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Synthesis of 5-substituted-3-[(2′*S*,3′*S*)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazoles and their epimers

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Abstract

5-Phenyl-3-[(2′*R*,3′*S*)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **10a** and its epimer **11a**, 5-methyl-3-[(2′*R*,3′*S*)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **10b** and its epimer **11b** were synthesized from cyanohydrin benzoates **8a**, **9a** and cyanohydrin acetates **8b**, **9b**, respectively, by treatment with hydroxylamine in methanol via intramolecular transacylation and subsequent cyclization of the corresponding amidoximes. Hydrolysis and reduction of the dimethoxymethyl groups in the above compounds gave the desired compounds **12a**, **13a**, **12b** and **13b.**

1. Introduction

The development of new classes of antiviral and antitumor agents have led, in our laboratory, to the preparation of isonucleosides[1,2] and *iso*-*C*-nucleosides.[3–5] *iso*-*C*-Nucleosides constitute a class of nucleoside analogues in which the nucleobases are linked via a carbon–carbon bond to the carbohydrate moiety at a position other than C-1′. It is anticipated that *iso*-*C*-nucleosides may have increased chemical and enzymatic stability under physiological conditions and may alter the biological profiles including catabolism. Recently a number of nucleosides with the unnatural L-configuration have been reported as potent chemotherapeutic agents against HIV, HBV and certain forms of cancer, and some of them show lower toxicity profiles than their D-counterparts.[6–10] Previously, we reported the synthesis of an *iso*-*C*-nucleoside in which the oxadiazole ring is linked at the 3′-position of D-xylose.[5] In this paper a series of L-configuration *iso*-*C*-nucleoside analogues bearing oxadiazole derivatives as nucleobases, 5-phenyl-3-[(2′*S*,3′*S*)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **12a**, 5-methyl-3-[(2′*S*,3′*S*)-3′-

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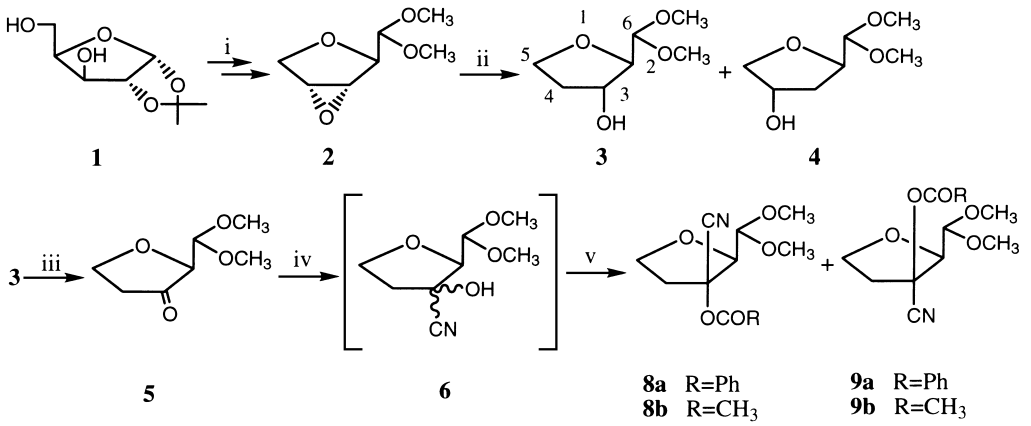
hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **12b** and their epimers, **13a**, **13b**, were synthesized for investigation of their biological activities.

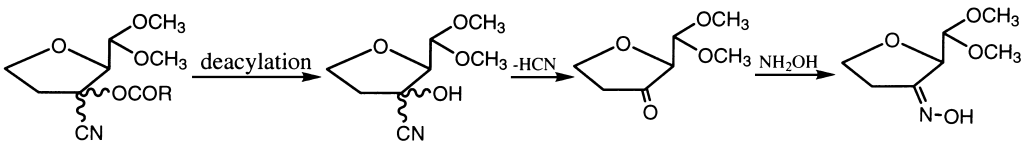
2. Results and discussion

The most frequently encountered route for the synthesis of substituted 1,2,4-oxadiazoles involves the acylation and subsequent cyclization of amidoximes, which can be obtained by condensation of nitriles with hydroxylamine.[11,12] For our purposes the key intermediate would be cyanohydrins **6**. Epoxide **2**, prepared from 1,2-*O*-isopropylidene-α-D-xylose **1**[13] in three steps,[1,14] was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to afford a 6:1 mixture of tetrahydrofuranols **3** and **4** in 58% and 9.3% yields, respectively. The predominance of tetrahydrofuranol **3** is probably attributable to the steric hindrance of the 2-dimethoxymethyl group to the coordinated reducing reagent; since the lithium aluminum hydride reduction takes place in an S_N2 fashion, the epoxide **2** will be opened from the β-face. The hydroxy group in **3** was oxidized with pyridinium dichromate (PDC) in dichloromethane to give ketone **5** in 92.6% yield. Addition of hydrogen cyanide (generated in situ from potassium cyanide and acetic acid) to **5** in dichloromethane–water gave an epimeric mixture of cyanohydrins **6** (Scheme 1). Due to almost the same chromatographic mobility of the two cyanohydrin epimers, no attempt was performed to separate them, and ^{1}H NMR spectroscopic data showed that the two epimers were present in about the same amount. When **6** was treated with hydroxylamine[15] in methanol under reflux, instead of the corresponding amidoximes, only a low yield of 3-oximido derivative **7** was obtained. Obviously, cyanohydrins **6** could undergo elimination of hydrogen cyanide under the slightly basic reaction conditions at elevated temperature to afford **5**, which condensed with hydroxylamine to give oxime **7** (Scheme 2). For this reason cyanohydrins **6** were protected with benzoyl chloride in pyridine to afford cyanohydrin benzoate **8a** and its epimer **9a** in 24.7% and 34.3% yields, respectively.



