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Synthesis of an Optically Active Carbocyclic Derivative of (+)-Hydantocidin

Hiromi Sano * and Soji Sugai

Agroscience Research Laboratories, Sankyo Co. Ltd., 1041 Yasu-cho, Yasu-gun, Shiga-ken 520-23, Japan

Abstract: Synthesis of an optically active carbocyclic analogue of (+)-hydantocidin is reported. The spirohydantoin ring formation of cyclopentanone **9**, derived from D-gulono-1,4-lactone **3** in 6 steps, was accomplished through α -aminonitrile **10**, followed by treatment with chlorosulfonyl isocyanate, to give spirohydantoin **13**, which was deprotected with 10% Pd/C, to afford an optically active carbocyclic analogue (+)-**2**.

During the course of our investigation on the structure-herbicidal-activity relationships of the first naturally occurring spironucleoside, (+)-hydantocidin,¹ which possesses a spirohydantoin at the anomeric center of D-ribofuranose and unique potent herbicidal activities against troublesome perennial weeds, we prepared a carbocyclic nucleoside analogue **2** in racemic form. We found that (\pm)-**2** maintained the herbicidal properties,^{2,3} in contrast to the modifications of the hydroxyl groups in D-ribofuranose: All diastereomers and deoxy derivatives of the natural compound exhibited no herbicidal activity. Only the anomeric epimer showed moderate activity. These results clearly indicate that all three hydroxy groups are required for herbicidal activities. Moreover, the enantiomer of (+)-hydantocidin was found to have no herbicidal activity in the greenhouse testing.⁴ In order to estimate the real herbicidal activity of the carbocyclic analogue, we undertook the synthesis of an optically active (+)-**2**, because the biological activities of carbocyclic nucleosides normally reside in one enantiomer, corresponding to the parent D-sugar.⁵ Furthermore, different features, such as metabolism, degradation, and biological activities, between the enantiomers of optically active agrochemicals have been reported.⁶

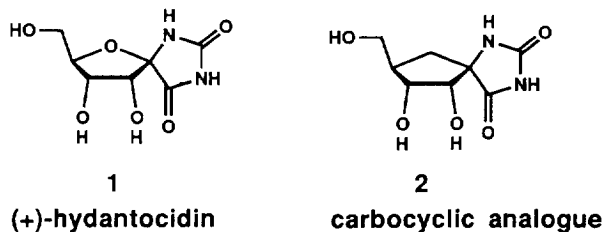
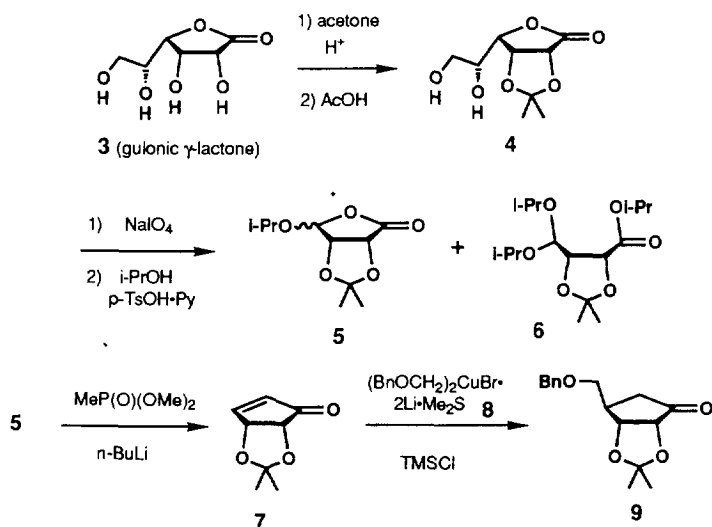


