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Synthesis of (±)-Carbocyclic Analogue of Spirohydantoin Nucleoside

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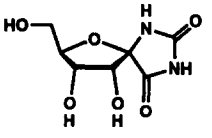
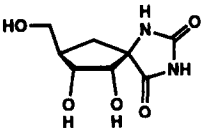
Abstract: Synthesis of (±)-carbocyclic spirohydantoin derivatives of (+)-hydantocidin is described. The pivotal step in the synthesis is spirohydantoin ring construction from cyclopentanone **9**. Using the Bucherer-Bergs condition predominately gave the epi-carbocyclic analogue **10**, whereas the alternative spiroring formation method through α-aminonitrile **13** provided the carbocyclic analogue **2** after deprotection.

Recently, carbocyclic nucleosides, in which the furanose ring oxygen atom is replaced by a carbon atom, have become considerable targets in the search for antiviral, antitumor, and especially anti-human-immunodeficiency-virus agents, due to the discovery of several carbocyclic derivatives with potent antiviral activity.[1] This replacement could enhance the metabolic stability toward phosphorylases, which cleave the *N*-glycosidic bond between heterocycle moiety and sugar of nucleosides.[2]

The first naturally occurring spironucleoside (+)-hydantocidin[3] has received wide attention[4,5,6] because of its unique features: spirohydantoin ring at the anomeric position of D-ribofuranose and its potent herbicidal activites aganst troublesome perennial weeds. As part of our continuing interest in the structure-activity relationship of (+)-hydantocidin,[7,8] we set out to make a carbocyclic analogue of (+)-hydantocidin, in an effort to explore the role of ether oxygen in the furanose ring. Although the metabolism of (+)-hydantocidin itself has not been clarified, the carbocyclic analogue would be chemically more stable than the parent compound: (+)-hydantocidin possessing *N,O*-hemiacetal functionality at the anomeric position could be easily isomerized to its 5-epimer; moreover, 5-*epi*-hydantocidin is thermodynamically more stable than the natural compound.[5,6]



1
(+)-hydantocidin



2
(±) carbocyclic analogue

Figure 1

Previous synthetic studies[7,8] from our laboratories have demonstrated that modifications of the

natural compound only led to a loss of herbicidal activity, except for the formation of spirosuccinimide analogue[7f]: All diastereoisomers and deoxy derivatives of the natural compound exhibited no herbicidal activity; only the 5-epimer showed a slight activity. A hydantoin ring expanded analogue, the spirodihydrouracil derivative, was also found to be inactive.[7e]

Our synthetic analysis is shown in **Figure 2**. We envisaged that spirohydantoin ring formation of the protected cyclopentanone **4** derived from 2,5-norbornadiene **3** would provide access to the desired compound **2**, after deprotection. The key to our plan is stereochemistry at the anomeric position during the spirohydantoin ring formation.

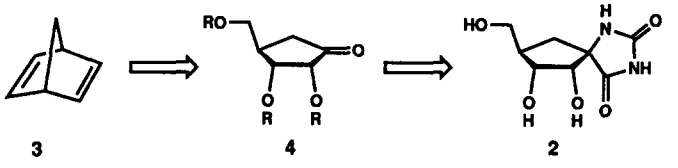
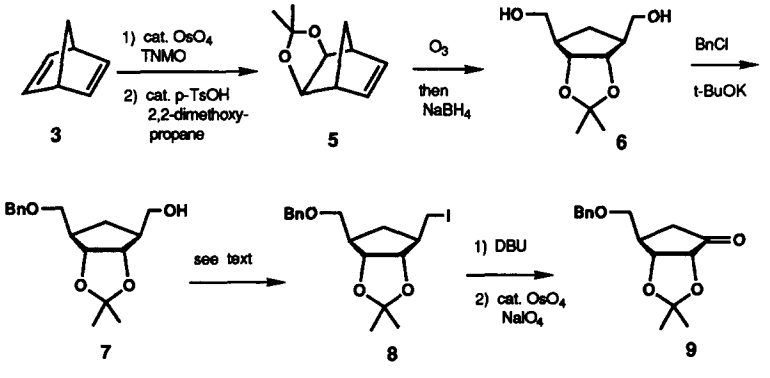


Figure 2

Preparation of the intermediate cyclopentanone **9** is represented in **Scheme 1**. Ozonolysis of **5**, prepared from 2,5-norbornadiene,[9] followed by reductive workup with sodium borohydride, gave diol **6** in 99% yield, which was treated with benzyl chloride and *t*-BuOK in DMSO to afford benzyl ether **7** in 55% yield. Iodide **8** was obtained through two methods: Direct conversion of the hydroxymethyl group in **7** was accomplished with methyltriphenoxyphosphonium iodide in DMF, affording **8** in 58% yield. However, isolation of **8** was tedious due to the resulting phosphonium salts. Alternatively, mesylation of **7** followed by treatment with sodium iodide in acetone provided **8** in 78% yield. The latter method was suitable for a large scale preparation. Elimination of hydrogen iodide from **8** was achieved by treatment with DBU in refluxing toluene to give an exoolefin, which was oxidized with sodium periodate in the presence of a catalytic amount of osmium tetroxide, to produce **9** in 61% yield from **8**.

