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SYNTHETIC STUDIES ON (+)-HYDANTOCIDIN (3): A NEW SYNTHETIC METHOD FOR CONSTRUCTION OF THE SPIRO-HYDANTOIN RING AT THE ANOMERIC POSITION OF D-RIBOFURANOSE

Shigeru Mio,* Yuko Kumagawa and Soji Sugai

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

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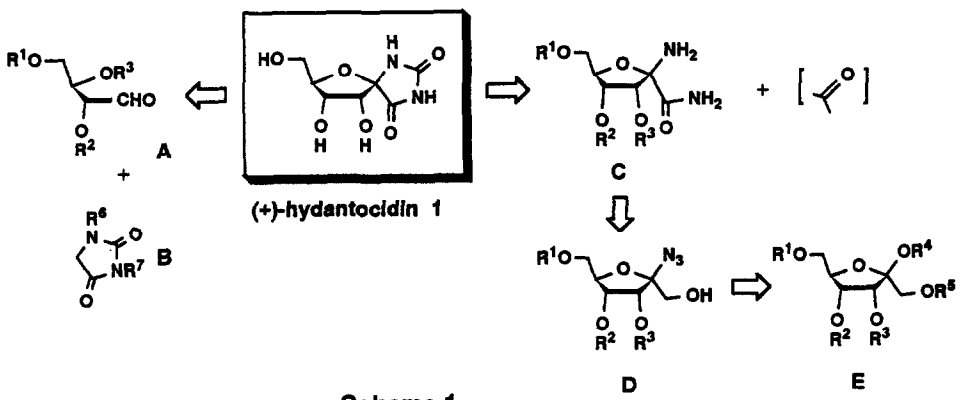
Abstract: A facile synthetic route for the large-scale preparation of a herbicidal natural product, (+)-hydantocidin, is described. The protected D-psicose **6**, prepared in five steps from D-fructose, was stereospecifically converted to azido-amide **14** by *N*-glycosidation ($TMSN_3$/TMSOTf), oxidation and amination. Hydantoin ring-construction on **14** was achieved by aza-Wittig reaction (PBu_3 /CO_2/ CH_3CN) to give **16** without epimerization at the anomeric center. After acetylation, stepwise deprotection of **24** afforded (+)-hydantocidin **1** in 16% overall yield from D-fructose.

In the preceding papers[1] we described the synthesis of (+)-hydantocidin **1**[2] and its stereoisomers on the basis of an aldol condensation methodology which employed D- and L-threose derivatives **A** and hydantoin **B** as starting materials (**Scheme 1**). The methodology was suitable for the synthesis of its stereoisomers, but disadvantageous for the large-scale synthesis of (+)-hydantocidin itself because of using costly starting materials and requiring a tedious chromatography. Since it become necessary to prepare large quantity of **1** for detailed evaluation of its herbicidal properties, we needed to develop a new synthetic method overcoming these problems. In this paper, we describe an efficient method for constructing the hydantoin ring at the anomeric position of a furanose in the complete synthesis of **1**.

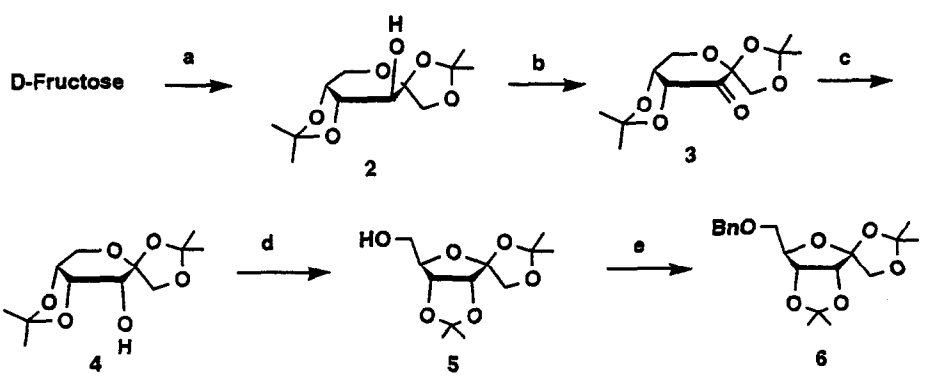
Our synthetic plan is shown in Scheme 1. The hydantoin ring is disconnected retrosynthetically into an amino-amide **C** and an carbonyl unit. The amino-amide **C** is obtainable by reduction of the azide group and the oxidation of the hydroxymethyl group in **D**, which can, in turn, be derived by stereoselective introduction of an azide group to the psicose derivative **E**. Although various synthetic methods for hydantoin formation[3] have been investigated, most of them are thought to be drastic to the *O,NH*-ketal functionality in **C** causing a furanose ring-opening and/or epimerization. Therefore, a mild condition is essential for the success of this spiro-formation. Another major problem is the choice of the suitable psicose **E**, which should be derived from a common sugar in a large scale and should be a good substrate for the *N*-glycosidation at β-position. Surprisingly, little attention has been paid to the *N*-glycosidation of D-psicofuranose derivatives, and, to our knowledge, only 2-bromo-1,3,4-tri-*O*-benzoylpsicofuranose derivatives[4] have been used as the substrate **E** for the synthesis of some ketohexose nucleoside[5].

With the above consideration in mind, we chose 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose **6** as the psicose **E**, which was prepared from D-fructose according to a literature procedure[4a] with several improvements

(Scheme 2). Catalytic ruthenium oxidation[6] of 1,2:3,4-di-*O*-isopropylidene-D-fructopyranose **2**, prepared from D-fructose by isopropylidenation using $HClO_4$ as an acid catalyst[4a], was adopted for large scale conversion to afford the corresponding ketone **3** in 99% yield. Stereoselective reduction of **3** followed by isomerization of the pyranose **4** into the furanose **5** was accomplished in 68% yield, and the resulting hydroxy group in **5** was protected with a benzyl group to give **6** (39% overall yield from D-fructose).



