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Synthesis of Spirothiohydantoin Analogues of Hydantocidin

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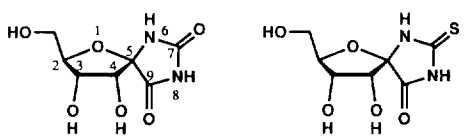
Abstract: Synthesis of spirothiohydantoin derivatives of hydantocidin is described. The key feature of the synthesis was spirothiohydantoin ring formation through an iminophosphorane intermediate. Spirothiohydantoin derivative **2** maintained comparable herbicidal activity to that of the natural compound except against fall panicum, when applied through a foliage of weeds at 1000 ppm. Surprisingly, its epimer **15** also demonstrated good herbicidal activity under the same condition, while 5-epi-hydantocidin **16** displayed fair activity.

Our previous study on the structure-herbicidal-activity relationships of hydantocidin **1**,[1] the first naturally occurring spironucleoside, demonstrated that 1) all stereoisomers and deoxy analogues except 5-epimer were found to be devoid of activity,[2] 2) replacement of an oxygen atom at *O*1 with a methylene unit was acceptable for biological activity,[3] 3) methylene group insertion at the anomeric position resulted in losing the activity,[4] 4) spirosuccinimide derivative,[5] being replacement of a nitrogen atom at *N*6 with a methylene unit, led to a moderately active compound, and 5) spiroimidazolidinone analogue,[6] with replacement of a *C*9 carbonyl group with a methylene group, had no activity. Because our previous drastic derivatization only led to diminished activity, our attention has turned to minimum modification without changing the basic structure, to design spirothiohydantoin analogue **2**, in which the *C*7 carbonyl group was replaced with a thiocarbonyl group (**Figure 1**). This modification would expose the role of the *C*7 carbonyl group and the possibility of a new derivatization of hydantocidin. Herein, we describe synthesis and herbicidal activity of thiohydantoin derivatives of hydantocidin.



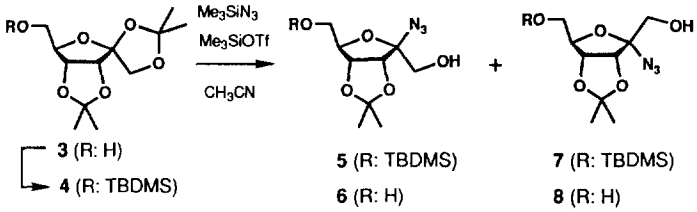
1 hydantocidin **2**

Figure 1

Among several synthetic studies on hydantocidin,[7] we focused on spirohydantoin ring construction reported from our laboratories previously[7b] using aza-Wittig reaction between α-azidoamide and carbon

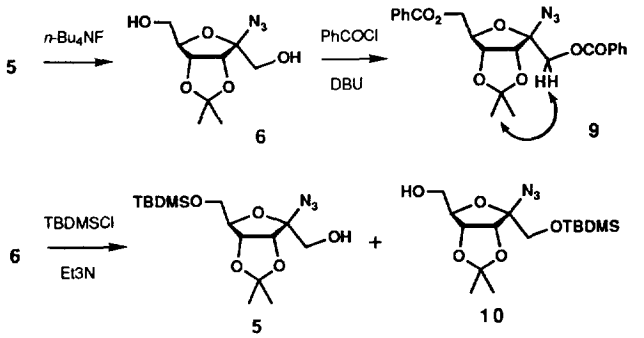
dioxide because of its high efficiency and mild reaction condition. Synthesis of the thiohydantoin derivative **2** was carried out starting with 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose **3**,[7b,8] prepared from D-fructose in 4 steps (**Scheme 1**). Protection of hydroxymethyl group in **3** as its *tert*-butyldimethylsilyl ether proceeded to a 98% chromatographed yield of ether **4**. Introduction of an azide group at the anomeric position of **4** was accomplished stereoselectively. Treatment of **4** with trimethylsilyl azide and trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetonitrile at 0 °C gave azido alcohol **5** in 28% yield and deprotected diol **6** in 24% yield, along with minor isomer **7** in 1.1% yield and diol **8** in 0.8% yield. Thus, cleavage of an isopropylidene group in **4** with TMSOTf was achieved regioselectively; however, the *tert*-butyldimethylsilyl group was also removed during this reaction to give diols **6** and **8**. Although the undesired diol **6** was produced, regioselective transformation of **6** to silylether **5** was accomplished (*vide infra*).

