Stereoselective synthesis of 2′-purine and pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy *D*-arabitol and *D*-altritol

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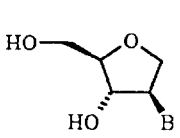
A series of 2′-purine and pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy-*D*-arabitol (1) and 1′,4′-anhydro-2′-deoxy-*D*-altritol (2) were synthesized regio- and stereo-selectively from *D*-sorbitol through some conversion in high yields.

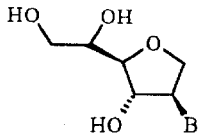
Keywords Stereoselective synthesis, 2′-isonucleosides, *D*-sorbitol

A number of nucleoside analogues have been proven to be with potential anticancer and antiviral activities.[1] Modifications in ribosyl ring result in the development of novel nucleoside derivatives with anticancer and/or antiviral activities, such as 2′,3′-dideoxynucleosides, acyclic nucleosides, carbocyclic nucleosides, nucleosides with a sugar moiety of four or six membered ring and isonucleosides *etc*.[2-8] Isonucleosides are a new kind of nucleoside analogues with the base being attached at 2′- or 3′-position of the ribose. Isonucleosides attracted much attention owing to the chemical and enzymatic stability and potential antiviral activities.[9] Some 2′-isonucleosides, 2′-purine and 2′-pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy-*D*-arabitol were synthesized from *D*-glucose and *L*-xylose.[9,10] Herein we report a convenient method of synthesizing some new 2′-isonucleosides, 2′-purine and pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy-*D*-arabitol (**1**) and 1′,4′-anhydro-2′-deoxy-*D*-altritol (**2**) from *D*-sorbitol with stereoselectivity and high yields.

As outlined in Scheme 1, the 1′,4′-anhydro-*D*-sorbitol (**3**), which was used as a chiral precursor in this protocol, was prepared from the dehydration of *D*-sorbitol and the yield was improved from 36% to 86% by careful control of the reaction temperature and the removed amount of water.[11]



1



2

The key intermediate, 5′,6′-*O*-isopropylidene-1′,4′:2′,3′-dianhydro-*D*-allitol, in which the configuration has been proved by ^{1}H-^{1}H 2D NOESY, was synthesized in 60% overall yield by the following four steps: 1) regioselective protection of the 5′,6′-dihydroxy group of **3** with acetone under acidic conditions to afford **4**; 2) regioselective benzoylation of 2′-OH with benzoyl chloride in pyridine to give **5** as a major component due to the result of the hindrance of 5′,6′-*O*-isopropylidene group; 3) methanesulfonylation of **5** on treatment with methanesulfonyl chloride in pyridine to **6** quantitatively; 4) treatment of **6** with sodium methoxide in methanol to produce the key intermediate **7** in 98% yield.

Introduction of nucleophilic bases into the modified sugar-ring to form the 2′-isonucleoside derivatives (1′,4′-anhydro-2′-deoxy-*D*-altritol derivatives) **8**[12] was proceeded under the conditions of potassium *tert*-butoxide, 18-crown-6 in DMF. Two active centers of epoxide can be substituted by nucleophilic reagents (SN_2) and the purine or pyrimidine bases prefer to attack the 2′-position to produce 2′-isonucleoside derivatives stereoselectively and the diastereoisomeric excesses (*d.e.*) of the products are 92—95% (HPLC on silica gel with eluant

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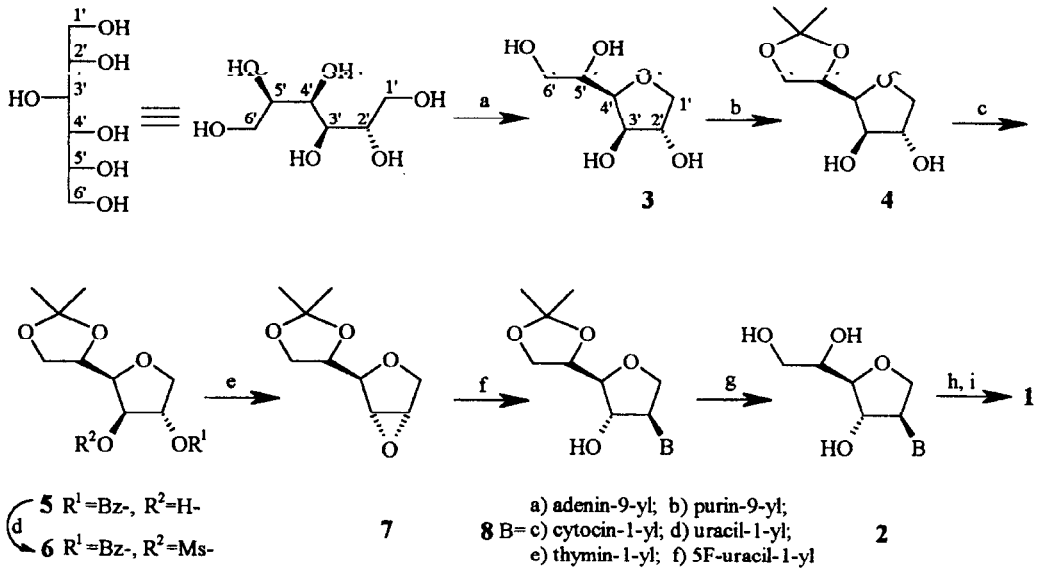
of dichloroethane-methanol, 13:1, *v/v*) owing to the hindrance of 5′,6′-*O*-isopropylidenyl group in compound **7**. The configurations of compounds **8** were confirmed to be arabinofuranose-form by the ^{1}H NMR GMQCOSY.

