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SYNTHETIC STUDIES ON (+)-HYDANTOCIDIN (1): A TOTAL SYNTHESIS OF (+)-HYDANTOCIDIN, A NEW HERBICIDAL METABOLITE FROM MICROORGANISM

Shigeru Mio,* Reiji Ichinose, Kuniko Goto, Soji Sugai

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

and Sadao Sato

Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan

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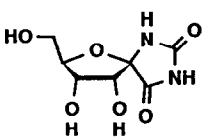
Abstract: A total synthesis of (+)-hydantocidin **1**, a new class of ribofuranose derivative exhibiting herbicidal activity, is reported. The spiro-hydantoin ring at the anomeric position of D-ribofuranose was constructed from substituted hydantoin derivatives **6**, **7**, and **12** through acid and base-promoted cyclization methods.

(+)-Hydantocidin **1**, isolated[1] from the cultured broth of *Streptomyces Hygroscopicus* SANK 63584, possesses an interesting profile of herbicidal and plant growth regulatory activity. The structure was determined[2] by the combination analysis of Mass and ^{1}H-NMR spectra which established the relative configuration of its stereochemistry. Both the novel structure, which contains the hydantoin nucleus at the anomeric position of ribofuranose in a spiro-form[3], and the unique herbicidal activity prompted us to investigate the synthesis of **1** and the related derivatives. Herein we report the total synthesis of **1** in an optically active form and establish its absolute configuration.

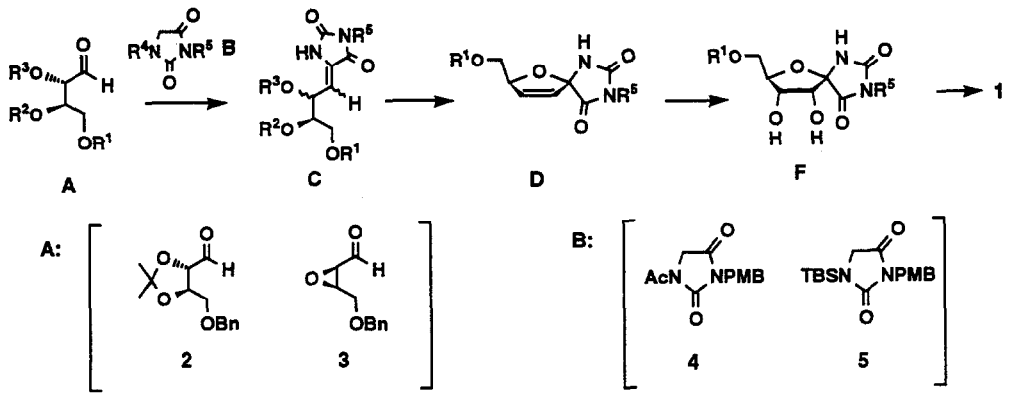


(+)-hydantocidin 1

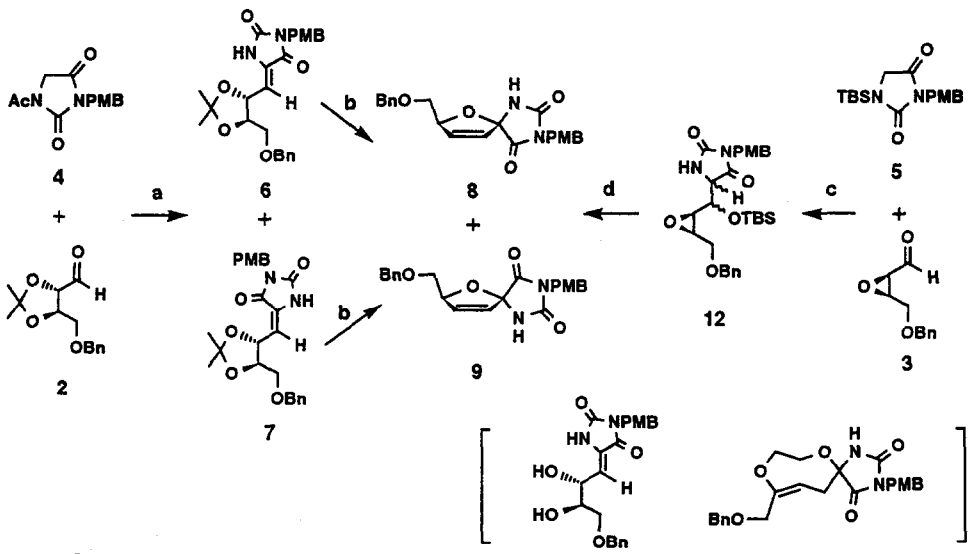
Our synthetic strategy is shown in Scheme 1. The required carbon framework can be derived from the tetrose derivative **A** and the hydantoin derivative **B** by condensation. The resulting condensate **C** can be cyclized into the key intermediate **D**, which will lead to the target molecule **1** after diastereoselective dihydroxylation and deprotection.

Aldehydes **2**[4] and **3**[5], in which the former was prepared from D-(-)-diethyl tartarate in four steps[4b] and the latter from (Z)-4-benzyloxy-2-buten-1-ol in two steps by Sharpless' asymmetric epoxidation[6] followed by Swern oxidation[7], were chosen as the tetrose **A**. The protected hydantoins[8] **4** and **5** were prepared by acetylation or silylation of *N*-(4-methoxybenzyl)hydantoin, respectively.

