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An Efficient Route to Acyclic *C*-Nucleosides and Fused-Ring Analogues of Uridine from *exo*-Glycals

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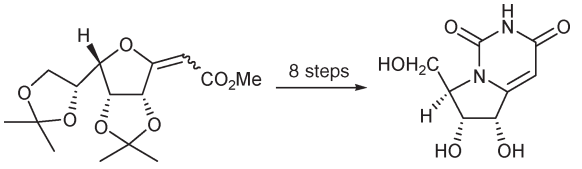

β-Amino esters prepared from activated *exo*-glycals are transformed into acyclic C-nucleoside with a C-4-substituted uracil derivative that can be cyclized under Mitsunobu conditions to provide a new family of fused-ring analogues of uridine nucleoside in which the N-1 nitrogen atom is embedded in an imino sugar ring. An analogue of uridine of D-*ribo* configuration is prepared.

Nucleosides are among the most widely studied compounds. As natural compounds they are part, included in their nucleotide forms, of DNA or RNA and their synthetic forms often show interesting biological activities as enzyme inhibitors and are used as antibiotics with antitumor and antiviral properties.

Many modifications of nucleoside basic structures are allowed which can be associated with the emergence of interesting biological properties as drug candidates or as biological tools.[1] A variety of nucleoside analogues have been proposed going from sugar- or base-modified ones, to conformationally restricted ones obtained by formation of links between the base and the sugar or by using multicyclic sugar moieties,[2] among them sugar- or base-modified nucleosides, acyclic nucleosides,[3] *C*-nucleosides,[4] and carbanucleosides.[5] Spironucleosides are also attractive analogues of nucleosides which can be regarded as *C*-nucleosides and as locked nucleosides. Recently, the discovery of the herbicidal nucleoside analogue hydantocidin[6] (Figure 1) has stimulated much interest in the synthesis of spironucleosides.[7,8a]

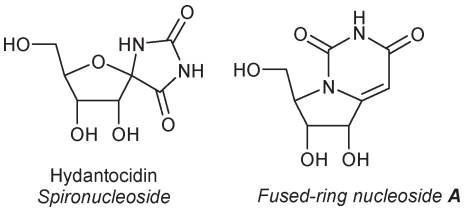

FIGURE 1. Some nucleoside analogues.

In this context, we are interested in opening new accesses to some representatives of these classes of compounds. Recently, we used *exo*-glycals[8b] easily obtained through the Wittig reaction of sugar lactones[9] as versatile starting compounds for the synthesis of spironucleoside analogues, obtained by cycloaddition reactions with nitrones[10] or by cyclization of intermediate β-amino esters.[8a] The present study reports the use of the latter to access new spirouracil derivatives, which led to the discovery of a yet unknown class of conformationally restricted uridine analogues **A** in which