Scheme 1



Reagents and conditions: a) conc. H_2SO_4-H_2O/140—120℃ (86%); b) acetone-conc. H_2SO_4/RT (88%); c) benzoyl chloride-pyridine/RT (70%); d) MsCl-pyridine/RT (100%); e) $NaOCH_3$-CH_3OH/RT (98%); f) Bases, Bu^tOK, 18-crown-6, DMF/90—100℃ (30—70%); g) TFA-H_2O/RT (99%); h) $NaIO_4$-H_2O/RT (93%); i) $NaBH_4$-H_2O/RT (98%).

Removal of the isopropylidene group of **8** afforded a class of new 2′-isonucleoside derivatives, 2′-purine and pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy-*D*-altritol **2**. Compounds **2** were oxidated with sodium periodate followed by reduction with sodium borohydride to give the 2′-isonucleoside derivatives, 2′-purine and pyrimidine derivatives of 1′,4′-anhydro-2′-deoxy-*D*-arabitol **1**.

In conclusion, we have developed a stereoselective route for synthesizing 2′-isonucleosides with 15—35% overall yields. The products **1** have the same spectra with those compounds synthesized from *D*-glucose and *L*-xylose.[9,10] The structures of **1** and **2** were confirmed by Elemental Analysis, ^{1}H NMR and MS.[12] The anticancer and antiviral tests of all these new compounds are in the progress.

References and notes

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12. Selected data for compounds **8a**, **8e**, , **2a**, **2e**, and **1a**, **1e**:

8a $[\alpha]_D^{20}$, -46.2(*c* 0.8, MeOH). δ_H(AM-300 300 MHz, $CDCl_3$, TMS): 8.30 and 7.91(2 × s, each 1H, H-2,8), 7.24(br, 2H, C6-NH_2), 5.98(br, 1H, 3'-OH), 4.92(ddd, *J* = 5.9, 4.3, 4.0 Hz, 1H, H-2'), 4.53(dd, *J* = 5.0, 4.0 Hz, 1H, H-3'), 4.45(dd, *J* = 9.9, 6.1 Hz, 1H, H-1'), 4.37—4.31(m, 2H, H-5', H-1'), 4.12 (dd, *J* = 8.5, 7.0 Hz, 1H, H-6'), 3.95—3.89(m, 2H, H-6',4'), 1.32 and 1.23(2 × s, each 3H, 2 × CH_3). *m/z* (%): 322(M^+ + 1, 5), 306(M^+ - CH_3, M + 1 - NH_2, 42.3), 263(M^+ - $[CH_3]_2CO$, 29.5), 246(M^+ - 1 - $[CH_3]_2CO_2$, 24.8), 136(Adenine + 1, 100). Anal. $C_1H_{19}N_5O_4 \cdot 1/2H_2O$. Calcd: C, 50.91; H, 6.06; N, 21.21. Found: C, 50.65; H, 6.06; N, 21.15.