The total synthesis began with the aldol condensation of 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose **2** and 1-*N*-acetyl-3-*N*-(4-methoxybenzyl)hydantoin **4** (**Scheme 2**). The treatment[9] of **2** with **4** in 1,4-dioxane in the



Scheme 1



Scheme 2

a) *t*-BuOK, dioxane, r.t. b) *p*-TsOH·H_2O, MS 4Å (cf. Table 1).
c) Li-enolate of **5**, THF, -78°C, 20min. d) $LI(TMS)_2$, THF,r.t.

presence of potassium *tert*-butoxide at 0°C to room temperature afforded a mixture of (*Z*)-isomer **6** (71%) and (*E*)-isomer **7** (14%) after their crystallization and chromatography. In the comparison of the olefin protons' NMR signals for them, a 0.31ppm downfield shift for **6** indicated the *cis*-relationship between the proton and the amide-carbonyl functionality on the basis of anisotropic effect.

The initial attempt to cyclize **6** into a spiro-furanose under a transketalization conditions[10] containing ethylene glycol and *p*-toluenesulfonic acid in dichloroethane at room temperature led to only the deacetonized product **10**, while heating of the reaction mixture for two hours afforded the cyclized product **8** (40%), **9** (15%) and **11**(0.8%). Elemental analyses and several spectral data indicated a diastereomeric relationship between **8** and **9**. The single crystal X-ray analysis of **9** confirmed the stereochemistry at the quaternary center (**Figure 1**), indicating that another isomer **8** had the desired stereochemistry. The by-product **11** might be formed by the attachment of ethylene glycol, suggesting the cyclization would prefer the conditions without ethylene glycol. Among several solvents screened, a halocarbon solvent such as chloroform and dichloroethane was found to be suitable for this transformation (**Table 1**). On the other hand, the cyclization of (*E*)-isomer **7** occurred at room temperature to yield **8** (38%) and **9** (23%). The cyclization employing various Lewis acids, *i.e.*, $SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$, ZnI_2 and others, instead of protic acid, met with failure.

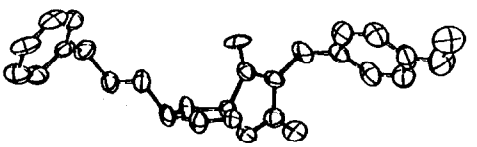


Figure 1

Perspective view of the crystallographic structure of **9** showing a *cis*-relationship between the benzyloxymethyl group and the carbonyl group on the dihydrofurane ring.

Table 1. Acid-Promoted Cyclization [a] of **6** and **7**.

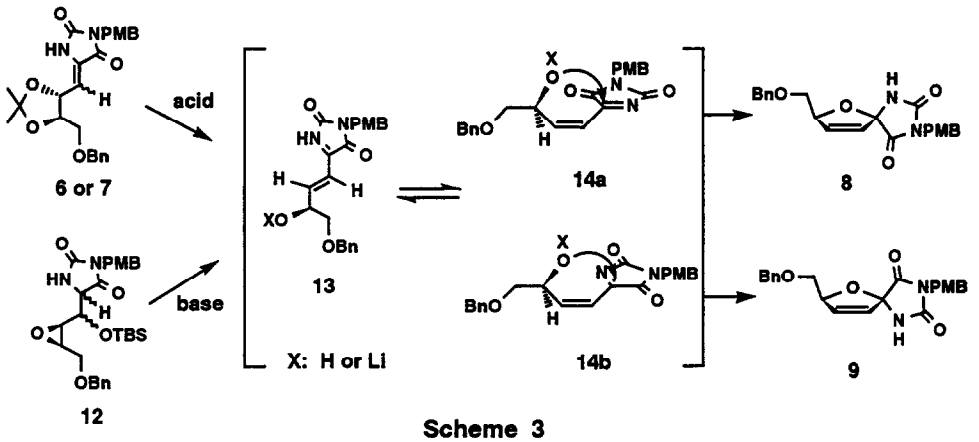
entry	substr.	solvent	%, yield (**8** + **9**)	Isomers ratio (**8**:**9**)
1	**6**	$ClCH_2CH_2Cl$	82	63 : 37
2	**6**	$CHCl_3$	85	60 : 40
3	**6**	benzene	62	64 : 36
4	**6**	CH_3CN	46	50 : 50
5	**6**	THF	0	- : -
6[b]	**7**	$ClCH_2CH_2Cl$	61	63 : 37

[a]All experiments were carried out at 70°C (except for entry **6**) for 2h in the presence of *p*-TsOH. [b]The reaction was performed at r.t.

We next turned our attention to the use of (*2R,3R*)-4-benzyloxy-2,3-epoxybutanal **3** in place of **2**. The addition[11,5a] of lithium enolate of the hydantoin **5** to **3** occurred in THF at -78°C accompanying with the migration of the silyl group to the resulting hydroxy group. The adduct **12**, which showed two spots on a silica gel TLC plate (Rf: 0.47 and 0.28, ethyl acetate-hexane 1:2), was obtained in 95% yield, consisting of four diastereoisomers[12] in a ratio of 4.5:1:3.2:1 analyzed by HPLC. The mixture was subjected to the cyclization conditions employing 2.2eq. of lithium bis(trimethylsilyl)amide in several solvents (THF, Et_2O, dioxane or

THF-hexane 1:3) at room temperature. In all cases, the stereoisomer **9** was obtained predominantly to the desired isomer **8** in a ratio of ca. 2:1 (20-50% combined yields) in spite of varying the solvents polarity. Interestingly, a series of addition-cyclization steps from **3** and **5** was able to perform in one pot by successive addition of lithium bis(trimethylsilyl)amide to the solution of resulting aldol adducts **12**. Similarly **9** and **8** were produced in a 41% combined yield in a ratio of *ca.* 2:1.