Scheme 1. (i) Refs. 1 and 14; (ii) $LiAlH_4$, THF, reflux; (iii) PDC, Ac_2O, CH_2Cl_2, reflux; (iv) KCN, HOAc, CH_2Cl_2–H_2O, 0°C; (v) BzCl, pyridine, rt; or Ac_2O, DMAP, CH_2Cl_2, rt

In general, amidoximes can be isolated during the synthesis of oxadiazoles,[11,12] but in our case, treatment of both cyanohydrin benzoates, **8a** and **9a**, with hydroxylamine in methanol afforded 5-phenyl-oxadiazole derivatives **10a** and **11a** in 42% and 40% yields, respectively, with a small

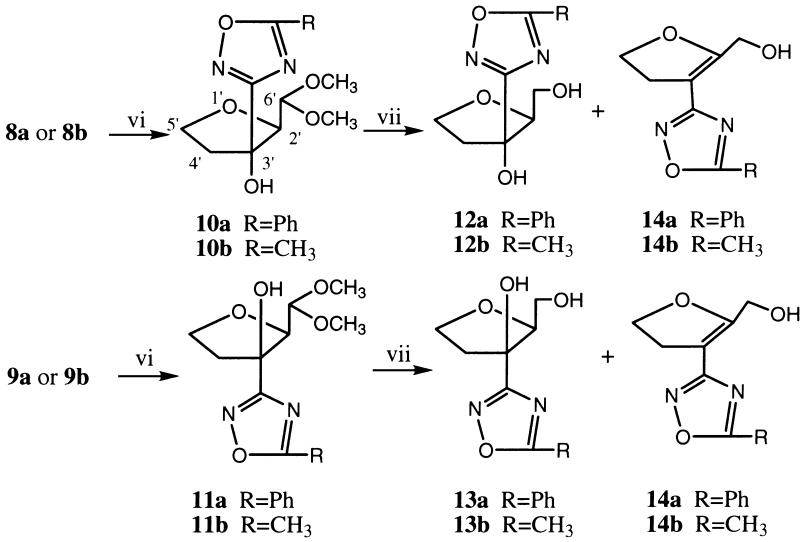


8a R=Ph
8b R=CH_3
9a R=Ph
9b R=CH_3

6 **5** **7**

Scheme 2. Reaction pathway to **7**

amount of compound **7** instead of the corresponding amidoximes (Scheme 3). The formation of **7** was not surprising and it can be ascribed to the debenzoylation of **8a** or **9a** to cyanohydrins **6** (see Scheme 2). This 'one-step cyclization' was possibly through two intermediates; intermediate **II** was formed from amidoximes **I** by intramolecular transacylation of the neighboring benzoyl group, and cyclization took place as a fast step (Scheme 4). The evidence to support the neighboring-group participation mechanism is that in the cases of the reaction of 2,3,5-tri-*O*-benzoyl-β-D-



10a R=Ph
10b R=CH_3

12a R=Ph
12b R=CH_3

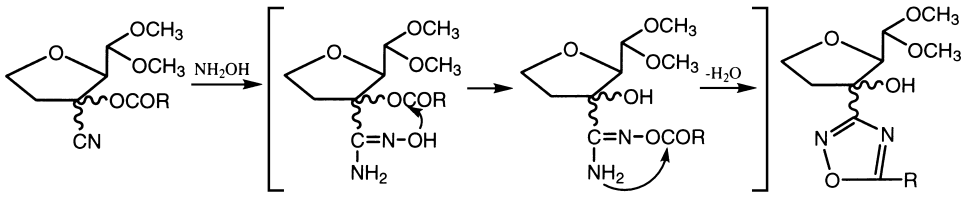
14a R=Ph
14b R=CH_3

11a R=Ph
11b R=CH_3

13a R=Ph
13b R=CH_3

14a R=Ph
14b R=CH_3

Scheme 3. (vi) NH_2OH, CH_3OH, reflux; (vii) 1% HCl–dioxane, 100°C; then $NaBH_4$, rt



8a R=Ph
8b R=CH_3
9a R=Ph
9b R=CH_3

I **II**

10a R=Ph
10b R=CH_3
11a R=Ph
11b R=CH_3

Scheme 4. Mechanism for neighboring-group participation, transacylation and cyclization

ribofuranosyl cyanide[11] and 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl cyanide[12] with hydroxylamine in methanol, the corresponding amidoximes were obtained and no such transacylation and cyclization products were noted. To demonstrate the generality of the mechanism, cyanohydrin acetates **8b** and **9b** were prepared by treatment of cyanohydrins **6** with acetic anhydride and 4-dimethylaminopyridine (DMAP) in dichloromethane. Treatment of both cyanohydrin acetates with hydroxylamine in methanol afforded 5-methyl-oxadiazole derivatives **10b** and **11b**, respectively, as expected.