Scheme 1



Determinations of the stereochemistry of **5** and **6** at the anomeric position are summarized in **Scheme 2**. Deprotection of the *tert*-butyldimethylsilyl group in **5** with tetra-*n*-butylammonium fluoride gave **6** in a quantitative yield, and conversion of diol **6** to **5** proceeded by exposure of **6** to *tert*-butyldimethylsilyl chloride and triethylamine in 57% yield together with regioisomer **10** in 4% yield, clearly demonstrating that **6** possessed the same stereochemistry as **5**. The stereochemistry of the anomeric position of **5** and **6** was confirmed by 2D-NOESY experiments of dibenzoate **9**, which was prepared by treatment of **6** with benzoyl chloride and DBU in THF in 78% yield. Cross peaks between methylene protons at *C*1 and methyl protons of isopropylidene were observed, indicating that azido nucleophile was introduced from the opposite side of the 3,4-*O*-isopropylidene unit.

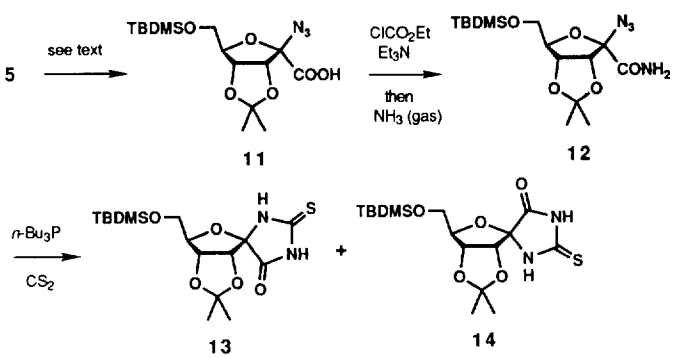
Scheme 2



Construction of the thiohydantoin ring is shown in **Scheme 3**. Swern oxidation of **5**, followed by further

oxidation with sodium chlorite, in the presence of sodium dihydrogen phosphate dihydrate and 2-methyl-2-butene,[9] afforded carboxylic acid **11**, which was converted to amide **12** by treatment of ethyl chloroformate and triethylamine followed by bubbling ammonia gas in 24% yield from **5**. Alternatively, direct oxidation using ruthenium tetraoxide *in situ* generated from ruthenium(III) chloride-sodium periodate yielded **11** more efficiently: Vigorous stirring of **5** with a catalytic amount of ruthenium(III) chloride hydrate and sodium periodate in acetonitrile-carbon tetrachloride-water at room temperature gave **11**, which was further transformed into the amide **12** in 66% yield from **5**. With the key intermediate α-azidoamide **12** in hand, the next stage was set to develop the method of spirothiohydantoin ring formation. Previous study on synthesis of hydantocidin from our laboratories[7b] has revealed that spirohydantoin ring formation from α-azidoamide and carbon dioxide smoothly proceeded without epimerization at the anomeric position *via* aza-Wittig reaction.[10] According to this finding, spirothiohydantoin ring formation at the anomeric position was achieved by treatment of **12** with tri-*n*-butylphosphine and carbon disulfide in acetonitrile at 50 °C to give spirothiohydantoin **13** in 16% yield along with its epimer **14** in 25% yield. To our knowledge this is the first example of spirothiohydantoin ring formation from α-azidoamide and carbon disulfide using aza-Wittig reaction. Unfortunately, all attempts to improve the efficiency and stereoselectivity of this thiohydantoin ring synthesis were unsuccessful. The low reactivity of carbon disulfide to the aza-Wittig intermediate resulted to the low yield and isomerization at the anomeric center.

Scheme 3



The final deprotection proceed without epimerization at the spiro center: Hydrolysis of *tert*-butyldimethylsilyl ether and isopropylidene acetal in **13** with Dowex 50W^R (H^+) in methanol-water at 60 °C afforded the target compound **2** in 77% yield (**Scheme 4**). Its epimer **15** was also prepared under the same conditions in 94% yield. The stereochemistries of **2** and **15** were determined by spectroscopic comparison with the corresponding spirohydantoin derivatives.[5,11] The signal of *C*2 methine proton in the ^{1}H NMR spectrum was distinct for the epimers at the spiro center; 4.27-4.23 ppm as a multiplet for **2** and 4.15-4.10 ppm as a multiplet for **15**, whereas a multiplet peak at 4.23-4.20 ppm for hydantocidin **1** and a triple of doublet peak at 4.09 ppm for 5-epimer **16**. Further heating of **2** with Dowex 50W^R (H^+) in methanol-water at

