3,4-dichlorophenyl)acetylamino]-4-*O*-methanesulfonyl-α- and β-D-*erythro*-1,5-hept-3-ulopyranoside (2)

Ketone **1**[6] (mixture of anomers, 192 mg, 0.51 mmol) was dissolved in CH_2Cl_2 (30 mL) under an N_2 atmosphere. At 0 °C, methanesulfonyl chloride (0.2 mL, 2.5 mmol) and Et_3N (0.5 mL, 3.6 mmol) were added, and the mixture was stirred at room temperature for 30 h. Then the solvent was evaporated in vacuo. The residue was purified by FC (2 cm, 95:5 EtOAc–acetone, fractions 2 mL, R_f 0.45) to give **2** (151 mg (70%)) as a colorless solid: mp 115 °C; IR (ATR, neat): $\tilde{\nu}$ 3271 (νN–H), 1734 (νC=O), 1638 (νO=C–NH, amide I), 1566 (δN–H, amide II), 1310, 1171, 1033 cm^{-1} (νC–O); ^{1}H NMR ($CDCl_3$): δ 1.79–1.94 (m, 1H, CH_2CH$_2$NH, α+β-is.), 1.96–2.13 (m, 1H, CH_2CH$_2$NH, α+β-is.), 2.66 (dd, J 14.3/9.3 Hz, 0.45H, 2-H$_{ax}$, β-is.), 2.75 (dd, J 14.3/4.1 Hz, 0.55H, 2-H$_{ax}$, α-is.), 2.82 (d, J 14.0 Hz, 0.55H, 2-H$_{eq}$, α-is.), 2.95 (dd, J 14.3/2.6 Hz, 0.45H, 2-H$_{eq}$, β-is.), 3.14–3.77 (m, 2H, CH$_2$CH_2NH, α+β-is./5-H, β-is.), 3.25 (s, 3 × 0.55H, OSO$_2$CH_3, α-is.), 3.26 (s, 3 × 0.45H, OSO$_2$CH_3, β-is.), 3.49 (s, 3 × 0.45H, OCH_3, β-is.), 3.50 (s, 3 × 0.55H, OCH_3, α-is.), 3.51 (s, 2 × 0.45H, COCH_2Ph, β-is.), 3.53 (s, 2 × 0.55H, COCH_2Ph, α-is.), 3.94–4.42 (m, 0.55H, 5-H, α-is.), 4.56 (dd, J 9.2/2.4 Hz, 0.45H, 1-H$_{ax}$, β-is.), 4.65 (d, J 10.1 Hz, 0.45H, 4-H, β-is.), 4.79 (d, J 10.1 Hz, 0.55H, 4-H, α-is.), 4.93 (d, J 4.0 Hz, 0.55H, 1-H$_{eq}$, α-is.), 5.65 (s, br, 0.45H, NH, β-is.), 5.78 (s, br, 0.55H, NH, α-is.), 7.12 (dd, J 8.2/2.1 Hz, 0.45H, arom. H, 6′-H, β-is.), 7.13 (dd, J 8.2/2.1 Hz, 0.55H, arom. H, 6′-H, α-is.), 7.38 (d, J 2.1 Hz, 0.45H, arom. H, 2′-H, β-is.), 7.39 (d, J 2.1 Hz, 0.55H, arom. H, 2′-H, α-is.), 7.42 (d, J 8.2 Hz, 0.45H, arom. H, 5′-H, β-is.), 7.43 (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 [%] 325/327/329 [M−HOCH$_3$−CH$_3$SO$_2$OH, 11/7/1], 159/161/163 [–CH$_2$PhCl$_2^+$, 100/59/11], 79 [–CH$_3$SO$_2^+$, 33]; CIMS (NH_3): m/z [%] 454/456/458 [MH$^+$, 53/30/6], 422/424/426 [M−OCH$_3$, 60/41/7], 328/330/332 [M−CH$_3$SO$_2$O, 100/44/11]. Anal. Calcd for $C_{17}H_{21}Cl_2N_1O_7S$ (454.3): C, 44.94; H, 4.66; N, 3.08. Found: C, 44.47; H, 4.36; N, 2.94.

4.3. Methyl 2,6,7-trideoxy-7-[(3,4-dichlorophenyl)acetylamino]-4-*O*-*p*-toluenesulfonyl-α- and β-D-*erythro*-1,5-hept-3-ulopyranoside (3)

Ketone **1**[6] (mixture of anomers, 270 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (25 mL). Then *p*-toluenesulfonyl chloride (953 mg, 5.0 mmol), Et_3N (1.3 mL, 9.3 mmol), and 4-(dimethylamino)pyridine (DMAP, 641 mg, 5.2 mmol) were added at 0 °C (ice cooling). The mixture was stirred at 0 °C for 10 min and at room temperature for 16 h. Then the reaction mixture was washed with N HCl (20 mL) and satd aq $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (2 cm, 80:20 EtOAc–petroleum ether, fractions 5 mL, R_f 0.43) to give **3** (294 mg (77%) as a pale-yellow solid: mp 66 °C; IR (ATR, neat): $\tilde{\nu}$ 3293 (νN–H), 2933 (νC–H), 1369 (R–SO$_2$–OR′), 1173, 1055 (νC–O), 811, 662 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 1.77–1.89 (m, 1H,

CH_2CH_2NH, α+β-is.), 2.00–2.18 (m, 1H, CH_2CH_2NH, α+β-is.), 2.45 (s, 3H, $PhCH_3$, α+β-is.), 2.60 (d, *J* 14.6 Hz, 0.6H, 2-H_{eq}, α-is.), 2.61 (dd, *J* 14.0/9.2 Hz, 0.4H, 2-H_{ax}, β-is.), 2.70 (dd, *J* 14.3/4.3 Hz, 0.6H, 2-H_{ax}, α-is.), 2.77 (dd, *J* 14.9/2.4 Hz, 0.4H, 2-H_{eq}, β-is.), 3.20 (s, 3 × 0.6H, OCH_3, α-is.), 3.26–3.61 (m, 2H, CH_2CH_2NH, α+β-is./0.4H, 5-H, β-is.), 3.49 (s, 2 × 0.4H, $COCH_2Ph$, β-is.), 3.50 (s, 3 × 0.4H, OCH_3, β-is.), 3.52 (s, 2 × 0.6H, $COCH_2Ph$, α-is.), 3.96 (td, *J* 9.2/2.7 Hz, 0.6H, 5-H, α-is.), 4.51 (dd, *J* 8.9/2.4 Hz, 0.4H, 1-H_{ax}, β-is.), 4.79 (d, *J* 10.1 Hz, 0.4H, 4-H, β-is.), 4.80 (d, *J* 10.1 Hz, 0.6H, 4-H, α-is.), 4.88 (d, *J* 3.7 Hz, 0.6H, 1-H_{eq}, α-is.), 5.78 (s, br, 0.4H, NH, β-is.), 5.88 (s, br, 0.6H, NH, α-is.), 7.11–7.15 (m, 1H, arom. H, 6′-H, α+β-is.), 7.33–7.44 (m, 2H, arom. H, Ts–H, *m*-pos., α+β-is./1H, arom. H, 5′-H, α+β-is./1H, arom. H, 2′-H, α+β-is.), 7.86 (d, *J* 8.2 Hz, 2 × 0.4H, arom. H, Ts–H, *o*-pos., β-is.), 7.87 (d, *J* 8.2 Hz, 2 × 0.6H, arom. H, Ts–H, *o*-pos., α-is.); the ratio of α and β anomers was 60:40; $C_{23}H_{25}Cl_2NO_7S$ (530.2); EIMS: *m*/*z* [%] 496/498/500 [M−$HOCH_3$, 12/8/2], 479/481/483 [M−$HOCH_3$−OH, 11/7/1.5], 159/161/163 [–$CH_2PhCl_2^+$, 46/27/6], 155 [–$SO_2PhCH_3^+$, 42].

4.4. Preparation of methyl 7-amino-2,6,7-trideoxy-α- and β-D-*erythro*-1,5-hept-3-ulopyranoside dimethyl ketal (8α/β)[6]

To a solution of **7α/β** (0.72 g, 3.1 mmol) in MeOH (60 mL) and 5 N NaOH (15 mL), Raney nickel was added, and the mixture was shaken under an H_2 atmosphere (4.1 bar) at room temperature for 24 h. The Raney nickel 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 (0.70 g, 97%), which was pure enough for further reactions. In order to characterize the primary amine **8α/β**, a sample (103 mg) of the residue was purified by FC [2 cm, 80:20 ethanol–acetone, 2% *N*-ethyl-*N*,*N*-dimethylamine, fractions 5 mL, R_f 0.11] to yield **8α/β** (17 mg, <10%): IR (neat): $\tilde{\nu}$ 2945 (νC–H), 1128, 1053 cm^{-1} (νC–O); ^1H 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.

4.5. Preparation of methyl 2,6,7-trideoxy-7-[2-(3,4-dichlorophenyl)acetylamino]-α- and β-D-*erythro*-1,5-hept-3-ulopyranoside dimethyl ketal (9α/β)[6]

Under an 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 **8α/β** (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 the nitrile **7α/β**) of **9α/β**; IR (neat): $\tilde{\nu}$ 3301 (νN–H), 2942 (νC–H), 1647 (νO=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, CH_2CH_2NH, 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, CH_2CH_2NH, 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, br, 0.5H, NH, α/β-is.), 6.13 (s, br, 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 50:50; 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.