The stereochemistry of **10a** was determined by single crystal X-ray analysis (Fig. 1). It was shown that the oxadiazole moiety of compound **10a** was on the same side as the dimethoxymethyl group. Correspondingly, the cyano group of cyanohydrin benzoate **8a** was deduced to be upon the tetrahydrofuran ring, and compounds **9a** and **11a** were the C3′ epimers of **8a** and **10a**, respectively. The stereochemistries of 5-methyl-oxadiazole derivatives **10b** and **11b** were determined by comparison of NMR spectra with those of the 5-phenyl-oxadiazole counterparts. Remarkable shifts were observed in ^{1}H NMR spectra for the protons of methoxy groups and $H_{6'}$ between **10a** and **11a**, where the protons of methoxy groups in **10a** (δ 2.87, 3.17) appeared at higher field than those of **11a** (δ 3.17, 3.26) and $H_{6'}$ signal of **10a** (δ 4.11, overlapped with signals of other protons) was at higher field compared with that of **11a** (δ 4.52, doublet, $J_{6',2'} = 7.5$ Hz), reflecting a steric interaction of the oxadiazole moiety with the dimethoxymethyl group in **10a**. Similar shifts in ^{1}H NMR spectra data between **10b** (chemical shifts for the protons of methoxy groups and $H_{6'}$: δ 2.89, 3.13; δ 3.99, overlapped) and **11b** (chemical shifts for the protons of methoxy groups and $H_{6'}$: δ 3.15, 3.35; δ 4.47, doublet, $J_{6',2'} = 7.5$ Hz) could infer that **10b** had the same configuration as **10a**, and **11b** was the C3′ epimer of **10b**.

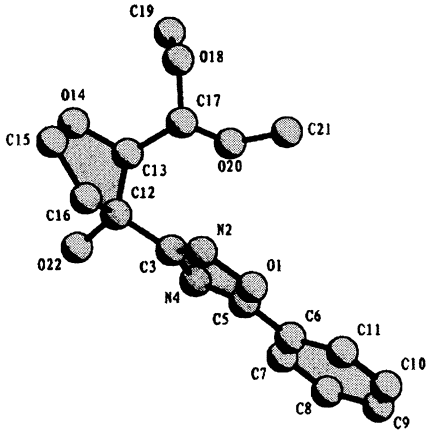


Figure 1. Crystal X-ray structure of compound **10a**

The dimethoxymethyl groups in compounds **10a**, **10b**, **11a** and **11b** were hydrolyzed in 1% hydrochloric acid–dioxane and reduced with sodium borohydride to afford the deoxy L-ribitol nucleosides **12a** and **12b**, and the deoxy L-xylitol nucleosides **13a** and **13b**. Two byproducts, 5-phenyl-3-(2′-hydroxymethyl-4′,5′-dihydrofuran-3′-yl)-1,2,4-oxadiazole **14a** and 5-methyl-3-(2′-hydroxymethyl-4′,5′-dihydrofuran-3′-yl)-1,2,4-oxadiazole **14b** were also obtained during the reaction by E1 elimination of water. The structures of **14a** and **14b** were identified by NMR spectra; the orientation of the double bond is consistent with the Saytzeff rule.

3. Experimental

3.1. General procedures

Melting points were determined on an XT-4A melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 243B polarimeter. IR spectra were recorded on a DE-983G spectrophotometer in KBr pellets. UV spectra were recorded on a Varian DMS200 UV–visible spectrophotometer. Mass spectra were obtained on either ZAB-HS or KYKY-ZHP-5 mass spectrometer. NMR spectra were recorded on a Varian-300 or JEOL AL300 spectrometer with TMS as internal standard. Exchangeable protons were detected by addition of D_2O. Column chromatography was performed on silica gel (200–300 mesh) purchased from Qingdao Chemical Company, China.

3.2. (2R,3R)-3-Hydroxy-2-dimethoxymethyltetrahydrofuran **3** and (2R,4S)-4-hydroxy-2-dimethoxymethyltetrahydrofuran **4**

To a solution of **2**[1,14] (10 g, 62 mmol) in dry THF (200 ml), $LiAlH_4$ (7.2 g, 190 mmol) was added and the reaction mixture was refluxed until compound **2** was consumed (checked by TLC). A mixture of THF (200 ml) and water (13 ml) was added dropwise to destroy the excess $LiAlH_4$ at 0°C, then the mixture was filtered and the filtrate was concentrated in vacuo. Silica gel column chromatography (petroleum ether–acetone) afforded compounds **3** (5.85 g, 58%) and **4** (0.94 g, 9.3%), each as a colorless oil.

Compound **3**: $[\alpha]_D^{15}$ –31.2 (*c* 0.16, MeOH). EI-MS (m/z): 131 $[M–OCH_3]^+$. ^1H NMR (DMSO-d_6) δ 1.68 (m, 1H, H_{4a}), 1.86 (m, 1H, H_{4b}), 3.28, 3.30 (2s, 3H each, $>C(OCH_3)_2$), 3.62 (dd, 1H, $J_{2,6}=5.7$ Hz, $J_{2,3}=1.2$ Hz, H_2), 3.76 (m, 2H, $H_{5a,}$ H_{5b}), 4.10 (d, 1H, $J_{6,2}=5.7$ Hz, H_6), 4.15 (m, 1H, H_3), 4.89 (d, 1H, D_2O exchangeable, 3-OH). ^{13}C NMR (DMSO-d_6) δ 35.2 (C_4), 53.5 (OCH_3), 55.0 (OCH_3), 66.7 (C_5), 71.6 (C_2), 85.9 (C_3), 104.1 (C_6). Anal. calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.59; H, 8.59.

