C-Nucleosides: Synthesis of Novel Ribavirin Analogues by Cycloaddition Reactions of D-Allononitrile-N-sulfide

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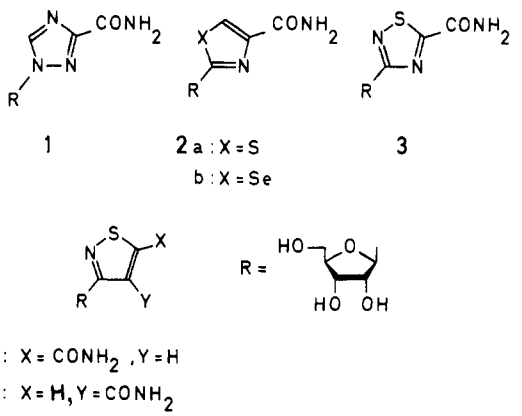
The preparation and synthetic application of O-benzoyl-protected 2,5-anhydro-D-allononitrile-N-sulfide was investigated. The O-benzoyl-protected 2,5-anhydro-D-allononitrile was hydrolyzed to the corresponding allonamide, which was converted to the protected 5-β-D-ribofuranosyl-1,3,4-oxathiazol-2-one. Generation of the nitrile sulfide by pyrolysis of the latter in the presence of ethyl cyanoformate and ethyl propiolate afforded thiadiazole and isothiazole carboxylate esters, which were elaborated to thiadizaole and isothiazole C-nucleoside analogues 3 and 4 of ribavirin. None of these compounds produced any significant inhibition either of in vitro L1210 cell growth or of viral replication in any of the tested systems. Analysis of the ^1H NMR spectra of ribavirin and the C-nucleoside analogues 3 and 4 showed that the conformational equilibrium of the ribose moiety, which lies at the N side for ribavirin, is shifted toward the S conformers in the compounds 3 and 4. Ribavirin and compound 4 have a similar rotameric distribution at the C_4–$C_{5'}$ exocyclic bond, but compound 3 behaves differently.

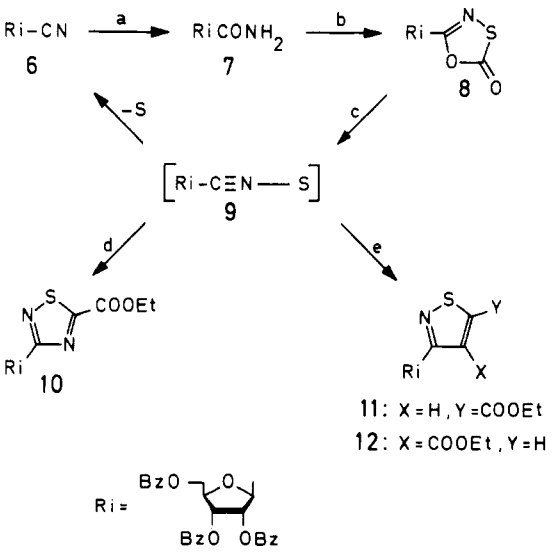
The synthetic nucleoside ribavirin **1**[2] was found to exhibit a broad spectrum antiviral activity both in vitro and in vivo.[3] The structurally similar 2-β-D-ribofuranosylthiazole-4-carboxamide (**2a**) and its selenium analogue **2b** (Chart I) have been found to be effective antitumor agents[4c,5a,b] in mice. Our interest in the synthesis of C-nucleosides prompted us to initiate the synthesis of 3-β-D-ribofuranosyl-1,2,4-thiadiazole-5-carboxamide (**3**), 3-β-D-ribofuranosylisothiazole-5-carboxamide (**4**), and the isomeric 4-carboxamide **5**, using the 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allononitrile-N-sulfide (**9**) as an intermediate (Scheme I). Nitrile sulfides, S homologues of nitrile oxides, can be generated by thermolysis or photolysis of various precursors; they can be trapped with dipolarophiles to yield isothiazoles[6] and thiadiazoles.[7]

In this work we describe the generation of the β-D-ribosylnitrile sulfide **9** by thermolysis of the oxathiazolone **8** in toluene or xylene at 220 °C and its trapping with ethyl cyanoformate and ethyl propiolate. The 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allononitrile (**6**)[8] was hydrolyzed to 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allonamide (**7**) in greater than 90% yield by using formic acid and hydrogen chloride in dichloromethane.[9a] When the nitrile **6** was hydrolyzed

Chart I



Scheme I[a]



[a] (a) HCOOH, HCl, CH_2Cl_2; (b) ClSCOCl, benzene, Δ; (c) 220 °C, m-xylene or toluene; (d) ethyl cyanoformate, m-xylene; (e) ethyl propiolate, toluene.

