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Synthesis of Surrogate Structures Related to the Herbicidal Agent Hydantocidin

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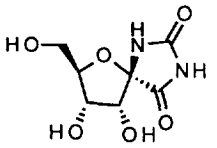
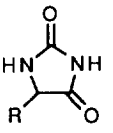
Abstract: The synthesis of a spirohydantoin derivative of D-erythrose has been accomplished in the quest to understand the functional requirements for the herbicidal activity of hydantocidin.

Over the years, there has been an overwhelming interest in the discovery and development of compounds with herbicidal activity.[1] Indeed, the agrochemical industry has made great strides in the search for herbicidal agents with specific action against a number of plant species. The literature in this area is replete with compounds of different origins, structure and chemical diversity.[2] Recent reports[3-4] have described the isolation of hydantocidin **1**, an unusual spirohydantoin structure obtained from *Streptomyces hygroscopicus*, and incorporating a D-ribofuranosyl unit (Figure 1). The hydantoin nucleus **2**, is found in the plant and animal kingdom in a number of diverse forms.[5] Several reports have appeared in the literature describing the synthesis of hydantocidin,[6] as well as a number of its analogs and stereoisomers.[7] Interestingly, the herbicidal activity of hydantocidin is associated with the D-ribo-configuration,[8] since other diastereisomers were found to be devoid of activity.

