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Synthesis of Novel 1,3-Dioxolane Nucleoside Analogues

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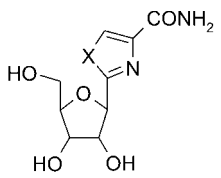
Novel 1,3-dioxolane C-nucleoside analogues of tiazofurin 2-(2-hydroxymethyl-1,3-dioxolan-4-yl)-1,3-thiazole-4-carboxamide as well as *N*-nucleoside analogues of substituted imidazoles 1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-4-nitroimidazole and 1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole were synthesized from methyl acrylate through a multistep procedure. Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis.

Keywords nucleoside, 1,3-dioxolane, tiazofurin, Ribavirin, imidazole

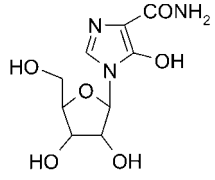
Introduction

2',3'-Dideoxynucleoside analogues such as AZT,[1] ddC,[2] ddI[2] and d4T[3] are amongst the most active agents against HIV-1 and HIV-2, the causive agents of AIDS. The use of 2',3'-dideoxynucleoside analogues in combination with protease inhibitors has been responsible for the marked reduction of opportunistic infections and mortality in HIV patients in the past decade.[4] Unfortunately these compounds possess undesirable pharmacological properties[5] and they are susceptible to the development of resistant strains of HIV.[6] In an attempt to overcome some of these detrimental side effects, dideoxynucleoside analogs such as (−)-*L*-*β*-1,3-oxathiolanyl cytosine (3TC, Lamivudine) and (−)-*L*-*β*-1,3-dioxolanyl cytosine [(−)-OddC], in which the 3'-methylene carbon of the normal nucleoside was replaced by a heteroatom, have been reported.[7-10] 3TC is being clinically used as an anti-AIDS and anti-HBV drug. (−)-OddC showed significant activity against both solid and lymphoid tumors both *in vitro* and *in vivo*, and also exhibited potent anti-AIDS and anti-HBV activities.

The synthetic *C*-nucleosides, tiazofurin (2-*β*-*D*-ribofuranosylthiazole-4-carboxamide, NSC-286193,[11] **1**) and selenazofurin (2-*β*-*D*-ribofuranosylselenazole-4-carboxamide, NSC-340847,[12] **2**), which exhibit distinguished antitumor and antiviral activities, have gained significant attention. On the other hand, imidazole nucleoside analogues such as Bredinin[13] (5-hydroxyl-1-*β*-*D*-ribofuranosylimidazole-4-carboxamide, **3**), AICAR[14] (5-amino-1-*β*-*D*-ribofuranosyl imidazole-4-carboxamide, **4**) and EICAR[15] (5-ethynyl-1-*β*-*D*-ribofuranosylimidazole-4-carboxamide, **5**) also exhibited broad spectrum of biological activities, and they are cytotoxic to certain cancer cells *in vitro* and *in vivo*, potent inhibitors of proliferation of certain RNA viruses,[16] and immunosuppressors,[17] respectively.



1 X = S
2 X = Se



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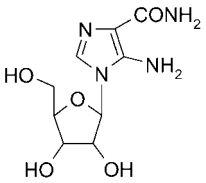

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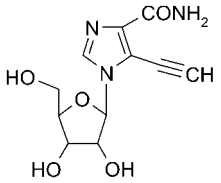

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Based on these findings, it was of interest to synthesize hybrid 1,3-dioxolane nucleoside analogues. This report describes the synthesis of novel 1,3-dioxolane *C*-nucleoside analogues of tiazofurin, 2-(2-hydroxymethyl-1,3-dioxolan-4-yl)-1,3-thiazole-4-carboxamide, as well as *N*-nucleoside analogues of substituted imidazole, 1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole and 1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-4-nitroimidazole. Compared with the literature reported lengthy and low yield synthetic steps of the 1, 3-dioxolane nucleoside analogues,[18-20] our synthetic route seems short and efficient.

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Results and discussion

Since 1,3-dioxolanyl moiety is an acetal, it can be constructed by reacting aldehyde with diol using Lewis acid as catalyst. Methyl acrylate was chosen as starting material, since it is cheap and convenient to obtain. Oxidation of methyl acrylate with potassium permanganate afforded racemic methyl glycerate (**7**). Condensation of benzyloxyacetaldehyde diethyl acetal (**6**) with (±)-methyl glycerate (**7**) in the presence of *p*-toluenesulfonic acid provided racemic dioxolane **8** in 67% yield.

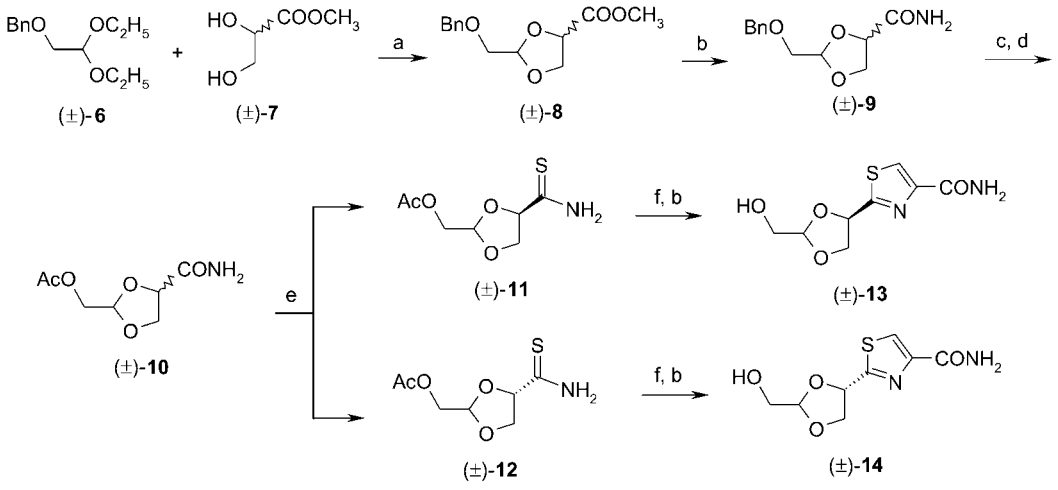
The synthetic route of 2-(2-hydroxymethyl-1,3-dioxolan-5-yl)-1,3-thiazole-4-carboxamide (**13** and **14**) is outlined in Scheme 1.

