Pergamon

Tetrahedron Vol. 51, No. 5, pp. 1387-1394, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01027-7

Stereocontrolled Synthesis of Spirosuccinimide Derivative of (+)-Hydantocidin

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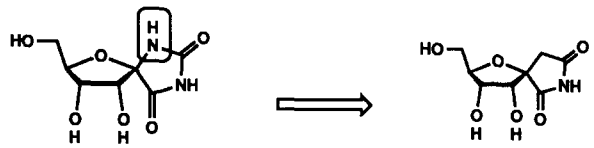
Abstract: Synthesis of the spirosuccinimide derivative of (+)-hydantocidin **2** is reported. The key step is a $SnCl_4$-promoted *C*-glycosidation of the protected D-psicose **3** with allyltrimethlsilane in dichloromethane, which proceeded in good yield and high selectivity; however, *C*-glycosidation of **3** in acetonitrile afforded the spirooxazoline **6**. Synthesis of **2** was achieved in 13% overall yield from **3**.

Since the isolation of (+)-hydantocidin **1**,[1] the first naturally occurring spironucleoside, the interest in this unusual class of compounds has grown rapidly.[2] Considerable synthetic works toward (+)-hydantocidin itself[3] and its derivatives[4] have been reported due to its unique structure, a spirohydantoin nucleus at the anomeric position of D-ribofuranose, as well as potent herbicidal activity with no toxicity against mammals.[1c]

From our previous investigation on the structure modification of the sugar moiety of (+)-hydantocidin, all three hydroxy groups existing in D-furanose ring are found to be essential for herbicidal activity.[4, 5] On the other hand, the study of the hydantoin part, in which two amido functions might take part in hydrogen bonding with a certain receptor in plants, has not been explored. Herein, we describe stereocontrolled synthesis of the spirosuccinimide derivative **2**, which has methylene group in stead of the NH group of the hydantoin ring in (+)-hydantocidin. This replacement would remove the hydrogen bonding ability at that site with minimal conformational change (**Figure 1**).



1
(+)-hydantocidin

2

Figure 1

Our approach to the spirosuccinimide skeleton **A** is described in **Figure 2**. We envisaged that a spirosuccinimide **A** would evolve from a protected D-psicose **C** by stereoselective *C*-glycosidation with a "carbonyl methyl" equivalent followed by oxidation of a hydroxymethyl group in **B** and subsequent succinimide ring formation. We chose allyltrimethylsilane which could serve as the carbonyl methyl nucleophile by

oxidative cleavage of the double bond after *C*-allylation.

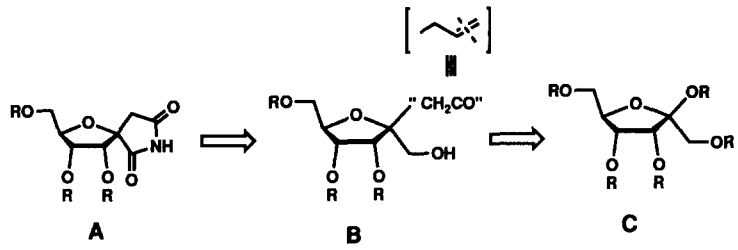
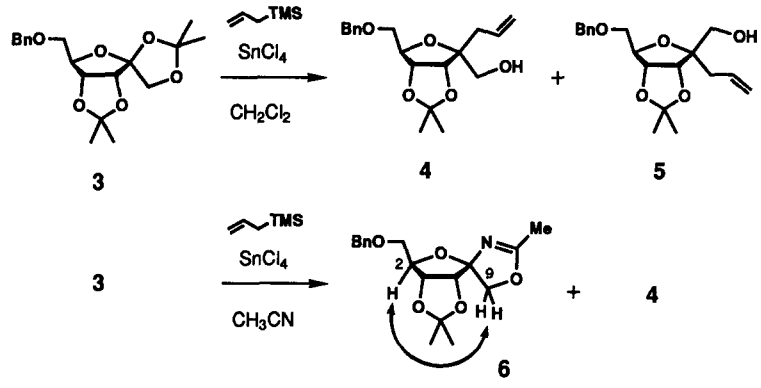


