Total Synthesis of 2′-Deoxy-2′-arafluorotoyocamycin and Related Nucleosides

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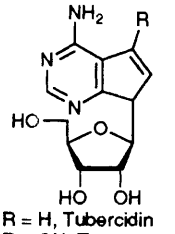
Total synthesis of 2′-deoxy-2′-arafluoro analogues of toyocamycin **11**, sangivamycin **12** and thiosangivamycin **13**, starting from 5-bromo-2-ethoxymethyleneaminopyrrole-3,4-dicarbonitrile **4** has been accomplished for the first time.

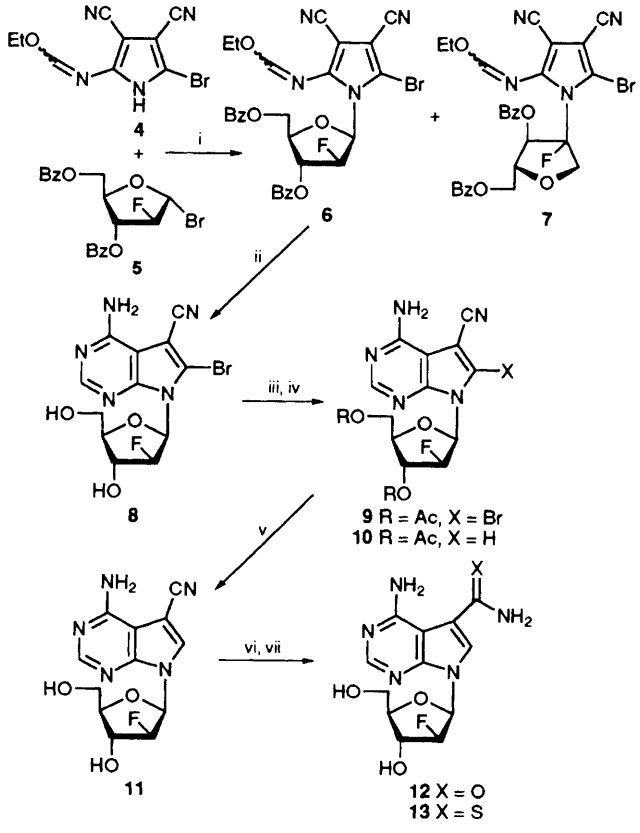
In the search for more effective antiviral agents, nucleoside analogues have been explored extensively. Since the isolation and structural elucidation of the naturally occurring pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics tubercidine **1**, toyocamycin **2** and sangivamycin **3**, a number of reports have appeared in the literature describing their biological activities and physicochemical properties.[1] Toyocamycin and sangivamycin exhibit significant antitumour activity *in vivo*.[2] In addition, the base as well as the sugar modified derivatives of **1** and **2** have shown significant antitumour/antiviral activities.[3] The sugar modifications, specifically the addition of a fluorine atom 'up' in the 2′-position makes certain purine nucleosides acid stable[4] and increases the metabolic stability by making it more resistant to hydrolysis by adenosine deaminase (ADA) as well as resistant to degradation by purine nucleoside phosphorylase (PNP).[5] Certain 5-substituted 2′-deoxy-2′-fluoroarabinosyl pyrimidine nucleosides, *e.g.* 5-iodo-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (FIAC) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (FMAU) have emerged as potent antiviral agents, active against herpes virus type 1 and type 2 (HSV-1 and HSV-2) *in vivo*.[6] This potent activity coupled with enzymatic stability, provided a good rationale for the synthesis of 2′-deoxy-2′-arafluoro nucleosides containing the pyrazolo[2.3-*d*]pyrimidine ring system.

We report herein for the first time the synthesis of novel nucleosides 2′-deoxy-2′-arafluoro analogues of toyocamycin **11**, sangivamycin **12** and thiosangivamycin **13**, starting from 5-bromo-2-ethoxymethyleneaminopyrrole-3,4-dicarbonitrile **4** *via* the sodium salt glycosylation method (Scheme 1).