60 °C led it to undergo isomerization to give an appreciable formation of **15** by HPLC analysis, although epimer **15** resisted isomerizing to **2** under the same acidic conditions. These phenomena resemble those observed in isomerization between hydantocidin and **16** (**Scheme 5**).[11]

Scheme 4

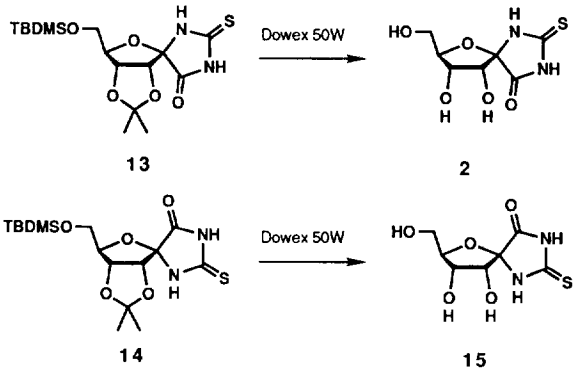


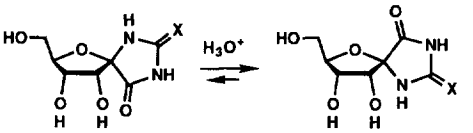
Table 1 summarizes the results obtained for the herbicidal test of hydantocidin derivatives when applied to foliage of ten troublesome weeds at 1000 ppm. Spirothiohydantoin analogue **2** maintained herbicidal activity and the activity was comparable to that of the natural compound except against fall panicum. Strikingly, its epimer **15** also demonstrated good herbicidal activity, while the epimer of hydantocidin **16** showed moderate activity. Although conversion of the carbonyl group to thiocarbonyl function may cause to change many properties of the parent molecule such as polarity, molecular size, and ability of hydrogen bonding, thiohydantoin analogue **2** maintains herbicidal activity. These results support the probability that the carbonyl group at *C*7 could be modified for herbicidal activities. Moreover, the unexpected results from the bioassay that the herbicidal activity of 5-epi-thiohydantoin **15**, which resisted epimerization to **2** under acidic condition, was superior to that of 5-epi-hydantocidin **16**, imply the possibility that the thiohydantoin ring could play a certain special role for herbicidal activity.

Table 1 Herbicidal Activity of 2 and 15 at 1000 ppm

compound	A	B	C	D	E	F	G	H	I	J
2	5	5	4	5	5	5	5	5	5	5
15	5	5	4	5	5	4	5	4	4	4
1	5	5	5	5	5	5	5	5	5	5
16	1	4	4	4	0	3	4	2	-	4

A: barnyardgrass; B: crabgrass; C: fall panicum; D: green foxtail; E : Johnsongrass; F: black nightshade; G: cocklebur; H: tall morningglory; I: ragweed; J: velvetleaf; - : not examined.

Scheme 5



1: X=O
2: X=S

16: X=O
15: X=S

In conclusion, we have synthesized spirothiohydantoin nucleosides **2** and **15** as hydantocidin analogues. The procedure involved thiohydantoin ring formation at the anomeric position of D-ribofuranose *via* an aza-Wittig intermediate. The results of herbicidal testing of the two analogues demonstrated that the carbonyl group at *C7* of the natural compound could be modified in the search for potent herbicides. Further research on the structure-herbicidal-activity relationships of hydantocidin is now in progress.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. ^{1}H-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 SiO_2 column chromatography. Merck TLC plate Art.5744 was used for preparative TLC.

6-*O*-*tert*-Butyldimethylsilyl-1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose 4

Imidazole (5.87 g, 86 mmol) and *tert*-butyldimethylsilyl chloride (6.80 g, 43 mmol) were added to a solution of 1,2:3,4-di-*O*-isopropylidene-β-D-psicofuranose **3** (9.35 g, 36 mmol) in DMF (50 ml), and the resulting mixture was stirred at room temperature for 10 h. The reaction mixture was partitioned between water and Et_2O, and the combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (hexane / EtOAc 50 : 3) to give silyl ether **4** (13.2 g, 98%) as a colorless oil.

