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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.

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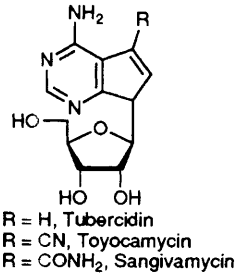
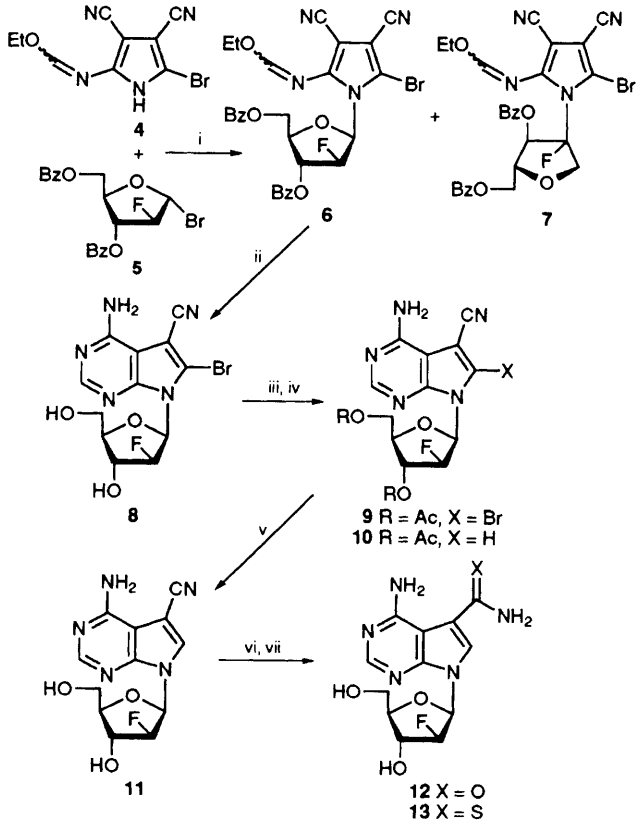
In the search for more effective antiviral agents, nucleoside analogues have been explored extensively. Since the isolation and structural elucidation of the naturally occurring pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics tubercidine **1**, toyocamycin **2** and sangivamycin **3**, a number of 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%

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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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