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RESEARCH ARTICLE

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Synthesis of 3-*O*-methyl-D-*chiro*-inositol adenosine analogues

Abstract Using 3-*O*-methyl-D-*chiro*-inositol as starting material, the title compound **5** was synthesized by condensation of adenine and methanesulfonate **3**. Additionally, compounds **8** and **9** were prepared through the opening of the epoxide ring in **7** by adenine. The key intermediate **7** was obtained in good yield *via* an epoxidation from mono-mesylate **6**. The process of opening of epoxide ring appeared to be regioselective in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Keywords 3-*O*-methyl-D-*chiro*-inositol, carbocyclic nucleoside analogues, adenine, regioselectivity

Recently, carbocyclic nucleosides in which the oxygen atom of the sugar moiety is replaced by a CH_2 group, have emerged as a promising class of nucleosides with interesting antitumor [1] and antiviral [2] activities. Due to the absence of the glycosidic linkage between the heterocycle and the sugar, these compounds have higher metabolic stability against the nucleoside phosphorylases [3]. Among numerous carbocyclic nucleosides, a great deal of work has focused on the development of novel synthetic five-membered nucleosides possessing a satisfactory preclinical profile [4]. Nevertheless, relatively little effort have been directed towards the synthesis of six-membered carbocyclic nucleoside analogues [5]. Despite the fact that a few of six-membered carbocyclic nucleosides have been synthesized and showed potent antiviral activities [6,7], there are very few reports on the synthesis of six-membered carbocyclic nucleosides with D-pinitol (= 3-*O*-methyl-D-*chiro*-inositol) as glycosyl donor. In this paper, a very short and efficient synthetic route (Scheme 1) to three novel six-membered carbocyclic adenosine analogues from D-pinitol, which occurs ubiquitously in plants, is presented.

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1 Methods and Experimental

1.1 General methods

Column chromatography (CC) was performed on silica gel (200–300 mesh) and precoated silica-gel plates (F_{254}: Qingdao Marine Chemical Co. Ltd., 20 × 10 cm, 0.5 mm thick) were used for TLC.

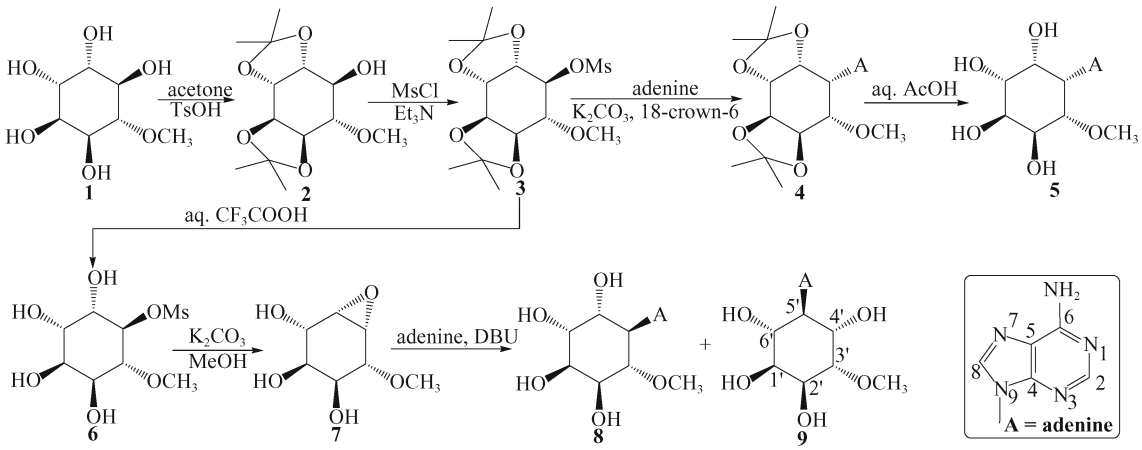
Instrumentation included an X-6 melting-point apparatus (Beijing TECH Instrument Co. Ltd.); a Nicolet Nexus 470 FT-IR apparatus (USA); a Bruker Avance-600 NMR spectrometer (δ, J in Hz); an ABI-API4000 mass spectrometer (in m/z); a Perkin Elmer 240C elemental analysis apparatus; and a Perkin Elmer 241 polarimeter.