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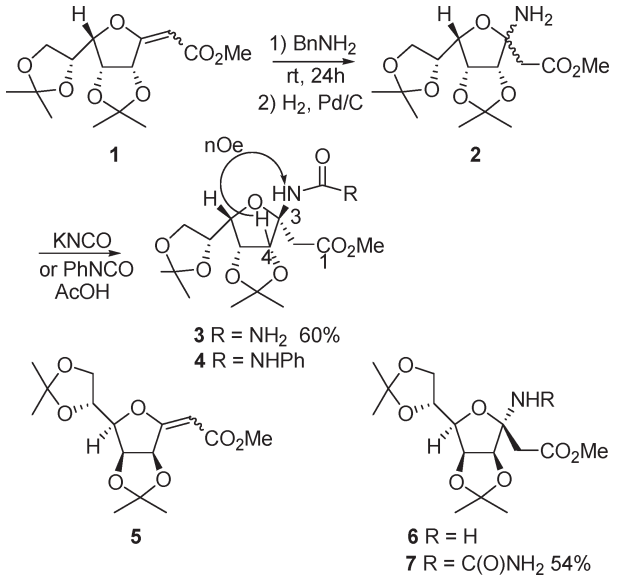
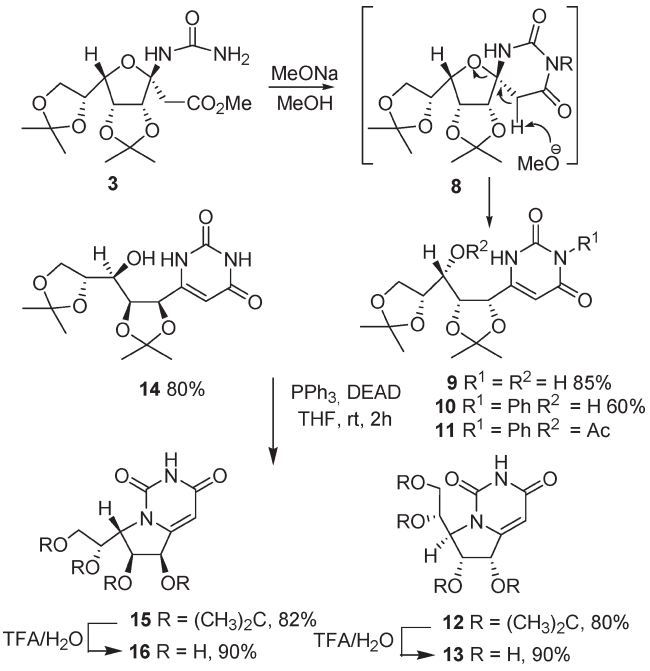
SCHEME 1. Synthesis of Anomeric Ureas



SCHEME 2. Synthesis of Acyclic and Bicyclic C-Nucleosides



the N1−C6 bond of the uracil ring is part of an imino-sugar ring (Figure 1). Reports on nucleoside analogues in which both the sugar and the aromatic ring systems are embedded and retain their functionalities are scarce.[11] Such conformationally restricted compounds may be useful for biological studies.

Exo-glycals are useful starting materials for the synthesis of glycoamino acids, which are considered valuable precursors of heterocycles. Thus starting from the *exo*-glycal **1**, the known amino ester **2** was obtained by addition of benzylamine followed by hydrogenation over Pd/C 10%.[8a] Reaction of **2**, isolated as a mixture of anomers, with potassium isocyanate in glacial acetic gave the expected urea **3** in good yield, this compound being isolated in 60% yield mainly as a β anomer.[12] NOe measurements confirmed a short distance between the anomeric N−H of the urea and H-4 of the sugar ring (*C*-glycoside numbering, see Scheme 1) establishing the β configuration of urea **3**. Crystals suitable for X-ray diffraction have been obtained and their analysis confirmed the NMR assignments (see the SI, Figure 2). The formation of the β urea from the anomeric mixture **2** is explained by a faster reaction of potassium isocyanate with less crowded β anomer **2** as compared to the α one, thus displacing the anomeric equilibrium toward the β anomer.

The *manno* derivative **5** behaved similarly and gave the amino-ester **6** again as an anomeric mixture, successfully transformed into the urea **7** in 54% yield isolated as the α anomer (trans arrangement of the urea and the O-4 substituent) as shown by ^{1}H NMR.

The reaction of phenyl isocyanate with compound **2** provided **4** in 80% yield. With these ureas in hands, we investigated their ring closure into uracil derivatives. Treatment of **3** in acidic medium (camphorsulfonic acid or methanesulfonic acid in dry DMF or THF) did not give any cyclized products. Prolonged heating under thermal or microwave activation also failed to give the expected uracil derivatives. Treatment of **3** with tetrabutylammonium fluoride (TBAF) gave an efficient but slow reaction taking about 2−3 days to go to completion. An excess of TBAF accelerated the reaction. The only compound isolated from this reaction was the acyclic uridine analogue **9**. No spironucleoside was isolated whatever the conditions used. Treatment of **3** with K_2CO_3 and DBU in a MeOH/H_2O mixture or with LiI in pyridine gave the same result. Finally, the most efficient conditions were the use of sodium methoxide in methanol, giving **9** in 85%.