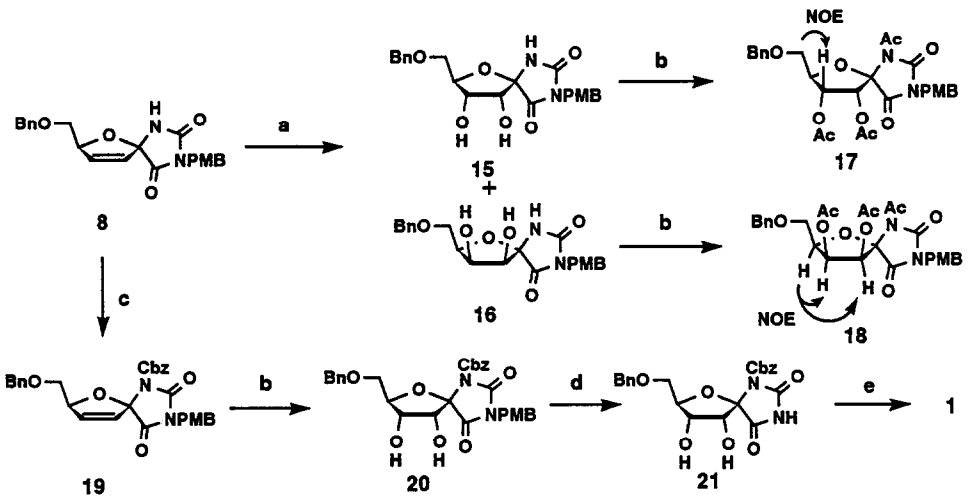
The probable cyclization processes are shown in Scheme 3. The elimination of allylic alkoxy group in **6** or **7** would give (*Z*)- and/or (*E*)-olefin, **13** and/or **14** (X=H), under the acidic condition. In the case of **12** tandem eliminations of alkoxy groups would give **13** and **14** (X=Li) under the basic conditions. During the isomerization between **13** and **14** in the reaction media, the cyclization would occur in the conformer **14a** and **14b** to produce **8** and **9**, respectively. Interestingly, the cyclization of **14a** predominated under the acidic conditions, while **14b** predominated under the basic conditions. Though it was difficult to clarify the factors governing the product distribution, the acid-promoted cyclization was favorable for our project.



Scheme 3

As a key intermediate **8** was in hand, we tried to introduce diastereoselectively dihydroxy groups to the olefin by catalytic osmium oxidation under VanRheenen's condition[13] (**Scheme 4**). It was difficult to predict the extent of the stereochemical predominance of the resulting diol because both faces of the olefin in **8** seemed to be affected sterically by the neighboring groups. Unfortunately, the osmium oxidation of **8** occurred predominantly at the β-face to produce **16** (58%) along with the desired isomer **15** (10%). The stereochemistry of the dihydroxylation were determined by the NOE measurement of the corresponding triacetyl derivatives **17** and **18**. In order to disturb sterically the β-face dihydroxylation, a benzyloxycarbonyl group was introduced at the amide-NH group in **8** by using potassium *tert*-butoxide and benzyl chloroformate.The osmium oxidation of the carbamate **19** proceeded slowly at room temperature. After stirring for five days, only one stereoisomer **20** was formed in 48% isolated yield (96% theoretical yield) along with the 50% recovery of **19**. Although the configuration of the diol was not established at this stage, further deprotection reaction were carried out. The 4-methoxybenzyl group at the hydantoin nucleus was removed with ceric ammonium nitrate by the slightly modified Yamaura's method[14] in 94% yield, and then both the benzyl and benzyloxycarbonyl groups in the

resulting product 21 were hydrogenated in methanol in the presence of Pd-C. After Diaion CHP 20P column chromatography followed by crystallization, the final product 1 was obtained in 89% yield. The comparison of ^{1}H-NMR (400MHz), Mass, IR, $[\alpha]_D$ and the herbicidal activity confirmed that the synthetic product 1 was identical with the natural product.



Cbz: benzyloxycarbonyl

Scheme 4

a) OsO_4, *N*-methylmorpholine-*N*-oxide, acetone-H_2O. b) Ac_2O, pyridine, *N,N*-dimethylpyridine, CH_2Cl_2. c) benzyl chloroformate, *t*-BuOK, THF. d) ceric ammonium nitrate, CH_3CN-H_2O. e) H_2 (3.5kg/cm^2) / Pd-C (5%), CH_3OH.

In conclusion, we have established the methods for constructing a spiro-hydantoin systems at the anomeric position of furanose, and completed the total synthesis of (+)-hydantocidin through 6 steps in 33% overall yield from 2. Finally, the absolute configuration of (+)-hydantocidin was determined as 1 on the basis of $[\alpha]_D$.

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We wish to thank Dr. T. Haneishi, International Drag Development Department of Sankyo Co. Ltd., and Mr. M. Nakajima, Fermentation Products Research Laboratories of Sankyo Co. Ltd., for the useful information about (+)-hydantocidin.

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 polarimeter. Merck Kieselgel 60, Art. 9385 was used for SiO_2 column chromatography.