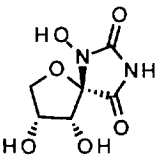
Figure 1



Hydantocidin, **1**



2

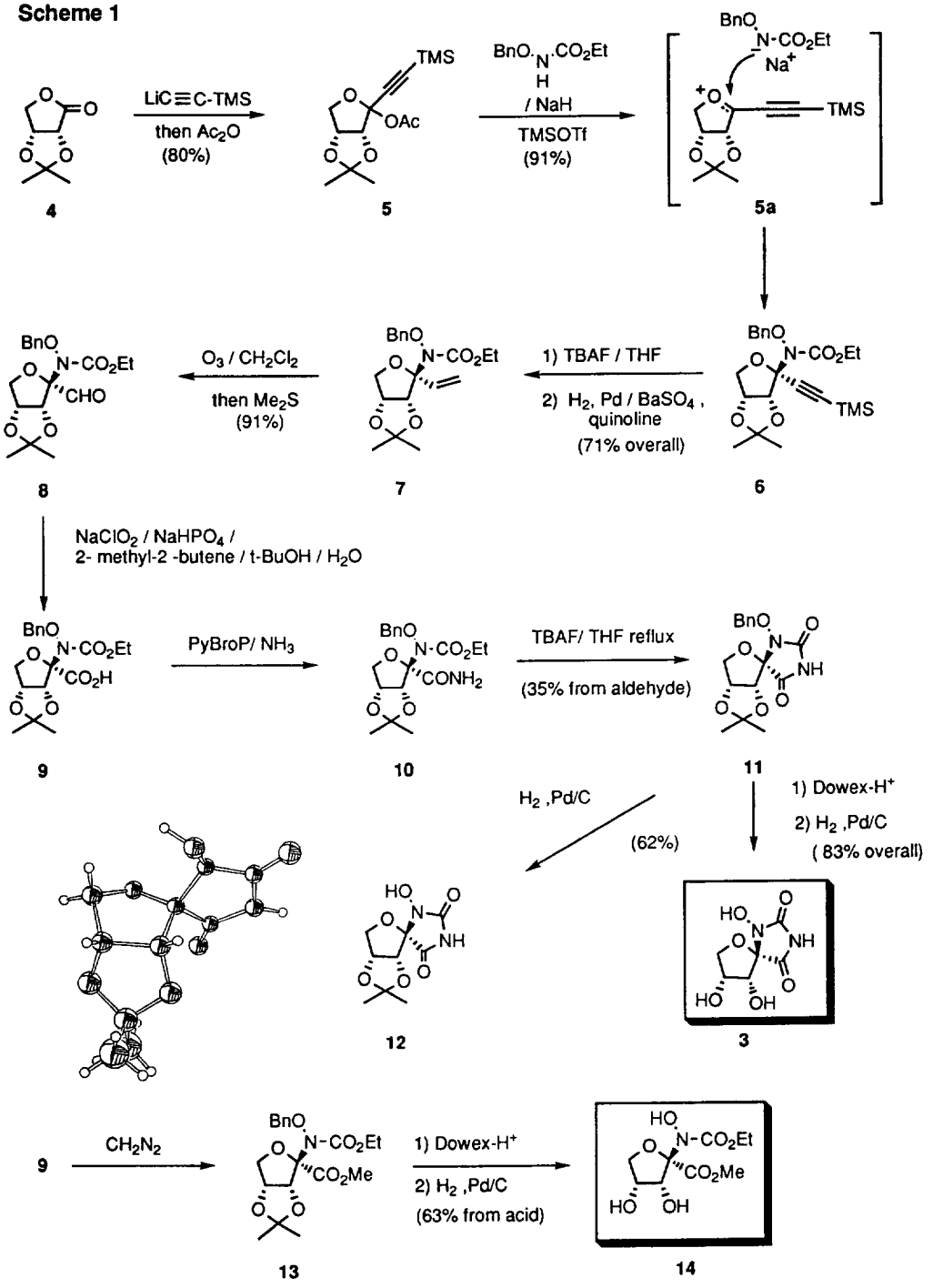


3

Little is known concerning the mode of herbicidal action of hydantocidin, and of the enzymes involved in such processes. The structural similarity of hydantocidin to D-ribonucleosides prompted us to initiate a program directed towards the synthesis of structural analogs that may shed some light on the functional requirements for herbicidal activity.

We describe in this paper the synthesis of a prototype structure that incorporates an N-hydroxy spirohydantoin motif as shown in expression **3** (Figure 1). It was anticipated that the presence of the N-hydroxy group should provide a site for possible H-bonding and a polar environment on the β-face of the molecule. We also wished to prove the importance of the hydroxymethyl group in **1**, hence the synthesis of the des-hydroxymethyl surrogate structure **3**. In a recent publication, it was shown that the replacement of the hydroxymethyl group in **1** by a methyl group resulted in loss of herbicidal activity.[9] In order to ensure the D-erythro configuration of the diol function, we chose the readily available 2,3-*O*-isopropylidene-D-erythronolactone **4**[10] as the chiral template (Scheme 1). The carboxyl equivalent was introduced by treatment of **4** with lithium trimethylsilylacetylide,[11] followed by addition of acetic anhydride to give **5**, presumably as an anomeric mixture. Treatment of **5** with ethyl N-benzyloxycarbamate in the presence of sodium hydride and trimethylsilyl triflate led to the formation of essentially a single product **6** in 91 % yield. The assignment of anomeric configuration was made at the stage of an advanced intermediate by means of single crystal X- ray analysis. Thus, the incipient cyclic oxonium ion **5a** undergoes nucleophilic attack by the carbamate from the side opposite to the 2,3-*O*-isopropylidene group, which follows the logic of steric control. Removal of the TMS group followed by hydrogenation of the triple bond under Lindlar conditions gave the anomeric C-vinyl derivative **7** in excellent overall yield. Ozonolysis afforded the corresponding aldehyde **8** which was oxidized to the corresponding acid **9** and the latter was transformed to the amide derivative **10** using PyBroP.[12] Several trials aimed at the cyclization of **10** to the desired hydantoin **11** were unsuccessful in the presence of a variety of bases. However, treatment of **10** with tetra n-butylammonium fluoride in refluxing THF[13] afforded **11** in good

Scheme 1


LiC≡C-TMS
then Ac2O
(80%)
TMSOTf
(91%)
1) TBAF / THF
2) H2, Pd / BaSO4, quinoline
(71% overall)
O3 / CH2Cl2
then Me2S
(91%)
NaClO2 / NaHPO4 /
2- methyl-2 -butene / t-BuOH / H2O
PyBroP/ NH3
TBAF/ THF reflux
(35% from aldehyde)
H2 ,Pd/C
(62%)
1) Dowex-H+
2) H2 ,Pd/C
(83% overall)
CH2N2
1) Dowex-H+
2) H2 ,Pd/C
(63% from acid)
4
5
5a
6
7
8
9
10
11
12
3
13
14

overall yield. Mild hydrolysis of the isopropylidene group in the presence of Dowex-50 (H^+), followed by hydrogenolysis of the N-benzyloxy group gave the intended hydantocidin analog. Removal of the benzyl group of compound **11** led to a nicely crystalline product **12** which was suitable for a crystallographic study (Scheme 1).