The structure of **9** was established on the basis of its ^{1}H NMR spectrum showing the absence of a methylene group and the presence of a vinylic proton at 5.7 ppm. Compound **9** gave an acetate (not shown) on acetylation confirming the presence of a free secondary hydroxyl group. The formation of **9** could proceed via the putative spironucleoside intermediate **8**. Subsequent abstraction of the acidic H-5 proton of the six-membered ring resulted in the elimination of the sugar ring oxygen leading to the acyclic *C*-nucleoside **9** (Scheme 2).[13] We have previously shown that such a sugar ring-opening occurred during cycloaddition of nitrile oxides with *exo*-glycals leading to acyclic isoxazoles instead of spiroisoxazoline. It is interesting to note that furanose spiroisoxazolidines obtained by cycloaddition of *exo*-glycals with nitrones are stable.[10] The driving force of this ring formation is obviously the formation of a conjugated double bond leading to aromatic rings.

Almost identical results were obtained in the ring closure of **7** giving the corresponding acyclic *C*-nucleosides **14** in

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80% yield. The N-3 substituted acyclic *C*-nucleoside **10** was obtained by cyclization of **4** in 60% yield. Acetylation of the latter gave the corresponding acetate **11**, which confirmed the open chain structure.

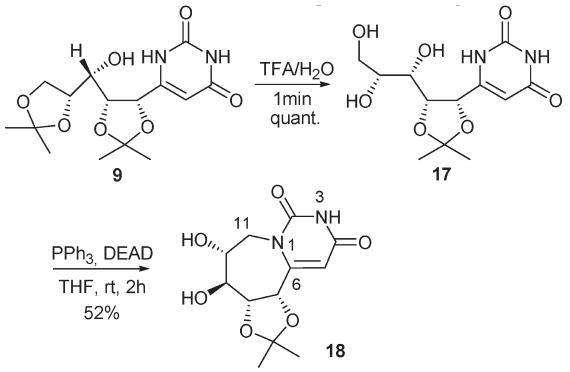
We reasoned that these acyclic *C*-nucleosides could be elaborated to a new class of bicyclic compounds. Indeed, under Mitsunobu activation of the O-6 group of **9**, cyclization took place with the N-1 of the uracil residue producing exclusively the fused-ring nucleoside **12** in 80% yield. Almost identical results were obtained in the formation of **15** in 82% yield from **14**. These bicyclic compounds **12** and **15** are the first members of a new class of modified nucleosides related to azanucleosides[14] and conformationally locked nucleosides.

The structures of **12** and **15** were supported by ^{1}H NMR, which showed no coupling constants between H-9 and H-8 indicative of a trans relationship as expected. This configuration was confirmed later on from the *ribo* derivative **20**. Finally, acidic treatment of both compounds produced gave the unprotected nucleosides **13** and **16**, respectively.