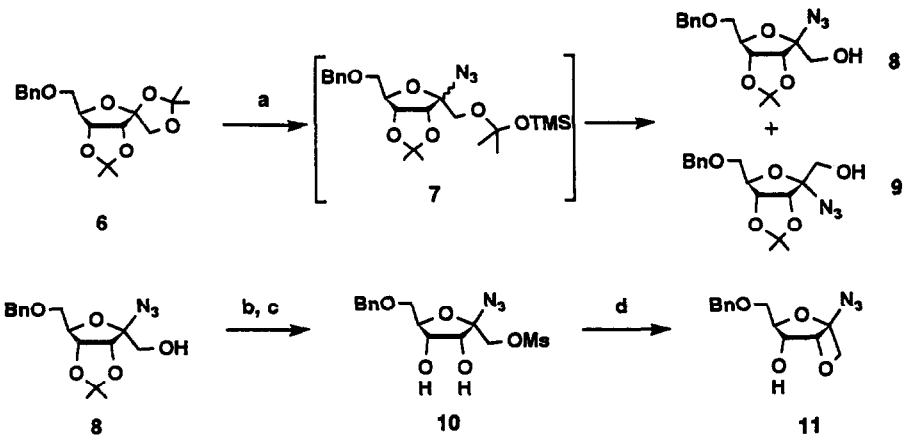
Scheme 1



Scheme 2

a) $HClO_4$, dimethoxyacetone, 58%. b) $RuCl_3 \cdot xH_2O$, $NaIO_4$, $BnN^+Et_3Cl^-$, K_2CO_3, $CHCl_3$-H_2O, 99%. c) $NaBH_4$, EtOH, 96%. d) $HClO_4$, dimethoxyacetone, 71%. e) BnCl, NaOH, $BnN^+Et_3Cl^-$, 99%.

While we intended to employ an azide nucleophile for the *N*-glycosidation of **6**, there exist several problems: (1) the site selectivity among the three reactable ketal functionalities with nucleophile under the Lewis acidic conditions, (2) the chemoselectivity in the desired oxonium intermediate whether accepting of the nucleophile or abstracting the neighboring protons, and (3) the stereoselectivity of the desired glycosidation. When **6** was actually treated with azidotrimethylsilane ($TMSN_3$) in the presence of tritylperchlorate ($TrClO_4$)[9] or trimethylsilyltriflate (TMSOTf)[10], the desired β-azide compound **8** was obtained predominantly in high yield (**Scheme 3**). Interestingly, an equimolar amount of the Lewis acid was required in dichloromethane, whereas the reaction in acetonitrile proceeded completely in the presence of only catalytic amounts of the acid (**Table 1**). Initial products, expected to be a mixture of anomeric stereoisomers **7**, were hydrolyzed



Scheme 3

a) $TMSN_3$, Lewis acid; see Table 1. b) MsCl, Et_3N, 96%. c) Dowex 50W(H^+), MeOH-H_2O, 79%. d) $NaN(TMS)_2$, THF, 73%.

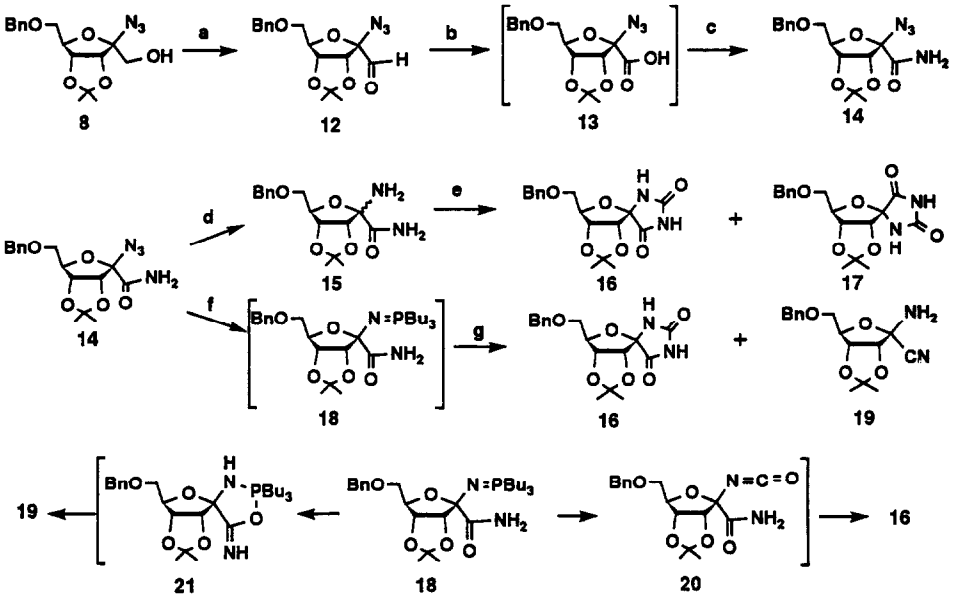
Table 1. N-glycosidation of **6** with $TMSN_3$

entry	solvent	Lewis acid	yield **8** + **9**	ratio **8** : **9**
1	CH_2Cl_2	$TrClO_4$ (1.0eq)	70%	8 : 1
2	CH_2Cl_2	TMSOTf (1.0eq)	63%	8 : 1
3	CH_3CN	$TrClO_4$ (0.3eq)	61%	13 : 1
4	CH_3CN	TMSOTf (0.3eq)	97%	18 : 1

into **8** and **9** during the aqueous work up. The stereochemistry at C-1 in **8** was confirmed chemically by oxetane-formation[11] on the furanose ring (**Scheme 3**). After mesylation and de-isopropylidenation of **8**, the resulting alcohol **10** was cyclized into an oxetane **11** by treatment with sodium bis(trimethylsilyl)amide. No 1,4-anhydroisomer, which could be easily distinguished from **11** by analysis of spin-system in the ^{1}H-NMR, was

formed in this procedure. This transformation indicates a *cis*-relationship between the C-1 hydroxymethyl group and the C-3 hydroxy group on the psicofuranose and confirms that the azido group is introduced at β-position. It turned out that the spiro-dioxacyclopentane ring in **6** was predominantly opened to form an oxonium intermediate at the anomeric position and it was attached by $TMSN_3$ from the β-side sterically and/or electronically owing to the C-2 substituent of the furanose ring. None of the enol ether or its hydrolytic products indicates a sufficient reaction rate in the oxonium intermediate with the azido nucleophile compared to the proton abstraction at C-1 and/or C-3 position.

