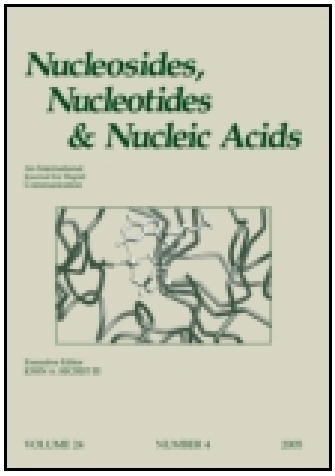

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An Economical Synthesis of Famciclovir

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AN ECONOMICAL SYNTHESIS OF FAMCICLOVIR

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ABSTRACT: An economical synthesis of famciclovir from N-2-acetyl-7-benzylguanine by a novel regioselective alkylation with the diester cyclopropane compound was developed.

We have recently developed a novel regioselective alkylation of the bromide or iodide side chain to N-2-acetyl-7-benzylguanine **1** leading eventually to famciclovir **7** which is potent anti-herpesvirus agent[1]. In order to obtain such acyclic guanine nucleoside derivatives, 2-amino-6-chloropurine is commonly used for the alkylation[2]. A problem associated with this method is that the alkylation is rarely regiospecific, and although the desired N-9 isomer is the major product, the N-7 isomer which is difficult to remove is also formed to a significant extent. From an industrial viewpoint, it should be noted that there is another serious disadvantage for using the halide as a side chain precursor due to its high production cost. In order to find a more economical synthetic pathway to famciclovir, we studied the alkylation of several side chain precursors. Among them, the readily available cyclopropane compound (6,6-dimethyl-5,7-dioxaspiro[2,5]-octan-4,8-dione) **2** was a choice of agent[3].

The alkylation of **1** was performed by heating with 3 equiv. of **2** in DMF at 60℃ for 24hrs to give the adduct **3** as a sole product which was easily obtained simply by adding ethyl acetate and filtration in 76% yield.

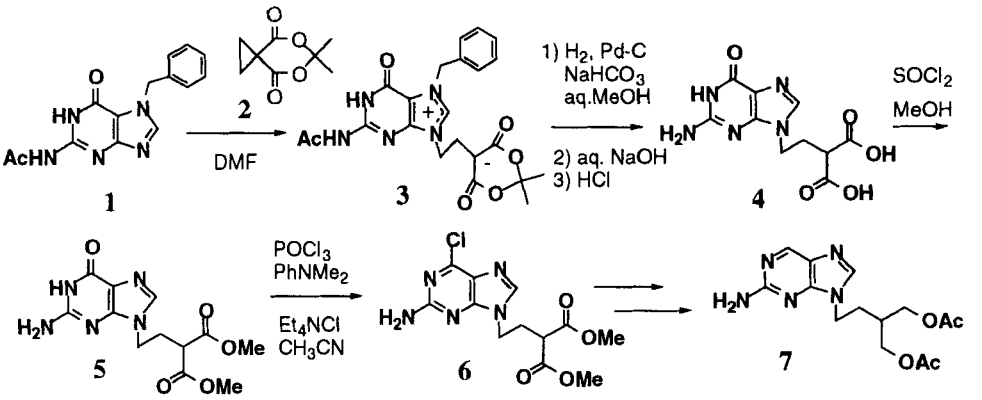
Deprotection of 7-benzyl group of **3** was achieved by catalytic hydrogenolysis in the presence of $NaHCO_3$ in aq. MeOH. After the catalyst was removed by filtration, the filtrate was concentrated and then basicified to pH 13 with aq. NaOH to remove N-2-acetyl group. After completion of the reaction, the cyclic dicarboxylic ester group was hydrolyzed at 65℃ under acidic condition (pH 2.5) with 6mol/L HCl. The mixture

was then brought to room temperature and adjusted to pH 3.5 with aq. NaOH. **4** was obtained as crystals in 90% yield after filtration.

4 was converted into the diester **5** in 94% yield by esterification with 2 equiv. of $SOCl_2$ in MeOH at 45℃ for 24hrs followed by neutralization with aq. NaOH and filtration.

The chlorination was performed by adding 4.5 equiv. of $POCl_3$ into the cooled mixture of **5**, 2 equiv. of tetraethylammonium chloride and 0.5 equiv. of N,N-dimethylaniline in MeCN followed by heating at 80℃ for 1hr. After cooling to room temperature, the mixture was evaporated to dryness and the residue was dissolved in dichloromethane and washed with aq. NaOH. The dichloromethane layer was evaporated and the residue was subjected to crystallization with MeOH. **6** was obtained as pale yellow crystals in 84% yield after filtration.

Famciclovir **7** was obtained from **6** in good yield according to the method described in the literature[3].



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