Crystal Data of 9: $C_{22}H_{22}N_2O_5$, *Mw*=394.4, orthorhombic, $P2_12_12_1$, *a*=9.966(1), *b*=20.224(3), *c*=10.0879(1)Å, *U*=2033.1Å^3, *Z*=4, *Dc*=1.29gcm^{-3}, μ(Cukα=1.5418Å)=8cm^{-1}, *F*(000)=832, *T*=297K, Intensity data were obtained on a Rigaku AFC-5R

diffractometer with graphite-monochromatized Cukα radiation using the θ-2θ scan technique ($2\theta<128°$). Among 1952 independent reflections measured, 1880 were considered as observed on the basis of the criterion $Fo>2\sigma(Fo)$. All intensities were corrected for Lorents and polarization effects but not for absorption. Structure was solved by MULTAN84[15] and refined by block-diagonal least-squares methods. Positions of the hydrogen atoms were estimated from standard geometry. The final refinements with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms lowered R value to 0.055(Rw=0.054, $w=1/\sigma^2(Fo)$). Fractional atomic coordinates, tables of bond lengths and angles and isotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.

3-(4-Methoxybenzyl)hydantoin. To a stirring solution of hydantoin (17.59g, 175.8mmol) and *t*-BuOK (21.70g, 193mmol) in DMSO (150ml) was added 4-methoxybenzyl chloride (27.53g, 175.8mmol) at room temperature. After being stirred for 4h, the mixture was poured into ice-water. The resulting solid was collected by filtration, washed with water and i-Pr_2O, and dried by passing air. The crude product was recrystallized from methanol to give the title compound (35.78g, 92%) as a white solid. m.p. 192-194°C; IR($CHCl_3$) 3480, 1775, 1715, 1610cm^{-1}; NMR(60MHz, DMSO-d_6) δ 7.94(1H, br.s), 7.15(2H, d, J=8.8Hz), 6.76(2H,d, J=8.8Hz), 4.40(2H, s), 3.88(2H, s), 3.70(3H, s); MS m/z 220(M^+), 191, 176, 162, 148, 136, 127, 77; Anal. found: C, 60.26; H, 5.59; N, 12.60. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72%.

1-Acetyl-3-(4-methoxybenzyl)hydantoin (4). A solution of 3-(4-methoxybenzyl)hydantoin (10.0g, 45mmol) in acetic anhydride (100ml) was heated under reflux for 15h. The reaction mixture was concentrated under reduced pressure and the crude solid was recrystallized from ether to give **4** (10.85g, 91%) as colourless prisms. m.p. 115-117°C; IR(Nujol) 1790, 1730, 1615cm^{-1}; NMR(60MHz, $CDCl_3$) δ 7.41(2H, d, J=8.8Hz), 6.87(2H, d, J=8.8Hz), 4.62(2H, s), 4.22(2H, s), 3.82(3H, s), 2.52(3H, s); MS m/z 262(M+), 220, 192, 186, 162, 134, 121; Anal. found: C, 59.25; H, 5.21; N, 10.37. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.34; N, 10.69%.

1-*t*-Butyldimethylsilyl-3-(4-methoxybenzyl)hydantoin (5). To a stirring solution of 3-(4-methoxybenzyl)hydantoin (60.0g, 272mmol) in THF (600ml) were added a solution of $LiN(TMS)_2$ (1.0M in THF, 300ml, 300mmol) and *t*-butyldimethylsilyl chloride (45.15g, 300mmol) at -60°C. After stirring at -20°C for 2h, 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 evaporated. The crude product was crystallized from a ether-hexane mixed solvent to give **5** (78.82g, 83%) as colourless prisms. m.p. 73-74°C; IR ($CHCl_3$) 1760, 1700, 1610, 1510cm^{-1}; NMR(60MHz, $CDCl_3$) δ 7.38(2H, d, J=9Hz), 6.84(2H, d, J=9Hz), 4.57(2H, s), 3.82(2H, s), 3.76(3H, s), 0.94(9H, s), 0.29(6H, s); MS m/z 334(M+), 277, 149, 121; Anal. found: C, 61.11; H, 7.62; N, 8.38. Calcd. for $C_{17}H_{26}N_2O_3Si$: C, 61.04; H, 7.84; N, 8.38%.

5-*Z*-[(2*R*,3*R*)-4-Benzyloxy-2,3-isopropylidenedioxy]butylidene-3-(4-methoxybenzyl)hydantoin (6) and **5-*E*-[(2*R*, 3*R*)-4-benzyloxy-2,3-*O*-isopropylidenedioxy]butylidene-3-(4-methoxybenzyl)hydantoin (7).** To a stirring solution of 2,3-*O*-isopropylidene-4-*O*-benzyl-D-threose **2** (46.71g, 187mmol) and 1-acetyl-3-(4-methoxybenzyl)hydantoin **4** (46.61g, 178mmol) in dioxane (1.5l) at 0°C was added *t*-BuOK (20.34g, 181mmol). After 30min stirring, the mixture was allowed to warm to room temperature and stirred for 5h. Then the mixture was concentrated under reduced pressure, and the residue was diluted with water and extracted with EtOAc(x3). The combined extract was washed with brine, dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from a mixture of ether-hexane to give **6** (50.27g, 62.5%) as colourless prisms. The filtrate was concentrated and the residue was chromatographed on silica gel (EtOAc-hexane 1:4) to give **6** (6.84g, 8.5%) as colourless prisms and **7** (11.26g, 14%) as a colourless syrup. **Data of 6:** m.p. 119-120°C; $[\alpha]_D^{24}$ +43.9° (c=1.40, $CHCl_3$); IR (KBr) 3260, 1780, 1725, 1685, 1255cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.86(1H, br.s), 7.3-7.4(7H, m), 6.84(2H, d, J=8.8Hz), 5.78(1H, d, J=3.7Hz), 4.64(1H, dd, J=8.1, 3.7Hz),