1.2 3-*O*-Methyl-1,2:5,6-bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (**2**)

To a suspension of D-pinitol **1** (10.0 g 51.5 mmol) in DMP and acetone (200 mL, 1:3) was added *p*-TsOH (380 mg, 2.0 mmol) and $MgSO_4$ (9 g). The mixture was stirred at room temperature for 16 h, after which a homogeneous solution was obtained. Solid $NaHCO_3$ (1.00 g, 11.9 mmol) was added. The bulk of DMF and acetone was removed under reduced pressure and the residue was filtrated. The obtained filtrate was extracted with AcOEt (3 × 100 mL), the filtration residue was washed with the same solvent AcOEt. The combination of the organic extracts was washed with water and brine and dried ($MgSO_4$). The organic phase was concentrated under reduced pressure to afford 12.13 g (89%) of **2** as a white crystalline solid with mp of 95°C–96°C and $[\alpha]_D^{20}$ of −41.5°C (c 0.021 g/mL, $CHCl_3$). ^1H and ^{13}C NMR spectral data matched that reported [8].

1.3 3-*O*-Methyl-1,2:5,6-bis-*O*-(1-methylethylidene)-4-[(methylsulfonyl)oxy]-D-*chiro*-inositol (**3**)

A cold (0°C–5°C) solution of diacetonide **2** (3.0 g, 11.58 mmol) in dry pyridine (15 mL) was stirred with $MgCl_2$ (0.41 g, 2.14 mmol) for 24 h at same temperature. The reaction mixture was poured into 200 mL ice-water containing 50 mL HCl. The resulting aqueous suspension was filtered under reduced pressure, and residue was



Scheme 1 Synthetic route of title compounds **5**, **8** and **9**

washed with anhydrous EtOH till neutral to afford **3** (4.04 g, 99%) as a white solid with mp of 120°C–122°C and $[\alpha]_D^{30}$ of +72.5(c 0.3 g/mL, $CHCl_3$). IR, ^1H and ^{13}C NMR spectral data matched that reported [9].

1.4 (1′S,2′S,3′S,4′S,5′R,6′R)-3′-*O*-Methyl-1′,2′:5′,6′-bis-*O*-(1-methylethylidene)-4′-deoxy-4′-(adeine-9-yl)-D-*chiro*- inositol (**4**)

A suspension of adenine (285 mg, 2.11 mmol), NaH (80% dispersion in mineral oil, 63 mg, 2.10 mmol) and 18-crown-6 (150 mg, 0.57 mmol) in 20 mL of DMF was stirred for 4 h at 80°C. To the solution of sodium adenine, the mesylate compound **3** (600 mg, 1.7 mmol) in 5 mL of DMF was added. The reaction mixture was stirred for 2–3 days at the same temperature and the bulk DMF was removed by rotary evaporation under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and the undissolved material was removed by filtration. The filtrate was concentrated to dryness and the solid was dissolved in a small amount of CHC1$_3$/MeOH (50:1) and passed through silica gel and 140 mg (21%) of compound **4** (140 mg, 21%) was collected as white solid. mp: 215°–217°. $[\alpha]_D^{30}$ + 67.5(c 0.3 g/mL $CHCl_3$). IR (KBr): 3356, 3296, 3155, 2924, 2904, 1676, 1606, 724, 675. ^1H-NMR (600 MHz, $CDCl_3$): 8.46 (*s*, 1 H); 8.35 (*s*, 1 H); 5.18 (*dd*, *J* = 3.08, 4.34 Hz, 1 H); 4.83 (*dd*, *J* = 2.32, 7.74 Hz, 1 H); 4.72 (*dd*, *J* = 2.33, 6.94 Hz, 1 H); 4.57 (*dd*, *J* = 0.98, 6.96 Hz, 1 H); 4.53 (m, *J* = 0.80, 0.78, 0.73, 0.72 Hz, 1 H); 3.38 (*s*, MeO); 3.35 (*dd*, *J* = 1.48, 1.48 Hz, 1 H); 1.66 (*s*, Me); 1.57 (*s*, Me); 1.42 (*s*, Me); 1.31 (*s*, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 155.1; 152.6; 150.2; 143.1; 118.6; 109.8; 108.5; 80.6; 73.5; 72.9; 71.8; 71.7; 58.1 (MeO); 49.1 (C-4′); 29.7; 26.6; 25.3; 23.9. Anal. Calcd for $C_{18}H_{25}N_5O_5$: C 55.23, H 6.44, N 17.89; Found: C 55.25, H 6.42, N 17.78. ESI-MS: (MH^+) 392.4.

