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SYNTHETIC STUDIES ON (+)-HYDANTOCIDIN (4): SYNTHESIS OF STEREOISOMERS OF (+)-HYDANTOCIDIN

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Abstract: The stereoisomers of (+)-hydantocidin were synthesized by diastereoselective dihydroxylation directly or epoxidation followed by ring opening of 1-oxa-6,8-diazaspiro[4.4]nonane-3-ene-7,9-dione systems.

A naturally occurring spiro-ribofuranose, (+)-hydantocidin **1**[1], shows a strong herbicidal activity against both annual weeds and perennial weeds with no toxicity to microorganisms or animals. The unique structure[2] and the striking selectivity implies a new characteristic mode of action functioning in only plant. Our interest was directed toward the elucidation of the structure-activity-relationship from the aspect of spatial arrangement of the functional groups in **1**. Therefore, we planned to prepare all the stereoisomers of (+)-hydantocidin which consist of sixteen stereoisomers arising from the four contiguous chiral centers (**Figure 1**). In the preceding papers[3], we reported the total synthesis of **1** and the stereoisomers **3**, **4**, **7** and **8**. Herein we wish to report a general synthetic route for all the diastereoisomers **1**-**8** which are corresponding to D-series of sugar.

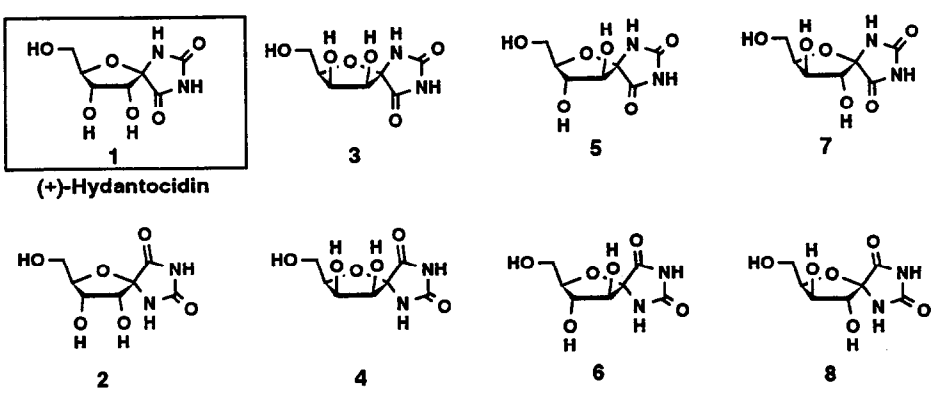


Figure 1

Our strategy is based on the diastereoselective dihydroxylation of spiro-2,5-dihydrofurane systems[4] **A** and **B** (**Figure 2**). We intended to control the selectivity by the choice of substituents at N-6 position. It is expected that the C-9 carbonyl side of the olefin face in both **A** and **B** is more congested and reacts more slowly with

electrophiles than the other face when R is H. The reverse selectivity , on the other hand, can be expected when the N-6 side is covered by a bulky substituent introduced at N-6 position.

Initially, we focused on the methodology for synthesis of 3,4-*cis*-stereoisomers **1-4** (**Scheme 1**). The previous findings[3a] of the face selectivities in type **A** support the above strategy: **9** was dihydroxylated with osmium tetroxide to afford **13** predominantly (**13**:**14**=5.8:1), and **11** gave only α-dihydroxy isomer **15**. In order

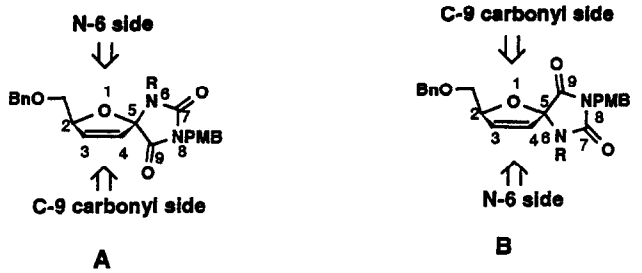
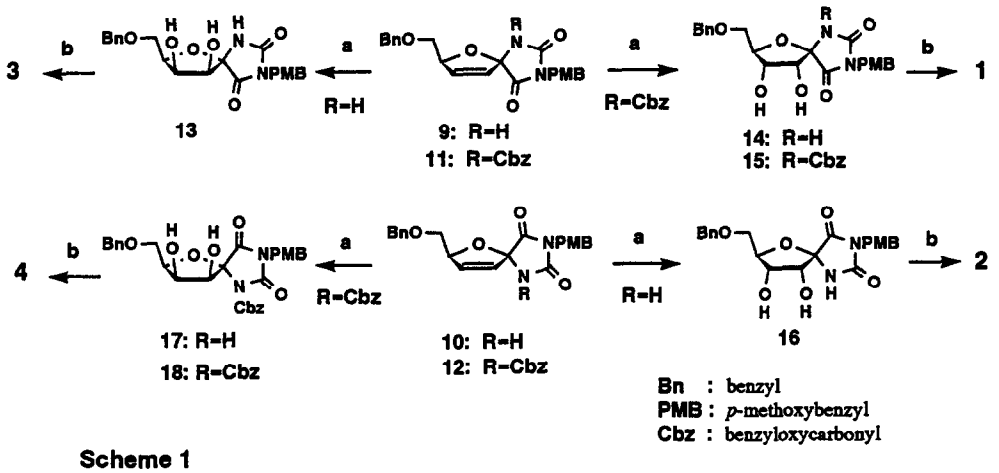