Figure 1

In our previous synthesis of (\pm)-**2**, cyclopentanone **9**, which was easily prepared from 2,3-norbornadiene, was a key intermediate to subject to spirohydantoin formation, using, respectively, the Read and Bucher-Berg reactions, affording the corresponding carbocyclic analogue and its anomeric epimer after deprotection. During planning of the synthesis of (+)-**2**, therefore, we focused on an efficient preparation of **9** in an optically active form, corresponding to the D-sugar. Several synthetic approaches to optically active hydroxy substituted cyclopentanone and cyclopentenone rings have been developed using natural chiral sources, asymmetric reactions, diastereomeric resolutions, and biochemical methods.^{7,8} With these reports in mind, our synthesis began with D-gulono-1,4-lactone **3**, following the work of Borchardt,⁸ as shown in **Scheme 1**. Treatment of D-gulono-1,4-lactone **3** with copper(II) sulfate in acetone in the presence of conc. sulfonic acid, followed by monocleavage with acetic acid, gave 2,3-*O*-isopropylidene-D-gulono-1,4-lactone **4** in 85% yield. Oxidative cleavage of the diol part of **4** with sodium periodate afforded L-erythrosine,⁹ which was directly converted to *i*-propyl acetal **5** in 51% yield along with the *i*-propyl ester **6** in 7% yield. Conversion of *i*-propyl acetal **5** to cyclopentenone **7**¹⁰ was accomplished with dimethyl methylphosphonate and *n*-butyl lithium at -78 °C in 51% yield. Conjugate 1,4-addition¹¹ of α -hydroxymethyl anion, derived from benzyloxymethyl tributylstannane,¹² to **7** in the presence of trimethylsilyl chloride, was efficiently performed to give cyclopentanone **9** in 99% yield as a single isomer. The stereochemistry at C4 of **9** was confirmed by comparison with authentic racemic samples² on the bases of spectroscopic data (¹H-NMR, IR, MS) and chromatographic behavior (TLC), indicating that the homo cuprate **8** attacked enone **7** from the less-hindered side.

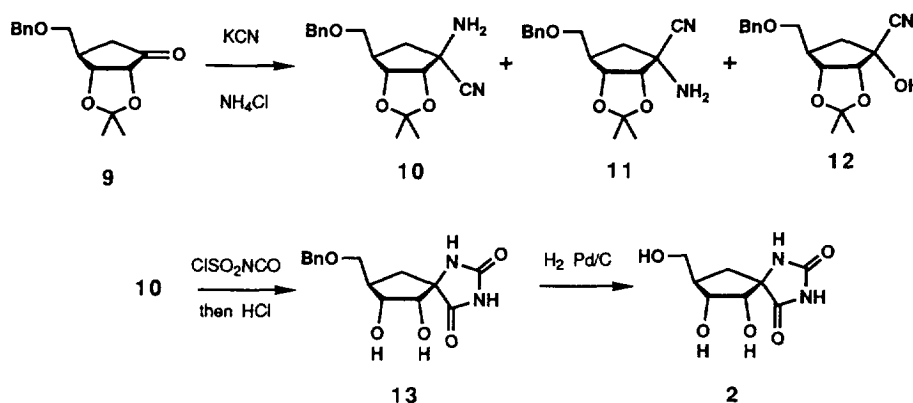
Scheme 1



Heating of **9** with potassium cyanide and ammonium chloride in MeOH-H₂O at 90 °C for 24 h provided the desired α -aminonitrile **10** in 33% yield and its epimer **11** in 11% yield together with cyanohydrin

12 in 25% yield, after careful chromatographic purification (**Scheme 2**). The stereochemistries of **10**, **11**, and **12** were unequivocally established by comparison with authentic racemic samples.² Treatment of **10** with chlorosulfonyl isocyanate,¹³ followed by hydrolysis with hydrochloric acid, afforded spirohydantoin **13** in 64% yield. Hydrogenolysis of benzyl ether with 10% Pd-C under H₂ atmosphere gave the optically active carbocyclic analogue **2** in 98% yield. The structure of the target molecule **2** was also confirmed by comparison with authentic racemic samples.²