4.64(2H, s), 4.59(2H, s), 3.96(1H, ddd, J=4.4, 5.1, 8.1Hz), 3.78(3H, s), 3.68(1H, dd, J=4.4, 10.3Hz), 3.60(1H, dd, J=5.1, 10.3Hz), 1.44(6H, s); MS *m/z* 452(M+), 437, 394, 361, 343, 260, 211, 121; HRMS. found:452.1948. Calcd. for $C_{25}H_{28}N_2O_6$: 452.1947. **Data of 7:** $[\alpha]_D^{24}$ -31.5° (c=2.31, $CHCl_3$); IR (KBr)3300,1770, 1720, 1680, 1610 cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.87(1H, br.s), 7.4-7.2(7H, m), 7.14(2H, d, J=8.8Hz), 5.55(1H, dd, J=7.7, 9.2Hz), 5.47(1H, d, J=9.2Hz), 4.57(2H, s), 4.53(2H, ABq, J=12.1Hz), 3.93(1H, ddd, J=4.0, 6.2, 7.7Hz), 3.76(3H, s), 3.69(1H, dd, J=6.2, 10.3Hz), 3.14(1H, dd, J=4.0, 10.3Hz), 1.44(6H, s); MS *m/z* 452(M+), 403, 394, 302, 286, 260, 122, 91; Anal. found: C, 66.04; H, 6.26; N, 6.16. Calcd. for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19%.

[2*S*,5*S*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-3-ene-7,9-dione (8), (2*S*,5*R*)-2-benzyloxymethyl-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-3-ene-7,9-dione (9) and 5-benzyloxymethyl-11-(4-methoxybenzyl)-1,4-dioxa-9,11-diazaspiro[7,4]dodecane-5-ene-10,12-dione (11).

Acid-promoted cyclization of 6 and 7. *(a) Dichloroethane as a solvent in the presence of ethylene glycol:* a mixture of hydantoin **6** (9.00g, 19.3mmol), ethylene glycol (1.87g, 30.4mmol) and *p*-TsOH·H_2O (0.90g, 4.73mmol) in dichloroethane (800ml) was heated under reflux for 2h. The mixture was washed with water and brine, dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (EtOAc-hexane 1:3) gave **8** (3.14g, 40%) as white needles, **9** (1.14g, 15%) as colourless prisms and **11** (0.07g, 0.8%).as a white solid. **Data of 8:** m.p. 101-103°C; $[\alpha]_D^{23}$ -145.1° (c=1.03, CH_3OH); IR (KBr) 3360, 1790, 1730, 1250cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.4-7.2(7H, m), 6.83(2H, d, J=8.8Hz), 6.25(1H, dd, J=1.5, 5.9Hz), 5.72(1H, br.s), 5.70(1H, dd, J=2.2, 5.9Hz), 5.15-5.05(1H, m), 4.53(2H, ABq, J=12.8Hz), 4.53(2H, ABq, J=11.7Hz), 3.78(3H, s), 3.67(1H, dd, J=2.9, 10.6Hz), 3.53(1H, dd, J=2.6, 10.6Hz); MS *m/z* 394(M^+), 364, 334, 288, 273, 211, 91; HRMS. found: 394.1535. Calcd. for $C_{22}H_{22}N_2O_5$: 394.1529. **Data of 9:** m.p. 92-94°C; $[\alpha]_D^{25}$ +27.8° (c=1.12, $CHCl_3$); IR (KBr) 3250, 1785, 1725, 1250cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.40-7.25(7H, m), 7.32(2H, d, J=8.4Hz), 6.35(1H, dd, J=1.5, 5.9Hz), 5.95(1H, br.s), 5.64(1H, dd, J=2.2, 5.9Hz), 5.2-5.1(1H, m), 4.59(2H, s), 4.56(2H, ABq, J=12.1Hz), 3.77(3H, s), 3.69(1H, dd, J=7.3, 9.9Hz), 3.57(1H, dd, J=5.5, 9.9Hz); MS *m/z* 394(M^+), 364, 334, 288, 273, 211, 121, 91; Anal. found: C, 66.81; H, 5.60; N, 7.08. Calcd. for $C_{22}H_{22}N_2O_5$: C, 67.00; H, 5.58; N, 7.10%. **Data of 11:** m.p. 111.5-120.5°C; IR (Nujol) 3210, 3100, 1760, 1725, 1690, 1620cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.36-7.25(7H, m), 6.83(2H, d, J=8.8Hz), 5.85(1H, br.s), 5.85(1H, t, J=8.4Hz), 4.62(2H, s), 4.56(2H, s), 3.95(4H, s), 3.76(2H, s), 3.37(2H, s), 2.59(1H, d, J=8.4Hz); MS *m/z* 438(M^+), 394, 317, 193, 121, 91; Anal. found: C, 64.11 H, 5.76; N, 6.26. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.75; H, 5.93; N, 6.39%.

(b) Dichloroethane as a solvent in the absence of ethylene glycol: a mixture of hydantoin **6** (9.00g, 19.3mmol), *p*-TsOH·H_2O (0.90g, 4.73mmol) and molecular sieves 4Å (9.0g) in dichloroethane (800ml) was heated under reflux for 2h. The same workup as described above gave **8** (3.96g, 52%) and **9** (2.29g, 30%).