8 was smoothly transformed into the corresponding amide **9** with ammonia in methanol. Removal of benzyl group by catalytic hydrogenation would be unsuccessful because sulfur inactivated the palladium catalyst. So the benzyl group was transformed to acetyl group before sulfur was introduced into the reaction system. **9** was deprotected via catalytic hydrogenation over Pd/C. The resulting compound was then reacted with acetic anhydride in pyridine to form **10**. **10** was subjected to thiation with tetraphosphorus decasulphide in refluxing dioxane to give **11** and **12**. **11** and **12** have different R_f values on TLC. They could be separated by column chromatography. The structure of the major product was determined to be (±)- β-2-acetyloxymethyl-1,3-dioxolane-4-yl thiocarboxamide (**11**), whereas the minor product was (±)-α-2-acetyloxymethyl-1,3-dioxolane-4-yl thiocarboxamide (**12**). These configurations were determined based on ^{1}H NMR spectral studies of **13** and **14**, obtained via the treatment of **11** and **12** with ethyl bromopyruvate in refluxing ethanol, followed by ammonolysis. The δ value of the anomeric proton of **13** shifted upfield relative to that of **14**. NOE experiments showed that when H-2 of **13** was irradiated, H-5 peak was enhanced, suggesting **13** in *cis* orientation, while irradiation of H-2 of **14**, no enhancement of H-5 was observed, indicating **14** in *trans* configuration.

Preparation of 1-(2-hydroxymethyl-1,3-dioxolan-5-yl)-4,5-dicyanoimidazole and 1-(2-hydroxymethyl-1,3-dioxolan-5-yl)-4-nitroimidazole was accomplished by the multistep synthetic sequence depicted in Scheme 2.

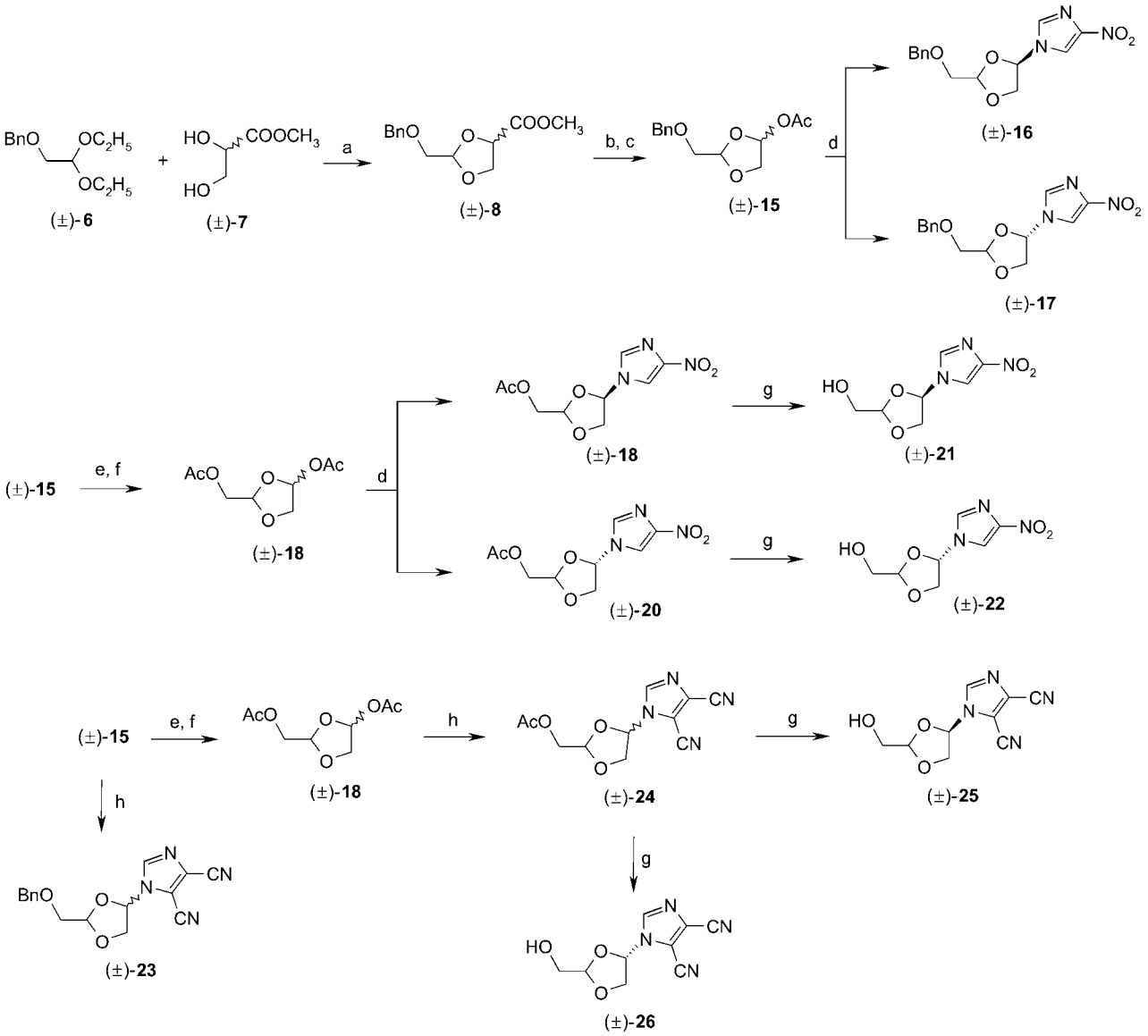
Saponification of the dioxolane methyl ester **8** with LiOH in aqueous THF followed by acidification afforded the carboxylic acids as a oil, which was used without further purification. Treatment of this crude acids with 1.1 equivalents of pyridine and 1.3 equivalents of $Pb(OAc)_4$ in dry acetonitrile effected a smooth, oxidative decarboxylation, producing acetate **15** as a mixture of *cis*- and *trans*-isomers. Condensation of acetate **15** with silylated 4-nitroimidazole in dry 1,2-dichloroethane using TMSOTf as the Lewis acid catalyst gave a mixture of **16** (β) and **17** (α) isomers, which could be separated carefully by column chromatography. The δ value of the anomeric proton of **16** shifted upfield relative to that of **17**. NOE experiments showed that when H-2 of **16** was irradiated, H-5 peak was enhanced, suggesting **16** in *cis*-orientation, while irradiation of H-2 of **17**, no enhancement of H-5 was observed, indicating **17** in *trans*-configuration. Furthermore, the H-2 proton of the β-isomer appeared upfield from that observed for the α-isomer because of the deshielding effect by base, and the H-6 proton of the β-isomer also appeared downfield from those observed for the α-isomer due to the same deshielding effect. Catalytic hydrogenation of **16** and **17** over Pd/C gave unstable 4-amino derivative, which quickly turned from colorless to dark brown when exposed to the air. The sequence was therefore revised. **15** was first deprotected via catalytic hydrogenation over palladium on charcoal. The hydroxyl group was then reacted with acetic anhydride in pyridine to form the acetyl-protected acetate **18**.