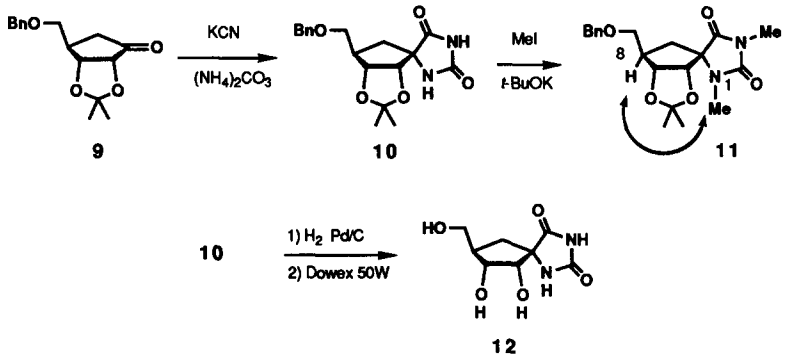
Scheme 1



Under Bucherer-Bergs condition, construction of a spirohydantoin ring from **9** was accomplished

(**Scheme 2**). Treatment of **9** with potassium cyanide and ammonium carbonate in MeOH-H_2O at 70 °C furnished spirohydantoin **10** in 91% yield as a single product possessing an undesired configuration at C5. Stereochemistry of **10** at its spiro center was assigned by a series of ^{1}H-NOE experiments of the dimethylated hydantoin **11**, which was derived from **10**: methylation of **10** with methyl iodide and *t*-BuOK in DMF afforded **11** in 48% yield. The NOE was observed between the N1 methyl protons and the C8 methine proton in **11**. Removal of the protecting groups was accomplished by hydrogenation with 5% Pd-C under a hydrogen atmosphere followed by hydrolysis of the dimethylmethylene moiety with Dowex 50W^R (H^+ form) in MeOH-H_2O to afford 5-epi-carbocyclic analogue **12** in 84% yield from **10**. Although the spiroring formation using the Bucherer-Bergs method was efficient, the undesirable stereochemistry at the spiro center led us to consider an alternative spirohydantoin ring formation method.

Scheme 2



Reversal stereoselectivity has been described[10] for spirohydantoin ring formation and α–amino acids synthesis after hydrolysis from some substituted cyclanones and bicyclo ketones. Edward[11] gave a coherent explanation that the Read reaction, hydantoin ring synthesis through an α-aminonitrile intermediate followed by cyclization, gives kinetically controlled products, whereas thermodynamically controlled spiro products are obtained under Bucherer-Bergs conditions. With this explanation in mind, we selected the Read reaction as an alternative ring construction method.

Table 1 summarized the results of intermediate α-aminonitrile synthesis. Exposure of **9** to potassium cyanide and ammonium chloride in MeOH-H_2O at room temperature for 7 d, provided only a trace of α-aminonitrile **14** (9% yield), whose configuration at C1 was opposite to the desired compound, and cyanohydrin **15**[12] (72% yield) as a major product (entry 1). An elevated reaction temperature in EtOH-H_2O at 65 °C gave the desired α-aminonitrile **13** in a low yield (12% yield) together with **14** and **15** (entry 2). Heating at 90 °C for a prolonged time (24 hr) furnished **13** in 40% yield (entry 4). The product ratio was dependent upon the reaction temperature and the reaction time: a higher reaction temperature and a longer heating time afforded more of the desired intermediate **13** (entry 2, 3, and 4). In contrast, irradiation of a mixture of **9**, potassium cyanide, ammonium chloride, and alumina in acetonitrile with ultrasound[13] at 60

°C afforded undesired **14** in 63% yield and **15** in 35% yield, but none of **13** (entry 5).

Scheme 3

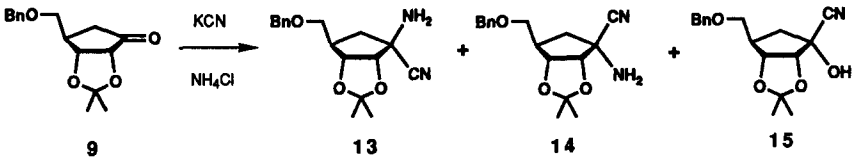


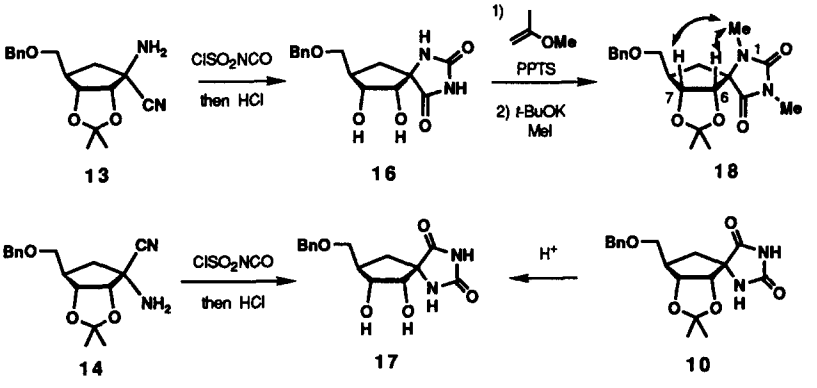
Table 1 The Results of α-Aminonitrile Synthesis from 9

entry	conditions	yields(%)[a] 13	14	15
1	r.t. 7 d	0	9	72
2	65 °C 9 h	12	42	30
3	90 °C 9 h	35	31	23
4	90 °C 24 h	40	15	22
5	60 °C 20 h[b]	0	63	35

a) isolated yields; b) irradiation with ultrasound

With **13** in hand, our attention was turned to the spiroring formation. Conversion of **13** to a hydantoin derivative proceeded smoothly with chlorosulfonyl isocyanide[14] in CH_2Cl_2, followed by hydrolysis to afford spirohydantoin **16** in 67% yield, whereas **14** afforded spiro-epimer **17** in 40% yield. Determination of

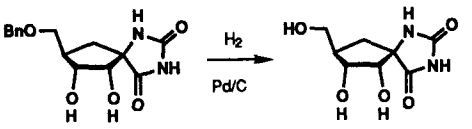
Scheme 4



the stereochemistry of **16** by NOE was performed on the dimethylated compound **18**: treatment of **16** with 2-methoxypropene in the presence of PPTS, followed by methylation with methyl iodide and *t*-BuOK, gave **18** in 66% yield. Irradiation of the signal for C1 methyl hydrogens enhanced the signals for C6 and C7 methine hydrogens of **18**, indicating that **16** possesses desired stereochemistry at the spiro center. 5-Epi-spirohydantoin **17** was identified by comparison to the authentic sample from **10** (**Scheme 4**).

Debenzylation of **16** with 5% Pd-C under H_2 atmosphere furnished the desired carbocyclic analogue **2** in 96% yield (**Scheme 5**).

