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A model study to carbocyclic formycin A and B analogues

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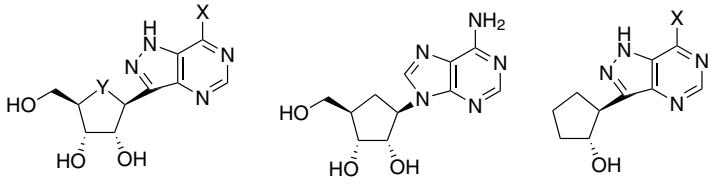
Abstract—An efficient synthesis of carbocyclic formycin analogues has been developed to serve as the foundation for the preparation of a variety of formycin-based antiviral agents.

Formycin A (**1**) and B (**2**, Fig. 1) are two naturally occurring nucleosides possessing significant antitumor and antiviral activities.[1,2] These two nucleosides, which are isomeric to adenosine and inosine, respectively, belong to the family of C-nucleosides in which the ribofuranosyl moiety is linked to the heterocyclic base by carbon–carbon bond at the anomeric center.[3] With this C-glycosidic linkage, formycins are enzymatically stable to the action of purine nucleoside phosphorylase (PNP).[3] However, the high toxicity associated with these compounds has restricted their development as potential therapeutic agents.

Carbocyclic nucleosides, where the furanose ring oxygen of the more common nucleosides is replaced by a methylene, are also stable to PNP.[4] A prominent example of this class of compounds is aristeromycin (**3**), which has shown considerable antiviral potential by inhibiting S-adenosylhomocysteine (AdoHcy) hydrolase.[5]

Combining the C-nucleoside and carbocyclic nucleoside features into one structural entity has received little attention because of the associated synthetic challenges,[6] including carbocyclic formycin (**4**).[7] Therefore, an efficient and expeditious synthetic procedure to carbocyclic C-nucleosides is desirable. In that direction, we wish to report a model study to formycin analogues **5** and **6** starting from a readily available epoxide.

Thus, addition of lithiated 3,3-diethoxy-1-propyne to cyclopentene oxide at −78 °C in the presence of $BF_3{\cdot}OEt_2$[8,9] afforded (±)-**7** (Scheme 1). Hydrolysis of (±)-**7** with a mixture of acetic acid and 10% aqueous hydrochloric acid followed by treatment of the resulting acetylenic aldehyde with hydrazine monohydrate gave a pyrazole derivative,[10–12] which was acetylated to provide the key intermediate (±)-**8**. Nitration of (±)-**8** with ammonium nitrate and trifluoroacetic anhydride in trifluoroacetic acid following literature conditions[13]



1, X=NH_2; Y=O
2, X=OH; Y=O
4, X=NH_2; Y=CH_2

3

5, X=NH_2
6, X=OH

Figure 1.

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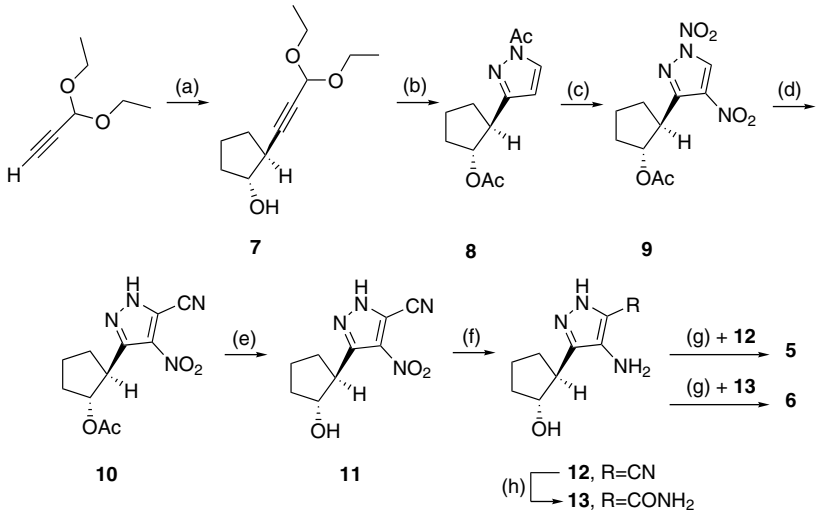

Scheme 1. Reagents and conditions: (a) i. *n*-BuLi/hexanes; ii. cyclopentene oxide, $BF_3{\cdot}Et_2O$, 64%; (b) i. 10% HCl, AcOH; ii. $N_2H_4{\cdot}H_2O$, AcOH; iii. Ac_2O, pyridine, DMAP, 73%; (c) NH_4NO_3, TFA, trifluoroacetic anhydride, 100%; (d) KCN, EtOH, 68%; (e) NaOMe, MeOH, 93%; (f) H_2, Pd/C, MeOH, 100%; (g) $HC(=NH)NH_2{\cdot}AcOH$, EtOH, 67% for **5** and 71% for **6**; (h) H_2O_2, MeOH, 77%.

resulted in the dinitropyrazole (±)-**9**. *cine*-Substitution[14] of the *N*-nitro of **9** with a cyano took place in a solution of potassium cyanide in ethanol to give nitronitrile (±)-**10**. Deacetylation of (±)-**10** to (±)-**11** was conducted in a solution of catalytic sodium methoxide in methanol. Hydrogenation of (±)-**11** in the presence of palladium/carbon afforded a quantitative amount of (±)-**12**. Treatment of (±)-**12** with formamidine acetate in refluxing ethanol proceeded with ring annulation to (±)-(1β,2α)-2-hydroxy-1-(7-aminopyrazolo-[4,3-*d*]pyrimid-3-yl)cyclopentane (**5**).[15]

Oxidation of (±)-**12** with hydrogen peroxide in methanol provided amide (±)-**13**. After refluxing (±)-**13** with formamidine acetate in ethanol, (±)-(1β,2α)-2-hydroxy-1-(7-hydroxypyrazolo[4,3-*d*]pyrimid-3-yl])cyclopentane (**6**) was obtained.[16]

In summary, an efficient means to carbocyclic formycin analogues has been developed. Application of this pathway employing more functionalized epoxides can produce a comprehensive and diverse library of carbocyclic C-nucleosides as antiviral candidates. This is being pursued in our laboratory and will be reported in due time.

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15. Compound **5**: mp 253–255 °C; ^{1}H NMR (DMSO-d_6) δ 12.40 (s, 1H), 8.16 (s, 1H), 7.29 (br s, 2H), 5.16 (s, 1H), 4.45–4.39 (m, 1H), 3.26–3.18 (m, 1H), 2.13–2.11 (m, 1H), 2.00–1.95 (m, 2H), 1.80–1.75 (m, 2H), 1.62–1.59 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 151.0, 150.5, 147.1, 139.6, 121.8, 76.7, 46.0, 33.9, 29.3, 22.0. Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.72; H, 5.98; N, 31.75.
16. Compound **6**: mp 282–284 °C; ^{1}H NMR (DMSO-d_6) δ 13.78 (br s, 1H), 12.10 (br s, 1H), 7.83 (s, 1H), 4.87 (s, 1H), 4.41–4.37 (m, 1H), 3.22–3.20 (m, 1H), 2.10–2.07 (m, 1H), 1.99–1.89 (m, 2H), 1.79–1.73 (m, 2H), 1.60–1.55 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 153.3; 148.0, 141.9, 136.7, 127.2, 76.8, 45.5, 34.1, 29.8, 22.0. Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.57; H, 5.44; N, 25.38.