Figure 2

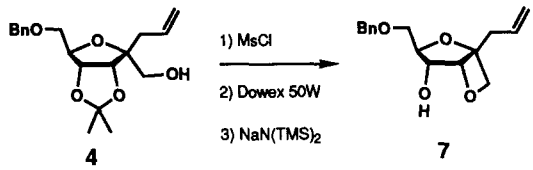
5-*O*-Benzyl-1,2:3,4-di-*O*-isopropylidene-D-psicofranose **3** which was easily prepared from D-fructose,[6] underwent $SnCl_4$-promoted *C*-glycosidation[7] with allyltrimethylsilane in dichloromethane at -40 ℃ to give predominately **4** in 83% yield and the epimer **5** in 4% (**Scheme 1**). Using other Lewis acids such as TMSOTf, BF_3•Et_2O, $TrClO_4$, and $TiCl_4$ resulted in recovery of starting material. When *C*-glycosidation of **3** was carried out in acetonitrile at -20 °C, spirooxazoline **6** was obtained in 42% yield together with **4** in 10% yield.[8, 9, 10] This result demonstrated that nitrile-nucleophile is more reactive to a cationic intermediate derived from **3** than allyltrimethylsilane.

Scheme 1



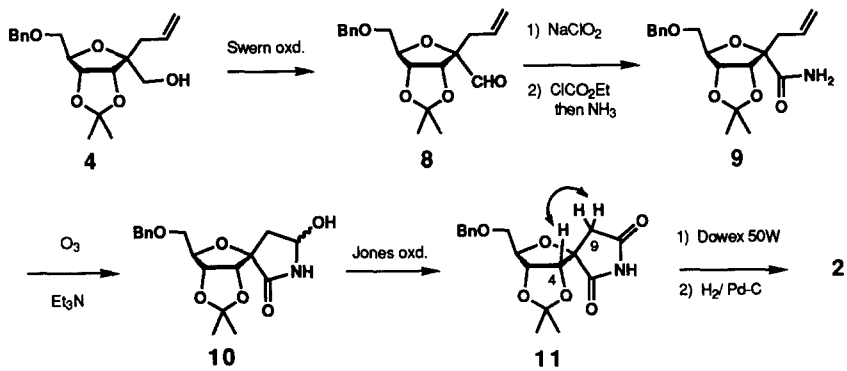
Stereochemistry of the major stereoisomer **4** at the anomeric position was determined by the following chemical transformation (**Scheme 2**): a) mesylation of the hydroxymethyl group in **4**, b) removal of the isopropylidene moiety with Dowex 50W ^{R} (H^+ form), and c) cyclization into oxetane **7** by treatment with sodium bis(trimethylsilyl)amide. This oxetane formation indicates that allyl nucleophile attacked from β–face at the anomeric center of **3**.

Scheme 2



Conversion of **4** to the target molecule **2** is summarized in **Scheme 3**. Swern oxidation of **4** gave aldehyde **8**, which was converted to amide **9** through a mixed carboxylic anhydride intermediate: oxidation of aldehyde **8** with sodium chlorite in the presence of 2-methyl-2-butene and sodium dihydrogen phosphate[10] gave the carboxylic acid, which was sequentially treated with triethylamine and ethyl chloroformate, and with gaseous ammonia to afford amide **9** in 58% overall yield from **8**. Ozonolysis of **9** followed by reductive workup with triethylamine afforded the aldehyde intermediate, which was isolated as a diastereomixture of hemiacetal **10** in 57% yield. The ratio of diastereomixture was found to be *ca.* 3 : 1 by HPLC analysis. Construction of the spirosuccinimide skeleton was accomplished by Jones oxidation of the mixture **10** to afford **11** in 79% yield. The stereochemistry of **11** at the anomeric position was confirmed by 2D-NOESY experiment: the cross peak between the C4 methine and the C9 methylene hydrogens of **11** was observed. Hydrolysis of the isopropylidene group in **11** with Dowex 50W* (H^{+} form) in MeOH-H_2O followed by debenzylation with 5% Pd-C under hydrogen atmosphere furnished the spirosuccinimide analogue **2** in 60% yield from **11**. The overall yield from **3** to **2** was 13% in 7 steps.