Our next attention was directed toward the hydantoin synthesis (**Scheme 4**). An appropriately functionalized azido-amide **14** was thought to be a suitable intermediate. The alcohol **8** was transformed in combination of



Scheme 4

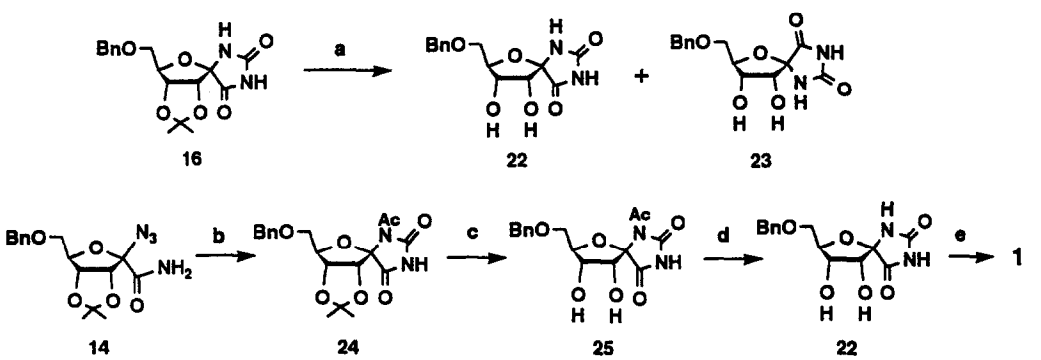
a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%. b) $NaClO_2$, $NaH_2PO_4 2H_2O$, 2-methylbutene, *t*-BuOH-H_2O. c) $ClCO_2Et$, Et_3N, THF, 0°C then NH_3 gas, 72% from **12**. d) Zn, NH_4Cl, THF-MeOH, 72%. e) $CO(Imd)_2$, benzene, **16** (25%) and **17** (30%). f) PBu_3, CH_3CN. g) CO_2, CH_3CN, **16** (68%) and **19** (4%).

Swern oxidation[12] and $NaOCl_2$ oxidation[13] into a carboxylic acid **13**, which was further converted to amide **14** through a mixed acid anhydride in high yield. The stereochemistry of the anomeric position was favorably retained during a series of transformations. Initially we attempted to construct a hydantoin ring by carbonylation on amino-amide **15**. Reduction of **14** unfortunately gave inseparable anomers (the ratio was ranging in 1:1 - 1:2 measured by ^{1}H-NMR) of **15** under three different conditions (Zn/NH_4Cl[14], NaTeH[15] and H_2/Pd-C[16]), respectively. Furthermore, the formation of the hydantoin[17] on the amino-amide **15** succeeded only by using carbonyldiimidazole in refluxing benzene to afford **16** (25%), but the undesired anomer **17** was also produced in 30% yield. Therefore, it become necessary to build the hydantoin nucleus on azido-amide **14** without the epimerization. It is well known that an azide reacts with a phosphorus (III) compound to afford an

iminophosphoran[18] which reacts with carbonyl compounds to produce the corresponding imine by aza-Wittig reaction[19]. Although this transformation has been utilized to construct various aza-heterocycles, there is no attempt for synthesis of hydantoin; therefore, our major interest is whether this process can be performed at the anomeric position with retention of stereochemistry. In the first trial, treatment of **14** with tri-*n*-butylphosphin (PBu_3) in THF afforded a polar intermediate, iminophosphoran **18**, and then the introduction of CO_2 to the reaction mixture gave the desired spiro-hydantoin **16** (35%) along with amino-cyanide **19**[20] (32%). The formation of **19** would be attributed to a cyclic *O,N*-phosphoran **21** formed through the prototropic shift[21] from amide to iminophosphoran followed by the elimination of tributylphosphin oxide. In order to prevent the formation of **19**, several solvents and phosphorus (III) reagents were examined, and the results are shown in Table 2. Among them, the use of PBu_3 in acetonitrile increased dramatically the yield of **16** with trace amounts

Table 2. Hydantoin formation of **14** *via* aza-Wittig reaction

entry	solvent	PR_3	%, yield 16	19	ratio 16 : 19
1	THF	PBu_3	35	32	1.1 : 1
2	dioxane	PBu_3	20	26	1 : 1.3
3	CH_2Cl_2	PBu_3	54	28	1.9 : 1
4	benzene	PBu_3	26	42	1 : 1.6
5	CH_3CN	PBu_3	68	4	17 : 1
6	CH_3CN	PPh_3	26	7.4	3.7 : 1
7	CH_3CN	$P(OEt)_3$	0	0	- : -



Scheme 5

a) Dowex 50(H^+), MeOH-H_2O, 95% (**22**:**23** = 85:15). b) PBu_3, CO_2 gas, CH_3CN, r.t., 5h, then Ac_2O, pyridine, DMAP, 90%. c) Dowex 50(H^+), MeOH-H_2O, 92%. d) $NH_2NH_2 \cdot H_2O$, MeOH, 96%. e) H_2 (3.5kg/cm^2), Pd-C (10%), MeOH, 55°C, 93%.

of **19**. Fortunately, no other spiro-isomer **17** was detected by HPLC, showing that the hydantoin formation proceeded with retention of stereochemistry. The spiro-stereochemistry of **16** was confirmed by its conversion into the natural product itself as described in the following section.

As shown in Scheme 5, the removal of the isopropylidene group in **16** under an acidic condition (Dowex 50W(H^+) in MeOH-H_2O) proceeded in 95% yield accompanied with epimerization at the spiro center (the ratio of **22**:**23** was 85:15). The epimerization was though to be caused in the presence of free NH group on the hydantoin ring; therefore, an acetyl group was introduced there by adding acetic anhydride and pyridine to the aza-Wittig reaction mixture. After silica gel chromatography, *N*-acetyl hydantoin **24** was isolated in 90% yield from **14**. The unexpected improvement of the yield may be attributed to the increased stability of **24** during silica gel chromatography. The removal of the isopropylidene group in **24** was achieved by treatment of Dowex 50W(H+), and deacetylation of **25** with hydrazine monohydrate afforded benzyl ether **22** in 88% yield without epimerization. The last step was accomplished by hydrogenolysis of **22** to furnish the final compound **1** in 93% yield after Diaion CHP 20P column chromatography. The synthetic compound was found to be identical in every respect with the natural product.

In summary, we have described an efficient synthesis of (+)-hydantocidin from the inexpensive starting material, D-fructose, in 12 steps with 19% overall yield. We are now investigating other glycosidations to the protected psicose **6** to construct other spiro-ribose heterocycles for elucidation of the herbicidal structure-activity-relationships and the results of these investigation will be reported elsewhere.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on JOEL GX-400, JOEL GX-270 and Varian EM 360A spectrometers. Infrared spectra were recorded on a Jasco A-102 spectrometer. Mass spectra were recorded on a JOEL JMS-D300 spectrometer. Optical rotations were measured on a Jasco DIP-360 polalimeter. Merck Kieselgel 60 Art. 9385 was used for SiO_2 column chromatography.