In order to assess the importance of the hydantoin ring, we prepared a hybrid derivative in which the hydantoin ring was replaced by ester groups. Thus, oxidation and esterification of the aldehyde derivative **8** gave the ester **13** which was sequentially deprotected to give **14**.

Compounds **3** and **14** were found to lack herbicidal activity against a number of monocot and dicot plants in greenhouse trials.

EXPERIMENTAL

Tetrahydrofuran was distilled over benzophenone and potassium prior to use. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel silica gel 60 F_{254} glass plates. Flash chromatography was performed according to the procedure of Still et al.[14] with Merck silica gel, 230-400 mesh. Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrometer. The wave numbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker WH-400 spectrometer at 400MHz for ^1H and 75.5 MHz for ^{13}C. ^1H multiplicities are recorded using the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; b, broad; *J*, coupling constant (Hertz). High-resolution FAB mass spectra were obtained by means of Kratos MS5OTCTA and AEI-MS 902 spectrometers at the University of Montréal. Melting points were measured on Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25°C.

1-Trimethylsilylethynyl-2,3- O-isopropylidene-D-erythrofuranosyl acetate, 5

To a solution of TMS-acetylene (1 mL, 7.23 mmol) in THF (5 mL) was added dropwise n-BuLi (2.5M in hexanes, 2.89ml) under argon at -10°C. After 15 min, the resulting pale yellow solution was slowly transferred via a cannula to a solution of 2,3-O-isopropylidene-D-erythronolactone, **4** (952 mg, 6 mmol) in THF (18 mL) at -70°C. The reaction mixture was stirred for 1h, then quenched with Ac_2O (2 mL). The resulting suspension was warmed to 0°C with vigorous stirring, diluted with water and then extracted with EtOAc (3X). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed

on silica gel (EtOAc-hexanes 8:2) to give the acetate **5** (1.43g, 80%) as an oil which crystallized at 0°C; mp 34-36°C; $[\alpha]_D$ -78.6° (*c* 0.89, $CHCl_3$); IR ν_{max} (film) : 2180, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.96 (d, *J*=6 Hz, 1H, H-2); 4.83 (dd, *J* = 3.6 Hz, 1H, H-3); 4.1(d, *J* =10.8 Hz, 1H, H-4); 3.84 (dd, 1H, H-4); 2.16 (s, 3H, $COCH_3$); 1.57 (s, 3H, Me); 1.35 (s, 3H, Me); 0.19 (s, 9H, TMS); ^{13}C NMR ($CDCl_3$) δ:116.96, 113.29, 99.3, 98.4, 92.6, 84.2, 78.8, 69, 25.6, 25.1, 20.6, -0.8; MS (FAB+) , *m/z* : 299 (MH^+).

N-Benzyloxy-N-carbethoxy-1-trimethylsilylethynyl-2,3-O-isopropylidene-β-D-erythrofuranosylamine, 6

A suspension of NaH (172 mg, 60% dispersion in mineral oil, 7.16 mmol) was washed with hexanes, suspended in dry CH_3CN (5 mL) and treated slowly under argon with a solution of N-benzyloxycarbamate (1.25 g, 6.3 mmol) in CH_3CN (5 mL). After 30 min, the white suspension was cooled to 0°C and treated with a solution of the acetate **5** (1.4g, 4.7 mmol). After cooling to -30°C, TMSOTf (1.38 mL) was slowly added and the resulting brownish solution was stirred for 1h. At this point, Et_3N was added and the mixture allowed to reach rt. The solvent was removed and the residue was partitioned between EtOAc and water. The water layer was extracted with EtOAc (2X) and the combined extracts were washed with brine and then dried ($MgSO_4$) . Evaporation of the solvent and chromatography of the residue on silica gel (EtOAc-hexanes 9:1) yielded the N-benzyloxycarbamate derivative **6** (1.85g, 91%) as an oil which crystallized after a few days at 0°C; mp 45-47°C ; $[\alpha]_D$ -49° (*c* 0.83, $CHCl_3$); IR ν_{max} (film): 2145, 1720, 1700, 1480, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.35-7.33 (m, 5H, Ph); 5.21 (d, *J* =5.7 Hz, 1H, H-3); 5.12 (d, *J* =9.4 Hz, 1H,CH_2 Ph); 4.9 (d, 1H,CH_2 Ph); 4.87 (dd, *J* =3.4 Hz,*J* =5.7 Hz, 1H, H-4); 4.24(m, 2H, CH_2 CH_3); 4.1(d, *J* =9.8 Hz, H-5); 4.04 (dd, *J* =9.8 Hz, *J* =5.8 Hz, 1H, H-5); 1.55 (s, 3H, Me); 1.36 (s, 3H, Me); 1.33 (t, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 1.57, 134.79, 128.8, 128.1, 127.94, 112.86, 97.54, 97.12, 93.16, 85.55, 81.14, 78.1, 74.25, 62.3, 26.06, 25.17, 13.93, -0.75; HRSM (FAB+), calcd for $C_{32}H_{24}NO_6Si$ (MH^+) : 434.1989, found : 434.1998.