Scheme 3



The results of bioassay showed that the designed compound **2** maintained herbicidal activity in some extent despite lacking the NH-group. Spirosuccinimide **2** gave 90% herbicidal control of cocklebur, 90% control of ragweed, and 70% control of crabgrass, when applied to a foliage of the weeds at 1000 ppm, whereas (+)-hydantocidin completely controlled all species at the same concentration. This finding might indicate the possibility that the NH-group attached at the anomeric position is a supplementary unit in (+)

hydantocidin for herbicidal activity. This is in contrast with distinct recognition of all three hydroxy groups in D-ribofuranose ring for herbicidal activity.[4, 5]

In conclusion, we have established an efficient route for the synthesis of spirosuccinimide derivative **2** at the anomeric position of nucleoside by employing *C*-glycosidation of the protected psicose **3** with allyltrimethylsilane. The result of bioassay might indicate that the NH-group at the anomeric position could be replaceable by a methylene unit. Further research on the structure-herbicidal-activity relationships of (+)-hydantocidin is now in progress.

Acknowledgment

We wish to thank Mr. T. Honma and Mr. M. Shindou, Agroscience Research Laboratories, Sankyo Co. Ltd., for testing the herbicidal activity of spirosuccinimide derivative **2**.

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.

2-Allyl-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-β-D-psicofuranose 4 and its α isomer 5.

To a cooled (-40 °C) solution of **3** (4.37 g, 12.5 mmol) and allyltrimethylsilane (2.19 ml, 37.4 mmol) in CH_2Cl_2 (100 ml), $SnCl_4$ (2.19 ml, 18.7 mmol) was added dropwise, and the mixture was maintained at -40 °C for 3 h. The reaction mixture was poured into sat. $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was subjected to chromatography on silica gel (hexane/EtOAc 8:1) to give **4** (3.45 g, 83%) and **5** (0.15 g, 4%) as colorless oils.

For **4**: $[\alpha]_D^{25}$ +12.2 (c = 1.42, $CHCl_3$); IR (neat) 3470, 3050, 2985, 2930, 1635, 1490, 1450, 1370, 1245, 1205, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.28 (5H, m), 5.92-5.76 (1H, m), 5.16 (1H, d, *J* = 6.5 Hz), 5.11 (1H, s), 4.64 (1H, dd, *J* = 6.9, 4.4 Hz), 4.58 (2H, s), 4.56 (1H, d, *J* = 6.9 Hz), 4.16 (1H, dd, *J* = 9.3, 4.4 Hz), 3.72 (1H, d, *J* = 11.7 Hz), 3.67 (1H, d, *J* = 11.7 Hz), 3.56 (2H, m), 2.45 (1H, dd, *J* = 14.5, 7.3 Hz), 2.44 (1H, dd, *J* = 14.5, 7.3 Hz), 2.26 (1H, s), 1.54 (3H, s), 1.33 (3H, s); MS *m/z* 334 (M^+), 320, 303, 293, 245, 235, 201, 185, 173, 117, 92; HRMS. found: 334.1780. Calcd. for $C_{19}H_{26}O_5$: 334.1782.

For **5**: $[\alpha]_D^{25}$ +8.6 (c = 1.01, $CHCl_3$); IR (neat) 3470, 3050, 2985, 2930, 1635, 1490, 1450, 1370, 1245, 1205, 1150, 1070 cm^{-1}; NMR ($CDCl_3$) δ 7.39-7.27 (5H, m), 5.95-5.80 (1H, m), 5.17-5.00 (2H, m), 4.90 (1H, dd, *J* = 6.0, 5.6 Hz), 4.69 (1H, d, *J* = 6.0 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.53 (1H, d, *J* = 11.7 Hz), 4.09 (1H, ddd, *J* = 5.6, 2.8, 2.0 Hz), 3.77 (1H, dd, *J* = 10.5, 2.8 Hz), 3.64 (1H, dd, *J* = 10.5, 2.0 Hz), 3.59-3.33 (3H, m), 2.50 (1H, dd, *J* = 14.1, 6.9 Hz), 2.45 (1H, dd, *J* = 14.1, 7.7 Hz), 1.54 (3H, s), 1.35 (3H, s); MS *m/z* 334 (M^+), 320, 303, 293, 245, 235, 201, 185, 173, 117, 92; HRMS. found: 334.1775. Calcd. for $C_{19}H_{26}O_5$: 334.1782.