$[\alpha]_D^{25}$ -73.4 (C=1.24, $CHCl_3$); IR ($CHCl_3$) 2990, 2950, 2850, 1470, 1250, 1060 cm^{-1}; NMR ($CDCl_3$) δ 4.77 (1H, dd, *J* = 6.0, 0.8 Hz), 4.59 (1H, d, *J* = 6.0 Hz), 4.27 (1H, d, *J* = 9.3 Hz), 4.11 (1H, ddd, *J* = 8.9, 5.6, 0.8 Hz), 4.02 (1H, d, *J* = 9.3 Hz), 3.64 (1H, dd, *J* = 8.9, 5.6 Hz), 3.59 (1H, dd, *J* = 8.9, 8.9 Hz), 1.44 (3H, s), 1.43 (3H, s), 1.37 (3H, s), 1.33 (3H, s), 0.90 (9H, s), 0.07 (6H, s); Mass *m/z* 359 (M^+-15), 259, 241, 201, 171, 143, 125, 117, 75; Anal. found: C, 58.01; H, 9.41. Calcd. for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15%.

Reaction of 4 with trimethylsilyl azide and trimethylsilyl trifluoromethanesulfonate

Trimethylsilyl azide (6.6 ml, 49.7 mmol) and trimethylsilyl trifluoromethanesulfonate (2.4 ml, 12.4 mmol) were added sequentially to a solution of silyl ether **4** (8.9 g, 24.0 mmol) in acetonitrile (70 ml) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined extracts were washed with brine, dried, and concentrated. Silica gel chromatography of the residue (hexane / EtOAc 10 : 1) afforded **2-azido-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose 5** (2.55 g, 28%) as a colorless oil and **2-azido-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose 6** (1.47 g, 24%) as a colorless solid, together with **2-azido-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-α-D-psicofuranose 7** (0.10 g, 1.1%) and **2-azido-2-deoxy-3,4-*O*-isopropylidene-α-D-psicofuranose 8** (46 mg, 0.8%) as colorless oils, respectively.

For 5: $[\alpha]_D^{25}$ -138.9 (C=1.29, $CHCl_3$); IR ($CHCl_3$) 3500, 2970, 2950, 2880, 2130, 1460, 1380, 1240, 1210, 1110, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.83 (1H, dd, *J* = 6.0, 1.6 Hz), 4.47 (1H, d, *J* = 6.0 Hz), 4.32 (1H, ddd, *J* = 6.8, 5.2, 1.6 Hz), 3.92 (2H, d, *J* = 7.2 Hz), 3.76 (1H, dd, *J* = 10.5, 5.2 Hz), 3.72 (1H, dd, *J* = 10.5, 6.8 Hz), 2.21 (1H, t, *J* = 7.2 Hz), 1.52 (3H, s), 1.33 (3H, s), 0.91 (9H, s), 0.09 (6H, s); Mass *m/z* 359 (M^+), 344, 317, 259, 217, 201, 187, 171, 159, 143, 129, 117, 101; Anal. found: C, 50.41; H, 7.84; N, 11.42. Calcd. for $C_{15}H_{29}N_3O_5Si$: C, 50.12; H, 8.13; N, 11.69%.

For 6: m.p. 78-79 °C; $[\alpha]_D^{25}$ -129.4 (C=1.21, $CHCl_3$); IR ($CHCl_3$) 3600, 3490, 3020, 2950, 2120, 1380, 1240, 1070 cm^{-1}; NMR ($CDCl_3$) δ 4.82 (1H, dd, *J* = 6.0, 1.4 Hz), 4.53 (1H, d, *J* = 6.0 Hz), 4.38 (1H, ddd, *J* = 6.0, 4.8, 1.4 Hz), 3.97 (2H, d, *J* = 7.3 Hz), 3.84-3.69 (2H, m), 2.35 (1H, t, *J* = 7.3 Hz), 2.23 (1H, t, *J* = 6.4 Hz), 1.53 (3H, s), 1.33 (3H, s); Mass *m/z* 230 (M^+-15), 203, 188, 172, 129, 115, 97; Anal. found: C, 43.84; H, 5.89; N, 16.84. Calcd. for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.14%.