Scheme 2



When applied through the foliage of troublesome weeds at 1000 ppm, herbicidal activities of the optically active carbocyclic analogue (+)-**2** were clearly superior to those of the racemate **2**: The optically active (+)-**2** gave 50% herbicidal control of fall panicum, 90% control of Johnson grass, and 100% control of ragweed, while the racemate **2** demonstrated 5% control of fall panicum, 50% control of Johnson grass, and 70% control of ragweed under the same conditions.¹⁴ The combination of these results and the previous findings from our laboratories,⁵ that the enantiomer of (+)-hydantocidin had no herbicidal activity, supports the possibility that only the one enantiomer of the carbocyclic nucleoside of (+)-hydantocidin shows herbicidal activities. The oxygen atom in the D-ribofuranose ring of the natural compound can be replaced with a carbon atom with almost no loss of herbicidal activities.

In summary, we prepared an optically active carbocyclic analogue of (+)-hydantocidin from D-gulonolactone in 9 steps, featuring 1,4-addition of cyclopentenone **7** with homobenzyloxymethyl cuprate **8** and spirohydantoin ring construction from cyclopentanone **9** through α -aminonitrile **10** as key steps. The herbicidal test results of (+)-**2** demonstrated that the herbicidal activities of (+)-**2** were more highly active than those of the racemate **2**. The replacement of an oxygen atom with a carbon in the D-ribofuranose ring of the natural compound can be acceptable for herbicidal activity. Further investigations on the structure-herbicidal-activity relationships of (+)-hydantocidin are now in progress.

Acknowledgment

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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. Optical rotations were measured on a Jasco DIP-360 polarimeter. Merck Kieselgel 60 was used for SiO₂ column chromatography. Merck TLC plate Art.5744 was used for preparative TLC.

2,3-*O*-Isopropylidene-D-gulono-1,4-lactone 4

A mixture of D-gulono-1,4-lactone 3 (25 g, 140 mmol) and anhydrous copper(II) sulfate (100 g) in acetone (1000 ml), was stirred at room temperature in the presence of conc. sulfuric acid (2 ml) for 18 h. After filtration through a pad of Celite[®], the filtrate was neutralized with 4N NaOH, dried, and concentrated. The residue was recrystallized from benzene-petroleum, to give 33.6 g of 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (93%) as a colorless solid.

m.p. 154-155 °C; IR (CHCl₃) 3000, 1790, 1375, 1110, 1070 cm⁻¹; ¹H-NMR (CDCl₃) δ 4.84 (1H, d, *J* = 5.6 Hz), 4.74 (1H, dd, *J* = 5.6, 3.2 Hz), 4.49-4.39 (2H, m), 4.25-4.19 (1H, m), 3.85-3.79 (1H, m), 1.48 (6H, s), 1.40 (3H, s), 1.38 (3H, s); MS *m/z* 259 (M⁺+1), 243, 125, 101, 59.

The above diacetonide (33.6 g, 130 mmol) was dissolved with a mixture of acetic acid (450 ml) and water (150 ml), and concentrated at room temperature for 3 d. A precipitated solid was dissolved with EtOAc (500 ml) and heated at 80 °C for 2 h. Filtration through a pad of Celite[®], followed by concentration, afforded 25.8 g of monoacetonide 4 (91%) as a colorless solid.

m.p. 140-142 °C; IR (KBr) 3550, 3400, 2980, 1775, 1375, 1190, 1105 cm⁻¹; ¹H-NMR (CDCl₃) δ 4.88-4.87 (2H, m), 4.60 (1H, td, *J* = 7.2, 1.6 Hz), 4.14 (1H, ddd, *J* = 7.2, 4.2, 3.6 Hz), 3.89 (1H, dd, *J* = 11.7, 3.6 Hz), 3.82 (1H, dd, *J* = 11.7, 4.2 Hz), 1.68 (2H, brd.), 1.48 (3H, s), 1.40 (3H, s); MS *m/z* 219 (M⁺+1), 203, 159, 116, 83.

