Pergamon

Tetrahedron Letters, Vol. 36, No. 45, pp. 8167-8170, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01763-1

1,3-Dioxolane C-Nucleosides: Asymmetric Synthesis of Four Stereoisomers of 2-[2-(Hydroxymethyl)-1,3-Dioxolan-5-yl)]-1,3-Thiazole-4-Carboxamide

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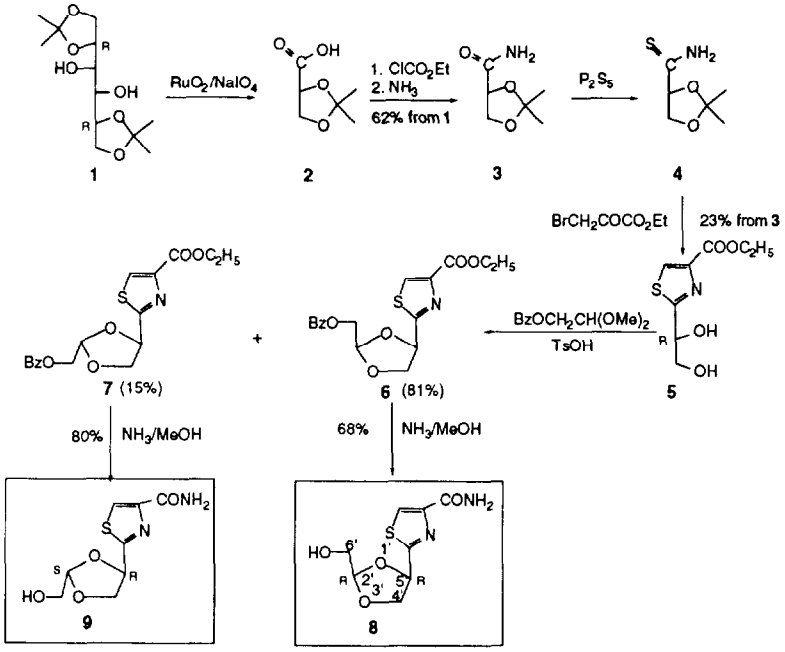
Abstract: Asymmetric synthesis of four novel C-nucleosides, (2'R,5'R)-, (2'S,5'R)-, (2'S,5'S)- and (2'R,5'S)-2-[2-hydroxymethyl)-1,3-dioxolan-5-yl]-1,3-thiazole-4-carboxamide has been accomplished by the condensation of key intermediates, 2-(1R- and 1S-glycol-1-yl)-4-ethoxycarbonyl-1,3-thiazole with 2-benzoyloxy acetaldehyde dimethyl acetal.

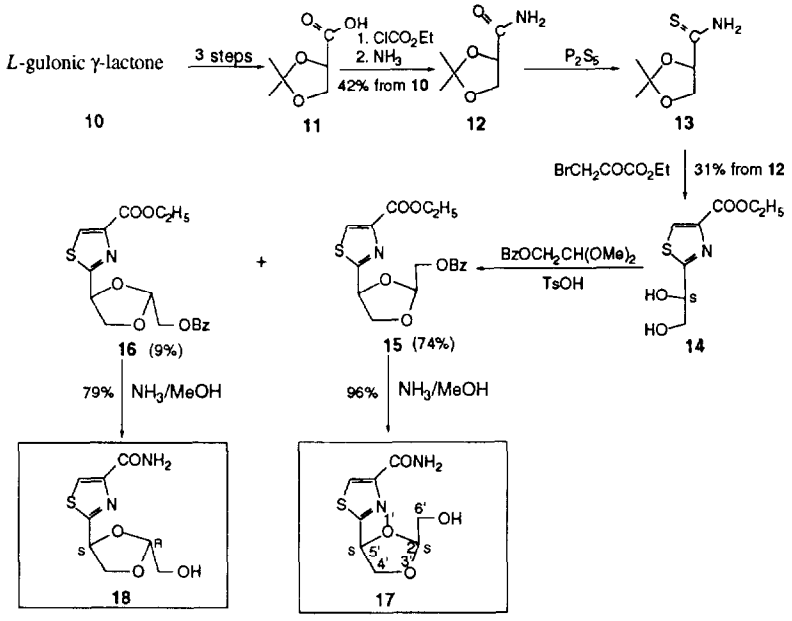
Tiazofurin, a synthetic thiazole C-nucleoside which has been undergoing phase II clinical trials against lung cancer,[5] exhibited interesting antitumor and antiviral activities.[1-4] Recently, a number of modified nucleosides with dioxolane[6-8] and oxathiolane[9-13] ring systems instead of classical ribose derivatives have been synthesized and found to show potent anti-HIV and anti-HBV activities. Among the dioxolane nucleosides, (-)-(2'R,5'R)-dioxolan-5'-yl-guanine (DG) and (2'R,5'R)-9-(dioxolan-5-yl)-2,6-diaminopurine (DAPD)[8] are currently undergoing preclinical evaluations as anti-HIV and anti-HBV agents. Based on promising biological activities of both tiazofurin and dioxolane nucleosides, we initiated the synthesis of a novel class of dioxolane C-nucleosides. Recently, in a related study we reported the asymmetric synthesis of (2'R,5'S)- and (2'S,5'R)-2-[5-(hydroxymethyl)-1,3-dioxolan-2-yl]-1,3-thiazole-4-carboxamide by the condensation of a 1,3-thiazole-4-carboxamide derivative with (S)- or (R)-glycol.[14] With this experience in constructing the chiral dioxolane ring, in this communication we wish to report the synthesis of another class of chiral 1,3-dioxolane C-nucleosides, which can be utilized for the synthesis of potential biologically active purine and pyrimidine 1,3-dioxolane C-nucleosides.

