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Note

Synthesis of azole nucleoside analogues of D-pinitol as potential antitumor agents

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Abstract—A convenient strategy is reported for the synthesis of azole nucleoside analogues of D-pinitol (=3-*O*-methyl-D-*chiro*-inositol). The key intermediate 3-*O*-methyl-4,5-epoxy-D-*chiro*-inositol was obtained in excellent yield via an epoxidation from monomethanesulfonate of D-pinitol. The process of opening of the epoxy ring by azole-bases appeared strongly regioselective in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. All newly synthesized carbocyclic azole nucleosides were assayed against lung and bladder cancer in vitro. Only the triazole and benzotriazole nucleoside analogues inhibited the growth of human lung cancer cell lines (PG) with EC_{50} of 11.3 and 22.6 μM, respectively, and showed much less inhibitory activity against human bladder cell lines (T_{24}).

Keywords: Carbocyclic azole nucleoside; D-Pinitol; 1,2,4-Triazole; Benzotriazole; Nitroindazole; Opening of epoxy ring reaction; Antitumor activity

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 antiviral and antitumor activities.[1] Due to the absence of the glycosidic linkage between the heterocycle and the sugar, these compounds have a higher metabolic stability against the nucleoside phosphorylases.[2] Natural as well as synthetic carbocyclic nucleosides such as abacavir[3] and entecavir[4] have shown interesting antitumor activities and antiviral activities against the human cytomegalovirus (HCMV),[5] herpes simplex virus (HSV),[6] hepatitis B virus (HBV),[7] and human immunodeficiency virus (HIV).[8] Based on their notable biological activities, it is not surprising that these targets have drawn substantial synthetic interest.

Another alteration to the nucleoside structure that has resulted in profound biological effects is modification of the heterocyclic base.[9] In this field, azole nucleosides were proven to be a large class of antimetabolites and have attracted considerable attention because of their broad bioactive spectrum.[10] Bredinin shows immunosuppressive properties and inhibits inosine 5′-monophosphate dehydrogenase (IMPDH) and depletes cells of guanine nucleotides.[11] Ribavirin, a broad spectrum antiviral agent, also displays antitumor activity.[12] Pyrazofurin exhibits remarkable anticancer and antiviral properties.[9,13] In addition to the above compounds, numerous other azole nucleoside analogues have also been synthesized and display strong antiviral activities, in which the base involves benzimidazole, indazole, and other azole derivatives.[12b,14] Despite significant progress, there are very few reports on the synthesis and bioactivity of carbocyclic azole nucleoside.[15]

D-Pinitol (=3-*O*-methyl-D-*chiro*-inositol) occurs ubiquitously in plants[16] and is a useful chiral starting material, as illustrated by the asymmetric synthesis of a putative insulin mediator.[17] Its structural features make it perfectly suited for the stereocontrolled synthesis of the title compounds (Scheme 1). For example, a cyclohexane ring is already present and a chiral center at C-4 and C-5 allows stereospecific introduction of the base moiety via transformation of the OH and MsO groups

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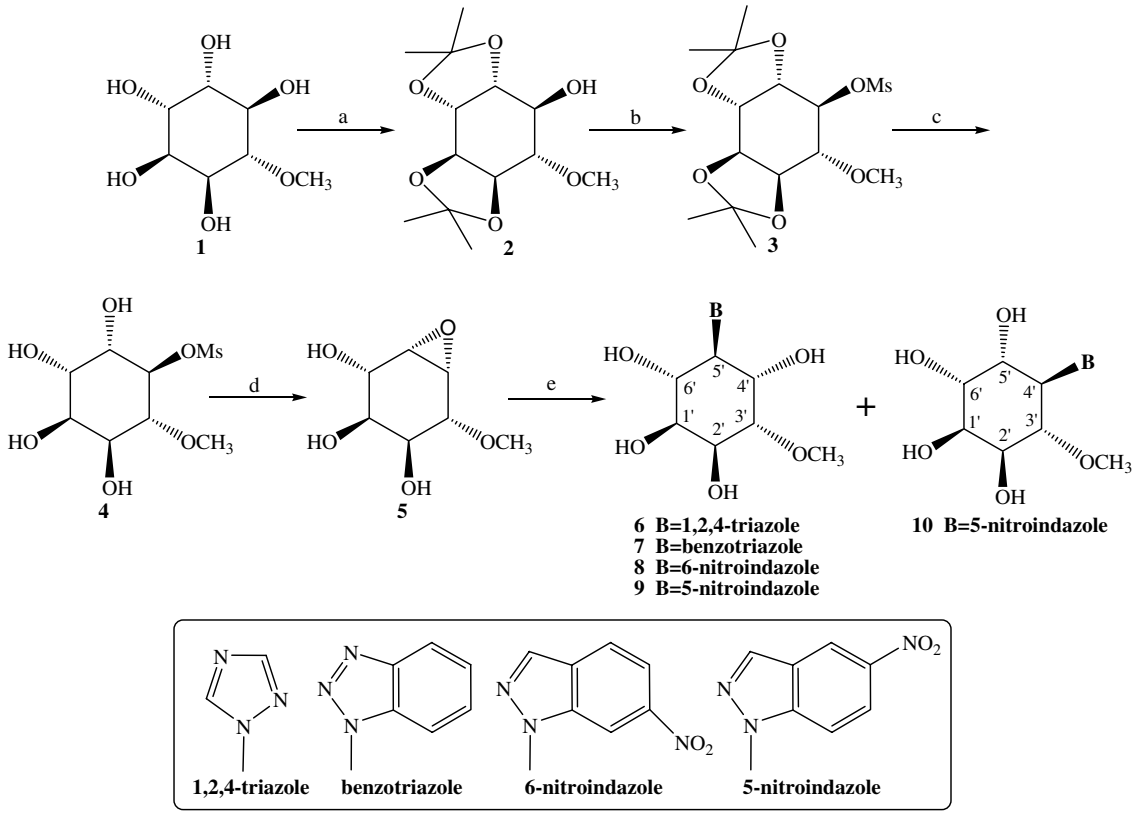