1.5 (1′S,2′S,3′S,4′S,5′R,6′R)-3′-*O*-Methyl-4′-deoxy-4′-(adenine-9-yl)-D-*chiro*-inositol (**5**)

A solution of fully protected 3-O-methyl-D-chiro-inositol adenine **4** (200 mg, 0.511 mmol) in 80% AcOH (10 mL) was heated at 80°C for 8 h. After cooling, the volatiles were removed by rotary evaporation. The residual acetic acid was stripped off by azeotropic distillation with toluene to give the adenine nucleoside **5** (148 mg, 87%) as a white solid, which was recrystallized with a mixture of MeOH and H_2O. The mp was 286°–289° and the $[\alpha]_D^{28}$ was +155 (*c* 0.2 H_2O). ^1H-NMR (600 MHz, DMSO-d_6): 3.22 (*s*, MeO); 3.44–3.47 (*m*, H-C(3′)); 3.72–3.75 (*m*, H-C (1′)); 3.80–3.83 (*m*, H-C(5′) and H-C(6′)); 4.05 (*d*, *J* = 2.55 Hz, H-C(2′)); 4.62 (*br. s*, D_2O exchange., OH); 4.72 (*br s*, D_2O exchange., OH); 4.96 (*m*, H-C(4′)); 5.20 (*br s*, D_2O exchange., OH); 7.22 (*br. s*, D_2O exchange., NH_2); 8.14 (*s*, H-C(8)); 8.37 (*s*, H-C(2)). ^{13}C-NMR (150 MHz, DMSO-d_6): 51.5 (C-4′); 58. 4(MeO); 67.3(C-5′); 68.3(C-2′); 69.6(C-1′); 72.0(C-6′); 83.3(C-3′); 117.7(C-5); 142.3 (C-8); 149.4(C-4); 152.3(C-2); 156.1(C-6). Anal. Calcd for $C_{12}H_{17}N_5O_5$: C 46.30, H 5.50, N 22.50; Found: C 46.44, H 5.46, N 22.61. ESI-MS: (MH^+) 312.6, (MNa^+) 334.7.

1.6 3-*O*-Methyl-4-[(mesyl-)oxy]-D-chiro-inositol (**6**)

Prepared according to the procedure [9].

1.7 3-*O*-Methyl-4,5-epoxyl-D-chiro-inositol (**7**)

Prepared according to the procedure [9].

1.8 (1′S,2′S,3′S,4′R,5′R,6′R)-3′-*O*-Methyl-4′-deoxy-4′-(adenine-9-yl)-D-*chiro*-inositol (**8**) and (1′S,2′S,3′S,4′S,5′R,6′R) -3′-*O*-Methyl-5′-deoxy-5′-adenine-9-yl)-D-*chiro*-inositol (**9**)

To a stirred suspension of **7** (544 mg, 2 mmol) and dry nucleobase (1.5 equiv.) in dry DMSO (4 mL), DBU (0.5 mL, 3.3 mmol) in 2 mL dry DMSO was added dropwise. The clear solution was stirred at 100°C for 36 h. After removal of DMSO in vacuo, the resulting brown residue was diluted with anhydrous methanol. Silica gel was added and the mixture evaporated to dryness. The dry

powder was applied to a silica gel column and eluted with chloroform-methanol to afford less polar **8** (103 mg, 17%) and more polar **9** (220 mg, 35%). Both compounds are obtained as white solids.