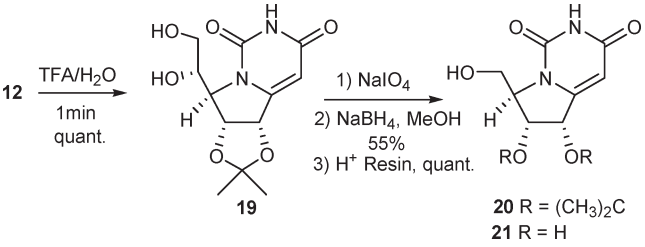
It seemed interesting to test this ring closure on the triol **17**, which was quantitatively obtained from **9** by selective acetal hydrolysis. The less strained azepane ring **18** was formed preferentially together with the pyrrolidine derivative **19** in a 33:1 ratio. The structure of compound **18** was established on the basis of ^{13}C NMR (δ C-11 45.2 ppm) indicative of the presence of a nitrogen atom on this carbon. Furthermore the chemical shifts (δ H-11 3.70 and 4.80 ppm) and the large *gem* coupling constant (16.2 Hz) between the two H-11 protons indicate a strong difference in their electronic environment in agreement with the seven-membered-ring structure shown in Scheme 3. Analysis of HMBC connectivities showed long-range couplings between C-2 and H-11, H-11′ and thus the existence of an N-1−C-11 bond. It is likely that this ring closure proceeds via direct activation of the more reactive C-11 hydroxyl group as is usual in the Mitsunobu activation of such polyol systems. Ring closure then occurs to give mostly the *gulo*-azepane **18** in 52% yield. As for **12** and **15**, compound **18** could be regarded as a member of a new class of imino-sugar.[15]

We next envisioned further transformation of **12** into a significant pentose uridine analogue of *ribo* configuration. Compound **12** was transformed by three conventional steps including the selective acid hydrolysis (TFA/H_2O 1/3) of the terminal isopropylidene protective group giving **19** in 95% yield. The cleavage of the diol function of **19** with Malaprade oxidation gave the corresponding aldehyde, which was reduced without purification to produce the alcohol **20** in 65% yield over the two steps. X-ray diffraction studies

SCHEME 3. Synthesis of an Azepane Imino-Sugar



SCHEME 4. Synthesis of a Bicyclic Nucleoside of *ribo* Configuration



confirmed the *ribo* configuration and the net inversion of configuration during the cyclization step (see the SI, Figure 3). The final step was the deprotection of **20** by acid hydrolysis, giving **21** in quantitative yield (Scheme 4).

Antibiograms of compounds **11**, **16**, **20**, and **21** on four different strains (*E. coli*, *E. faecalis*, *S. aureus*, *P. aeruginosa*) did not reveal any antibacterial activity.

In conclusion, β-amino esters readily obtained from *exo*-glycals are useful intermediates for the preparation of uracil heterocycles. Spironucleosides cannot be obtained because of spontaneous elimination of the sugar ring oxygen leading to new acyclic *C*-nucleosides. The latter can be cyclized to provide the first representatives of two classes of yet unknown fused nucleoside analogues of uridine.

Experimental Section

Methyl 2,3-Dideoxy-4,5:7,8-di-*O*-isopropylidene-3-ureido-α-D-*gulo*-3-octulofuranoate, 3. To a solution of β-amino-ester **2**, in neat acetic acid (2.55 g, 7.7 mmol), was added potassium isocyanate (2.5 g, 31 mmol) and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted in CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtrated, and evaporated. Purification by column chromatography (hexane/ethylacetate 4:6 to 2:8) gave **3** (1.78 g, 60%) as a white solid, mp 188−190 °C (from CH_2Cl_2): R_f 0.3 (CH_2Cl_2/MeOH 95:5); $[\alpha]^{20}_D$ −23.5 (*c* 1.1; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.29, 1.38, 1.42, 1.45 (4s, 12H, 4 × CH_3), 1.60 (m, 1H, NH), 2.98 (d, 1H, J_{gem} = 17.0 Hz, H-2), 3.17 (d, 1H, J_{gem} = 17.0 Hz, H-2′), 3.72 (s, 3H, CO_2CH_3), 3.77 (dd, 1H, J_{gem} = 8.8 Hz, $J_{7,8}$ = 6.6 Hz, H-8), 4.03 (dd, 1H, $J_{5,6}$ = 3.6 Hz, $J_{6,7}$ = 8.0 Hz, H-6), 4.21 (dd, 1H, J_{gem} = 8.8 Hz, $J_{7,8}$ = 6.6 Hz, H-8′), 4.36 (m, 1H, H-7), 4.67 (d, 1H, $J_{4,5}$ = 5.8 Hz, H-4), 4.72 (dd, 1H, $J_{5,6}$ = 3.6 Hz, $J_{4,5}$ = 5.8 Hz, H-5), 5.11 (m, 1H, NH), 5.35 (m, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.7, 25.4,