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with hydrogen peroxide and potassium carbonate in dioxane–water,[9b] various side products were observed, probably due to the lability of the anomeric proton and of the protecting benzoyl groups; with manganese dioxide in dichloromethane[9c] the reaction proceeded too slowly. A minor portion (1%) of the anomer was also isolated. Anomeric assignments were made by comparing the ^1H NMR spectra of both isomers. The less polar (major) product showed a narrow multiplet absorption containing the anomeric proton at δ 4.7. The more polar (minor) product had a doublet at δ 4.94. According to the "syn upfield rule",[10] a proton syn with respect to a substituent (β-anomer) resonates at a higher field than when this substituent is anti (α-anomer). Consequently the $H_{1'}$ resonances at δ 4.94 and 4.7 are assigned to the α- and β-anomer, respectively.

Amides react very efficiently with chlorocarbonylsulfenyl chloride to give oxathiazolones.[11] Upon reflux of **7** with this reagent in benzene and further workup the 5-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-1,3,4-oxathiazol-2-one (**8**) was obtained in 85% yield.

When **8** was gradually heated, its decomposition started at 120–130 °C, giving a mixture of nitrile **6** and sulfur. However, when **8** was heated (sealed tube) in the presence of ethyl cyanoformate in *m*-xylene at 220 °C, the thiadiazole **10** was isolated in 40% yield. Ammonolysis with methanolic ammonia afforded the desired amide **3** in 60% yield after recrystallization. The structure of **3** was assigned by analogy with the known additions of nitrile sulfides to nitriles.[7] This is also consistent with electronic and steric factors affecting 1,3-dipolar cycloadditions.[12,13] However, in order to get more convincing information we recorded the ^{13}C NMR spectrum of the known thiadiazole **13**, which we obtained by pyrolysis of 5-phenyloxathiazolone and ethyl cyanoformate.[7a] The noise-decoupled ^{13}C NMR spectrum of **13** exhibited three quaternary carbon atoms to be assigned to C_3, C_5, and the ester function. In the off-resonance spectrum the peaks at 174.5 and 158.4 ppm appeared as multiplets and the peak at 178 ppm as a singlet. The assignment was performed by using a selective decoupling at low intensity, at the ester methylene protons. In these conditions the C_3 atom appeared as a multiplet at 174.5 ppm, whereas the C_5 atom and the ester carbonyl appeared as singlets at 178 and 158.4 ppm, respectively. This spectrum is in fairly good accordance with the ^{13}C NMR spectrum of compound **3** in D_2O; this shows three peaks in the relevant region, at 184.5, 174.6, and 161.2 ppm, for the C_5, C_3, and amide function. The absorption at 174.6 ppm with the highest NOE was assigned to the ribosyl-substituted C_3 atom. The remaining absorptions at 184.5 and 161.2 ppm were attributed to the C_5 atom and the amide carbonyl, respectively. In order to determine the anomeric configuration, the isopropylidene acetal **14** was synthesized by using dimethoxypropane in acidic conditions. Its ^1H NMR spectrum showed two singlets at δ 1.41 and δ 1.61 with a difference in shift value of 0.20 ppm; a value of less than 0.10 ppm should be expected in the case of an α-anomer.[14] The proton at $C_{4'}$ showed a triplet of doublets (J = 3 and 7 Hz), and the absorption of $H_{3'}$ was well resolved; the coupling of $H_{3'}$ and $H_{4'}$ was about 3 Hz (first-order analysis). In α-anomers this coupling constant should be zero, resulting in an apparent triplet for $H_{4'}$.[15]