Scheme 5



16 **2**

The results of bioassay indicated that the carbocyclic compound **2** retained herbicidal activities in spite of its racemic form. The carbocyclic analogue **2** exhibited 90% herbicidal control of barnyard grass, 70% control of crabgrass, and 70% control of velvetleaf when applied to a foliage of the weeds at 1000 ppm, whereas the 5-epi-carbocyclic analogue **12** was inactive against these weeds at the same concentration.[15] This finding shows that replacement of the oxygen atom in D-ribofuranose ring of (+)-hydantocidin with a methylene unit is acceptable for maintaining herbicidal activity. Thus, we have succeeded in preparing a hydantoin analogue with herbicidal activity that is chemically stable and that does not undergo isomerization.

In summary, we have described synthesis of a carbocyclic analogue of (+)-hydantocidin and its epimer at the spiro center, involving two spirohydantoin ring formation methods: 1) the Bucherer-Bergs method exclusively afforded the 5-epi isomer, and 2) α-aminonitrile intermediate **13**, derived from cyclopentanone **9**, was smoothly converted to the desired carbocyclic spirohydantoin. The results of bioassay indicated that the D-furanose ring oxygen atom can be replaced with a methylene unit for herbicidal activity. Synthesis of an optically active carbocyclic analogue of (+)-hydantocidin is in progress.

Acknowledgments

We wish to thank Mr. T. Honma and Mr. M. Shindou, Agroscience Research Laboratories, Sankyo Co. Ltd., for testing the herbicidal activity of derivatives **2** and **12**. And the authors thank Mr. H. Kajino, Agroscience Research Laboratories, Sankyo Co. Ltd., for ^{1}H-NOE experiments of compounds **11**, **18**, and **19**.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. 1H-NMR spectra (270MHz) were recorded on a JEOL GX-270 spectrometer. IR spectra were recorded on a Jasco A-102 spectrometer. Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Merck Kieselgel 60 was used for SiO_2 column chromatography. Merck TLC plate Art.5744 was used for preparative TLC.

(*exo, exo*)-5,6-Dimethylmethylenedioxy-bicyclo[2.2.1]hept-2-ene 5.

A solution of 2,5-norbornadiene **3** (169 g, 1.83 mol) in THF (300 ml) was added to a mixture of trimethylamine *N*-oxide dihydrate (203 g, 1.83 mol) and osmium tetraoxide (1 g, 3.9 mmol) in *t*-BuOH (500 ml), THF (500 ml), and H_2O (250 ml). After being stirred for 2 d, the reaction mixture was quenched with aqueous $Na_2S_2O_4$ solution, and filtered through a pad of Celite^R. The filtrate was concentrated and extracted with EtOAc. The combined organic layers were dried, evaporated, and chromatographed on silica gel (hexane/EtOAc 2:1 to 1:3) to give **(*exo, exo*)-bicyclo[2.2.1]hept-5-ene-2,3-diol** (69 g, 30%) as a colorless solid.

m.p. 100-104 °C; IR ($CHCl_3$) 3380, 2980, 2940, 1390, 1160, 1050 cm^{-1}; NMR ($CDCl_3$) δ 6.04 (2H, t, J = 1.8 Hz), 3.71 (2H, t, J = 1.8 Hz), 3.11-3.06 (2H, m), 2.70 (2H, td, J = 1.8, 1.8 Hz), 1.89 (1H, d, J = 9.3 Hz), 1.63 (1H, td, J = 9.3, 1.8 Hz); MS *m/z* 126 (M^+), 107, 95, 79, 77.

A solution of the above diol (48.5 g, 0.38 mol) and 2,2-dimethoxypropane (52 g, 0.5 mol) in acetone (200 ml) was stirred in the presence of p-TsOH•H_2O (0.5 g) at room temperature for 15 h. The reaction solution was poured into H_2O and extracted with EtOAc. The organic phases were washed with brine, dried, and concentrated. Purification of the residue with silica gel chromatography (hexane/EtOAc 20:1) gave 58 g of acetonide **5** (92%) as a colorless oil.

For **5**: IR ($CHCl_3$) 2980, 2930, 1450, 1380, 1270, 1210, 1060 cm^{-1}; NMR ($CDCl_3$) δ 6.07-6.06 (2H, M), 4.20 (2H, d, J = 1.5 Hz), 2.78 (2H, t, J = 1.5 Hz), 1.98 (1H, d, J = 9.1 Hz), 1.69 (1H, dd, J = 9.1, 1.5 Hz), 1.48 (3H, s), 1.34 (3H, s); MS *m/z* 167 (M^++1), 149, 113, 97, 71.

t-4,t-5-Dimethylmethylenedioxy-r-1,c-3-cyclopentanedimethanol 6.

Ozone was bubbled through a solution of acetonide **5** (22.5 g, 135 mmol) in MeOH (400 ml) at -70 °C for 7 h, and the reaction mixture was allowed to warm up to 0 °C. Sodium borohydride (30.7 g, 0.81 mol) was added in many portions with vigorously stirring, and the resulting mixture was heated at 50 °C for 3 h, then stood at room temperature overnight. After removal of the solvent, brine was added to the residue, and the product mixture was extracted with EtOAc. The combined extracts were dried and evaporated in vacuo. The residue was purified with chromatography on silica gel (hexane/EtOAc 1:2 to EtOAc only) to afford diol **6** (27.1 g, 99%) as a colorless oil.

For **6**: IR ($CHCl_3$) 3430, 3000, 2940, 2880, 1705, 1370, 1230 cm^{-1}; NMR ($CDCl_3$) δ 4.42 (2H, ABqd, J = 6.1, 0.8 Hz), 3.68 (4H, dd, J = 10.4, 6.0 Hz), 2.34-2.22 (2H, m), 2.07 (1H, td, J = 12.9, 7.2 Hz), 1.82 (2H, brd.), 1.51 (3H, s), 1.32 (3H, s), 1.26 (1H, d, J = 12.9 Hz); MS *m/z* 187 (M^+-15), 145, 127, 109, 79; Anal. found: C, 59.18; H, 8.90. Calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97%.