Scheme 1. Reagents and conditions: (a) DMP, acetone, *p*-TsOH, rt, 16 h, 89%; (b) MsC1, Et_3N, CH_2Cl_2, 0 °C, 24 h, 99%; (c) 75% aqueous TFA, 80 °C, 12 h, 81%; (d) anhydrous methanol, K_2CO_3, rt, 6 h, 73%; (e) azole-bases, DBU, DMSO, 90–100 °C, 48 h.

into an epoxy ring, and then regioselective opening of the epoxide by heterocyclic bases. In this paper, a very short and efficient synthetic route to novel azole nucleoside analogues of D-pinitol and their cytotoxicity effects are reported.

Diacetonide derivative **2**, a key intermediate, was synthesized according to an efficient procedure in quantitative yield,[17,18] and then mesylated to obtain methanesulfonate **3** as the glycosyl donor. Subsequently, the common intermediate, diacetonide methanesulfonate **3**, was subjected to 1-methylethylidene deprotection with aqueous CF_3COOH, and afforded mono-methanesulfonate of D-pinitol **4**, which was subsequently converted to epoxide **5** in the presence of K_2CO_3 in anhydrous MeOH[19] in 73% yield. Since most of the reactions gave very high yields, intermediates **2**, **3**, **4**, and **5** involved in the procedure could be subjected directly to the next reaction without further purification. The epoxy ring of **5** was identified from its ^1H NMR spectrum showing an upfield signal for H-4 at 3.58 ppm, a salient feature of the epoxy ring. The regioselective opening of the epoxy ring with various azole-bases was achieved in reasonable yields in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), affording the corresponding carbocyclic azole nucleosides. In the case of the glycose-base coupling reaction, a mixture of C-5′ and C-4′ isomers was theoretically produced. In fact, the reaction of triazole-bases appeared strongly regioselective, giving only the predominant C-5′ isomers **6** and **7**. On the other hand, the reaction of nitroindazole was moderate regioselective, in which the C-5′ isomers were always contaminated with small amounts of C-4′ regioisomers. As a result, the two diastereoisomers **9** and **10** were obtained as a mixture (C-5′/C-4′ = 1.71; see Table 1, entry 4), which was not isolated independently due to their similar chromatographic mobilities on RPC-18 HPLC. These results can be explained by the nucleophilicities of nitroindazole-bases being weaker than those of the triazole base owing to the high electron withdrawing effect of the $-NO_2$ group.[20]

Structural assignments of products **6**–**10** were accomplished by 1D and 2D NMR spectroscopic methods.

Table 1. Opening of epoxy ring reaction of 4,5-epoxyl-D-pinitol (**5**) with azole-bases[a]

Entry	Azole-bases	Product	Yield[b] (%)	5′/4′ Ratio
1	1,2,4-Triazole	**6**	74	+∞[c]
2	Benzotriazole	**7**	68	+∞[c]
3	6-Nitroindazole	**8**	66	+∞[c]
4	5-Nitroindazole	**9/10**	62	1.71[d]

[a] Reaction was carried out at 100 °C.
[b] Isolated yields.
[c] Isolated yields of two regioisomers.
[d] Ratio was determined by ^1H NMR analysis.