For 7: $[\alpha]_D^{25}$ +56.2 (C=1.18, $CHCl_3$); IR ($CHCl_3$) 3580, 3420, 2960, 2920, 2860, 2130, 1450, 1380, 1260, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (1H, dd, *J* = 6.2, 4.2 Hz), 4.80 (1H, d, *J* = 6.2 Hz), 4.36 (1H, ddd, *J* = 4.2, 2.4, 1.8 Hz), 3.96 (1H, dd, *J* = 11.3, 2.4 Hz), 3.79 (1H, dd, *J* = 11.3, 1.8 Hz), 3.65 (1H, dd, *J* = 11.4, 3.0 Hz), 3.50 (1H, dd, *J* = 11.4, 10.6 Hz), 3.13 (1H, dd, *J* = 10.6, 3.0 Hz), 1.63 (3H, s), 1.39 (3H, s), 0.92 (9H, s), 0.12 (6H, s); Mass *m/z* 344 (M^+-15), 317, 257, 239, 229, 217, 201, 186, 171, 159, 143, 131, 117, 101; Anal. found: C, 49.91; H, 7.93; N, 11.67. Calcd. for $C_{15}H_{29}N_3O_5Si$: C, 50.12; H, 8.13; N, 11.69%.

For 8: $[\alpha]_D^{25}$ +74.7 (C=1.16, $CHCl_3$); IR ($CHCl_3$) 3480, 3030, 3000, 2940, 2120, 1450, 1250, 1090 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (1H, dd, *J* = 6.3, 3.5 Hz), 4.83 (1H, d, *J* = 6.3 Hz), 4.43-4.40 (1H, m), 3.95 (1H, dd, *J* = 11.8, 2.4 Hz), 3.78-3.71 (2H, m), 3.64-3.60 (1H, m), 3.13 (1H, brd.), 2.72 (1H, brd.), 1.64 (3H, s), 1.38 (3H, s); Mass *m/z* 230 (M^+-15), 214, 203, 172, 149, 127, 115, 85, 59; Anal. found: C, 44.01; H, 6.35; N, 16.84. Calcd. for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.14%.

Conversion of 5 to 6

Tetrabutylammonium fluoride (1.0 M in THF, 0.84 ml, 0.84 mmol) was added to a solution of **5** (0.20 g, 0.56 mmol) in THF (3 ml) at room temperature. After 20 min, the mixture was poured into water and extracted

with EtOAc. The combined organic layers were washed with brine, dried, and evaporated to give a crude oil, which was chromatographed on silica gel (hexane / EtOAc 5 : 1 to 1 : 1) to afford **6** (0.14 g, quantitative yield).

2-Azido-2-deoxy-1:6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-psicofuranose 9

Benzoyl chloride (0.37 ml, 3.2 mmol) was added to a solution of diol **6** (0.26 g, 1.1 mmol) and DBU (0.6 ml, 4.2 mmol) in 1,2-dichloroethane (5 ml) at room temperature, and it was stirred there for 3 h. The reaction mixture was quenched with 1N HCl and extracted with dichloromethane. The combined organic layers were dried and evaporated to give a residual oil, which was purified by chromatography on silica gel (hexane / EtOAc 6 : 1) to afford dibenzoate **9** (0.37 g, 78%) as a colorless oil.

$[\alpha]_D^{25}$ -85.0 (C=1.08, $CHCl_3$); IR ($CHCl_3$) 3030, 2990, 2120, 1720, 1450, 1380, 1270, 1110 cm^{-1}; NMR ($CDCl_3$) δ 8.12-8.07 (4H, m), 7.62-7.55 (2H, m), 7.49-7.42 (4H, m), 4.93 (1H, dd, *J* = 5.8, 1.7 Hz), 4.79 (1H, d, *J* = 12.0 Hz), 4.69 (1H, td, *J* = 6.1, 1.7 Hz), 4.63 (1H, d, *J* = 12.0 Hz), 4.58 (1H, d, *J* = 5.8 Hz), 4.53 (2H, ABqd, *J* = 11.6, 6.1 Hz), 1.54 (3H, s), 1.35 (3H, s); Mass *m/z* 438 (M^+-15), 411, 318, 232, 163, 149, 105, 77; Anal. found: C, 61.01; H, 4.83; N, 9.10. Calcd. for $C_{23}H_{23}N_3O_7$: C, 60.92; H, 5.11; N, 9.27%.

Conversion of 6 to 5

A mixture of **6** (0.22 g, 0.92 mmol), triethylamine (0.19 ml, 1.4 mmol), and *tert*-butyldimethylsilyl chloride (0.16 g, 1.1 mmol) in DMF (6 ml) was stirred in the presence of DMAP (20 mg) at room temperature for 14 h. The reaction mixture was quenched with water and extracted with EtOAc. The extracts were washed with brine and dried. After removal of the solvent, silica gel chromatography (hexane / EtOAc 8 : 1 to 1 : 1) of the residue gave **5** (0.19 g, 57%) as a colorless oil and **2-azido-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose 10** (14 mg, 4%) as a colorless solid together with diol **6** (50 mg, 22% recovery) as a colorless solid.