N-Benzyloxy-N-carbethoxy-1-vinyl-2,3-O-isopropylidene-β-D-erythrofuranosylamine, 7

Carbamate **6** (2.5g, 2.9 mmol) was dissolved in THF (10 mL) and treated with TBAF (1M in THF, 3.5 mL). The reaction mixture was stirred for 5 min then concentrated. Flash chromatography of the residue on silica gel (EtOAc-hexanes 8:2) provided the alkyne as white crystals (900 mg, 86%); mp 65-69°C; $[\alpha]_D$ 79.6° (*c* 0.78, $CHCl_3$); IR ν_{max} (nujol): 3260, 2100, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ:7.47-7.37 (m, 5H, Ph); 5.18 (d, *J* = 5.7 Hz, 1H, H-2); 5.09 (d, *J* = 9.34 Hz, 1H, CH_2 Ph); 4.91 (d, 1H, CH_2 Ph); 4.87 (m, 1H, H-3); 4.27 (q, 2H, CH_2 CH_3); 4.12 (d, *J* =10.1 Hz, 1H, H-4); 4.02 (dd, *J* =10 Hz, *J*=3.81 Hz, 1H, H-4); 2.83 (s, 1H, C*H*); 1.58 (s, 3H, Me); 1.36 (s+t, 6H, Me, CH_2CH_3); HRMS (FAB+), calcd for $C_{19}H_{24}NO_6$ (MH^+): 362.1589; found: 362.1603.

A solution of the above alkyne (455 mg, 1.25 mmol) in a mixed solvent system (EtOAc-hexanes, 1:2, 3 mL) was treated with 5% Pd-on-$BaSO_4$ (45 mg) and 5 drops of quinoline. The mixture was stirred under 1 atm of H_2 until complete consumption of the starting material (TLC, 2h). The catalyst was filtered off, and the solvent was evaporated. After dilution with EtOAc and washing with 10% HCl, flash chromatography of the residue on silica gel (EtOAc-hexanes 8:2) yielded the desired alkene **7** (379mg, 83%) as a colorless liquid; $[\alpha]_D$ -100.4° (*c* 1.1, $CHCl_3$); IR ν_{max} (film): 1750, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.4-7.35 (m, 5H, Ph); 6.07(dd, *J*=10.8 Hz, *J* =17.3 Hz, 1H, CH=*CH*$_2$); 5.54 (d, *J* =17.2 Hz, 1H, CH=*CH*$_2$); 5.38 (d, 1H, *CH* =CH_2); 5.05 (d, *J* =5.9 Hz, 1H, H-32); 4.93 (d, *J* =9.52 Hz, 1H,*CH*$_2$ Ph); 4.87 (m, 2H, *CH*$_2$ Ph, H-3); 4.25 (q, 2H, *CH*$_2$ CH_3); 4.11 (dd, *J* =3.85 Hz, *J* =10.1 Hz, 1H, H-4); 4.05 (d, *J* =10 Hz, 1H, H-4); 1.45 (s, 3H, Me); 1.33 (t, 3H, CH_2*CH*$_3$); 1.31(s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ: 156.9, 134.49, 133.21, 128.93, 128.33, 128.11, 116.35, 112.2, 101.89, 84.51, 80.97, 78.36, 73.63, 62.03, 25.74, 24.67, 13.94; HRSM (IE), calcd for $C_{18}H_{22}NO_6$: 348.1447, found: 348.1441.

