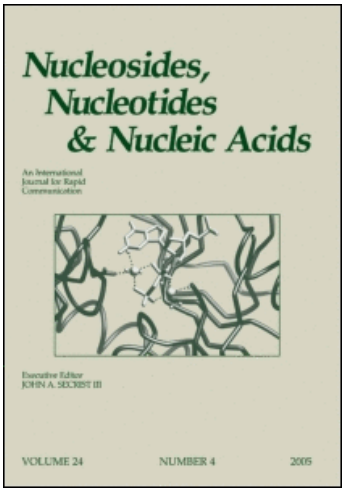

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SYNTHESIS OF CARBOCYCLIC ANALOGS OF 2',3'-DIDEOXYSANGIVAMYCIN, 2',3'-DIDEOXYTOYOCAMYCIN, AND 2',3'-DIDEOXYTRICIRIBINE

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SYNTHESIS OF CARBOCYCLIC ANALOGS OF 2′,3′-DIDEOXYSANGIVAMYCIN, 2′,3′-DIDEOXYTOYOCAMYCIN, AND 2′,3′-DIDEOXYTRICIRIBINE

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ABSTRACT

Syntheses and antiviral activity of new carbocyclic analogs of 2′, 3′-dideoxysangivamycin, 2′,3′-dideoxytoyocamycin and 2′,3′-dideoxytriciribine is described. The key intermediate, carbocyclic 4-chloro-5-iodopyrrolopyrimidine, was synthesized in good yield via a novel iodination method using I_2 and CF_3COOAg. This carbocyclic 4-chloro-5-iodopyrrolopyrimidine then allowed for a concise synthesis of the desired 4,5-disubstituted carbocyclic nucleosides.

INTRODUCTION

2′,3′-Dideoxyribofuranosides have received considerable attention as this class of nucleosides includes several compounds with potent anti-HIV activity (*e.g.* ddC and ddI)[1]. Besides the syntheses of the natural purine and pyrimidine analogs, several heterocycle-modified 2′,3′-dideoxyribofurnosides, such as the pyrrolopyrimidines 2′,3′-dideoxysangivamycin, 2′,3′-dideoxytoyocamycin[2], and the tricyclic nucleoside triciribine[3] have been synthesized. These have all demonstrated antiviral activity. We became interested in the

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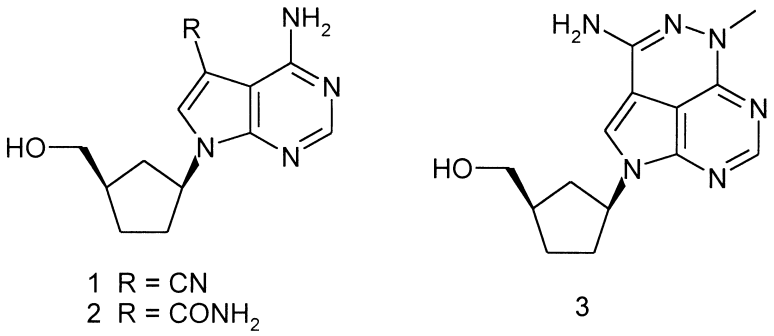


Figure 1.

synthesis of the carbocyclic dideoxy-analogs as these would have a more stable glycosidic bond. While many carbocyclic-2′,3′-dideoxynucleoside analogs have been synthesized[4], the carbocyclic analogs of 2′,3′-dideoxy-sangivamycin, 2′,3′-dideoxytoyocamycin and 2′,3′-dideoxytriciribine, have to our knowledge not been reported.

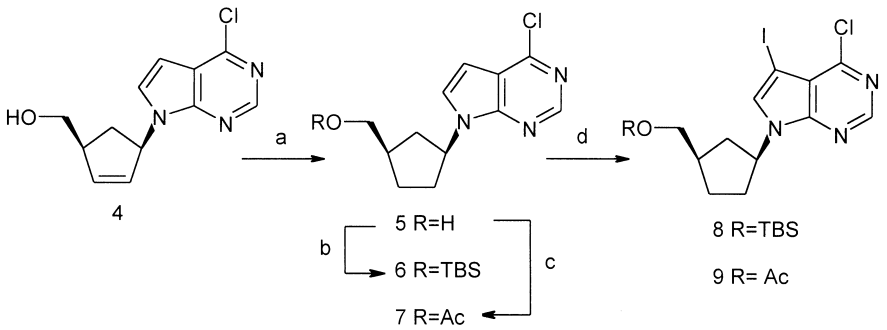
Herein we describe a facile route for the synthesis of these 4,5-disubstituted pyrrolopyrimidines (**1–3**) via a novel carbocyclic 4-chloro-5-iodopyrrolopyrimidine intermediate.