***C*-Glycosidation in acetonitrile:**

To a solution of **3** (0.25 g, 0.71 mmol) and allyltrimethylsilane (0.33 ml, 2.1 mmol) in acetonitrile (6 ml) was added $SnCl_4$ (0.13 ml, 1.1 mmol) at -20 °C. After being stirred for 4 h, the reaction mixture was quenched with sat. $NaHCO_3$, and extracted with EtOAc. The combined extracts were washed with brine and dried. Removal of the solvent followed by purification with silica gel chromatography (hexane/EtOAc 8:1)

gave **(2*R*,3*R*,4*R*,5*R*)-2-benzyloxymethyl-3,4-(dimethylmethylenedioxy)-6,7-didehydro-7-methyl-1,8-dioxa-6-azaspiro[4.4]nonane 6** (0.10 g, 42%) and **4** (24 mg, 10%) as colorless oils.
For **6**: $[\alpha]_D^{25}$ -69.3 (c = 1.80, $CHCl_3$); IR ($CHCl_3$) 1650, 1450, 1385 cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.27 (5H, m), 4.80 (1H, dd, *J* = 6.0, 1.6 Hz), 4.58 (2H, ABq, *J* = 12.1 Hz), 4.53 (1H, d, *J* = 10.9 Hz), 4.49 (1H, d, *J* = 10.9 Hz), 4.30 (1H, td, *J* = 7.3, 1.6 Hz), 1H, d, *J* = 10.9 Hz), 3.64 (2H, ABq, *J* = 9.8, 7.3 Hz), 1.99 (3H, s), 1.46 (3H, s), 1.33 (3H, s) ; MS *m/z* 334 (M^++1), 318, 242, 227, 154, 126, 98, 84; Anal. found: C, 64.55; H, 7.25; N, 3.91. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20%.

2-Allyl-1,3-anhydro-6-*O*-benzyl-2-deoxy-β-D-psicofuranose 7
Methanesulfonyl chloride (0.24 ml, 3.2 mmol) was added to a solution of **4** (0.35 g, 1.0 mmol) and Et_3N (0.73 ml, 5.2 mmol) in CH_2Cl_2 (10 ml) at 0 °C, and the mixture was stirred for 15 min. The reaction mixture was partitioned between water and ether. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel (hexane/EtOAc 3:1) to give **2-allyl-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropyridene-1-*O*-methanesulfonyl-β-D-psicofuranose** (0.34 g, 79%) as a colorless oil:
$[\alpha]_D^{25}$+9.9 (c = 1.08, $CHCl_3$); IR (neat) 3070, 3030, 3000, 2950, 2860, 1600, 1495, 1450, 1350, 1210, 1175, 1075 cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.29 (5H, m), 5.87-5.72 (1H, m), 5.21-5.15 (2H, m), 4.68 (1H, dd, *J* = 6.9, 4.8 Hz), 4.57 (2H, s), 4.56 (1H, d, *J* = 6.9 Hz), 4.39 (1H, d, *J* = 10.9 Hz), 4.24 (1H, d, *J* = 10.9 Hz), 4.19 (1H, ddd, *J* = 6.0, 4.8, 4.0 Hz), 3.59 (1H, dd, *J* = 10.5, 4.0 Hz), 3.57 (1H, dd, *J* = 10.5, 6.0 Hz), 3.06 (3H, s), 2.55-2.34 (2H, m), 1.52 (3H, s), 1.32 (3H, s) ; MS *m/z* 412 (M^+), 397, 371, 305, 245, 145, 137, 121, 92; HRMS. found: 412.1552. Calcd. for $C_{20}H_{28}O_7S$: 412.1548.