Chart II

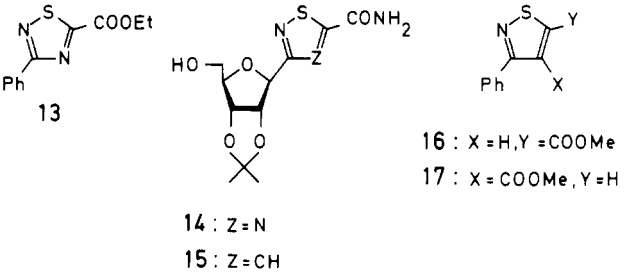

Table I. Calculated[a] Conformational Parameters for the Ribose Moiety of Ribavirin 1 and the Analogues 3 and 4

cmpd	P_N	P_S	N_{τ_m}	S_{τ_m}	X_N
3	39.3	141.9	42.2	44.6	0.48
4	37.0	141.9	44.3	47.3	0.41
1[b]	10.5	172.8	35.4	38.1	0.61

[a] From ^1H NMR coupling constants, based on the graphs of ref 17. The parameters P_N and P_S describe the phase angles of the N and S conformer in the pseudorotational model of ref 18. N_{τ_m} and S_{τ_m} are the ring pucker values and X_N is the molar fraction of N in the N ⇌ S equilibrium. [b] On the basis of the spectrum reported in ref 19.

The intermediate nitrile sulfide **9** was also trapped with ethyl propiolate in toluene (sealed tube, 220 °C). After purification by high-performance liquid chromatography, the carboxylic ester **11** (48% yield) was obtained as an oil; the 4-position substituted isothiazole **12** was isolated in 16% yield. In the cycloaddition reaction of the analogous allononitrile oxide with ethyl propiolate, only the 5-position substituted isomer was reported,[16] whereas with allononitrile sulfide **9** we found a 3 to 1 ratio of the 5- and 4-position substituted isothiazoles. Benzonitrile oxide gives predominantly the 5-position substituted isomer,[13] and in the benzonitrile sulfide addition reaction the 4- and 5-position substituted products are formed in equal amounts.[6b] The striking lack in regiospecificity for the nitrile sulfide reactions in comparison with the nitrile oxides could be explained by the high temperature needed for the thermolysis of the oxathiazolones (180–200 °C), whereas the nitrile oxides can be generated at −20 °C.[16] However, Frontier Orbital theory[13] can give an explanation for this behavior. Theoretical calculations[12] indicate that nitrile sulfides have a higher HOMO energy level than do nitrile oxides. This energy difference can be responsible for a more pronounced dipole–HOMO control and the higher yield of the 4-position substituted product in the cycloaddition of nitrile sulfides. The difference between the allono- and benzonitrile sulfide (the former giving more of the 5-position substituted product) can be due to steric interactions.

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Table II. Calculated[a] Rotameric Distribution at the $C_{4'}$–$C_{5''}$ Bond in Ribavirin 1 and the Analogues 3 and 4

cmpd	ρ_{gg}	ρ_{gt}	ρ_{tg}
3	0.45	0.55	0.00
4	0.51	0.39	0.10
1[b]	0.50	0.40	0.10

[a] From ^{1}H NMR coupling constants, according to Haasnoot's method (ref 20); ρ_{gg}, ρ_{gt}, and ρ_{tg} are the gauche–gauche, gauche–trans, and trans–gauche ($H_{4'}$–$H_{5'}$; $H_{4'}$–$H_{5''}$) conformer populations, respectively. [b] Based on the reported spectrum in ref 19.

Ammonolysis of the esters 11 and 12 in methanolic ammonia afforded the desired amides 4 and 5 in a 55% and 58% yield after recrystallization. The isomers could be distinguished by comparing their NMR spectra with those of the analogous 3-phenyl-substituted isothiazoles.[6b] The H absorptions at 7.8 ppm in 4 and 11, respectively, related best to the value of 8.0 ppm in compound 16, whereas the 9.40 and 9.9 ppm absorptions in 5 and 12 correspond with the H-5 absorption at 9.1 ppm in 17 (Chart II). Carboxamide 4 was converted to the isopropylidene derivative 15. The chemical shift difference of the methyl absorptions in this compound was 0.24 ppm, and $H_{4'}$ appeared as a multiplet with $J_{3'4'} = 2.5$ Hz, pointing out the β-anomeric configuration.[14,15]