1,2:4,5-Di-*O*-isopropylidene-D-psicopyranose (2). To a suspension of D-fructose (18.42g, 0.10mol) in a mixture of acetone (370ml) and 2,2-dimethoxypropane (7.4ml, 60ml) was added 70% perchloric acid (4.3ml, 48mmol) at 0°C, and the mixture was stirred for 6h. To this mixture, conc. ammonium hydroxide (4.8ml) was added and the mixture was evaporated leading to a crystalline residue which was dissolved in CH_2Cl_2 (200ml). The solution was washed with brine (x3), dried (Na_2SO_4) and evaporated. The residue was crystallized from CH_2Cl_2-hexane to give **2** (15.19g, 58%) as white needles; NMR (270MHz, $CDCl_3$) δ 4.23-4.09(4H, m), 4.00(1H, br. d, J=12.9Hz), 3.98(1H, d, J=8.9Hz), 3.67(1H, dd, J=6.8, 8.5Hz), 1.98(1H, d, J=8.5Hz), 1.54(3H, s), 1.52(3H, s), 1.44(3H, s), 1.37(3H, s).

1,2:4,5-Di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose (3). To a mechanically stirring mixture of **2** (350.1g, 1.345mol), $PhCH_2(Et_3)NCl$ (15.32g, 67.25mmol), $NaIO_4$ (427.0g, 2.00mol) and K_2CO_3 (28.52g, 0.206mol) in $CHCl_3$-H_2O (1:1, 2.3l) was added $RuCl_3.H_2O$ (10.40g, 46.1mmol). The reaction temperature was gradually elevated to reflux. After 2h, 2-propanol (400ml) was added. The mixture was stirred for 1h and then filtered through Celite. The organic layer was separated and the water layer was extracted with CH_2Cl_2 (x2). the combined organic layer was washed with sat. Na_2SO_3, water and brine and dried (Na_2SO_4). Evaporation of the solvent gave **3** (343.24g, 99%) as a white solid; NMR (270MHz, $CDCl_3$) δ 4.73(1H, d, J=5.2Hz),

4.61(1H, d, J=9.3Hz), 4.54(1H, ddd, J=1.0, 2.0, 5.2Hz), 4.39(1H, dd, J=2.0, 13.3Hz), 4.12(1H, d, J=13.3Hz), 3.99(1H, d, J=9.3Hz), 1.55(3H, s), 1.64(3H, s), 1.40(3H, s).

1,2:4,5-Di-*O*-isopropylidene-D-psicopyranose (4). To a stirring solution of 3 (83.27g, 0.322mol) in EtOH (820ml) was added $NaBH_4$ (6.10g, 0.162mol) at 15°C. After 1h, the solvent was removed under reduced pressure. Ether (500ml) and sat. NH_4Cl (300ml) were added to the residue and stirred for 4h. The mixture was partitioned between ether and water and the water layer was extracted with ether (x3). The combined extract was dried (Na_2SO_4) and evaporated to give 4 (80.47g, 96%) as a white solid. NMR (270MHz, $CDCl_3$) δ 4.44(1H, dd, J=4.0, 6.4Hz), 4.25(1H, d, J=9.3Hz), 4.25-4.20(1H, m), 4.04(1H, d, J=9.3Hz), 4.01-4.00(2H, m), 3.74(1H, dd, J=4.0, 6.4Hz), 2.30(1H, d, J=6.4Hz), 1.55(3H, s), 1.41(3H, s), 1.38(3H, s).

1,2:3,4-Di-*O*-isopropylidene-D-psicofuranose (5). To a solution of 4 (2.60g, 10mmol) in a mixture of acetone (26ml) and 2,2-dimethoxypropane (0.62ml, 5.0mmol) was added 70% perchloric acid (0.15ml, 1,7mmol) at 5°C. The mixture was stirred for 3h. After conc. ammonium hydroxide (0.3ml) was added, the solvent was evaporateed. The residue was partitioned between ether and water and the water layer was extracted with ether (x3). The combined extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (EtOAc-hexane 1:6) to give 5 (1.84g, 71%) as a white solid. NMR (270MHz, $CDCl_3$) δ 4.92(1H, dd, J=0.8, 6.0Hz), 4.65(1H, d, J=6.0Hz), 4.34(1H, d, J=10.1Hz), 4.30(1H, br. t, J=2.8Hz), 4.07(1H, d, J=10.1Hz), 3.77(1H, ddd, J=2.4, 3.2, 12.5Hz), 3.64(1H, ddd, J=3.2, 10.5, 12.5Hz), 3.17(1H, dd, J=3.2, 10.5Hz), 1.51(3H, s), 1.45(3H, s), 1.41(3H, s), 1.33(3H, s).

5-*O*-Benzyl-1,2:3,4-*O*-isopropylidene-D-psicofuranose (6). To a mixture of benzyl chloride (0.35ml, 3.07mmol) and the psicofuranose 5 (200mg, 0.768mmol) was added a solution of benzyltriethylammonium chloride (10.5mg, 0.046mmol) and NaOH (307mg, 7.68mmol) in water (0.60ml) at room temperature. The mixture was heated at 100°C with vigorous stirring for 2h. After being cooled, the reaction mixture was extracted with ether (x3), and the combined extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (EtOAc-hexane 1:10) to give 6 (254.0mg, 99%) as a oil. $[\alpha]_D^{23}$ -65.2° (c=1.44, $CHCl_3$); IR ($CHCl_3$) 1450, 1370cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.28-7.20(5H, m), 4.75(1H, dd, J=1.2, 6.0Hz), 4.60(1H, d, J=6.0Hz), 4.56(2H, ABq, J=12.1Hz), 4.30(1H, ddd, J=0.8, 6.4, 8.0Hz), 4.28(1H, d, J=9.7Hz), 4.04(1H, d, J=9.7Hz), 3.58(1H, dd, J=6.0, 10.0Hz), 3.52(1H, dd, J=8.0, 10.0Hz), 1.44(3H, s), 1.43(3H, s), 1.37(3H, s), 1.32(3H, s); HRMS. found: 350.1702. Calcd. for $C_{19}H_{26}O_6$: 350.1729.

2-Azido-2-deoxy-3,4-*O*-isopropylidene-6-*O*-benzyl-β-D-psicofuranose (8) and α-isomer (9).