A mixture of the above mesylate (0.34 g, 0.94 mmol) and Dowex 50W^R (H^+ form) (1.4 g) in H_2O (3 ml) and methanol (6 ml) was heated at 60 °C for 3 h. The reaction mixture was filtered through a pad of Celite^R, and the filtrate was evaporated in vacuo. Silica gel chromatography (hexane/EtOAc 1:1 to 1:2) of the residue afforded **2-allyl-6-*O*-benzyl-2-deoxy-1-*O*-methanesulfonyl-β-D-psicofuranose** (0.30 g, 85%) as a colorless oil:
$[\alpha]_D^{25}$ +9.0 (c = 3.29, $CHCl_3$); IR (neat) 3500, 3050, 2950, 2880, 1640, 1495, 1450, 1350, 1170, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.38-7.25 (5H, m), 5.88-5.73 (1H, m), 5.17 (1H, s), 5.11 (12H, d, *J* = 5.6 Hz), 4.57 (1H, d, *J* = 12.1 Hz), 4.56 (1H, d, *J* = 12.1 Hz), 4.36 (1H, d, *J* = 10.5 Hz), 4.34 (1H, d, *J* = 10.5 Hz), 4.11 (1H, dd, *J* = 6.8, 5.6 Hz), 4.04 (1H, d, *J* = 5.6 Hz), 4.02 (1H, ddd, *J* = 6.8, 4.4, 4.0 Hz), 3.62 (1H, dd, *J* = 10.5, 4.0 Hz), 3.61 (1H, dd, *J* = 10.5, 4.4 Hz), 3.15-2.60 (2H, m), 3.05 (3H, s), 2.40 (1H, dd, *J* = 6.9, 1.2 Hz), 2.37 (1H, dd, *J* = 6.9, 1.2 Hz); MS *m/z* 372 (M^+), 331, 263, 245, 235, 217, 179, 155, 107, 92; HRMS. found: 372.1233. Calcd. for $C_{17}H_{24}O_7S$: 372.1242.

To a solution of the above diol (0.25 g, 0.67 mmol) in THF (10 ml) was added $NaN(TMS)_2$ (1M in THF, 1.0 ml) at 0 °C. After 10 min, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with ether. The organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent followed by chromatography on silica gel (hexane/EtOAc 1:1) gave oxetane **7** (0.14 g, 77%) as a colorless syrup.
For **7**: $[\alpha]_D^{25}$ +54.1 (c = 1.32, $CHCl_3$); IR (neat) 3400, 3050, 3020, 2930, 2860, 1635, 1490, 1445, 1245, 1165, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.38-7.24 (5H, m), 5.86-5.71 (1H, m), 5.20-5.10 (2H, m), 4.82 (1H, d, *J* = 4.8 Hz), 4.72 (1H, d, *J* = 7.7 Hz), 4.64 (2H, s), 4.57 (1H, d, *J* = 7.7 Hz), 4.21 (1H, ddd, *J* = 8.5, 6.0, 2.4 Hz), 3.85 (1H, dd, *J* = 10.5, 2.4 Hz), 3.69 (1H, dd, *J* = 10.5, 6.0 Hz), 3.79 (1H, ddd, *J* = 10.9, 8.5, 4.8 Hz), 2.62-2.47 (2H, m), 2.43 (1H, d, *J* = 10.9 Hz); MS *m/z* 276 (M^+), 259, 246, 181, 155, 137, 125, 107, 99; HRMS. found: 276.1360. Calcd. for $C_{16}H_{20}O_4$: 276.1356.

2-Allyl-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-β-D-*ribo*-hexos-2-ulo-2,5-furanose 8.
A solution of DMSO (1.50 ml, 21.1 mmol) in CH_2Cl_2 (5 ml) was added to a cold (-60 °C) solution of oxalyl

chloride (0.90 ml, 10.5 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred for 5 min. A solution of alcohol **4** (1.41 g, 4.2 mmol) in CH_2Cl_2 (5 ml) was added to the mixture, and the resulting mixture was stirred at -60 °C for 15 min. Triethylamine (5.87 ml, 42.1 mmol) was added, and after 30 min at room temperature, the reaction mixture was poured into H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane/EtOAc 7:1) to give aldehyde **8** (1.36 g, 97%) as a colorless oil.