(c) Chloroform, benzene, actonitrile and tetrahydrofurane as solvent: Each solvent system was used in the same manner as described above and results are given in Table 1.

(d) Cyclization of 7: a mixture of hydantoin **7** (52.4mg, 0.116mmol), *p*-TsOH·H_2O (10mg, 0.052mmol) and molecular sieves 4Å (0.10g) in dichloroethane (5.0ml) was stirred at room temperature for 20h. The same workup as described in (a) gave **8** (17.7mg, 38%) and **9** (10.5mg, 23%).

5-[(2*R*,3*R*)-4-Benzyloxy-2,3-epoxy-1-*t*-butyldimethylsilyloxy]butyl-3-(4-methoxybenzyl)hydantoin (12). To a stirring solution of hydantoin **5** (19.22g, 57.46mmol) in THF (500ml) at -78°C were added $LiN(TMS)_2$ (1.0M in THF, 57.5ml, 57.5mmol) and after 30min, a solution of the aldehyde **3** (9.85g, 51.25mmol) in THF (25ml). After 20min stirring, 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 under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **12** (25.56g, 95%) which consists of four diastereomers. HPLC analysis (Lichrosorb Si60; flow rate, 3.0ml/min; EtOAc-hexane 1:3 as eluent) of **12** indicated each

retention time as 7.96, 9.56, 11.77 and 14.47min which are numbered as **12a-d**, respectively. The ratio of **12a:12b:12c:12d** was 4.5:1:3.2:1. After further purification by silica gel chromatography (EtOAc-hexane 1:3), the mixture was separated into four fractions: **12a**, a mixture of **12a** and **12b** (1:6), a mixture of **12c** and **12d** (6:1), and a mixture of **12c** and **12d** (1:2). **Data of 12a:** ^{1}H-NMR(270MHz, $CDCl_3$) δ 7.40-7.31(7H, m), 6.83(2H, d, J=8.4Hz), 6.08(1H, br.s), 4.68-4.49(4H, m), 4.33(1H, dd, J=1.8, 5.5Hz), 4.08(1H, d, J=1.8Hz), 3.80(1H, d, J=6.2, 10.3Hz), 3.78(3H, s), 3.69(1H, dd, J=5.1, 10.3Hz), 3.26(1H, ddd, J=3.7, 5.1, 6.2Hz), 2.95(1H, dd, J=3.7, 5.5Hz), 0.76(9H, s), 0.02(3H, s), -0.06(3H, s); IR($CHCl_3$) 1785, 1720, 1610, 1450cm^{-1}; MS *m/z* 511(M^+-15), 469, 361, 211, 121, 91; Anal. found: C, 63.63 H, 7.16; N, 5.21. Calcd. for $C_{28}H_{38}N_2O_6Si$: C,63.85; H, 7.27; N, 5.23%. ^{1}H-NMR(270MHz) of **12b**: δ 7.40-7.31(7H, m), 6.80(2H, d, J=8.8Hz), 5.07(1H, br.s), 4.57-4.30(4H, m), 4.07(1H, br. d), 3.76(3H, s), 3.71(1H, dd, J=2.4, 8.1Hz), 3.66-3.57(2H, m), 3.60(1H, q, J=4.4Hz), 3.29(1H, dd, J=4.4, 8.1Hz), 0.78(9H, s), 0.07(3H, s), -0.05(3H, s). ^{1}H-NMR (270MHz) of **12c**: δ 7.37-7.30(7H, m), 6.81(2H, d, J=8.4Hz), 5.75(1H, br.s), 4.61-4.49(4H, m), 4.18(1H, d, J=2.4Hz), 3.89(1H, dd, J=2.4, 7.2Hz), 3.76(1H, dd, J=4.4, 11.0Hz), 3.75(3H, s), 3.60(1H, dd, J=5.8, 11.0Hz), 3.23-3.16(2H, m), 0.81(9H, s), 0.02(3H, s), -0.01(3H, s). ^{1}H-NMR (270MHz) of **12d**: δ 7.36-7.28(7H, m), 6.83(2H, d, J=8.8Hz), 5.81(1H, br.s), 4.60-4.47(4H, m), 4.07(1H, d, J=2.8Hz), 3.94(1H, dd, J=2.8, 8.2Hz), 3.78(3H, s), 3.70(1H, dd, J=5.8, 10.7Hz), 3.56(1H, dd, J=5.0, 10.7Hz), 3.27(1H, ddd, J=4.2, 5.0, 5.8Hz), 3.00(1H, dd, J=4.2, 8.2Hz), 0.80(9H, s), 0.10(3H, s), -0.02(3H, s).

Base promoted cyclization of 12. To a stirring solution of epoxy-alcohol **12** (330mg, 0.626mmol) in THF (25ml) was added $LiN(TMS)_2$ (1.0M in THF, 1.3ml, 1.3mmol) at 0°C and the mixture was stirred at room temperature for 10 h. The reaction mixture was poured into water, acidified with diluted HCl and then extracted with ether. The combined extract was washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **8** and **9** (133.1mg, 54%combined yield, **8**:**9** ~1:2 (HPLCanalysis)).

One pot synthesis of 8 and 9 from 3. To the stirring solution of **3** (242.5mg, 0.460mmol) in THF were added $LiN(TMS)_2$ (1.0M in THF, 0.85ml, 0.85mmol) and after 30min, a solution of **5** (0.87M in THF, 0.92ml, 0.80mmol) at -78°C. After stirring for 30min, $LiN(TMS)_2$ (1.0M in THF, 0.85ml, 0.85mmol) was added to the reaction mixture, and solution was stirred at 0°C for 1h. The reaction mixture was worked up as described above to give **8** and **9** (74mg, 41% combined yield, **8**:**9** ~1:2 (HPLC analysis)).