(1*SR*,2*SR*,3*RS*,4*RS*)-4-Benzyloxymethyl-2,3-dimethylmethylenedioxy-cyclopentanemethanol 7.

To a solution of diol **6** (27.1 g, 134 mmol) in DMSO (350 ml) was added t-BuOK (15.8 g, 141 mmol), and the mixture was maintained at room temperature for 2 h. Benzyl chloride (16.2 ml, 141 mmol) was added to the black mixture, and it was stirred for 1.5 h. Ice water was added, and the product mixture was extracted with EtOAc. The combined layers were washed with brine, dried, concentrated, and purified with silica gel chromatography (hexane/EtOAc 5:1 to 1:2) to give monobenxyl ether **7** (21.5 g, 55%) as a colorless oil.

For **7**: IR ($CHCl_3$) 3450, 3000, 2940, 2860, 1370, 1090 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (5H, brd.), 4.53 (2H, s), 4.39 (2H, ABqd, J = 7.0, 4.0 Hz), 3.68 (1H, dd, J = 10.8, 5.6 Hz), 3.61 (1H, dd, J = 10.8, 6.8 Hz), 3.48 (2H, ABqd, J = 5.2, 2.0 Hz), 2.36 (1H, m), 2.25 (1H, m), 2.10 (1H, ddd, J = 12.9, 7.3, 5.6 Hz), 1.66 (1H, brd.), 1.50 (3H, s), 1.31 (3H, s); MS *m/z* 291 (M^+-1), 277, 237, 203, 107, 91; Anal. found: C, 69.59; H, 8.22. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

(1*RS*,2*SR*,3*RS*,4*RS*)-4-Benzyloxymethyl-2,3-dimethylmethylenedioxy-1-iodomethylcyclopentane 8.

Method A:

Triphenyl phosphite (31.6 g, 102 mmol) and methyl iodide (9.3 ml, 150 mmol) were heated under N_2 atmosphere at 70 °C for 1 h and then at 130 °C for 15 h. After the mixture was allowed to cool to room temperature, a solution of monobenzyl ether **6** (8.5 g, 29 mmol) in DMF (40 ml) was added, and followed by stirring for 2 h. The reaction mixture was partitioned between H_2O and EtOAc, and the combined organic extracts were washed with brine and H_2O prior to drying and evaporation. The residue was purified by silica gel chromatography (hexane/EtOAc 20:1) to give iodide **8** (6.72 g, 58%) as a slightly red oil.

method B:

Methanesulfonyl chloride (6.63 ml, 85.7 mmol) was added at -20 °C to a solution of monobenzyl ether **6**

(20.9 g, 71.4 mmol) and triethylamine (11.9 ml, 85.7 mmol) in CH_2Cl_2 (250 ml). After being stirred for 30 min, the mixture was poured into H_2O, and extracted with CH_2Cl_2. The organic layers were dried, evaporated, and chromatographed on silica gel (hexane/EtOAc 3:1) to give **(1'*SR*,2'*SR*,3'*RS*,4'*RS*)-4'-benzyloxymethyl-2',3'-dimethylmethylenedioxy-cyclopentylmethyl methanesulfonate** (25.6 g, 97%) as a colorless oil.

IR (neat) 3500, 2940, 2870, 1710, 1450, 1350, 1170 cm^{-1}; NMR ($CDCl_3$) δ 7.42-7.28 (5H, m), 4.52 (2H, ABq, *J* = 12.5 Hz), 4.41 (1H, dd, *J* = 6.9, 4.4 Hz), 4.34 (1H, dd, *J* = 6.9, 5.2 Hz), 4.24 (2H, ABqd, *J* = 14.1, 6.4 Hz), 3.48 (2H, d, *J* = 5.6 Hz), 2.98 (3H, s), 2.48-2.31 (2H, m), 2.17 (1H, td, *J* = 13.3, 7.2 Hz), 1.49 (3H, s), 1.41 (1H, td, *J* = 13.3, 10.2 Hz), 1.30 (3H, s); MS *m/z* 370 (M^+), 355, 264, 203, 169, 110, 91, 79; HRMS. found: 370.1447. Calcd. for $C_{18}H_{26}O_6S$: 370.1450.

A mixture of the above mesylate (25.6 g, 69.2 mmol) and sodium iodide (183.1 g, 1.2 mol) in acetone (150 ml) was stirred at room temperature for 17 h. The reaction mixture was quenched by the addition of aq. Na_2SO_3 solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Silica gel chromatography (hexane/EtOAc 7:1) of the residue afforded iodide **8** (22.4 g, 80%) as a slightly red oil:

For **8**: IR ($CHCl_3$) 3000, 2920, 2850, 1375, 1065 cm^{-1}; NMR ($CDCl_3$) δ ; 7.39-7.28 (5H, m), 4.53 (2H, ABq, *J* = 12.5 Hz), 4.43 (1H, dd, *J* = 6.8, 4.8 Hz), 4.20 (1H, dd, *J* = 6.8, 5.4 Hz), 3.47 (2H, d, *J* = 6.0 Hz), 3.36 (1H, dd, *J* = 10.0, 5.2 Hz), 3.20 (1H, dd, *J* = 10.0, 7.0 Hz), 2.41-2.31 (1H, m), 2.26-2.16 (2H, m), 1.50 (3H, s), 1.37-1.28 (1H, m), 1.31 (3H, s); MS *m/z* 402 (M^+), 387, 238, 217, 92; Anal. found: C, 50.56; H, 5.72; I, 31.84. Calcd. for $C_{17}H_{23}IO_3$: C, 50.76; H, 5.76; I, 31.55%.

(2*RS*,3*RS*,4*RS*)-4-Benzyloxymethyl-2,3-dimethylmethylenedioxy-cyclopentanone 9.

A solution of iodide **8** (22.39 g, 55.6 mmol) and DBU (9.89 ml, 66.8 mmol) in toluene (150 ml) was heated at 100 °C under N_2 atmosphere for 14 h. The reaction mixture was poured into H_2O, and extracted with Et_2O. The organic layers were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography on silica gel (hexane/EtOAc 8:1) to give 10.4 g of **(1*SR*,2*RS*,3*RS*)-3-benzyloxymethyl-1,2-dimethylmethylenedioxy-5-methylenecyclopentane** (68%) as a colorless oil.

