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# Syntheses of hydantocidin and C-2-thioxohydantocidin

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Dedicated to Professor Derek Horton on the occasion of his 70th birthday

**Abstract**

Hydantocidin (**12**), a naturally occurring strong herbicide, was synthesized in 35.2% overall yield, with accompanying 5-*epi*-hydantocidin (**12′**) in 9.6% overall yield via isothiocyanate (**13**) and spiro-hydantoin (**10**) from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**). C-2-Thioxo-hydantocidin (**24**) was also synthesized in 16.5% overall yield with accompanying 5-*epi*-C-2-thioxohydantocidin (**24′**, 9.2% yield) via isothiocyanate (**22**). © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* Spironucleoside; Furanoid spirohydantoin; Glycosyl isothiocyanate; Herbicide

## 1. Introduction

Together with the explosive increase in the world population, deficiency of provisions, environmental destruction and pollution, and global warming have become serious problems. Means for grain production to maintain this large population have come under increased development. One aspect is the use of herbicides. Glyphosate has become one of the most popular herbicides in the world. However, glyphosate-resistant weeds have been reported recently. In addition, proteins produced by grain plants recombinated by a glyphosate-resistant gene are a cause for concern, because of the awareness of the existence of pathogenic proteins.

Hydantocidin produced from *Streptomyces hygroscopicus*,[1] the first naturally occurring spiro-ribofuranose having strong herbicidal activity toward annual, biennial and perennial weeds by action as an adenylosuccinate synthetase inhibitor[2] without showing toxicity to microorganisms and animals and without remaining for a long period in the soil, may be used in the near future as a potential herbicide against glyphosate-resistant weeds. However, the high cost of hydantocidin production, whether by fermentation or by total synthesis,[3] has made its use as a herbicide impractical. Therefore, economical production of hydantocidin is being sought. At this time, the author has accomplished a fairly good overall yield for hydantocidin, that is, hydantocidin **12** was synthesized in 35.2% overall yield accompanying *epi*-hydantocidin **12′** in 9.6% overall yield from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**). And also C-2-thioxohydantocidin **24** was synthesized from **1** in 16.5% overall yield via isothiocyanate **22**. Therefore, I would like to report the synthetic procedure in detail here.[4]

## 2. Results and discussion

The starting material, 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**),[5] was converted to 5-*O*-benzyl ether **2** or 5-*O*-(4-methoxybenzyl) ether **15** in 95 or 77% yield, respectively, by treatment with benzyl bromide or 4-methoxybenzyl chloride using NaH as a base. Treatment of **2** with $CBrCl_3$ using tris(dimethylamino)phosphine $[(Me_2N)_3P]$ as a base according to Chapleur's procedure[6] gave dichloroolefin **3**[7] in 86% yield. Compound **15** also gave **16** in 95% yield. In this reaction, Lakhrissi and Chapleur[6] used $CCl_4$ instead of $CBrCl_3$. However, in the case of using $CCl_4$, the reac-

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tion, on occasion, did not proceed. The dichloroolefin **3** was further converted to methyl α-chlorourosonates **4** and **4′** in 68% yield as a 4:1 diastereomeric mixture via C-1–C-2 epoxide by treatment with 3-chloroperoxybenzoic acid.[6] The mixture of **4** and **4′** was separated chromatographically. The configuration of **4** was determined by measurement of the nuclear Overhauser effect (NOE) between H-3 (the proton attached to the 3-position carbon) and $^{13}$C-1 (methyl ester carbonyl carbon) of compounds **4** and **4′**. The NOE between H-3 and $^{13}$C-1 of **4** was detected. However, the NOE between H-3–$^{13}$C-1 of **4′** was not detected. This result indicates that the configurations of the carbonyl carbon of the C-1 methyl ester and the C-3 proton in compound **4** are on the same side of the molecule, while those of **4′** are trans to one another. Compound **16** was also converted to a 4:1 mixture of **17** and **17′** (epimer of **17**) in 67% yield in the same treatment. The mixture of **17** and **17′** was separated chromatographically.

Firstly, a route through carbodiimide **7** and ureido **9** was attempted. Treatment of **4** with sodium azide in DMF at room temperature gave azide **5** in 95% yield with inversion of configuration. Conversion of **5** to phosphine imide **6** by treatment of triphenylphosphine, and successive treatment of **6** with 4-mehoxybenzyl isocyanate yielded carbodiimide **7** (90%) as a single product. Treatment of **7** with aq 1 M HCl in THF afforded urea **8** quantitatively. Deprotection of the 4-methoxybenzyl group from **8** was carried out by treatment with ammonium cerium(IV) nitrate (CAN) to give **9** in 97% yield. Hydantoin formation from **9** with $NH_3$ in MeOH proceeded smoothly to give spiro-hydantoin **10** in 99% yield. Hydrogenolysis of **10** using Pd-on-charcoal afforded **11** quantitatively. Treatment of **11** with 1:3 $CF_3COOH$–water at 0 °C according to the reported method[3f] yielded hyantocidin **12** quantitatively. This synthetic hydantocidin was identical with natural hydantocidin in all respects, including herbicidal activity toward many kinds of weeds (Schemes 1 and 2).

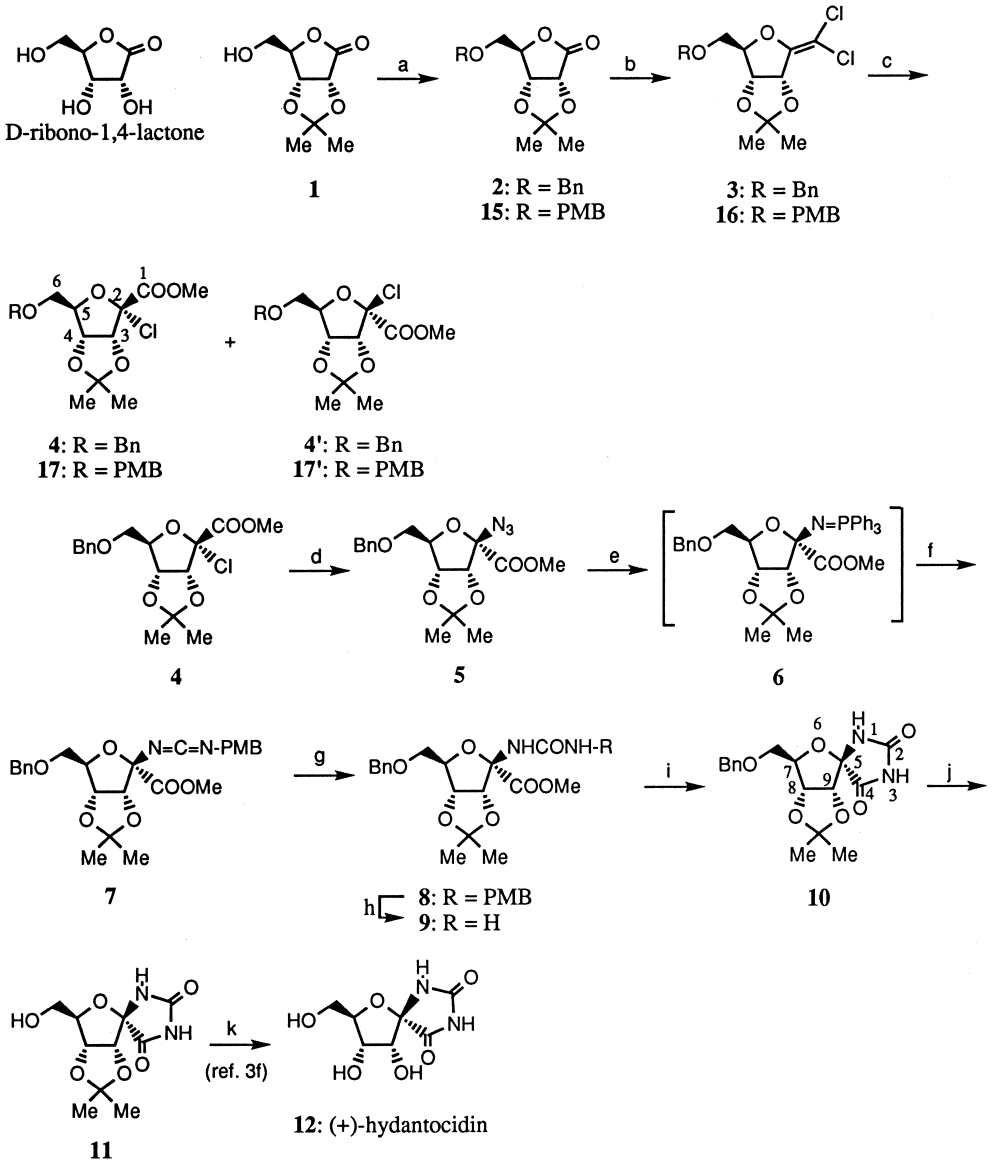
The spiro-*epi*-hydantocidin (**12′**) was also synthesized by the same procedure as for the synthesis of **12** from methyl α-chlorourosonate **4′** through the corresponding epimeric intermediates **5′**–**11′**. In the preparation of ureido **8′** (67% yield) from **7′**, a fair amount of **8″** (14%) was obtained by acidic cleavage of the acetonide protecting group. Compound **10′** was also obtained in 91% yield from **9** by both epimerization and hydantoin formation using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Necessarily, compound **10** was epimerized to **10′** in 87% yield (with 12% recovery of **10**) using the same conditions.

However, this route was not economical because of the high cost of the reagents for agricultural chemicals used, such as sodium azide, triphenylphosphine and 4-methoxybenzyl isocyanate. Therefore, another synthetic route via isothiocyanates **13** and **22** was investigated (Scheme 3).