Compound **4**: $[\alpha]_D^{15}$ +2.7 (*c* 0.185, MeOH). EI-MS (m/z): 131 $[M–OCH_3]^+$. ^1H NMR (DMSO-d_6) δ 1.77 (m, 2H, $H_{3a,}$ H_{3b}), 3.29, 3.30 (2s, 3H each, $>C(OCH_3)_2$), 3.51 (d, 1H, $J_{5a,5b}=8.7$ Hz, H_{5a}), 3.73 (dd, 1H, $J_{5b,5a}=8.7$ Hz, $J_{5b,4}=3.9$ Hz, H_{5b}), 4.01 (m, 1H, H_2), 4.18 (d, 1H, $J_{6,2}=5.4$ Hz, H_6), 4.27 (m, 1H, H_4), 4.85 (d, 1H, D_2O exchangeable, 4-OH). ^{13}C NMR (DMSO-d_6) δ 36.2 (C_3), 53.6 (OCH_3), 54.8 (OCH_3), 70.3 (C_5), 75.0 (C_2), 77.3 (C_4), 105.6 (C_6). Anal. calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.47; H, 8.76.

3.3. 2-(S)-Dimethoxymethyl-3-keto-tetrahydrofuran **5**

To a stirred solution of **3** (11.0 g, 68 mmol) in dry CH_2Cl_2 (50 ml) were added pyridium dichromate (PDC, 15.3 g, 40 mmol) and Ac_2O (18.8 ml, 200 mmol), and the mixture was refluxed for 1 h. After being cooled to ambient temperature, Et_2O (200 ml) was added, and the mixture was applied to a short silica gel column and eluted by Et_2O. The combined eluant was concentrated and coevaporated with toluene (3×20 ml) to afford **5** (10.1 g, 92.6%) as a pale yellow oil. Compound **5** was used without further purification. IR (KBr): 1755 cm^{-1} (CO). EI-MS (m/z): 129 $[M–OCH_3]^+$. ^1H NMR (DMSO-d_6) δ 2.46 (overlapped, 2H, $H_{4a,}$ H_{4b}), 3.29, 3.33 (2s, 3H each, $>C(OCH_3)_2$), 3.89 (d, 1H, $J_{2,6}=2.1$ Hz, H_2), 4.14 (m, 2H, $H_{5a,}$ H_{5b}), 4.42 (d, 1H, $J_{6,2}=2.1$ Hz, H_6). ^{13}C NMR (DMSO-d_6) δ 36.6 (C_4), 54.6 (OCH_3), 54.9 (OCH_3), 64.9 (C_5), 78.4 (C_2), 103.4 (C_6), 213.1 (C_3).

3.4. 2-(R)-Dimethoxymethyl-3-oximido-tetrahydrofuran 7

To a mixture of **5** (880 mg, 5.5 mmol), CH_2Cl_2 (10 ml), water (5 ml) and potassium cyanide (720 mg, 11 mmol) at 0°C, HOAc (0.5 ml, 8.2 mmol) was added. The mixture was stirred at 0°C for 2 h, then the organic phase was separated and dried (Na_2SO_4). After evaporation in vacuo, the residue was dissolved in methanol (10 ml) containing free base hydroxylamine [from 800 mg (11 mmol) of the hydrochloride][15] and the mixture was refluxed for 2 h. The solvent was then evaporated and the residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate) to afford **7** (180 mg, 19%) as a syrup. $[\alpha]_D^{15}$ –102.8 (*c* 0.105, MeOH). FAB-MS (m/z): 176 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.57 (overlapped, 2H, $H_{4a,}$ H_{4b}), 3.30, 3.33 (2s, 3H each, $>C(OCH_3)_2$), 3.86 (m, 1H, H_{5a}), 4.01 (m, 1H, H_{5b}), 4.28 (d, 1H, $J_{2,6}=3.6$ Hz, H_2), 4.35 (d, 1H, $J_{6,2}=3.6$ Hz, H_6), 10.88 (s, 1H, D_2O exchangeable, N-OH). ^{13}C NMR (DMSO-d_6) δ 27.3 (C_4), 54.5 (OCH_3), 54.8 (OCH_3), 66.6 (C_5), 76.9 (C_2), 104.5 (C_6), 159.0 (C_3). Anal. calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 7.99. Found: C, 47.59; H, 7.44; N, 7.74.

3.5. (2R,3S)-3-Benzoyloxy-3-cyano-2-dimethoxymethyltetrahydrofuran **8a** and (2R,3R)-3-benzoyloxy-3-cyano-2-dimethoxymethyltetrahydrofuran **9a**

To a mixture of **5** (3.6 g, 23 mmol), CH_2Cl_2 (40 ml), water (20 ml) and potassium cyanide (3.0 g, 46 mmol) at 0°C, HOAc (2.0 ml, 34.5 mmol) was added. The mixture was stirred at 0°C for 2 h, then the organic phase was separated and dried (Na_2SO_4). After evaporation in vacuo, the residue was dissolved in dry pyridine (20 ml), BzCl (2.7 ml, 23 mmol) was added and the mixture was stirred overnight. Most of the solvent was removed and the residue was partitioned between ice-cold water (20 ml) and CH_2Cl_2 (2×20 ml). The organic extracts were washed in sequence with 1 M H_2SO_4 (10 ml), saturated $NaHCO_3$ solution (10 ml) and brine (10 ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel chromatography (petroleum ether–acetone) to yield **8a** (1.62 g, 24.7%) and **9a** (2.25 g, 34.3%), each as a syrup.