IR($CHCl_3$) 3000, 2950, 2865, 1375, 1105 cm^{-1}; NMR ($CDCl_3$) δ 7.34-7.27 (5H, m), 5.19 (1H, d, *J* = 1.4 Hz), 5.09 (1H, dd, *J* = 2.4, 1.4 Hz), 4.69 (1H, d, *J* = 5.8 Hz), 4.50 (1H, d, *J* = 5.8 Hz), 4.49 (2H, s), 3.26 (2H, d, *J* = 7.6 Hz), 2.83-2.72 (1H, m), 2.44 (1H, dd, *J* = 7.6, 7.2 Hz), 2.11 (1H, d, *J* = 15.7 Hz), 1.47 (3H, s), 1.32 (3H, s); MS *m/z* 275 (M^++1), 259, 217, 91; Anal. found: C, 74.11; H, 8.00. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08%.

Sodium periodate (20.3 g, 94.7 mmol) was added in many portions to a cooled (0 °C) solution of the above exo-methylene compound (10.4 g, 37.9 mmol) and osmium tetraoxide (0.30 g, 1 mmol) in THF (200 ml) and H_2O (200 ml). The black mixture was stirred at room temperature for 36 h, and it was poured into H_2O. The product mixture was extracted with EtOAc, and the organic phases were washed with brine prior to drying and evaporation. Silica gel chromatography (hexane/EtOAc 5:1) of the residue gave ketone **9** (9.41 g, 90%) as a colorless oil.

For **9**: IR ($CHCl_3$) 3000, 2940, 2860, 1755, 1380, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.37-7.20 (5H, m), 4.66 (1H, d, *J* = 5.6 Hz), 4.46 (2H, ABq, *J* = 12.5 Hz), 4.28 (1H, d, *J* = 5.6 Hz), 3.64 (1H, dd, *J* = 9.1, 2.8 Hz), 3.43 (1H, dd, *J* = 9.1, 3.2 Hz), 2.75 (1H, dd, *J* = 18.1, 9.3 Hz), 2.59-2.55 (1H, m), 2.14 (1H, dd, *J* = 18.1, 1.2 Hz), 1.43 (3H, s), 1.33 (3H, s); MS *m/z* 276 (M^+), 261, 185, 127, 91; HRMS. found: 276.1354. Calcd. for $C_{16}H_{20}O_4$: 276.1361.

(5*SR*,6*SR*,7*RS*,8*RS*)-8-Benzyloxymethyl-6,7-dimethoxymethylenedioxy-1,3-diazaspiro[4.4]nonane-2,4-dione 10.

Potassium cyanide (0.52 g, 8.0 mmol) was added to a solution of ketone **9** (1.11 g, 4.0 mmol) in MeOH (20

ml), and stirred at room temperature for 15 min. Ammonium carbonate (3.84 g, 40 mmol) and H_2O (20 ml) were added to the mixture. The resulting mixture was heated at 70 °C for 4.5 h, and the solvent was removed in vacuo. H_2O was added, and the mixture was carefully acidified with 6N HCl, and extracted with EtOAc. (Caution: HCN can be evolved!) The organic layers were washed with brine, and dried. After removal of solvents, the residue was purified by silica gel chromatography (hexane/EtOAc 2:1 to 1:1) to give 5-*epi*-spirohydantoin **10** (1.26 g, 91%) as a colorless solid.

For **10**: m.p. 89-90 °C; IR ($CHCl_3$) 3450, 3205, 3000, 2950, 2870, 1780, 1730, 1380, 1230, 1090 cm^{-1}; NMR ($CDCl_3$) δ 7.90 (1H, brd.), 7.38-7.27 (5H, m), 5.69 (1H, brd.), 4.64 (1H, d, J = 6.0 Hz), 4.56 (1H, dd, J = 6.0, 3.0 Hz), 4.54 (2H, s), 3.55 (2H, d, J = 6.4 Hz), 2.50-2.39 (1H, m), 2.24-2.07 (2H, m), 1.54 (3H, s), 1.32 (3H, s); MS *m/z* 346 (M^+), 331, 255, 240, 197, 91; Anal. found: C, 62.15; H, 6.40; N, 7.87. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09%.

(5*SR*,6*SR*,7*RS*,8*RS*)-8-Benzyloxymethyl-1,3-dimethyl-6,7-dimethylmethylenedioxy-1,3-diazaspiro[4.4]nonane-2,4-dione 11.

To a solution of spirohydantoin **10** (50 mg, 0.14 mmol) in THF was added t-BuOK (40 mg, 0.36 mmol), and the mixture was stirred at room temperature for 30 min. Methyl iodide (0.087 ml, 1.4 mmol) was added, and the resulting mixture was stirred for 1.5 h. Brine was added, and the product mixture was extracted with EtOAc. The organic layers were dried and evaporated. The residue was purified with chromatography on silica gel (hexane/EtOAc 2:1) to give dimethyl product **11** (25 mg, 48%) as a colorless oil.

For **11**: IR ($CHCl_3$) 3000, 2950, 2870, 1770, 1710, 1470, 1380, 1240, 1090 cm^{-1}; NMR ($CDCl_3$) δ 7.38–7.28 (5H, m), 4.62-4.57 (2H, m), 4.55 (2H, s), 3.64 (1H, dd, J = 8.9, 7.2 Hz), 3.52 (1H, dd, J = 8.9, 7.0 Hz), 3.11 (3H, s), 3.10 (3H, s), 2.67-2.61 (1H, m), 2.33 (1H, dd, J = 14.5, 9.0 Hz), 2.00 (1H, dd, J = 14.5, 8.9 Hz), 1.54 (3H, s), 1.30 (3H, s); MS *m/z* 374 (M^+), 359, 283, 266, 225, 208, 195, 140, 91; HRMS. found: 374.1851. Calcd. for $C_{20}H_{26}N_2O_5$: 374.1842.