N-Benzyloxy-N-carbethoxy-1-formyl-2,3-O-isopropylidene-β-D-erythrofuranosylamine, 8

A stream of ozone was passed through a solution of alkene **7** (379 mg, 1.04 mmol) in CH_2Cl_2 (15 mL) at -78°C until a blue color was persistent (45 min). After addition of Me_2S (1 mL), the cooling bath was removed and the mixture allowed to warm gradually. Evaporation of CH_2Cl_2 and flash chromatography of the residue using EtOAc-hexanes (8:2) provided the aldehyde **8** as a colorless oil (348 mg, 91%); $[\alpha]_D$ -160.8° (*c* 1.09, $CHCl_3$); IR ν_{max} (film): 1770 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.5 (s, 1H, CHO); 7.5 (s, 5H, Ph); 5.24 (d, *J* =10 Hz, 1H *CH*$_2$ Ph); 5.18 (d, *J* =5.9 Hz, 1H, H-2); 5.01(d, 1H, *CH*$_2$ Ph); 4.95 (m, 1H, H-3); 4.42 (m, 2H, *CH*$_2$ CH_3); 4.32 (m, 2H, H-4); 1.6 (s, 3H, Me); 1.5 (t, 3H, CH_2*CH*$_3$); 1.43 (s, 3H, Me);^{13}C NMR ($CDCl_3$) δ: 190.3, 156.5, 133.9, 128.9, 128.7, 128.3, 128.1, 112.8, 100.5, 84.02, 80.54, 78.9, 75.5, 63.1, 25.6, 24.6, 13.8; HRMS (IE), calcd for $C_{17}H_{22}NO_6$(*M-CHO*): 336.1448, found: 336.1447.

N-Benzyloxy-N-carbethoxy-1-carboxy-2,3-O-isopropylidene-β-D-erythrofuranosylamine, 9

Aldehyde **8** (292 mg, 0.79 mmol), $NaHPO_4$ (328 mg, 2.38 mmol) and $NaClO_2$ (323 mg, 3.58 mmol) were dissolved in a mixture of t-BuOH-H_2O (2:1, 7.5 mL). After addition of 2-methyl-2-butene (2M in THF, 1.2 mL) the reaction mixture was stirred for 3h, diluted with water, acidified with 10% HCl and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give the free acid **9** in nearly quantitative yield as an amorphous white solid, which was used without further purification; ^1H NMR($CDCl_3$) δ: 7.4 (s, 5H, Ph); 5.1 (m, 2H, *CH*$_2$ Ph, H-2); 4.91 (d, *J* =9.9 Hz, 1H, *CH*$_2$ Ph); 4.8 (m, 1H, H-3);

4.3 (m, 2H, CH_2 CH3); 4.16 (s, 2H, H-4); 1.34 (s, 3H, Me); 1.29 (s, 3H, CH_2CH_3); MS (FAB+), *m/z* : 382 (MH^+), 404 (MNa^+).

[3R,4R,5S]-6-N-Benzyloxy-3,4-O-isopropylidenedioxy-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione, 11