Figure 2



Scheme 1

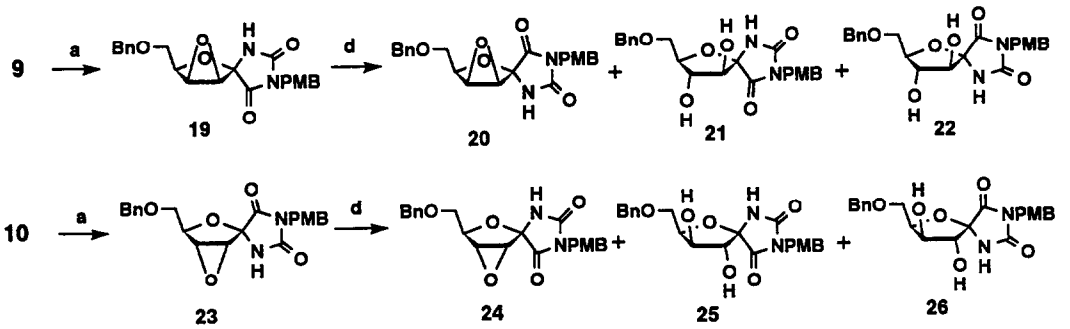
a) OsO_4, *N*-methylmorpholine-*N*-oxide, acetone-H_2O. b) CAN, acetonitrile-H_2O; H_2/Pd-C(5%), MeOH, 55°C.

to generalize this strategy, we examined the dihydroxylation of type **B** ,**10** and **12**, which have unnatural configuration at the spiro-center. Catalytic osmium tetroxide oxidation[5] of **10** proceeded smoothly at room temperature to afford a single isomer **16** (76%), and the oxidation of *N*-benzyloxycarbonyl derivative **12** at 35°C for 3 days gave β-dihydroxy isomer **18** (53%) with recovery of the starting olefin (30%). The *cis*-isomers **16** and **18** were independently converted to desired stereoisomers **2** and **4** by demethoxybenzylation with celic ammonium nitrate (CAN)[6] and hydrogenolysis of the benzyl group with H_2/ Pd-C, respectively.

Next, we tried to synthesize the 3,4-*trans*-stereoisomers **5-8** *via* the opening of the corresponding 3,4-epoxides in an acidic medium (**Scheme 2**). Epoxidation of **9** with *m*-chloroperbenzoic acid (*m*CPBA) in refluxing dichloroethane for 3.5h afforded one isomer **19** (59%), while spiro-isomer **10** gave a single epoxide **23** (22%) with recovery of **10** (41%). In each case, *m*CPBA attacked the opposite face to the C-9 carbonyl side,

the selectivity of which was consistent with the osmium oxidation mentioned above. Although the α-face in **10** was thought to be less hindered than the β-face in **9** owing to the C-2 substituent, the epoxidation of **10** proceeded slowly and didn't completed by either prolonged reaction time or elevated temperature. The fact implies an additional factor influencing the reactivity of epoxydation compared with the case of the osmium oxidation.

With epoxides **19** and **23** in hand, the ring-opening was examined in an acidic medium (**Scheme 2**). After several attempts, a rather drastic condition (50% aq. H_2SO_4 in DME at 50°C) was required to afford two isomeric diols **21**(39%) and **22** (21%) along with the epimerized epoxide **20** (9%). The similar result was obtained in the case of epoxide **23** affording dihydroxy compound **25** (30%) and **26** (17%) together with an epimerized epoxide **24** (13%) after chromatography. Interestingly, it was found that the epoxide-opening occurred at only the 3-position on the furanose ring in both cases. While the detailed factor of the regioslectivity of epoxide-opening is unclear at this stage, C-9 and N-6 functionalities on the spiro-hydantoin are presume to play an important role for the selectivity. The deprotection of **21** and **22** were accomplished by successive treatment with CAN and H_2/Pd-C to afford the desired 3,4-*trans*-dihydroxy isomers **5** (21%) and **6** (27%) in two steps, respectively.



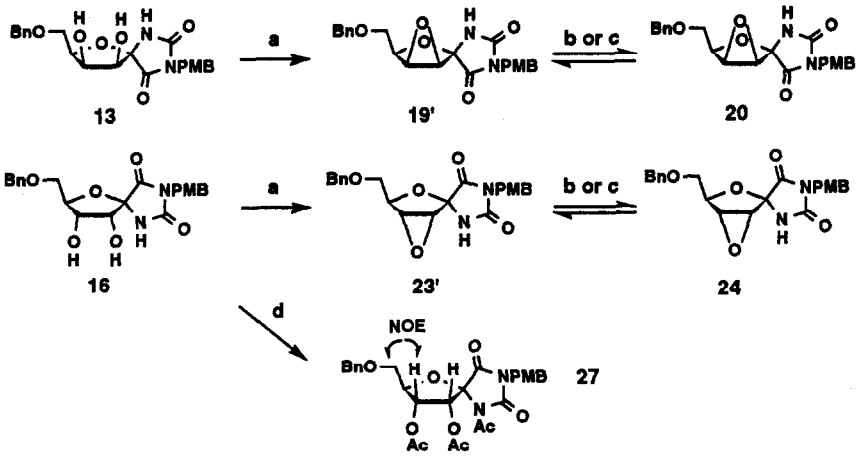
Scheme 2

a) *m*-CPBA, dichloroethane, reflux. b) 50% aq.H_2SO_4, DME, 50°C.