(5*SR*,6*SR*,7*RS*,8*RS*)-7,6-Dihydroxy-8-hydroxymethyl-1,3-diazaspiro[4.4]nonane-2,4-dione 12.

A solution of spirohydantoin **10** (0.27 g, 0.77 mmol) in MeOH (120 ml) was heated at 55 °C in the presence of 5% Pd/C (0.50 g) under H_2 atmosphere (3 Kg/cm^2) for 5 h. The reaction mixture was filtered through a pad of Celite^R and concentrated in vacuo to give **(5*SR*,6*SR*,7*RS*,8*RS*)-6,7-dimethylmethylenedioxy-8-hydroxymethyl-1,3-diazaspiro[4.4]nonane-2,4-dione** (0.20 g, quantitative yield).

NMR (CD_3OD) δ 4.57 (2H, ABq, J = 6.4 Hz), 3.65 (2H, d, J = 6.4 Hz), 2.47-2.34 (1H, m), 2.05 (2H, d, J = 9.3 Hz), 1.53 (3H, s), 1.31 (3H, s).

A mixture of the above alcohol (0.20 g, 0.77 mmol) and Dowex^R 50W X2 (H^+ form) (0.50 g) in MeOH (4 ml) and H_2O (4 ml) was stirred at room temperature for 4 h, and filtered through a pad of Celite^R. The filtrate was concentrated and subjected to chromatography on Dianion CHP 20P (H_2O only) to give 5-*epi*-spirohydantoin **12** (0.14 g, 84%) as a colorless solid.

For **12**: m.p. 167-168 °C; IR (KBr) 3380, 3290, 3040, 1760, 1700, 1410, 1330, 1120, 1010 cm^{-1}; NMR (CD_3OD) δ 4.02-3.96 (2H, m), 3.55 (2H, ABqd, J = 10.9, 6.4 Hz), 2.31-2.20 (1H, m), 2.08 (1H, dd, J = 14.1, 9.3 Hz), 1.92 (1H, dd, J = 14.1, 7.3 Hz); MS *m/z* 217 (M^++1), 198, 152, 113, 86; Anal. found: C, 44.20; H, 5.53; N, 12.76. Calcd. for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.59; N, 12.96%.

Synthesis of α-aminonitrile from cyclopentanone 9

At room temperature

A mixture of cyclopentanone **9** (0.19 g, 0.71 mmol), potassium cyanide (0.13 g, 2.1 mmol), and ammonium chloride (0.11 g, 2.1 mmol) in MeOH (3 ml) and H_2O (3 ml) was stirred at room temperature for 7 d. The reaction mixture was partitioned between H_2O and EtOAc, and the organic layers were dried and evaporated.

Purification of the residue with silica gel chromatography (hexane/EtOAc 5:2) gave **(1*RS*,2*SR*,3*RS*,4*RS*)-1-amino-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-cyclopentanecarbonitrile 14** (19 mg, 9%) and **(1*RS*,2*RS*,3*RS*,4*RS*)-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-hydroxy-1-cyclopentane-carbonitrile 15** (0.15 g, 72%) as colorless oils.

Irradiation with ultrasound

A mixture of potassium cyanide (0.13 g, 2.0 mmol), ammonium chloride (0.12 g, 2.2 mmol), and neutral alumina (0.36 g) in MeCN (7 ml) was irradiated with ultrasound at 60 °C. After 10 min, a solution of cyclopentanone **9** (0.28 g, 1.0 mmol) in MeCN (3 ml) was added, followed by irradiation for 20 h. After filtration through a pad of Celite^R, the filtrate was concentrated in vacuo followed by purification by chromatography on silica gel (hexane/EtOAc 4:1 to 2:1) to give **14** (0.19 g, 63%) and **15** (0.11 g, 35%) as colorless oils.

Heating at 90 °C

A mixture of cyclopentanone **9** (1.05 g, 3.8 mmol), potassium cyanide (1.73 g, 26.6 mmol), and ammonium chloride (1.42 g, 26.6 mmol) in MeOH (15 ml) and H_2O (15 ml) was heated at 90 °C for 9 h. The black mixture was poured into H_2O and extracted with EtOAc. The organic phases were washed with brine, dried, and evaporated. The residue was purified by silica gel chromatography (hexane/EtOAc 6:1 to 2:1) to afford **(1*SR*,2*SR*,3*RS*,4*RS*)-1-amino-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-cyclopentane-carbonitrile 13** (0.46 g, 40%), **14** (0.17 g, 15%), and **15** (0.25 g, 22%) as colorless oils.

For **13**: IR ($CHCl_3$) 3550, 3420, 3350, 3020, 2960, 2890, 2250, 1730, 1455, 1380, 1240, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.40-7.27 (5H, m), 4.63 (1H, d, *J* = 5.6 Hz), 4.51 (2H, ABq, *J* = 12.1 Hz), 4.29 (1H, d, *J* = 5.6 Hz), 3.61 (1H, dd, *J* = 9.3, 7.3 Hz), 3.52 (1H, dd, *J* = 9.3, 6.2 Hz), 2.63-2.49 (2H, m), 1.91-1.82 (1H, m), 1.74 (2H, brd.), 1.55 (3H, s), 1.31 (3H, S); MS *m/z* 302 (M^+), 287, 276, 211, 196, 153, 123, 92; HRMS. found: 302.1632. Calcd. for $C_{17}H_{22}N_2O_3$: 302.1631.

For **14**: IR ($CHCl_3$) 3500, 3400, 3320, 3000, 2940, 2860, 2220, 1600, 1450, 1370, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.38-7.27 (5H, m), 4.66 (1H, d, *J* = 7.0 Hz), 4.59 (1H, dd, *J* = 7.0, 3.6 Hz), 4.53 (2H, s), 3.55 (1H, dd, *J* = 9.3, 5.6 Hz), 3.49 (1H, dd, *J* = 9.3, 5.6 Hz), 2.70-2.57 (1H, m), 2.17 (2H, d, *J* = 8.4 Hz), 1.77 (2H, brd.), 1.53 (3H, s), 1.34 (3H, s); MS *m/z* 302 (M^+), 287, 275, 260, 174, 154, 96, 91; HRMS. found: 302.1636. Calcd. for $C_{17}H_{22}N_2O_3$: 302.1631.