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25.9, 26.8 (4 × CH_3), 37.7 (C-2), 51.9 (CO_2CH_3), 65.9 (C-8), 75.1, 80.0, 82.0, 86.0 (4C, C-4, C-5, C-6, C-7), 92.6 (C-3), 109.9, 113.3 (2C acetal), 158.1 ($CO(NH_2)_2$), 170.3 (CO_2CH_3); IR (KBr, ν, cm^{-1}) 3366 (NH), 1738 (COOMe), 1674 ($CO(NH_2)_2$). Anal. Calcd for $C_{16}H_{26}N_2O_8$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.49; H, 6.88; N, 7.49.

(1′*S*,2′*R*,3′*S*,4′*R*)-6[(3′-Hydroxy-1′,2′,4′,5′-diisopropylidenedioxy)-pentyl]uracil, 9. Compound **3** (1.5 g, 4.0 mmol) was dissolved in anhydrous methanol (40 mL), and a fresh solution (0.5 M) of sodium methoxide was added (8 mL, 1 equiv). After 15 min the reaction was completed. The mixture was cooled at 0 °C and an aqueous solution of HCl was added until the mixture was neutral. The methanol was evaporated and the crude residue was purified by column chromatography to afford compound **9** (1.3 g, 85%) as a white solid: R_f 0.66 (A); $[\alpha]^{20}_D$ +40.7 (*c* 0.9; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36, 1.42, 1.65 (3s, 12H, 4 × CH_3), 3.36 (m, 1H, OH), 3.65 (m, 1H, H-3′), 3.79 (dd, 1H, J_{gem} = 8.0 Hz, $J_{4',5'}$ = 6.5 Hz, H-5′), 4.05 (dd, 1H, J_{gem} = 8.0 Hz, $J_{4',5''}$ = 6.5 Hz, H-5″), 4.22 (m, 1H, H-4′), 4.31 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-2′), 4.95 (d, 1H, H-1′), 5.68 (s, 1H, H-5), 9.20 (m, 1H, NH), 9.83 (m, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 25.3, 25.7, 26.3, 26.9 (4 × CH3), 66.2 (C-5′), 70.0, 75.5, 77.4, 78.5 (4C, C-3′, C-1′, C-4′, C-2′), 100.2 (C-5), 110.2, 111.3 (2C acetal), 151.9 (C-6), 152.1 (C-2), 165.4 (C-4); IR (KBr, ν, cm^{-1}) 3422 (OH), 3330 (NH), 1717 (CO), 1660 ((CO(NH)$_2$); MS (HR-ESI) calcd for $C_{15}H_{22}N_2O_7Na$ 365.1324, found 365.1311 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{22}N_2O_7$: C, 52.62; H, 6.47; N, 8.18. Found: C, 52.78; H, 6.51; N, 8.08.