4.6. Methyl 2,6,7-trideoxy-7-[(3,4-dichlorophenyl)acetylamino]-4-*O*-(imidazol-1-ylthiocarbonyl)-α- and β-D-*erythro*-1,5-hept-3-ulopyranoside dimethyl ketal (10α/β)

Under N_2, 1,1′-thiocarbonyldiimidazole (380 mg, 2.1 mmol) was added to a solution of **9α,β** (160 mg, 0.38 mmol) in toluene (15 mL). The mixture was heated to reflux for 21 h. After completion of the reaction, the mixture was extracted with N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by FC (2 cm, 70:30 EtOAc–acetone, fractions 5 mL, R_f 0.39) to give **10α/β** (121 mg, 60%) as a pale-yellow oil: IR (ATR, film): $\tilde{\nu}$ 3286 (νN–H), 2940 (νC–H), 1648 (νO=C–NH, amide I), 1554 (δN–H of amide II), 1227 (νC=S), 1111, 1004 (νC–O), 734, 654 cm^{-1} (γCH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 1.50–1.92 (m, 2H, CH_2CH_2NH, α+β-is.), 1.76 (dd, *J* 13.7/8.6 Hz, 0.45H, 2-H_{ax}, β-is.), 2.09 (d, *J* 4.6 Hz, 2 × 0.55H, 2-H_{eq}, α-is.+2-H_{ax}, α-is.), 2.33 (dd, *J* 13.7/2.1 Hz, 0.45H, 2-H_{eq}, β-is.), 3.16–3.65 (m, 2H, CH_2CH_2NH, α+β-is.), 3.22 (s, 3 × 0.45H, OCH_3, β-is.), 3.22 (s, 3 × 0.55H, OCH_3, α-is.), 3.23 (s, 3 × 0.55H, OCH_3, α-is.), 3.32 (s, 3 × 0.55H, OCH_3, α-is.), 3.33 (s, 3 × 0.45H, OCH_3, β-is.), 3.44 (s, 3 × 0.45H, OCH_3, β-is), 3.46 (s, 2 × 0.45H, $COCH_2Ph$, β-is.), 3.47 (s, 2 × 0.55H, $COCH_2Ph$, α-is.), 3.81–3.89 (m, 0.45H, 5-H, β-is.), 4.14–4.20 (m, 0.55H, 5-H, α-is.), 4.58 (dd, *J* 8.6/2.4 Hz, 0.45H, 1-H_{ax}, β-is.), 4.60 (t, *J* 4.6 Hz, 0.55H, 1-H_{eq}, α-is.), 4.48 (d, *J* 5.8 Hz, 0.45H, 4-H, β-is.), 4.63 (d, *J* 8.6 Hz, 0.55H, 4-H, α-is.), 5.76 (s, br, 0.45H, NH, β-is.), 5.83 (s, br, 0.55H, NH, α-is.), 7.05–7.07 (m, 1H, imidazole-H, 2″-H, α+β-is.), 7.10 (dd, *J* 8.2/1.2 Hz, 1H, arom. H, 6′-H, α+β-is.), 7.36 (s, br, 1H, arom. H, 2′-H, α+β-is.), 7.40 (dd, *J* 8.2/1.2 Hz, 1H, arom. H, 5′-H, α+β-is.), 7.60 (t, 0.45H, *J* 1.5 Hz, imidazole-H, pos. 4″-H, β-is.), 7.62 (t, 0.55H, *J* 1.5 Hz, imidazole-H, pos. 4″-H, α-is.), 8.33 (t, *J* 1.2 Hz, 0.45H, imidazole-H, 5″-H, β-is.), 8.35 (t, *J* 0.9 Hz, 0.55H, imidazole-H, 5″-H, α-is.); the ratio of α and β anomers was 55:45; EIMS: *m*/*z* [%] 111 [thiocarbonyliimidazole, 20], 88 [–$C(OCH_3)_2$–CH_2^+–, 50]; CIMS (isobutane): *m*/*z* [%] 532/534/536 [MH^+, 11.4/7.1/1.6], 342/344/346 [M^+−thiocarbonylimidazole−2 × OCH_3, 67/37/9]. Anal. Calcd for $C_{22}H_{27}Cl_2N_3O_6S$ (532.4): C, 49.63; H, 5.11; N, 7.89; S. 6.02. Found: C, 48.99; H, 5.35; N, 8.20; S, 5.85.

4.7. Methyl 6-cyano-2,6-dideoxy-4-*O*-(imidazol-1-ylthiocarbonyl)-α- and β-D-*erythro*-1,5-hex-3-ulopyranoside dimethyl ketal (11α/β)

Under N_2, thiocarbonyldiimidazole (2.9 g, 16.3 mmol) was added to a solution of **7α/β** (750 mg, 3.2 mmol) in toluene (40 mL). The mixture was heated to reflux for 27 h. After completion of the reaction, the mixture was extracted with N HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (3 cm, EtOAc, fractions 10 mL, R_f 0.57) to give **11α/β** (931 mg, 90%) as a yellow oil: IR (ATR, film): $\tilde{\nu}$ 2923 (νC–H), 1226 (νC=S), 1285, 1048 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 2.02–2.15 (m, 1.5H, 2-H_{eq}, β-is./2-H_{eq}, α-is./2-H_{ax}, β-is.), 2.21 (dd, *J* 14.3/3.7 Hz, 0.5H, 2-H_{ax}, α-is.), 2.71 (dd, *J* 16.9/4.7 Hz, 0.5H, CH_2CN, α/β-is.), 2.79 (dd, *J* 16.8/5.2 Hz, 0.5H, CH_2CN, α/β-is.), 2.87 (dd, *J* 16.8/9.2 Hz, 0.5H, CH_2CN, α/β-is.), 3.00 (dd, *J* 16.8/8.9 Hz, 0.5H, CH_2CN, α/β-is.), 3.24 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.25 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.25 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.27 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.47 (s, 3 × 0.5H, OCH_3, α/β-is.), 3.51 (s, 3 × 0.5H, OCH_3, α/β-is.), 4.32 (dt, *J* 8.9/5.3 Hz, 0.5H, 5-H, α/β-is.), 4.48 (dt, *J* 9.2/5.3 Hz, 0.5H, 5-H, α/β-is.), 4.76 (dd, *J* 9.2/4.6 Hz, 0.5H, 1-H_{ax}-β), 4.80 (d, *J* 3.7 Hz, 0.5H, 1-H_{eq}-α), 5.54 (d, *J* 5.8 Hz, 0.5H, 4-H, α/β-is.), 5.62 (dd, *J* 5.8/0.9 Hz, 0.5H, 4-H, α/β-is.), 7.05 (t, *J* 0.9 Hz, 0.5H, imidazole-H, 2′-H, α/β-is.), 7.05 (t, *J* 0.9 Hz 0.5H, imidazole-H, 2′-H, α/β-is.), 7.61 (t, *J* 1.5 Hz, 0.5H, imidazole-H, 4′-H, α/β-is.), 7.63 (t, *J* 1.5 Hz, 0.5H, imidazole-H, 4′-H, α/β-is.), 8.31 (t, *J* 0.9 Hz, 0.5H, imidazole-H, 5′-H, α/β-is.), 8.34 (t, *J* 0.9 Hz, 0.5H, imidazole-H, 5′-H, α/β-is.); the ratio of the α and β anomers was 50:50; ^{13}C NMR ($CDCl_3$): δ 20.4 (0.5C, CH_2CN), 21.9 (0.5C, CH_2CN), 35.0 (0.5C, C-2), 35.1 (0.5C, C-2), 48.7 (0.5C, OCH_3), 49.0 (0.5C, OCH_3), 49.2 (1C, OCH_3), 56.1 (0.5C, OCH_3), 56.9 (0.5C, OCH_3), 76.7 (0.5C, C-5), 70.0 (0.5C, C-5), 79.1 (0.5C, C-4), 79.1 (0.5C, C-4), 96.7 (0.5C, C-1-*o* C-3), 97.0 (0.5C, C-3-*o* C-1), 98.2 (0.5C, C-1-*o* C-3), 100.0 (0.5C, C-3-*o* C-1), 118.1 (0.5C, CH_2CN), 118.2 (0.5C, CH_2CN), 131.2 (1C, imidazole-C), 131.3 (1C, imidazole-C), 136.9 (0.5C, imidazole-C), 137.0 (0.5C, imidazole-C), 182.9 (0.5C, S=C), 183.0 (0.5C, S=C); CIMS (isobutane): *m*/*z* [%] 398 [M+$C_4H_9^+$, 11], 342 [MH^+, 100], 311 [MH^+−OCH_3, 11]; Anal. Calcd for $C_{14}H_{19}N_3O_5S$ (341.4): C, 49.26; H, 5.61; N, 12.31; S, 9.39. Found: C, 49.19; H, 5.51; N, 12.82; S, 8.78.