Compound **8a**: $[\alpha]_D^{15}$ –62.0 (*c* 0.15, MeOH). FAB-MS (m/z): 292 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.76 (m, 2H, $H_{4a,}$ H_{4b}), 3.41, 3.42 (2s, 3H each, $>C(OCH_3)_2$), 3.92 (m, 1H, H_{5a}), 4.11 (m, 1H, H_{5b}), 4.31 (d, 1H, $J_{2,6}=5.4$ Hz, H_2), 4.60 (d, 1H, $J_{6,2}=5.4$ Hz, H_6), 7.59 (t, 2H, arom. H), 7.75 (t, 1H, arom. H), 8.02 (d, 2H, arom H). ^{13}C NMR (DMSO-d_6) δ 38.5 (C_4), 54.3 (OCH_3), 54.9 (OCH_3), 66.5 (C_5), 76.5 (C_2), 83.8 (C_3), 102.7 (C_6), 116.2 (CN), 128.0, 128.9, 129.6, 134.4 (arom. C), 164.2 (CO). Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.80. Found: C, 62.17; H, 5.83; N, 4.56.

Compound **9a**: $[\alpha]_D^{15}$ +48.3 (*c* 0.12, MeOH). FAB-MS (m/z): 292 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.79 (m, 2H, $H_{4a,}$ H_{4b}), 3.38, 3.42 (2s, 3H each, $>C(OCH_3)_2$), 3.96 (m, 2H, $H_{5a,}$ H_{5b}), 4.19 (d, 1H, $J_{2,6}=7.2$ Hz, H_2), 4.84 (d, 1H, $J_{6,2}=7.2$ Hz, H_6), 7.60 (t, 2H, arom. H), 7.75 (t, 1H, arom. H), 8.02 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 38.2 (C_4), 53.4 (OCH_3), 55.3 (OCH_3), 66.2 (C_5), 74.8 (C_2), 83.6 (C_3), 101.5 (C_6), 116.5 (CN), 128.1, 129.1, 129.5, 134.4 (arom. C), 163.8 (CO). Anal. calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.80. Found: C, 61.35; H, 5.79; N, 4.86.

3.6. (2R,3S)-3-Acetoxy-3-cyano-2-dimethoxymethyltetrahydrofuran **8b** and (2R,3R)-3-acetoxy-3-cyano-2-dimethoxymethyltetrahydrofuran **9b**

To a mixture of **5** (3.4 g, 21 mmol), CH_2Cl_2 (40 ml), water (20 ml) and potassium cyanide (2.7 g, 42 mmol) at 0°C, HOAc (1.8 ml, 31.5 mmol) was added and the mixture was stirred at 0°C for

2 h. The organic phase was separated and dried over anhydrous Na_2SO_4. 4-Dimethylaminopyridine (DMAP, 3.7 g, 30 mmol) and Ac_2O (2.3 ml, 26 mmol) were added and the mixture was stirred overnight. After water (10 ml) was added, the organic phase was separated and washed in sequence with 1 M H_2SO_4 (10 ml), saturated $NaHCO_3$ solution (10 ml) and brine (10 ml), and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether–acetone) to yield **8b** (1.65 g, 33.3%) and **9b** (1.57 g, 31.7%), each as a syrup.

Compound **8b**: $[\alpha]_D^{15}$ –48.1 (*c* 0.185, MeOH). FAB-MS (m/z): 230 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.13 (s, 3H, $COCH_3$), 2.50 (overlapped, 1H, H_{4a}), 2.64 (m, 1H, H_{4b}), 3.36 (s, 6H, $>C(OCH_3)_2$), 3.82 (m, 1H, H_{5a}), 4.04 (overlapped, 2H, $H_{5b,}$ H_2), 4.51 (d, 1H, $J_{6,2}=5.4$ Hz, H_6). ^{13}C NMR (DMSO-d_6) δ 20.6 ($COCH_3$), 38.4 (C_4), 54.2 (OCH_3), 54.7 (OCH_3), 66.4 (C_5), 75.8 (C_2), 83.9 (C_3), 102.5 (C_6), 116.3 (CN), 169.2 (CO). Anal. calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.59; N, 6.11. Found: C, 52.01; H, 6.54; N, 5.83.

Compound **9b**: $[\alpha]_D^{15}$ –3.5 (*c* 0.115, MeOH). FAB-MS (m/z): 230 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.15 (s, 3H, $COCH_3$), 2.57 (m, 1H, H_{4a}), 2.72 (m, 1H, H_{4b}), 3.34, 3.39 (2s, 3H each, $>C(OCH_3)_2$), 3.92 (m, 2H, $H_{5a,}$ H_{5b}), 4.03 (d, 1H, $J_{2,6}=7.5$ Hz, H_2), 4.57 (d, 1H, $J_{6,2}=7.5$ Hz, H_6). ^{13}C NMR (DMSO-d_6) δ 20.5 ($COCH_3$), 38.0 (C_4), 53.3 (OCH_3), 55.5 (OCH_3), 66.0 (C_5), 73.9 (C_2), 83.2 (C_3), 101.5 (C_6), 116.6 (CN), 168.8 (CO). Anal. calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.59; N, 6.11. Found: C, 52.20; H, 6.62; N, 5.90.