In this second route, treatment of **4** with KSCN at 80 °C in DMF gave a 4:1 mixture of isothiocyanate **13** and **13′** in 84% yield without yielding corresponding thiocyanates.[4,8,9] Similarly, the same treatment of **4′** gave a 5:2 mixture of **13** and **13′** in 69% yield. Separation of isothiocyanates **13** and **13′** was difficult by chromatography. However, a sample of the mixture was partially separated on a TLC plate by development with 3:1 cyclohexane–EtOAc (**13**, $R_f$ 0.500; **13′**, $R_f$ 0.467) to measure the physical data. The $^{13}$C NMR spectra of **13** and **13′** indicated the presence of the isothiocyanates ($\delta$ 143.2 and 144.4 ppm, respectively).[9] This mixture was treated with $NH_3$ in MeOH to give C-2-thioxohydantoins **14** and **14′**, quantitatively. The ratio of **14** and **14′** was in parallel with that of the starting **13** and **13′**. And the same reaction of compounds **17** and **17′** also gave a 5:1 mixture of corresponding isothiocyanates **18** and **18′** in 74% yield from **17**, and a 3:1 mixture of **18** and **18′** in 72% yield from **17′**. These compounds **18** and **18′** were also inseparable by chromatography. And the mixture of **18** and **18′** was also treated by $NH_3$ to give hydantoins **19** and **19′** quantitatively in the same ratio as that of the starting **18** and **18′**. These 4-methoxybenzyl-protected spiro-hydantoins **19** and **19′** were also used for unnatural C-2-thioxohydantocidin **24** as mentioned later. Treatment of thioxo-hydantoins **14** and its spiro epimer **14′** with $H_2O_2$–aq $NaHCO_3$ quantitatively gave hydantoin **10** and its epimer **10′**, respectively.[10] And thioxo-compounds **19** and **19′** were also converted to oxo-compounds **20** and **20′** in 96 and 95% yields, respectively. This procedure was also applicable for the oxidation of thiourea, thiohydantoin and cyclic thiocarbamate to yield corresponding urea, hydantoin and carbamate as reported in a communication.[4]

Spiro-hydantoin **10** and its spiro epimer **10′** were converted quantitatively to hydantocidin **12** and its spiro epimer **12′** in two steps as mentioned above. And compounds **20** and **20′** were also converted quantitatively to hydantocidin **12** and **12′** via the hydrogenolyzed compounds **11** and **11′**, respectively.

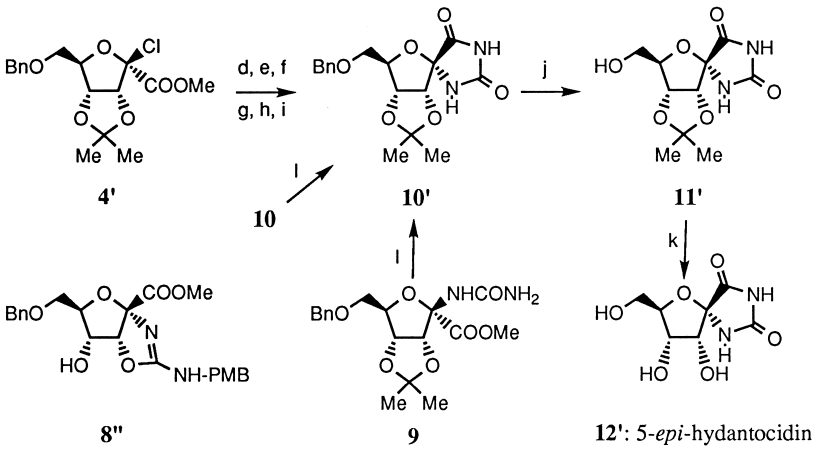
Thus, hydantocidin **12** was synthesized in eight steps from **1** via isothiocyanate **13**, and the overall yield was 35.2% accompanied by 9.6% yield of spiro-*epi*-hydantocidin **12′**. Also, hydantocidin was synthesized in eight steps from **1** via isothiocyanates **18** and **18′** in 30.0% overall yield accompanied by spiro-*epi*-hydantocidin **12′** (6.3%). The yield of this route was lower than that of the route via **13**. Besides, the 4-methoxybenzyl group is much more expensive than the benzyl group for synthesis. In either case, the difference is little, that is, one is benzyl, and the other is 4-methoxybenzyl.




Scheme 1. Reagents and conditions: Bn = benzyl; PMB = 4-methoxybenzyl; (a) NaH, BnBr, or PMB–Cl, DMF, 24 °C, 16 h, 95% (**2**) and 77% (**15**); (b) $CBrCl_3$, $(Me_2N)_3P$, $CH_2Cl_2$, −78–24 °C, 16 h, 86% (**3**) and 95% (**16**); (c) *m*-CPBA, MeOH, $CH_2Cl_2$, 24 °C, 16 h, 54% (**4**) and 14% (**4′**), and 54% (**17**) and 13% (**17′**); (d) $NaN_3$, DMF, 24 °C, 16 h, 95%; (e) $PPh_3$, THF, 24 °C, 2 h; (f) PMB–N=C=O, THF, 24 °C, 16 h, two steps 90%; (g) 1:20 aq 1 M HCl–THF, rt, 15 min, quant; (h) $Ce(NH_4)_2(NO_3)_6$, 2:1 MeCN–water, rt, 20 min, 97%; (i) 0.2 M $NH_3$ in MeOH, 27 °C, 4 h, 99%; (j) $H_2$, Pd/C, EtOAc, 24 °C, 30 min, quant; (k) (Ref. 3f) 1:3 $CF_3COOH$–water, 0 °C, 2 h, quant.

Thirdly, C-2-thioxohydantocidin **24**, which has been reported along with its spiro epimer **24′** as being comparable with hydantocidin **12** in herbicidal activity to many different types of weeds,[3k,11] is not found in nature and, therefore, has to be synthesized.

Methyl α-chlorourosonate **4** was hydrogenolyzed to deprotect the benzyl group, and the resulting alcohol was acetylated with acetic anhydride and pyridine to give **21** in 90% yield. On the other hand, compound **4′** just decomposed to unknown materials in the same procedure without yielding **21′**. However, considering that treatment of **4′** itself at 80 °C for 1 h in DMF gave ca. 1:1 mixture of **4** and **4′** by thermal equilibration, this problem (unavailability of **4′**) should be resolved in further studies. Methyl α-chlorourosonate **21** was also converted to isothiocyanate **22** (68%) and its epimer **22′** (13%) by treatment with potassium thiocyanate (KSCN) at 80 °C in DMF. The $^{13}C$ NMR spectra of **22** and **22′** showed resonances for isothiocyanate groups ($\delta$ 144.5 and 145.0 ppm, respectively).[9] Reaction of **22** and **22′** with $NH_3$ in MeOH gave the deacetylated spiro-hydantoins **23** and **23′** quantitatively, respectively. On the other hand, treatment of **19** and **19′** in $CH_2Cl_2$ with PhSH and $SnCl_4$ at −78 °C under $N_2$ gave **23** and **23′**




Scheme 2. Reagents and conditions: Bn = benzyl; PMB = 4-methoxybenzyl; (d) $NaN_3$, DMF, 24 °C, 16 h, 89%; (e) $PPh_3$, THF, 24 °C, 2 h; (f) PMB–N=C=O, THF, 24 °C, 16 h, two steps 69%; (g) 1:20 aq 1 M HCl–THF, rt, 15 min, 67% (**8′**) and 14% (**8″**); (h) $Ce(NH_4)_2(NO_3)_6$, 2:1 MeCN–water, rt, 20 min, 72%; (i) 0.2 M $NH_3$ in MeOH, 27 °C, 4 h, quant; (j) $H_2$, Pd/C, EtOAc, 24 °C, 30 min, quant; (k) (Ref. 3f) 1:3 $CF_3COOH$–water, 0 °C, 2 h, quant; (l) DBU, THF–DMF, rt, 7 days, 91% from **9**, and 87% from **10** (12% recovery of **10**).

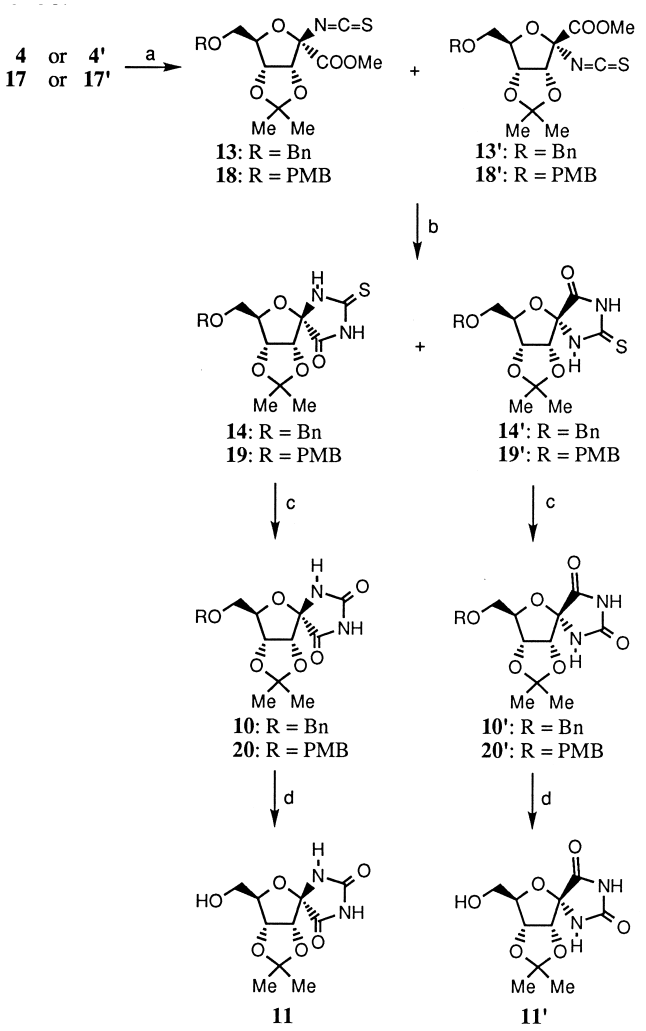
in 81 and 72% yields, respectively, accompanying recovery of **19** (6%) and **19′** (13%), respectively.[12] Finally, the protecting isopropylidene group of **23** was cleaved by treatment with 3:1 $CF_3COOH$–water at 0 °C for 2 h and −5 °C for 16 h to give a chromatographically separable mixture of **24** (61%) and **24′** (16%).[3f] However, the same treatment of **23′** only gave **24′** in 94% yield. As a result, C-2-thioxohyantocidin **24** was synthesized from **1** in eight steps via the acetylated isothiocyanates **22** and **22′** in 16.5% overall yield, along with the accompanying spiro epimer **24′** (9.2% yield). These compounds were also synthesized from **1** in seven steps via isothiocyanate intermediates **19** and **19′** in 15.4% overall yield, along with the accompanying spiro epimer **24′** (4.2% yield). The yield of this route was a little lower than that of the route via **22** (Scheme 4).

Thus, hydantocidin **12** and spiro-*epi*-hydantocidin **12′** were synthesized from 2,3-*O*-isopropylidene-D-ribono-1,4-lactone **1** in overall yields of 35.2 and 9.6% via isothiocyanate intermediates **13** and **13′**, and 30.0 and 6.3% via intermediates **19** and **20**, and **19′** and **20′**, respectively. C-2-Thioxohydantocidin **24** and spiro-*epi*-C-2-thioxohydantocidin **24′** were synthesized from **1** in overall yields of 16.5 and 9.2% via isothiocyanate intermediates **22** and **22′**, and 15.4 and 4.2% via intermediates **19** and **19′**.

