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A practical synthesis of antiviral cyclopropane nucleoside A-5021

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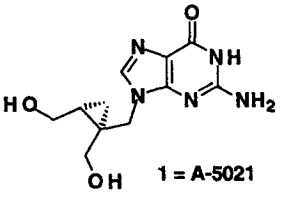
Abstract

(1′*S*,2′*R*)-9-[[1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl]guanine (A-5021, **1**) was synthesized from optically active cyclopropane lactone **2** by employing: (1) selective reduction of the ester; (2) alkylation of 2-amino-6-chloropurine; and (3) reductive opening of the lactone ring. This route eliminates the protection steps to give **1** in a good yield and is of practical value.

We have recently reported the synthesis and antiviral activity of (1′*S*,2′*R*)-9-[[1′,2′-bis(hydroxymethyl)-cycloprop-1′-yl]methyl]guanine (A-5021, **1**).[1,2] It appeared that **1** shows extremely potent antiherpetic activity against herpes simplex virus and varicella zoster virus and exhibits remarkable therapeutic efficiency over acyclovir in the animal models.[3] A-5021 (**1**) has a unique structural characteristic with two asymmetric centers on the cyclopropane ring as the acyclosugar moiety. The previous synthesis of **1** includes multiple protection/deprotection steps and is unpractical as a large scale process for further evaluation of **1** as a clinical candidate. We report here a practical route for the preparation of **1** developed by exploiting the reactivity of cyclopropane-lactone **2**.



1 = A-5021

Ethyl (1*R*,2*R*)-1,2-bis(hydroxymethyl)-1-cyclopropanecarboxylate **2**, which is prepared from chiral epichlorohydrin with high optical purity,[1,4] was used as a starting material (Scheme 1). The lactone ring of **2** is reactive under reductive and hydrolytic conditions because of the structural constraint caused by a fused cyclopropane ring. Reduction of **2** with $NaBH_4$ resulted in the reduction of the lactone ring and protection of the diol is required for further use.[1] The overall strategy for the synthetic scheme of

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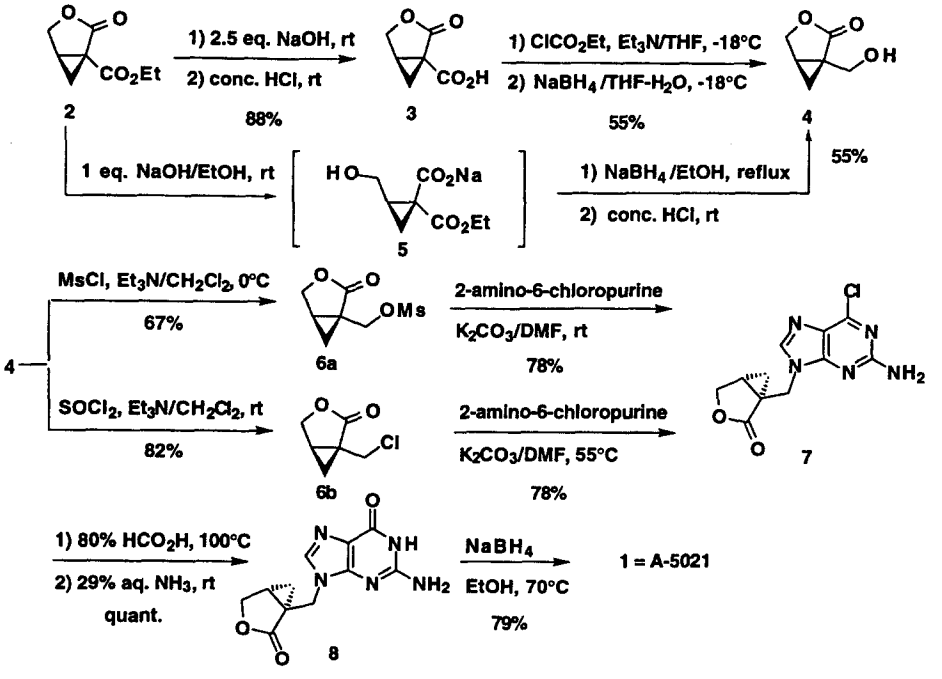
1 is to eliminate the protection steps and to use the lactone as a protective group. For that purpose, the ethyl ester moiety of **2** has to be reduced selectively. Treatment of **2** in 1N NaOH (2.5 equiv.) at room temperature for 4 h resulted in the formation of a hydroxydicarboxylic acid, which was converted into lactone-carboxylic acid **3** under acidic conditions.[5] The carboxylic acid **3** was successfully reduced to the alcohol **4** by $NaBH_4$ via the mixed anhydride at −18°C whilst keeping the reactive lactone ring intact.[6] Alternatively, the lactone moiety of **2** was selectively hydrolyzed to give the hydroxycarboxylic acid ester **5** by treatment with 1 equiv. NaOH, and subsequent reduction of **5** with $NaBH_4$ under reflux gave **4** in one-pot in 55% yield.[7]



Scheme 1.

The alcohol **4** was, then, converted to the mesylate **6a**[8] which was used for the coupling with 2-amino-6-chloropurine. The cyclopylmethyl mesylate or halide like **6** is more reactive than a normal alkyl mesylate or halide and sometime is difficult to isolate or handle.[9] They are more reactive with electron donating groups on the cyclopropane ring. The lactone group involved in **6** makes it stable during purification on chromatography. The alkylation of 2-amino-6-chloropurine by **6a** took place smoothly at room temperature with regioselectivity of 6.5:1 at positions 9 and 7, respectively.[10] Alternatively, the chloride **6b** formed by treatment with $SOCl_2$[11] also gave good results both in the formation of halide and alkylation reaction. Alkylation with **6b** required higher temperature but showed slightly better regioselectivity (7.0:1 for at positions 9 and 7).[10] Use of 2-amino-6-chloropurine as a precursor of the guanine base is better than others such as 2-amino-6-benzyloxy or 2-amino-6-diphenylcarbamoyloxypurine[12] in terms of regioselectivity of the alkylation.[13] The major alkylation product **7** was purified by chromatography and treated with 80% HCO_2H[14] to give the guanine derivative **8**. Finally, **8** was reduced with $NaBH_4$ in EtOH at 70°C to give **1** in 79% yield.[15] Reduction of **8** proceeds at room temperature, but since the solubility of **7** in EtOH is limited, reduction at higher temperatures gives better results.