Using TMSOTf in CH_3CN: To a stirring solution of 6 (28.30g, 80.8mmol) and azidotrimethylsilane (21.4ml, 161.5mmol) in acetonitrile (280ml) was added trimethylsilyltrifrate (4.7ml, 24.2mmol) After the mixture was stirred at 0°C for 30min and at room temperature for 1h, ether (150ml) and sat. NH_4Cl (30ml) were added and the mixture was stirred for 1h to hydrolyze the silyl ether intermediates. The water layer was extracted with ether (200ml) and the combined extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give a mixture of 8 and 9 (26.27g, 97%) in a ratio of 18:1 (8:9). **Data of 8:** $[\alpha]_D^{25}$ -124.3° (c=0.43, $CHCl_3$); IR ($CHCl_3$) 3600, 2130, 1730, 1450, 1370cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.64-7.27(5H, m), 4.80(1H, dd, J=1.2, 6.0Hz), 4.59(2H, s), 4.47(1H, d, J=6.0Hz), 4.47(1H, dt, J=1.4, 6.0Hz), 3.93(2H, m), 3.62(2H, d, J=6.5Hz), 2.19(1H, t, J=6.8Hz), 1.52(3H, s), 1.32(3H, s). MS *m/z* 320(M^+-15), 304, 292, 277, 127, 92; Anal. found: C, 57.24; H, 6.20; N, 12.43. Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.30; H ,6.31; N , 12.53%. **Data of 9:** $[\alpha]_D^{23}$ +24.4° (c=1.06, $CHCl_3$); IR ($CHCl_3$) 3420, 2105cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.41-7.29(7H, m), 4.89(1H, dd, J=4.2, 6.2Hz), 4.83(1H, d, J=6.2Hz), 4.58(2H, ABq, J=11.7Hz), 4.42(1H, ddd, J=2.2, 2.8, 4.2Hz), 3.80(1H, dd, J=2.8, 10.6Hz), 3.64(1H, br.

d, J=12.1Hz), 3.62(1H, dd, J=2.2, 10.6Hz), 3.47(1H, br. d, J=12.1Hz), 3.3-3.0(1H, br. s), 1.62(3H, s), 1.37(3H, s); MS *m/z* 320(M^+-15), 304, 293, 276, 149, 91; Anal. found: C, 57.08; H, 6.24; N, 12.39. Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.30; H ,6.31; N , 12.53%.

Using $TrClO_4$ in CH_3CN: Treatment of **6** (227.0mg, 0.648mmol) in CH_3CN (2.3ml) with $TrClO_4$ (63.1mg, 0.194mmol) and $TMSN_3$ (0.22ml, 1.6mmol) in the same manner described above gave the mixture of **8** and **9** (140.4mg, 61%) in a ratio of 13:1 (**8**:**9**).

Using TMSOTf in CH_2Cl_2: Treatment of **6** (549.8mg, 1.57mmol) in CH_2Cl_2 (5.3ml) with TMSOTf (0.10ml, 0.52mmol) and $TMSN_3$ (0.45ml, 3.39mmol) in the same manner described above gave the mixture of **8** and **9** (330.7mg, 63%) in a ratio of 8:1 (**8**:**9**).

Using $TrClO_4$ in CH_2Cl_2: Treatment of **6** (197.4mg, 0.563mmol) in CH_2Cl_2 (2.0ml) with $TrClO_4$ (1931mg, 0.563mmol) and $TMSN_3$ (0.19ml, 1.4mmol) in the same manner as described above gave the mixture of **8** and **9** (141.3mg, 70%) in a ratio of 8:1 (**8**:**9**).

2-β-Azido-2-deoxy-6-*O*-benzyl-1-*O*-methanesulfonyl-D-psicofuranose (10). To a solution of **8** (3.27g, 9.75mmol) and Et_3N (2.7ml, 19.5mmol) in CH_2Cl_2 (70ml) at 0°C was added MsCl (0.9ml, 12mmol) and the mixture was stirred for 30min. The reaction mixture was poured into water and the water layer was extracted with ether (x3). The combined extract was washed with 0.5M HCl, water and brine. After drying (Na_2SO_4) and evaporation of the solvent, the residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **2-β-azido-2-deoxy-6-*O*-benzyl-3,4-*O*-isopropylidene-1-*O*-methanesulfonyl-D-psicofuranose** (3.86g, 96%) as a colourless syrup; NMR (270MHz, $CDCl_3$) δ 7.39-7.30(5H, m), 4.59(2H, ABq, J=12.1Hz), 4.84(1H, dd, J=1.6, 5.6Hz), 4.52(1H, d, J=11.0Hz), 4.50(1H, dt, J=1.6, 5.6Hz), 4.45(1H, d, J=11.0Hz), 4.45(1H, d, J=5.6Hz), 3.11(3H, s), 1.51(3H, s), 1.31(3H, s); MS *m/z* 398(M^+-15), 371, 275, 242, 98. To a solution of the mesylate (569.1mg, 1.38mmol) in a mixture of MeOH and water (2:1, 12ml) was added Dowex 50W(H^+) (2.03g) at 50°C and then the mixture was stirred overnight. After filtration through Celite, the filtrate was concentrated. The resulting residue was chromatographed on silica gel (EtOAc-hexane 3:1) to give **10** (409.6mg, 79%) as a colourless syrup; $[\alpha]_D^{23}$ -47.1° (c=1.38, $CHCl_3$); IR ($CHCl_3$) 3550, 3450, 2125cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.36-7.27(5H, m), 4.60(2H, ABq, J=12.1Hz), 4.59(1H, d, J=11.3Hz), 4.43(1H, br. d, exchanged with D_2O into dd, J=4.6, 7.6Hz), 4.39(1H, d, J=11.3Hz), 4.18(1H, ddd, J=4.4, 5.2, 7.6Hz), 3.97(1H, br. d, exchanged with D_2O into d, J=4.6Hz), 3.71(1H, dd, J=4.4, 10.6Hz), 3.66(1H, dd, J=5.2, 10.6Hz), 3.38(1H, br. s, exchanged with D_2O), 3.11(3H, s), 2.69(1H, br. s, exchanged with D_2O); MS *m/z* 331(M^+-42), 314, 264, 242, 234. Anal. found: C, 44.76; H, 5.11; N, 11.16 Calcd. for $C_{14}H_{19}N_3O_7S$: C, 45.04; H ,5.13; N ,11.25%.

2-β-Azido-2-deoxy-6-*O*-benzyl-1,3-anhydro-D-psicofuranose (11). To a solution of **10** (172.9mg, 0.463mmol) in THF (10ml) at 0°C was added $NaN(TMS)_2$ (1.0M in THF, 0.55ml, 0.55mmol) and the mixture was stirred ar room temperature for 10min. The reaction mixture was poured into sat. NH_4Cl and extracted with ether (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:2) to give **11** (94.1mg, 73%) as a colourless syrup; $[\alpha]_D^{23}$ +13.5° (c=1.14, $CHCl_3$); IR ($CHCl_3$) 3450, 2125, 1330cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.37-7.27(5H, m), 5.04(1H, d, J=4.8Hz), 4.78(1H, d, J=7.6Hz), 4.62(2H, ABq, J=12.1Hz), 4.60(1H, d, J=7.6Hz), 4.28(1H, ddd, J=2.8, 5.2, 7.6Hz), 4.06(1H, br. q, exchanged with D_2O into dd, J=4.8, 7.6Hz), 3.86(1H, dd, J=2.8, 10.9Hz), 3.75(1H, dd, J=5.2, 10.9Hz); MS *m/z* 277M^+), 249, 149, 107, 92; HRMS. found: 277.1068. Calcd. for $C_{13}H_{15}N_3O_4$:277.1063.