## 3. Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were obtained by the use of a JASCO P-1030 polarimeter. $^1$H NMR spectra were recorded with a JEOL-GSX 400 spectrometer (400 MHz) using TMS as the internal standard, and $^{13}$C NMR spectra were recorded at 125 MHz using TMS as the internal standard. IR absorption spectra were determined with an IR A-2 spectrophotometer, and mass spectra were obtained with a JMS-700 mass spectrometer. Separation of the compounds by column chromatography was done with Silica Gel 60 (230–400 mesh ASTM, E. Merck) under a slightly elevated pressure (1.1–1.5 atm) for easy elution, and the quantity of silica gel used was 50–100 times the weight charged on the column. Thin-layer chromatography was performed on E. Merck no. 5715 Silica Gel 60-$F_{254}$ plates. Tetrahydrofuran (THF) was distilled in the presence of radical anions generated by sodium-benzophenone ketyl. Dichloromethane was dried by being passed through an ICN Alumina B-Super I, and DMF and pyridine were dried by storage over 4 Å molecular sieves.

*5-O-Benzyl-2,3-O-isopropylidene-D-ribono-1,4-lactone* (**2**).—To a solution of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**1**, 7.45 g, 39.58 mmol) and benzyl bromide (8.12 g, 47.50 mmol) in DMF (30 mL) was added NaH (60–72% oil dispersion, 1.90 g) under ice cooling. The mixture was stirred at 0 °C for 30 min, and then rt for 16 h. The mixture was then diluted with EtOAc, washed with aq 0.1 M HCl, satd aq $NaHCO_3$, and brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo to give an oily mixture. The mixture was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave **2** (10.45 g, 95%). $^1$H NMR ($CDCl_3$): $\delta$ 1.37 (3 H, s), 1.47 (3 H, s), 3.68 (1 H, dd, *J* 1.5, 11.0 Hz), 4.72 (1 H, dd, *J* 2.2, 11.0 Hz), 4.47, 4.56 (2 H, AB-q, *J* 11.7 Hz), 4.65 (1 H, dd, *J* 1.5, 2.2 Hz), 4.71 (1 H, d, *J* 5.9 Hz), 4.79 (1 H, d, *J*

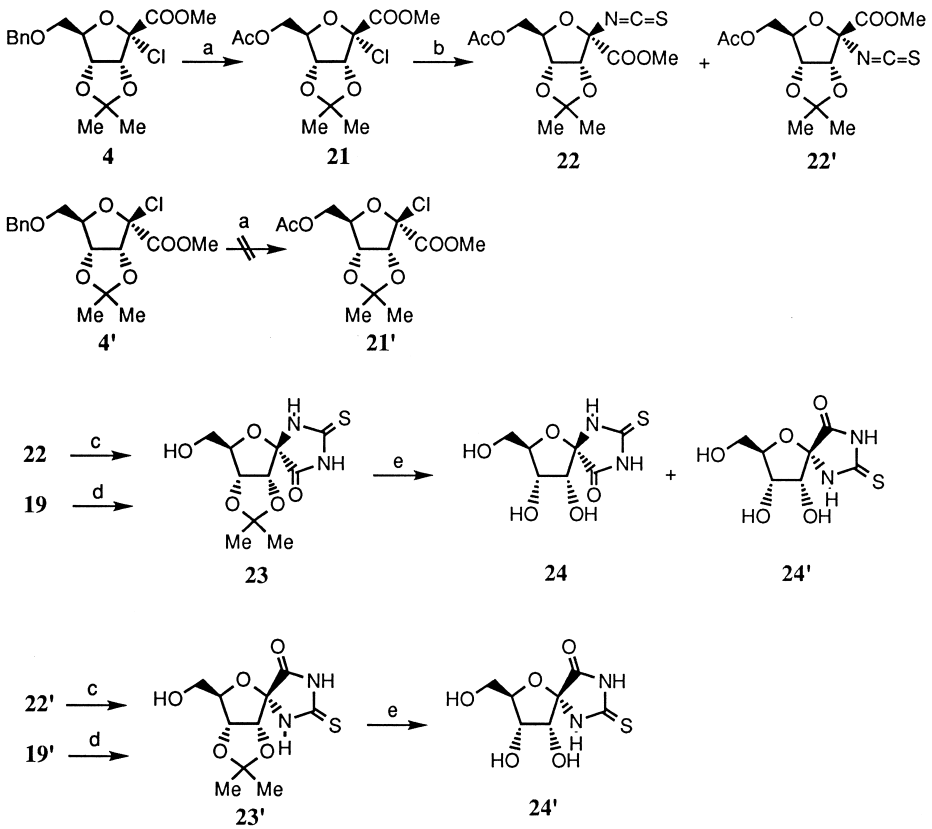



Scheme 3. Reagents and conditions: Bn = benzyl; PMB = 4-methoxybenzyl; (a) KSCN, DMF, 80 °C, 5 h, 84% (a 4:1 mixture of **13** and **13′** from **4**), 69% (a 5:2 mixture of **13** and **13′** from **4′**), 73% (a 5:1 mixture of **18** and **18′** from **17**), and 72% (a 3:1 mixture of **18** and **18′** from **17′**); (b) $NH_3$, MeOH, rt, 30 min, quant; (c) $H_2O_2$, $NaHCO_3$, MeCN–water, rt, 15 min, quant (**10** and **10′**), 96% (**20**), and 95% (**20′**); (d) $H_2$, Pd/C, EtOAc, rt, quant.

5.9 Hz), 7.24–7.38 (5 H, m). FABMS (positive-ion) $m/z$: 279 $[M+H]^+$.

*2,5-Anhydro-6-*O*-benzyl-1,1-dichloro-1-deoxy-3,4-*O*-isopropylidene-*D*-ribo-hex-1-enitol* (**3**).—To a solution of **2** (6.00 g, 21.56 mmol) and $BrCCl_3$ (21.37 g, 107.80 mmol) in $CH_2Cl_2$ (60 mL) was added dropwise a solution of $P(NMe_2)_3$ (35.20 g, 46.08 mmol) in $CH_2Cl_2$ (40 mL) at −78 °C over 1.5 h under nitrogen. The temperature was gradually elevated to −40 °C during 4 h stirring, and then to rt with stirring for 16 h. The reaction mixture was diluted with $CH_2Cl_2$, washed with aq 0.5 M HCl, water, aq $NaHCO_3$, and brine, and the organic layer was then dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give a mixture, which was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave **3** (6.37 g, 86%) as an oil and starting **2** (0.45 g, 7.5% recovery). IR $\nu_{max}$(film) 1765, 1731 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.39 (3 H, s), 1.49 (3 H, s), 3.65 (2 H, s), 4.51 (2 H, s), 4.65 (1 H, s), 4.80, 5.26 (2 H, AB-q, $J$ 6.0 Hz), 7.27–7.40 (5 H, m). FABMS (positive-ion) $m/z$: 344 $[M^{+\bullet}]$. HRFABMS (positive-ion), Calcd for $C_{16}H_{18}{}^{35}Cl_2O_4$: 344.0582; Found: 344.0599. Anal. Calcd for $C_{16}H_{18}Cl_2O_4$: C, 55.67; H, 5.26; Cl, 20.54. Found: C, 55.94; H, 5.16; Cl, 20.11.

*Methyl 2,5-anhydro-6-*O*-benzyl-2-chloro-3,4-*O*-isopropylidene-α-*D*-ribo-2-hexulofuranosonate* (**4**) *and methyl 2,5-anhydro-6-*O*-benzyl-2-chloro-2-deoxy-3,4-*O*-isopropylidene-β-*D*-ribo-2-hexulofuranosonate* (**4′**).—To a solution of **3** (345 mg, 1.00 mmol) in $CH_2Cl_2$ (20 mL) containing MeOH (300 mg) were added hydroquinone (50 mg) and 4-chloroperoxybenzoic acid (1.20 g, purity ca 77%, Aldrich Chemical Co.) under $N_2$ at rt. The mixture was stirred for 16 h at rt, and then the reaction mixture was diluted with $CH_2Cl_2$ and washed with 10% aq $NaHSO_3$ (two times), satd aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave 2-epimer **4′** (0.51 g, 14%, $R_f$ 0.508) as an amorphous solid and **4** (1.94 g, 54%, $R_f$ 0.398) as a gum. Physical data of **4′**: mp 48–48.5 °C (from hexane); $[\alpha]_D^{25}$ −99.5° ($c$ 0.5, $CHCl_3$). IR $\nu_{max}$(KBr) 1762 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.33 (3 H, s), 1.44 (3 H, s), 3.75 (2 H, d, $J$ 7.3 Hz, C-6–$H_2$), 3.89 (3 H, s), 4.58, 4.60 (2 H, AB-q, $J$ 12.5 Hz), 4.66 (1 H, dt, $J$ 2.2, 7.3 Hz, C-5–H), 4.93 (1 H, dd, $J$ 1.5, 5.9 Hz, C-4–$H$), 5.14 (1 H, d, $J$ 5.9 Hz, C-3–$H$), 7.27–7.35 (5 H, m). $^{13}C$ NMR (100 MHz, $CDCl_3$): 25.44, 26.25, 53.48 ($OCH_3$), 68.81, 73.30, 81.71, 88.51, 89.80, 103.09, 114.14, 127.63 (3 C), 128.31 (2 C), 137.35, 164.89. NOE between H-3 and $^{13}C$-1 was not detected. FABMS (positive-ion) 355 $[M-H]^+$, 357 $[M+H]^+$, 379 $[M+Na]^+$ (on addition of aq NaI). HRFABMS (positive-ion), Calcd for $C_{17}H_{21}ClNaO_6$: 379.0924; Found: 379.0940. Physical data of **4**: $[\alpha]_D^{23}$ +41.4° ($c$ 3.2, $CHCl_3$). IR $\nu_{max}$(film) 3089–2867, 1750 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.40 (3 H, s), 1.70 (3 H, s), 3.69 (1 H, dd, $J$ 3.2, 11.3 Hz, C-6–$H$), 3.73 (1 H, dd, $J$ 3.2, 11.3 Hz, C-6–$H$), 3.83 (3 H, s), 4.53, 4.58 (2 H, AB-q, $J$ 12.2 Hz), 4.59 (1 H, q, $J$ 3.2 Hz, C-5–$H$), 4.81 (1 H, dd, $J$ 3.2, 7.1 Hz, C-4–$H$), 5.02 (1 H, d, $J$ 7.1 Hz, C-3–$H$), 7.28–7.39 (5 H, m). $^{13}C$ NMR (100 MHz , $CDCl_3$): 25.29 (2 C), 53.48 ($OCH_3$), 68.58, 73.41, 79.80, 83.68 (2 C), 102.44, 116.78, 127.55 (2 C), 127.75, 128.31 (2 C), 137.21, 166.22. NOEs between H-3 and $^{13}C$-1, H-3 and $^{13}C$-2, H-3 and $^{13}C$-4, H-3 and $^{13}C$-5, and H-3 and $^{13}C$-benzylic were detected. Anal. Calcd for $C_{17}H_{21}ClO_6$: C, 57.23; H, 5.93; Cl, 9.94. Found: C, 57.01; H, 5.77; Cl, 10.14.



