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Studies for the transformation of carbocycles into carbohydrates: approach toward the synthesis of higher sugar derivatives

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Abstract—A highly stereocontrolled synthesis of a β-D-*ribo*-hept-6-ulopyranosuronamide derivative, a useful intermediate for the synthesis of other higher sugars, has been developed using naturally occurring (−)-quinic acid as a chiral starting material. The transformation of carbocycle to carbohydrate, a key step in this sequence, occurred in a one-pot reaction: an ozonolysis carried out under mild conditions.

Keywords: Higher sugars; Quinic acid; Heptulopyranosuronamide

1. Introduction

The term higher sugars is customarily employed with monosaccharides containing seven or more consecutive carbon atoms in the chain. They have been identified as subunits in various natural products and it is now well recognized that they play prominent roles in numerous biological processes.[1] For example, some seven- and eight-carbon atom sugars are important components in bacterial lipopolysaccharides,[2] the nine-carbon sialic acids, the core class of higher sugars, occur as terminal residues of glycoconjugates involved in recognition phenomena,[3] and some C_{10} to C_{12} sugars,[4] the rarest higher aldoses, have been identified as components of antibiotics (see Fig. 1). Such higher sugars have attracted considerable attention, and the expanding knowledge of their biological properties, allied with their limited availability from natural sources, make the elaboration of practical routes to derivatives or analogues an attractive challenge.[5] Herein we report our studies on the synthesis of a higher sugar from quinic acid.

(−)-Quinic acid [(1s_n,3*R*,4s_n,5*R*)-tetrahydroxycyclohexanecarboxylic acid[6]] (**1**), a widespread natural product, isolated in high enantiomeric purity either from its main plant source, *Chinchona* bark,[7] or from recombinant microbial biocatalyses,[8] is commercially available and a very attractive starting material for stereocontrolled multistep synthesis of naturally occurring substances and related compounds.[9] In the past, it has seen only limited use as a chiral synthetic precursor, but over the years its applications in this field have been growing rapidly, and a broad spectrum of compounds have been synthesized. Considering the basic cyclohexane skeleton of quinic acid, rich in functional groups as well as in asymmetric and pseudoasymmetric carbons, it is natural that its major use has been for the preparation of compounds featuring cyclohexane-substituted frameworks, and these syntheses are well documented in the literature.[9–11†] The structural features of quinic acid also ensure a measure of regio- and stereo-control in chemical manipulations that are not easily matched by other organic compounds, and its application in organic synthesis has been extended to the preparation of

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† For the synthesis of polycyclic compounds from quinic acid see Ref. 11.

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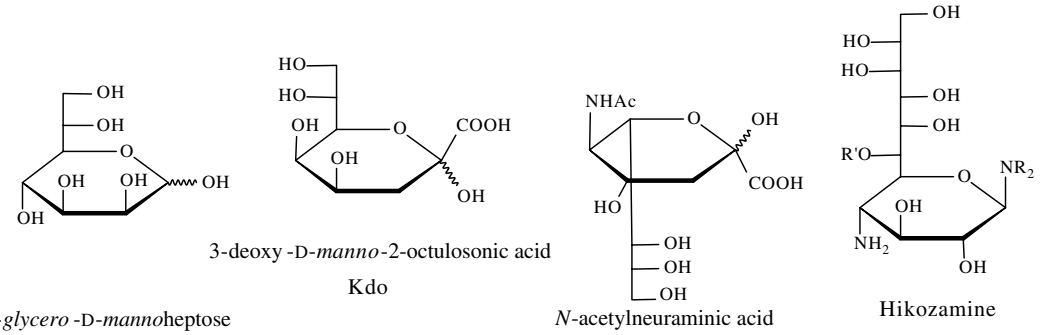


Figure 1. Representative examples of higher sugars.