Scheme 1



Reagents and conditions: (a) *p*-TsOH, benzene, reflux; (b) NH_3/MeOH, r.t.; (c) Pd/C, H_2, ethanol; (d) Ac_2O/Py, r.t.; (e) P_4S_{10}, dioxane, reflux; (f) $BrCH_2COCOOEt$/EtOH, reflux.

Scheme 2



Reagents and conditions: (a) *p*-TsOH, benzene, reflux; (b) LiOH, THF∶H_2O (4∶1, *V*∶*V*), reflux; (c) $Pb(OAc)_4$, pyridine, CH_3CN; (d) 4-nitroimidazole, TMSOTf, $ClCH_2CH_2Cl$, r.t.; (e) Pd/C, H_2, methanol; (f) Ac_2O/Py, r.t.; (g) NH_3/MeOH, r.t.; (h) 4,5-dicyanoimidazole, TMSOTf, $ClCH_2CH_2Cl$, r.t.

Condensation of acetate **18** with silylated 4-nitro imidazole in dry 1,2-dichloroethane using TMSOTf as the Lewis acid catalyst gave **19** and **20**. They could be separated by column chromatography. Ammonolysis of **19** and **20** in methanolic ammonia afforded the final products **21** and **22**, respectively. Compound **23** was prepared by similar procedure as that of **16** and **17** from acetate **15** with silylated 4,5-dicyanoimidazole as a mixture of α and β isomers in a ratio of 1∶2 based on ^{1}H NMR spectroscopy, in which the major compound (β-isomer) showed the upfield shift of H-2 (δ 5.23), compared to the minor compound (α-isomer) for H-2 (δ 5.68). The mixture of α and β isomers gave only one spot on a silica gel TLC in various solvent systems. Therefore, it could not be separated into single isomer at this stage. Considerable difficulties were encountered in removing the benzyl groups of **23** by catalytic hydrogenation over Pd/C. So the sequence was also revised. Silylated 4,5-dicyanoimidazole reacted with acetate **18** to yield compound **24** as a mixture of α and β isomers. Recrystallization from petroleum ether and ethyl acetate afforded the major isomer (β) as white solid. Ammonolysis of **24** in methanolic ammonia afforded the final products **25** and **26**, respectively. The assignments of anomeric configuration of **21**, **22** and **25, 26** were based on the comparison of the ^{1}H NMR patterns of **16** and **17**.

Experimental

Melting points were determined on an XT4A instrument and are uncorrected. IR spectra were recorded

on a Bruker VETOR 22 spectrometer. NMR spectra were recorded on a Bruker 400 or 300 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (δ). Column chromatography was performed on silica gel (200—300 mesh) and silica gel GF254 used for TLC purchased from Qingdao Chemical Company, China.