In order to elucidate the stereochemistry of the *cis*-diol **16** , the *trans*-diols (**21, 22, 25** and **26**) and the epoxides (**19, 20, 23** and **24**) , the following experiments were carried out (**Scheme 3** and **Scheme 4**). While the structure of *cis*-diol **13, 14, 15** and **17** have already been confirmed as depicted in Scheme 1 in our previous reports[3a], the remaining *cis*-diol **16** was derivatized into a triacetate **27** to analyze the stereochemistry. In the ^{1}H-NMR experiment in **27**, the NOE was observed between the protons at C-2α and C-3 showing an α-arrangement of the diol group.

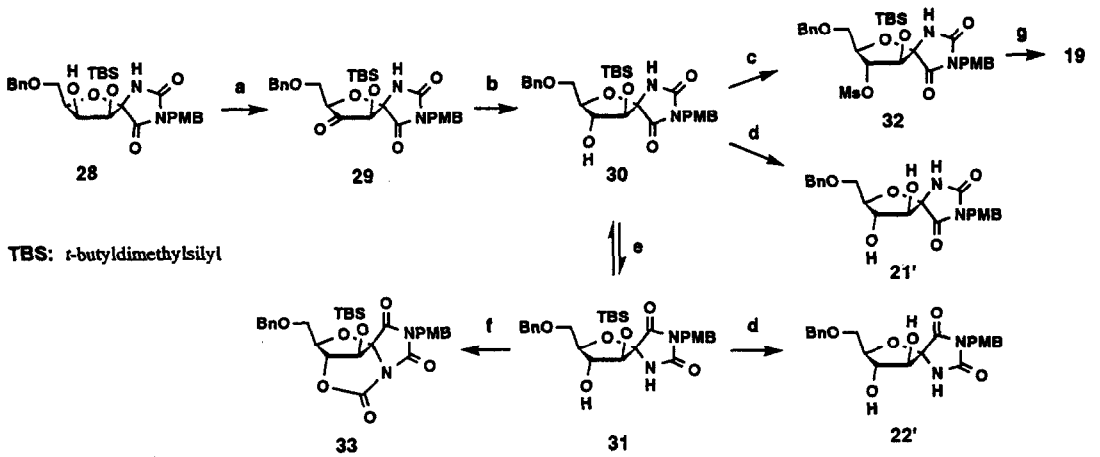
Next, the stereochemistry of the epoxide **19** and **23** were determined on the basis of Moffatt's method[7] which converted a geminal-*cis*-diol into the corresponding epoxide with retention of their stereochemistry in a nucleoside system. Treatment of **13** with 2-acetoxyisobutylyl chloride in acetonitrile gave 3,4- and 4,3-chlorohydrine intermediates which were successfully cyclized into **19'** by employing NaH in the mixed solvent of THF and DMF. The epoxide **19'** was identical in every respects to **19** derived by *m*CPBA-epoxidation. The same sequence was applied to **16** affording **23'** which was also identical with **23**. Analysis of ^{1}H-NMR, IR and

Mass spectra between **19** and **20** strongly supports an epimeric relationship of the spiro-center, furthermore; the isomerization between them could achieved in protic solvent (methanol or water) under both acidic (*p*-TsOH) and basic (aq. NH_3) conditions with no change of epoxy-functionality on the furanose ring. Similarly, **24** was postulated to be the epimer at the spiro-center of **23**.



Scheme 3

a) 2-acetoxyisobutylyl chloride, CH_3CN; NaOMe, MeOH; NaH, THF-DMF. b) aq.NH_3, EtOH, 50°C. c) *p*-TsOH, MeOH, 70°C. d) Ac_2O, Py, DMAP, CH_3CN.



TBS: *t*-butyldimethylsilyl

Scheme 4

a) $COCl_2$, DMSO, Et_3N, CH_2Cl_2. b) $NaBH_4$, MeOH. c) MsCl, Et_3N, CH_2Cl_2. d) *n*-Bu_4NF, THF. e) aq.NH_3, EtOH, 70°C f) $COCl_2$, Et_3N, CH_2Cl_2. g) *n*-Bu_4NF then NaH, THF

While the stereochemistry of the *trans*-diols **25** and **26** have been already elucidated in our aldol-addition approach[3b], the confirmation of the *trans*-diols **21** and **22** was carried out by derivatization from the stereo-defined spiro-hydantoin **28** (**Scheme 4**). Swern oxidation[8] of **28** gave the corresponding ketone **29** (23%) with recovery of the starting alcohol (52%) and subsequent reduction of **29** with sodium borohydride in methanol produced diastereomeric alcohols **30** and **28** (95%, **30**:**28**=14:1). The stereochemistry at C-3 was determined by formation of 3,4-epoxide **19** from **30** which process consists of desilylation with *n*-Bu_4NF followed by base-promoted cyclization. Finally, the stereochemistry of **22** was confirmed by the comparison of the authentic sample **22'** which was derived from **30** in two steps. Epimerization of **30** into **31** was succeeded in a mixture of ethanol and ammonium hydroxide at 80°C to yield **31** (34%) together with **30** (44%). The analysis of ^{1}H-NMR Mass and IR in **31** showed the existence of the unchanged furanose part, the result of which indicated the epimeric relationship at the spiro center. Finally, its stereochemistry was confirmed by the formation of **33** which was carbonylated between hydroxy group at C-3 and NH group at N-6. The resulting alcohol **31** was desilylated with *n*-Bu_4NF to furnish the *trans*-diol **22'** which was identical with **22** derived from the epoxide-opening.