For **15**: IR ($CHCl_3$) 3300, 3000, 2940, 2860, 2250, 1450, 1370 cm^{-1}; NMR ($CDCl_3$) δ 7.42-7.27 (5H, m), 5.24 (1H, s), 4.63 (1H, d, *J* = 5.2 Hz), 4.57 (2H, s), 4.45 (1H, dd, *J* = 5.2, 1.6 Hz), 3.65 (1H, dd, *J* = 9.3, 3.6 Hz), 3.50 (1H, dd, *J* = 9.3, 3.2 Hz), 2.78 (1H, dd, *J* = 14.5, 9.7 Hz), 2.52-2.46 (1H, m), 2.02 (1H, dd, *J* = 14.5, 1.2 Hz), 1.50 (3H, s), 1.31 (3H, s), ; MS *m/z* 303 (M^+), 288, 235, 185, 154, 127, 92; HRMS. found: 303.1465. Calcd. for $C_{17}H_{21}NO_4$: 303.1471.

(5*RS*,6*SR*,7*RS*,8*RS*)-8-Benzyloxymethyl-6,7-dihydroxy-1,3-diazaspiro[4.4]nonane-2,4-dione 16.

Chlorosulfonyl isocyanide (0.082 ml, 0.95 mmol) was added at room temperature under N_2 atmosphere to a solution of aminonitrile **13** (0.26 g, 0.86 mmol) in CH_2Cl_2(10 ml). The reaction mixture was stirred for 20 min, and concentrated. 1N HCl (4 ml) was added to the residue, and the resulting mixture was stirred at room temperature for 20 min, and further stirred at 100 °C for 1 h. The reaction mixture was poured into H_2O, and extracted with EtOAc. The organic layers were washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (hexane/EtOAc 1:5 to EtOAc only) to give spirohydantoin **16** (0.17 g, 67%) as a colorless solid.

For **16**: m.p. 136 °C; IR (KBr) 3250, 2930, 2870, 1775, 1720, 1405, 1050 cm^{-1}; NMR (CD_3OD) δ 7.36-7.23 (5H, m), 4.53 (2H, s), 3.97 (1H, d, *J* = 6.0 Hz), 3.89 (1H, dd, *J* = 6.0, 3.6 Hz), 3.52 (2H, ABqd, *J* = 9.3, 5.2 Hz), 2.55-2.42 (1H, m), 2.30 (1H, dd, *J* = 13.7, 9.7 Hz), 1.68 (1H, dd, *J* = 13.7, 8.5 Hz); MS *m/z* 306 (M^+), 288, 215, 197, 137, 108; HRMS. found 306.1222. Calcd. for $C_{15}H_{18}N_2O_5$: 306.1216.

(5*SR*,6*SR*,7*RS*,8*RS*)-8-Benzyloxymethyl-6,7-dihydroxy-1,3-diazaspiro[4.4]nonane-2,4-dione 17.
From **14**: 5-*Epi* spirohydantoin **17** (72 mg) was obtained from aminonitrile **14** (0.18 g, 0.59 mmol) and chlorosulfonyl isocyanate (0.057ml, 0.65mmol) in 40% yield as a colorless solid under the same procedure used for **13**.
From **10**: A mixture of 5-*epi* spirohydantoin **10** (0.10 g, 0.29 mmol) and Dowex^R 50W (H^+ form) (0.50 g) in MeOH (3 ml) and H_2O (3 ml) was stirred at room temperature for 14 h. After filtration through a pad of Celite^R, the filtrate was concentrated, and subjected to chromatography on silica gel (hexane/EtOAc 1:5) to give 5-*epi*-spirohydantoin **17** (88 mg, 99%) as a colorless solid.
For **17**: m.p. 139-140 °C; IR (KBr) 3360, 3220, 2940, 2855, 1775, 1740, 1400, 1330, 1275 cm^{-1}; NMR (CD_3OD) δ 7.37-7.24 (5H, m), 4.52 (2H, ABq, J = 12.4 Hz), 4.04 (1H, d, J = 4.8 Hz), 3.99 (1H, dd, J = 4.8, 3.2 Hz), 3.49 (2H, d, J = 6.0 Hz), 2.43-2.31 (1H, m), 2.09 (1H, dd, J = 14.2, 9.4 Hz), 1.98 (1H, dd, J = 14.2, 7.8 Hz); MS *m/z* 306 (M^+), 288, 215, 197, 149, 91; HRMS. found 306.1221. Calcd. for $C_{15}H_{18}N_2O_5$: 306.1216.

(5*RS*,6*SR*,7*RS*,8*RS*)-6,7-Dihydroxy-8-hydroxymethyl-1,3-diazaspiro[4.4]nonane-2,4-dione 2.
A mixture of spirohydantoin **16** (0.12 g, 0.41 mmol) and 5% Pd/C (0.10 g) in MeOH (125 ml) was heated at 55 °C under H_2 atmosphere (3 Kg/cm^2) for 6 h. Filtration through a pad of Celite^R followed by concentration and purification with chromatography on Dianion CHP 20P (H_2O only) afforded carbocyclic analogue **2** (84 mg, 96%) as a colorless solid.
For **2**: m.p. 158-160 °C; IR (KBr) 3300, 2930, 1770, 1730, 1410, 1270, 1030 cm^{-1}; NMR (CD_3OD) δ 3.96 (1H, d, J = 6.0 Hz), 3.87 (1H, dd, J = 6.0, 3.2 Hz), 3.58 (2H, ABqd, J = 10.8, 5.2 Hz), 2.44-2.34 (1H, m), 2.29 (1H, dd, J = 12.9, 9.2 Hz), 1.62 (1H, dd, J = 12.9, 7.6 Hz); MS *m/z* 217 (M^++1), 198, 180, 152, 128, 114, 104, 100, 96; Anal. found: C, 44.15; H, 5.50; N, 12.70. Calcd. for $C_8H_{12}N_2O_5$: C, 44.44; H, 5.59; N, 12.96%.