In contrast to our previous approach, in which (R)- and (S)-glycols were condensed with an appropriate heterocyclic moiety,[14] for the synthesis of the titled nucleosides, dioxolane rings were constructed by the condensation of chiral glycols, containing the heterocyclic moiety with 2-benzoyloxy acetaldehyde dimethyl acetal (Scheme 1). 1,2:5,6-O-Diisopropylidene-*D*-mannitol (**1**) was selected as starting material for the synthesis of the β-*D*-isomer, which should provide the desired stereochemistry in **8**. Compound **1** was oxidized by $NaIO_4/RuO_2$ to directly give acid **2**, which was treated with ethyl chloroformate and triethylamine in THF followed by amidation with conc. ammonium hydroxide to give **3** in 62% yield from **1**. The amide **3** was converted to a thioamide **4** by P_2S_5 in 1,4-dioxane at rt for 1 h, which, after filtration through a Celite pad, was diluted with an equal volume of EtOH and refluxed with ethyl bromopyruvate for 2 h to give a thiazole derivative **5** in 23% yield. Condensation of **5** with 2-benzoyloxy acetaldehyde dimethyl acetal, catalyzed by p-toluenesulfonic acid in benzene gave β-*D*-**6** and α-*L*-**7** after silica gel chromatographic separation with ethyl acetate in hexanes (0-40%) in 81% and 15% yields, respectively. The treatment of **6** and **7** with saturated methanolic ammonia afforded the final desired nucleosides **8**[15] and **9**[16] in good yields. The structures of **6-9** were confirmed by elemental

Scheme 1



Scheme 2



analysis, ^{1}H NMR and ^{13}C NMR experiments. Downfield chemical shift of 2'-H for the α isomer **7** (5.59 ppm) and **9** (5.21 ppm) due to the deshielding of the thiazole ring while upfield chemical shifts for the β isomer **6** (5.34 ppm) and **8** (5.02 ppm) were observed, which is another indication of the correct assignments of the structures. Single X-ray crystallographic studies of the β isomer **8** unambiguously supported the above configurational assignments (Figure 1).

By similar procedures used for **8** and **9**, the corresponding enantiomers **17**[17] and **18**[18] were also synthesized from *L*-O-isopropylidene (S)-glyceric acid (**11**), which was prepared from *L*-gulonic γ-lactone (**10**) in three steps (Scheme 2). Assignment of the structures of **17** and **18** was based on the comparison of the chemical, physical and optical data to that of the corresponding enantiomers **8** and **9**. Biological evaluation of **8**, **9**, **17** and **18** is in progress, which will be published elsewhere.