Scheme 4. Reagents and conditions: (a) (i) $H_2$, Pd/C, EtOAc, rt, 20 min; (ii) $Ac_2O$, pyridine, EtOAc, rt, 15 h, 2 steps 90%; (b) KSCN, DMF, 80 °C, 15 h, 68% (**22**) and 13% (**22′**); (c) $NH_3$ in MeOH, rt, 6 h, quant; (d) $SnCl_4$, PhSH, $CH_2Cl_2$, −78 °C, 30 min, 81% (**23**), or 76% (**23′**) and 13% (recovery of **19′**); (e) 1:3 $CF_3COOH$–water, 0 °C, 3 h, 68% (**24**) and 13% (**24′**) from **23**, or 20 °C, 2 h, 94% (**24′**) from **23′**.

*Methyl 2,5-anhydro-2-azido-6-*O*-benzyl-3,4-*O*-isopropylidene-β-*D*-ribo-2-hexulofuranosonate* (**5**).—To a solution of **4** (835 mg, 2.34 mmol) in DMF (10 mL) was added $NaN_3$ (457 mg, 7.02 mmol). After 5 h stirring at rt, the reaction mixture was diluted with EtOAc, washed with water, and brine. The organic extract was dried over $MgSO_4$, filtered, and then concentrated in vacuo (finally with a pump) to give **5** (808 mg, 95%). IR $\nu_{max}$(film) 2117, 1764 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (3 H, s), 1.45 (3 H, s), 3.63 (1 H, dd, *J* 6.2, 10.1 Hz, C-6–H), 3.65 (1 H, dd, *J* 5.2, 10.1 Hz, C-6–H), 3.87 (3 H, s), 4.56, 4.61 (2 H, AB-q, *J* 12.0 Hz), 4.63–4.67 (2 H, m), 4.87 (1 H, dd, *J* 1.5, 5.8 Hz), 7.34–7.36 (5 H, m). FABMS (positive-ion) *m*/*z*: 386 $[M + Na]^+$ (on addition of NaI). Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83; N, 11.57. Found: C, 56.02; H, 5.76; N, 11.50.

*Methyl 2,5-anhydro-2-azido-6-*O*-benzyl-3,4-*O*-isopropylidene-α-*D*-ribo-2-hexulofuranosonate* (**5′**).—Compound **5′** was also obtained in 89% yield as an oil from **4′** according to the same procedure described above. IR $\nu_{max}$(film) 3065–2866, 2127, 1751 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 (3 H, s), 1.65 (3 H, s), 3.61–3.63 (2 H, m), 3.70 (3 H, s), 4.45, 4.54 (2 H, AB-q, *J* 12.0 Hz), 4.52 (1 H, m), 4.79 (1 H, dd, *J* 1.6, 6.2 Hz), 5.13 (1 H, d, *J* 6.2 Hz), 7.26–7.34 (5 H, m). FABMS (positive-ion) *m*/*z*: 362 $[M - H]^+$, 386 $[M + Na]^+$.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-[3-*N*-(4-methoxybenzyl)carbodiimido]-β-*D*-ribo-2-hexulofuranosonate* (**7**).—To a solution of **5** (760 mg, 2.09 mmol) in THF (35 mL) was added $PPh_3$ (1.20 g, 4.57 mmol) to yield phosphine imide **6**. After 2 h stirring at rt, 4-methoxybenzyl isocyanate (1.00 g, 6.13 mmol) was added to this solution. The mixture was stirred for 3 days at rt. The reaction mixture was concentrated in vacuo to give a mixture that was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave carbodiimide **7** (904 mg, 90%) as an oil. IR $\nu_{max}$(film) 3063–2840, 2130, 1767, 1745, 1612 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.29 (3 H, s), 1.44 (3 H, s), 3.60–3.74 (2 H, m), 3.78 (6 H, s), 4.10 (1 H, m), 4.19 (1 H, m), 4.37, 4.52 (2 H, AB-q, *J* 11.5 Hz), 4.58 (1 H, s), 4.69 (1 H, m), 4.85 (1 H, m), 6.81–6.84 (2 H, m), 7.10–7.12 (2 H, m), 7.26–7.27 (5 H, m). FABMS (positive-ion) *m*/*z*: 483 $[M + H]^+$. HRFABMS (positive-ion), Calcd for $C_{26}H_{31}N_2O_7$: 483.2131; Found: 483.2153. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.36; H, 6.37; N, 5.75.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-[3-*N*-(4-methoxybenzyl)carbodiimido]-α-*D*-ribo-*

*2-hexulofuranosonate* (**7′**).—Compound **7′** was also obtained in 69% yield from **5′** via phosphazene **6′** according to the same procedure described above. IR $\nu_{max}$(film) 3063–2838, 2134, 1744, 1613, 1587 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.37 (3 H, s), 1.61 (3 H, s), 3.59–3.61 (2 H, m), 3.64 (3 H, s), 3.79 (3 H, s), 4.43–4.57 (5 H, m), 4.75 (1 H, dd, *J* 2.2, 6.6 Hz), 5.02 (1 H, d, *J* 6.6 Hz), 6.84–6.87 (2 H, m), 7.24–7.36 (7 H, m). FABMS (positive-ion) *m/z*: 483 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{26}H_{31}N_2O_7$: 483.2131; Found: 483.2126.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-[3-*N*-(4-methoxybenzyl)ureido]-β-*D*-ribo-2-hexulofuranosonate* (**8**).—To a solution of **7** (452 mg, 0.94 mmol) in THF (20 mL) was added aq 1 M HCl (1.00 mL) at rt. After stirring for 40 min, the reaction mixture was diluted with EtOAc. The solution was washed with satd aq $NaHCO_3$ and brine, and the organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give ureido **8** (469 mg, quant) as a solid; mp 149–151 °C (from EtOAc). $[\alpha]_D^{25}$ −84° (*c* 0.05, $CHCl_3$). IR $\nu_{max}$(KBr) 3350, 3088–2838, 1754, 1656, 1614, 1564, 1513 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.29 (3 H, s), 1.44 (3 H, s), 3.65 (1 H, dd, *J* 4.1, 10.3 Hz), 3.69 (1 H, dd, *J* 3.8, 10.3 Hz), 3.77 (3 H, s), 3.78 (3 H, s), 4.10 (1 H, dd, *J* 4.8, 14.6 Hz, changed to a doublet, *J* 14.6 Hz, on addition of $D_2O$), 4.19 (1 H, dd, *J* 5.8, 14.6 Hz, changed to a doublet, *J* 14.6 Hz, on addition of $D_2O$), 4.37, 4.51 (2 H, AB-q, *J* 11.4 Hz), 4.58 (1 H, m), 4.69 (1 H, d, *J* 6.2 Hz), 4.85 (1 H, m, changed to dd, *J* 2.2, 6.2 Hz, on addition of $D_2O$), 5.20 (1 H, bs, NH, exchanged on addition of $D_2O$), 5.65 (1 H, s, NH, not exchanged on addition of $D_2O$), 6.82 (2 H, d, *J* 8.3 Hz), 7.11 (2 H, m), 7.19–7.21 (2 H, m), 7.26–7.30 (3 H, m). FABMS (positive-ion) *m/z*: 501 $[M+H]^+$, 523 $[M+Na^+]$. HRFABMS (positive-ion), Calcd for $C_{26}H_{32}N_2NaO_8$: 523.2057; Found: 523.2065. Anal. Calcd for $C_{26}H_{32}N_2O_8$: C, 62.39; H, 6.44; N, 5.60. Found: C, 62.28; H, 6.10; N, 5.55.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-[3-*N*-(4-methoxybenzyl)ureido]-α-*D*-ribo-2-hexulofuranosonate* (**8′**).—Compound **8′** was also obtained in 67% yield as a powder by treatment of **7′** for 2 h, instead of 40 min according to the procedure as described above, and a byproduct (**8″**) was obtained in 14% yield. Physical data of **8′**: IR $\nu_{max}$($CHCl_3$) 4214, 3411, 3088–2839, 1753, 1678, 1613 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.39 (3 H, s), 1.62 (3 H, s), 3.62 (3 H, s), 3.64 (1 H, dd, *J* 4.4, 11.0 Hz), 3.70 (1 H, dd, *J* 4.4, 11.0 Hz), 3.79 (3 H, s), 4.26 (1 H, dd, *J* 5.9, 14.6 Hz), 4.37–4.42 (2 H, m), 4.49, 4.57 (2 H, AB-q, *J* 12.1 Hz), 4.78 (1 H, dd, *J* 2.9, 6.6 Hz), 4.83 (1 H, d, *J* 7.3 Hz), 5.66 (1 H, bs, NH, exchanged on addition of $D_2O$), 5.73 (1 H, s, NH), 6.83–6.85 (2 H, m), 7.19–7.22 (2 H, m), 7.27–7.35 (5 H, m). FABMS (positive-ion) *m/z*: 501 $[M+H]^+$, 523 $[M+Na]^+$. HRFABMS (positive-ion), Calcd for $C_{26}H_{33}N_2O_8$: 501.2237; Found: 501.2233. Physical data of **8″**: IR $\nu_{max}$($CHCl_3$) 3350, 3365–2840, 1746, 1654, 1612, 1587, 1514 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.69–3.72 (3 H, m), 3.76 (6 H, s), 4.14 (1 H, m), 4.34 (2 H, s), 4.53, 4.56 (2 H, AB-q, *J* 11.2 Hz), 5.05 (1 H, d, *J* 5.9 Hz), 6.82–6.85 (2 H, m), 7.19–7.22 (2 H, m), 7.25–7.35 (5 H, m). FABMS (positive-ion) *m/z*: 443 $[M+H]^+$, 481 $[M+K]^+$ (on addition of KI). HR-FABMS (positive-ion), Calcd for $C_{23}H_{26}KN_2O_7$: 481.1377; Found: 481.1374. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.21; H, 6.13; N, 6.20.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-ureido-β-*D*-ribo-2-hexulofuranosonate* (**9**).—To a solution of **8** (230 mg, 0.46 mmol) in MeCN (20 mL) was added a solution of ammonium cerium(IV) nitrate (4.11 g, 7.50 mmol) in water (10 mL) at rt with stirring. After 20 min, the reaction mixture was diluted with EtOAc, washed with sat aq $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture, which was chromatographed on a silica gel column. Elution with 3% MeOH in EtOAc gave **9** (170 mg, 97%) as a solid; mp 201–202 °C (from MeOH). IR $\nu_{max}$(KBr) 3365, 3207, 3088–2864, 2557–2385, 1751, 1658 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.31 (3 H, s), 1.45 (3 H, s), 3.68 (1 H, dd, *J* 4.1, 10.4 Hz), 3.74 (1 H, dd, *J* 4.1, 10.4 Hz), 3.80 (3 H, s), 4.49, 4.57 (2 H, AB-q, *J* 11.4 Hz), 4.59 (1 H, m), 4.81 (1 H, d, *J* 6.4 Hz), 4.90 (1 H, dd, *J* 2.5, 6.4 Hz), 4.94 (2 H, bs, $NH_2$, exchanged on addition of $D_2O$), 6.23 (1 H, s, NH, not exchanged on addition of $D_2O$), 7.28–7.40 (5 H, m). FABMS (positive-ion) *m/z*: 381 $[M+H]^+$, 403 $[M+Na^+]$. HRFABMS (positive-ion), Calcd for $C_{18}H_{25}N_2O_7$: 381.1662; Found: 381.1668. Anal. Calcd for $C_{18}H_{24}N_2O_7$: C, 56.83; H, 6.36; N, 7.36. Found: C, 56.29; H, 6.78; N, 6.92.