(5*RS*,6*SR*,7*RS*,8*RS*)-8-Benzyloxymethyl-1,3-dimethyl-6,7-dimethylmethylenedioxy-1,3-diaza-spiro[4.4]nonane-2,4-dione 18.
A solution of spirohydantoin **16** (0.19 g, 0.63 mmol) and 2-methoxypropene (0.18 ml, 1.9 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature in the presence of p-TsOH•Py (20 mg) for 1 h. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 prior to drying and evaporation. Chromatography on silica gel of the residue (hexane/EtOAc 3:2) afforded **(5*RS*,6*SR*,7*RS*,8*RS*)-8-benzyloxymethyl-6,7-dimethylmethylenedioxy-1,3-diazaspiro[4.4]nonane-2,4-dione** (0.20 g, 94%) as a colorless syrup.
IR ($CHCl_3$) 3440, 3200, 3000, 2950, 2870, 1780, 1730, 1380, 1240, 1060 cm^{-1}; NMR ($CDCl_3$) δ 7.58 (1H, brd.), 7.44-7.30 (5H, m), 6.49 (1H, brd.), 4.62 (1H, d, J = 5.4 Hz), 4.56 (1H, ABq, J = 11.4 Hz), 4.54 (1H, d, J = 5.4 Hz), 3.66 (1H, dd, J = 9.5, 3.0 Hz), 3.54 (1H, dd, J = 9.5, 3.0 Hz), 2.88 (1H, dd, J = 14.1, 9.4 Hz), 2.56-2.53 (1H, m), 1.74 (1H, dd, J = 14.1, 1.0 Hz), 1.54 (3H, s), 1.27 (3H, s); MS *m/z* 346 (M^+), 331, 238, 197, 149, 91; HRMS. found: 346.1535. Calcd. for $C_{18}H_{22}N_2O_5$: 346.1528.
A solution of the above spirohydantoin (32 mg, 0.092 mmol) and *t*-BuOK (83 mg, 0.74 mmol) in THF (3 ml) was stirred at room temperature for 30 min, and methyl iodide (0.07 ml, 1.1 mmol) was added. The resulting mixture was stirred at room temperature for 24 h, before dilution with water and extraction with EtOAc. The organic layers were washed with brine, dried, and purified with silica gel chromatography (hexane/EtOAc 3:1) to afford dimethylspirohydantoin **18** (24 mg, 70%) as a colorless oil.
For **18**: IR ($CHCl_3$) 3670, 3470, 3000, 2920, 2860, 1765, 1710, 1460, 1380, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.39-7.29 (5H, m), 4.68 (1H, d, J = 8.1 Hz), 4.63 (1H, dd, J = 8.1, 5.2 Hz), 4.55 (2H, ABq, J = 12.1 Hz), 3.61 (1H, dd, J = 9.5, 4.8 Hz), 3.52 (1H, dd, J = 9.5, 4.4 Hz), 3.18-3.05 (1H, m), 3.00 (3H, s), 2.91 (3H, s),

2.12 (1H, t, J = 13.3 Hz), 1.95 (1H, dd, J = 13.3, 7.3 Hz), 1.49 (3H, s), 1.28 (3H, s); MS m/z 374(M^+), 359, 266, 225, 208, 195, 140, 91; HRMS. found 374.1848. Calcd. for $C_{20}H_{26}N_2O_5$: 374.1842.

(5*SR*,6*RS*,7*RS*,8*RS*)-8-Benzyloxymethyl-6,7-dimethylmethylenedioxy-1-oxa-3-azaspiro[4.4]nonan-2-one 19.

A solution of cyanohydrin **15** (0.13 g, 0.43 mmol) in Et_2O (3 ml) was added at 0 °C to a suspension of lithium aluminum hydride (35 mg, 0.86 mmol) in Et_2O (5 ml), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with 4N NaOH and extracted with EtOAc. The combined organic layers were washed with brine, dried, and concentrated. The residue was diluted with CH_2Cl_2 (10 ml), and stirred with triethylamine (0.85 ml, 6.1 mmol) and phosgene (1.3 M in toluene, 5.3 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was poured into H_2O, and extracted with CH_2Cl_2. The organic layers were washed, dried, evaporated, and purified with silica gel chromatography (hexane/EtOAc 3:1 to 1:1) to afford spirooxazolidone **19** (60 mg) in 44% yield from **15** as a colorless oil.

For **19**: IR ($CHCl_3$) 3460, 3260, 2980, 2930, 1750, 1370, 1260, 1070 cm^{-1}; NMR ($CDCl_3$) δ 7.35-7.28 (5H, m), 5.28 (1H, brd.) 4.67 (1H, d, J = 5.6 Hz), 4.53 (2H, s), 4.48 (1H, dd, J = 5.6, 1.4 Hz), 3.90 (1H, d, J = 9.1 Hz), 3.55 (1H, dd, J = 9.3, 9.3 Hz), 3.45 (1H, dd, J = 9.3, 7.2 Hz), 3.36 (1H, d, J = 9.1 Hz), 2.51-2.42 (1H, m), 2.15 (1H, dd, J = 14.3, 8.1 Hz), 2.01 (1H, d, J = 14.3 Hz), 1.42 (3H, s), 1.30 (3H, s); MS m/z 333 (M^+), 318, 214, 201, 149, 91; HRMS. found: 333.1569. Calcd. for $C_{18}H_{23}NO_5$: 333.1576.

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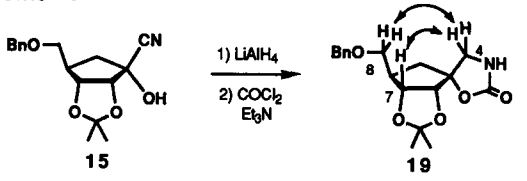
Scheme 6



15 19

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15. (+)-Hydantocidin exhibited complete control of all species under the same condition.

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