In conclusion, we have developed a general route for the synthesis of all the diastereoisomers of (+)-hydantocidin in D-series by the diastereoselective dihydroxylation of the spiro-2,5-dihydrofurane systems **9**-**12** as key steps. This method is also applicable to the antipode-synthesis of **1**-**8** by employing L-tartrate as a starting material and the research are now in progress.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. ^{1}H-NMR spectra (270MHz) were recorded on a JOEL GX-270 spectrometer. IR 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 was used for SiO_2 column chromatography. Merck TLC plate Art.5744 was used for preparative TLC.

[2*R*,5*R*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-6-benzyloxycarbonyl-1-oxa-6,8-diazaspiro[4.4]nonane-3-ene-7,9-dione (12). To a stirring solution of **10** (770mg, 1.45mmol) in THF (80ml) was added *t*-BuOK (0.22g, 1.45mmol) at 0°C. After 5 min, benzyl chloroformate (0.34ml, 1.60mmol) was added, and the mixture was stirred at r.t. for 1.5h. The mixture was diluted with water and extracted with EtOAc (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **12** (880mg, 84%) as a colourless syrup. $[\alpha]_D^{26}$ -54.2° (c=1.19, $CHCl_3$); IR ($CHCl_3$) 1820, 1760, 1745cm^{-1}; NMR ($CDCl_3$) δ 7.38-7.30(7H, m), 7.27(2H, d, J=8.8Hz), 6.83(1H, dd, J=2.2, 6.6Hz), 5.61(1H, dd, J=2.6, 6.6Hz), 5.23(2H, s), 5.21(1H, dddd, J=2.2, 2.6, 5.1, 7.3Hz), 4.65(2H, s), 4.55(2H, ABq, J=12.4Hz), 3.78(3H, s), 3.64(1H, dd, J=7.3, 10.2Hz), 3.57(1H, dd, J=5.1, 10.2Hz); MS *m/z* 428(M+), 337, 262, 121. Anal. found: C, 68.16; H, 5.57; N, 5.35. Calcd. for $C_{30}H_{28}N_2O_7$: C, 68.18; H, 5.30; N, 5.30%.

[2*R*,3*S*,4*R*,5*R*]-2-Benzyloxy-8-(4-methoxybenzyl)-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (16). To a solution of **10** (500mg, 1.17mmol) in a mixture of pyridine-water-*t*-butanol (2:15:50, 10ml) were added trimethylamine-*N*-oxide dihydrate (212mg, 1.91mmol) and OsO_4 (0.10g) and then the mixture was stirred at 70°C for 6h. The mixture was quenched with 20% aq. $NaHSO_3$ (2.0ml) and extract with EtOAc (x3). The combined extract was dried (Na_2SO_4) and concentrated. The residue was

chromatographed on silica gel (EtOAc-hexane 1:1 then 6:1) to give **16** (415.0mg, 76%) as a colourless syrup. $[\alpha]_D^{26}$ -25.0° (c=1.01, $CHCl_3$); IR ($CHCl_3$) 3400, 1790, 1720cm^{-1}; NMR ($CDCl_3$) δ 7.37-7.27(7H, m), 6.81(2H, d, J=8.4Hz), 6.43(1H, br.s), 4.56(2H, ABq, J=12.1Hz), 4.55(2H, s), 4.37(1H, dd, J=4.4, 7.3Hz), 4.2-4.3(2H, m), 3.75(3H, s), 3.62(1H, dd, J=4.8, 10.6Hz), 3.54(1H, dd, J=5.1, 10.6Hz), 3.32(1H, d, J=7.3Hz), 3.04(1H, d, J=3.3Hz); MS *m/z* 428(M+), 337, 262, 121; HRMS. found: 428.1589. Calcd. for $C_{22}H_{24}N_2O_7$: 428.1584.

[2*R*,3*R*,4*S*,5*R*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-6-benzyloxycarbonyl-3,4-dihydroxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (18). To a solution of *N*-methylmorpholine-*N*-oxide (139mg, 1.21mmol) in a mixture of acetone-water (2:1, 0.6ml) were added a solution of **12** (0.57g, 1.1mmol) in a mixture of acetone-*t*-BuOH (5:2, 1.4ml) and OsO_4(45mg). After stirring at 35°C for 67h, the mixture was quenched with 20% aq.$NaHSO_3$ 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 **18** (320mg, 53%) as a colourless syrup with recovery of **12** (170mg, 30%). $[\alpha]_D^{25}$ +5.1° (c=1.38, $CHCl_3$); IR ($CHCl_3$) 3550-3350, 1820, 1810, 1740cm^{-1}; NMR ($CDCl_3$) δ 7.45-7.25(7H, m), 7.28(2H, d, J=8.8Hz), 5.32(2H, ABq, J=12.1Hz), 5.18(1H, dd, J=4.4, 9.9Hz), 4.67(1H, ddd, J=2.6, 4.4, 6.6Hz), 4.63(2H, s), 4.56(2H, ABq, J=12.1Hz), 4.22(1H, br.s), 4.19(1H, dd, J=2.6, 4.4Hz), 3.81(1H, dd, J=4.4, 11.0Hz), 3.77(3H, s), 3.73(1H, dd, J=6.6, 11.0Hz), 2.95(2H, d, J=9.9Hz); MS *m/z* 544(M^+-18, H_2O), 454, 333, 121, 91. Anal. found: C, 63.63; H 5.47; N, 4.86. Calcd. for $C_{30}H_{30}N_2O_9$: C, 64.05; H, 5.33; N, 4.98%.