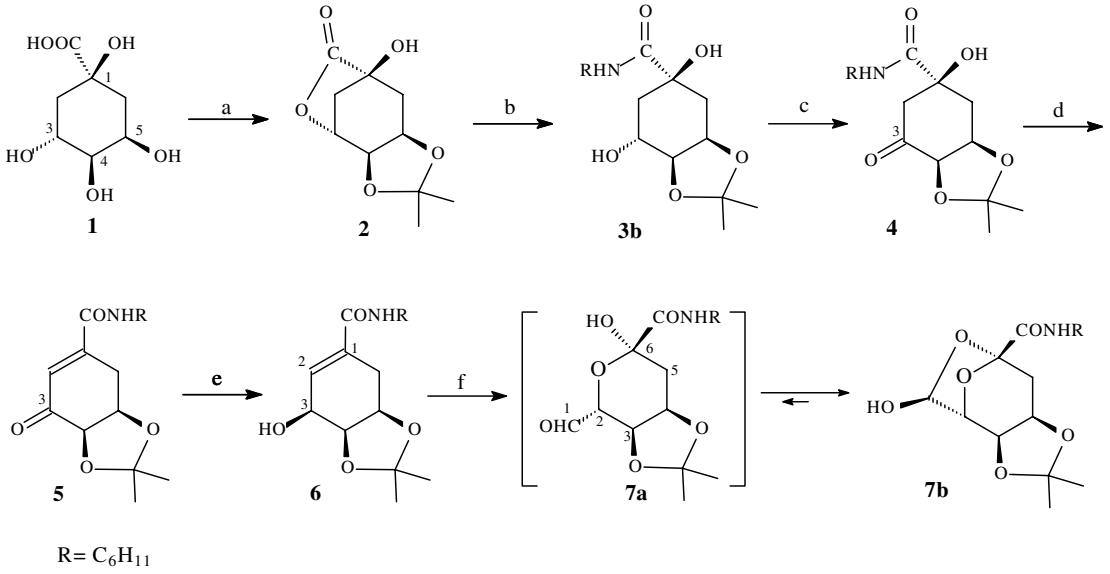
open-chain compounds,[9,12] substituted cyclopentane skeletons,[9,13] and nitrogenous heterocyclic targets.[9,14] Surprisingly, only two publications describe the use of quinic acid as starting material for the preparation of oxygenated heterocycles, a δ-lactone[15] and a tetrahydropyran[16] and, to the best of our knowledge, the synthesis of carbohydrates from this versatile substrate has not yet been reported.

In this paper, we disclose a concise, stereocontrolled route for the conversion of the quinic acid (**1**) into a heptulopyranosuronamide derivative, a seven-carbon sugar that may be considered as a useful intermediate for the synthesis of other higher carbohydrates. The pattern of substitutions created in the six-membered ring of quinic acid permitted the carbocycle to carbohydrate transformation in a one-pot reaction, a key step in this sequence being an ozonolysis carried out under mild conditions.

2. Results and discussion

Starting with quinic acid, Scheme 1 illustrates the synthetic pathway toward the β-D-*ribo*-hept-6-ulopyranosuronamide derivative **7**. The reproducible acid-catalyzed reaction of (−)-**1** with acetone, according to Stoodley and co-workers[13], led to the isopropylidene quinide acetal **2** in excellent yield.

To have a compound with the C-3 secondary alcohol free, which satisfies the requirements of functional group compatibilities for the next steps, a ring-opening aminolysis of the lactone was performed. It is known that,



Scheme 1. Reagents and conditions: (a) acetone, H_2SO_4, Na_2SO_4, reflux, 1 h, quant.; (b) $C_6H_{11}NH_2$, microwave irradiation (see Table 1); (c) PCC, CH_2Cl_2, MS 4 Å, rt, 3 h, 81%; (d) $POCl_3$, py, rt, 25 h, 85%; (e) $NaBH_4$, MeOH, 0 °C, 25 min, 77%; (f) O_3, CH_2Cl_2, −78 °C, 5 min, then $(CH_3)_2S$, −78 °C to rt, 81%.