Data for 8: mp: 219–221°. $[\alpha]_D^{28}$ − 78.5 (*c* 0.2 H_2O). ^{1}H-NMR (600 MHz, D_2O): 3.01 (*s*, MeO); 4.03 (*dd*, *J* = 2.85, 9.68 Hz, H-C(3′)); 4.12 (*t*, *J* = 10.65 Hz, H-(4′)); 4.17–4.20 (*m*, H-C(1′) and H-C(6′)); 4.62 (*t*, *J* = 10.79 Hz, H-(5′)); 4.72–4.74 (*m*, H-C(2′)); 8.27 (*s*, H-C(8)); 8.33 (*s*, H-C (2)). ^{13}C-NMR (150 MHz, D_2O): 57.1(C-1′); 62.0 (MeO); 70.1(C-5′); 73.2(C-2′); 74.2(C-4′); 74.2(C-6′); 82.7(C-3′); 121.7(C-5); 144.9(C-8); 152.4(C-4); 155.4 (C-2); 158.5(C-6). Anal. Calcd for $C_{12}H_{17}N_5O_5$: C 46.30, H 5.50, N 22.50; Found: C 46.36, H 5.42, N 22.58. ESI-MS: (MH^+) 312.6, (MNa^+) 334.7.

Data for 9: mp: 252–256°. $[\alpha]_D^{28}$ − 32.5 (*c* 0.2 OH). ^{1}H-NMR (600 MHz, D_2O): 3.43 (*s*, 3 H, MeO); 3.69 (*dt*, *J* = 3.60, 14.57 Hz, H-C(3′)); 3.78 (*dd*, *J* = 3.3, 9.6 Hz, H-C(1′)); 4.23–4.27 (*m*, H-C(2′) and H-C(4′)); 4.37 (*t*, *J* = 10.84 Hz, H-C(5′)); 4.56 (*dd*, *J* = 3.18, 11.10 Hz, H-C(6′)); 8.06 (*s*, H-C(2)); 8.09 (*s*, H-C(8)). ^{13}C-NMR (150 MHz, D_2O): 61.3(MeO); 63.6(C-5′); 69.9(C-6′); 70. 6(C-2′); 72.1(C-4′); 73.7(C-1′); 83.8(C-3′); 121.5(C-5); 144.5(C-8); 152.2(C-4); 155.0(C-2); 158.1(C-6). Anal. Calcd for $C_{12}H_{17}N_5O_5$: C 46.30, H 5.50, N 22.50; Found: C 46.26, H 5.62, N 22.44. ESI-MS: (MH^+) 312.6, (MNa^+) 334.7.

2 Results and discussion

Firstly, we report the synthesis of adenosine **5** by the classical SN_2 type reaction between adenine and mesylate, in which the key condensation of the glycolsyl donor and adenine leads to protected nucleoside **4** in 21% yield for 2–3 days. So, opening of the epoxide ring was employed to afford 4- and 5-substituted adenosine analogues **8** and **9**. It is important to mention that the yield of 5-substituted adenosine **9** (35%) is two times higher than that of 4-substituted adenosine **8** (17%) indicating a certain regioselectivity of the epoxy-opening reaction.

Structural characterization of the adenosine analogues **8** and **9** has been done by analyzing the 1D, 2D HMQC, 2D HMBC, 2D ^{1}H–^{1}H NOESY spectra. The HMBC spectra of **9** showed the expected cross-peaks between H-8 proton and the carbon C-5′ (63.59) indicating clearly the N-9 regiochemistry of the nucleobase in amination under epoxide-opening reactions. Moreover, the NOESY spectra showed correlation between H-8 and H-4′ (4.26), H-8 and H-6′ (4.56) protons, respectively, clearly indicating that the nucleobase was above the plane of the six-membered ring (e.g. β configuration). In the same way, spectroscopic analysis of compound **8** demonstrated a similar configuration except for adenine coupling at C-4′.

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