Methyl (2-benzyloxymethyl-1,3-dioxolan-4-yl) carboxylate (8)

To a stirred solution of methyl glycerate (3.36 g, 28 mmol) in dry benzene (100 mL), benzyloxyacetaldehyde diethyl acetal (5.0 g, 25.5 mmol) and *p*-TsOH•H_2O (1.0 g) were added sequentially. The mixture was refluxed gently in the Dean-Stark apparatus to remove water. The reaction mixture was cooled down to room temperature and neutralized with Et_3N. Evaporation of the solvent afforded a syrup, which was purified by silic gel column chromatography to give **3** as a light yellow oil (4.3 g, 67%). ^{1}H NMR (acetone-d_6) δ: 7.35—7.25 (m, 5H, arom-H), 5.23, 5.15 (2×t, J=3.7, 4.2 Hz, 1H, H-2), 4.68, 4.63 (2×dd, J=5.0, 2.3, 3.8, 3.5 Hz, 1H, H-5), 4.59, 4.57 (2×s, 2H, $PhCH_2O$), 4.27—3.92 (m, 2H, H-4), 3.72, 3.68 (2×s, 3H, $COOCH_3$), 3.63—3.55 (m, 2H, H-6); IR (NaCl) ν: 3444, 2953, 1758, 1454, 1212, 1154, 1114 cm^{-1}. Anal. calcd for $C_{13}H_{16}O_5$ (252.27): C 61.90, H 6.39; found C 61.75, H 6.53.

(2-Benzyloxymethyl-1,3-dioxolan-4-yl) carboxamide (9)

Crude ester **8** (1.96 g, 7.8 mmol) was dissolved in methanolic ammonia (50 mL) and was stirred at r.t. overnight. Column chromatography provided **9** (1.75 g, 95%) as a viscous syrup. ^{1}H NMR (acetone-d_6) δ: 7.34—7.27 (m, 5H, arom H), 6.82, 6.70 (m, 2H, $CONH_2$), 5.28, 5.11 (2×t, J=3.8, 4.2 Hz, 1H, H-2), 4.61, 4.57 (2×s, 2H, $PhCH_2O$), 4.48, 4.40 (2×dd, J=5.7, 1.4, 3.6, 3.8 Hz, 1H, H-5), 4.28—3.88 (m, 2H, H-4), 3.72—3.56 (m, 2H, H-6); IR (NaCl) ν: 3416, 2878, 1691, 1454, 1401, 1155, 1095 cm^{-1}. Anal. calcd for $C_{12}H_{15}NO_4$ (237.26): C 60.75, H 6.37, N 5.90; found C 60.34, H 6.58, N 5.57.

(2-Acetoxymethyl-1,3-dioxolan-4-yl) carboxamide (10)

Amide **9** (1.5 g, 6.3 mmol) was dissolved in absolute methanol, followed by the addition of 5% Pd/C catalyst (0.4 g). Hydrogen was introduced into the reaction mixture and the solution was stirred at r.t. until TLC showed completion of the reaction. The Pd/C was filtered off, and washed with MeOH repeatedly. The filtrate was evaporated and an oily residue, which was of sufficient purity for further reaction, was obtained. It was dissolved in 20 mL of pyridine and 10 mL of acetic anhydride was added. The mixture was stirred at r.t. under nitrogen for 12 h. Solvent was removed under reduced pressure and the residue was coevaporated with toluene (3×50 mL). The resulting yellow syrup was of sufficient purity for further reaction (1.16 g, 97%). ^{1}H NMR ($CDCl_3$) δ: 7.01, 6.61, 6.39, 5.84 (4×s, 2H, $CONH_2$), 5.31, 5.17 (2×t, J=3.9, 3.6 Hz, 1H, H-2), 4.52, 4.50 (2×dd, J=3.2, 1.5, 3.4, 2.6 Hz, 1H, H-5), 4.45—4.15 (m, 2H, H-4), 4.12—4.04 (m, 2H, H-6), 2.05, 2.03 (2×s, 3H, CH_3CO); IR (NaCl) ν: 3449, 2899, 1742, 1685, 1595, 1376, 1236, 1151, 1053 cm^{-1}. Anal. calcd for $C_7H_{11}NO_5$ (189.16): C 44.45, H 5.86, N 7.41; found C 44.11, H 6.19, N 7.56.

(±)-(2-Acetoxymethyl-1,3-dioxolan-4-yl) thiocarboxamide (11 and 12)

Compound **10** (1.1 g, 5.8 mmol) was dissolved in absolute dioxane (50 mL) and boiled with tetraphosphorus decasulphide (1.5 g, 6.8 mmol) for 1 h. TLC showed two new spots, which have very similar R_f values. Solvent was removed under reduced pressure and the syrup obtained was separated carefully by column chromatography to yield (±)-**11** (0.42 g, 35%) and (±)-**12** (0.23 g, 19%).

Compound **11**: m.p. 102—103 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.03, 7.61 (2s, each 1H, $CSNH_2$), 5.34 (t, J=3.8 Hz, 1H, H-2), 4.88 (dd, J=7.4, 7.8 Hz, 1H, H-5), 4.60 (dd, J=7.8, 8.4 Hz, 1H, H-4b), 4.17—4.22 (m, 2H, H-6), 3.98 (dd, J=7.5, 8.4 Hz, 1H, H-4a), 2.12 (s, 3H, CH_3CO); ^{13}CNMR (CDCl3) δ: 204.75 ($CSNH_2$), 171.14 (C=O), 103.43 (C-2), 81.43 (C-5), 71.86 (C-4), 64.08 (C-6), 21.36 (CH_3); IR (KBr) ν: 3300, 3140, 2920, 1729, 1648, 1434, 1260, 1151, 1045 cm^{-1}. Anal. calcd for $C_7H_{11}NO_4S$ (205.23): C 40.97, H 5.40, N 6.82; found C 41.33, H 5.09, N 6.37.