Table 1. Comparative results in representative aminolysis reactions of **2** using classical and microwave-induced procedures

Entry	Conditons	Reaction time	Product (yields)[a]
1[21a]	Benzylamine (1 equiv), $AlMe_3$–toluene 2 M (1 equiv), CH_2Cl_2, rt → 40 °C	48 h	Starting material **2** recovered
2	Benzylamine (2 equiv), chlorobenzene, reflux	24 h	(20%)
3	Benzylamine (1.5 equiv), MW[b] (500–600 W)	6 min[c]	(90%)
			3a
4	Cyclohexylamine (2 equiv), MW[b] (500–600 W)	15 min[c]	(84%)
5	Cyclohexylamine (2 equiv), MW[d] (550 W/50 W)	10 min[e]	(82%)
6	Cyclohexylamine (1 equiv), MW[d] (550 W/50 W)	20 min[e]	(97%)
			3b

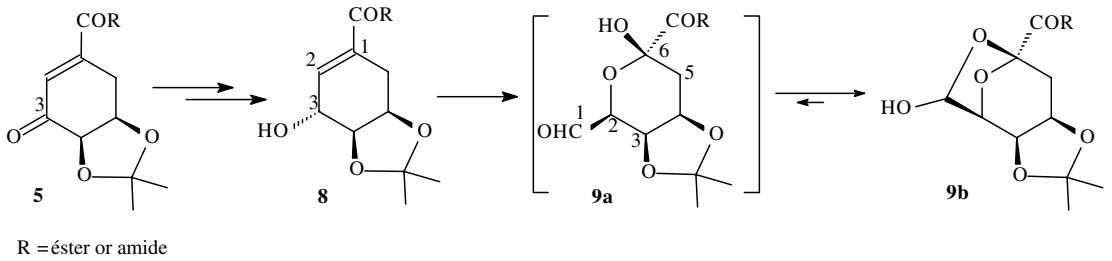
[a]The yields are based on isolated products.
[b]Reactions carried out in a domestic microwave equipment, in a screw-capped Teflon vessel.
[c]Periods of heating intercalated with periods of standing without irradiation in the oven.
[d]Reactions carried out in a microwave equipment intended for organic synthesis, operating with power control.
[e]Periods of heating at 550 W intercalated with periods at 50 W.

in general, the conversion of lactones to amides requires rather harsh conditions, such as high temperatures and/or long reaction times,[17] high pressures,[18] or strong alkali-metal catalysts.[19] The use of milder catalysts[20] or other amidating agents, including transition-metal derivatives,[21] has also been reported, but we decided to explore a direct method for the conversion of the inactivated lactone **2** into a highly stable hydroxy amide derivative by employing a microwave-assisted reaction. In synthetic organic chemistry, the advantages of this methodology, when compared with conventional heating methods, are described by several reviews.[22] In the present particular case, treatment of **2** with freshly distilled primary amines, such as benzylamine and cyclohexylamine, gave, after few minutes under microwave irradiation either in a household oven or in equipment intended for organic synthesis (power control), excellent yields of the corresponding hydroxy amides **3**. These results, including comparison with classical heating methods, are given in Table 1. Thus, faster, cleaner, solvent-free, and higher yield microwave-assisted aminolysis reactions, without any catalysis, could be achieved with **2**.[23]

From **3b**, a classical synthetic sequence was used to promote a regioselective C-1–C-2 elimination of the tertiary hydroxyl moiety. First, the secondary alcohol group of **3b** was oxidized with pyridinium chlorochromate (PCC) in the presence of molecular sieves, and then the isolated ketone **4** was treated with freshly distilled phosphorus oxychloride–pyridine, furnishing enone **5** in 69% overall yield (Scheme 1). Tests for a concomitant oxidation–β-elimination of the chemical groups involved with PCC in pyridine, as proposed by Shing and Tang[24] with analogous compounds, were also performed, but in this case **5** was obtained from **3b** in only 53% yield.

Mild reduction of the carbonyl group in **5** was accomplished with $NaBH_4$, giving the allylic alcohol **6** in 77% yield. As expected, this condition guaranteed a chemo- and stereo-selective reduction, the hydride attack proceeding almost exclusively from the less hindered α-face of the keto group. A 2D NOESY experiment shows interactions, which demonstrate the C-3-(*S*) configuration on **6**, as for example NOE correlations between H-3 and H-5 and between H-3 and H-6(α). Small signals, always presented on the ^1H NMR spectra of crude **6**, were attributed to the C-3 epimer of **6** (less than 8% yield).