The conformational equilibrium of the ribose moiety of the ribavirin analogues 3 and 4 was studied by ^{1}H NMR spectroscopy (using a 250-MHz spectrometer and a D_2O solution at room temperature). The first-order coupling constants $J_{H_{1'}2'}$, $J_{H_{2'}3'}$ and $J_{H_{3'}4'}$ were subjected to the graphical analysis developed by Davies and Danyluk,[17] based upon the pseudorotational model of Altona and Sundaralingam.[18] The results of this analysis are collected in Table I together with conformational parameters for ribavirin, obtained from the reported spectrum[19] by using Davies and Danyluk's method.

Both the thiadiazole 3 and the isothiazole 4 seem to deviate from ribavirin 1 in regard of the ribose conformation: the phase angles of the N and the S conformer occupy rather extreme positions on the pseudorotational circle and the pucker values N_{τ_m} and S_{τ_m} are higher than in most known N-nucleosides. The equilibrium, which lies at the N side for ribavirin, is shifted toward the S conformers in our products. The rotameric distributions at the $C_{4'}$–$C_{5'}$ exocyclic bond were also calculated for these compounds. Here we used Haasnoot's method[20] based on a generalized Karplus equation[21] which includes corrections for electronegativity influences. The AB part of the $H_{4'}$ – $H_{5'}H_{5''}$ ABX spectrum was subjected to second-order analysis[22] to get the accurate coupling constants. The obtained rotameric populations are represented in Table II, and the parameters for ribavirin, calculated from the reported spectrum,[19] are included.

The similarity between the isothiazole 4 and ribavirin is striking and is in accord with the general trend[20] that the most important (gauche–gauche) rotamer has the 5'-OH oriented over the ribose ring, toward the base. For the thiadiazole there is a slight preference for the gauche–trans rotamer, where the 5'-OH is oriented away from the ribose ring, gauche to $O_{1'}$ and trans to $C_{3'}$.

The biological activities of the compounds 3, 4, and 5 were tested. None of these showed any significant inhibition either of in vitro L1210 cell growth or of viral replication in any of the tested systems (HSV-2, measles, polio-1, VSV, vaccinia, Reovirus-1, parainfluenza-3, coxsackie B4).

Experimental Section

Melting points, determined with a Leitz melting point microscope, are uncorrected. The ^{1}H NMR data are presented in ppm downfield from Me_4Si used as an internal standard; the spectra were taken on a Jeol JNM-MH-100 spectrometer at 100 MHz, on a Varian EM 390 at 90 MHz, and a Bruker WM 250 at 250 MHz; for the ^{13}C NMR spectra a Bruker WP 80 spectrometer was used. The mass spectra were recorded on a AEI-MS-12 apparatus with direct injection and an ionization energy of 70 eV. Infrared spectra were obtained from a Perkin-Elmer 250 grating apparatus. For the chromatographic separations Merck silicagel 60 (0.063–0.200 mm) was used unless otherwise stated.

2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allonamide (7). To an ice-cooled solution of 6 (28.0 g, 59.5 mmol)—obtained from 30 g of the corresponding acetate by the Bobek and Farkas procedure[8] and used without further purification–in 200 mL of dichloromethane was added 9.2 mL of formic acid. The mixture was saturated with dry HCl gas, brought to room temperature, and concentrated under vacuum. The residual oil was chromatographed on a silicagel column with toluene gradually mixed with up to 30% ethyl acetate. The fractions containing pure 7 were concentrated under vacuum, yielding 26.8 g (92%) of the amide as a crystallizing oil: mp 63–65 °C; IR ($CHCl_3$) 3450–3320 (NH_2), 1730 (COOR), 1690 cm^{-1} ($CONH_2$); ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 6, Ar H), 7.4 (m, 9, Ar H), 6.95 (br s, 1, NH), 6.40 (br s, 1, NH), 5.8 (m, 2, H_3, H_4), 4.7 (m, 4, H_2, H_5, H_6, $H_{6'}$); mass spectrum, *m/e* 489, 445, 367, 354, 245, 105; exact mass calcd for $C_{27}H_{23}O_8N$ 489.142, found 489.113 ± 0.04. Anal. Calcd for $C_{27}H_{23}O_8N$: C, 66.25; H, 4.73; N, 2.86. Found: C, 65.80; H, 4.90; N, 2.69.