(2*R*,3*S*)-2,3-Dimethylenedioxy-4-hydroxy-4-(2-propyloxy)-butanoic acid γ -lactone 5

A solution of sodium periodate (34.65 g, 162 mmol) in water (150 ml) was added dropwise to a solution of monoacetonide 4 (14.72 g, 67.4 mmol) and NaOH (3.23 g, 80.9 mmol) in water (200 ml) at room temperature with pH maintained at 7 by addition of 0.5N NaOH. After 10 min, barium chloride (6.5 g) was added, and the resulting mixture was stirred vigorously for 2 min. After filtration through a pad of Celite[®], the filtrate was acidified with 2N-HCl to pH 3 and extracted with EtOAc. The combined organic layers were dried and evaporated to give 10.5 g of a solid. The residual solid was dissolved with *i*-PrOH (500 ml) and heated at 90 °C in the presence of PPTS (1.58 g) and molecular sieves 4 A (2 g) under N₂ atmosphere for 2 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite[®] and evaporated. The residue was diluted with Et₂O and washed with water, dried, and concentrated. The residue was chromatographed

on silica gel (hexane/EtOAc 5:1), to afford γ -lactone **5** (7.46 g, 51%) as a colorless solid, and **(2R,3S)-2-propyl 2,3-dimethylmethylenedioxy-4-di-(2-propyloxy)-butanoate 6** (1.5 g, 7%) as a colorless oil.

For γ -lactone **5**: m.p. 36-37 °C; $[\alpha]_D^{25} +54.4$ (c=2.22, CHCl₃); IR (CHCl₃) 2970, 1785, 1375, 1105 cm⁻¹; ¹H-NMR (CDCl₃) δ 5.54 (1H, s), 4.82 (1H, d, *J* = 5.6 Hz), 4.53 (1H, d, *J* = 5.6 Hz), 4.03 (1H, heptet, *J* = 6.0 Hz), 1.46 (3H, s), 1.38 (3H, s), 1.22 (3H, d, *J* = 6.0 Hz), 1.21 (3H, d, *J* = 6.0 Hz); MS *m/z* 217 (M⁺+1), 201, 145, 131, 89; HRMS. found: 201.0769. Calcd. for C₁₀H₁₆O₅(-CH₃): 201.0763.

For 2-propyl ester **6**: $[\alpha]_D^{25} -51.2$ (c = 1.97, CHCl₃); IR (CHCl₃) 2980, 1735, 1370, 1095 cm⁻¹; ¹H-NMR (CDCl₃) δ 5.02 (1H, heptet, *J* = 6.0 Hz), 4.78 (1H, d, *J* = 6.6 Hz), 4.52 (1H, d, *J* = 6.6 Hz), 4.25 (1H, t, *J* = 6.6 Hz), 3.96 (1H, heptet, *J* = 6.0 Hz), 3.90 (1H, heptet, *J* = 6.0 Hz), 1.57 (3H, s), 1.36 (3H, s), 1.29 (3H, d, *J* = 6.0 Hz), 1.28 (3H, d, *J* = 6.0 Hz), 1.22 (3H, d, *J* = 6.0 Hz), 1.20 (3H, d, *J* = 6.0 Hz), 1.17 (3H, d, *J* = 6.0 Hz), 1.09 (3H, d, *J* = 6.0 Hz); Mass *m/z* 318 (M⁺), 303, 259, 217, 175, 145, 132; HRMS. found: 303.1811. Calcd. for C₁₀H₃₀O₆(-CH₃): 303.1808.