3.7. 5-Phenyl-3-[(2′R,3′S)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole ***10a***

A solution of **8a** (840 mg, 2.9 mmol) and free base hydroxylamine [from 610 mg (8.7 mmol) of the hydrochloride] in methanol (10 ml) was refluxed for 2 h. The solvent was then evaporated and the residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate) to afford **7** (42 mg, 8.2%) and **10a** (385 mg, 42%). Recrystallization from ethyl acetate–cyclohexane gave **10a** as colorless needles.

Compound **10a**: mp 101–102°C. $[\alpha]_D^{15}$ –26.2 (*c* 0.145, MeOH). UV λ_{max}^{MeOH} (lg ε): 204.0 (4.31), 251.9 (4.29). FAB-MS (m/z): 307 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.17 (m, 1H, $H_{4'a}$), 2.62 (m, 1H, $H_{4'b}$), 2.87, 3.17 (2s, 3H each, $>C(OCH_3)_2$), 3.95 (overlapped, 2H, $H_{2',}$ $H_{5'a}$), 4.11 (overlapped, 2H, $H_{5'b,}$ $H_{6'}$), 6.13 (s, 1H, D_2O exchangeable, 3′-OH), 7.69 (m, 3H, arom. H), 8.14 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 38.6 ($C_{4'}$), 52.3 (OCH_3), 53.6 (OCH_3), 66.4 ($C_{5'}$), 77.8 ($C_{2'}$), 86.4 ($C_{3'}$), 101.7 ($C_{6'}$), 123.4, 127.7, 129.6, 133.2 (arom. C), 172.6 (C_3), 174.4 (C_5). Anal. calcd for $C_{15}H_{18}N_2O_5$: C, 58.84; H, 5.92; N, 9.15. Found: C, 58.80; H, 5.85; N, 9.18. Crystal data: empirical formula, $C_{15}H_{18}N_2O_5$; formula weight, 306.31; crystal system, monoclinic; space group, $P2_1$; $a=10.586(1)$, $b=6.751(1)$, $c=11.348(1)$ Å, $\beta=109.37(1)°$, $V=765.09(15)$ Å^3, $Z=2$, $D=1.330$ g/cm^3.

3.8. 5-Phenyl-3-[(2′R,3′R)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole ***11a***

The above procedure applied to **9a** (1.22 g, 4.0 mmol) with hydroxylamine (840 mg, 12 mmol) afforded **7** (80 mg, 11%) and **11a** (490 mg, 40%).

Compound **11a**: mp 76–76°C $[\alpha]_D^{15}$ –35.0 (*c* 0.14, MeOH). UV λ_{max}^{MeOH} (lg ε): 204.0 (4.36), 251.5 (4.35). FAB-MS (m/z): 307 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.28 (m, 1H, $H_{4'a}$), 2.50 (overlapped, 1H, $H_{4'b}$), 3.17, 3.26 (2s, 3H each, $>C(OCH_3)_2$), 4.02 (overlapped, 3H, $H_{5'a,}$ $H_{5'b}$ and $H_{2'}$), 4.52

(d, 1H, $J_{6',2'}=7.5$ Hz, $H_{6'}$), 6.03 (s, 1H, D_2O exchangeable, 3′-OH), 7.68 (m, 3H, arom. H), 8.10 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 41.2 ($C_{4'}$), 52.8 (OCH_3), 55.3 (OCH_3), 66.2 ($C_{5'}$), 77.2 ($C_{2'}$), 83.9 ($C_{3'}$), 102.7 ($C_{6'}$), 123.4, 127.7, 129.5, 133.2 (arom. C), 173.7 (C_3), 174.6 (C_5). Anal. calcd for $C_{15}H_{18}N_2O_5$: C, 58.84; H, 5.92; N, 9.15. Found: C, 58.72; H, 6.14; N, 9.17.

3.9. 5-Methyl-3-[(2′R,3′S)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole *10b*

The above procedure applied to **8b** (890 mg, 3.9 mmol) with hydroxylamine (700 mg, 10 mmol) afforded **7** (160 mg, 23.4%) and **10b** (360 mg, 37.8%).

Compound **10b**: $[\alpha]_D^{15}$ –59.3 (*c* 0.145, MeOH). UV λ_{max}^{MeOH} (lg ε): 201.4 (3.61). FAB-MS (m/z): 245 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.05 (m, 1H, $H_{4'a}$), 2.49 (overlapped, 1H, $H_{4'b}$), 2.58 (s, 3H, 5-CH_3), 2.89, 3.13 (2s, 3H each, $>C(OCH_3)_2$), 3.87 (overlapped, 2H, $H_{2'}$, $H_{5'a}$), 3.99 (overlapped, 2H, $H_{5'b}$, $H_{6'}$), 5.94 (s, 1H, D_2O exchangeable, 3′-OH). ^{13}C NMR (DMSO-d_6) δ 11.9 (5-CH_3), 40.6 ($C_{4'}$), 52.6 (OCH_3), 53.9 (OCH_3), 66.7 ($C_{5'}$), 77.9 ($C_{2'}$), 86.6 ($C_{3'}$), 102.0 ($C_{6'}$), 172.1 (C_3), 176.4 (C_5). Anal. calcd for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47. Found: C, 49.26; H, 6.66; N, 11.30.