A second fraction contained the D-altronamide (280 mg, 1%); ^{1}H NMR ($CDCl_3$) δ 8.2–7.8 (m, 6, Ar H), 7.6–7.4 (m, 9, Ar H), 6.85 (br s, 1, NH), 6.45 (br s, 1, NH), 6.14 (dd, 4.5 and 5 Hz, 1, $H_{2'}$), 5.86 (dd, 4.5 and 7.5 Hz, 1, $H_{3'}$), 4.94 (d, 5 Hz, 1, $H_{1'}$), 4.8–4.4 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$); mass spectrum, *m/e* 489, 445, 367, 245, 105.

5-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,3,4-oxathiazol-2-one (8). A solution of 7 (26.8 g, 49.0 mmol) and ClSCOCl[11] (7.1 g, 54 mmol) in dry benzene (550 mL) was refluxed for 24 h. Then the mixture was cooled and concentrated under vacuum. The resulting oil was coevaporated with toluene and chromatographed on a silicagel column with 10% ethyl acetate in benzene. The yield of pure compound 8 was 25.10 g (83.5%): mp 114–116 °C (recrystallized from methanol–ethyl ether); IR ($CHCl_3$) 1775, 1730 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 7.8 (m, 6, Ar H), 7.4 (m, 9, Ar H), 5.9 (m, 2, $H_{2'}$, $H_{3'}$), 5.1 (d, $J = 6$ Hz, 1, $H_{1'}$), 4.7 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$); ^{13}C NMR ($CDCl_3$) δ 173.1 (C_2), 157.6 (C_5); mass spectrum, *m/e* 547, 503, 471, 445, 425; exact mass calcd for $C_{28}H_{21}NO_9S$: 547.094, found 547.096 ± 0.002. Anal. Calcd for $C_{28}H_{21}NO_9S$: C, 61.42; H, 3.87; N, 2.56; S, 5.86. Found: C, 61.81; H, 4.04; N, 2.50; S, 5.64.

Pyrolysis of 8 with Ethyl Cyanoformate and Ethyl Propiolate. Ethyl 3-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-thiadiazole-5-carboxylate (10). A solution of oxathiazolone 8 (200 mg, 0.37 mmol) and ethyl cyanoformate (400 mg, 4 mmol) in *m*-xylene (4 mL) was degassed and heated in a sealed tube for 1.5 h at 220 °C. Evaporation of excess ethyl cyanoformate and fast chromatography on a silicagel suction column with 5% ethyl acetate in toluene yielded 90 mg (40%) of a clean slightly yellow oil: IR (film) 1730 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 8.2–7.9 (m, 6, Ar H), 7.6–7.3 (m, 9, Ar H), 6.24 (t, 5 Hz, 1, $H_{2'}$), 6.12 (dd, 5 and 7 Hz, 1, $H_{3'}$), 5.8 (d, 5 Hz, 1, $H_{1'}$), 4.84 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.56 (q, 7.5 Hz, 2, CH_2), 1.45 (t, 7.5 Hz, 3, CH_3); mass spectrum, *m/e* 602, 587, 556, 480, 467, 358, 105; exact mass calcd for $C_{31}H_{26}O_9N_2S$ 602.136, found 602.137 ± 0.001.

Ethyl 3-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)isothiazole-5-carboxylate (11) and the Isomeric 4-Carboxylate

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(12). A solution of 8 (300 mg, 0.53 mmol) and ethyl propiolate (600 mg, 6 mmol) in toluene (4 mL) was pyrolyzed in a sealed tube for 1 h at 220 °C. Excess ethyl propiolate was removed by fast chromatography on a silicagel suction column, and the residue was separated by using high-performance liquid chromatography (Jobin-Yvon Chromatospac Prep 100, column diameter 8 cm, silicagel from Merck, art. 7736; eluted with 30% ethyl acetate in dichloromethane at 8 bar, 35 mL/min; detection with RI). In this way 0.160 g (48%) of compound 11 and 0.051 g (16%) of the 4-position substituted isothiazole 12 was obtained.