2-β-Azido-2-deoxy-6-*O*-benzyl-1-didehydro-3,4-*O*-isopropylidene-D-psicofuranose (12). To a stirring solution of oxaryl chloride (7.5ml, 85.8mmol) in CH_2Cl_2 (460ml) was added a solution of DMSO (12.2ml, 171mmol) in CH_2Cl_2 (32ml) at -60°C. After 20min, a solution of **8** (22.92g, 68.34mmol) in CH_2Cl_2 (43ml) was added and stirred at -60°C. After 50 min, Et_3N (47.8ml, 343mmol) was added and the mixture was stirred for 20 min then at 0°C for 80 min. To this reaction mixture were added sat. NH_4Cl (100ml) and 1N HCl (170ml) and the mixture was poured into water. The water layer was extracted with ether (x3) and the combined extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **12** (21.98g, 96%) as a colourless syrup; $[\alpha]_D^{25}$ -83.5° (c=1.08, $CHCl_3$); IR ($CHCl_3$) 3300, 2150, 1750,

1500, 1460cm^{-1}; NMR (270MHz, $CDCl_3$) δ 9.45(1H, s), 7.40-7.29(5H, m), 4.87(1H, dd, J=1.2, 6.0Hz), 4.68(1H, ddd, J=1.2, 5.6, 6.8Hz), 4.64(1H, d, J=5.6Hz), 4.64(2H, ABq, J=12.1Hz), 3.65(2H, m), 1.48(3H, s), 1.28(3H, s); MS *m/z* 318(M^+-15), 305, 291, 276, 105, 91; Anal. found: C, 57.43; H, 5.70; N, 12.55. Calcd. for $C_{16}H_{19}N_3O_5$: C, 57.65; H ,5.75; N ,12.61%.

1-β-Azido-1-dehydro-1-α-carbamoyl-1-deoxy-2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribofuranose (14). To a stirring solution of **12** (10.90g, 31.56mmol) and 2-methyl-2-butene (6.7ml, 63mmol) in *t*-BuOH (180ml) was added a solution of $NaClO_2$ (8.56g, 94.7mmol) and $NaH_2PO_4{\cdot}2H_2O$ (9.85g, 63.1mmol) in water (110ml) at room temperature. After 2.5 h, sat. Na_2SO_3 (30ml) was added and the resulting mixture was stirred for 10 min. The mixture was poured into diluted HCl solution and extracted with CH_2Cl_2 (x3). The combined extract was washed with brine, dried (Na_2SO_4) and evaporated. Removal of the solvent in vacuo gave **1-β-azido-1-dehydro-1-α-caboxy-1-deoxy-2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribofuranose 13** (11.00g) which was used directly in the next reaction; IR ($CHCl_3$) 3450, 2130, 1740, 1450cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.38-7.27(5H, m), 4.87(1H, dd, J=1.6, 5.6Hz), 4.68(1H, d, J=5.6Hz), 4.67(1H, dt, J=1.6, 6.0Hz), 4.59(2H, m), 3.66(2H, m), 1.50(3H, s), 1.32(3H, s); MS *m/z* 276(M^+-15), 262, 219. To the stirring solution of the above carboxylic acid **13** (11.00g) in THF (250ml) were added Et_3N (13.2ml, 94.7ml) and $ClCO_2Et$ (4.5ml, 47.3mmol). After 10 min, NH_3 gas was introduced into the reaction mixture over 5 min and the mixture was stirred at room temperature for 30 min. After being concentrated to 1/3 volume, the mixture was poured into water and extracted with CH_2Cl_2 (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexane 3:1) gave **14** (7.87g, 72% from **12**) as white needles; m.p. 103-104°C; $[\alpha]_D^{23}$ -105.7° (c=1.16, $CHCl_3$); IR ($CHCl_3$) 3520, 3480, 3400, 2110, 1705, 1575cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.41-7.27(5H, m), 6.65(1H, br. s), 5.79(1H, br. s), 4.77(1H, dd, J=1.2, 5.6Hz), 4.69(1H, d, J=5.6Hz), 4.60(2H, s), 4.58(1H, dt, J=1.2, 6.5Hz), 3.64(2H, dABq, J=6.5, 10.1Hz), 1.48(3H, s), 1.31(3H, s); MS *m/z* 333(M^+-15), 304, 276, 177, 91; Anal. found: C, 54.91; H, 5.62 N, 15.92 Calcd. for $C_{16}H_{20}N_4O_5$: C, 55.17; H, 5.79; N, 16.08%.

1-Amino-1-carbamoyl-1-dehydro-1-deoxy-2,3-*O*-isopropylidene-5-*O*-benzyl-D-ribofuranose (15).

Reduction of 14 by using Zn: To a stirring solution of **14** (0.85g, 2.44mmol) in a mixture of THF (17ml) and MeOH (34ml) were added NH_4Cl (0.81g, 15.1mmol) and Zn powder (0.46g, 7.03mmol) at room temperature. After 1h, ether (100ml) was added and the mixture was stirred for 30min. After filtration of the reaction mixture through Celite, the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (EtOAc-hexane 10:1) to give **15** (572.0mg, 72%) as a colourless syrup (the ratio of the anomers is 2:1); the one anomer: NMR (270MHz, $CDCl_3$) δ 7.64-7.27(m), 6.69(br. s), 5.50(br. s), 4.57(ABq, J=11.4Hz), 4.55(d, J=5.0Hz), 4.81(dd,J=1.4, 5.8Hz), .4.46(dt, J=1.4, 5.0Hz), 3.68(m), 2.34(br. s), 1.48(s), 1.30(s); the other anomer: 7.64-7.27(m), 7.25(br. s), 5.24(br. s), 4.57(ABq, J=12.1Hz), 4.72(d, J=6.4Hz), 4.77(dd, J=4.0, 6.4Hz), 3.72(dd,J=3.5, 10.5Hz),3.63(dd, J=3.5, 10.5Hz), 1.59(s), 1.36(s); the mixture of the anomers: MS *m/z* 323(M^++1), 307, 278, 201, 91; IR ($CHCl_3$) 3540, 3420, 1700, 1570cm^{-1}.