Protection of the amino group of 2-amino-5-bromopyrrole-3,4-dicarbonitrile[7] was effected by treatment with triethylorthoformate in refluxing MeCN to afford the ethoxymethylene derivative **4** in quantitative yield. The sodium salt of **4** produced *in situ* by the treatment with NaH in anhydrous MeCN, was treated with 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide **5**[8] at ambient temperature. The resulting mixture containing mainly two nucleoside products was separated by silica gel column chromatography. The fast moving product with R_f = 0.41 (hexane–EtOAc; 7 : 3; *v/v*) was isolated (mp 110–111 °C, 63%) and characterized as 2-ethoxymethyleneamino-5-bromo-1-(2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-β-D-arabinofuranosyl)pyrrole-3,4-dicarbonitrile **6**.† The anomeric proton of **6** resonates at δ 6.49 as a doublet, $J_{1',2'}$ = 5.10, J_{HF} = 12.21 Hz, characteristic of the β-anomer of certain 2′-deoxy-2′-arafluoro nucleosides.[4] The slow moving nucleoside product with R_f = 0.38 was identified as the α-anomer **7** (mp 150–152 °C, 15%) and the anomeric proton resonates at δ 7.05 as a doublet of doublet, $J_{1',2'}$ = 5.61, J_{HF} = 9.3 Hz. The formation of the β- and α-anomers (**6** and **7**) indicted that the sodium salt glycosylation of **4** with **5** is not stereospecific, whereas the sodium salt glycosylation of **4** with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose in MeCN is stereospecific.[9] Treatment of **6** with MeOH–NH_3 at room temperature effected a ring annulation with concomitant removal of the benzoyl groups to afford 4-amino-6-bromo-7-(2-deoxy-2-fluoro-β-D-arabinofuranosyl-)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile **8**. Selective acetylation[10] of **8** with Ac_2O in the presence of 4-dimethylaminopyridine (DMAP) in dry DMF at −25 °C gave the 3′,5′-di-*O*-acetyl derivative **9**, which on reductive debromination[11] with 5% Pd/C in the presence of MgO under hydrogen atmosphere at 40 psi gave 3′,5′-di-*O*-acetyl-2′-deoxy-2′-arafluorotoyocamycin **10**. Deacetylation of **10** by the treatment with Na_2CO_3 in 1,4-dioxane–H_2O at room temperature furnished 2′-deoxy-2′-arafluorotoyocamycin **11**.† It was observed that deacetylation of **10** with MeOH–NH_3 at room temperature gave a 1 : 1 mixture of desired **11** and presumably 2′-deoxy-2′-arafluorotubercidin-5-methylformamidate. Treatment of **11** with NH_4OH–H_2O_2 in dioxane–MeOH–H_2O gave 2′-deoxy-2′-arafluorosangivamycin **12**. 2′-Deoxy-2′-arafluorothiosangi-vamycin **13** was obtained by the treatment of **11** with H_2S in dry pyridine in the presence of Et_3N at room temperature.



1 R = H, Tubercidin
2 R = CN, Toyocamycin
3 R = $CONH_2$, Sangivamycin



Scheme 1 *Reagents and conditions*: i, NaH, MeCN, 18 h, room temp., 63% of **6**; ii, MeOH–NH_3, room temp., 90%; iii, Ac_2O, DMF, −25 °C, 3 h, 80%; iv, 5% Pd/C, EtOH–1,4-dioxane, MgO, 40 psi, 84%; v, Na_2CO_3, H_2O, 1,4-dioxane, room temp., 72 h, 96%; vi, 30% H_2O_2, NH_4OH, 1,4-dioxane, MeOH–H_2O, room temp., 14 h, 70%; *vii*, H_2S, pyridine, Et_3N, room temp., 12 h, 93%

In conclusion, a total synthesis of 2′-deoxy-2′-arafluorotoyocamycin **11**, 2′-deoxy-2′-arafluorosangivamycin **12** and 2′-deoxy-2′-arafluorothiosangivamycin **13** was achieved for the first time in good yield *via* sodium salt glycosylation method starting from the aglycone 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile.

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Footnote

† Selected ^{1}H NMR [400 MHz, in $(CD_3)_2SO$] data for **6**: δ 1.24 (t, 3 H, OCH_2CH_3), 4.40 (m, 2 H, OCH_2CH_3), 4.69 (m, 2 H, 5′-H_2), 4.99 (dd, J_{HF} = 12.21 Hz, 1 H, 4′-H), 6.04 (tt, J_{HF} = 9.44 Hz, 1 H, 3′H), 6.33 (tt, J_{HF} = 45.49 Hz, 1 H, 2′-H), 6.49 (dd, J_{HF} = 12.21, $J_{1',2'}$ = 5.10 Hz, 1 H, 1′-H), 7.47–7.73 (m, 6 H, phenyl-H), 8.01, (4 H, orthophenyl-H), 8.57 (s, 1 H, CH=N): satisfactory elemental analysis (C, H, N, F) were obtained. For **11**: δ 3.60 (m, 2 H, 5′-H_2), 4.40 (m, 2 H, 4′-H, 3′-H), 5.0 (s, 1 H, 5′-OH), 5.63 (tt, J_{HF} = 45.36 Hz, 1 H, 2′-H), 5.99 (s, 1 H, 3′-OH), 6.40 (dd, J_{HF} = 12.36 Hz, $J_{1',2'}$ = 3.08 Hz, 1 H, 1′-H), 6.94 (br, s, 2 H, NH_2), 8.26 (s, 1 H, 6-H), 8.37 (s, 1 H, 2-H): IR (KBr) 2235 (CN); UV λ_{max}/nm (pH 1) 272 (ε 9700), 236 (11 200); λ_{max}/nm (pH 7) 272 (ε 10 100), 232 (9300); (pH 11) 270 (ε 8600), 230 (7800). For **13** δ 3.62 (m, 2 H, 5′-H_2), 4.30 (q, 1 H, 4′-H), 4.39 (tt, J_{HF} = 10.92 Hz, 1 H, 3′-H), 5.01 (t, 1 H, 5′-OH), 5.58 (tt, J_{HF} = 45.44 Hz, 1 H, 2′-H), 5.97 (d, J = 4.24 Hz, 1 H, 3′-OH), 7.94 (s, 2 H, NH_2), 7.97 (s, 1 H, 6-H), 8.15 (s, 1 H, 2-H), 9.64 (2 br s, 2 H, $CSNH_2$); IR (KBr) 1255 (C=S); UV λ_{max}/nm (pH 1) 296 (ε 7600), 242 (10 400); λ_{max}/nm (pH 7) 286 (ε 8600), 248 (7900); λ_{max}/nm (pH 11) 286 (ε 7800), 246 (7100).

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