[2*R*,3*S*,4*R*,5*R*]-3,4-Dihydroxy-2-hydroxymethyl-6,8-diaza-1-oxaspiro[4.4]nonane-7,9-dione (2). To a stirring solution of ceric ammonium nitrate (1.34g, 2.44mmol) in water (1.8ml) was added a solution of **16** (70mg, 0.16mmol) in CH_3CN (3.7ml) at r.t.. After 15min, the reaction mixture was diluted with brine and the aqueous layer was extracted with EtOAc (x4). The combined extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (EtOAc-hexane 2:1 then 10:1) to give **[2*R*,3*S*,3*R*,5*R*]-2-benzyloxymethyl-3,4-dihydroxy-6,8-diaza-1-oxaspiro[4.4]nonane-7,9-dione** (26mg, 50%) as a colourless syrup, which was used directly in the next reaction. IR ($CHCl_3$) 3300, 3040, 1785, 1740cm^{-1}; NMR ($CDCl_3$) δ 7.2-7.4(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, dt, J=3.3, 4.8Hz), 3.60(2H, d, J=4.8Hz); MS *m/z* 308(M+), 230, 202. A mixture of the above diol (218mg, 0.707mmol) and 5% Pd-C (220mg) in MeOH (300ml) was heated at 55°C under hydrogen atmosphere (3.0kg/cm^2) for 6h. After filtration of the mixture through Celite, the filtrate was concentrated under reduced pressure. Chromatography of the residue on Diaion CHP 20P (water) gave **2** (102.4mg, 66%) as a white amorphous solid. $[\alpha]_D^{22}$ -11.0° (c=0.30, CH_3OH); IR (KBr) 3650-2700, 1785, 1725cm^{-1}; NMR (CD_3OD) δ 4.24(1H, d, J=5.1Hz), 4.16(1H, dd, J=3.3, 5.1Hz), 3.66(1H, dd, J=4.4, 12.1Hz), 3.59(1H, dd, J=5.1, 12.1Hz), 3.29(1H, ddd, J=3.3, 4.4, 5.1Hz); MS *m/z* 219(M+), 187, 171, 129. Anal. found: C, 38.38; H, 4.55; N, 12.43. Calcd. for $C_7H_{10}N_2O_6$: C, 38.53; H, 4.62; N, 12.84%.

[2*R*,3*R*,4*S*,5*S*]-2-Benzyloxymethyl-3,4-epoxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (19). A mixture of **9** (500mg, 1.3mmol), *m*-CPBA (1.09g, 5.0mmol) and 2,6-di-*t*-butyl-4-methylphenol (219mg, 0.99mmol) in 1,2-dichloroethane (50ml) was refluxed for 4h. After cooled, the resulting crystals were filtered off and the filtrate was diluted with CH_2Cl_2. The solution was washed with saturated Na_2SO_3 and brine, and then dried (Na_2SO_4). Evaporation of the solvent and chromatography of the residue on silica gel (EtOAc-hexane 1:4) gave **19** (240mg, 59%) as a colourless syrup. $[a]_D^{25}$ -27.4° (c=0.96, $CHCl_3$); IR ($CHCl_3$) 3300, 1795, 1730cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.27(7H, m), 6.84(2H, d, J=8.8Hz), 5.73(1H, br.s), 4.58(2H, s), 4.57(2H, ABq, J=12.1Hz), 4.48(1H, dt, J=0.7, 6.2Hz), 3.96(1H, dd, J=0.7, 2.9Hz), 3.78(3H, s), 3.75(1H, d, J=2.9Hz), 3.63(2H, d, J=6.2Hz); MS *m/z* 410(M+), 304, 260, 121. Anal. found: C, 64.11; H, 5.54; N, 6.50. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.37; N, 6.83%.

[2*R*,3*S*,4*R*,5*R*]-2-Benzyloxymethyl-3,4-epoxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (23). Compound **10** (1.00g, 2.5mmol) was converted to **23** (0.45g, 22%) as a colourless syrup with recovery of **10** (0.41g, 41%) in the same manner as described above. $[\alpha]_D^{25}$ -23.9° (c=0.65, CH_3OH); IR ($CHCl_3$) 3450, 1790, 1740cm^{-1}; NMR ($CDCl_3$) δ 7.04-7.20(7H, m), 6.84(2H, d, J=8.8Hz), 5.71(1H, br.s), 4.59(2H, ABq, J=14.7Hz), 4.56(2H, s), 4.48(1H, dd, J=6.6, 7.7Hz), 3.99(1H, d, J=2.6Hz), 3.78(3H, s), 3.77(1H, d, J=2.6Hz), 3.73(1H, dd, J=7.7, 9.9Hz), 3.63(1H, dd, J=6.6, 9.9Hz); MS *m/z* 410(M+), 319, 304, 259, 121. Anal. found: C, 64.01; H, 5.40; N, 6.57. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.36; N, 6.82%.