Isothiazole 11 (oil): IR (oil film) 1740 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 8.1–7.85 (m, 6, Ar H), 7.80 (s, 1, H_4), 7.60–7.20 (m, 9, Ar H), 6.1 (t, 4.5 Hz, 1, $H_{2'}$), 5.90 (t, 4.5 Hz, 1, $H_{3'}$), 5.47 (d, 5 Hz, 1, $H_{1'}$), 4.9–4.6 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.35 (q, 7 Hz, 2, CH_2), 1.26 (t, 7 Hz, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 1.68 (C_3), 166.0–165.2 (COOPh), 159.5 (COOEt), 158.3 (C_5), 133–128 (Ar C), 125.9 (C_4), 80–63 (ribosyl C), 61.8 (CH_2), 13.9 (CH_3); mass spectrum, m/e 601, 573, 556, 479, 357, 105; exact mass calcd for $C_{32}H_{27}NO_9S$ 601.141, found 601.141 ± 0.001.

Isothiazole 12 (oil): ^1H NMR ($CDCl_3$) δ 9.2 (s, 1, H_5), 8.1–7.8 (m, 6, Ar H), 7.5–7.2 (m, 9, Ar H), 6.2 (m, 3, $H_{1'}$, $H_{2'}$, $H_{3'}$), 4.8 (m, 3, $H_{4'}$, $H_{5'}$, $H_{5''}$), 4.3 (q, 6 Hz, 2, CH_2), 1.26 (t, 6 Hz, 3, CH_3); mass spectrum, m/e 601, 584, 572, 556, 479, 357, 105; exact mass calcd for $C_{32}H_{27}NO_9S$, 601.141, found 601.140 ± 0.001.

Ammonolysis of Compounds 10–12: Preparation of the Amides 3–5. A solution of compounds 10–12 (0.2 mmol) in methanol (2 mL) saturated with ammonia was stirred at room temperature for 80 h. After every 24-h period the solvent was evaporated and replaced by freshly prepared methanolic ammonia. After the reaction was completed, the solvent was evaporated and the residue was taken up in water (3 mL) and washed (3 times) with chloroform. The water layer was freeze-dried and the residue was recrystallized from 2-propanol to yield the very hygroscopic amides 3–5.

3-β-D-Ribofuranosyl-1,2,4-thiadiazole-5-carboxamide (3): yield 60%; mp 155–156 °C; IR (oil film) 3310 (OH, NH_2), 1675 cm^{-1} (CO); ^1H NMR (D_2O) δ 5.17 (d, J = 5.6 Hz, 1, $H_{1'}$), 4.48 (dd, 5.6 and 5.3 Hz, 1, $H_{2'}$), 4.29 (t, J = 5.3 Hz, 1, $H_{3'}$), 4.17 (ddd, 5.3, 2.3, and 6.4 Hz, 1, $H_{4'}$), 3.87 (dd, 2.3 and −12.5 Hz, 1, $H_{5'}$), 3.77 (dd, 6.4 and −12.5 Hz, 1, $H_{5''}$); ^{13}C NMR (D_2O) δ 61.6, 71.2, 79.2, 80.8, 84.9 (ribosyl C), 161.2 ($CONH_2$), 174.6 (C_3), 184.5 (C_5); mass spectrum (+4Me_3Si), m/e 549, 534, 459, 446, 356, 316, 256, 244, 230, 217, 159, 158, 129, 103, 73. Anal. Calcd for $C_8H_{11}N_3O_5S$: C, 36.78; H, 4.24; N, 16.08. Found: C, 36.61; H, 3.90; N, 15.66.