For **8**: $[\alpha]_D^{25}$ -5.4 (c = 2.26, $CHCl_3$); IR (neat) 3060, 3030, 2990, 2930, 2850, 2710, 1735, 1635, 1490, 1450, 1425, 1375, 1245, 1210, 1155, 1070 cm^{-1}; NMR ($CDCl_3$) δ 9.62 (1H, s), 7.39-7.27 (5H, m), 5.83-5.68 (1H, m), 5.15-5.07 (2H, m), 4.75 (1H, dd, *J* = 6.5, 3.6 Hz), 4.67 (1H, d, *J* = 6.5 Hz), 4.59 (1H, s), 4.58 (1H, s), 4.44 (1H, ddd, *J* = 4.0, 4.0, 3.6 Hz), 3.64 (1H, *J* = 10.5, 4.0 Hz), 3.62 (1H, dd, *J* = 10.5, 4.0 Hz), 2.59 (1H, m), 2.52 (1H, m), 1.46 (3H, s), 1.29 (3H, s); MS *m/z* 332 (M^+), 317, 303, 245, 199, 149, 117, 92; HRMS. found: 332.1630. Calcd. for $C_{19}H_{24}O_5$: 332.1623.

2-Allyl-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-β-D-*ribo*-hexulofuranosonamide 9.

A solution of sodium dihydrogen phosphate dihydrate (2.2 g, 14.1 mmol) and sodium chlorite (2.0 g, 22.1 mmol) in H_2O (20 ml) was added to a stirred solution of aldehyde **8** (2.35 g, 7.1 mmol) and 2-methyl-2-butene (1.5 ml, 14.1 mmol) in *t*-BuOH (40 ml). After being stirred at room temperature for 30 min, the reaction mixture was quenched with saturated Na_2SO_3 solution, acidified to pH 1 with 1N-HCl, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and evaporated to give 1.65 g of **2-allyl-6-*O*-benzyl-2-deoxy--3,4-*O*-isopropylidene-β-D-*ribo*-hexulofuranosonoic acid** (67%) as a colorless oil:

$[\alpha]_D^{25}$ -26.9 (c = 1.46, $CHCl_3$); IR (neat) 3090, 3000, 2950, 2600, 1730, 1640, 1495, 1450, 1370, 1250, 1210, 1130, 1070 cm^{-1}; NMR ($CDCl_3$) δ 7.40-7.23 (5H, m), 5.82-5.66 (1H, m), 5.15-5.09 (1H, m), 4.81 (1H, dd, *J* = 6.0, 3.6 Hz), 4.64 (1H, d, *J* = 6.0 Hz), 4.57 (2H, s), 4.47 (1H, ddd, *J* = 4.0, 3.6, 3.6 Hz), 3.62 (1H, dd, *J* = 10.5, 3.6 Hz), 3.61 (1H, dd, *J* = 10.5, 4.0 Hz), 2.81 (1H, dd, *J* = 14.1, 7.3 Hz), 2.58 (1H, dd, *J* = 14.1, 6.9 Hz), 1.50 (3H, s), 1.32 (3H, s); MS *m/z* 348 (M^+), 333, 303, 293, 245, 155, 145, 117, 107, 90; HRMS. found: 348.1565. Calcd. for $C_{19}H_{24}O_6$: 348.1573.

Triethylamine (1.93 ml, 13.9 mmol) and ethyl chloroformate (0.66 ml, 6.9 mmol) were sequentially added to a solution of the above carboxylic acid (1.61 g, 4.6 mmol) in THF (15 ml) at 0 °C, and the resulting mixture was stirred at 0 °C for 10 min. Ammonia gas was bubbled through the reaction mixture at 0 °C for 30 min, and the reaction mixture was quenched by the addition of 1N-HCl and saturated NH_4Cl solution. The product mixture was extracted with CH_2Cl_2, and the combined extracts were washed with brine and dried. Silica gel chromatography (hexane/EtOAc 1:1 to 1:2) of the residue gave amide **9** (1.39 g, 87%) as a colorless oil.

For **9**: $[\alpha]_D^{25}$ -29.8 (c = 1.18, $CHCl_3$); IR (neat) 3470, 3320, 2990, 2930, 1680, 1580, 1490, 1450, 1375, 1245, 1205, 1155, 1100, 1060 cm^{-1}; NMR ($CDCl_3$) δ 7.40-7.28 (5H, m), 6.76 (1H, brd.), 5.82-5.67 (2H, m), 5.13-5.07 (2H, m), 4.72 (1H, dd, *J* = 5.6, 4.0 Hz), 4.63 (1H, d, *J* = 5.6 Hz), 4.58 (2H, s), 4.33 (1H, m), 3.58 (1H, dd, *J* = 14.1, 6.8 Hz), 2.43 (1H, dd, *J* = 14.1, 7.3 Hz), 1.50 (3H, s), 1.32 (3H, s); MS *m/z* 347 (M^+), 332, 303, 245, 199, 183, 168, 155, 139, 117, 91; HRMS. found: 347.1731. Calcd. for $C_{19}H_{25}NO_5$: 347.1726.