RESULTS AND DISCUSSION

Reduction of carbocyclic 4-chloropyrrolopyrimidine **4**[5] with PtO_2/H_2 as outlined in Scheme 1 gave the cyclopentane **5**[6], which was silylated or acetylated to give, respectively, **6** or **7**. Table 1 outlines several conditions for attempted iodination of the protected pyrrolopyrimidines **6** and **7**.

While iodination of furanose derivatives, corresponding to **5**, with NBS, NIS or ICl have been reported[7], these conditions were unsuccessful in iodinating the carbocycle **5** or its protected derivatives. Treatment of **5**, **6** or **7** with NIS or I_2 under various conditions resulted in no reaction, while treatment of **6** or **7** with ICl required excess reagent and was complicated by gradual formation of several byproducts. When **6** was used as the substrate, the reaction was complicated by partial loss of the silyl protecting group. Addition of potassium carbonate to neutralize the reaction conditions (entry 4 in Table 1) did not improve the yield. Similarly, when **7** was treated with ICl in the absence or presence of base (entry 5 and 6 in Table 1, respectively) the desired product **9** was isolated in only low yield[8].

Therefore, it was clear that the iodination of carbocyclic pyrrolopyrimidines required a more powerful iodination reagent than had previously been used for corresponding furanose derivatives. At this point our attention was turned to iodotrifluoroacetate[9] as a more rigorous iodonium source.



Scheme 1. Reagents and conditions: (a) PtO_2, H_2 (30 psi), EtOH, r.t. quant. (b) TBSCl, pyr, DMAP, CH_2Cl_2, r.t., 90% (c) Ac_2O, pyridine, CH_2Cl_2, r.t., 77% (d) For conditions see Table 1.

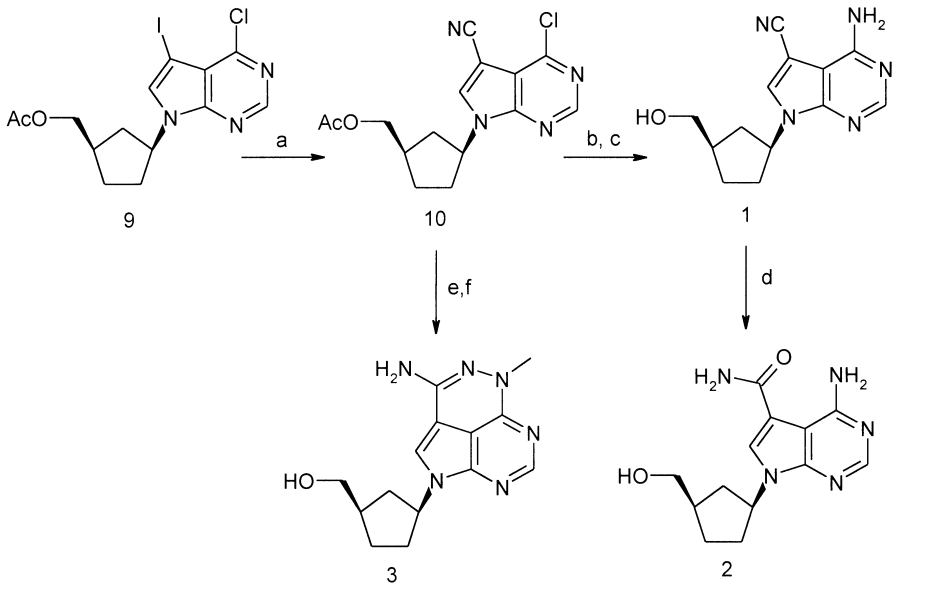
We were pleased to observe that exposure of **6** or **7** to iodine in the presence of CF_3COOAg in CH_2Cl_2 (generating CF_3COOI), gave the desired 5-iodo-pyrrolopyrimidines (**8** and **9**, respectively) consistently in 70–80% yield (entries 7 and 8 in Table 1)[10].