3-β-D-Ribofuranosylisothiazole-5-carboxamide (4): yield 55%; mp 135–137 °C; IR (KBr) 3310 (OH, NH_2), 1670 cm^{-1} (CO); ^1H NMR (D_2O) δ 7.8 (s, 1, H_4), 5.0 (d, 6.4 Hz, 1, $H_{1'}$), 4.3 (dd, 6.4 and 5.1 Hz, 1, $H_{2'}$), 4.18 (dd, 5.1 and 4.7 Hz, 1, $H_{3'}$), 4.12 (ddd, 4.7, 3.3, and 5.1 Hz, 1, $H_{4'}$), 3.83 (dd, 3.3 and −12.5 Hz, 1, $H_{5'}$), 3.74 (dd, 5.1 and −12.5 Hz, 1, $H_{5''}$); mass spectrum (+4Me_3Si) m/e 548, 533, 458, 445, 368, 355, 315, 255, 230, 229, 227, 217, 157, 103, 73. Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76. Found: C, 41.91; H, 5.03; N, 10.40.

3-β-D-Ribofuranosylisothiazole-4-carboxamide (5): yield 58%; mp 89–90 °C; the product decomposed on attempted purification preventing proper combustion analysis, but it was stable in aqueous solution or in vacuum; IR (KBr) 3300 (OH, NH_2), 1675, 1620 cm^{-1} (CO); ^1H NMR (D_2O, MeOD) δ 9.41 (s, 1, H_5), 5.45 (d, 5 Hz, 1, $H_{1'}$), 4.48 (dd, 5 and 5.6 Hz, 1, $H_{2'}$), 4.16 (t, 5.6 Hz, 1, $H_{3'}$), 4.16 (ddd, 5.6, 3.3, and 5.1 Hz, 1, $H_{4'}$), 3.89 (dd, 3.3 and −12.4 Hz, 1, $H_{5'}$), 3.77 dd, 5.1 and −12.4 Hz, 1, $H_{5''}$); mass spectrum (+3Me_3Si), m/e 476, 461, 386, 296, 283, 217, 73.

Acetalization of Compounds 3 and 4. Compound 3 (4) (10 mg), 1 mL of dimethoxypropane, and a pinch of *p*-toluenesulfonic acid was stirred at room temperature for 30 min. The mixture was placed directly on a preparative thin layer plate (silicagel) and eluted with 2% methanol in ethyl acetate to yield the desired compound as a clean, slightly yellow oil.

(2′,3′-*O*-Isopropylidene)-β-D-ribofuranosyl-1,2,4-thiadiazole-5-carboxamide (14): yield 8 mg; $_1H$ NMR (D_2O) δ 5.34 (d, 4 Hz, 1, $H_{1'}$), 5.28 (dd, 4 and 6.5 Hz, 1, $H_{2'}$), 4.93 (dd, 6.5 and 3 Hz, 1, $H_{3'}$), 4.38 (td, 3 and 7 Hz, 1, $H_{4'}$), 3.65 (m, 2, H_5 and $H_{5'}$), 1.61 (s, 3, CH_3), 1.41 (s, 3, CH_3).

3-(2′,3′-*O*-Isopropylidene)-β-D-ribofuranosylisothiazole-5-carboxamide (15): yield 5 mg; ^1H NMR ($CDCl_3$) 5.16 (d, 4 Hz, 1, $H_{1'}$), 4.89 (dd, 4 and 6.5 Hz, 1, $H_{2'}$), 4.86 (dd, 6.5 and 2.5 Hz, 1, $H_{3'}$), 4.37 (m, 1, $H_{4'}$), 3.66 (m, 2, $H_{5'}$ and $H_{5''}$), 1.64 (s, 3, CH_3), 1.40 (s, 3, CH_3).

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Use of D-Ribonolactone in Organic Synthesis. 2. Scope and Utility

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The scope and utility of D-ribonolactone (1) as a chiral template for the synthesis of optically active γ-lactones which are important precursors for many natural products are discussed. The regio- and stereoselective functionalization of 1 is examined.

Chiral γ-lactones are important precursors in natural product syntheses. These compounds have been obtained either from the cyclization of acyclic starting materials, such as the stereoselective iodolactonization of unsaturated 3-hydroxy acids,[1] or from sugars such as D-ribofuranose[2] or D-glucosamine.[3] The concept of using "chiral templates" derived from carbohydrates has been ingeniously and widely used in synthesis.[4] Most efforts in this area have traditionally focused on sugars such as D-ribose, D-glucose, etc. Manipulations involving carbohydrates,

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