For 10: m.p. 40 °C; $[\alpha]_D^{25}$ -65.1 (C=0.64, $CHCl_3$); IR ($CHCl_3$) 3470, 2950, 2920, 2860, 2120, 1460, 1370, 1250, 1110, 1030 cm^{-1}; NMR ($CDCl_3$) δ 4.79 (1H, dd, *J* = 5.8, 1.8 Hz), 4.46 (1H, d, *J* = 5.8 Hz), 4.33 (1H, td, *J* = 6.5, 1.8 Hz), 4.00 (2H, ABq, *J* = 10.7 Hz), 3.77-3.72 (2H, m), 2.19 (1H, t, *J* = 6.4 Hz), 1.49 (3H, s), 1.32 (3H, s), 0.92 (9H, s), 0.12 (3H, s); Mass *m/z* 344 (M^+-15), 317, 302, 259, 201, 171, 129, 117, 85, 73; Anal. found: C, 49.83; H, 8.00; N, 11.63. Calcd. for $C_{15}H_{29}N_3O_5Si$: C, 50.12; H, 8.13; N, 11.69%.

2-Azido-6-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-β-D-*ribo*-hexulofuranosonamide 12

Direct oxidation method

A mixture of alcohol **5** (0.37 g, 1.0 mmol) and sodium periodate (1.12 g, 5.2 mmol) in acetonitrile (5.4 ml), carbon tetrachloride (5.4 ml), and water (8 ml) was stirred vigorously in the presence of ruthenium(III) chloride hydrate (0.12 g, 0.52 mmol) at room temperature for 90 min. The reaction mixture was diluted with water and filtered through a pad of Celite.[R] The filtrate was acidified with 2N HCl, extracted with dichloromethane, washed with saturated sodium sulfate solution and brine, and dried. Removal of the solvent gave 0.36 g of crude carboxylic acid **11**, which was diluted with THF (10 ml) and treated with triethylamine

(0.20 ml, 2.1 mmol) and ethyl chloroformate (0.40 ml, 2.9 mmol) at 0 °C. After 5 min, ammonia gas was bubbled through the mixture for 10 min, and then the mixture was poured into water, extracted with ether, and washed with brine prior to drying and evaporation. Purification of the residue by chromatography on silica gel (hexane / EtOAc 3 :2) afforded 0.26 g of amide **12** (66% from **5**) as a colorless solid.

Stepwise oxidation method

A solution of dimethylsulfoxide (2.5 ml, 35.5 mmol) in dichloromethane (5 ml) was added dropwise to a solution of oxalyl chloride (1.55 ml, 17.8 mmol) in dichloromethane (80 ml) at -70 °C, and the mixture was stirred for 10 min. A solution of alcohol **5** (4.44 g, 12.7 mmol) in dichloromethane (15 ml) was added, and after 15 min at 70 °C, triethylamine (8.8 ml, 63.4 mmol) was added. The resulting mixture was stirred at -70 °C for 30 min and at 0 °C for 30 min; then it was poured into water, and extracted with dichloromethane. The combined organic layers were washed with brine, dried, and concentrated to give 4.6 g of the crude aldehyde, which was subjected to the next oxidation reaction without further purification. NMR ($CDCl_3$) δ 9.44 (1H, s), 4.88 (1H, dd, J = 5.8, 1.2 Hz), 4.63 (1H, d, J = 5.8 Hz), 4.55 (1H, ddd, J = 6.0, 5.0, 1.2 Hz), 3.79 (1H, dd, J = 10.8, 5.0 Hz), 3.76 (1H, dd, J = 10.8, 5.0 Hz), 1.48 (3H, s), 1.30 (3H, s), 0.92 (9H, s), 0.10 (6H, s). The crude aldehyde (4.6 g) was dissolved in *tert*-butanol (80 ml). Sodium dihydrogen phosphate dihydrate (3.96 g, 25.4 mmol) and sodium chlorite (3.45 g, 38.1 mmol) in water (40 ml), and 2-methyl-2-butene (4.0 ml, 38.1 mmol) were added to the solution. After 2 h, the reaction mixture was poured into water, acidified to pH 2 with 2N HCl, and extracted with dichloromethane. The organic extracts were dried and evaporated to afford 4.5 g of the crude corresponding carboxylic acid **11**, which was dissolved in THF (150 ml) and cooled to 0 °C. Ethyl chloroformate (1.8 ml, 19.0 mmol) and triethylamine (5.3 ml, 38.1 mmol) were added. After 10 min, ammonia gas was bubbled through the mixture for 10 min. The reaction mixture was quenched by addition of water and extracted with EtOAc, and the combined organic layers were washed with brine and dried. Silica gel chromatography (hexane EtOAc 3 :2) afforded amide **12** (1.15 g, 24%) as a colorless solid.