Finally, with the desired functionality on the C-1–C-3 fragment of the carbocyclic system, an ozonolysis reaction was applied with **6**. After 5 min of treatment with ozone at −78 °C, reductive decomposition of the crude ozonide, also at low temperature, led to a product identified as the hemiacetal **7b**. This result suggests that the transformation of carbocycle to sugar actually occurred as expected, namely in sequence with



Scheme 2. Partial route for the preparation of α-D-*arabino*-hept-6-ulopyranosuronic derivative from quinic acid.

ozonolysis product formation. Compound **7a** may be suggested as an intermediate, but it was never isolated. The hydroxyl group at C-1 on **7b** was proposed to be *exo* by examination of the ^{1}H NMR spectral data, which shows $^3J_{1,2} \approx 0$ Hz ($\phi \approx 90°$).

It is noteworthy that slight modifications of this sequence (Scheme 2) may permit preparation of the C-3 epimer of the allylic alcohol **6** and, from it, higher sugars of other series, for example derived from α-D-*arabino*-hept-6-ulopyranosuronic compounds as **9**, could be stereoselectively prepared.[25]

In conclusion, we have demonstrated the possibility of obtaining optically pure heptoses employing (−)-quinic acid as a chiral template through a synthetic sequence, which could, in principle, be applied to the preparation of more complex structures of higher sugars and their analogues.

3. Experimental

3.1. General methods

(−)-Quinic acid was purchased from Aldrich (98%). All solvents were distilled before use and, when necessary, purified according to known procedures.[26] The ozone generator was constructed at IQ-UNICAMP according to a literature reference.[27] Column chromatography (CC) was performed with silica gel (silica 60 Å, 70–230 mesh). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} glass-backed plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate–ammonium molybdate solution, followed by heating. Preparative TLC was performed using silica gel F_{254} glass-backed plates (1 mm). Compounds were visualized under UV light. The microwave reactions were conducted: (a) in a domestic oven (Brastemp) operating at 2.45 GHz, 950 W of delivered power, without temperature control; (b) in a microwave labstation intended for organic synthesis (MicroSynth from Milestone) operating at 2.45 GHz, dual magnetron system with delivered microwave power of 1000 W, pulsed magnetron power supply, equipped with a thermocouple temperature control system and an automatic magnetic stirrer, controlled via a Pentium-based terminal. Optical rotations were measured on a Carl Zeiss Polamat polarimeter using a Hg lamp and are corrected. IR spectra were measured for KBr pellets or films on KBr disks using a Bomem MB-series FT-IR spectrometer. NMR spectra were recorded on Bruker AC.P-300, Varian Gemini 300 or Varian Inova 500 spectrometers, using $CDCl_3$ as solvent. Mass spectra and high resolution MS were recorded on VG Autospec equipment, with electron impact of 70 eV or chemical ionization with isobutane.

3.2. 4,5-*O*-isopropylidene quinide (2)