Each step requires only inexpensive reagents and the overall process is shorter than the method previously reported[1] by eliminating the protection/deprotection steps. Further optimization in the reaction

conditions is required, but, this method is suitable for a large scale synthesis as well as for the synthesis of the deuterium-labeled compound. Additionally, **2** is useful as a chiral cyclopropane precursor for the other targets[4] such as unnatural amino acids. The procedure described here will also be applicable for the preparation of compounds with highly functionalized cyclopropanes.

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5. The lactone-ester **2** was treated in 1N NaOH (2.5 equiv.) for 4 h at room temperature, and conc. HCl was added to bring pH<1. The lactone-carboxylic acid **3** was purified by absorption to Sepabead SP-207 equilibrated with 0.1N HCl followed by elution with 20% MeOH to give a white solid in 88% yield. ^{1}H NMR ($CDCl_3$) δ 1.56 (dd, J=4.5, 5.6 Hz, 1H), 2.15 (dd, J=4.5, 7.8 Hz, 1H), 2.96–3.03 (m, 1H), 4.31 (d, J=9.6 Hz, 1H), 4.47 (dd, J=5.0, 9.6 Hz, 1H); FD MASS *m/z* 143 (MH^+).
6. The lactone-carboxylic acid **3** was treated with 1.2 equiv. of Et_3N and ethyl chloroformate at −18°C for 30 min in THF, and aq. solution of 3 equiv. of $NaBH_4$ was added. After stirring for 20 min at −18°C, excess of 2N HCl was added. The product was extracted and purified by silica gel chromatography to give **4** as a colorless oil in 55% yield. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, J=4.8 Hz, 1H), 1.32 (dd, J=4.8, 7.7 Hz, 1H), 2.26–2.33 (m, 1H), 3.69 (d, J=12.6 Hz, 1H), 4.05 (d, J=12.6 Hz, 1H), 4.18 (d, J=9.3 Hz, 1H), 4.34 (dd, J=4.7, 9.6 Hz, 1H); FD MASS *m/z* 129 (MH^+).
7. The lactone-ester **2** was treated with 1 equiv. of NaOH in EtOH for 16 h. Then, 5 equiv. of $NaBH_4$ was added and the mixture was refluxed for 3 h. After evaporation in vacuo, the product was treated with excess of 2N HCl for 18 h at room temperature and purified as above to give **4** in 55% yield.
8. The mesylate **6a** was prepared by treatment of **4** with 1.2 equiv. of MsCl and 1.5 equiv. of Et_3N in CH_2Cl_2 at 0°C for 21 h. **6a** was extracted at pH 7 and purified by silica gel chromatography. ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J=5.1 Hz, 1H), 1.44 (dd, J=5.1, 8.0 Hz, 1H), 2.47–2.54 (m, 1H), 3.08 (s, 3H), 4.13 (d, J=11.9 Hz, 1H), 4.21 (d, J=9.3 Hz, 1H), 4.38 (dd, J=4.8, 9.3 Hz, 1H), 4.87 (d, J=11.9 Hz, 1H).
9. We often encountered such problems especially with the halides derived from three hydroxymethyl groups on a cyclopropane ring, two of which are protected by ether-type protective groups.
10. The coupling was carried out with 1 equiv. of 2-amino-6-chloropurine, K_2CO_3 and **6** in DMF at room temperature (**6a**) or at 55°C (**6b**) for 20 h. The 7- and 9-alkylated products were separated by silica gel chromatography to give **7** as a white solid. ^{1}H NMR (CD_3OD) δ 1.16 (t, J=4.8 Hz, 1H), 1.65 (dd, J=4.8, 7.8 Hz, 1H), 2.70–2.76 (m, 1H), 4.20 (d, J=9.3 Hz, 1H), 4.29 (dd, J=4.5, 9.3 Hz, 1H), 4.37 (d, J=15 Hz, 1H), 4.69 (d, J=15.0 Hz, 1H), 8.71 (s, 1H); FD MASS *m/z* 280 (MH^+).
11. The chloride **6b** was prepared by treatment of **4** with 1.5 equiv. of $SOCl_2$ and Et_3N in CH_2Cl_2 at room temperature for 90 min. The product was extracted at pH 7 and purified by silica gel chromatography. ^{1}H NMR ($CDCl_3$) δ 1.16 (t, J=5.1 Hz, 1H), 1.47 (dd, J=5.1, 8.0 Hz, 1H), 2.35–2.42 (m, 1H), 3.48 (d, J=12.0 Hz, 1H), 4.19 (d, J=9.3 Hz, 1H), 4.27 (d, J=12.0 Hz, 1H), 4.36 (dd, J=4.5, 9.3 Hz, 1H).
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15. The alkylation product **7** was heated in 80% formic acid at 100°C for 2 h and then treated with 29% aq. ammonia for 1 h at room temperature to give **8** quantitatively. After evaporation, **8** was treated with 3 equiv. $NaBH_4$ in EtOH at 70°C for 3 h, and **1** was purified by reversed-phase chromatography.