*Methyl 2,5-anhydro-6-*O*-benzyl-3,4-*O*-isopropylidene-2-ureido-α-*D*-ribo-2-hexulofuranosonate* (**9′**).—Compound **9′**, accompanied by a small amount of chromatographycally inseparable 4-epimer (**9**), was also obtained from **8′** in 72% yield according to the same procedure described above. IR $\nu_{max}$($CHCl_3$) 4214, 3514, 3403, 3020–2860, 1755, 1690, 1594 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.39 (3 H, s), 1.63 (3 H, s), 3.64–3.70 (5 H, m, containing 3 H, s, at d 3.68 ppm), 4.41 (1 H, m), 4.48–4.58 (2 H, m), 4.77–4.88 (2 H, m), 5.10 (2 H, bs, $NH_2$), 5.83 (1 H, s, NH), 7.29–7.37 (5 H, m). FABMS (positive-ion) *m/z*: 381 $[M+H]^+$, 403 $[M+Na^+]$. HR-FABMS (positive-ion), Calcd for $C_{18}H_{25}N_2O_7$: 381.1662; Found: 381.1642.

*[5S-(5α,7α,8β,9β)]-7-(Benzyloxymethyl)-8,9-isopropylidenedioxy-6-oxa-1,3-diazaspiro[4.4]nonane-2,4-dione* (**10**).—(a) To a solution of **9** (48.0 mg, 0.13 mmol) in MeOH (5 mL) was added a solution of 2 M $NH_3$ in MeOH (0.5 mL) at 37 °C with stirring. After 4 h, the reaction mixture was concentrated in vacuo to

give a solid, which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc gave **10** (43.5 mg, 99%) as a solid; mp 164–166 °C (from EtOAc–hexane). $[\alpha]_D^{24}$ −85.8° (*c* 0.4, $CHCl_3$). IR $\nu_{max}$(KBr) 3410–2870, 1786, 1734 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.31 (3 H, s), 1.61 (3 H, s), 3.60 (1 H, dd, *J* 1.9, 10.5 Hz), 3.75 (1 H, dd, *J* 1.9, 10.5 Hz), 4.53, 4.63 (2 H, AB-q, *J* 11.4 Hz), 4.59 (1 H, m), 4.77 (1 H, d, *J* 5.7 Hz), 4.80 (1 H, d, *J* 5.7 Hz), 6.31 (1 H, bs, NH), 7.31–7.45 (5 H, m), 7.68 (1 H, bs, NH, exchanged on addition of $D_2O$). FABMS (positive-ion) *m*/*z*: 349 $[M+H]^+$, 403 $[M+Na^+]$. HRFABMS (positive-ion), Calcd for $C_{17}H_{21}N_2O_6$: 349.1400; Found: 349.1388. Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.73; H, 5.77; N, 8.05.

(b) To a solution of **14** (100 mg, 2.74 mmol) in MeCN (3 mL) was added a solution of 1 M aq $NaHCO_3$ (2 mL) and aq 30% $H_2O_2$ (0.3 mL). After stirring for 15 min at rt, the reaction mixture was diluted with EtOAc, which was washed with 10% aq $NaHSO_3$ and brine. The organic extract was dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo to give **10** (96 mg, quant), which was identical with that obtained from **9**.

*[5*R*-(5α,7β,8α,9α)]-7-(Benzyloxymethyl)-1,3-diaza-8,9-isopropylidenedioxy-6-oxaspiro[4.4]nonane-2,4-dione* (**10′**).—(a) Compound **10′** was also obtained quantitatively as a powder from **9′** using $NH_3$ according to the same procedure described in the above procedure (a) to obtain **10** from **9**. IR $\nu_{max}$($CHCl_3$) 3432, 1801, 1756, 1385, 1091 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.36 (3 H, s), 1.57 (3 H, s), 3.61–3.68 (2 H, m), 4.40 (1 H, m), 4.57, 4.60 (2 H, AB-q, *J* 12.0 Hz), 4.76–4.82 (2 H, m), 6.05 (1 H, bs, NH), 7.25–7.40 (5 H, m), 8.00 (1 H, bs, NH, exchanged on addition of $D_2O$). FABMS (positive-ion) *m*/*z*: 349 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{17}H_{21}N_2O_6$: 349.1400; Found: 349.1395.

(b) To a solution of **9** (60 mg, 0.518 mmol) or **10** (60 mg) in DMF (4 mL) and THF (24 mL) was added DBU (60 mg). The solution was stirred at rt for 7 days, diluted with EtOAc, and washed with 0.01 M aq HCl, water, and brine. The organic extract was dried over $MgSO_4$ and filtered, and the filtrate was evaporated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc gave an epimer **10′** [50 mg (91%) from **9**; or 52 mg (87%) from **10** accompanying the recovered starting **10** (7 mg, 12%)].

(c) Compound **10′** was also obtained quantitatively from **14′** according to the procedure described above to obtain **10** from **14**. This compound was identical with that obtained above from **9′**.

*[5*S*-(5α,7α,8β,9β)]-1,3-Diaza-7-(hydroxymethyl)-8,9-isopropylidenedioxy-6-oxaspiro[4.4]nonane-2,4-dione* (**11**).—(a) A solution of **10** (50 mg, 0.14 mmol) in EtOAc (10 mL) containing 10% Pd-on-charcoal (25 mg) was stirred under hydrogen at rt for 30 min. After filtration of the reaction mixture, the filtrate was concentrated in vacuo to give **11** (37 mg, quant) as a solid; mp 188–190 °C (from EtOAc). $[\alpha]_D^{23}$ −64.5° (*c* 0.07, MeOH). IR $\nu_{max}$(KBr) 3531, 3466, 3434, 3407, 3240, 2987, 2936, 1790, 1745, 1725 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 1.32 (3 H, s), 1.54 (3 H, s), 3.68 (1 H, dd, *J* 3.4, 11.9 Hz), 3.71 (1 H, dd, *J* 3.3, 11.9 Hz), 4.46 (1 H, m), 4.81–4.93 (2 H, m). FABMS (positive-ion) *m*/*z*: 517 $[2M+H]^+$, 259 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{10}H_{15}N_2O_6$: 259.0930. Found: 259.0922.

(b) Compound **20** was treated as described in the formation of **11** from **10** to give **11** (quant), which was identical with that obtained from **10**.

*[5*R*-(5α,7β,8α,9α)]-1,3-Diaza-8,9-isopropylidenedioxy-7-(hydroxymethyl)-6-oxaspiro[4.4]nonane-2,4-dione* (**11′**).—(a) Compound **11′** was also obtained quantitatively as a powder from **10′** according to the procedure described above in the formation of **11** from **10**. IR $\nu_{max}$(KBr) 3700–2940, 1790, 1737 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 1.32 (3 H, s), 1.54 (3 H, s), 3.68 (1 H, dd, *J* 3.4, 11.9 Hz), 3.71 (1 H, dd, *J* 3.3, 11.9 Hz), 4.46 (1 H, m), 4.81–4.93 (2 H, m). FABMS (positive-ion) *m*/*z*: 259 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{10}H_{15}N_2O_6$: 259.0930; Found: 259.0934.

(b) Compound **20′** was treated as described in the formation of **11** from **10** to give **11′** (quant), which was identical with that obtained from **10′**.

*[5*S*-(5α,7α,8β,9β)]-1,3-Diaza-8,9-dihydroxy-7-(hydroxymethyl)-6-oxaspiro[4.4]nonane-2,4-dione (***12***, hydantocidin).*—A solution of **11** (31 mg, 0.12 mmol) in 1:3 $CF_3COOH$–water (5 mL) was stirred at 0 °C for 2 h, and concentrated in vacuo to give **12** (26 mg, quant) as a solid, mp 190–192 °C (from MeOH–EtOAc). $[\alpha]_D^{23}$ +28.3° (*c* 0.44, water) [lit. +29.0° (*c* 0.62, water)].[3c] IR $\nu_{max}$(KBr) 3470–2770, 1780, 1740, 1710 $cm^{-1}$. $^1H$ NMR ($D_2O$, $Me_3SiCD_2CD_2COONa$ as an internal standard): $\delta$ 3.68 (1 H, dd, *J* 4.6, 12.7 Hz), 3.78 (1 H, dd, *J* 3.0, 12.7 Hz), 4.22 (1 H, dd, *J* 4.4, 5.8 Hz), 4.34 (1 H, m), 4.40 (1 H, d, *J* 5.8 Hz). FABMS (positive-ion) *m*/*z*: 219 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_7H_{11}N_2O_6$: 219.0617; Found: 219.0623. Anal. Calcd for $C_7H_{10}N_2O_6$: C, 38.53; H, 4.62; N, 12.84. Found: C, 38.50; H, 4.73; N, 12.85.