(7*S*,8*R*,9*R*)-1,3-Diaza-2,4-dioxo-7,8-*O*-isopropylidene-9-[(4′*S*)-2′,2′-dimethyl-1,3-dioxolan-4′-yl]bicyclo[4.3.0]non-5-ene, 12. Acyclic *C*-nucleoside **9** (0.45 g, 1.31 mmol) and triphenylphosphine (1 g, 3.9 mmol) were dissolved in anhydrous THF (10 mL), the mixture was stirred at room temperature under nitrogen atmosphere. Diethylazodicarboxylate (1.35 g, 7.8 mmol) was added slowly with a syringe, then the mixture was stirred for 2 h. TLC confirmed total disappearance of starting material. The solvent was evaporated and the crude product was chromatographed on a silica gel column giving the fused nucleoside **12** (0.34 g, 80%) as a solid: R_f 0.5 (H/A 3:7); $[\alpha]^{20}_D$ −228.7 (*c* 0.7; $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28, 1.37, 1.39, 1.45 (4s, 12H, 4 × CH_3), 3.92 (dd, 1H, $J_{5',5''}$ = 9.2 Hz, $J_{4',5'}$ = 5.2 Hz, H-5′), 4.23 (dd, 1H, $J_{5',5''}$ = 9.2 Hz, $J_{4',5''}$ = 8.0 Hz, H-5″), 4.53 (d, 1H, $J_{8,9}$ = 1.0 Hz, H-9), 4.67 (dd, 1H, $J_{7,8}$ = 5 Hz, H-8), 4.75 (dd, 1H, H-4′), 5.31 (d, 1H, H-7), 5.80 (s, 1H, H-5), 9.47 (br s, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.9, 26.2, 26.3, 27.8 (4 × CH_3), 66.1 (C-5′), 66.9 (C-9), 72.6 (C-4′), 77.1 (C-8), 80.1 (C-7), 98.4 (C-5), 110.8, 113.6 (2C acetal), 150.0 (C-6), 158.4 (CO(N)(NH)), 165.0 (CO); IR (KBr, ν, cm^{-1}) 3195 NH, 1700 (CONH), 1660 (CONH). Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.54; H, 6.21; N, 8.63. Found: C, 55.37; H, 6.30; N, 8.58.

(7*S*,8*R*,9*R*)-1,3-Diaza-2,4-dioxo-7,8-*O*-isopropylidene-9-[(1′*S*)-2′-dihydroxyethyl]bicyclo[4.3.0]non-5-ene, 19. A suspension of compound **12** (0.35 g, 1.2 mmol) in a 1/3 mixture of trifluoroacetic acid and water (4 mL) was stirred vigorously at 0 °C until total dissolution, i.e., for 1 min. The mixture was concentrated under vacuum at room temperature and coevaporated several times with toluene giving crude compound **19** (340 mg, 100%) as a gum: R_f 0.2 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (250 MHz, MeOH-d_4) δ 1.39, 1.41 (2s, 6H, 2 × CH_3), 3.72 (m, 2H, 2 H-2′), 4.17 (m, 1H, H-1′), 4.64 (d, 1H, $J_{1',9}$ = 1.9 Hz, H-9), 4.96 (d, 1H, $J_{7,8}$ = 5.1 Hz, H-8), 5.40 (d, 1H, $J_{7,8}$ = 5.1 Hz, H-7), 5.73 (s, 1H, H-5); ^{13}C NMR (62.9 MHz, D_2O) δ 30.2, 32.0 (2 × CH_3), 68.1 (C-2′), 71.7 (C-9), 71.3 (C-1′), 82.0 (C-8), 85.1 (C-7), 101.6 (C-5′), 117.0 (C-5), 154.6 (C-6), 163.7 (C-2), 169.1 (C-4).