(2*R*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-3,4-isopropylidenedioxy-8-hydroxy-1-oxa-7-azaspiro[4.4]nonan-6-one 10.

Ozone was bubbled through a solution of amide **9** (0.59 g, 1.71 mmol) in CH_2Cl_2 (10 ml) at -70 °C for 2 h. Triethylamine (1.67 ml, 12.0 mmol) was added, and the mixture was stirred at -70 °C for 30 min and at 0 °C for 1 h. The reaction mixture was partitioned between water and CH_2Cl_2, and the combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was purified by silica gel chromatography (hexane/EtOAc 2:5 to EtOAc only) to give a diastereomeric mixture of hemiacetal **10** (0.34 g, 57%) as a colorless oil. The ratio of the diastereomer was found to be *ca.* 3 : 1 by HPLC analysis. For

analytical purpose, the diastereomer could be separated by careful silica gel chromatography.
For the less polar isomer of **10**: $[\alpha]_D^{25}$ +5.9 (c = 2.42, $CHCl_3$); IR ($CHCl_3$) 3670, 3610, 3025, 2400, 1720, 1720, 1600, 1510, 1475, 1420, 1380, 1075, 1040 cm^{-1}; NMR ($CDCl_3$) δ 7.38-7.25 (5H, m), 5.20 (1H, dd, *J* = 6.0, 5.6 Hz), 4.84 (1H, s), 4.79 (1H, dd, *J* = 6.9, 2.8 Hz), 4.66-4.61 (1H, m), 4.59 (1H, d, *J* = 6.9 Hz), 4.55 (1H, d, *J* = 12.1 Hz), 4.51 (1H, d, *J* = 12.1 Hz), 3.56 (2H, m), 2.59 (1H, dd, *J* = 13.3, 5.6 Hz), 2.11 (1H, s), 2.07 (1H, dd, *J* = 13.3, 3.6 Hz), 1.51 (3H, s), 1.29 (3H, s); MS *m/z* 349 (M^+), 334, 316, 305, 273, 240, 226, 199, 182, 175, 145, 126, 105, 92; HRMS. found: 349.1523. Calcd. for $C_{18}H_{23}NO_6$: 349.1519.
For the more polar isomer of **10**: $[\alpha]_D^{25}$ +18.6 (c = 1.54, $CHCl_3$); IR ($CHCl_3$) 3670, 3610, 3025, 2400, 1720, 1600, 1510, 1475, 1420, 1380 cm^{-1}; NMR ($CDCl_3$) δ 7.39-7.27 (5H, m), 7.12 (1H, s), 5.22 (1H, m), 4.84 (2H, s), 4.71-4.64 (1H, m), 4.55 (2H, s), 3.57 (3H, d, *J* = 4.0 Hz), 2.40 (1H, dd, *J* = 13.3, 5.6 Hz), 2.24 (1H, d, *J* = 13.3 Hz), 1.55 (3H, s), 1.34 (3H, s); MS *m/z* 349 (M^+), 334, 316, 305, 273, 240, 226, 199, 182, 175, 145, 126, 105, 92; HRMS. found: 349.1514. Calcd. for $C_{18}H_{23}NO_6$: 349.1519.

(2*R*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-3,4-isopropylidenedioxy-1-oxa-7-azaspiro[4.4]nonane-6,8-dione 11.
Jones reagent was added to a cold (0 °C) solution of hemiacetal **10** (0.33 g, 0.92 mmol) in acetone (15 ml), and the mixture was stirred at 0 °C for 10 min. The excess oxidant was quenched by the addition of *i*-PrOH, and the product mixture was filtered through a pad of Celite^R. The filtrate was diluted with ether, washed sequentially with saturated $NaHCO_3$ and brine, dried, and evaporated. Purification of the residue by silica gel chromatography (hexane/EtOAc 5:2) gave spirosuccinimide **11** (0.25 g, 79%) as a colorless syrup.
For **11**: $[\alpha]_D^{25}$ +12.4 (c = 2.53, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2850, 1790, 1730, 1450, 1375, 1340, 1260, 1180, 1155, 1130, 1080 cm^{-1}; NMR ($CDCl_3$) δ 8.34 (1H, brd.), 7.41-7.28 (5H, m), 4.86 (1H, dd, *J* = 6.5, 2.8 Hz), 4.73 (1H, d, *J* = 6.5 Hz), 4.69 (1H, dd, *J* = 5.6, 2.8 Hz), 4.54 (2H, ABq, *J* = 12.0 Hz), 3.60 (2H, m), 2.90 (2H, s), 1.53 (3H, s), 1.32 (3H, s); MS *m/z* 347 (M^+), 332, 289, 241, 224, 198, 181, 168, 145, 126, 105, 92; HRMS. found: 347.1368. Calcd. for $C_{18}H_{21}NO_6$: 347.1363.