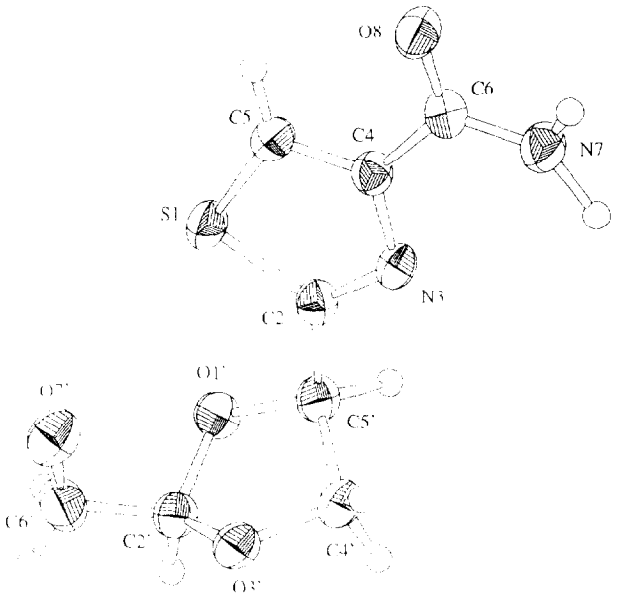


Fig. 1 ORTEP Drawing of Compound **8**

Acknowledgement: This research was supported by U.S. Public Health Service Research grants (AI 33655 and AI 32351) from the National Institute of Allergy and Infectious Diseases.