3.10. 5-Methyl-3-[(2′R,3′R)-3′-hydroxy-2′-dimethoxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole *11b*

The above procedure applied to **9b** (810 mg, 3.5 mmol) with hydroxylamine (620 mg, 8.8 mmol) afforded **7** (80 mg, 13%) and **11b** (344 mg, 40.2%).

Compound **11b**: $[\alpha]_D^{15}$ –10.8 (*c* 0.12, MeOH). UV λ_{max}^{MeOH} (lg ε): 202.0 (3.68). FAB-MS (m/z): 245 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.18 (m, 1H, $H_{4'a}$), 2.38 (m, 1H, $H_{4'b}$), 2.57 (s, 3H, 5-CH_3), 3.15, 3.35 (2s, 3H each, $>C(OCH_3)_2$), 3.96 (overlapped, 3H, $H_{2'}$, $H_{5'a}$, $H_{5'b}$), 4.47 (d, 1H, $J_{6',2'}=7.5$ Hz, $H_{6'}$), 5.89 (s, 1H, D_2O exchangeable, 3′-OH). ^{13}C NMR (DMSO-d_6) δ 11.9 (5-CH_3), 41.3 ($C_{4'}$), 52.6 (OCH_3), 55.4 (OCH_3), 66.2 ($C_{5'}$), 77.2 ($C_{2'}$), 83.6 ($C_{3'}$), 102.7 ($C_{6'}$), 172.9 (C_3), 176.5 (C_5). Anal. calcd for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.60; N, 11.47. Found: C, 48.96; H, 6.64; N, 11.27.

3.11. 5-Phenyl-3-[(2′S,3′S)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole *12a*

A solution of **10a** (260 mg, 0.86 mmol) in dioxane (5 ml) and 1% HCl (5 ml) was heated at 100°C for 1.5 h, then cooled to room temperature. After neutralization, the mixture was treated with $NaBH_4$ (34 mg, 0.86 mmol) for 30 min, then neutralized again. The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether–acetone) to afford **12a** (175 mg, 78.6%) and 5-phenyl-3-(2′-hydroxymethyl-4′,5′-dihydrofuran-3′-yl)-1,2,4-oxadiazole **14a** (17 mg, 8.2%).

Compound **12a**: mp 74–76°C. $[\alpha]_D^{15}$ –81.6 (*c* 0.125, MeOH). UV λ_{max}^{MeOH} (lg ε): 204.3 (4.33), 251.2 (4.31). FAB-MS (m/z): 263 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.15 (m, 1H, $H_{4'a}$), 2.62 (m, 1H, $H_{4'b}$), 3.33 (overlapped, 2H, $H_{5'a}$, $H_{5'b}$), 3.93 (m, 2H, $H_{6'a}$, $H_{6'b}$), 4.07 (t, 1H, $J_{2',6'}=7.5$ Hz, $H_{2'}$), 4.49 (s, 1H, D_2O exchangeable, 6′-OH), 6.13 (s, 1H, D_2O exchangeable, 3′-OH), 7.66 (m, 3H, arom. H), 8.10 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 38.0 ($C_{4'}$), 61.2 ($C_{6'}$), 65.9 ($C_{5'}$), 77.1 ($C_{2'}$), 88.1 ($C_{3'}$), 123.5, 127.8, 129.6, 133.2 (arom. C), 172.4 (C_3), 174.6 (C_5). Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.39; H, 5.58; N, 10.54.

Compound **14a**: mp 118–119°C. UV λ_{max}^{MeOH} (lg ε): 203.7 (4.24), 259.1 (4.49). FAB-MS (m/z): 245 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 3.01 (t, 2H, $J_{4',5'}=9.6$ Hz, $H_{4'a}$, $H_{4'b}$), 4.51 (t, 2H, $J_{5',4'}=9.6$ Hz, $H_{5'a}$, $H_{5'b}$), 4.60 (d, 2H, $J_{6',OH}=6.0$ Hz, $H_{6'}$), 5.20 (t, 1H, $J_{OH,6'}=6.0$ Hz, D_2O exchangeable, 6′-OH), 7.66 (m, 3H, arom. H), 8.09 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 29.9 ($C_{4'}$), 54.7 ($C_{6'}$), 69.8 ($C_{5'}$), 97.4 ($C_{3'}$), 123.4, 127.8, 129.5, 133.2 (arom. C), 163.4 ($C_{2'}$), 165.3 (C_3), 173.9 (C_5). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.10; H, 4.97; N, 11.53.

3.12. 5-Phenyl-3-[(2′S,3′R)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **13a**

A solution of **11a** (360 mg, 1.2 mmol) in dioxane (10 ml) and 1% HCl (10 ml) was heated at 100°C for 1.5 h, then cooled to room temperature. After neutralization, the mixture was treated with $NaBH_4$ (45 mg, 1.2 mmol) for 30 min, then neutralized again. The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether–acetone) to afford **13a** (133 mg, 48.0%) and **14a** (78 mg, 27.1%).