*[5*R*-(5α,7β,8α,9α)]-1,3-Diaza-8,9-dihydroxy-7-(hydroxymethyl)-6-oxaspiro[4.4]nonane-2,4-dione (***12′***, spiro-epi-hydantocidin).*—Compound **12′** was also obtained from **11′** as a powder according to the same procedure described above. $[\alpha]_D^{23}$ −9.8° (*c* 0.75, MeOH) [lit. −11.0° (*c* 0.3, MeOH)].[3j] IR $\nu_{max}$(KBr) 3470–2770, 1780, 1740, 1710 $cm^{-1}$. $^1H$ NMR ($CD_3OD$), $\delta$ 3.59 (1 H, dd, *J* 5.2, 12.2 Hz, C-6–*H*), 3.78 (1 H, dd, *J* 4.3, 12.2 Hz, C-6–*H*), 4.08 (1 H, ddd, *J* 3.4, 4.3, 5.2 Hz, C-5–*H*), 4.16 (1 H, dd, *J* 3.4, 5.0 Hz, C-4–*H*), 4.24 (1 H, d, *J* 5.0 Hz, C-3–*H*). FABMS (positive-ion) *m*/*z*: 219 $[M+H]^+$.

HRFABMS (positive-ion), Calcd for $C_7H_{11}N_2O_6$: 219.0617; Found: 219.0598. Anal. Calcd for $C_7H_{10}N_2O_6$: C, 38.54; H, 4.62; N, 12.84. Found: C, 38.33; H, 4.86; N, 12.70.

*Methyl 6-O-benzyl-3,4-O-isopropylidene-2-isothiocyanato-β-D-ribo-2-hexulofuranosonate* (**13**) *and Methyl 6-O-benzyl-3,4-O-isopropylidene-2-isothiocyanato-α-D-ribo-2-hexulofuranosonate* (**13′**).—To a solution of **4** (3.57 g, 10.00 mmol) in DMF (36 mL) was added KSCN (3.00 g, 30.87 mmol). After 5 h stirring at 80 °C, the reaction mixture was diluted with EtOAc, and washed with water and brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo (finally with a pump) to give a residue, which was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave a 4:1 mixture of **13** and **13′** (3.26 g, 84%). The mixture was partially separated on a TLC plate by development with 3:1 cyclohexane–EtOAc (**13**, $R_f$ 0.500; **13′**, $R_f$ 0.467) to measure the physical data. Physical data of **13**: $[\alpha]_D^{24}$ −118.8° (*c* 3.9, $CHCl_3$). IR $\nu_{max}$(film) 3090–2860, 2016, 1773, 1756 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (3 H, s), 1.44 (3 H, s), 3.60–3.68 (2 H, m), 3.89 (3 H, s), 4.55, 4.65 (2 H, AB-q, *J* 11.7 Hz), 4.64 (1 H, m), 4.89–4.92 (2 H, m), 7.30–7.37 (5 H, m). $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.0 ($CH_3$), 25.8 ($CH_3$), 53.4 ($OCH_3$), 69.6 ($CH_2$), 73.8 ($CH_2$), 82.1 (CH), 86.9 (CH), 89.2 (CH), 98.1 (anomeric C), 114.2 ($O_2CMe_2$), 127.8 (aromatic CH × 2), 127.9 (aromatic CH), 128.4 (aromatic CH × 2), 137.5 (aromatic C), 143.2 (–NCS), 165.0 (COOMe). FABMS (positive-ion) *m*/*z*: 402 $[M+Na]^+$, 380 $[M+H]^+$. Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69; S, 8.45. Found: C, 57.19; H, 5.57; N, 3.17; S, 8.17. Physical data of **13′**: $[\alpha]_D^{24}$ −36.3° (*c* 0.2, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ 1.39 (3 H, s), 1.69 (3 H, s), 3.63–3.70 (2 H, m), 3.79 (3 H, s), 4.50 (1 H, m), 4.51, 4.57 (2 H, AB-q, *J* 12.0 Hz), 4.78 (1 H, m), 5.03 (1 H, d, *J* 6.6 Hz), 7.30–7.42 (5 H, m). $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.3 ($CH_3$), 26.1 ($CH_3$), 53.6 ($OCH_3$), 69.5 ($CH_2$), 73.5 ($CH_2$), 81.1 (CH), 83.7 (CH), 84.3 (CH), 95.3 (anomeric C), 116.4 ($O_2CMe_2$), 127.6 (aromatic CH × 2), 128.4 (aromatic CH × 2), 137.5 (aromatic C), 144.4 (–NCS), 166.2 (COOMe). FABMS (positive-ion) *m*/*z*: 402 $[M+Na]^+$, 380 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{18}H_{22}NO_6S$: 380.1168; Found: 380.1169.

*[5S-(5α,7α,8β,9β)]-7-(Benzyloxymethyl)-1,3-diaza-8,9-isopropylidenedioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one* (**14**) *and [5R-(5α,7β,8α,9α)]-7-(benzyloxymethyl)-1,3-diaza-8,9-isopropylidenedioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one* (**14′**).—To a solution of a 4:1 mixture of **13** and **13′** (600 mg, 1.58 mmol) in MeOH (6.0 mL) was added a solution of 2 M $NH_3$ in MeOH (2.0 mL) at 24 °C with stirring. After 2 h the reaction mixture was concentrated in vacuo to give a solid, which was chromatographed on a silica gel column. Elution with 3:1 cyclohexane–EtOAc gave **14′** (113 mg, 19.6%; $R_f$ 0.449 (2:1 cyclohexane–EtOAc)) and **14** (466 mg, 80.5%; $R_f$ 0.359 (2:1 cyclohexane–EtOAc)). Physical data of **14**: $[\alpha]_D^{24}$ −169.7° (*c* 3.7, $CHCl_3$). IR $\nu_{max}$(KBr) 3400–2860, 1781, 1498 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (3 H, s), 1.61 (3 H, s), 3.62 (1 H, dd, *J* 1.5, 10.3 Hz), 3.78 (1 H, dd, *J* 1.5, 10.3 Hz), 4.56, 4.64 (2 H, AB-q, *J* 11.4 Hz), 4.61 (1 H, t, *J* 1.5 Hz), 4.78 (1 H, d, *J* 5.9 Hz), 4.81 (1 H, d, *J* 5.9 Hz), 7.38–7.47 (5 H, m), 7.78 (1 H, s, NH, exchanged on addition of $D_2O$), 8.16 (1 H, s, NH, exchanged on addition of $D_2O$). FABMS (positive-ion) *m*/*z*: 365 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{17}H_{21}N_2O_5S$: 365.1171; Found: 365.1167. Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 55.57; H, 5.67; N, 7.44; S, 8.56. Physical data of **14′**: $[\alpha]_D^{24}$ −61.5° (*c* 1.3, $CHCl_3$). IR $\nu_{max}$(KBr) 3450–2850, 1755, 1505 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.36 (3 H, s), 1.59 (3 H, s), 3.62 (1 H, dd, *J* 6.2, 10.4 Hz), 3.67 (1 H, dd, *J* 6.2, 10.4 Hz), 4.43 (1 H, t, *J* 6.2 Hz), 4.59 (2 H, s), 4.81 (2 H, s), 7.26 (1 H, bs, NH, exchanged on addition of $D_2O$), 7.28–7.36 (5 H, m), 8.39 (1 H, bs, NH, exchanged on addition of $D_2O$). FABMS (positive-ion) *m*/*z*: 365 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{17}H_{21}N_2O_5S$: 365.1171; Found: 365.1183. Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.43; H, 5.46; N, 7.44; S, 8.50.

*2,3-O-Isopropylidene-5-O-(4-methoxybenzyl)-D-ribono-1,4-lactone* (**15**).—Compound **15** (10.37 g, 77%) was also obtained as an oil from **1** (8.2 g, 43.57 mmol), 4-methoxybenzyl chloride (8.20 g, 52.36 mmol) and NaH (60–70% oil dispersion, 2.09 g) in DMF (30 mL) according to the same procedure described in the formation of **2** from **1**. IR $\nu_{max}$(film) 3030–2840, 1785, 1614, 1587, 1515 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.36 (3 H, s), 1.47 (3 H, s), 3.64 (1 H, dd, *J* ~1.0, 10.3 Hz), 3.68 (1 H, dd, *J* 1.8, 10.3 Hz), 3.81 (3 H, s), 4.40, 4.48 (2 H, AB-q, *J* 11.7 Hz), 4.63 (1 H, dd, *J* 1.0, 1.8 Hz), 4.68 (1 H, d, *J* 5.5 Hz), 4.76 (1 H, d, *J* 5.5 Hz), 6.88 (2 H, d, *J* 8.4 Hz), 7.18 (2 H, d, *J* 8.4 Hz). FABMS (positive-ion) *m*/*z*: 308 $[M^+]$, 309 $[M+H]^+$, 331 $[M+Na]^+$ HRFABMS (positive-ion), Calcd for $C_{16}H_{20}O_6$: 308.1260; Found: 308.1263. Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 61.98; H, 6.75.

*2,5-Anhydro-1,1-dichloro-1-deoxy-3,4-O-isopropylidene-6-O-(4-methoxybenzyl)-D-ribo-hex-1-enitol* (**16**).—Compound **15** (4.77 g) was treated as described in the formation of **3** from **2** to give **16** (5.54 g, 95%) as a solid, mp 62–65 °C (thread-like needles from EtOAc–hexane). $[\alpha]_D^{24}$ −147.3° (*c* 1.1, $CHCl_3$). IR $\nu_{max}$(KBr) 3040–2830, 1733, 1664, 1610, 1585, 1513 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 3 H, s), 1.48 (3 H, s), 3.59 (1 H, dd, *J* 2.9, 11.0 Hz), 3.63 (1 H, dd, *J* 2.9, 11.0 Hz), 3.82 (3 H, s), 4.42, 4.45 (2 H, AB-q, *J* 11.7 Hz), 4.64 (1 H, t, *J* 2.9 Hz), 4.77 (1 H, d, *J* 5.9 Hz), 5.23 (1 H, d, *J* 5.9 Hz), 6.88–6.90 (2 H, m), 7.18–7.21 (2 H,

m). FABMS (positive-ion) $m/z$: 374 [$M^+$]. HRFABMS (positive-ion), Calcd for $C_{17}H_{20}{}^{35}Cl_2O_5$: 374.0688; Found: 374.0691. Anal. Calcd for $C_{17}H_{20}Cl_2O_5$: C, 54.41; H, 5.37; Cl, 18.90. Found: C, 54.30; H, 5.38; Cl, 18.66.