Subsequently, compound **9** was converted to the 4-chloro-5-cyano-pyrrolopyrimidine derivative **10** via palladium-catalyzed cross coupling with tributyltin cyanide[11]. Displacement of chlorine with ammonia followed by removal of the acetyl protecting group gave carbocyclic dideoxy-toyocamycin (**1**, Scheme 2). The carbocyclic dideoxysangivamycin (**2**) was formed in quantitative yield by treatment of **1** with H_2O_2 in aqueous ammonia. Carbocyclic dideoxytriciribine (**3**) was obtained by treating compound **10** with methylhydrazine in DMF, followed by deacetylation with potassium carbonate.

Table 1. Selected Conditions That Were Attempted for Iodination of **6** and **7**, to Yield **8** or **9**.

Entry	Starting Material	Iodinating Agent	Solvent	Other Reagents	Yield (% of 8 or 9)
1[a]	**6**	NIS	CH_2Cl_2	–	0
2[a]	**6**	I_2	CH_2Cl_2	–	0
3	**6**	ICl	CH_2Cl_2	–	< 20
4	**6**	ICl	CH_2Cl_2	K_2CO_3	< 20
5	**7**	ICl	CH_2Cl_2	–	< 10
6	**7**	ICl	CH_2Cl_2	K_2CO_3	< 10
7	**6**	I_2	CH_2Cl_2	CF_3COOAg	76
8	**7**	I_2	CH_2Cl_2	CF_3COOAg	74

[a]Also attempted using CH_3CN and DMF as solvents.



Scheme 2. Reagents and conditions: (a) Bu_3SnCN, $Pd(PPh_3)_4$, $ClCH_2CH_2Cl$, reflux, 74%, (b) NH_3(l), 70°C, 3 days, (c) NH_3/MeOH, r.t., 77% from **10**, (d) NH_4OH, H_2O_2, r.t., 99%, (e) CH_3NHNH_2, DMF, reflux, (f) K_2CO_3, MeOH, H_2O, r.t., 92% from **10**.

Antiviral testing showed that none of these derivatives had activity separate from cytotoxicity against HIV[12]. Compounds **1** and **2** had activity against HBV that was separate from cytotoxicity (for compound **1**: IC_{50} 3 μM and CC_{50} 42 μM and for compound **2**: IC_{50} 0.7 μM and CC_{50} 16 μM), while compound **3** had no activity against HBV[13]. The synthetic strategy outlined above is currently being used for preparation of additional 4,5-disubstituted carbocyclic pyrrolopyrimidines to try to identify compounds with better separation between antiviral activity and cytotoxicity.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz on Varian Unity Plus NMR spectrophotometer. The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as an internal standard. Elemental analysis were performed by Atlantic Microlab Inc. Flash column chromatography was performed using Merck Silica gel 60 (230–400 mesh), and the stated solvent system under pressure. Mass spectra were obtained on Micromass Platform mass spectrometers from Micromass Ltd., Altrincham, UK, using Electrospray Ionization.

[(1R,3S)-3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7yl)cyclopentyl]methanol (5)[6]. To a solution of [(1S,4R)-4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7yl)-2-cyclopentene-1yl]methanol (**4**[5], 2.29 g, 9.17 mmol) in ethanol was added platinum (IV) oxide (0.25 g, 0.92 mmol). The suspension was shaken at room temperature for 16 h under 30 psi of hydrogen. The catalyst was removed by filtration. Concentration of the resulting filtrate gave compound **5** (2.3 g, quant.) as a clear oil: ^{1}H-NMR ($CDCl_3$): δ 8.61 (s, 1H), 7.38 (d, 1H), 6.61 (d, 1H), 5.18 (m, 1H), 3.72 (m, 2H), 2.46-2.26 (m, 3H), 2.02-1.78 (m, 4H); MS m/z 274 (M+Na).