4.8. Methyl 6-cyano-2,4,6-trideoxy-α- and β-D-*glycero*-1,5-hex-3-ulopyranoside dimethyl ketal (12α/β)

Under N_2, tris(trimethylsilyl)silane (0.9 mL, 2.9 mmol) and AIBN (0.08 g, 0.49 mmol) were added to a solution of **11α/β** (787 mg, 2.3 mmol) in toluene (20 mL). The mixture was heated to reflux for 7 h. Then the solvent was concentrated in vacuo. The residue was purified by FC (3 cm, 50:50 petroleum ether–EtOAc, fractions 10 mL, R_f 0.52) to give **12α/β** (441 mg, 89%) as a yellow oil: IR (ATR, film): $\tilde{\nu}$ 2942 (νC–H), 2250 (νCN), 1121,

1047 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.33–1.51 (m, 1H, 2-H_{ax}, α-is.+2-H_{ax}, β-is.), 1.69 (dd, *J* 14.3/4.6 Hz, 1H, 2-H_{eq}, α-is.+2-H_{eq}, β-is.), 2.03–2.25 (m, 2H, 4-H_{ax}+4-H_{eq}, α+β-is.), 2.52–2.62 (m, 2H, CH_2CN, α+β-is.), 3.18 (s, 3 × 0.35H, OCH_3, α-is.), 3.18 (s, 3 × 0.65H, OCH_3, β-is.), 3.20 (s, 3 × 0.35H, OCH_3, α-is.), 3.21 (s, 3 × 0.65H, OCH_3, β-is.), 3.37 (s, 3 × 0.35H, OCH_3, α-is.), 3.50 (s, 3 × 0.65H, OCH_3, β-is.), 3.82 (dddd, *J* 11.6/6.7/6.1/2.4 Hz, 0.65H, 5-H, β-is.), 4.15 (dtd, *J* 11.9/6.1/2.1 Hz, 0.35H, 5-H, α-is.), 4.46 (dd, *J* 9.8/2.4 Hz, 0.65H, 1-H_{ax}, β-is.), 4.82 (d, *J* 4.0 Hz, 0.35H, 1-H_{eq}, α-is.); ^{13}C NMR ($CDCl_3$): δ 23.9 (0.65C, *C*H_2CN), 24.0 (0.35C, *C*H_2CN), 35.3 (0.35C, C-2), 37.5 (0.65C, C-2), 37.8 (0.35C, C-4), 38.0 (0.65C, C-4), 47.1 (0.35C, OCH_3), 47.7 (0.65C, OCH_3), 47.8 (0.65C, OCH_3), 48.4 (0.35C, OCH_3), 55.4 (0.35C, OCH_3), 56.5 (0.65C, OCH_3), 62.7 (0.35C, C-5), 67.1 (0.65C, C-5), 97.3 (0.35C, C-1-*o* C-3), 98.4 (0.65C, C-1-*o* C-3), 99.0 (0.35C, C-3-*o* C-1), 100.7 (0.65C, C-3-*o* C-1), 116.7 (0.65C, CH_2CN), 116.9 (0.35C, CH_2CN); the ratio of α and β anomers was 35:65; EIMS: *m*/*z* [%] 184 [M−OCH_3, 46], 175 [M−CH_2CN, 4], 152 [M−$HOCH_3$−OCH_3, 44], 88 [–C$(OCH_3)_2$–CH_2^+–, 60]; CIMS (NH_3): *m*/*z* [%] 233 [M+NH_4^+, 32], 184 [M−OCH_3, 8], 152 [M−$HOCH_3$−OCH_3, 100]; Anal. Calcd for $C_{10}H_{17}NO_4$ (215.3): C, 55.80; H, 7.96; N, 6.51. Found: C, 55.31; H, 7.99; N, 6.22.

4.9. Methyl 7-amino-2,4,6,7-tetradeoxy-α- and β-D-*glycero*-1,5-hept-3-ulopyranoside dimethyl ketal (13α/β)

A mixture of nitrile **12α/β** (1.1 g, 5.3 mmol), MeOH (40 mL), 2 N NaOH (15 mL), and Raney nickel was shaken under an H_2 atmosphere (4 bar) at room temperature for 24 h. Then the Raney nickel was separated by filtration through Celite®AFA, the solvent was evaporated, and after addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (4 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting crude **13α/β** (yellow oil, 929 mg, 81%) was used for the next reaction without further purification. $C_{10}H_{21}NO_4$ (219.3); IR (ATR, film): $\tilde{\nu}$ 3356 (νN–H), 2926 (νC–H), 1657 (δN–H), 1342, 1172, 1042 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.23–1.39 (m, 1H, 2-H_{ax}, α+β-is./0.6H, 2-H_{eq}, β-is.), 1.41 (s, 2H, $CH_2CH_2NH_2$, α+β-is.), 1.51–1.74 (m, 2H, C$H_2CH_2NH_2$, α+β-is./0.4H, 2-H_{eq}, α-is.), 1.85–1.95 (m, 1H, 4-H_{ax}, α+β-is.), 2.12–2.19 (m, 1H, 4-H_{eq}, α+β-is.), 2.75–2.85 (m, 2H, $CH_2CH_2NH_2$, α+β-is.), 3.13 (s, 3 × 0.6H, OCH_3, β-is.), 3.14 (s, 3 × 0.4H, OCH_3, α-is.), 3.16 (s, 3 × 0.4H, OCH_3, α-is.), 3.16 (s, 3 × 0.6H, OCH_3, β-is.), 3.29 (s, 3 × 0.4H, OCH_3, α-is.), 3.44 (s, 3 × 0.6H, OCH_3, β-is.), 3.52–3.61 (m, 0.6H, 5-H, β-is.), 3.85–3.94 (m, 0.4H, 5-H, α-is.), 4.38 (dd, *J* 9.8/2.1 Hz, 0.6H, 1-H_{ax}, β-is.), 4.75 (d, *J* 4.3 Hz, 0.4H, 1-H_{eq}, α-is.); the ratio of α and β anomers was 40:60; EIMS: *m*/*z* [%] 156 [M−$HOCH_3$−OCH_3, 59]; CIMS (NH_3): *m*/*z* [%] 220 [MH^+, 100], 188 [M−OCH_3, 50], 156 [M−$HOCH_3$−OCH_3, 44].

4.10. Methyl 2,4,6,7-tetradeoxy-7-[(3,4-dichlorophenyl)-acetylamino]-α- and β-D-*glycero*-1,5-hept-3-ulopyranoside dimethyl ketal (14α/β)

4.10.1. Method A. Under N_2, Bu_3SnH (0.1 mL, 0.38 mmol) and AIBN (2 mg, 0.01 mmol) were added to a cooled (ice) solution of thiocarbamate **10α/β** (52 mg, 0.10 mmol) in toluene (8 mL). The mixture was heated under reflux for 29 h. Then the solvent was evaporated in vacuo, and the residue was purified by FC [2 cm, 80:20 EtOA–acetone, fractions 5 mL, R_f 0.27] to give **14α/β** (28 mg, 70%).

4.10.2. Method B. Under N_2, (3,4-dichlorophenyl)acetic acid (788 mg, 3.8 mmol) was dissolved in CH_2Cl_2 (15 mL). 1,1′-Carbonyldiimidazole (625 mg, 3.9 mmol) was added, and the mixture was stirred at room temperature for 1 h. Then a solution of unpurified primary amine **13α/β** (633 mg, 2.9 mmol) in CH_2Cl_2 (10 mL) was added slowly under ice cooling. The mixture was stirred at room temperature for 6 h. The solvent was evaporated in vacuo, and the residue was purified by FC (3 cm, 95:5 EtOAc–acetone, fractions 10 mL, R_f 0.44) to give **14α/β** (1.2 g, 79% based on the nitrile **12α/β**) as a yellow oil: IR (ATR, film): $\tilde{\nu}$ 2940 (νC–H), 1645 (νO=C–NH, amide I), 1552 (δN–H, amide II), 1119, 1047 cm^{-1} (νC–O); ^1H NMR ($CDCl_3$): δ 1.22–1.41 (m, 0.45H, 2-H_{ax}, α-is.), 1.29 (d, *J* 13.1 Hz, 0.45H, 2-H_{eq}, α-is.), 1.32 (dd, *J* 13.4/1.8 Hz, 0.55H, 2-H_{eq}, β-is.), 1.37 (dd, *J* 13.1/9.8 Hz, 0.55H, 2-H_{ax}, β-is.), 1.50–1.84 (m, 2H, CH_2CH_2NH, α+β-is.), 1.86–1.94 (m, 1H, 4-H_{ax}/4-H_{eq}, α+β-is.), 2.15–2.23 (m, 1H, 4-H_{ax}/4-H_{eq}, α+β-is.), 3.16 (s, 3 × 0.45H, OCH_3, α-is.), 3.16 (s, 3 × 0.55H, OCH_3, β-is.), 3.18 (s, 3 × 0.45H, OCH_3, α-is.), 3.18 (s, 3 × 0.45H, OCH_3, α-is.), 3.20 (s, 3 × 0.55H, OCH_3, β-is.), 3.23–3.37 (m, 1H, CH_2CH_2NH, α+β-is.), 3.41–3.66 (m, 1H, CH_2CH_2NH, α+β-is./0.55H, 5-H, β-is.), 3.43 (s, 3 × 0.55H, OCH_3, β-is.), 3.47 (s, 2 × 0.55H, COCH_2Ph, β-is.), 3.50 (s, 2 × 0.45H, COCH_2Ph, α-is.), 3.85–3.94 (m, 0.45H, 5-H, α-is.), 4.37 (dd, *J* 9.8/2.1 Hz, 0.55H, 1-H_{ax}, β-is.), 4.54 (d, *J* 4.6 Hz, 0.45H, 1-H_{eq}, α-is.), 5.98 (s, br, 0.55H, NH, β-is.), 6.16 (s, br, 0.45H, NH, α-is.), 7.11 (dd, *J* 8.2/2.1 Hz, 0.45H, arom. H, 6′-H, α-is.), 7.12 (dd, *J* 8.2/1.8 Hz, 0.55H, arom. H, 6′-H, β-is.), 7.36 (d, *J* 2.4 Hz, 0.45H, arom. H, 2′-H, α-is.), 7.37 (d, *J* 2.1 Hz, 0.55H, arom. H, 2′-H, β-is.), 7.41 (d, *J* 8.2 Hz, 0.55H, arom. H, 5′-H, β-is.), 7.42 (d, *J* 8.2 Hz, 0.45H, arom. H, 5′-H, α-is.); the ratio of α and β anomers was 45:55; ^{13}C NMR ($CDCl_3$): δ 34.1 (0.55C, *C*H_2CH_2NH), 34.4 (0.45C, *C*H_2CH_2NH), 35.5 (0.55C, C-4), 37.1 (0.45C, CH_2CH_2NH), 37.6 (0.55C, CH_2CH_2NH), 37.9