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15. **(2'R,5'R)-2-(2-Hydroxymethyl-1,3-dioxolan-5-yl)-thiazole-4-carboxamide (8)**. mp 116.5-118.5°C; $[\alpha]_D^{25}$ +59.4 (c 0.66, MeOH); UV $(H_2O)\lambda_{max}$ 237.5 nm (ε 7764, pH2), 237.5 nm (ε 8535, pH7), 237.0 nm (ε 8356, pH11); IR (KBr) 3451, 3333, 2867, 1694, 1659, 1619, 1144 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H, 5-H), 7.71, 7.55 (2s, 2H, NH_2, D_2O exchangeable), 5.41 (dd, $J_{5',4'a}$=3.6, $J_{5',4'b}$=6.8, 1H, 5'-H), 5.11 (t, J=6.0Hz, 1H, OH, D_2O exchangeable), 5.02 (t, J=4.0Hz, 1H, 2'-H), 4.24 (dd, $J_{4'b,5'}$=6.8, $J_{4'b,4'a}$=8.4Hz, 1H, 4'-H_b), 4.17 (dd, $J_{4'a,5'}$=3.6, $J_{4'a,4'b}$=8.4Hz, 1H, 4'-H_a), 3.56 (m, 2H, 6'-H). ^{13}C NMR (DMSO-d_6) δ 172.3 (C=O), 162.6 (C_2), 150.5 (C_4), 125.0 (C_5), 105.9 ($C_{2'}$), 74.7 ($C_{5'}$), 71.0 ($C_{6'}$), 62.0 ($C_{4'}$); Anal. Calcd for $C_8H_{10}NO_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93; Found: C, 41.80; H, 4.37; N, 12.21; S, 13.83; MS *m/e* 231.0 (MH+).
16. **(2'S,5'R)-2-(2-Hydroxymethyl-1,3-dioxolan-5-yl)-thiazole-4-carboxamide (9)**. mp 118-120 °C; $[\alpha]_D^{25}$+54.04 (c 0.63, MeOH); UV $(H_2O)\lambda_{max}$ 237.5 nm (ε 8444, pH2), 237.0 nm (ε 8293, pH7), 237.5 nm (ε 8603, pH11); IR (KBr) 3467, 3193, 1680, 1595, 1071 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.24 (s, 1H, 5-H), 7.73, 7.56 (2s, 2H, NH_2, D_2O exchangeable), 5.45 (dd, $J_{5',4'a}$=5.2, $J_{5',4'b}$=6.4Hz, 1H, 5'-H), 5.21 (t, J=3.6Hz, 1H, 2'-H), 5.0 (br s, 1H, OH, D_2O exchangeable), 4.41 (dd, $J_{4'b,5'}$=6.4, $J_{4'b,4'a}$=8.4Hz, 1H, 4'$_b$-H), 4.06 (dd, $J_{4'a,5'}$=5.2, $J_{4'a,4'b}$=8.4Hz, 1H, 4'$_a$-H), 3.49 (d, J=3.6Hz, 2H, 6'-H). ^{13}C NMR (DMSO-d_6) δ 171.2 (C=O), 162.5 (C_2), 150.8 (C_4), 125.0 (C_5), 105.2 ($C_{2'}$), 74.7 ($C_{5'}$), 70.4 ($C_{6'}$), 62.3 ($C_{4'}$); Anal. Calcd for $C_8H_{10}NO_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93; Found: C, 41.81; H, 4.34; N, 12.06; S, 13.85; MS *m/e* 230.8 (MH+).
17. **(2'S,5'S)-2-(2-Hydroxymethyl-1,3dioxolan-5-yl)-thiazole-4-carboxamide (17)**. mp 117-119 °C; $[\alpha]_D^{25}$-61.27 (c 0.76, MeOH); UV $(H_2O)\lambda_{max}$ 237.5 nm (ε 9087, pH2), 237.5 nm (ε 9456, pH7), 236.5 nm (ε 7716, pH11); ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1H, 5-H), 7.73, 7.58 (2s, 2H, NH_2, D_2O exchangeable), 5.43 (dd, $J_{5',4'a}$=3.6, $J_{5',4'b}$=6.7, 1H, 5'-H), 5.12 (t, J=6.0Hz, 1H, OH, D_2O exchangeable), 5.03 (t, J=4.1Hz, 1H, 2'-H), 4.25 (dd, $J_{4'b,5'}$=6.9, $J_{4'b,4'a}$=8.6Hz, 1H, 4'-H_b), 4.19 (dd, $J_{4'a,5'}$=3.6, $J_{4'a,4'b}$=8.6Hz, 1H, 4'-H_a), 3.56 (m, 2H, 6'-H). ^{13}C NMR (DMSO-d_6) δ 172.3 (C=O), 162.6 (C_2), 150.6 (C_4), 125.0 (C_5), 105.9 ($C_{2'}$), 74.6 ($C_{5'}$), 71.0 ($C_{6'}$), 62.5 ($C_{4'}$); Anal. Calcd for $C_8H_{10}NO_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93; Found: C, 41.82; H, 4.34; N, 12.06; S, 13.81; MS *m/e* 231.0 (MH+).
18. **(2'R,5'S)-2-(2-Hydroxymethyl-1,3-dioxolan-5-yl)-thiazole-4-carboxamide (18)**. mp 119-120 °C; $[\alpha]_D^{25}$-54.72 (c 0.96, MeOH); UV $(H_2O)\lambda_{max}$ 237.5 nm (ε 8806, pH2), 237.0 nm (ε 9091, pH7), 236.5 nm (ε 9106, pH11); ^{1}H NMR (DMSO-d_6) δ 8.26 (s, 1H, 5-H), 7.75, 7.60 (2s, 2H, NH_2, D_2O exchangeable), 5.47 (dd, $J_{5',4'a}$=3.2, $J_{5',4'b}$=6.3Hz, 1H, 5'-H), 5.21 (t, J=3.6Hz, 1H, 2'-H), 5.03 (br s, 1H, OH, D_2O exchangeable), 4.43 (dd, $J_{4'b,5'}$=6.4, $J_{4'b,4'a}$=8.3Hz, 1H, 4'$_b$-H), 4.08 (dd, $J_{4'a,5'}$=5.2, $J_{4'a,4'b}$=8.3Hz, 1H, 4'$_a$-H), 3.49 (d, J=3.7Hz, 2H, 6'-H). ^{13}C NMR (DMSO-d_6) δ 171.1 (C=O), 162.5 (C_2), 150.9 (C_4), 125.0 (C_5), 105.3 ($C_{2'}$), 74.7 ($C_{5'}$), 70.4 ($C_{6'}$), 62.3 ($C_{4'}$); Anal. Calcd for $C_8H_{10}NO_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93; Found: C, 41.52; H, 4.29; N, 12.04; S, 13.77; MS *m/e* 230.8 (MH+).

(*Received in USA* 16 *August* 1995; *accepted* 15 *September* 1995)