[(1R,3S)-3-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7yl)cyclopentyl]methyl acetate (7). To a solution of compound **5** (1.7 g, 6.75 mmol) in dry dichloromethane (15 mL) was added pyridine (5.4 mL, 67.5 mmol). Subsequently, acetic anhydride (1.0 g, 10.1 mmol) was added slowly to the reaction mixture. The mixture was stirred at room temperature for 16 h, water (30 mL) was added and the mixture stirred for additional 2 h. Ethyl acetate (100 mL) and additional water were added and the phases were separated, the organic phase washed with water and brine and dried over magnesium sulfate. Filtration and concentration followed by purification by flash chromatography (10% methanol in chloroform) gave 7 (1.52 g, 77%) as a clear oil: ^{1}H NMR ($CDCl_3$): δ 8.57 (s, 1H), 7.30 (d, 1H), 6.58 (d, 1H), 5.18 (m, 1H), 4.08 (m, 2H), 2.42 (m, 2H), 2.22 (m, 1H), 2.03 (s, 3H), 1.94 (m, 2H), 1.67 (m, 2H); MS m/z 316 (M+Na).

[(1R,3S)-3-(4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidinyl-7yl)cyclopentyl]-methyl acetate (9). Iodine (1.42 g, 5.6 mmol in 15 mL of dichloromethane) was added dropwise to a solution of 7 (1.37 g, 4.65 mmol) and silver trifluoroacetate (1.65 g, 7.46 mmol) in dichloromethane (20 mL). Addition of the iodine resulted in formation of a yellow precipitate. The resulting suspension was stirred at room temperature for 1.5 h. Filtration and concentration followed by purification by flash chromatography (5–40% ethyl acetate-hexanes) gave compound **9** (1.45 g, 74%) as a white foam: ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H), 7.44 (s, 1H), 5.15 (m, 1H), 4.08 (m, 2H), 2.40 (m, 2H), 2.23 (m, 1H), 2.04 (s, 3H), 1.91 (m, 2H), 1.64 (m, 2H); MS m/z 420 (M+H). Anal. Calcd for $C_{14}H_{15}N_3ClIO_2$: C, 40.10; H, 3.60; N, 10.01; Found: C, 40.61; H, 3.80; N 9.93.

[(1R,3S)-3-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7yl)cyclopentyl]-methyl acetate (10). Tributyltin cyanide (4.30 g, 13.6 mmol) and tetrakis(triphenylphosphine) palladium (0) (1.57 g, 1.36 mmol) were dissolved in dichloroethane (100 mL) and the resulting solution was heated at reflux for 30 minutes under nitrogen. Then **9** (2.86 g, 6.8 mmol) was added. The reaction mixture was heated at reflux for 24 h. Concentration followed by purification by flash chromatography (0–40%

ethyl acetate-hexanes) gave **10** (1.59 g, 76%) as a white crystalline solid: mp 117–119 °C; ^{1}H-NMR ($CDCl_3$): δ 8.73 (s, 1H), 8.00 (s, 1H), 5.21 (m, 1H), 4.14 (d, 2H), 2.53 (m, 2H), 2.38 (m, 1H), 2.09 (s, 3H), 2.03 (m, 1H), 1.79 (m, 2H), 1.63 (m, 1H); MS m/z 319 (M+H); IR (neat) 2235 cm^{-1} (cyano). Anal. Calcd for $C_{15}H_{15}N_4ClO_2$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.55; H, 4.72; N, 17.63.