(0.45C, C-4), 38.4 (1C, C-2), 42.6 (0.45C, CO*C*H_2Ph), 42.7 (0.55C, CO*C*H_2Ph), 46.9 (0.55C, O*C*H_3), 47.5 (0.45C, O*C*H_3), 47.6 (0.45C, O*C*H_3), 48.3 (0.55C, O*C*H_3), 55.0 (0.55C, O*C*H_3), 56.3 (0.45C, O*C*H_3), 66.4 (0.55C, C-5), 70.2 (0.45C, C-5), 97.3 (0.55C, C-3), 98.3 (0.55C, C-1), 99.2 (0.45C, C-3), 100.8 (0.45C, C-1), 128.5/128.8/130.6/130.6/131.0/131.3/132.7/135.2 (6C, arom. C), 169.4 (0.55C, NH*C*OCH$_2$) 169.5 (0.45C, NH*C*OCH$_2$); EIMS: *m*/*z* [%] 406 [M^+, 1], 344 [M−2 × OCH$_3$, 16]; CIMS (NH_3): *m*/*z* [%] 423/425/427 [M+NH_4^+, 4.5/3.1/0.5], 345/347/349 [MH^+−2 × OCH$_3$, 58/32/5], 314/316/318 [MH^+−3 × OCH$_3$, 100/64/11]; Anal. Calcd for $C_{18}H_{25}Cl_2NO_5$ (406.3): C, 53.21; H, 6.20; N, 3.45. Found: C, 53.17; H, 6.30; N, 3.34.

4.11. Methyl 7-(benzoylamino)-2,4,6,7-tetradeoxy-α- and β-D-*glycero*-1,5-hept-3-ulopyranoside dimethyl ketal (15α/β)

Under N_2, PhCOCl (0.4 mL, 3.5 mmol) and Et_3N (0.7 mL, 5.0 mmol) were added to a solution of unpurified primary amine **13α/β** (561 mg, 2.6 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 8 h. After concentration of the mixture in vacuo, the residue was purified by FC (3 cm, EtOAc, fractions 10 mL, R_f 0.46) to give **15α/β** (747 mg, 73% based on the nitrile **12α/β**) as a pale-yellow oil: IR (ATR, film): $\tilde{\nu}$ 3323 (*ν*N–H), 2940 (*ν*C–H), 1638 (*νO*=*C*–NH, amide I), 1538 (*δ*N–H, amide II), 1117, 1049 (*ν*C–O), 710, 694 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): *δ* 1.39–1.48 (m, 1H, 2-H$_{ax}$, α+β-is.), 1.66–1.72 (m, 1H, 2-H$_{eq}$, α+β-is.), 1.73–1.91 (m, 2H, C*H*$_2$CH$_2$NH, α+β-is.), 1.91–2.03 (m, 1H, 4-H$_{ax}$, α+β-is.), 2.19–2.26 (m, 1H, 4-H$_{eq}$, α+β-is.), 3.18 (s, 3 × 0.4H, OC*H*$_3$, β-is.), 3.19 (s, 3 × 0.6H, OC*H*$_3$, α-is.), 3.21 (s, 3 × 0.6H, OC*H*$_3$, α-is.), 3.21 (s, 3 × 0.4H, OC*H*$_3$, β-is.), 3.32 (s, 3 × 0.6H, OC*H*$_3$, α-is.), 3.44 (s, 3 × 0.4H, OC*H*$_3$, β-is.), 3.41–3.57 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 3.67–3.85 (m, 0.4H, 5-H, β-is./1H, CH$_2$C*H*$_2$NH, α+β-is.), 4.01–4.11 (m, 0.6H, 5-H, α-is.), 4.46 (dd, *J* 9.8/2.1 Hz, 0.4H, 1-H$_{ax}$, β-is.), 4.86 (d, *J* 4.0 Hz, 0.6H, 1-H$_{eq}$, α-is.), 4.92 (s, br, 1H, NH, α+β-is.), 7.38–7.51 (m, 3H, arom. H, α+β-is.), 7.76 (tt, *J* 6.7/1.4 Hz, 2H, arom. H, *m*-pos., α+β-is.); the ratio of α and β anomers was 60:40; EIMS: *m*/*z* [%] 260 [M−HOCH$_3$−OCH$_3$, 12], 105 [$PhCO^+$, 100], 88 [–C(OCH$_3$)$_2$–CH_2^+–, 23]; CIMS (NH_3): *m*/*z* [%] 292 [M−OCH$_3$, 28], 260 [M−HOCH$_3$−OCH$_3$, 100]; Anal. Calcd for $C_{17}H_{25}NO_5$ (323.4): C, 63.14; H, 7.79; N, 4.33. Found: C, 62.41; H, 7.79; N, 4.45.

4.12. Methyl 2,4,6,7-tetradeoxy-7-[(3,4-dichlorophenyl)acetylamino]-α- and β-D-*glycero*-1,5-hept-3-ulopyranoside (18α/β)

A solution of **14α/β** (961 mg, 2.4 mmol) and *p*-toluenesulfonic acid (100 mg, 0.53 mmol) in CH_2Cl_2 (40 mL) was stirred at 0 °C for 4 h. The reaction mixture was extracted with satd aq $NaHCO_3$ (2 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (3 cm, 90:10 EtOAc–acetone, fractions 10 mL, R_f 0.39) to give **18α/β** (539 mg, 63%) as a colorless solid: mp 141 °C; IR (ATR, neat): $\tilde{\nu}$ 3275 (*ν*N–H), 2929 (*ν*C–H), 1716 (*ν*C=O), 1641 (*νO*=*C*–NH, amide I), 1559 (*δ*N–H, amide II), 1114, 1033 (*ν*C–O), 734 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): *δ* 1.65–1.84 (m, 2H, C*H*$_2$CH$_2$NH, α+β-is.), 2.21–2.38 (m, 2H, 4-H$_{ax}$+4-H$_{eq}$, α+β-is.), 2.36–2.47 (m, 0.15H, 2-H$_{ax}$, β-is.), 2.44 (dt, *J* 14.9/1.5 Hz, 0.85H, 2-H$_{eq}$, α-is.), 2.55 (dd, *J* 14.8/4.4 Hz, 0.85H, 2-H$_{ax}$, α-is.), 2.64 (dd, *J* 14.7/2.4 Hz, 0.15H, 2-H$_{eq}$, β-is.), 3.16–3.29 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 3.20 (s, 3H, OC*H*$_3$, α+β-is.), 3.47 (s, 2 × 0.85H, COC*H*$_2$Ph, α-is.), 3.51 (s, 2 × 0.15H, COC*H*$_2$Ph, β-is.), 3.54–3.65 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 4.00–4.10 (m, 1H, 5-H, α+β-is.), 4.52 (dd, *J* 8.6/2.7 Hz, 0.15H, 1-H$_{ax}$, β-is.), 4.88 (d, *J* 4.3 Hz, 0.85H, 1-H$_{eq}$, α-is.), 5.86 (s, br, 0.15H, NH, β-is.), 5.99 (s, br, 0.85H, NH, α-is.), 7.12 (dd, *J* 8.2/2.1 Hz, 1H, arom. H, 6′-H, α+β-is.), 7.38 (d, *J* 1.8Hz, 1H, arom. H, 2′-H, α+β-is.), 7.41 (d, *J* 8.2 Hz, 0.15H, arom. H, 5′-H, β-is.), 7.43 (d, *J* 8.2 Hz, 0.85H, arom. H, 5′-H, α-is.); the ratio of α and β anomers was 85:15; EIMS: *m*/*z* [%] 159/161/163 [–$CH_2PhCl_2^+$, 67/43/7]; CIMS (NH_3): *m*/z [%] 377/379/381 [M+NH_4^+, 12.1/7.4/1.2], 314/316/318 [M−CH_2OCH_3, 100/63/11] ; CIMS (isobutane): *m*/*z* [%] 416 [M+$C_4H_9^+$, 4], 328/330/332 [M−OCH$_3$, 52/35/7]; Anal. Calcd for $C_{16}H_{19}Cl_2NO_4$ (360.2): C, 53.35; H, 5.32; N, 3.89. Found: C, 53.21; H, 5.55; N, 3.68.