Compound **12**: m.p. 100—102 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.49, 7.71 (2s, each 1H, $CSNH_2$), 5.25 (t, J=3.0 Hz, 1H, H-2), 4.90 (dd, J=3.8, 4.4 Hz, 1H, H-5), 4.52 (dd, J=7.8, 4.4 Hz, 1H, H-4b), 4.29 (m, 2H, H-6), 4.09 (dd, J=3.8, 7.8 Hz, 1H, H-4a), 2.13 (s, 3H, CH_3CO); ^{13}CNMR ($CDCl_3$) δ: 205.53 ($CSNH_2$), 171.98 (C=O), 104.26 (C-2), 81.86 (C-5), 72.41 (C-4), 64.77 (C-6), 22.27 (CH_3); IR (KBr) ν: 3334, 3180, 2890, 1736, 1640, 1433, 1257, 1154, 1045 cm^{-1}. Anal. calcd for $C_7H_{11}NO_4S$ (205.23): C 40.97, H 5.40, N 6.82; found C 40.60, H 5.48, N 6.35.

(±)-β-2-(2-Hydroxymethyl-1,3-dioxolan-4-yl)-1,3-thiazole-4-carboxamide (13)

Thioamide **11** (0.2 g, 0.98 mmol) was dissolved in 15 mL of ethanol and reacted with ethyl bromopyruvate (0.5 mL, 2.94 mmol) at 80 ℃ for 2 h. In the first 10 min, a deep yellow color was formed, probably associated with formation of the intermediate, which, upon further heating, turned pale yellow. After evaporation and extraction, a deep yellow residue was obtained. It was dissolved in methanolic ammonia (20 mL) and stirred at r.t. for 3 d. The solvent was evaporated and the residue was purified on a silica gel column chromatography to yield **13** as a white solid (80 mg, 36%). m.p. 114—116 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.22 (s, 1H, H-5'), 7.29, 7.06 (2s, each 1H, $CONH_2$), 5.38 (t, J=5.1 Hz, 1H, H-2), 5.22 (dd, J=5.4, 4.7 Hz, 1H, H-5), 4.33 (dd, J=5.4, 6.0 Hz, 1H, H-4b), 3.91 (dd, J=6.0, 4.7 Hz, 1H,

H-4a), 3.49—3.55 (m, 2H, H-6), 3.49 (brs, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 172.97 (C=O), 163.31 (C-2'), 150.87 (C-4'), 125.85 (C-5'), 104.80 (C-2), 75.75 (C-5), 71.54 (C-6), 63.22 (C-4); IR (KBr) ν: 3450, 3164, 2924, 1680, 1595, 1306, 1282 cm^{-1}; MS *m/z*: 230.03. Anal. calcd for $C_8H_{10}N_2O_4S$ (230.24): C 41.73, H 4.38, N 12.17; found C 41.95, H 4.48, N 11.92.

(±)-α-2-(2-Hydroxymethyl-1,3-dioxolan-4-yl)-1,3-thiazole-4-carboxamide (14)

Compound **14** was obtained from **12** by the same procedure as **13**. m.p. 111—114 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.22 (s, 1H, H-5'), 7.32, 7.16 (2s, each 1H, $CONH_2$), 5.44 (t, J=5.7 Hz, 1H, H-2), 5.37 (dd, J=6.8, 6.3 Hz, 1H, H-5), 4.58 (dd, J=6.8, 7.8 Hz, 1H, H-4b), 4.14 (dd, J=7.8, 6.3 Hz, 1H, H-4a), 3.76—3.85 (m, 2H, H-6), 3.52 (brs, 1H, OH); IR (KBr) ν: 3443, 3187, 2926, 1691, 1589, 1276 cm^{-1}; MS *m/z*: 230.11. Anal. calcd for $C_8H_{10}N_2O_4S$ (230.24): C 41.73, H 4.38, N 12.17; found: C 41.92, H 4.50, N 12.28.

5-Acetoxy-2-benzyloxymethyldioxolane (15)

LiOH • H_2O (0.72 g, 17.2 mmol) was added to a solution of ester **8** (4.2 g, 16.7 mmol) in 50 mL of THF/H_2O (4/1, *V*/*V*). The mixture was stirred at room temperature until TLC indicated the disappearance of starting material. The reaction mixture was neutralized with acetic acids and THF removed under reduced pressure. The residue was extracted with EtOAc and the organic layer was washed three times with H_2O, dried ($MgSO_4$) and evaporated to give 3.6 g (91%) of the crude acid, which was used without further purification. To a solution of the crude acid (3.6 g, 15.1 mmol) in dry acetonitrile (50 mL) were added pyridine (2.5 mL, 30.2 mmol) and $Pb(OAc)_4$ (9.3 g, 21 mmol), and the mixture was stirred at r.t. for 5 h. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was separated by column chromatography to give **15** as syrup (2.5 g, 60%). ^{1}H NMR ($CDCl_3$) δ: 7.35—7.29 (m, 5H, arom H), 6.39, 6.33 (2×dd, J=2.0, 2.3, 3.4, 3.7 Hz, 1H, H-5), 5.37, 5.28 (2×t, J=3.7, 4.0 Hz, 1H, H-2), 4.60, 4.62 (2×s, 2H, $PhCH_2O$), 4.25—3.92 (m, 2H, H-4), 3.64, 3.60 (m, 2H, H-6), 2.10, 2.03 (2×s, 3H, OAc); ^{13}C NMR($CDCl_3$) δ: 170.37 (C=O), 137.75, 128.53, 128.10, 127.86 (arom C), 103.80 (C-5), 94.58 (C-2), 73.83 ($PhCH_2O$), 70.87 (C-4), 70.17 (C-6), 21.20 (CH_3); IR(NaCl) ν: 3387, 2965, 1760, 1449, 1201, 1163, 1120 cm^{-1}. Anal. calcd for $C_{13}H_{16}O_5$ (252.27): C 61.90, H 6.39; found C 61.44, H 6.69.