4-Amino-7-[(1S,3R)-3-(hydroxymethyl)cyclopentyl]-7H-pyrrolo[2,3-d]-pyrimidine-5-carbonitrile (carbocyclic D-2′,3′-dideoxytoyocamycin, 1). Compound **10** (300 mg, 0.94 mmol) was placed in a steel bomb. Liquid ammonia was added to the bomb at −78 °C. The bomb was sealed and heated at 70 °C for 4 days with stirring. The bomb was subsequently cooled to −78 °C and opened. Methanol (5 mL) was added dropwise and the bomb was sealed again and allowed to stand at room temperature for 1 day. The bomb was cooled to −78 °C and opened, the methanolic ammonia was allowed to evaporate slowly as the bomb warmed to room temperature. Ethyl acetate was added and the content of the bomb poured into a separation funnel. The organic phase was washed with a saturated sodium bicarbonate solution, water and brine. The organics were dried ($MgSO_4$), filtered and concentrated to give, after purification by flash chromatography (10% methanol-ethyl acetate), compound **1** (186 mg, 77%) as a white solid: mp 195–196 °C; ^{1}H NMR (d_6-DMSO): δ 8.37 (s, 1H), 8.21 (s, 1H), 6.79 (broad s, 2H), 5.01 (m, 1H), 4.62 (m, 1H), 3.41 (m, 2H), 2.29-2.07 (m, 3H), 1.91 (m, 1H), 1.76 (m, 1H), 1.63 (m, 2H); MS m/z 258 (M+H); IR (neat) 2217 cm^{-1} (cyano). Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.36; H, 6.01; N, 26.84.

4-Amino-7-[(1S,3R)-3-(hydroxymethyl)cyclopentyl]-7H-pyrrolo[2,3-d]-pyrimidine-5-carboxamide (carbocyclic D-2′,3′-dideoxysangivamycin, 2). To a solution of compound **1** (18 mg, 0.07 mmol) in methanol (1 mL) was added 30% ammonium hydroxide (1 mL). The solution was cooled to 0 °C and 30% aqueous hydrogen peroxide (0.1 mL) was added. The reaction mixture was warmed to room temperature and stirred for 1 h. The solvent was removed under reduced pressure to give, after recrystallization from methanol, **2** as a crystalline solid (20 mg, quant): mp > 250 °C (dec.); ^{1}H-NMR (d_6-DMSO): δ 8.80 (broad s), 8.09 (s, 1H), 8.01 (s, 1H), 7.78 (broad s, 1H), 7.19 (broad s, 2H), 4.93 (m, 1H), 4.56 (m, 1H), 3.37 (m, 2H), 2.21-2.06 (m, 3H), 1.75 (m, 2H), 1.59-1.47 (m, 2H); MS m/z 276 (M+H). Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.53; H, 6.23; N, 25.19.

[(1R,3S)-3-(5-amino-3-methyl-1,3,4,6,8-pentaazaacenaphthylen-1(3H)-yl)-cyclopentyl]methanol (carbocyclic D-2′,3′-dideoxytriciribine, 3). To a solution of compound **10** (400 mg, 1.25 mmol) in dry DMF (20 mL) was

added methyl hydrazine (0.17 mL, 3.14 mmol). The reaction mixture was heated at reflux for 4 h, then cooled to room temperature. The reaction mixture was concentrated, followed by purification with flash chromatography (10% methanol-chloroform) to give 348 mg (85%) of [(1R,3S)-3-(5-amino-3-methyl-1,3,4,6,8-pentaazaacenaphthylen-1(3H)-yl)cyclopentyl]methyl acetate: ^{1}H-NMR ($CDCl_3$): δ 7.79 (s, 1H), 6.50 (s, 1H), 4.88 (broad s, 2H), 4.66 (m, 1H), 3.84 (m, 2H), 3.29 (s, 3H), 2.18 (m, 2H), 2.02 (m, 1H), 1.82 (s, 3H), 1.80-1.65 (m, 2H), 1.43 (m, 2H). The acetate derivative was dissolved in methanolic ammonia (1 M, 5 mL) and the solution was stirred at 40 °C for 2 days in a sealed tube. Removal of volatiles, followed by purification by flash column chromatography (5–20% methanol-chloroform) gave **3** (295 mg, 97%) as a yellow hygroscopic foam: ^{1}H-NMR ($CDCl_3$): δ 8.13 (s, 1H), 6.63 (s, 1H), 4.80 (m, 1H), 4.38 (broad s, 2H), 3.65 (m, 2H), 3.48 (s, 3H), 3.42 (s, 1H), 2.38 (m, 1H), 2.27 (m, 1H), 2.16 (m, 1H), 2.02 (m, 1H), 1.85 (m, 1H), 1.78 (m, 2H); MS m/z 287 (M+H). Anal. Calcd for $C_{14}H_{18}N_6O$: C, 58.73; H, 6.34; N, 29.35. Found: C, 58.49; H, 6.31; N, 29.25.

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