m.p. 129-130 °C; $[\alpha]_D^{25}$ -133.7 (C=0.89, $CHCl_3$); IR ($CHCl_3$) 3520, 3400, 2955, 2860, 2120, 1710, 1570, 1380, 1110, 1080 cm^{-1}; NMR ($CDCl_3$) δ 6.64 (1H, brd.), 5.84 (1H, brd.), 4.80 (1H, dd, J = 5.6, 1.6 Hz), 4.68 (d, J = 5.6 Hz), 4.42 (1H, ddd, J = 7.0, 5.8, 5.6 Hz), 3.78 (1H, dd, J = 10.5, 5.8 Hz), 3.73 (1H, dd, J = 10.5, 7.0 Hz), 1.49 (3H, s), 1.32 (3H, s), 0.91 (9H, s), 0.10 (6H, s); Mass *m/z* 357 (M^+-15), 330, 315, 287, 272, 257, 217, 186, 159, 129, 117, 75; Anal. found: C, 48.08; H, 7.30; N, 15.03. Calcd. for $C_{15}H_{28}N_4O_5Si$: C, 48.37; H, 7.58; N, 15.04%.

***(2R,3R,4R,5S)*-2-*tert*-Butyldimethylsilyloxymethyl-3,4-dimethylenedioxy-6,8-diaza-1-oxa-spiro[4.4]nonane-7-thione-9-one 13 and its epimer 14**

n-Tributylphosphine (1.82 ml, 7.3 mmol) was added to a solution of amide **12** (2.48 g, 6.6 mmol) in acetonitrile (25 ml) at room temperature. After 20 min, carbon disulfide (15.2 ml, 120 mmol) was added, and the resulting mixture was maintained at 50 °C for 7 h. The product mixture was concentrated and purified by silica gel chromatography (hexane / EtOAc 8 : 1 to 6 : 1) to afford the desired spirothiohydantoin **13** (0.42 g, 16%) as a colorless solid and ***(2R,3R,4R,5R)*-2-*tert*-butyldimethylsilyloxymethyl-3,4-dimethylenedioxy-6,8 diaza-1-oxa-spiro[4.4]nonane-7-thione-9-one 14** (0.64 g, 25%) as a colorless syrup, respectively.

For 13: m.p. 159-160 °C; $[\alpha]_D^{25}$ -172.6 (C=0.79, $CHCl_3$); IR ($CHCl_3$) 3440, 1780, 1490, 1375, 1120, 1100,

1080 cm^{-1}; NMR ($CDCl_3$) δ 8.16 (1H, brd.), 7.89 (1H, brd.), 4.84 (1H, d, *J* = 6.2 Hz), 4.81 (1H, d, *J* = 6.2 Hz), 4.58 (1H, t, *J* = 1.6 Hz), 3.94 (1H, dd, *J* = 11.3, 1.6 Hz), 3.81 (1H, dd, *J* = 11.3, 1.6 Hz), 1.63 (3H, s), 1.33 (3H, s), 0.99 (9H, s), 0.22 (3H, s), 0.20 (3H, s); Mass *m/z* 388 (M^+), 373, 331, 313, 185, 149, 126, 117, 75; Anal. found: C, 49.24; H, 7.01; N, 7.24; S, 8.13. Calcd. for $C_{16}H_{28}N_2O_5SSi$: C, 49.46; H, 7.27; N, 7.21; S, 8.25%.