4.13. Methyl 7-(benzoylamino)-2,4,6,7-tetradeoxy-α- and β-D-*glycero*-1,5-hept-3-ulopyranoside (19α/β)

A solution of **15α/β** (811 mg, 2.51 mmol) and *p*-toluenesulfonic acid (100 mg, 0.53 mmol) in CH_2Cl_2 (40 mL) was stirred at 0 °C for 2 h. After completion of the reaction, the mixture was extracted with satd aq $NaHCO_3$ (2 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residual solid was purified by recrystallization from 2-Pr_2O. R_f 0.52 (80:20 TBME–acetone) to give **19α/β** (636 mg, 91%) as a colorless solid: mp 131 °C; IR (ATR, neat): $\tilde{\nu}$ 3318 (*ν*N–H), 2929 (*ν*C–H), 1730 (*ν*C=O), 1638 (*νO*=*C*–NH, amide I), 1535 (*δ*N–H, amide II), 1290 cm^{-1} (*ν*C–O); ^{1}H NMR ($CDCl_3$): *δ* 1.89–1.96 (m, 2H, C*H*$_2$CH$_2$NH, α+β-is.), 2.36–2.52 (m, 2H, 4-H$_{eq}$ and 4-H$_{ax}$, α+β-is./0.1H, 2-H$_{eq}$, β-is./0.1H, 2-H$_{ax}$, β-is), 2.49 (dd, *J* 14.9/1.5 Hz, 0.9H, 2-H$_{eq}$, α-is.), 2.64 (dd, *J* 14.9/4.7 Hz, 0.9H, 2-H$_{ax}$, α-is.), 3.33 (s, 3 × 0.9H, OC*H*$_3$, α-is.), 3.50 (s, 3 × 0.1H, OC*H*$_3$, β-is.), 3.46–3.65 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.) 3.73–3.84 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 4.16–4.25 (m,

1H, 5-H, α+β-is.), 4.60 (dd, *J* 8.7/2.9 Hz, 0.1H, 1-H_{ax}), 5.14 (dd, *J* 4.6/1.5 Hz, 0.9H, 1-H_{eq}), 6.23 (s, br, 0.1H, NH, β-is.), 6.68 (s, br, 0.9H, NH, α-is.), 7.39–7.52 (m, 3H, arom. H, α+β-is.), 7.70–7.78 (m, 2H, arom. H, α+β-is.); the ratio of α and β anomers was 90:10; ^{13}C NMR ($CDCl_3$): δ 35.0 (1C, *C*H_2CH$_2$NH), 37.5 (1C, CH$_2$*C*H$_2$NH), 46.3 (1C, C-2), 47.2 (1C, C-4), 55.0 (1C, OCH_3), 68.1 (1C, C-5), 99.7 (1C, C-1), 126.7 (1C, arom. C), 128.6 (3C, arom. C), 131.4 (2C, arom. C), 167.7 (1C, NH*C*OPh), 203.7 (1H, C-3); in the ^{13}C NMR spectrum the intensities of the β anomer signals were too weak; EIMS: *m*/*z* [%] 245 [M−HOCH$_3$, 5], 105 [PhCO$^+$, 100], 77 [Ph$^+$, 40]; CIMS (NH_3): *m*/*z* [%] 295 [M+NH_4^+, 100], 278 [MH$^+$, 76], 346 [M−OCH$_3$, 67]; CIMS (isobutane): *m*/*z* [%] 278 [MH$^+$, 16], 247 [MH$^+$−OCH$_3$, 15]; Anal. Calcd for $C_{15}H_{19}NO_3$ (277.3): C, 64.97; H, 6.91; N, 5.05. Found: C, 64.97; H, 6.85; N, 4.85.

4.14. 1,5-Anhydro-2,4,6,7-tetradeoxy-7-(3,4-dichlorophenyl)acetylamino-D-*glycero*-hept-1-en-3-ulose (20) {2-(3,4-dichlorophenyl)-*N*-{2-[(2*R*)-4-oxo-2,3-dihydropyran-2-yl]ethyl}-acetamide (20)}

Under N_2, a solution of **14α/β** (77 mg, 0.19 mmol) and $BF_3{\cdot}Et_2O$ (seven drops) in THF (10 mL) was heated to reflux for 3 days. Then H_2O (10 mL) and Et_2O (10 mL) were added. After separation of the organic layer, the aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (1 cm, 80:20 EtOAc–acetone, fractions 2 mL, R_f 0.31) to give **20** (53 mg, 86%) as a colorless solid: mp 126 °C; IR (ATR, neat): $\tilde{\nu}$ 3283 (*ν*N–H), 1663 (*ν*C=O), 1638 (*νO*=*C*–NH, amide I), 1557 (δN–H, amide II), 1270, 1031 cm^{-1} (*ν*C–O); ^{1}H NMR ($CDCl_3$): δ 1.87–1.97 (m, 2H, C*H*$_2$CH$_2$NH), 2.40 (ddd, *J* 16.8/4.0/1.2 Hz, 1H, 3-H_{eq}), 2.53 (dd, *J* 16.8/13.4 Hz, 1H, 3-H_{ax}), 3.33–3.48 (m, 2H, CH$_2$C*H*$_2$NH), 3.51 (s, 2H, COC*H*$_2$), 4.42 (ddt, *J* 13.4/8.0/4.3 Hz, 1H, 2-H), 5.41 (dd, *J* 6.1/1.2 Hz, 1H, 5-H), 5.68 (s, br, 1H, NH), 7.12 (dd, *J* 8.2/2.1 Hz, 1H, arom. H, 6′-H), 7.23 (d, *J* 6.1 Hz, 1H, 6-H), 7.37 (d, *J* 2.1 Hz, 1H, arom. H, 2′-H), 7.43 (d, *J* 8.2 Hz, 1H, arom. H, 5′-H); ^{13}C NMR ($CDCl_3$): δ 33.9 (1C, *C*H$_2$CH$_2$NH), 36.3 (1C, CH$_2$*C*H$_2$NH), 41.8 (1C, C-3), 42.6 (1C, CO*C*H$_2$Ph), 78.0 (1C, C-2), 107.4 (1C, C-5), 28.7/130.8/131.3/131.6/132.9/134.9 (6C, arom. C), 162.4 (1C, C-6), 169.7 (1C, *C*OCH$_2$Ph), 191.7 (1H, C-4); EIMS: *m*/*z* [%] 327/329/331 [M$^+$, 24/16/3], 159/161/163 [–CH$_2$PhCl$_2^+$, 56/38/7]. CIMS (NH_3): *m*/*z* [%] 345/347/349 [M+NH_4^+, 100/66/12], 328/330/332 [MH$^+$, 97/66/13], 294/296 [MH$^+$−Cl, 97/35]. APCIMS: *m*/*z* [%] 328/330/332 [MH$^+$, 100/57/7]; Anal. Calcd for $C_{15}H_{15}Cl_2NO_3$ (328.2): C, 54.90; H, 4.61; N, 4.27. Found: C, 54.60; H, 4.75; N, 4.11.

4.15. 1,5-Anhydro-7-benzoylamino-2,4,6,7-tetradeoxy-D-*glycero*-hept-1-en-3-ulose (20) {*N*-{2-[(2*R*)-4-oxo-2,3-dihydropyran-2-yl]ethyl}benzamide (21)}

Under N_2, a solution of **19α/β** (100 mg, 0.36 mmol) and $BF_3{\cdot}Et_2O$ (12 drops) in THF (12 mL) was heated to reflux for 28 h. Then H_2O (8 mL) and Et_2O (15 mL) were added. After separation of the organic layer, the aqueous layer was extracted with Et_2O (15 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (2 cm, 90:10 EtOAc–petroleum ether, fractions 2 mL, R_f 0.29) to give **21** (57 mg, 64%) as an orange oil: IR (ATR, film): $\tilde{\nu}$ 3321 (*ν*N–H), 2924 (*ν*C–H), 1717 (*ν*C=O), 1637 (*ν*O=C–NH, amide I), 1591 (*ν*C=C), 1537 (δN–H, amide II), 1275 (*ν*C–O), 697 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$): δ 2.02–2.15 (m, 2H, C*H*$_2$CH$_2$NH), 2.47 (ddd, *J* 16.8/4.0/1.0 Hz, 1H, 3-H_{eq}), 2.59 (dd, *J* 16.8/13.1 Hz, 1H, 3-H_{ax}), 3.59–3.72 (m, 2H, CH$_2$C*H*$_2$NH), 4.50–4.60 (m, 1H, 2-H), 5.43 (dd, *J* 6.0/0.9 Hz, 1H, 5-H), 6.46 (s, br, 1H, NH), 7.36 (d, *J* 5.8 Hz, 1H, 6-H), 7.40–7.54 (m, 3H, arom. H), 7.74–7.77 (m, 2H, arom. H); EIMS: *m*/*z* [%] 245 [M$^+$, 1], 140 [M−PhCO, 6], 105 [PhCO$^+$, 100], 77 [Ph$^+$, 40]; Anal. Calcd for $C_{14}H_{15}NO_3$ (245.3): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.02; H, 6.23; N, 5.21.