Into a solution of crude acid **9** (286 mg, 0.74 mmol) and Py BroP (12) (417 mg, 0.89 mmol) in dry CH_2Cl_2 (10 mL) was introduced over 10 min dry NH_3. After 45 min of stirring, the reaction mixture was poured into 5% $NaHCO_3$ then extracted with EtOAc. The combined extracts were washed with 5% HCl, brine, dried (Na_2SO_4) then concentrated. Filtration of the crude residue on silica gel (CH_2Cl_2-MeOH 95:5) afforded a white amorphous solid (200 mg) which was directly used in the next step. According to its ^1H NMR this material was the primary amide **10** contaminated by phosphine oxide derivatives. A mixture of the above solid and TBAF (3 mL, 1M THF) in THF (5 mL) was refluxed overnight. The reaction mixture was diluted with water, concentrated and extracted with EtOAc. The combined extracts were washed with 5% HCl, brine and dried over Na_2SO_4. After concentration, the crude residue was chromatographed (EtOAc-hexanes 2:1) to afford the spirohydantoin **11** as a white solid (89 mg, 35%); mp 114-116°; $[\alpha]_D$ -35.9° (*c* 0.53, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3150, 1780, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.1 (s, 1H, NH); 7.5-7.4 (s, 5H, Ph); 5.18 (d, *J* = 10.25 Hz, 1H, CH_2 Ph); 5.13 (d, *J* = 5.8 Hz, H-3); 4.92 (d, *J* =10.2 Hz, 1H, CH_2 Ph); 4.88 (ddd, *J*=1.3 Hz, *J*=2.8 Hz, *J*=5.9 Hz, 1H, H-4); 4.28 (d, *J*=10.4 Hz, 1H, H-5); 3.96 (dd, 1H, H-5); 1.55 (s, 3H, Me); 1.3 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ:163.93, 154.3, 133.78, 129.28, 128.86, 128.28. 114.53, 98.31 (*Cspiro*), 82.11, 80.11, 79.83, 74.35, 25.04, 24.50; HRSM (FAB+), calcd for $C_{16}H_{19}N_2O_6$ (MH^+): 335.122, found: 335.124.

[3R,4R,5S]-3,4,6-N-Trihydroxy-1-oxa-6,8-diazaspiro[4.4] nonane-7,9-dione, 3

Hydantoin **11** (45 mg) was dissolved in a mixture of MeOH-H_2O (2:1, 5 mL) and the solution was heated at 60°C in the presence of Dowex50X8 (H^+, prewashed with deionized water) for 5h. After filtration , removal of solvent and purification by flash chromatography (CH_2Cl_2-EtOAc-MeOH 2:2:1), the diol was isolated as a syrup (32 mg, 83%); $[\alpha]_D$ + 9.3° (*c* 0.7, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3500, 3380, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.38-7.34 (m, 5H, Ph); 5.1 (d, *J*=10.7 Hz,1H, CH_2 Ph); 4.9 (d, 1H, CH_2Ph); 4.61 (d, *J* =4.9 Hz, 1H, H-4); 4.15 (m, 1H, H-3); 4.04 (d, *J* =10.5 Hz, 1H, H-2); 3.9 (dd, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ: 169.88, 153.5, 134.48, 129.67, 128.47, 98.02 (*Cspiro*), 80.77, 75.20, 71.29; MS (FAB+), *m /z* : 295 (MH^+), 317 (MNa^+); HRMS (FAB+), calcd for $C_{13}H_{15}N_2O_6$ (MH^+): 295.093, found: 295.091.

Hydrogenolysis of the above diol (30 mg) with Pd/C (8 mg) in MeOH for 5h afforded after filtration and evaporation, the spirohydantoin **3** (20 mg, quant.) as a white amorphous solid; $[\alpha]_D$ -176.8° (*c* 0.95, MeOH); ^1H

NMR (CD_3OD) δ: 4.77 (d, *J*=4.9 Hz, 1H, H-4); 4.2 (m, 2H, H-3); 4.07 (d, *J*=8.8 Hz, 1H, H-2); ^{13}C NMR (CD_3OD) δ: 172.23, 156.70, 99.13 (*Cspiro*), 76.77, 72.97, 71.94; MS (FAB+), *m/z* :205 (MH^+).

*[3R,4R,5S]-6-N-Hydroxy-3,4-isopropylidenedioxy-1-oxa-6,8-diazaspiro[4.4] nonane-7,9-dione, **12***

Debenzylation of hydantoin **11** was carried out as described above. Purification by flash chromatography gave the N-hydroxyhydantoin **12** as a white solid. Recrystallization of this material from CH_2Cl_2 afforded white needles (62%) suitable for X-ray analysis; m.p 180-182°; $[\alpha]_D$ -71.8° (*c* 0.51, MeOH); IR ν_{max} ($CHCl_3$): 3340,3200,1790,1710 cm^{-1}; ^1H NMR (CD_3OD) δ: 5.31 (d, *J*=5.8Hz, 1H, H-4); 5.21 (m, 1H, H-3) ; 4.44 (dd, *J*=3.9Hz, *J*=10.3Hz, 1H, H-2); 4.35 (d, *J*=10.4Hz, 1H, H-2); 1.66 (s, 3H, Me); 1.48 (s, 3H, Me); ^{13}C NMR (CD_3OD) δ: 167.13, 157.13, 115.33, 99.47 (*Cspiro*), 83.8, 81.94, 75.65, 25.8, 25.06; HRMS (FAB+), calcd for $C_9H_{13}N_2O_6$ (MH^+): 245.0773, found: 245.078.