[2*R*,3*R*,4*S*,5*R*]-2-Benzyloxymethyl-3,4-epoxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (20), [2*R*,3*S*, 4*S*,5*S*]-2-benzyloxycarbonyl-3,4-dihydroxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]-nonane-7,9-dione (21) and its [2*R*,3*S*,4*S*,5*R*]-isomer (22). A stirring solution of **19** (1.00g, 24mmol) in a mixture of dimethoxyethane (20ml) and 50% aq. H_2SO_4 (10ml) was heated at 50°C for 7h. After being cooled, the mixture was neutralised with sat. Na_2CO_3 and extracted with EtOAc (x3). The combined extract was dried (Na_2SO_4) and concentrated under reduced pressure to give the residue which was chromatographed on silica gel (EtOAc-hexane 2:3) to yield **20** (94mg, 9.4%) as a colourless syrup, **21** (406mg, 39%) as a white solid and **22** (420mg, 40%) as a white solid, respectively. **Data of 20:** $[\alpha]_D^{25}$ +12.1° (c=0.97, CH_3OH); IR ($CHCl_3$) 3330, 1850, 1745cm^{-1}; NMR ($CDCl_3$) δ 7.34-7.25(7H, m), 6.86(2H, d, J=8.8Hz), 4.58(2H, ABq, J=15.4Hz), 4.57(1H, br.s), 4.22(1H, dt, J=2.2, 6.2Hz), 3.96(1H, d, J=2.2Hz), 3.91(1H, t, J=2.2Hz), 3.76(3H, s), 3.75(1H, dd, J=6.2, 9.9Hz), 3.67(1H, dd, J=6.2, 9.9Hz); MS *m/z* 410(M+), 260, 121. Anal. found: C, 64.01; H, 5.36; N, 6.73. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.37; N, 6.83%. **Data of 21:** mp. 125-128°C; $[\alpha]_D^{25}$ +20.7° (c=0.64, CH_3OH); IR (KBr) 3300, 1785, 1715cm^{-1}; NMR (CD_3OD) δ 7.34-7.24(7H, m), 6.85(2H, d, J=8.8Hz), 4.56(1H, br.s), 4.55(2H, ABq, J=14.6Hz), 4.29(1H, ddd, J=1.8, 2.2, 5.1Hz), 3.97(1H, dd, J=1.1, 1.8Hz), 3.95(1H, d, J=1.1Hz), 3.76(3H, s), 3.68(1H, dd, J=2.2, 11.0Hz), 3.57(1H, dd, J=5.1, 11.0Hz); MS *m/z* 428(M+), 365, 262, 121. Anal. found: C, 61.69; H, 5.77; N, 6.54. Calcd. for $C_{22}H_{24}N_2O_7$: C, 61.89; H, 5.61; N, 6.54%. **Data of 22:** mp. 106-107°C; $[\alpha]_D^{25}$ +5.3° (c=0.45, $CHCl_3$); IR $CHCl_3$) 3440, 1785, 1730cm^{-1}; NMR (CD_3OD) δ 7.34-7.22(7H, m), 6.83(2H, d, J=8.4Hz), 4.54(2H, ABq, J=15.0Hz), 4.53(2H, ABq, J=11.9Hz), 4.28(1H, t, J=8.4Hz), 4.14(1H, d, J=8.4Hz), 4.04(1H, ddd, J=3.3, 6.6, 8.4Hz), 3.75(3H, s), 3.74(1H, dd, J=3.3, 7.7Hz), 3.69(1H, dd, J=6.6, 7.7Hz); MS *m/z* 428(M+), 317, 262, 121. Anal. found: C, 61.39; H, 5.26; N, 6.33. Calcd. for $C_{22}H_{24}N_2O_7$: C, 61.68; H, 5.61; N, 6.54%.

[2*R*,3*S*,4*R*,5*S*]-2-Benzyloxymethyl-3,4-epoxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione(24), [2*R*,3*R*, 4*R*,5*S*]-2-benzyloxymethyl-3,4-dihydroxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro-[4.4]nonane-7,9-dione (25) and its [2*R*,3*R*,4*R*,5*S*]-isomer (26). The epoxide **23** (887mg, 2.16mmol) was treated in the same manner as described above to yield **24** (112.2mg, 13%) as white needles, **25** (277.7mg, 30%) and **26** (157.5mg, 17%), respectively. **Data of 24:** mp. 126.5-127.5°C; $[\alpha]_D^{25}$ -85.4° (c=0.39, CH_3OH); IR (KBr) 3400, 1790, 1730cm^{-1}; NMR (CD_3OD) δ 7.40-7.30(5H, m), 7.26(2H, d, J=8.8Hz), 6.86(2H, d, J=8.8Hz), 4.58(2H, s), 4.57(2H, ABq, J=14.7Hz), 4.38(1H, t, J=3.7Hz), 3.92(2H, s), 3.76(3H, s), 3.76(1H, dd, J=3.7, 10.6Hz), 3.66(1H, dd, J=3.7, 10.6Hz); MS *m/z* 410(M+), 319, 304, 259, 121. Anal. found: C, 64.39; H, 5.32; N, 6.87. Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.39; H, 5.36; N, 6.82%. The data of **25** and **26** were reported in the preceding paper[3b].

Preparation of 19′ and 23′ by Moffatt's procedure.

To a stirring solution of **13** (166.7mg, 0.389mmol) in CH_3CN (4ml) was added 2-acetoxyisobutylyl chloride (0.11ml, 0.78mmol) and the mixture was heated at 80°C for 3h. After being cooled, the mixture was evaporated under reduced pressure to give a syrup which was dissolved in THF (6.0ml). To this solution was added NaOMe (0.94ml, 2.1M in MeOH) at 0°C and the mixture was stirred at r.t. for 5h. After quenching with sat. NH_4Cl, the mixture was extracted with Et_2O (x3), and then the combined extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was then dissolved in THF-DMF (4ml, 3:1). To this

solution was added NaH (23mg, 0.57mmol) at r.t. and then the mixture was stirred for 30min. The same work up as described above was carried out to give a residue which was chromatographed on preparative TLC affording **19'** (81.4mg, 51%) which was identical with **19**.

The same procedure on **16** (32.3mg) gave the corresponding epoxide **23'** (13.8mg, 44%) which was identical eith **23**.

Isomerization of epoxides 19, 20, 23 and 24.

Method A: A mixture of the epoxide **19** (49.0mg, 0.119mmol) and *p*-TsOHH_2O (11.4mg, 0.060mmol) in MeOH (1.0ml) was stirred at 70°C for 6h. The resulting mixture was diluted with water and extracted with EtOAc (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (EtOAc-hexane 1:1) to give **19** (21.9mg, 45%) and **20** (18.6mg, 38%).