[2*R*,3*S*,4*R*,5*S*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (15) and [2*R*,3*R*,4*S*,5*S*]-isomer (16). To a solution of **8** (1.57g, 3.98mmol) in *t*-BuOH-acetone (2:3) (25.5ml) were added OsO_4 (0.10g) and a solution of *N*-methylmorpholin-*N*-oxide (1.20g, 8.71mmol) in acetone-water (1:1) (20.4ml). The mixture was stirred at room temperature for 24h and then $Na_2S_2O_4$ (1.20g) was added. After the mixture was stirred for 30min, Celite (4.0g) was added and then filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (EtOAc-hexane 1:1) to give **15** (280mg, 10%) as white needles and **16** (1.63g, 58%) as white needles. **Data of 15**: m.p. 82.5-84.0°C; $[\alpha]_D^{24}$ -1.18° (c=1.56, $CHCl_3$); IR (KBr) 3450, 1790, 1720, 1250cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.45-7.20(7H, m), 6.83(2H, d, J=8.8Hz), 5.85(1H, br.s), 4.58(2H, s), 4.52(2H, s), 4.38(2H, m), 4.33(1H, d, J=12.1Hz), 4.14(1H, ddd, J=1.0, 5.4, 12.2Hz), 3.77(3H, s), 3.60(2H, d, J=1.0Hz), 3.06(1H, d, J=8.8Hz), MS *m/z* 428(M^+), 136, 121; HRMS. found: 428.1571. Calcd. for $C_{22}H_{24}N_2O_7$:428.1584. **Data of 16**: m.p. 125.0-126.5°C; $[\alpha]_D^{24}$ +19.21° (c=2.28, $CHCl_3$); IR (KBr) 3520, 3250, 1785, 1725, 1250 cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.45-7.25(7H, m), 6.81(2H, d, J=8.8Hz), 6.25(1H, br. s), 4.55(4H, s), 4.44(1H, t, J=4.4Hz), 4.36(1H, dt, J=4.4, 9.8Hz), 4.30(1H, t, J=4.4Hz), 3.76(3H, s), 3.75(2H, d, J=4.4H), 3.61(1H, d, J=9.8Hz), 3.58(1H, d, J=4.4Hz); MS *m/z* 428(M^+), 317, 248, 220, 121; Anal. found: C, 61.58; H, 5.67; N, 6.54. Calcd. for $C_{22}H_{24}N_2O_7$: C, 61.68; H,5.60; N,6.54%.

[2*R*,3*R*,4*R*,5*S*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-3,4-diacetoxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (17). A solution of talcohol **15** (118.1mg, 0.276mmol), pyridine (0.16ml, 1.93mmol), 4-*N*,*N*-dimethylaminopyridine (34.0mg, 0.079mmol) and acetic anhydride (0.18ml, 1.93mmol) in acetonitrile (2.4ml) was stirred overnight at room temperature. The reaction mixture was

then diluted with ether and washed with dil. HCl, water and brine. After drying (Na_2SO_4) and evaporation of the solvent, the resulting residue was chromatographed on silica gel (EtOAc-hexane 3:1) to afford **17** (93.8mg, 62%) as a col,ourless syrup; $[\alpha]_D^{24}$ +70.69° (c=1.16, $CHCl_3$); IR ($CHCl_3$) 1800, 1740, 1720, 1610, 1510, 1445cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.34-7.28(7H, m), 6.84(2H, d, J=8.8Hz), 5.62(1H, d, J=7.2Hz), 5.36(1H, dd, J=7.2, 8.5Hz), 4.73-4.66(1H, m), 4.62-4.50(4H, m), 3.76-3.67(2H, m), 2.57(3H, s), 2.08(3H, s), 1.84(3H, s); MS *m/z* 554(M^+), 511, 448, 405, 121, 91; HRMS. found: 554.1909. Calcd. for $C_{28}H_{30}N_2O_{10}$: 554.1910.

[2*R*,3*S*,4*S*,5*S*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-3,4-diacetoxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (18). A alcohol **16** (299.8mg, 0.700mmol) was acetylated in the same manner as described above to yield **18** (245.4mg, 63%) as a colourless syrup; $[\alpha]_D^{24}$ -19.15° (c=2.26, $CHCl_3$); IR($CHCl_3$) 1800, 1740, 1610, 1510, 1435, 1410cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.35-7.27(7H, m), 6.85(2H, d, J=8.8Hz), 5.68(1H, dd, J=5.0, 6.8Hz), 5.50(1H, d, J=6.8HZ), 4.72(1H, dt, J=5.0, 7.0Hz), 4.62(1H, d, J=12.2Hz), 4.62(2H, ABq, J=14.5Hz), 4.45(1H, d, J=12.2Hz), 3.81(1H, dd, J=7.0, 10.5Hz), 3.79(3H, s), 3.74(1H, dd, J=5.0, 10.5Hz), 2.49(3H, s), 2.13(3H, s), 1.98(3H, s); MS *m/z* 554(M^+), 511, 405, 121, 91; HRMS. found: 554.1895. Calcd for $C_{28}H_{30}N_2O_{10}$: 554.1901.