*N-Benzyloxy-N-carbethoxy-1-carbomethoxy-2,3-O-isopropylidene-β-D-erythrofuranosylamine, **13***

The crude acid **9** (100 mg) was treated at 0°C in CH_2Cl_2 solution with an excess of diazomethane to provide after flash chromatography (EtOAc-hexanes 7/3) the carbamate **13** as a syrup (108 mg, 95%); $[\alpha]_D$ -119.5° (*c* 0.64, $CHCl_3$), IR ν_{max} (film): 1770 and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.38 (s, 5H, Ph); 5.1 (d, *J*=9.9 Hz, 1H, CH_2 Ph); 5.07 (d, *J*=5.3 Hz, 1H, H-2); 4.9 (d, 1H, CH_2Ph); 4.79 (dd, 1H, H-3); 4.25 (q, 2H, CH_2CH_3); 4.15 (d, *J*=2.6 Hz, 2H, H-4); 3.84 (s, 3H, Me); 1.44 (s, 3H, Me); 1.32 (t, 3H, CH_2CH_3); 1.3 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ: 165.11, 156.21, 134.13, 128.8, 128.56, 128.24, 112.7, 100.77, 84.33, 80.37, 78.33, 75.53, 62.82, 52.50, 25.6, 24.78, 13.76; MS (FAB+), *m/z* : 201, 396, HRMS, calcd for $C_{19}H_{26}NO_8$ (MH^+): 396.1643, found : 396.1658.

*N-Carbethoxy-N-hydroxy-1-carbomethoxy-β-D-erythrofuranosylamine, **14***

Hydrolysis of ester **13** (40 mg, 0.11 mmol) was carried out as described for preparation of **3** (Dowex 50X8H^+, 70°, 2hr). Purification by flash chromatography (CH_2Cl_2-MeOH 95:5) of the residue, gave the diol (29 mg, 81%) as a syrup; $[\alpha]_D$ -47.5° (*c* 1.35, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.42-7.35 (m, 5H, Ph); 4.97 (d, *J* =3.3 Hz, 2H, CH_2Ph); 4.73 (dd, *J* =5 Hz, 1H, H-2); 4.4 (m, 1H, H-3); 4.27 (q, 2H, CH_2CH_3); 4.15 (dd, 2H, H-4); 3.84 (s, 3H, Me); 3.8 (d, *J* ~5 Hz, 1H, OH); 3.15 (d, *J* ~5 Hz, 1H, OH); 1.35 (t, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.36, 157.92, 134.38, 129.26, 128.37, 128.03, 99.47, 19.14, 16.44, 73.8, 71.42, 62.8, 53.04, 13.81; HRMS (FAB+), calcd for $C_{16}H_{22}NO_8$ (MH^+): 356.1331, found: 356.1345.

The above diol (39 mg, 0.11 mmol) was dissolved in MeOH (5 mL), 10% Pd/C (15 mg) was added and the reaction mixture was stirred for 5 h under 1 atm of H_2, then filtered. Removal of the solvent and chromatography on silica gel (MeOH-EtOAc-CH_2Cl_2 1:4:4) afforded the hydroxamic acid derivative **14** (24 mg, 82%) as a syrup; $[\alpha]_D$ -140° (*c* 1.2, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3620, 3500, 1720 cm^{-1}; ^1H NMR (CD_3OD) δ: 4.5 (s, 2H, H-2, H-3); 4.15 (m, 3H, CH_2CH_3+H-4); 3.74 (s+m, 4H, Me, H-5); 1.24 (t, 3H, CH_2CH_3); ^{13}C NMR (CD_3OD) δ: 168.75, 157.78, 100.0, 75.89, 73.63, 70.58, 63.52, 53.28, 14.07; HRMS (FAB+), calcd for $C_9H_{16}NO_8$ (MH^+): 266.0875, found: 266.0885.

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