Compound **13a**: mp 109–110°C. $[\alpha]_D^{15}$ –22.4 (*c* 0.14, MeOH). UV λ_{max}^{MeOH} (lg ε): 204.3 (4.25), 251.5 (4.27). FAB-MS (m/z): 263 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.28 (m, 1H, $H_{4'a}$), 2.56 (m, 1H, $H_{4'b}$), 3.58 (m, 1H, $H_{5'a}$), 3.73 (m, 1H, $H_{5'b}$), 3.90 (m, 1H, $H_{2'}$), 4.02 (m, 2H, $H_{6'a}$, $H_{6'b}$), 4.60 (s, 1H, D_2O exchangeable, 6′-OH), 5.98 (s, 1H, D_2O exchangeable, 3′-OH), 7.68 (m, 3H, arom. H), 8.12 (d, 2H, arom. H). ^{13}C NMR (DMSO-d_6) δ 40.2 ($C_{4'}$), 59.9 ($C_{6'}$), 65.6 ($C_{5'}$), 76.7($C_{2'}$), 85.8 ($C_{3'}$), 123.3, 127.8, 129.6, 133.3 (arom. C), 173.3 (C_3), 175.0 (C_5). Anal. calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.62; H, 5.38; N, 10.67.

3.13. 5-Methyl-3-[(2′S,3′S)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **12b**

A solution of **10b** (250 mg, 1 mmol) in dioxane (5 ml) and 1% HCl (5 ml) was heated at 100°C for 1.5 h, then cooled to room temperature. After neutralization, the mixture was treated with $NaBH_4$ (38 mg, 1 mmol) for 30 min, then neutralized again. The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether–acetone) to afford **12b** (154 mg, 75.2%) and 5-methyl-3-(2′-hydroxymethyl-4′,5′-dihydrofuran-3′-yl)-1,2,4-oxadiazole **14b** (16 mg, 8.6%).

Compound **12b**: $[\alpha]_D^{15}$ –105.7 (*c* 0.105, MeOH). UV λ_{max}^{MeOH} (lg ε): 201.3 (3.39). FAB-MS (m/z): 201 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.08 (m, 1H, $H_{4'a}$), 2.51 (overlapped, 1H, $H_{4'b}$), 2.57 (s, 3H, 5-CH_3), 3.08 (m, 1H, $H_{5'a}$), 3.20 (m, 1H, $H_{5'b}$), 3.89 (m, 2H, $H_{6'a}$, $H_{6'b}$), 4.00 (m, 1H, $H_{2'}$), 4.42 (t, 1H, D_2O exchangeable, 6′-OH), 5.94 (s, 1H, D_2O exchangeable, 3′-OH). ^{13}C NMR (DMSO-d_6) δ 11.9 (5-CH_3), 37.8 ($C_{4'}$), 61.2 ($C_{6'}$), 65.8 ($C_{5'}$), 76.9 ($C_{2'}$), 88.0 ($C_{3'}$), 171.5 (C_3), 176.4 (C_5). Anal. calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 48.33; H, 6.62; N, 13.64.

Compound **14b**: mp 68–71°C. UV λ_{max}^{MeOH} (lg ε): 204.3 (3.81), 260.8 (4.34). FAB-MS (m/z): 183 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.56 (s, 3H, 5-CH_3), 2.94 (t, 2H, $J_{4',5'}=9.6$ Hz, $H_{4'a}$, $H_{4'b}$), 4.46 (overlapped, 4H, $H_{5'a}$, $H_{5'b}$, $H_{6'a}$, $H_{6'b}$), 5.13 (s, 1H, D_2O exchangeable, 6′-OH). ^{13}C NMR (DMSO-d_6) δ 11.9 (5-CH_3), 29.9 ($C_{4'}$), 54.5 ($C_{6'}$), 69.6 ($C_{5'}$), 97.5 ($C_{3'}$), 162.7 ($C_{2'}$), 164.6 (C_3), 175.8 (C_5). Anal. calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.56; N, 15.37. Found: C, 52.57; H, 5.53; N, 15.09.

3.14. 5-Methyl-3-[(2′S,3′R)-3′-hydroxy-2′-hydroxymethyltetrahydrofuran-3′-yl]-1,2,4-oxadiazole **13b**

A solution of **11b** (250 mg, 1 mmol) in dioxane (5 ml) and 1% HCl (5 ml) was heated at 100°C for 1.5 h, then cooled to room temperature. After neutralization, the mixture was treated with

$NaBH_4$ (38 mg, 1 mmol) for 30 min, then neutralized again. The solvent was evaporated and the residue was purified by silica gel column chromatography (petroleum ether–acetone) to afford **13b** (165 mg, 83.2%) and **14b** (5 mg, 3.3%).

Compound **13b**: $[\alpha]_D^{15}$ –20.0 (*c* 0.125, MeOH). UV λ_{max}^{MeOH} (lg ε): 201.8 (3.47). FAB-MS (m/z): 201 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.18 (m, 1H, $H_{4'a}$), 2.42 (m, 1H, $H_{4'b}$), 2.58 (s, 3H, 5-CH_3), 3.54 (m, 1H, $H_{5'a}$), 3.64 (m, 1H, $H_{5'b}$), 3.84 (m, 2H, $H_{6'a,}$ $H_{6'b}$), 3.98 (m, 1H, $H_{2'}$), 4.54 (t, 1H, D_2O exchangeable, 6′-OH), 5.80 (s, 1H, D_2O exchangeable, 3′-OH). ^{13}C NMR (DMSO-d_6) δ 11.9 (5-CH_3), 40.2 ($C_{4'}$), 59.9 ($C_{6'}$), 65.2 ($C_{5'}$), 76.6 ($C_{2'}$), 85.8 ($C_{3'}$), 172.5 (C_3), 177.0 (C_5). Anal. calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99. Found: C, 47.77; H, 5.83; N, 13.49.

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