(7*S*,8*R*,9*R*)-1,3-Diaza-2,4-dioxo-9-(hydroxymethyl)-7,8-*O*-isopropylidenebicyclo[4.3.0]non-5-ene, 20. To a solution of crude compound **19** (0.050 g, 0.175 mmol) in methanol (3 mL), cooled at 0 °C, was slowly added a solution of sodium periodate (0.043 g, 0.20 mmol). The reaction was stirred for 1 h at room temperature. 1,2-Ethanediol (0.1 mL) was added, the white precipitate was filtered off, and water was added (3 mL). The aqueous phase was extracted twice with ethyl acetate (20 mL) and the combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuo to provide the crude aldehyde (0.044 g, 0.17 mmol), which was dissolved in anhydrous methanol (3 mL). The solution was stirred and cooled at 0 °C and then sodium borohydride (0.061 g, 0.34 mmol) was added. After 1 h, a few drops of 3 N hydrochloric acid and water (20 mL) was added. The aqueous layer was extracted twice with diethyl ether (20 mL) and the combined organic phases were dried over magnesium sulfate. Filtration and evaporation under vacuum gave the crude alcohol, which was purified by column chromatography giving **20** (0.028 g, 65%) as a white solid, mp 230−2 °C: R_f 0.5 (CH_2Cl_2/MeOH 9:1); $[\alpha]^{20}_D$ −217 (*c* 1; $CHCl_3$); ^{1}H NMR (250 MHz, D_2O) δ 1.40, 1.42 (2s, 6H, 2 × CH_3), 3.34 (m, 1H, OH), 3.80 (dd, 1H, *J* = 1.9 Hz, $J_{1,1'}$ = 12.2 Hz, H-1′), 4.02 (dd, 1H, *J* = 2.5 Hz, $J_{1',1''}$ = 12.2 Hz, H-1″), 4.52 (m, 1H, H-9), 4.83 (d, 1H, $J_{7,8}$ = 5.5 Hz, H-8), 5.43 (d, 1H, $J_{7,8}$ = 5.5 Hz, H-7), 5.71 (s, 1H, H-5); ^{13}C NMR (62.9 MHz, D_2O) δ 25.9, 27.7 (2 × CH_3), 60.2 (C-1′), 67.5 (C-9), 81.0 (C-8), 81.1 (C-7), 97.7 (C-5), 113.8 (C acetal), 151.3 (C-6), 161.18 (C-2), 167.6 (C-4); IR (KBr, ν, cm^{-1}) 3365 (NH), 3156.25 (OH), 1678 ((CO), (CO(N)(NH)), (C=C)); MS (HR-ESI) calcd for $C_{11}H_{14}N_2O_5$ 255.0981, found 255.0986 $[M + H]^+$, 277.0798 $[M + Na]^+$, 531.1670 $[2M + Na]^+$, 785.2621 $[3M + Na]^+$.

(7*S*,8*R*,9*R*)-1,3-Diaza-2,4-dioxo-9-(hydroxymethyl)bicyclo[4.3.0]non-5-ene, 21. To a solution of compound **20** (0.033 g, 0.13 mmol) in water (1 mL) was added Amberlite IR-120, H^+ form, previously washed with methanol and water. The mixture was stirred for 2 h. The resin was filtered off and the filtrate was freeze-dried to yield compound **21** (0.026 g, 95%) as a white foam: R_f 0.1 (CH_2Cl_2/MeOH 9:1); $[\alpha]^{20}_D$ −81.6 (*c* 0.6; H_2O); ^{1}H NMR (250 MHz, D_2O) δ 3.85 (dd, 1H, *J* = 2.5 Hz, J_{gem} = 12.3 Hz, H-1′), 3.93 (dd, 1H, *J* = 4.8 Hz, J_{gem} = 12.3 Hz, H-1″), 4.35 (t, 1H, $J_{8,9}$ = 3.4 Hz, $J_{9,1'}$ = 2.9 Hz, H-9), 4.47 (d, 1H, $J_{7,8}$ = 4.7 Hz, H-8), 5.22 (dd, 1H, $J_{5,7}$ = 1.7 Hz, $J_{7,8}$ = 4.7 Hz, H-7), 5.89 (d, 1H, $J_{5,7}$ = 1.7 Hz, H-5); ^{13}C NMR (62.9 MHz, D_2O) δ 61.7 (C-1′), 71.0 (C-9), 74.9 (C-8), 75.1 (C-7), 99.3 (C-5), 153.7 (C-6), 163.9 (C-2), 170.2 (C-4); MS (HR-ESI) calcd for $C_8H_{10}N_2O_5Na$ 237.0482, found 237.0491 $[M + Na^+]$.

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Supporting Information Available: Full experimental procedures, characterization data, copies of ^{1}H and ^{13}C spectra, and crystallographic data of compounds **7** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.