Reduction of 14 by using H_2/Pd-C: A mixture of **14** (2.58g, 7.41mmol) and Pd-C (5%) (0.52g) in MeOH (250ml) was heated at 55°C under hydrogen atmosphere (3.0kg/cm^2) for 5h. After filtration of the reaction mixture through Celite, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (EtOAc-MeOH 10:1) to give **15** (1.774g, 75%). The ratio of the anomers is 1:1.

Reduction of 14 by using NaTeH: To a suspension of Te powder (3.27g, 25.6mmol) in EtOH (50ml) under nitrogen was added $NaBH_4$ (2.33g, 61.5mmol) at room temperature and the mixture was refluxed for 30 min. After the mixture was cooled, a solution of **14** (3.57g, 10.25mol) in a mixture of ether (40ml) and EtOH (10ml) was added dropwise to the resulting solution of NaTeH. After 4h, the mixture was stirred vigorously under air for 1h. Filtration of the mixture through Celite and concentration of the filtrate gave the residue, which was chromatographed on silica gel (EtOAc-MeOH 10:1) to give **15** (2.75g, 83%). The ratio of the anomers is 1:1.

[2*R*,3*R*,4*R*,5*S*]-2-Benzyloxymethyl-3,4-isopropylidenedioxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (16) and its [2*R*,3*R*,4*R*,5*R*]-isomer (17). To a solution of **15** (224.6mg,, 0.697mmol) in benzene (12ml) was added carbonyl diimidazole (0.34g, 2.09mmol) and stirred at 70°C for 5.5h. After cooled, the reaction mixture was poured into water and extracted with EtOAc (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel (EtOAc-hexane 1:2) gave **16** (73.6mg, 30%) as a white solid and **17** (61.7mg, 25%) as a colourless syrup. **Data of 16:** $[\alpha]_D^{23}$ -34.4° (c=0.89, CH_3OH); IR ($CHCl_3$) 3500, 1795, 1740, 1120, 1080cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.55(1H, br. s), 7.50-7.26(5H, m), 6.28(1H, br. s), 4.80(1H, d, J=6.0Hz), 4.77(1H, d, J=6.0Hz), 4.58(2H, ABq, J=11.3Hz), 4.58(1H, t, J=1.6Hz), 3.76(1H, dd, J=1.6, 10.5Hz), 3.60(1H, dd, J=1.6, 10.5Hz), 1.61(3H, s), 1.31(3H, s); MS *m/z* 333(M^+), 242, 199, 149, 126, 92; HRMS. found: 348.1319. Calcd for $C_{17}H_{20}N_2O_6$: 348.1321. **Data of 17:** $[\alpha]_D^{23}$ -50.1° (c=0.91, $CHCl_3$); IR ($CHCl_3$) 3350, 1790, 1750, 1380cm^{-1}; NMR (270MHz, $CDCl_3$) δ 8.02(1H, br. s), 7.35-7.27(5H, m), 6.05(1H, br. s), 4.81-4.75(2H, m), 4.58(2H, s), 4.40(1H, dt, J=1.6, 6.4Hz), 3.65(2H, d·ABq, J=6.4, 10.4Hz), 1.57(3H, s), 1.36(3H, s); MS *m/z* 348(M^+), 333, 290, 257, 242, 149, 91; HRMS. found: 348.1312. Calcd. for $C_{17}H_{20}N_2O_6$: 348.1321.

Hydantoin formation by aza-Wittig reaction of 14.

THF as a solvent: To a stirring solution of **14** (505.8mg, 1.45mmol) in THF (20ml) was added PBu_3 (0.32ml, 1.6mmol) and then CO_2 gas was bubbled over 10 min at room temperature. After beingstirred for 5h, the reaction mixture was concentrated and the residue was chromatographed on silica gel (EtOAc-hexane 1:1) to give **16** (179.1mg, 35%) and **1-amino-1-cyano-1-dehydro-1-deoxy-2,3-*O*-isopropylidene-5-*O*-benzyl-*D*-ribofuranose 19** (144.2mg, 33%) as a colourless syrup; $[\alpha]_D^{23}$ +205.6° (c=1.26, $CHCl_3$); IR ($CHCl_3$) 3400, 1450, 1370, 1270cm^{-1}; NMR (270MHz, $CDCl_3$) δ 7.41-7.27(5H, m), 4.78(1H, dd, J=1.2, 5.8Hz), 4.56(2H, s), 4.45(1H, d, J=5.8Hz), 4.44(1H, m), 3.63(1H, dd, J=3.2, 10.5Hz), 3.58(1H, dd, J=3.2, 10.5Hz), 1.65(3H, s), 1.35(3H, s); MS *m/z* 304(M^+), 276(M^+-26, CN), 262, 220, 171, 127, 91; HRMS. found: 304.1429 Calcd for $C_{16}H_{20}N_2O_4$: 304.1423.

Dioxane as a solvent: Treatment of **14** (480.1mg, 1.38mmol) in dioxane (30ml) with PBu_3 (0.38ml, 1.52mmol) and CO_2 in the same manner as described above gave **16** (107.5mg, 26%) and **19** (95.7mg, 20%).

CH_2Cl_2 as a solvent: Treatment of **14** (371.0mg, 1.06mmol) in CH_2Cl_2 (25ml) with PBu_3 (0.298ml, 1.17mmol) and CO_2 in the same manner as described above gave **16** (202.0mg, 54%) and **19** (90.9mg, 28%).

Benzene as a solvent: Treatment of **14** (555.5mg, 1.1.59mmol) in benzene (37ml) with PBu_3 (0.44ml, 1.75mmol) and CO_2 in the same manner as described above gave **16** (145.1mg, 26%) and **19** (202.8mg, 42%).

CH_3CN as a solvent: Treatment of **14** (434.8mg, 1.25mmol) in CH_3CN (28ml) with PBu_3 (0.34ml, 1.37mmol) and CO_2 in the same manner as described above gave **16** (297.6mg, 68%) and **19** (15.9mg, 4.2%).

PPh_3 as a phosphine: Treatment of **14** (498.6mg, 1.43mmol) in CH_3CN (30ml) with PPh_3 (413ml, 1.57mmol) and CO_2 in the same manner as described above gave **16** (129.2mg, 26%) and **19** (32.1mg, 7.4%).