(2*R*,3*S*,4*R*,5*S*)-3,4-Dihydroxy-2-hydroxymethyl--1-oxa-7-azaspiro[4.4]nonane-6,8-dione 2.
A mixture of **11** (0.40 g, 1.14 mmol) and Dowex 50W^R (H^+ form) (0.6 g) in MeOH (12 ml) and water (12 ml) was heated at 60 °C for 4.5 h. After filtration through a pad of Celite^R, the filtrate was extracted with EtOAc, and the combined extracts were washed with brine, dried, and concentrated to give **(2*R*,3*S*,4*R*,5*S*)-2-benzyloxymethyl-3,4-dihydroxy-1-oxa-7-azaspiro[4.4]nonane-6,8-dione** (0.35 g, quantitative yield) as a colorless solid. An analytical sample was obtained by recrystallization from EtOAc - MeOH (10:1):
m.p. 191-193 °C; $[\alpha]_D^{25}$ +57.1 (c = 0.41, MeOH); IR (KBr) 3450, 3350, 3150, 3040, 2950, 2880, 2830, 1760, 1700, 1485, 1440, 1400, 1350, 1310, 1300, 1260, 1195, 1160, 1120, 1095 cm^{-1}; NMR (CD_3OD) δ 7.38-7.24 (5H, m), 4.54 (2H, s), 4.35 (1H, dd, *J* = 6.9, 3.2 Hz), 4.24 (1H, d, *J* = 6.0 Hz), 4.07 (1H, dd, *J* = 6.0, 3.2 Hz), 3.60 (1H, s), 3.58 (1H, d, *J* = 6.9 Hz), 2.89 (2H, s); MS *m/z* 307 (M^+), 289, 273, 201, 128, 105, 91; HRMS. found: 307.1048. Calcd. for $C_{15}H_{17}NO_6$: 307.1051.
A solution of the above diol (0.16 g, 0.52 mmol) in MeOH (150 ml) was heated at 55 °C in the presence of 5% Pd/C (0.20 g) under hydrogen (3 kg/cm^2) atmosphere for 6 h. The mixture was filtered through a pad of Celite^R, and the filtrate was evaporated in vacuo. The residue was chromatographed on Dianion CHP 20P (water) to afford **2** (68 mg, 60%) as a white solid.
For **2**: m.p. 143-146 °C; $[\alpha]_D^{25}$ +41.2 (c = 1.28, CH_3OH); IR (KBr) 3480, 3350, 3070, 2960, 2770, 1770, 1710, 1415, 1360, 1290, 1260, 1215, 1140, 1115, 1100, 1060 cm^{-1}; NMR (CD_3OD) δ 4.24 (1H, ddd, *J* = 3.6, 3.2, 3.0 Hz), 4.18 (1H, d, *J* = 6.0 Hz), 4.05 (1H, dd, *J* = 6.0, 3.6 Hz), 3.66 (1H, dd, *J* = 12.1, 3.2 Hz), 3.59 (1H, dd, *J* = 12.1, 3.0 Hz), 2.93 (1H, s), 2.92 (1H, s); MS *m/z* 217 (M^+), 199, 187, 181, 128, 115, 97, 83; Anal. found: C, 44.05; H, 5.33; N, 6.30. Calcd. for $C_8H_{11}NO_6$: C, 44.24; H, 5.11; N, 6.45%.

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(*Received in Japan* 24 *October* 1994; *accepted* 18 *November* 1994)