4.16. Methyl 3-(benzylamino)-2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-β-D-*threo*-1,5-heptopyranoside (22β), methyl 3-(benzylamino)-2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-α-D-*threo*-1,5-heptopyranoside (22α) and methyl 3-(benzylamino)-2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-α-D-*erythro*-1,5-heptopyranoside (23α)

Benzylamine (0.3 mL, 2.8 mmol) was dissolved in a small amount of abs MeOH and the solution was brought to pH 6 with 5 N HCl in MeOH. Then a small amount of 3 Å molecular sieves was added to a solution of the ketone **18α/β** (103 mg, 0.29 mmol) in abs MeOH (10 mL), and afterwards the benzylamine solution was added. Under N_2, $NaBH_3CN$ (35 mg, 0.56 mmol) was added, and the mixture was stirred at room temperature for 5 days. After completion of the reaction, satd aq $NaHCO_3$ (5 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FC (2 cm, 90:10 CH_2Cl_2–MeOH, fractions 2 mL) gave the isomerically pure secondary amine **22β** and a mixture of **22β**, **22α**, and **23α**.

4.16.1. Data for 22β. Colorless oil; yield 6.0 mg (6%); R_f 0.31; $[\alpha]_{589}$ +18.9 (*c* 0.018, MeOH); IR (ATR, film): $\tilde{\nu}$ 3289 (*ν*N–H), 2928 (*ν*C–H), 1646 (*νO*=*C*–NH, amide I), 1555 (δN–H, amide II), 1470 (δC–H), 1122, 1032 (*ν*C–O), 733 cm^{-1} (γCH$_{oop}$, arom.); ^{1}H NMR ($CDCl_3$):

δ 1.15 (q, J 12.2H, 1H, 2-H_{ax}-*o* 4-H_{ax}), 2.20 (q, J 11.9 Hz, 1H, 2-H_{ax}-*o* 4-H_{ax}), 1.58–1.87 (m, 1H, 2-H_{eq}-*o* 4-H_{eq}/2H, CH_2CH_2NH/1H, benzyl-N*H*), 2.09–2.15 (m, 1H, 2-H_{eq}-*o* 4-H_{eq}), 2.78 (tt, J 11.6/4.0 Hz, 1H, 3-H), 3.28 (td, J 12.5/6.1 Hz, 1H, 5-H), 3.42 (s, 3H, OCH_3), 3.46 (s, 2H, $COCH_2Ph$), 3.36–3.59 (m, 2H, CH_2CH_2NH), 3.82 (s, 2H, $NHCH_2Ph$), 4.23 (dd, J 9.8/2.1 Hz, 1H, 1-H_{ax}), 5.96 (s, br, 1H, N*H*CO), 7.11 (dd, J 8.2/2.1 Hz, 1H, arom. H, 6′-H), 7.23–7.43 (m, 5H, arom. H, phenyl), 7.38 (d, J 2.1 Hz, 1H, arom. H, 2′-H), 7.40 (d, J 8.2 Hz, 1H, arom. H, 5′-H); EIMS: m/z [%] 392/394/396 [M−$CH_2CH(OCH_3)$–, 9.5/5.8/1.1], 106 [$PhCH_2NH^+$, 89], 91 [$PhCH_2^+$, 100]; LC–APCI-MS: m/z [%] 451/453/455 [MH^+, 100/60/10], 419/421/423 [M−OCH_3, 12.4/6.6/0.9]; CIMS (isobutane): m/z [%] 451/453/455 [MH^+, 100/66/11], 419/421/423 [M−OCH_3, 55/33/6.7]; Anal. Calcd for $C_{23}H_{28}Cl_2N_2O_3$ (451.4): C, 61.20; H, 6.25; N, 6.21. Found: C, 61.35; H, 6.05; N, 6.47.

4.16.2. Data for a mixture of 22β, 22α, and 23α. Pale-yellow oil; yield 39 mg (31%); R_f 0.28; ^{1}H NMR ($CDCl_3$): δ 1.04–2.15 (m, 2H, 4-H_{eq}+4-H_{ax}, isomer 1, 2, and 3/2H, 4-H_{eq}+4-H_{ax}, isomer 1, 2, and 3/2H, CH_2CH_2NH, isomer 1, 2, and 3/benzyl-NH, isomer 1, 2, and 3), 2.75 (tt, J 11.6/4.0 Hz, 0.33H, 3-H_{ax}, isomer 1), 2.96–3.07 (m, 0.40H, 3-H_{ax}, isomer 2/0.27H, 3-H_{eq}, isomer 3), 3.09–3.97 (m, 2H, CH_2CH_2NH, isomer 1, 2, and 3/1H, 5-H, isomer 1, 2, and 3), 3.15 (s, 3 × 0.27H, OCH_3, isomer 3), 3.17 (s, 3 × 0.40H, OCH_3, isomer 2), 3.42 (s, 3 × 0.33H, OCH_3, isomer 1), 3.46 (s, 2 × 0.33H, $COCH_2Ph$, isomer 1), 3.49 (s, 2 × 0.27H, $COCH_2Ph$, isomer 3), 3.50 (s, 2 × 0.40H, $COCH_2Ph$, isomer 2), 3.78 (s, 2 × 0.40H, $NHCH_2Ph$, isomer 2), 3.81 (s, 2 × 0.33H, $NHCH_2Ph$, isomer 1, 2 × 0.27H, $NHCH_2Ph$, isomer 3), 4.24 (dd, J 9.8/1.8 Hz, 0.33H, 1-H_{ax}, isomer 1), 4.56 (d, J 3.4 Hz, 0.27H, 1-H_{eq}, isomer 3), 4.57 (d, J 3.9 Hz, 0.40H, 1-H_{eq}, isomer 2), 5.95 (s, br, 0.33H, N*H*CO, isomer 1), 6.15 (s, br, 0.27H, N*H*CO, isomer 3), 6.47 (s, br, 0.40H, N*H*CO, isomer 2), 7.09–7.15 (m, 1H, arom. H, isomer 1, 2, and 3), 7.28–7.43 (m, 7H, arom. H, isomer 1, 2, and 3); the ratio of the isomers 1 (**22β**), 2 (**22α**), and 3 (**23α**) was 33:40:27; $C_{23}H_{28}Cl_2N_2O_3$ (451.4).

4.17. Methyl 2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-3-(methylamino)-α- and β-D-*threo*-1,5-heptopyranoside (24α/β) and methyl 2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-3-(methylamino)-pentadeoxy-α-D-*erythro*-1,5-heptopyranoside (25β)

An ethanolic solution of methylamine (8 M, 0.45 mL, 3.6 mmol) was dissolved in a small amount of abs MeOH. The solution was brought to pH 6 with 5 N HCl in MeOH. This solution was added to a mixture of ketone **18α/β** (210 mg, 0.58 mmol), 3 Å molecular sieves and abs MeOH (10 mL). Under N_2, $NaBH_3CN$ (40 mg, 0.64 mmol) was added, and the mixture was stirred at room temperature for 5 days. After completion of the reaction, satd aq $NaHCO_3$ (10 mL) was added, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by FC (2 cm, 80:20 CH_2Cl_2–MeOH, fractions 5 mL) gave the isomerically pure amine **25β**, a mixture of **24α**, **24β**, and **25β** [colorless oil, yield 11 mg (5%)] and an anomeric mixture of **24α** and **24β**.

4.17.1. Data for 24α/24β. Colorless oil; yield 55 mg (25%); R_f 0.07; $[\alpha]_{589}$ +11.5 (c 0.013, MeOH); IR (ATR, film): $\tilde{\nu}$ 3297 (νN–H), 2943 (νC–H), 1638 ($\nu O{=}C$–NH, amide I), 1554 (δN–H, amide II), 1471 (δC–H), 1125, 1066, 1032 cm^{-1} (νC–O). ^{1}H NMR ($CDCl_3$): δ 1.21–1.80 (m, 2H, 4-H_{ax}+2-H_{ax}, α+β-is./2H, CH_2CH_2NH, α+β-is.), 1.90–2.19 (m, 2H, 4-H_{eq}+2-H_{eq}, α+β-is.), 2.48 (s, 3H, $NHCH_3$, α+β-is.), 2.86–2.96 (m, 1H, 3-H, α+β-is.), 3.13–3.59 (m, 0.65H, 5-H, β-is.), 3.16 (s, 3 × 0.35H, OCH_3, α-is.), 3.26 (dt, J 18.9/6.1 Hz, 2H, CH_2CH_2NH, α+β-is.), 3.42 (s, 3 × 0.65H, OCH_3, β-is.), 3.47 (s, 2 × 0.65H, $COCH_2Ph$, β-is.), 3.49 (s, 2 × 0.35H, $COCH_2Ph$, α-is.), 3.70–3.78 (m, 0.35H, 5-H, α-is.), 4.25 (d, J 8.2 Hz, 0.65H, 1-H_{ax}, β-is.), 4.61 (d, J 1.8 Hz, 0.35H, 1-H_{eq}, α-is.), 6.24 (s, br, 0.65H, N*H*CO, β-is.), 6.51 (s, br, 0.35H, N*H*CO, α-is.), 7.11 (dd, J 8.2/1.8 Hz, 0.35H, arom. H, 6′-H, α-is.), 7.12 (dd, J 8.2/1.5 Hz, 0.65H, arom. H, 6′-H, β-is.), 7.37 (d, J 2.1 Hz, 0.65H, arom. H, 2′-H, β-is.), 7.38 (d, J 2.4 Hz, 0.35H, arom. H, 2′-H, α-is.), 7.39 (d, J 8.5 Hz, 0.65H, arom. H, 5′-H, β-is.), 7.41 (d, J 8.2 Hz, 0.35H, arom. H, 5′-H, α-is.); a signal for the N*H*-proton was not seen in the spectrum; the ratio of α and β anomers was 35:65; EIMS: m/z [%] 315/317/319 [M^+−OCH_3−$NHCH_3$, 5/3/0.5], 159/161/163 [–$CH_2PhCl_2^+$, 25/18/3]; CIMS (NH_3): m/z [%] 375/377/379 [MH^+, 100/56/9], 343/345/347 [M^+−OCH_3, 27/13/2]; Anal. Calcd for $C_{17}H_{24}Cl_2N_2O_3$ (375.3): C, 54.41; H, 6.45; N, 7.46. Found: C, 54.30; H, 7.03; N, 7.10.