[2*R*,3*S*,4*R*,5*S*]-2-Benzyloxymethyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane7,9-dione (22) and [2*R*,3*S*,4*R*,5*R*]-isomer (23). To a solution of **14** (4.10g, 11.8mmol) in a mixture of MeOH (80ml) and H_2O (80ml) was added Dowex 50W(H^+) (7.90g) and the mixture was stirred at 50°C for 2h. After filtration of the mixture through Celite, the filtrate was concentrated to give a mixture of **22** and **23** (3.46g, 95%) in a ratio of 85:15 (**22**:**23**) (HPLC analysis) Compounds **22** and **23** were partly separated by silica gel chromatography (EtOAc). **Data of 22:** m.p. 135-136°C; $[\alpha]_D^{25}$ +13.7° (c=0.99, CH_3OH); IR ($CHCl_3$) 3300, 1795, 1730, 1120, 1090cm^{-1}; NMR (270MHz, CD_3OD) δ 7.37-7.25(5H, m), 4.56(2H, ABq, J=12.1Hz), 4.31(1H, dt, J=2.0, 4.0Hz), 4.27(1H, d, J=6.0Hz), 4.05(1H, dd, J=2.0, 6.0Hz), 3.57(2H, d, J=4.0Hz); MS *m/z* 308(M^+), 279, 265, 199, 167, 91; HRMS. found: 308.1010 Calcd for $C_{14}H_{16}N_2O_6$: 308.1008. **Data of 23:** IR ($CHCl_3$) 3300, 3040, 1785, 1740, 1195cm^{-1}; NMR (270MHz, CD_3OD) δ 7.4-7.2(5H,

m), 4.57(2H, ABq, J=11.7Hz), 4.28(1H, d, J=4.8Hz), 4.21(1H, dd, J=3.3, 4.8Hz), 4.16(1H, dd, J=3.3, 4.8Hz), 3.60(2H, d, J=4.8Hz); MS *m/z* 308(M^+), 230, 202, 129, 91; HRMS. found: 308.1002. Calcd for $C_{14}H_{16}N_2O_6$: 308.1008.

[2*R*,3*R*,4*R*,5*S*]-6-*N*-Acetyl-2-benzyloxymethyl-3,4-isopropylidene-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (24). To a solution of **14** (76.84g, 220.6mmol) in CH_3CN (1.5l) at room temperature was added PBu_3 (56.6ml), 227mmol). After 5 min, CO_2 gas was introduced into the reaction mixture over 75min and then stirred for 5h. To this mixture were added Ac_2O (31.2ml, 331mmol), pyridine (26.7ml, 330mmol) and 4-*N*,*N*-dimethylaminopyridine (2.15g, 17.6mmol) and the mixture was stirred for 20h. After evaporation of the solvent, the residue was partitioned between EtOAc and water. The water layer was extracted with EtOAc (x2) and the combined extract was washed with diluted HCl, water and brine and then dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on silica gel (EtOAc-hexane 1:1) gave **24** (100.89g, 90%) as a colourless syrup; $[\alpha]_D^{23}$ -2.7° (c=1.31, CH_3OH); IR ($CHCl_3$) 3420, 1810, 1760, 1720, 1450, 1370cm^{-1}; NMR (270MHz, CD_3OD) δ 8.0(1H, br. s), 7.38-7.27(5H, m), 5.30(1H, d, J=6.8Hz), 4.84(1H, dd, J=4.0, 6.8Hz), 4.69(1H, dt, J=4.0, 6.4Hz), 4,58(2H, ABq, 12.1Hz), 3.69(2H, d, J=6.4Hz), 2.53(3H, s), 1.58(3H, s), 1.31(3H, s); MS *m/z* 390(M^+), 375, 332, 241, 149, 91; HRMS. found: 390.1427. Calcd. for $C_{19}H_{22}N_2O_7$: 390.1427.

[2*R*, 3*R*,4*R*,5*S*]-6-*N*-Acetyl-2-benzyloxymethyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (25). To a solution of **24** (15.48g, 39.65mmol) in a mixture of MeOH (200ml) and water (100ml) at 60°C was added Dowex 50W(H^+) (20.0g) and the mixture was stirred for 10min. After filtration through Celite, the filtrate was concentrated under reduced pressure. The residue was crystallized from MeOH to give **25** (12.76g, 92%) as white needles; m.p. 171-172°C; $[\alpha]_D^{23}$ -17.3° (c=1.02, CH_3OH); IR (Nujol) 3300, 3200-2600, 1800, 1730, 1690, 1150cm^{-1}; NMR (270MHz, CD_3OD) δ 7.36-7.23(5H, m), 5.03(1H, d, J=6.8Hz), 4.55(2H, s), 4.42(1H, ddd, J=3.6, 5.2, 6.8Hz), 4.14(1H, dd, J=3.6, 6.8Hz), 3.71(1H, dd, J=6.8, 10.9Hz), 3.69(1H, dd, J=5.2, 10.9Hz), 2.51(3H, s); MS *m/z* 350(M^+), 244, 184, 170, 142, 129, 91; HRMS. found: 350.1106 Calcd. for $C_{16}H_{18}N_2O_7$:350.1114.

Deacetylation of 15 with hydrazine monohydrate. To a solution of **25** (42.25g, 120.6mmol) in MeOH (500ml) at room temperature was added hydrazine monohydrate (6.4ml, 133mmol). After 1h , the mixture was concentrated and the residue was chromatographed on silica gel (EtOAc-hexane 5:1) to give **22** (35.69g, 96%). The spectroscopic data were identical with that of the hydrolysis of **14**.

[2*R*,3*S*,4*R*,5*S*]-3,4-Dihydroxy-2-hydroxymethyl-1-oxa-6,8-diazaspiro[4.4]-nonane-7,9-dione (1). A mixture of **22** (12.98g, 42.10mmol) and Pd-C(10%) (1.02g) in MeOH (300ml) was heated at 55°C under hydrogen atmosphere (3.5kg/cm^2) for 15h. After filtration of the mixture through Celite, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on Diaion CHP 20P (water) to give **1** (8.56g, 93%)as colourless prisms; m.p. 188-189°C; $[\alpha]_D^{23}$ +29.0° (c=0.62, H_2O); IR (KBr) 3700-2800, 1780, 1720cm^{-1}; NMR (400MHz, D_2O) δ 4.21(1H, d, J=5.8Hz), 4.15(1H, ddd, J=3.4, 3.9, 4.9Hz), 4.03(1H, dd, J=3.9, 5.8Hz), 3.59(1H, dd, J=3.4, 12.7Hz), 3.49(1H, dd, J=4.9, 12.7); MS *m/z* 219M^++1), 187, 171, 141, 129, 116, 100, 86, 73; Anal. found: C, 33.44; H, 4.52; N, 12.76. Calcd. for $C_7H_{10}N_2O_6$: C, 38.53; H , 4.58; N, 12.84%.

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