(2R,3R)-2,3-Dimethylmethylenedioxy-cyclopentanone 7

A solution of dimethylmethylphosphonate (1.35 g, 12.5 mmol) in THF (100 ml) was treated with 1.6M solution of *n*-butyl lithium in *n*-hexane (7.5 ml, 11.9 mmol) at -78 °C. After 15 min, a solution of γ -lactone **5** (2.47 g, 11.4 mmol) in THF (20 ml) was added, and the resulting mixture was maintained at -78 °C for 2.5 h, and then at room temperature for 1 h. The reaction mixture was diluted with Et₂O and washed with brine, prior to drying and concentration. Silica gel chromatography (hexane/Et₂O 2:1) of the residue afforded 2-cyclopentenone **7** (0.89 g, 51%) as a colorless solid.

m.p. 66-67 °C; $[\alpha]_D^{25} -79.0$ (c = 2.66, CHCl₃); IR (CHCl₃) 3005, 2940, 1730, 1375, 1095 cm⁻¹; ¹H-NMR (CDCl₃) δ 7.60 (1H, dd, *J* = 6.0, 2.4 Hz), 6.22 (1H, d, *J* = 6.0 Hz), 5.26 (1H, dd, *J* = 5.6, 2.4 Hz), 4.46 (1H, d, *J* = 5.6 Hz), 1.42 (6H, s); Mass *m/z* 154 (M⁺), 139, 96, 68; HRMS. found: 154.0600. Calcd. for C₈H₁₀O₃: 154.0630.

(2R, 3R, 4R)-4-Benzyloxymethyl-2,3-dimethylmethylenedioxy-cyclopentanone 9

A solution of benzyloxymethyl tributylstannane (4.44 g, 10.8 mmol) in THF (100 ml) was treated with 1.6M solution of *n*-BuLi in *n*-hexane (6.9 ml, 11.0 mmol) at -78 °C under N₂ atmosphere. After stirring for 15 min, this solution was added dropwise via cannula to a cooled (-78 °C) solution of CuBr•SMe₂ (1.16 g, 5.63 mmol) in THF (13 ml), and was maintained at -78 °C for 15 min. Trimethylsilylchloride (3.43 ml, 27 mmol) was added, and the resulting mixture was added via cannula to a cold (-78 °C) solution of cyclopentenone **7** (0.69 g, 4.5 mmol) in THF (15 ml). The reaction mixture was stirred at -78 °C for 30 min, then at -40 °C for 20 min, and finally at 0 °C for 5 min. Saturated ammonium chloride solution, ammonia water, and CH₂Cl₂ were added to the mixture, and vigorous stirring was continued at room temperature for 30 min to quench the reaction. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried and concentrated. The residue was diluted with THF and 0.5N HCl, and stirred vigorously at room temperature for 15 min, and extracted with CH₂Cl₂. The organic phases were dried, evaporated, and purified by silica gel chromatography (hexane/EtOAc 6:1), to furnish cyclopentanone **9** (1.24 g, 99%) as a colorless oil.

$[\alpha]_D^{25}$ -63.1 ($c = 1.98$, CHCl_3); IR (CHCl_3) 3000, 2860, 1750, 1700, 1360, 1085 cm^{-1} ; $^1\text{H-NMR}$ (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, $J = 8.9, 2.8$ Hz), 3.43 (1H, dd, $J = 8.9, 3.0$ 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), 1.34 (3H, s); Mass m/z 276 (M^+), 261, 185, 127, 100, 91; HRMS. found: 276.1362. Calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_4$: 276.1362.

Strecker reaction of ketone 9

A mixture of cyclopentanone **9** (0.75 g, 2.7 mmol), potassium cyanide (1.4 g, 21.6 mmol), and ammonium chloride (1.2 g, 21.6 mmol) in methanol (15 ml) and water (15 ml) was heated at 90 °C for 24 h. The black mixture was diluted with water and filtered through a pad of Celite[®]. The filtrate was extracted with EtOAc, and the combined 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 give (1*S*,2*S*,3*R*,4*R*)-1-amino-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-cyclopentanecarbonitrile **10** (0.27 g, 33%) and (1*R*,2*S*,3*R*,4*R*)-1-amino-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-cyclopentanecarbonitrile **11** (0.09 g, 11%) as colorless oil, respectively, along with (1*R*,2*R*,3*R*,4*R*)-4-benzyloxymethyl-2,3-dimethylmethylenedioxy-1-hydroxy-1-cyclopentane-carbonitrile **12** (0.19 g, 25%) as a colorless solid.