4.17.2. Data for 25β. Colorless oil; yield 24 mg (11%); R_f 0.19; $[\alpha]_{589}$ +10.8 (c 0.011, MeOH); IR (ATR, film): $\tilde{\nu}$ 3288 (νN–H), 2928 (νC–H), 1645 ($\nu O{=}C$–NH, amide I), 1554 (δN–H, amide II), 1471 (δC–H), 1132, 1032 (νC–O), 682 cm^{-1} (γCH_{oop}, arom.); ^{1}H NMR ($CDCl_3$): δ 1.66–2.15 (m, 2H, CH_2CH_2NH/2H, 2-H_{ax}+2-H_{eq}/2H, 4-H_{ax}+4-H_{eq}), 2.49 (s, 3H, $NHCH_3$), 3.14 (quint., br, J 3.5 Hz, 1H, 3-H), 3.27–3.51 (m, 2H, CH_2CH_2NH), 3.43 (s, 3H, OCH_3), 3.51 (s, 2H, $COCH_2Ph$), 3.96–4.05 (m, 1H, 5-H), 4.75 (dd, J 9.3/2.0 Hz, 1H, 1-H_{ax}), 6.16 (s, br, 1H, NH), 7.15 (dd, J 8.2/1.8 Hz, 1H, arom. H, *o*-pos.-6′), 7.40 (d, J 8.5 Hz, 1H, arom. H, *m*-pos.-5′), 7.41 (d, J 1.5 Hz, 1H, arom. H, *o*-pos.-2′); Anal. Calcd

for $C_{17}H_{24}Cl_2N_2O_3$ (375.3): C, 54.41; H, 6.45; N, 7.46. Found: C, 54.02; H, 6.18; N, 7.20.

4.18. Methyl 2,3,4,6,7-pentadeoxy-7-[(3,4-dichlorophenyl)acetylamino]-3-(dimethylamino)-α- and β-D-*threo*-1,5-heptopyranoside (26α/β)

A methanolic solution of dimethylamine (2 M, 0.6 mL, 1.2 mmol) was dissolved in a small amount of abs MeOH. The solution was brought to pH 6 with 5 N HCl in MeOH. This solution was added to a mixture of ketone **18α/β** (89 mg, 0.25 mmol), a small amount of 4 Å molecular sieves and abs MeOH (10 mL). Under N_2, $NaBH_3CN$ (32 mg, 0.50 mmol) was added, and the mixture was stirred at room temperature for 4 days. Then satd aq $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (2 cm, 80:20 CH_2Cl_2–MeOH, fractions 2 mL, R_f 0.14) to give **26α/β** as a yellow oil (30 mg, 31%): $[\alpha]_{589}$ +14.4 (*c* 0.013, MeOH); IR (film): $\tilde{\nu}$ 3293 (*ν*N–H), 2938 (*ν*C–H), 1647 (*νO*=*C*–NH, amide I), 1555 (*δ*N–H, amide II), 1470 (*δ*C–H), 1123, 1046 cm^{-1} (*ν*C–O); ^1H NMR ($CDCl_3$): *δ* 1.18–1.37 (m, 0.35H, 2-H_{ax}, β-is.), 1.22 (q, *J* 11.9H, 1H, 4-H_{ax}, α+β-is.), 1.42 (td, *J* 12.5/3.7H, 0.65H, 2-H_{ax}, α-is.), 1.53–1.87 (m, 2H, C*H*$_2$CH$_2$NH, α+β-is.), 1.89–1.96 (m, 1H, 2-H_{eq}, α+β-is.), 1.98–2.06 (m, 1H, 4-H_{eq}, α+β-is.), 2.27 (s, 3 × 0.35H, N(C*H*$_3$)$_2$, β-is.), 2.28 (s, 3 × 0.65H, N(C*H*$_3$)$_2$, α-is.), 2.46 (tt, *J* 11.9/4.0 Hz, 0.35H, 3-H, β-is.), 2.76 (tt, *J* 12.1/3.8 Hz, 0.65H, 3-H, α-is.), 3.11–3.22 (m, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 3.16 (s, 3 × 0.65H, OC*H*$_3$, α-is.), 3.35–3.45 (m, 0.35H, 5-H, β-is.), 3.43 (s, 3 × 0.35H, OC*H*$_3$, β-is.), 3.47 (s, 2 × 0.35H, COC*H*$_2$Ph, β-is.), 3.50 (s, 2 × 0.65H, COC*H*$_2$Ph, α-is.), 3.58 (td, *J* 13.5/6.5 Hz, 1H, CH$_2$C*H*$_2$NH, α+β-is.), 3.74 (ddt, *J* 11.7/8.7/2.6 Hz, 0.65H, 5-H, α-is.), 4.25 (dd, *J* 9.6/2.0 Hz, 0.35H, 1-H_{ax}, β-is.), 4.59 (d, *J* 2.7 Hz, 0.65H, 1-H_{eq}, α-is.), 5.99 (s, br, 0.35H, NH, β-is.), 6.16 (s, br, 0.65H, NH, α-is.), 7.11 (dd, *J* 8.2/2.0 Hz, 0.65H, arom. H, 6′-H, α-is.), 7.12 (dd, *J* 8.2/2.1 Hz, 0.35H, arom. H, 6′-H, β-is.), 7.37 (d, *J* 2.1 Hz, 0.35H, arom. H, 2′-H, β-is.), 7.38 (d, *J* 2.1 Hz, 0.65H, arom. H, 2′-H, α-is.), 7.41 (d, *J* 7.9 Hz, 0.35H, arom. H, 5′-H, β-is.), 7.42 (d, *J* 7.9 Hz, 0.65H, arom. H, 5′-H, α-is.); the ratio of the α and β anomers was 65:35; ^{13}C NMR ($CDCl_3$): *δ* 32.0 (0.65C, C-2), 33.6 (0.35C, C-2), 33.8 (0.35C, C-4), 34.1 (0.65C, C-4), 34.6 (0.65C, *C*H$_2$CH$_2$NH), 34.8 (0.35C, *C*H$_2$CH$_2$NH), 37.3 (0.35C, CH$_2$*C*H$_2$NH), 37.8 (0.65C, CH$_2$*C*H$_2$NH), 41.0 (2 × 0.65C, N(*C*H3)$_2$), 41.3 (2 × 0.35C, N(*C*H3)$_2$), 42.8 (0.35C, CO*C*H$_2$Ph), 42.8 (0.65C, CO*C*H$_2$Ph), 54.4 (0.65C, O*C*H$_3$), 55.8 (0.65C, C-3), 56.3 (0.35C, O*C*H$_3$), 59.8 (0.35C, C-3), 68.3 (0.65C, C-5), 72.5 (0.35C, C-5), 98.7 (0.65C, C-1), 102.5 (0.35C, C-1), 128.6 (0.35C, arom. C, *o*-pos.6′), 128.9 (0.65C, arom. C, *o*-pos.6′), 130.7 (1C, arom. C, *o*-pos.2′), 131.1, 131.4, 132.8 (3C, arom. C, *m*-pos.3′ and 5′, *p*-pos.4′), 135.2 (0.35C, arom. C, pos.1′), 135.3 (0.65C, arom. C, pos.1′), 169.4 (0.65C, NH*C*OCH$_2$), 169.5 (0.35C, NH*C*OCH$_2$); the ratio of α and β anomers was 65:35; $C_{18}H_{26}Cl_2N_2O_3$ (389.3); EIMS: *m*/*z* [%] 159/161/163 [–CH$_2$PhCl$_2^+$, 37/21/4]; CIMS (isobutane): *m*/*z* [%] 389/391/393 [MH^+, 100/64/11], 358/360/362 [MH^+−OCH_3, 13.2/9.6/1.5]; HREIMS: Calcd for $C_{18}H_{26}Cl_2N_2O_3$ *m*/*z* 388.1321; found 388.1322.