8e $[\alpha]_D^{20}$, -23.6(*c* 0.3, MeOH). δ_H($CDCl_3$): 9.99 (br, 1H, 3-NH), 7.44(s, 1H, H-6), 4.92(d, *J* = 5.4 Hz, 1H, H-2'), 4.44—4.38(m, 1H, H-5'), 4.29(d, *J* = 4.1, 1H, H-3'), 4.22(dd, *J* = 11.2, 5.4 Hz, 1H, H-1'), 4.11(dd, *J* = 8.4, 7.4 Hz, 1H, H-6'), 4.09(d, *J* = 11.2 Hz, 1H, H-1'), 3.85(dd, *J* = 8.4, 6.4 Hz, 1H, H-6'), 3.80(t, *J* = 4.1 Hz, 1H, H-4'), 1.91(s, 3H, 5-CH_3), 1.33, 1.30(2 × s, 2 × 3H, 2CH_3). *m/z* (%): 312(M^+, 18.4), 296(M^+ - 1 - CH_3, 39.1), 186 (M^+ - 1 - Thymin-1-yl, 7.6), 126(Thymine, 18), 101 ($C_5H_9O_2$, 100). Anal. $C_{14}H_{20}N_2O_6$. Calcd: C, 53.85; H, 6.41; N, 8.97. Found: C, 53.55; H, 6.36; N, 8.50.

2a δ_H(DMSO-d_6): 8.20(s, 1H, H-2), 8.16(s, 1H, H-8), 7.27(br, 2H, 6-NH_2), 5.68(br, 1H, 3'-OH), 5.02 (br, 1H, OH), 4.86—4.81(m, 1H), 4.55(br, 1H, OH), 4.52—4.48(m, 1H), 4.17—4.08(m, 2H), 3.71—3.61(m, 2H), 3.51—3.05(m, 2H). *m/z*(%): 282(M^+ + 1, 1.3), 264(M^+ - OH, 1.1), 250(M^+ - CH_2OH, 4.3), 162(M^+ + 1 - $C_4H_8O_4$, 29.3), 136(Adenine + 1, 100). Anal. $C_{11}H_{15}N_5O_4 \cdot 2/3H_2O$. NCalcd: C, 45.05; H, 5.57; N, 23.89. Found: C, 44.96; H, 5.22; N, 23.54.

2e δ_H(DMSO-d_6): 11.29(s, 1H, 3-NH), 7.60(s, 1H, H-6), 5.54 (br, 1H, - OH), 5.15(br, 1H, - OH), 4.78 (dt, *J* = 6.4, 3.2, 3.2 Hz, 1H), 4.63(br, 1H, - OH), 4.26(s, 1H), 3.97(dd, *J* = 10.2, 6.6 Hz, 1H), 3.87 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.74(dd, *J* = 6.4, 5.5 Hz, 1H), 3.59(dd, *J* = 5.6, 3.2 Hz, 1H), 3.44(dd, *J* = 11.0, 5.4 Hz, 1H), 3.35(dd, *J* = 11.0, 5.6 Hz, 1H), 1.75(s, 3H, 5-CH_3). *m/z*(%): 273(M^+ + 1, 3), 241 (M^+ - CH_2OH, 7.2), 211(M^+ - $C_2H_5O_2$, 3.2), 146 (M^+ - Thymine, 4.5), 126(Thymine, 100). Anal. $C_{11}H_{16}N_2O_6 \cdot 1/3H_2O$. Calcd: C, 47.48; H, 5.99; N, 10.07. Found: C, 47.48; H, 6.10; N, 9.91.

1a δ_H(DMSO-d_6): 8.20(s, 1H, H-2), 8.15(s, 1H, H-8), 7.28(br, 2H, 6-NH_2), 5.78(d, 1H, 3'-OH), 4.93 (br, 1H, OH), 4.89—4.83(m, 1H), 4.39—4.36(m, 1H): 4.19—4.07(m, 2H), 3.71—3.68(m, 1H), 3.64—3.51(m, 2H). *m/z*(%): 252(M^+ + 1, 12.6), 234(M^+ - HOH, 1.3), 162(M^+ + 1 - $C_3H_6O_3$, 25.8), 135(Adenine, 100).

1e δ_H(DMSO-d_6): 11.31(br, 1H, 3-NH), 7.55(s, 1H, H-6), 5.63(br, 1H, - OH), 4.95(br, 1H, - OH), 4.81 (dt, *J* = 7.1, 4.3 Hz, 1H), 4.11(dd, *J* = 6.0, 4.4 Hz, 1H), 3.99(dd, *J* = 10.1, 7.1 Hz, 1H), 3.83(dd, *J* = 10.0, 4.3 Hz, 1H), 3.67—3.60(m, 1H), 3.60—3.50 (m, 2H), 1.76(s, 3H, 5-CH_3). *m/z*(%): 243(M^+ + 1, 48.3), 225(M^+ - OH, 4.2), 211(M^+ - CH_2OH, 1.9), 127(Thymine + 1, 100), 116(M^+ - Thymine, 7.9).

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