For **10**: $[\alpha]_D^{25}$ -29.2 ($c = 1.70$, CHCl_3); IR (CHCl_3) 3300, 3000, 2930, 2860, 1450, 1370, 1155, 1080 cm^{-1} ; $^1\text{H-NMR}$ (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); Mass m/z 302 (M^+), 287, 211, 153, 123, 91; HRMS. found: 302.1632. Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$: 302.1630.

For **11**: $[\alpha]_D^{25}$ -25.9 ($c = 2.59$, CHCl_3); IR (CHCl_3) 3400, 3000, 2930, 2860, 1450, 1375, 1055 cm^{-1} ; $^1\text{H-NMR}$ (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); Mass m/z 302 (M^+), 287, 211, 153, 123, 91; HRMS. found 302.1631; Calcd. for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$: 302.1630.

For **12**: m.p. 92 °C; $[\alpha]_D^{25}$ -42.9 ($c = 2.05$, CHCl_3); IR (CHCl_3) 3300, 2950, 2930, 2870, 1370, 1155 cm^{-1} ; $^1\text{H-NMR}$ (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, 127, 91; HRMS. found: 303.1465. Calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_4$: 303.1471.

(5*R*,6*S*,7*R*,8*R*)-8-Benzyloxymethyl-6,7-dihydroxy-1,3-diazaspiro[4.4]nonane-2,4-dione. **13**

Chlorosulfonyl chloride (0.11 ml, 1.2 mmol) was added to a solution of α -aminonitrile **10** (0.32 g, 1.1 mmol) in CH_2Cl_2 (15 ml) at room temperature under N_2 atmosphere, and the reaction mixture was stirred for 20 min. After concentration, 1N HCl (4 ml) was added to the residue, and the resulting mixture was stirred at room temperature for 20 min, and then at 100 °C for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layers were washed with brine, prior to drying and evaporation. The residue was

chromatographed on silica gel (hexane/EtOAc 1:5 to EtOAc only) to give spirohydantoin **13** (0.22 g, 64%) as a colorless solid.

m.p. 146-149 °C; $[\alpha]_D^{25} +9.4$ ($c = 1.28$, MeOH); IR (KBr) 3330, 2800, 1760, 1710, 1410, 1230, 1140 cm^{-1} ; $^1\text{H-NMR}$ (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, 91; HRMS. found: 306.1222. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_5$: 306.1216.

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

A mixture of spirohydantoin **13** (0.20 g, 0.65 mmol) and 10% Pd-C (0.15 g) in methanol (120 ml) was heated at 55 °C under H_2 atmosphere for 7.5 h. Filtration through a pad of Celite[®], followed by concentration in vacuo, gave a residue, which was subjected to chromatography on Dianion CHP 20P (water) to afford **2** (0.14 g, 98%) as a colorless solid.

m.p. 168-171 °C; $[\alpha]_D^{25} +12.4$ ($c = 2.19$, MeOH); IR (KBr) 3350, 1760, 1710, 1410, 1330, 1130, 1070 cm^{-1} ; $^1\text{H-NMR}$ (CD_3OD) δ 3.96 (1H, d, $J = 6.0$ Hz), 3.87 (1H, dd, $J = 6.0, 3.2$ Hz), 3.58 (2H, ABq, $J = 10.8, 5.2$ 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); Mass m/z 217 ($\text{M}^+ + 1$), 198, 180, 152, 112, 100; HRMS. found: 216.0740. Calcd. for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_5$: 216.0746; Anal. found: C, 44.24; H, 5.51; N, 12.80. Calcd. for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_5$: C, 44.44; H, 5.59; N, 12.96%.

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