(±)-1-(2-Benzyloxymethyl-1,3-dioxolan-4-yl)-4-nitroimidazole (16 and 17)

A mixture of 4-nitroimidazole (0.56 g, 5 mmol) in hexamethyldisilazane (50 mL) and ammonium sulfate (catalytic amount) was refluxed under nitrogen for 12h. The resulting clear solution was allowed to cool to room temperature and HMDS removed under reduced pressure under anhydrous condition to yield silylated 4-nitroimidazole as white crystals. Dry 1,2-dichloroethane (15 mL) was added to the silylated 4-nitroimidazole followed by the acetate **15** (0.88 g, 3.5 mmol) in dry 1,2-dichloroethane (25 mL). This suspension was cooled in an ice/water bath to 0 ℃ and treated with trimethylsilyl triflate (0.5 mL, 2.63 mmol), and the reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was poured into ethyl acetate (100 mL) and saturated $NaHCO_3$ (20 mL) solution and the resulting mixture stirred for 20 min. The organic layer was separated, washed with saturated $NaHCO_3$ (20 mL) solution and water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to yield **16** (0.47 g, 43%) and **17** (0.32 g, 29%) as white solid.

Compound **16**: m.p. 185—186 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.09 (s, 1H, imidazole H-5), 7.69 (s, 1H, imidazole H-2), 7.26—7.40 (m, 5H, arom H), 5.98 (dd, J=3.4, 0.8 Hz, 1H, H-5), 5.23 (t, J=2.7 Hz, H-2), 4.61 (s, 2H, $PhCH_2O$), 4.40—4.24 (m, 2H, H-4), 3.70—3.81 (m, 2H, H-6); IR (NaCl) ν: 3441, 3135, 2925, 1540, 1486, 1390, 1346, 1285, 1131, 1088, 1027 cm^{-1}. Anal. calcd for $C_{14}H_{15}N_3O_5$ (305.29): C 55.08, H 4.95, N 13.76; found C 54.83, H 4.64, N 13.31.

Compound **17**: m.p. 182—183 ℃; ^{1}H NMR ($CDCl_3$) δ: 7. 90 (s, 1H, imidazole H-5), 7.63 (s, 1H, imidazole H-2), 7.27—7.39 (m, 5H, arom H), 6.08 (dd, J=3.8, 1.0 Hz, 1H, H-5), 5.61 (t, J=3.0 Hz, H-2), 4.61 (s, 2H, $PhCH_2O$), 4.53—4.25 (m, 2H, H-4), 3.58—3.71 (m, 2H, H-6); IR (NaCl) ν: 3443, 3137, 2924, 1541, 1485, 1390, 1346 cm^{-1}. Anal. calcd for $C_{14}H_{15}N_3O_5$ (305.29): C 55.08, H 4.95, N, 13.76; found C 55.42, H 4.77, N 13.98.

5-Acetoxy-2-acetoxylmethyldioxolane (18)

Acetate **15** (2.3 g, 9.1 mmol) was dissolved in absolute methanol, followed by the addition of 10% Pd/C catalyst (0.4 g), hydrogen was introduced into the reaction mixture and the solution was stirred at r.t. until TLC showed completion of the reaction. The Pd/C was filtered off, and washed with MeOH repeatedly. The filtrate was evaporated and a colorless oil, which was of sufficient purity for further reaction, was obtained. It was dissolved in 20 mL of pyridine and 10 mL of acetic anhydride were added. The mixture was stirred at r.t. under nitrogen for 12 h. Solvent was removed under reduced pressure and the residue was coevaporated with toluene (3×50 mL). A yellow syrup was obtained (1.6 g, 89%). ^{1}H NMR ($CDCl_3$) δ: 6.42, 6.36 (2×dd, J=2.0, 2.4, 3.4, 3.7 Hz, 1H, H-5), 5.40, 5.33 (2×t, J=3.7, 4.4 Hz, 1H, H-2), 4.25—4.17 (m, 2H, H-4), 4.03—3.96 (m, 2H, H-6), 2.10 (2×s, 3H, OAc); IR (NaCl) ν: 2960, 1749, 1648, 1371, 1233, 1156, 1058, 1009 cm^{-1}. Anal. calcd for $C_8H_{12}O_6$ (204.17): C 47.06, H 5.92; found C 47.58, H 6.24.

(±)-1-(2-Acetyloxymethyl-1,3-dioxolan-4-yl)-4-ntroimidazole (19 and 20)

A mixture of 4-nitroimidazole (0.57 g, 5 mmol) in hexamethyldisilazane (50 mL) and ammonium sulfate

(catalytic amount) was refluxed under nitrogen for 12 h. The resulting clear solution was allowed to cool to room temperature and HMDS removed under reduced pressure under anhydrous condition to yield silylated 4-nitroimidazole as white crystals. Dry 1,2-dichloroethane (15 mL) was added to the silylated 4-nitroimidazole followed by the acetate **18** (0.71 g, 3.5 mmol) in dry 1,2-dichloroethane (25 mL). This suspension was cooled in an ice/water bath to 0 ℃ and treated with trimethylsilyl triflate (0.5 mL, 2.63 mmol), and the reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was poured into ethyl acetate (100 mL) and saturated $NaHCO_3$ (20 mL) solution and the resulting mixture stirred for 20 min. The organic layer was separated, washed with saturated $NaHCO_3$ (20 mL) solution and water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to yield **19** (0.31 g, 34%) and **20** (0.22 g, 24%) as white crystal.