Method B: To a solution of **19** (62.3mg, 0.152mmol) in MeOH (3.0ml) was added 28% aq.NH_3 (0.5ml). After stirring at 70°C for 6h, the mixture was diluted with water and extracted with EtOAc (x3). The combined extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (EtOAc-hexane 1:1) to give **19**(31.8mg, 51%) and **20** (13.7mg, 22%).

The epoxide **23** was also isomerized to **24** by method A (88%, **23**:**24**= 2.2:1) and method B (76%, **23**:**24**= 1:1.5), respectively.

[2*R*,3*R*,4*R*,5*R*]-2-Benzyloxymethyl-8-(4-methoxybenzyl)-3,4,6-triacetyl-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (27). To a stirring solution of **16** (28.6mg, 0.067mmol) in CH_3CN were added Ac_2O (44ml, 0.47mmol), pyridine (38ml, 0.48mmol) and 4-*N*,*N*-dimethylaminopyridine (10mg) at r.t.. After 1h, the mixture was diluted with water and then extracted with EtOAc (x3). The combined extract was washed with dil. HCl and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on preparative TLC (EtOAc-hexane 1:1) to give **27** (28.1mg, 76%) as a colourless syrup. $[\alpha]_D^{25}$ +29.0° (c=0.77, $CHCl_3$); IR ($CHCl_3$) 1805, 1740cm^{-1}; NMR ($CDCl_3$) δ 7.34-7.27(7H, m), 6.86(2H, d, J=8.8Hz), 5.43(1H, d, J=8.5Hz), 5.28(1H, dd, J=7.2, 8.5Hz), 4.98(1H, m), 4.65(1H, ABq, J=11.4Hz), 4.59(2H, ABq, J=17.6Hz), 3.79(3H, s), 3.72-3.63(2H, m), 2.52(3H, s), 2.10(3H, s), 1.99(3H, s); MS *m/z* 554(M^+), 511, 448, 276, 121; HRMS. found: 554.1913. Calcd. for $C_{28}H_{30}N_2O_{10}$: 554.1910.

[2*R*,4*R*,5*S*]-2-Benzyloxymethyl-4-*t*-butyldimethylsilyloxy-3-oxo-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (29). To a stirring solution of oxaryl chloride (1.7ml, 19.4mmol) in CH_2Cl_2 (90ml) was added a solution of DMSO (2.75ml, 38.8mmol) in CH_2Cl_2 (3ml) at -60°C. After 30min, a solution of **28** (4.39g, 8.39mmol) in CH_2Cl_2 (8ml) was added and the mixture was stirred for 35min. The reaction was quenched by adding Et_3N (6.8ml, 48.5mmol). After the solution was warmed to 0°C and stirred for 20min, it was diluted with water and extracted with CH_2Cl_2 (x3). The combined extract was dried (Na_2SO_4) and concentrated. The crude residue was chromatographed on silica gel (EtOAc-hexane 1:3) to afford **29** (1.04g, 24%) with recovery of **28** (2.30g, 52%). mp. 93.0-93.5°C; $[\alpha]_D^{22}$ -53.3° (c=1.30, $CHCl_3$); IR (KBr) 3370, 1780, 1730cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.24(7H, m), 6.82(2H, ABq, J=8.8Hz), 6.32(1H, br.s), 4.65(1H, d, J=1.1Hz), 4.59(2H, ABq, J=14.3Hz), 4.55(2H, ABq, J=11.0Hz), 4.43(1H, dt, J=1.1, 2.2Hz), 3.81(1H, dd, J=2.2, 10.6Hz), 3.78(3H, s), 3.74(1H, dd, J=2.2, 10.6Hz), 0.75(9H, s), 0.06(3H, s), -0.16(3H, s); MS *m/z* 541(M^++1), 483, 395, 377. Anal. found: 62.19; H, 6.66; N, 5.27. Calcd. for $C_{28}H_{36}N_2O_7Si$: C, 62.20; H, 6.71; N, 5.18%.

[2*R*,3*R*,4*S*,5*S*]-4-*t*-Butyldimethylsilyloxy-2-benzyloxymethyl-3-hydroxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (30). To a stirring solution of **29** (166.3mg, 0.308mmol) in MeOH (5.5ml) was added $NaBH_4$ (11.6mg, 0.307mmol) at 0°C. After 5 min, the mixture was diluted with water and extracted with EtOAc (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. The resulting residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **30** (146.3mg,

88%) and **28** (8.9mg, 5.3%). **Data of 30**: $[\alpha]_D^{22}$ +27.7° (c=1.03, $CHCl_3$); IR ($CHCl_3$) 2450, 1790, 1710cm^{-1}; NMR ($CDCl_3$) δ 7.36-7.29(7H, m), 6.83(2H, d, J=8.8Hz), 5.69(1H, br.s), 4.63-4.51(4H, m), 4.25-4.21(2H, m), 4.02(1H, dt, J=4.4, 9.2Hz), 3.78(3H, s), 3.63-3.53(2H, m), 3.42(1H, d, J=9.2Hz), 0.81(9H, s), 0.05(3H, s), -0.07(3H, s); MS *m/z* 543(M^++1), 485, 467, 211. Anal. found: C, 61.83; H, 7.07; N, 5.03. Calcd. for $C_{28}H_{38}N_2O_7Si$: 61.97; H, 7.06; N, 5.16%.