[2*R*,5*S*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-6-benzyloxycarbonyl-1-oxa-6,8-diazaspiro[4.4]nonane-3-ene-7,9-dione (19). To a solution of **8** (6.50g, 16.48mmol) in THF (325ml) was added *t*-BuOK (1.94g, 17.29mmol) at 0°C and the mixture was stirred for 5 min. A solution of chlorobenzylformate (2.8ml, 19.7mmol) in THF (30ml) was added and the resulting mixture was stirred at 0°C for 20min and at r.t. for 40min. After diluted with EtOAc, the mixture was washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:2) to give **19** (8.45g, 97%) as white needles; m.p. 97.0-98.0°C; $[\alpha]_D^{25}$ +8.96° (c=0.40, CH_3OH); IR (KBr) 1835, 1735, 1240cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.40-7.25(12H, m), 6.83(2H, d, J=8.8Hz), 6.32(1H, dd, J=1.5, 5.9Hz), 5.69(1H, dd, J=2.6, 5.9Hz), 5.3-5.2(1H, m), 5.19(2H, ABq, J=12.1Hz), 4.63(2H, s), 4.47(2H, ABq, J=12.1Hz), 3.78(3H, s), 3.56(1H, dd, J=7.9, 10.3Hz), 3.48(1H, dd, J=4.8, 10.3Hz); MS *m/z* 528(M^+), 498, 422, 393, 335, 211, 121, 91; HRMS. found: 528.1898. Calcd for $C_{30}H_{28}N_2O_7$: 528.1896.

[2*R*,3*S*,4*R*,5*S*]-Benzyloxymethyl-8-(4-methoxybenzyl)-6-benzyloxycarbonyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (20). To a solution of **19** (19.37g, 36.6mmol) in acetone (250ml) were added OsO_4 (1.0g) and a solution of *N*-methylmorpholin-*N*-oxide (4.72g, 40.3mmol) in *t*-BuOH-H_2O (1:2, 108ml). The mixture was stirred at room temperature for five days and then $Na_2S_2O_4$ (12.70g, 72.9mmol) was added. After 20min stirring, the mixture was filtered through Celite. Evaporation of the solvent and chromatography of the residue (EtOAc-hexane 2:1 then 1:1) gave **20** (9.85g, 48%, 96% theoretical yield) as a white solid with recovery of the starting material **19** (9.66g, 50%). **Data of 20:** m.p. 106.0-107.0°C; $[\alpha]_D^{25}$ +3.66° (c=0.30, CH_3OH); IR (KBr) 3350, 1805, 1750, 1725, 1245cm^{-1}; NMR(270MHz, $CDCl_3$) δ 7.4-7.2(12H, m), 6.83(2H, d, J=8.8Hz), 5.28(2H, s), 5.14(1H, dd, J=6.6, 8.8Hz), 4.63(2H, s), 4.6-4.5(1H, m), 4.50(2H, ABq, J=12.1Hz), 4.32(1H, d, J=8.8Hz), 4.10(1H, ddd, J=1.8, 6.6, 12.4Hz), 3.78(3H, s), 3.59(1H, dd, J=2.9, 6.6Hz), 3.54(1H, dd, J=2.9, 6.6Hz), 2.98(1H, d, J=8.8Hz); MS *m/z* 544(M^+-18), 454, 410, 363, 348, 320, 162, 121, 91; Anal. found: C, 64.36; H, 5.52; N, 4.98. Calcd. for $C_{30}H_{30}N_2O_9$: C, 64.05; H, 5.38; N, 4.98%.

[2*R*,3*S*,4*R*,5*S*]-2-Bezyloxymethyl-6-benzyloxycarbonyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (21). To a solution of ceric ammonium nitrate (37.57g, 68.53mmol) in water (69ml) was added **20** (2.57g, 4.57mmol) in acetonitrile (138ml) at room temperature. After stirring for 20min, the mixture was diluted with EtOAc (500ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue (EtOAc-hexane 1:1 then 2:1) gave **21** (1.89g, 94%) as a white amorphous solid; $[\alpha]_D^{25}$ +6.20° (c=0.58, CH_3OH); IR ($CHCl_3$) 3500-3300, 1730, 1600, 1290, 1270, 1120cm^{-1}; NMR(270MHz,

CD_3OD) δ 7.5-7.2(10H, m), 5.23(2H, ABq, J=12.1Hz), 4.91(1H, d, J=6.8Hz), 4.47(2H, s), 4.39(1H, ddd, J=4.0, 4.8, 6.4Hz), 3.98(1H, dd, J=4.0, 6.8Hz), 3.54(1H, dd, J=4.8, 10.5Hz), 3.47(1H, dd, J=6.4, 10.5Hz); MS *m/z* 442(M^+), 423, 397, 354, 333, 245, 205, 129, 107.

[2*R*,3*S*,4*R*,5*S*]-2-Hydroxymethyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (1). A solution of **21** (9.72g, 22.2mmol) and Pd-C (5%, 4.0g) in methanol (300ml) was heated at 55°C under hydrogen atmosphere (3.0kg/cm^2) for 6h. After filtration of the mixture, the filtrate was concentrated under reduced pressure. Chromatography of the residue on Diaion CHP-20P (water) and crystallization from acetone gave **1** (4.27g, 89%) as colourless prisms; m.p. 188.0-180.5°C; $[\alpha]_D^{23}$ +28.96° (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, 12.7Hz); MS *m/z* 219(M+1), 187, 171, 141, 129, 116, 100, 86, 73, 57; Anal. found: C, 36.41; H, 4.66; N, 11.70. Calcd. for $C_7H_{10}N_2O_6$+3/4H_2O): C, 36.29; H, 5.00; N, 12.09%.

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