Compound **19**: m.p. 204—206 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.12 (s, 1H, imidazole H-5), 7.69 (s, 1H, imidazole H-2), 6.01 (dd, J=4.6, 1.2 Hz, 1H, H-5), 5.30 (t, J=2.1 Hz, H-2), 4.47—4.40 (m, 2H, H-4), 4.20—4.39 (m, 2H, H-6), 2.12 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ: 170.3 (C=O), 148.8 (C-4'), 134.79 (C-2'), 117.40 (C-5'), 103.95 (C-2), 83.15 (C-5), 72.27 (C-4), 61.47 (C-6), 20.71 (CH_3); IR (KBr) ν: 3442, 3162, 3105, 2905, 1735, 1544, 1491, 1295, 1128, 1038 cm^{-1}. Anal. calcd for $C_9H_{11}N_3O_6$ (257.20): C 42.03, H 4.31, N 16.34; found C 41.88, H 4.73, N 16.01.

Compound **20**: m.p. 201—203 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.96 (s, 1H, imidazole H-5), 7.61 (s, 1H, imidazole H-2), 6.12 (dd, J=3.8, 2.0 Hz, 1H, H-5), 5.68 (t, J=2.8Hz, H-2), 4.58—4.44 (m, 2H, H-4), 4.02—4.14 (m, 2H, H-6), 2.13 (s, 3H, OAc); IR (KBr) ν: 3440, 3156, 2909, 1737, 1546, 1485, 1288, 1079, 1034 cm^{-1}. Anal. calcd for $C_9H_{11}N_3O_6$ (257.20): C 42.03, H 4.31, N, 16.34; found C 42.39, H 3.98, N 16.17.

(±)-β-1-(2-Hydroxymethyl-1,3-dioxolan-4-yl)-4-nitroimidazole (21)

19 (0.2 g, 0.78 mmol) was dissolved in methanolic ammonia (20 mL), and stirred at r.t. overnight. Solvent was evaporated and the residue was purified on a silic gel column chromatography to yield **21** as white crystal (0.15 g, 88%). m.p. 225—228 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.10 (s, 1H, imidazole H-5'), 7.75 (s, 1H, imidazole H-2'), 6.00 (dd, J=4.3, 1.4 Hz, 1H, H-5), 5.18 (t, J=2.4 Hz, H-2), 4.44—4.26 (m, 2H, H-4), 3.85—4.02 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ: 148.90 (C-4'), 136.28 (C-2'), 119.26 (C-5'), 107.07 (C-2), 84.36 (C-5), 73.02 (C-4), 61.60 (C-6); IR (KBr) ν: 3279, 3164, 3088, 1537, 1495, 1390, 1287, 1157, 1085 cm^{-1}; MS *m/z*: 215.56. Anal. calcd for $C_7H_9N_3O_5$ (215.17): C 39.08, H 4.22, N 19.53; found C 39.41, H 4.66, N 19.12.

(±)-α-1-(2-Hydroxymethyl-1,3-dioxolan-4-yl)-4-nitroimidazole (22)

20 (0.15 g, 0.58 mmol) was dissolved in methanolic ammonia (20 mL), and stirred at r.t. overnight. Solvent was evaporated and the residue was purified on a silic gel column chromatography to yield **22** as white crystal (0.11 g, 81%). m.p. 222—224 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.99 (s, 1H, imidazole H-5'), 7.64 (s, 1H, imidazole H-2'), 6.09 (dd, J=4.1, 1.9 Hz, 1H, H-5), 5.44 (t, J=2.4 Hz, H-2), 4.62—4.56 (m, 2H, H-4), 3.72—3.88 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ: 149.30 (C-4'), 136.62 (C-2'), 119.33 (C-5'), 106.95 (C-2), 84.87 (C-5), 73.31 (C-4), 61.44 (C-6); IR (KBr) ν: 3284, 3156, 3100, 1541, 1497, 1294, 1162, 1090 cm^{-1}; MS *m/z*: 215.03. Anal. calcd for $C_7H_9N_3O_5$ (215.17): C 39.08, H 4.22, N 19.53; found C 38.89, H 4.06, N 19.79.

(±)-1-(2-Benzyloxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole (23)