A suspension of (−)-quinic acid (**1**) (1.00 g, 5.2 mmol), anhydrous Na_2SO_4 (5.00 g, 35 mmol), concentrated H_2SO_4 (0.03 mL) and previously purified acetone (50 mL) was heated under reflux for 1 h. After cooling, the pH was adjusted to 6–7 with saturated $NaHCO_3$, the mixture was filtered, and the solvent was evaporated. The residue was partitioned between water and CH_2Cl_2, the organic layer was separated, dried with $MgSO_4$, and filtered and the solvent was evaporated. Crystallization of the crude product with 1:1 hexane–EtOAc gave **2** in quantitative yield (1.11 g); mp 140 °C [lit.[28] 143 °C]; $[\alpha]_D$ −38° (*c* 1.18, $CHCl_3$), [lit.[28] $[\alpha]_D$ −34.46 ($CHCl_3$)]; IR (KBr): ν_{max} 3428, 1774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 and 1.51 (2×s, 2×3H, 2×CH_3), 2.15 (dd, 1H, $J_{6ax,5}$ 3, J_{6gem} 15 Hz, H-6ax), 2.27–2.35 (m, 1H, H-2eq), 2.38 (ddd, 1H, $J_{4,6eq}$ 2, $J_{6eq,5}$ 7, J_{6gem} 15 Hz, H-6eq), 2.64 (d, 1H, J_{2gem} 12 Hz, H-2ax), 3.10 (br s, 1H, OH), 4.30 (ddd, 1H, $J_{4,6eq}$ 2, $J_{3,4}$ 3, $J_{4,5}$ 7 Hz, H-4), 4.49 (dt, 1H, $J_{5,6ax}$ 3, $J_{5,6eq} = J_{4,5}$ 7 Hz, H-5), 4.71 (dd, 1H, $J_{3,4}$ 3, $J_{2eq,3}$ 7 Hz, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.2 and 26.9 (2×CH_3), 34.2 (C-2), 38.1 (C-6), 71.5 (C-5), 72.1 (C-4), 71.4 (C-1), 75.8 (C-3), 109.8 ($C_{isoprop.}$), 179.3 (C=O); HRMS (EI): *m*/*z* found 214.0841, *m*/*z* calcd for **2** 214.0841.

3.3. *N*-Benzyl 4,5-*O*-isopropylidene quinamide (3a)

An 80 mL Pyrex flask containing a mixture of 4,5-*O*-isopropylidene quinide (**2**) (2.00 g, 9.3 mmol) and freshly distilled benzylamine (1.5 mL, 13.7 mmol) was placed

inside a screw-capped Teflon vessel, and the apparatus was irradiated in a domestic microwave oven, at 500–600 W, intercalating periods of heating (2×3 min) with periods of storage in the oven (30 s). After cooling, the mixture was dissolved in CH_2Cl_2 and the solution washed with cold aq 0.5 mol L^{-1} HCl and with saturated aq $NaHCO_3$. The organic layer was separated, dried with Na_2SO_4, filtered and the solvent was evaporated. Crystallization of the crude product with CH_2Cl_2–hexane gave **3a** in 90% yield (2.70 g); mp 99 °C; $[\alpha]_D$ −9.8° (*c* 1.02, $CHCl_3$); IR (KBr): ν_{max} 3372, 3025, 1650, 1583 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.35 and 1.50 (2×s, 2×3H, 2×CH_3), 2.02–2.14 (m, 2H, H-2, H-6), 2.30 (ddd, 1H, $J_{2eq,4}$ 1.5, $J_{2eq,3}$ 3, J_{gem} 15 Hz, H-2eq), 2.49 (dd, 1H, $J_{5,6eq}$ 5, J_{gem} 15 Hz, H-6eq), 3.42 (br s, 1H, OH), 3.85 (dt, 1H, $J_{2eq,3} = J_{3,4}$ 3, $J_{2ax,3}$ 5 Hz, H-3), 4.18 (ddd, 1H, $J_{2eq,4}$ 1.5, $J_{3,4}$ 3, $J_{4,5}$ 7 Hz, H-4), 4.47 (d, J_{gem} 6 Hz, $CH_{2benzyl}$), 4.58 (dt, 1H, $J_{5,6eq} = J_{5,6ax}$ 5, $J_{4,5}$ 7 Hz, H-5), 4.72 (br s, 1H, OH), 7.26–7.40 (m, 6H, NH and $CH_{arom.}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3 and 26.9 (2×CH_3), 34.4 (C-6), 37.1 (C-2), 43.3 ($CH_{2benzyl}$), 65.8 (C-3), 72.1 (C-5), 72.9 (C-1), 75.9 (C-4), 108.7 ($C_{isoprop.}$), 127.5, 127.6, 128.8, 137.5 ($C_{arom.}$), 176.5 (C=O).