*Methyl 2,5-anhydro-2-chloro-3,4-*O*-isopropylidene-6-*O*-(4-methoxybenzyl)-α-*D*-ribo-2-hexulofuranosonate* (**17**) *and methyl 2,5-anhydro-2-chloro-3,4-*O*-isopropylidene-6-*O*-(4-methoxybenzyl)-β-*D*-ribo-2-hexulofuranosonate* (**17′**).—Compound **16** (3.752 g) was treated as described in the formation of **4** from **3** to give **17′** (507 mg, 13%) and **17** (2.07 g, 54%). Physical data of **17′**: IR $\nu_{max}$(film) 3000–2830, 1766, 1613, 1587, 1514 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.33 (3 H, s), 1.43 (3 H, s), 3.71 (2 H, d, $J$ 7.2 Hz),), 3.81 (3 H, s), 3.89 (3 H, s), 4.50, 4.53 (2 H, AB-q, $J$ 11.0 Hz), 4.63 (1 H, dt, $J$ 1.6, 7.2 Hz), 4.92 (1 H, dd, $J$ 1.8, 5.6 Hz, C-4–*H*), 5.13 (1 H, d, $J$ 5.6 Hz), 6.88 (2 H, d, $J$ 8.8 Hz), 7.27 (2 H, d, $J$ 8.8 Hz). FABMS (positive-ion) 386 [$^{35}Cl$, $M^+$]. HRFABMS (positive-ion), Calcd for $C_{18}H_{23}{}^{35}ClO_7$: 386.1123; Found: 386.1125. Physical data of **17**: IR $\nu_{max}$(film) 2990–2860, 1762, 1751, 1613, 1587, 1514 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.39 (3 H, s), 1.70 (3 H, s), 3.63–3.70 (2 H, m), 3.81 (3 H, s), 3.83 (3 H, s), 4.45, 4.51 (2 H, AB-q, $J$ 11.7 Hz), 4.57 (1 H, dd, $J$ 2.9, 5.8 Hz), 4.78 (1 H, dd, $J$ 2.9, 6.8 Hz, C-4–*H*), 5.00 (1 H, d, $J$ 7.8 Hz), 6.88 (2 H, d, $J$ 8.8 Hz), 7.22 (2 H, d, $J$ 8.8 Hz). FABMS (positive-ion) $m/z$: 386 [$^{35}Cl$, $M^+$], 387 $[M+H]^+$, 425 $[M+K]^+$ (on addition of KI). HRFABMS (positive-ion), Calcd for $C_{18}H_{23}{}^{35}ClO_7$ K: 425.0770; Found: 425.0779.

*Methyl 2,5-anhydro-3,4-*O*-isopropylidene-2-isothiocyanato-6-*O*-(4-methoxybenzyl)-α-*D*-ribo-2-hexulofuranosonate* (**18**) *and methyl 2,5-anhydro-3,4-*O*-isopropylidene-2-isothiocyanato-6-*O*-(4-methoxybenzyl)-β-*D*-ribo-2-hexulofuranosonate* (**18′**).—Compound **17** (193 mg) was treated as described in the formation of **13** and **13′** from **4** to give a chromatographically inseparable 5:1 mixture of **18** and **18′** (149 mg, 73%). IR $\nu_{max}$(film) 3000–2830, 2017, 1772, 1756, 1613, 1587, 1514 $cm^{-1}$. Anal. Calcd for $C_{19}H_{23}NO_7S$ (409.4): C, 55.73; H, 5.66; N, 3.42; S, 7.83. Found: C, 55.29; H, 5.78; N, 3.24; S, 7.70. $^1H$ NMR ($CDCl_3$) of **18**: $\delta$ 1.29 (3 H, s), 1.43 (3 H, s), 3.57–3.63 (2 H, m), 3.82 (3 H, s), 3.88 (3 H, s), 4.49, 4.57 (2 H, AB-q, $J$ 11.7 Hz), 4.63 (1 H, dt, $J$ 1.0, 4.8 Hz), 4.87 (1 H, dd, $J$ 1.0, 5.7 Hz), 4.89 (1 H, d, $J$ 5.7 Hz), 6.89 (2 H, d, $J$ 8.7 Hz), 7.28 (2 H, d, $J$ 8.7 Hz). $^1H$ NMR ($CDCl_3$) of **18′**: $\delta$ 1.38 (3 H, s), 1.68 (3 H, s), 3.57–3.63 (2 H, m), 3.81 (3 H, s), 3.82 (3 H, s), 4.43, 4.50 (2 H, AB-q, $J$ 11.7 Hz), 4.48 (1 H, m), 4.75 (1 H, dd, $J$ 2.5, 6.6 Hz), 5.02 (1 H, d, $J$ 6.6 Hz), 6.88 (2 H, d, $J$ 8.7 Hz), 7.21 (2 H, d, $J$ 8.7 Hz).

*[5S-(5α,7α,8β,9β)]-8,9-Isopropylidenedioxy-7-[4-(methoxbenzyloxy)methyl]-6-oxa-2-thioxo-1,3-diazaspiro[4.4]nonan-4-one* (**19**) *and [5R-(5α,7β,8α,9α)]-8,9-isopropylidenedioxy-7-[4-(methoxbenzyloxy)methyl]-6-oxa-2-thioxo-1,3-diazaspiro[4.4]nonan-4-one* (**19′**).—A 5:1 mixture of **18** and **18′** (130 mg, 0.317 mmol) was treated as described in the formation of **14** and **14′** from a mixture of **13** and **13′** to give **19′** (20 mg, 16%, $R_f$ 0.474 in 3:2 cyclohexane–EtOAc) and **19** (105 mg, 84%, $R_f$ 0.382 in 3:2 cyclohexane–EtOAc). Physical data of **19′**: $[\alpha]_D^{24}$ −58.1° ($c$ 0.32, $CHCl_3$). IR $\nu_{max}$(film) 3226, 2993–2838, 1768, 1613, 1587, 1513, 1465 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.36 (3 H, s), 1.59 (3 H, s), 3.58–3.65 (2 H, m), 3.80 (3 H, s), 4.41 (1 H, m), 4.52 (2 H, s), 4.77–4.82 (2 H, m), 6.88 (2 H, d, $J$ 8.8 Hz), 7.28 (2 H, d, $J$ 8.8 Hz), 7.40 (1 H, bs, NH), 8.79 (1 H, broad, NH). FABMS (positive-ion) $m/z$: 395 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{18}H_{23}N_2O_6S$: 395.1276. Found: 395.1274. Physical data of **19**: $[\alpha]_D^{24}$ −154.4° ($c$ 1.3, $CHCl_3$). IR $\nu_{max}$(film) 3392, 3225, 2986–2838, 1781, 1613, 1586, 1513, 1500 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (3 H, s), 1.61 (3 H, s), 3.60 (1 H, dd $J$ 1.8, 10.6 Hz), 3.75 (1 H, dd $J$ 1.8, 10.6 Hz), 3.84 (3 H, s), 4.50, 4.56 (2 H, AB-q, $J$ 11.0 Hz), 4.61 (1 H, m), 4.76 (1 H, d, $J$ 5.5 Hz), 4.80 (1 H, d, $J$ 5.5 Hz), 6.96 (2 H, d, $J$ 8.8 Hz), 7.31 (2 H, d, $J$ 8.8 Hz), 7.80 (1 H, s, NH), 8.53 (1 H, broad, NH). FABMS (positive-ion) $m/z$: 395 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{18}H_{23}N_2O_6S$: 395.1276; Found: 395.1279. Anal. Calcd for $C_{18}H_{22}N_2O_6S$: C, 54.81; H, 5.62; N, 7.10; S, 8.13. Found: C, 54.54; H, 5.61; N, 7.01; S, 8.06.

*[5S-(5α,7α,8β,9β)]-8,9-Isopropylidenedioxy-7-[(4-methoxybenzyl)oxymethyl]-6-oxa-1,3-diazaspiro[4.4]-nonane-2,4-dione* (**20**).—Compound **19** was treated as described in the formation of **10** from **14** to give **20** (96% after chromatographic purification) as a solid, mp 180–181 °C (from EtOAc). IR $\nu_{max}$(KBr) 3500–2830, 1793, 1740, 1612 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (3 H, s), 1.61 (3 H, s), 3.57 (1 H, dd, $J$ 1.8, 10.6 Hz), 3.71 (1 H, dd, $J$ 1.8, 10.6 Hz), 3.83 (3 H, s), 4.47, 4.54 (2 H, AB-q, $J$ 11.0 Hz), 4.57 (1 H, m), 4.75 (1 H, d, $J$ 5.9 Hz), 4.77 (1 H, d, $J$ 5.9 Hz), 6.36 (1 H, s, NH), 6.94 (2 H, d, $J$ 8.8 Hz), 7.26 (2 H, d, $J$ 8.8 Hz), 7.86 (1 H, bs, NH). FABMS (positive-ion) $m/z$: 379 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{18}H_{23}N_2O_7$: 379.1506; Found: 379.1508.

*[5R-(5α,7β,8α,9α)]-8,9-Isopropylidenedioxy-7-[(4-methoxybenzyl)oxymethyl]-6-oxa-1,3-diazaspiro[4.4]-nonane-2,4-dione* (**20′**).—Compound **19′** was treated as described in the formation of **10** from **14** to give **20′** (95% after chromatographic purification) as an amorphous solid. IR $\nu_{max}$(film) 3259 (broad), 1793, 1740, 1613 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.35 (3 H, s), 1.56 (3 H, s), 3.60 (1 H, dd, $J$ 6.5, 10.3 Hz), 3.62 (1 H, dd, $J$ 6.4, 10.3 Hz), 3.80 (3 H, s), 4.37 (1 H, dt, $J$ 1.4, 6.5 Hz), 4.49, 4.52 (2 H, AB-q, $J$ 11.7 Hz), 4.77 (2 H, singlet-like), 6.38 (1 H, s, NH), 6.88 (2 H, d, $J$ 8.8 Hz), 7.27 (2 H, d, $J$ 8.8 Hz), 8.85 (1 H, bs, NH). FABMS (positive-ion) $m/z$: 378 [$M^+$]. HRFABMS (positive-ion), Calcd for $C_{18}H_{22}N_2O_7$: 378.1427. Found: 378.1424.