[*2R,3R,4S,5S*]-2-Benzyloxymethyl-4-*t*-butyldimethylsilyloxy-3-methanesulfonyloxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (32). To a stirring solution of **30** (64.9mg, 0.12mmol) and Et_3N (85ml, 0.61mmol) was added MsCl (14ml, 0.18mmol) at 0°C. After 10min, the mixture was diluted with water and extracted with Et_2O (x3). The combined extract was washed with dil. HCl and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (EtOAc-hexane 1:2) of the residue gave **32** (70.0mg, 99%) as a colourless syrup. $[\alpha]_D^{22}$ +3.2° (c=0.91, $CHCl_3$); IR ($CHCl_3$) 3430, 1790, 1730cm^{-1}. NMR ($CDCl_3$) δ 7.39-7.32(7H, m), 6.82(2H, d, J=8.8Hz), 6.19(1H, br.s), 5.12(1H, dd, J=5.1, 6.2Hz), 4.68(1H, d, J=6.2Hz), 4.62(2H, m), 4.56(2H, ABq, J=14.3Hz), 4.38(1H, dt, J=5.1, 2.2Hz), 3.78(1H, dd, J=2.2, 11.0Hz), 3.78(3H, s), 3.67(1H, dd, J=2.2, 11.0Hz), 3.02(3H, s), 0.76(9H, s), 0.01(3H, s), -0.25(3H, s); MS *m/z* 563(M^+-57, *t*-Bu), 467, 211, 121. Anal. found: C, 55.94; H, 6.55; N, 4.30. Calcd. for $C_{29}H_{40}N_2O_9SiS$: C, 56.10; N, 6.49; N, 4.51%.

Preparation of 19 from 32. To a stirring solution of **32** (16.3mg, 0.028mmol) in THF (0.3ml) was added a solution of *n*-Bu_4NF (60μl, 1.0M in THF) at r.t.. After 5 min, NaH (5mg, 60% in mineral oil) was added. After stirring for 25min, the reaction was quenched with sat. NH_4Cl, and extracted with Et_2O (x3). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (EtOAc-hexane 1:1) to give **19** (11.0mg, 97%) as an syrup which was identical with the **19** derived by the epoxidation of **9**.

Isomerization of 30 to 31. To a solution of **30** (146.3mg,) in EtOH (7.5ml) was added 28% aq.NH_3 (2.0ml). After stirring at 80°C for 3.5h, the mixture was diluted with water and extracted with EtOAc (x3).The combined extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (EtOAc-hexane 1:3) to give **31** (49.5mg, 34%) as a white solid and **30** (64.9mg, 44%). **Data of 31**: mp. 152.5-153.0°C; $[\alpha]_D^{22}$ -27.4° (c=0.68, $CHCl_3$); IR ($CHCl_3$) 3450, 1790, 1730cm^{-1}; NMR ($CDCl_3$) δ 7.35-7.28(7H, m), 6.81(2H, d, J=8.8Hz), 5.82(1H, br. s), 4.56(2H, m) 4.52(2H, m), 4.50(1H, t, J=8.1Hz), 4.15(1H, d, J=8.1Hz), 4.11(1H, dt, J=8.1, 12.1Hz), 3.79-3.70(2H, m), 3.77(3H, s), 1.60(1H, br. s), 0.71(9H, s), 0.06(3H, s), -0.07(3H, s); MS *m/z* 485 (M^+-57, *t*-Bu), 211, 121. Anal. found: C, 61.76; H, 6.93; N, 5.33. Calcd. for $C_{28}H_{38}N_2O_7Si$: C, 61.97; H, 7.06; N, 5.16%.

Desilylation of 30: To a stirring solution of **30** (335.8mg, 0.619mmol) in THF (6ml) was added *n*-Bu_4NF (1.2ml, 1.0M in THF) at 0°C. After 20min, the reaction mixture was diluted with water and extracted with Et_2O (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 3:1) to give **21'** (153.8mg, 58%) which was identical with **21** in all respects.

Desilylation of 31: The same procedure as described above gave **22'** (77%) which was identical with **22** in all respects.

[*1R,5R,6R,8S*]-6-Benzyloxymethyl-8-*t*-butyldimethylsilyloxy-10-(4-methoxybezyl)-2,10-diaza-4,7-dioxatricyclo[3.2.1.3^{1,2}]-undecane-3,9,11-trione (33). To a stirring solution of **31** (12.7mg, 0.0234mmol) in CH_2Cl_2 (1.0ml) were added Et_3N (33ml, 0.23mmol) and phosgene (0.12ml, 2.0M in toluene) at 0°C. After 10min, the reaction mixture was diluted with water and extracted with Et_2O (x3). The combined extract was washed with dil. HCl and brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on preparative TLC (EtOAc-hexane 1:1) to give **33** (9.4mg, 71%) as a colourless syrup. $[\alpha]_D^{25}$ +5.5° (c=0.36, $CHCl_3$); IR ($CHCl_3$) 1830, 1770, 1730cm^{-1}; NMR ($CDCl_3$) δ 7.35-7.27(7H, m), 6.82(2H, d, J=8.5Hz), 4.67(2H, s), 4.65-4.58(2H, m),

4.53(2H, ABq, J=12.1Hz), 4.44(1H, d, J=1.6Hz), 3.78(3H, s), 3.78-3.68(2H, m), 0.87(9H, s), 0.07(3H, s), 0.00(3H, s); MS *m/z* 511(M-57, *t*-Bu), 414, 211, 121. HRMS. found: 511.1540. Calcd. for $C_{25}H_{27}N_2O_8Si$ (M-*t*-Bu): 511.1537.

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