3.4. *N*-Cyclohexyl 4,5-*O*-isopropylidene quinamide (3b)

(a) An 80-mL Pyrex flask containing a mixture of 4,5-*O*-isopropylidene quinide (**2**) (0.30 g, 1.4 mmol) and freshly distilled cyclohexylamine (0.32 mL, 2.8 mmol) was placed inside a screw-capped Teflon vessel, and the apparatus was irradiated in a domestic microwave oven, at 500–600 W, intercalating periods of heating (3×5 min) with periods of storage in the oven (30 s). After cooling, the mixture was dissolved in CH_2Cl_2 and the solution was washed with cold aq 0.5 mol L^{-1} HCl and with saturated aq $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and filtered and the solvent was evaporated. Crystallization of the crude product with CH_2Cl_2–hexane gave **3b** in 84% yield (0.37 g); mp 119 °C; $[\alpha]_D$ −10.0° (*c* 0.39, $CHCl_3$); IR (KBr): ν_{max} 3436, 3416, 3285, 1663, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 and 1.25 (2×s, 2×3H, 2×CH_3), 0.88–1.70 (m, 10H, cyclohex.), 1.76 (2×dt, 2H, *J* 4, J_{gem} 15 Hz, H-6 and H-2), 2.03 (ddd, 1H, $J_{2eq,4}$ 1.5, $J_{2eq,3}$ 5, J_{gem} 15 Hz, H-2eq), 2.19 (dd, 1H, $J_{5,6eq}$ 2.5, J_{gem} 15 Hz, H-6eq), 3.07 (s, 1H, OH), 3.44–3.47 (m, 1H, $CH_{cyclohex.}$), 3.54 (m, 1H, H-5), 3.91 (ddd, 1H, $J_{4,2eq}$ 1.5, $J_{3,4}$ 3, $J_{4,5}$ 7 Hz, H-4), 4.32 (ddd, 1H, $J_{5,6eq}$ 2.5, $J_{5,6ax}$ 3, $J_{4,5}$ 7 Hz, H-5), 4.73 (d, 1H, *J* 4 Hz, OH), 6.60 (d, 1H, *J* 8 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6 and 27.3 (2×CH_3), 25.2, 25.8, 33.2, 33.3 ($C_{cyclohex.}$), 34.8 (C-6), 37.3 (C-2), 48.7 ($CH_{cyclohex.}$), 66.0 (C-3), 72.4 (C-5), 72.9 (C-1), 76.1 (C-4), 109.0 ($C_{isoprop.}$), 176.1 (C=O); HRMS (IE): *m*/*z* found 313.1588, *m*/*z* calcd for **3b** 313.1889.

(b) A 50-mL microwave vessel (for reactions up to 6 bar) containing a mixture of 4,5-*O*-isopropylidene quinide (**2**) (0.30 g, 1.4 mmol) and freshly distilled cyclohexylamine (0.16 mL, 1.4 mmol) was connected to a temperature sensor, and the apparatus was irradiated for 20 min in microwave equipment programmed for power control: 30 s at 550 W, 30 s at 55 W. After cooling, the mixture was dissolved in CH_2Cl_2 and the solution was washed with cold aq 0.5 mol L^{-1} HCl and with saturated aq $NaHCO_3$. The organic layer was separated, dried with Na_2SO_4, and filtered and the solvent was evaporated. Crystallization of the crude product with CH_2Cl_2–hexane gave **3b** in 97% yield (0.43 g).

3.5. *N*-Cyclohexyl (1*S*,4*R*,5*R*)-1-hydroxy-4,5-*O*-isopropylidene-3-oxo-cyclohexane-1- carboxamide (4)