For 14: $[\alpha]_D^{25}$ -53.7 (C=1.14, $CHCl_3$); IR ($CHCl_3$) 3450, 1770, 1490, 1080 cm^{-1}; NMR ($CDCl_3$) δ 8.24 (1H, brd.), 7.19 (1H, brd.), 4.85 (1H, dd, *J* = 6.0, 2.0 Hz), 4.79 (1H, d, *J* = 6.0 Hz), 4.28 (1H, td, *J* = 6.0, 2.0 Hz), 3.75 (2H, d, *J* = 6.0 Hz), 1.59 (3H, s), 1.38 (3H, s), 0.90 (9H, s), 0.09 (3H, s), 0.07 (3H, s); Mass *m/z* 389 (M^++1), 373, 331, 273, 255, 185, 158, 145, 126, 89, 75; Anal. found: C, 49.21; H, 7.10; N, 6.95; S, 8.50. Calcd. for $C_{16}H_{28}N_2O_5SSi$: C, 49.46; H, 7.27; N, 7.21; S, 8.25%.

***(2R,3R,4R,5S)*-3,4-Dihydroxy-2-hydroxymethyl-6,8-diaza-1-oxa-spiro[4.4]nonane-7-thione-9-one 2**

A mixture of spirothiohydantoin **13** (0.31 g, 0.79 mmol) and Dowex 50W^R (H^+, 0.90 g) in methanol (6 ml) and water (3 ml) was heated at 60 °C for 3 h. The reaction mixture was filtered through a pad of Celite^R and evaporated. The residue was purified by preparative TLC (EtOAc only) to afford the desired product **2** (0.14 g, 77%) as a colorless syrup.

$[\alpha]_D^{25}$ -52.7 (C=0.84, MeOH); IR (KBr) 3450, 3400, 3350, 3280, 3000, 1750, 1520, 1410, 1320, 1210, 1100 cm^{-1}; NMR (CD_3OD) δ 4.30 (1H, d, *J* = 5.6 Hz), 4.27-4.23 (1H, m), 4.07 (1H, dd, *J* = 5.6, 2.6 Hz), 3.66 (1H, dd, *J* = 12.0, 3.8 Hz), 3.61 (1H, dd, *J* = 12.0, 4.2 Hz); Mass *m/z* 234 (M^+), 200, 145, 132, 116, 86, 73; Anal. found: C, 35.87; H, 4.15; N, 11.69; S, 13.43. Calcd. for $C_7H_{10}N_2O_5S$: C, 35.90; H, 4.30; N, 11.96; S, 13.69%.

***(2R,3R,4R,5R)*-3,4-Dihydroxy-2-hydroxymethyl-6,8-diaza-1-oxa-spiro[4.4]nonane-7-thione-9-one 15**

A mixture of spirothiohydantoin **14** (28 mg, 0.073 mmol) and Dowex 50W^R (H^+, 90 mg) in methanol (0.6 ml) and water (0.6 ml) was stirred at 50 °C for 6 h. After filtration through a pad of Celite^R and concentration, the residue was subjected to preparative TLC (EtOAc only) to give the epimer **15** (16 mg, 94 %) as a colorless syrup.

$[\alpha]_D^{25}$ +36.8 (C=0.90, MeOH); IR (KBr) 3410, 3200, 2950, 2870, 1760, 1630, 1510, 1400, 1320, 1260, 1090 cm^{-1}; NMR (CD_3OD) δ 4.27 (1H, d, *J* = 4.8 Hz), 4.18 (1H, dd, *J* = 4.8, 3.2 Hz), 4.15-4.10 (1H, m), 3.66 (1H, dd, *J* = 12.1, 4.2 Hz), 3.59 (1H, dd, *J* = 12.1, 5.0 Hz); Mass *m/z* 234 (M^+), 198, 132, 116, 88, 73, 60, 56, 40; Anal. found: C, 35.57; H, 4.56; N, 11.66; S, 13.47. Calcd. for $C_7H_{10}N_2O_5S$: C, 35.90; H, 4.30; N, 11.96; S, 13.69%.

Herbicidal activity

Plastic pots (150 cm^2) were filled with sterilized sandy clay loam soil. Seeds of ten weeds were sown in the soil at a depth of about 0.5 cm. After 10-15 days of cultivation in a greenhouse, when the weeds had grown to the 3-leaf stage, a diluted suspension of each compound (1000 ppm) containing Gramin-S and water was uniformly sprayed on the foliage. Ten days after the treatment, the herbicidal activity against each weed was visually evaluated by the following ratings.

Herbicidal effect: 5, 95 to 100% weed control (plant growth inhibition); 4, 80 to 94% control; 3, 50 to 79% control; 2, 30 to 49% control; 1 10 to 29% control; 0, 0 to 9% control.

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