*Methyl 6-O-acetyl-2,5-anhydro-2-chloro-3,4-O-isopropylidene-α-D-ribo-2-hexulofuranosonate* (**21**).—A solution of **4** (350 mg, 0.981 mmol) in AcOEt (25 mL) was hydrogenolyzed at rt for 20 min using 10% Pd-on-charcoal (50 mg) as a catalyst. The catalyst was filtered, and to this filtrate was added $Ac_2O$ (2 mL) and pyridine (1 mL). This solution was stirred for 15 h at rt and concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with 1:1 cyclohexane–EtOAc gave **21** (273 mg, 90%) as a solid, mp 105–107 °C (from EtOAc–hexane). IR $\nu_{max}$(film) 3000–2950, 1743 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.41 (3 H, s), 1.71 (3 H, s), 2.10 (3 H, s), 3.89 (3 H, s), 4.29 (1 H, dd, *J* 4.9, 12.2 Hz), 4.38 (1 H, dd, *J* 3.9, 12.2 Hz), 4.64 (1 H, dd, *J* 3.9, 7.8 Hz), 4.71 (1 H, dd, *J* 3.9, 6.8 Hz), 5.03 (1 H, d, *J* 7.8 Hz). Anal. Calcd for $C_{12}H_{17}ClO_7$: C, 46.69; H, 5.55; Cl, 11.48. Found: C, 46.78; H, 5.53; Cl, 11.39.

*Methyl 6-O-acetyl-2,5-anhydro-3,4-O-isopropylidene-2-isothiocyanato-β-D-ribo-2-hexulofuranosonate* (**22**) *and methyl 6-O-acetyl-2,5-anhydro-3,4-O-isopropylidene-2-isothiocyanato-α-D-ribo-2-hexulofuranosonate* (**22′**).—To a solution of **21** in DMF (2 mL) was added KSCN (94 mg, 0.967 mmol). After 15 h stirring at 80 °C, the reaction mixture was diluted with EtOAc and washed with water and brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo (finally with a pump) to give a residue, which was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave **22** (73 mg, 68%, $R_f$ 0.547) and **22′** (14 mg, 13%, $R_f$ 0.453). Physical data of **22**: IR $\nu_{max}$(film) 2990–2950, 2011, 1773, 1749 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.33 (3 H, s), 1.46 (3 H, s), 2.14 (3 H, s), 3.91 (3 H, s), 4.20 (1 H, dd, *J* 5.9, 12.1 Hz), 4.31 (1 H, dd, *J* 5.9, 12.1 Hz), 4.68 (1 H, ddd, *J* 1.5, 5.1, 5.9 Hz), 4.86 (1 H, dd, *J* 1.5, 5.9 Hz), 4.94 (1 H, d, *J* 5.1 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.8 ($CH_3$), 25.1 ($CH_3$), 25.9 ($CH_3$), 53.6 ($OCH_3$), 63.4 ($CH_2$), 81.9 (CH), 85.8 (CH), 89.0 (CH), 97.7 (anomeric C), 114.7 ($O_2CMe_2$), 144.5 (–NCS), 164.7 (COOMe), 170.4 (MeCOO). FABMS (positive-ion) *m*/*z*: 332 $[M+H]^+$, 354 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{17}NO_7S$: C, 47.12; H, 5.17; N, 4.23; S, 9.68. Found: C, 47.27; H, 5.15; N, 4.21; S, 9.33. Physical data of **22′**: IR $\nu_{max}$(film) 2990–2950, 2022, 1750 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 1.40 (3 H, s), 1.70 (3 H, s), 2.12 (3 H, s), 3.89 (3 H, s), 4.18 (1 H, dd, *J* 4.8, 12.1 Hz), 4.37 (1 H, dd, *J* 3.7, 12.1 Hz), 4.54 (1 H, m), 4.71 (1 H, dd, *J* 2.8, 6.9 Hz), 5.02 (1 H, d, *J* 7.3 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.8 ($CH_3$), 25.4 ($CH_3$), 26.1 ($CH_3$), 53.9 ($OCH_3$), 63.2 ($CH_2$), 80.9 (CH), 82.5 (CH), 84.3 (CH), 94.9 (anomeric C), 117.3 ($O_2CMe_2$), 145.0 (–NCS), 166.0 (COOMe), 170.4 (MeCOO). FABMS (positive-ion) *m*/*z*: 332 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{13}H_{18}NO_7S$: 332.0804; Found: 332.0797.

*[5S-(5α,7α,8β,9β)]-1,3-Diaza-7-hydroxymethyl-8,9-isopropylidenedioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one* (**23**).—(a) To a solution of **22** (18 mg, 0.054 mmol) in MeOH (1 mL) was added a solution of 2 M $NH_3$ in MeOH (0.5 mL). The solution was stirred for 6 h at rt, and concentrated in vacuo to give thioxohydantoine **23** quantitatively as a solid, mp 158–161 °C (from $CHCl_3$). $[\alpha]_D^{24}$ −174.9° (*c* 0.3, MeOH). IR $\nu_{max}$(KBr) 3500–3000, 1763, 1509 $cm^{-1}$. $^1H$ NMR ($CDCl_3 + D_2O$): $\delta$ 1.34 (3 H, s), 1.64 (3 H, s), 3.87 (1 H, dd, *J* 1.8, 11.4 Hz), 3.93 (1 H, dd, *J* 1.8, 11.4 Hz), 4.63 (1 H, s), 4.92 (1 H, d, *J* 5.9 Hz), 4.95 (1 H, d, *J* 5.9 Hz). FABMS (positive-ion) *m*/*z*: 275 $[M+H]^+$. HRFABMS (positive-ion), Calcd for $C_{10}H_{15}N_2O_5S$: 275.0702; Found: 275.0705. Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.79; H, 5.14; N, 10.21; S, 11.69. Found: C, 43.67; H, 5.01; N, 10.23; S, 11.87.

(b) To a solution of **19** (64 mg, 0.160 mmol) and PhSH (45 mg, 0.408 mmol) in $CH_2Cl_2$ (4 mL) was added $SnCl_4$ (1 M solution in $CH_2Cl_2$, 0.40 mL) at −78 °C under nitrogen. After stirring for 30 min at −78 °C, the reaction mixture was diluted with EtOAc, and the solution was washed with satd aq $NaHCO_3$ and brine. The organic extract was dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with 2:1 cyclohexane–EtOAc gave the starting **19** (4 mg, 6% recovery) and **23** (36 mg, 81%), which was identical with that obtained from **22**.

*[5R-(5α,7β,8α,9α)]-1,3-Diaza-7-hydroxymethyl-8,9-isopropylidenedioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one* (**23′**).—(a) Compound **23′** was also obtained in 72% yield as a powder from **22′** according to the procedure described above to obtain **23** from **22**. $[\alpha]_D^{24}$ −43.6° (*c* 0.3, MeOH). IR $\nu_{max}$(KBr) 4215, 3420, 3000–2870, 1760 $cm^{-1}$. $^1H$ NMR ($CDCl_3 + D_2O$): $\delta$ 1.39 (3 H, s), 1.62 (3 H, s), 3.71 (1 H, dd, *J* 2.9, 13.2 Hz, on addition of $D_2O$), 3.87 (1 H, dd, *J* 2.2, 13.2 Hz), 4.08 (1 H, bs, OH), 4.51 (1 H, m), 4.92 (1 H, d, *J* 5.9 Hz), 5.04 (1 H, dd, *J* 1.5, 5.9 Hz), 7.31 (1 H, bs, HH), 9.23 (1 H, bs, NH). FABMS (positive-ion) *m*/*z*: 275 $[M+H]^+$. HR-FABMS (positive-ion), Calcd for $C_{10}H_{15}N_2O_5S$: 275.0702; Found: 275.0707. Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.79; H, 5.14; N, 10.21; S, 11.69. Found: C, 43.46; H, 4.91; N, 10.49; S, 12.17.

(b) Compound **19′** was treated as described in the formation of **23** from **19** to give starting **19′** (13% recovery) and **23′** (76%), which was identical with that obtained from **22′**.

*[5S-(5α,7α,8β,9β)]-1,3-Diaza-7-hydroxymethyl-8,9-dioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one (***24***, C-2-thioxo-hydantocidin) and its spiro-epimer* (**24′**).—A solution of **23** (18 mg, 0.066 mmol) in 1:3 $CF_3COOH$–water (0.4 mL) was stirred at 0 °C for 2 h, then −5 °C for 16 h. The solution was concentrated in vacuo to give a mixture, which was chromatographed on a preparative silica gel plate. Development with 9:1 EtOAc–MeOH gave two bands of products. The products from each

band were eluted with 9:1 EtOAc–MeOH, and the eluants were diluted with EtOAc. Each diluted solution was washed with brine. The organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo to give **24** (9.4 mg, 61%, $R_f$ 0.400) as a powder, and also **24′** (2.4 mg, 16%, $R_f$ 0.433, identical with that obtained from **23′**), respectively. Physical data of **24**: $[\alpha]_D^{24}$ −41.0° (*c* 0.4, MeOH) (lit.[3k] $[\alpha]_D^{24}$ −52.7° (*c* 0.8, MeOH)). IR $\nu_{max}$(KBr) 3329 (broad), 1760, 1676, 1516 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 3.62 (1 H, dd, *J* 4.1, 12.1 Hz), 3.65 (1 H, dd, *J* 3.8, 12.1 Hz), 4.07 (1 H, dd, *J* 2.6, 5.9 Hz), 4.25 (1 H, m), 4.30 (1 H, dd, *J* 1.4, 5.9 Hz). FABMS (positive-ion) *m*/*z*: 235 $[M+H]^+$. Anal. Calcd for $C_7H_{10}N_2O_5S{\cdot}1.2\ H_2O$: C, 32.86; H, 4.89; N, 10.95; S, 12.58. Found: C, 33.11; H, 5.01; N, 10.61; S, 12.23.

*[5R-(5α,7β,8α,9α)]-1,3-Diaza-7-hydroxymethyl-8,9-dioxy-6-oxa-2-thioxo-spiro[4.4]nonan-4-one* (**24′**).—A solution of **23′** (25 mg, 0.09 mmol) in 1:3 $CF_3COOH$–water (2.5 mL) was stirred at 20 °C for 2 h. The solution was concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with EtOAc gave **24′** (20 mg, 94%) as a powder. $[\alpha]_D^{24}$ +35.0° (*c* 0.4, MeOH) (lit.[3k] $[\alpha]_D^{24}$ +36.8° (*c* 0.9, MeOH)). IR $\nu_{max}$(KBr) 3334 (broad), 2930, 1763, 1630 (w), 1510 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 3.60 (1 H, dd, *J* 5.1, 12.4 Hz), 3.66 (1 H, dd, *J* 4.0, 12.4 Hz), 4.13 (1 H, m), 4.18 (1 H, dd, *J* 3.7, 4.4 Hz), 4.28 (1 H, d, *J* 4.4 Hz). FABMS (positive-ion) *m*/*z*: 235 $[M+H]^+$. HR-FABMS (positive-ion), Calcd for $C_7H_{11}N_2O_5S$: 235.0389; Found: 235.0381.

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