A suspension of the hydroxyl amide **3b** (0.33 g, 1.05 mmol), pyridinium chlorochromate (0.45 g, 2.09 mmol) and 4 Å molecular sieves (0.80 g, ground and previously activated for 3 h at 300 °C) in anhydrous CH_2Cl_2 (60 mL) was stirred at room temperature, under an inert atmosphere, for 3 h. The solvent was evaporated and anhydrous ethyl ether (20 mL) was added, stirring for another 1 h. The mixture was filtered through a small silica gel column, the column was washed with 10% ethyl ether–CH_2Cl_2 and the solvent was evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH 1%) to give pure **4** in 81% yield (0.26 g); $[\alpha]_D$ −72.1° (*c* 0.23, $CHCl_3$); IR (KBr): ν_{max} 3370, 3332, 1731, 1650, 1520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.39 and 1.47 (2×s, 2×3H, 2×CH_3), 1.11–1.91 (m, 10H, cyclohex.), 2.40 (dt, 1H, $J_{2eq,6eq} = J_{5,6}$ 3, J_{gem} 16 Hz, H-6eq), 2.63 (dd, 1H, $J_{2eq,6eq}$ 3, J_{gem} 15 Hz, H-2eq), 2,77 (dd, 1H, $J_{5,6ax}$ 3, J_{gem} 16 Hz, H-6), 3.15 (d, 1H, J_{gem} 15 Hz, H-2ax), 3.66–3.74 (m, 1H, $CH_{cyclohex.}$), 4.08 (s, 1H, OH), 4.46 (d, 1H, $J_{4,5}$ 5 Hz, H-4), 4.76– 4.79 (m, 1H, H-5), 6.90 (d, 1H, *J* 8 Hz, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.6, 24.7, 25.4, 32.8, 32.9 ($C_{cyclohex.}$), 25.8 and 27.2 (2×CH_3), 33.9 (C-6), 47.9 ($CH_{cyclohex.}$), 49.6 (C-2), 77.3 (C-1), 78.2 (C-5), 78.6 (C-4), 110.5 ($C_{isoprop.}$), 170.7 (C=O), 205.9 (C-3); HRMS (EI): *m*/*z* found 311.1733, *m*/*z* calcd for **4** 311.1732.

3.6. *N*-Cyclohexyl (4*R*,5*R*)-4,5-*O*-isopropylidene-3-oxo-1-cyclohexene-1-carboxamide (5)

Phosphorus oxychloride (freshly distilled, 0.045 mL, 0.48 mmol) was added via a syringe to a solution of **4** (0.15 g, 0.48 mmol) in anhydrous pyridine (10 mL) and the mixture was stirred at room temperature for 25 h. Ethyl ether (20 mL) and saturated aq NH_4Cl solution (15 mL) were added and the aq layer was separated and extracted two times with ethyl ether (10 mL). The combined organic layers were washed with water (2×10 mL) and brine (10 mL), separated and dried with $MgSO_4$. After filtration, the solvent was concentrated and the residue was purified by preparative TLC (0.5%

CH_2Cl_2–MeOH) to give **5** in 85% yield (0.12 g); $[\alpha]_D$ −14.7° (*c* 1.16, $CHCl_3$); IR (KBr): ν_{max} 3406, 3338, 3060, 1683, 1649, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 and 1.40 (2×s, 2×3H, 2×CH_3), 1.10–2.00 (m, 10H, cyclohex.), 3.01 (ddd, 1H, $J_{2,6eq}$ 2.5, $J_{5,6eq}$ 5, J_{gem} 20 Hz, H-6eq), 3.14 (br d, 1H, J_{gem} 20 Hz, H-6ax), 3.77–3.89 (m, 1H, $CH_{cyclohex.}$), 4.30 (d, 1H, $J_{4,5}$ 5 Hz, H-4), 4.69 (td, 1H, $J_{5,6ax}$ 2, $J_{4,5} = J_{5,6eq}$ 5 Hz, H-5), 5.97 (d, 1H, *J* 7 Hz, NH), 6.35 (d, 1H, $J_{2,6eq}$ 2.5 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.3, 27.1, 32.7 ($C_{cyclohex.}$), 25.8 and 27.4 (2×CH_3), 32.8 (C-6), 48.8 ($CH_{cyclohex.}$), 72.4 (C-5), 75.0 (C-4), 109.5 ($C_{isoprop.}$), 125.6 (C-2), 150.6 (C-1), 165.4 (C=O), 197.4 (C-3); HRMS (IE): *m*/*z* found 293.1627, *m*/*z* calcd for **5** 293.1626.