A mixture of 4,5-dicyanoimidazole (0.12 g, 1.02 mmol) in hexamethyldisilazane (10 mL) and ammonium sulfate (catalytic amount) was refluxed under nitrogen for 12 h. The resulting clear solution was allowed to cool to room temperature and HMDS removed under reduced pressure under anhydrous condition to yield silylated 4,5-dicyanoimidazole as white crystals. Dry 1,2-dichloroethane (5 mL) was added to the silylated 4,5-dicyanoimidazole followed by the acetate **15** (0.18 g, 0.7 mmol) in dry 1,2-dichloroethane (10 mL). This suspension was cooled in an ice/water bath to 0 ℃ and treated with trimethylsilyl triflate (0.1 mL, 0.52 mmol), and the reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was poured into ethyl acetate (30 mL) and saturated $NaHCO_3$ (10 mL) solution and the resulting mixture stirred for 20 min. The organic layer was separated, washed with saturated $NaHCO_3$ (20 mL) solution and water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to yield **23** as white solid (mixture of α and β isomers). Yield 82% (0.18 g). m.p. 211—213 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.32, 7.86 (2×s, 1H, imidazole H-2) 7.37—7.27 (m, 5H, arom H), 6.25, 6.12 (2×dd, J=4.3, 1.4, 2.1, 3.5 Hz, 1H, H-5), 5.68, 5.24 (2×t, J=3.7, 2.2 Hz, H-2), 4.62, 4.60 (s, 2H, $PhCH_2O$), 4.29—4.11 (m, 2H, H-4), 3.80—3.66 (m, 2H, H-6), IR (KBr) ν: 3118, 2904, 2239, 1471, 1360, 1304, 1230, 1157, 1099 cm^{-1}. Anal. calcd for $C_{16}H_{14}N_4O_3$ (310.31): C 61.93, H 4.55, N 18.05; found C 61.28, H 4.87, N 18.33.

(±)-β-1-(2-Acetyloxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole (24)

A mixture of 4,5-dicyanoimidazole (0.6 g, 5 mmol) in hexamethyldisilazane (50 mL) and ammonium sulfate (catalytic amount) was refluxed under nitrogen for 12 h. The resulting clear solution was allowed to cool to room temperature and HMDS removed under reduced pressure under anhydrous condition to yield silylated 4,5-dicyanoimidazole as white crystals. Dry 1,2-dichloroethane (15 mL) was added to the silylated 4,5-dicyanoimidazole followed by the acetate **18** (0.71 g, 3.5 mmol) in dry 1,2-dichloroethane (25 mL). This suspension was

suspension was cooled in an ice/water bath to 0 ℃ and treated with trimethylsilyl triflate (0.5 mL, 2.63 mmol), and the reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was poured into ethyl acetate (100 mL) and saturated $NaHCO_3$ (20 mL) solution and the resulting mixture stirred for 20 min. The organic layer was separated, washed with saturated $NaHCO_3$ (20 mL) solution and water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to yield **24** as mixture of α and β isomers (0.74 g, 81%). It was recrystallized from petroleum ether and ethyl acetate, and the major isomer (β) was obtained as white solid. m.p. 195—196 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.15 (s, 1H, imidazole H-2), 6.15 (dd, J=4.7, 1.0 Hz, 1H, H-5), 5.33 (t, J=2.4 Hz, H-2), 4.56—4.43 (m, 2H, H-4), 4.37—4.31 (m, 2H, H-6), 2.08 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ: 170.04 (C=O), 139.76 (C-2'), 123.59 (C-5'), 111.34 (C-4'), 107.56 (CN), 104.49 (C-2), 83.02 (C-5), 71.98 (C-4), 61.35 (C-6), 20.68 (CH_3); IR (KBr) ν: 3131, 2958, 2242, 1744, 1475, 1366, 1232, 1152, 1053 cm^{-1}. Anal. calcd for $C_{11}H_{10}N_4O_4$ (262.22): C 50.38, H 3.84, N 21.37; found C 50.65, H 3.32, N 20.90.

(±)-β-1-(2-Hydroxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole (25)

24 (0.2 g, 0.76 mmol) was dissolved in methanolic ammonia (20 mL) and stirred at r.t. overnight. Solvent was evaporated and the residue was purified on a silic gel column chromatography to yield **25** as white crystal (0.15 g, 89%). m.p. 236—237 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.52 (s, 1H, imidazole H-2), 6.61 (dd, J=1.3, 3.2 Hz, 1H, H-5), 5.17 (t, J=1.7 Hz, H-2), 4.35—4.29 (m, 2H, H-4), 3.94—4.06 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ: 140.73 (C-2'), 127.09 (C-5'), 121.79 (C-4'), 113.46 (CN), 106.03 (C-2), 84.78 (C-5), 73.81 (C-4), 61.17 (C-6); IR (KBr) ν: 3459, 3298, 3237, 2242, 1660, 1384, 1323, 1226, 1157, 1077 cm^{-1}; MS *m/z*: 220.51. Anal. calcd for $C_9H_8N_4O_3$ (220.19): C 49.09, H 3.66, N 25.45; found C 49.44, H 3.29, N 25.01.

(±)-α-1-(2-hydroxymethyl-1,3-dioxolan-4-yl)-4,5-dicyanoimidazole (26)

The mother liquor of **24** was evaporated, the residue was dissolved in methanolic ammonia (20 mL) and stirred at r.t. overnight. Solvent was evaporated and the residue was purified on a silic gel column chromatography to yield **26** as white crystal. m.p. 233—235 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.50 (s, 1H, imidazole H-2), 6.67 (dd, J=1.5, 3.3 Hz, 1H, H-5), 5.42 (t, J=2.2 Hz, H-2), 4.41—4.34 (m, 2H, H-4), 3.80—3.96 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ: 140.49 (C-2'), 127.21 (C-5'), 121.70 (C-4'), 113.23 (CN), 106.15 (C-2), 84.82 (C-5), 73.78 (C-4), 61.09 (C-6); IR (KBr) ν: 3453, 3295, 3229, 2240, 1658, 1387, 1324, 1221, 1148 cm^{-1}; MS *m/z*: 219.87. Anal. calcd for $C_9H_8N_4O_3$ (220.19): C 49.09, H 3.66, N 25.45; found C 49.56, H 3.34, N 25.87.

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