4.19. Methyl 7-(benzoylamino)-3-(benzylamino)-2,3,4,6,7-pentadeoxy-α-D-*erythro*-1,5-heptopyranoside (29α)

Benzylamine (0.8 mL, 7.3 mmol) was dissolved in a small amount of abs MeOH. The solution was brought to pH 6 with 5 N HCl in MeOH. This solution was added to a mixture of ketone **19α/β** (277 mg, 1.0 mmol), a small amount of 4 Å molecular sieves and abs MeOH (10 mL). Under N_2, $NaBH_3CN$ (64 mg, 1.02 mmol) was added, and the mixture was stirred at room temperature for 6 days. After completion of the reaction, 2 N NaOH (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (2 cm, 80:20 CH_2Cl_2–MeOH, fractions 2 mL, R_f 0.45) to give **29α** as a yellow oil (99 mg, 27%): $[\alpha]_{589}$ +60.0 (*c* 0.014, MeOH); IR (ATR, film): $\tilde{\nu}$ 3314 (*ν*N–H), 2927 (*ν*C–H), 1637 (*νO*=*C*–NH, amide I), 1539 (*δ*N–H, amide II), 1119, 1039 (*ν*C–O), 693 cm^{-1} (γCH$_{oop}$, arom.); ^1H NMR ($CDCl_3$): *δ* 1.57 (ddd, *J* 13.7/11.6/4.0 Hz, 1H, 4-H_{ax}), 1.77–1.99 (m, 1H, 4-H_{eq}/2H, 2-H_{ax}+2-H_{eq}/2H, C*H*$_2$CH$_2$NH), 3.01–3.06 (m, 1H, 3-H), 3.23 (s, 3H, OC*H*$_3$), 3.38–3.47 (m, 1H, CH$_2$C*H*$_2$NH), 3.77–3.89 (m, 1H, CH$_2$C*H*$_2$NH), 3.88 (s, 2H, NHC*H*$_2$Ph), 4.07–4.16 (m, 1H, 5-H), 4.84 (d, *J* 3.1 Hz, 1H, 1-H_{eq}), 7.12 (s, br, 1H, N*H*CO), 7.28–7.49 (m, 8H, arom. H), 7.77–7.81 (m, 2H, arom. H); the signal for the Bn–N*H*-proton was not observed in the spectrum; ^{13}C NMR ($CDCl_3$): *δ* 32.0, 34.7, 34.8 (3C, C-2, C-4, C-6), 37.9 (1C, CH$_2$*C*H$_2$NH), 48.5 (1C, C-3), 50.9 (1C, NH*C*H$_2$Ph), 55.3 (1C, O*C*H$_3$), 63.8 (1C, C-5), 99.3 (1C, C-1), 126.7, 126.8, 127.2, 128.1, 128.3, 128.4, 128.5, 131.2, 134.7 (12C, arom. C), 167.1 (1C, NH*C*OPh); $C_{22}H_{28}N_2O_3$ (368.5); EIMS: *m*/*z* [%] 105 [PhCO$^+$, 91], 91 [PhCH$_2^+$, 100], 77 [Ph$^+$, 22]; CIMS (NH_3): *m*/*z* [%] 369 [MH^+, 100], 337 [MH^+−$HOCH_3$, 4].

4.20. Methyl 7-(benzoylamino)-2,3,4,6,7-pentadeoxy-3-(dimethylamino)-α- and β-D-*threo*-1,5-heptopyranoside (30α/β)

An ethanolic solution of dimethylamine (5 M, 0.85 mL, 4.9 mmol) was dissolved in a small amount of abs

MeOH. The solution was brought to pH 6 with 5 N HCl in MeOH. This solution was added to a mixture of ketone **19α/β** (270 mg, 0.97 mmol), a small amount of 4 Å molecular sieves and abs MeOH (15 mL). Under N_2, $NaBH_3CN$ (61 mg, 0.97 mmol) was added, and the mixture was stirred at room temperature for 6 days. After completion of the reaction, 2 N NaOH (10 mL) was added and the mixture was extracted with Et_2O (3×15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (2 cm, 80:20 CH_2Cl_2–MeOH, fractions 5 mL, R_f 0.23) to give **30α/β** as a yellow oil (107 mg, 36%): $[\alpha]_{589}$ +44.3 (*c* 0.016, MeOH); IR (ATR, film): $\tilde{\nu}$ 3312 (*ν*N–H), 2936 (*ν*C–H), 1637 (*νO*=*C*–NH, amide I), 1541 (*δ*N–H, amide II), 1122, 1045 (*ν*C–O), 696 cm^{-1} (*γ*CH_{oop}, arom.); ^1H NMR ($CDCl_3$): δ 1.24–1.42 (m, 0.2H, 2-H_{ax}, β-is./0.2H, 4-H_{ax}, β-is.), 1.35 (q, *J* 12.2 Hz, 0.8H, 4-H_{ax}, α-is.), 1.57 (td, *J* 12.5/3.7 Hz, 0.8H, 2-H_{ax}, α-is.), 1.76–2.03 (m, 2H, C$H_2$$CH_2$NH, α+β-is./1H, 2-$H_{eq}$, α+β-is./1H, 4-$H_{eq}$, α+β-is.), 2.29 (s, 6×0.2H, N(CH_3)$_2$, β-is.), 2.32 (s, 6×0.8H, N(CH_3)$_2$, α-is.), 2.86 (tt, *J* 12.2/4.0 Hz, 1H, 3-H, α+β-is.), 3.31 (s, 3×0.8H, OCH_3, α-is.), 3.40–3.50 (m, 1H, CH_2CH_2NH, α+β-is.), 3.46 (s, 3×0.2H, OCH_3, β-is.), 3.80 (ddd, *J* 13.7/11.9/6.4 Hz, 1H, CH_2CH_2NH, α+β-is.), 3.92 (ddt, *J* 11.4/9.2/2.7 Hz, 1H, 5-H, α+β-is.), 4.35 (dd, *J* 9.5/2.1 Hz, 0.2H, 1-H_{ax}, β-is.), 4.91 (d, *J* 3.4 Hz, 0.8H, 1-H_{eq}, α-is.), 6.90 (s, br, 1H, NH, α+β-is.), 7.39–7.52 (m, 3H, arom. H, α+β-is.), 7.74–7.80 (m, 2H, arom. H, α+β-is.); the ratio of α and β anomers was 80:20; ^{13}C NMR ($CDCl_3$): δ 32.2 (0.8C, C-2), 33.4 (0.2C, C-2), 33.9 (0.2C, C-4), 34.3 (0.8C, C-4), 34.6 (0.2C, C$H_2$$CH_2$NH), 34.8 (0.8C, C$H_2$$CH_2$NH), 37.8 (0.2C, CH_2CH_2NH), 38.1 (0.8C, CH_2CH_2NH), 41.0 (2×0.8C, N(C$H3$)$_2$), 41.3 (2×0.2C, N(C$H3$)$_2$), 54.7 (0.8C, OCH_3), 55.9 (1C, C-3), 56.4 (0.2C, OCH_3), 68.4 (1C, C-5), 98.9 (0.8C, C-1), 102.5 (0.2C, C-1), 126.7, 126.8, 128.4, 128.5, 131.2, 134.7 (6C, arom. C), 167.1 (0.8C, NHCOCH_2), 167.2 (0.2C, NHCOCH_2); $C_{17}H_{26}N_2O_3$ (306.4); EIMS: *m*/*z* [%] 306 [M^+, 7], 105 [$PhCO^+$, 92], 77 [Ph^+, 31]; CIMS (NH_3): *m*/*z* [%] 307 [MH^+, 100], 275 [$MH^+ - HOCH_3$, 20].

5. Receptor-binding studies

5.1. General information

The following equipment was used: Homogenizer, Potter®S (B. Braun Biotech International); Ultraturrax, Euroturrax® T20 (Ika Labortechnik); centrifuge, high-speed cooling centrifuge model J2-HS (Beckman); filter, Whatman glass fiber filters GF/B, presoaked in 0.5% polyethylenimine in water for 2 h at 4 °C before use. Filtration was performed with a Brandel 24-well cell harvester. The scintillation cocktail was Rotiscint Eco Plus (Roth). Liquid scintillation analyzer was a TriCarb 2100 TR (Canberra–Packard), with a counting efficiency of 66%. All experiments were carried out in triplicate. IC_{50}-values were determined from competition experiments with at least six concentrations of test compounds and were calculated with the program, GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. K_i-values were calculated according to Cheng and Prusoff.[20] The K_i-values are given as the mean value ± SEM from three independent experiments.

5.2. σ_1 Assay procedures[14c]

For the σ_1 assay, guinea pig-brain membranes were prepared as described in the literature.[14c] The test was performed with the radioligand [^3H]-pentazocine (1036 GBq/mmol; NEN™ Life Science Products). The thawed membrane preparation (about 150 μg of protein) was incubated with various concentrations of the test compound, 3 nM [^3H]-pentazocine, and buffer (50 mM Tris–HCl, pH 7.4) in a total volume of 500 μL for 120 min at 37 °C. The incubation was terminated by rapid filtration through presoaked Whatman GF/B filters (0.5% polyethylenimine in water for 2 h at 4 °C) using a cell harvester. After washing four times with 2 mL of cold buffer, 3 mL of scintillation cocktail was added to the filters. After at least 8 h, bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Nonspecific binding was determined with 10 μM haloperidol.

5.3. σ_2 Assay procedures[14c]

For the σ_2-assay, rat-liver membranes were prepared as described in the literature.[14c] The membrane preparation (about 60 μg of protein) was incubated with 3 nM [^3H]-ditolylguanidine (2220 GBq/mmol, American Radiolabeled Chemicals, Inc.), and different concentrations of test compounds in buffer (50 mM Tris–HCl, pH 8.0) in the presence of 100 nM (+)-pentazocine. The total volume was 250 μL. The incubation (120 min, 25 °C) was stopped by addition of 2 mL of ice-cold buffer (10 mM Tris–HCl, pH 8.0), followed by rapid filtration through presoaked Whatman GF/B filters using a cell harvester. After the sample was washed three times with 2 mL of cold buffer, a total volume of 3 mL of scintillation cocktail was added to the filters. After at least 8 h, bound radioactivity trapped on the filters was counted in a liquid scintillation analyzer. Nonspecific binding was determined with 10 μM nonradiolabeled ditolylguanidine.

5.4. NMDA, κ-opioid, and μ-opioid receptor-assay procedures

These were conducted according to the published method.[14c]

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