3.7. *N*-Cyclohexyl (3*S*,4*S*,5*R*)-3-hydroxy-4,5-*O*-isopropylidene-1-cyclohexene-1-carboxamide (6)

A suspension of **5** (0.070 g, 0.24 mmol) and $NaBH_4$ (0.010 g, 0.26 mmol) in anhydrous MeOH (20 mL) was stirred at 0 °C (ice bath) for 20 min. A saturated aq solution of NH_4Cl (1 drop) was added and the solvent was evaporated. Purification of the residue by column chromatography (1% CH_2Cl_2–MeOH) gave **6** in 77% yield (0.054 g); $[\alpha]_D$ +23.8° (*c* 0.74, $CHCl_3$); IR (KBr): ν_{max} 3330, 3071, 1652, 1615, 1534 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 6 H, 2 x CH_3), 1.09–1.95 (m, 10H, cyclohex.), 1.99–2.02 (m, 1H, H-6eq), 2.83 (dd, 1H, $J_{5,6ax}$ 2.5, J_{gem} 16 Hz, H-6ax), 2.92 (br s, 1H, OH), 3.76–3.84 (m, 1H, $CH_{cyclohex.}$), 4.07 (br s, 1H, H-3), 4.53 (ddd, 1H, $J_{4,6eq}$ 1.5, $J_{3,4}$ 4.5, $J_{4,5}$ 7 Hz, H-4), 4.62 (ddd, 1H, $J_{5,6ax}$ 2.5, $J_{5,6eq}$ 4, $J_{4,5}$ 7 Hz, H-5), 5.70 (d, 1H, *J* 8 Hz, NH), 6.37 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3 and 25.8 (2×CH_3), 24.8, 25.4, 27.5 ($C_{cyclohex.}$), 33.0 (C-6), 48.2 ($CH_{cyclohex.}$), 67.5 (C-3), 75.5 (C-4), 76.2 (C-5), 108.9 ($C_{isoprop.}$), 133.3 (C1), 134.0 (C-2), 166.2 (C=O); HRMS (EI): *m*/*z* found 295.1784, *m*/*z* calcd for **6** 295.1784.

3.8. *N*-Cyclohexyl 5-deoxy-β-D-*ribo*-hept-6-ulopyranosuronamide derivative 7b

A stirred solution of compound **6** (0.050 g, 0.17 mmol) in anhydrous CH_2Cl_2 (15 mL), at −78 °C, was placed in an ozone reactor, coupled to a trap containing saturated aq KI solution, and ozone bubbling was maintained for 5 min. The end of the reaction was indicated by the blue color of the solution and by the brown color of the saturated KI solution. Still at −78 °C, a stream of N_2 was passed through the solution, dimethyl sulfide (0.02 mL, 0.27 mmol) was added and the stirring was maintained for 2 h. The solution was warmed to room temperature and the solvent was evaporated. Purification of the residue by column chromatography (3% CH_2Cl_2–MeOH) gave **7b** in 81% yield (45 mg); $[\alpha]_D$ +29.9° (*c* 0.84, $CHCl_3$); IR (film): ν_{max} 3410, 1656, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 and 1.54 (2×s, 2×3H, 2×CH_3), 1.10–1.98 (m, 10H, cyclohexyl.), 1.86 (dd, 1H, $J_{4,5}$ 6, J_{gem} 14 Hz, H-5), 2.51 (dd, 1H, $J_{4,5'}$ 8, J_{gem} 14 Hz, H5′), 3.65–3.84 (m, 2H, $CH_{cyclohex.}$ and OH), 4.08 (dd, 1H, $J_{2,3}$ 1.5, $J_{3,4}$ 6 Hz, H-3), 4.39 (dt, 1H, $J_{3,4} = J_{4,5}$ 6, $J_{4,5'}$ 8 Hz, H-4), 4.74 (s, 1H, H-2), 5.39 (s, 1H, H-1), 6.66 (d, 1H, *J* 6.5 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.4, 32.6, 32.7 ($C_{cyclohex.}$), 25.9 and 27.7 (2×CH_3), 35.3 (C-5), 48.0 ($CH_{cyclohex.}$), 69.9 (C-4), 70.9 (C-3), 82.0 (C-2), 95.4 (C-1), 105.1 (C-6), 110.3 ($C_{isoprop.}$), 165.8 (C=O amide); HRMS (EI): *m*/*z* found 327.1682, *m*/*z* calcd for **7b** 327.1681.

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