Total and Stereospecific Synthesis of 2′-Deoxycadeguomycin

Kandasamy Ramasamy, Roland K. Robins, and Ganapathi R. Revankar*

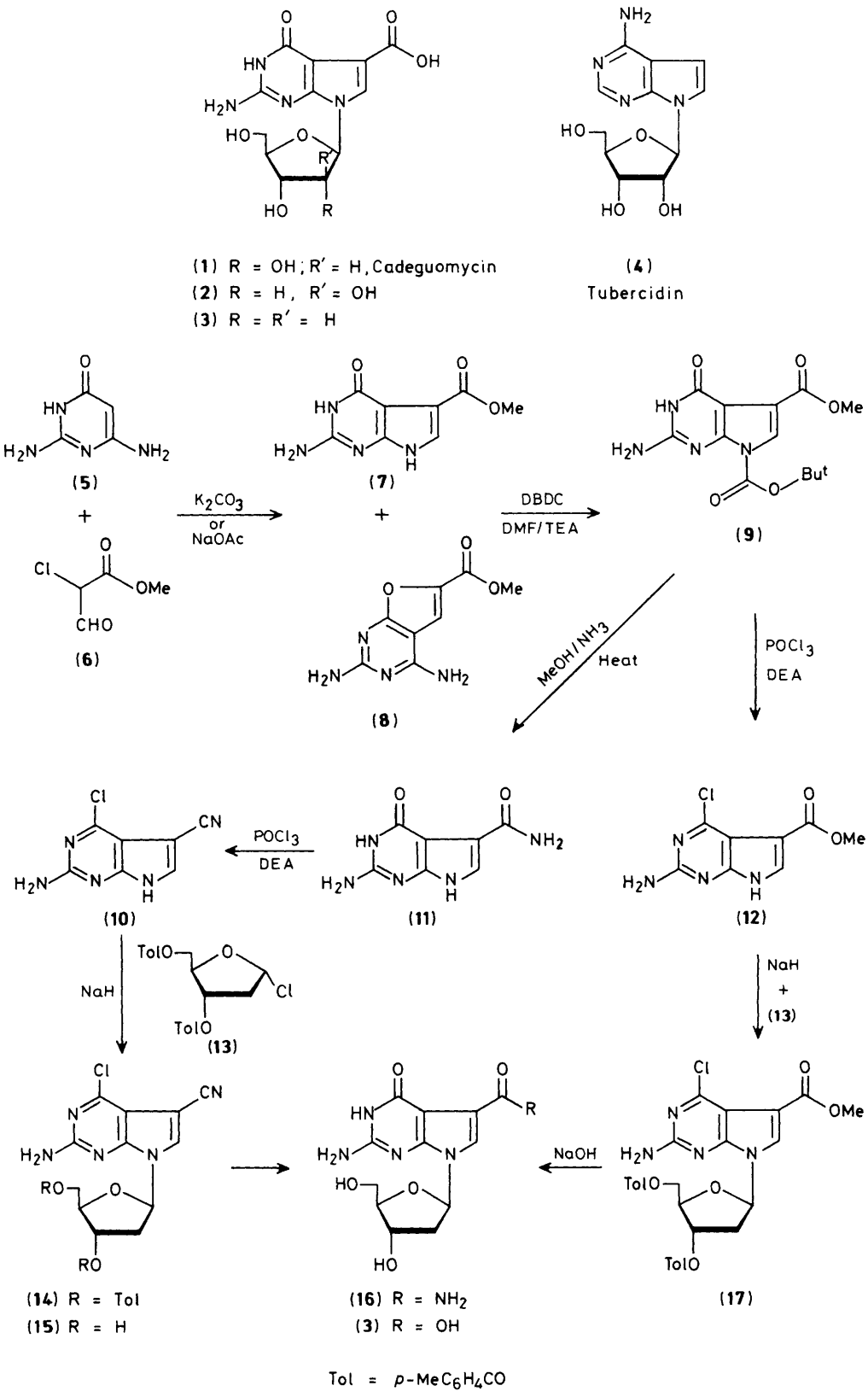
Department of Medicinal Chemistry, ICN Nucleic Acid Research Institute, 3300 Hyland Avenue, Costa Mesa, CA 92626, U.S.A.

An efficient and stereospecific synthesis of 2′-deoxycadeguomycin (**3**) from the novel 7-deazapurine derivatives 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**10**) or methyl 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**12**) has been accomplished.

Cadeguomycin (**1**) is a novel nucleoside antibiotic isolated recently[1] from the culture broth of *Streptomyces hygroscopicus* IM7912T as a minor component together with tubercidin (**4**), and characterized as 2-amino-4-oxo-3,4-dihydro-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid.[2] This nucleoside inhibited the growth of solid IMC carcinoma and pulmonary metastasis of Lewis lung carcinoma in mice with appreciably low toxicity.[3] It also enhanced cell-mediated immunity and macrophage activity.[3] Cadeguomycin displayed a unique property of enhancing uptake of pyrimidine nucleosides into K562 human myelogenous leukaemic cells and YAC-1 murine lymphoma cells, and it potentiated cytotoxicity of ara-C[3—5] as well as 5-fluoro-2′-deoxycytidine[6] both *in vitro* and *in vivo*. This interesting and potent activity, coupled with its biogenetic relationship with guanosine, resulted in the multistep syntheses of cadeguomycin[7—9] and *ara*-cadeguomycin (**2**).[10] However, the synthesis of 2′-deoxycadeguomycin (**3**) has not yet been realized. We now report the first stereospecific and total synthesis of (**3**) from the hitherto inaccessible aglycones 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**10**) or methyl 2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine-5-carboxylate (**12**).

Our approach was to build the substituted pyrrole ring onto a preformed 2,6-diaminopyrimidin-4(3*H*)-one (**5**) so that the pyrrolo[2,3-*d*]pyrimidine precursor (**7**) thus generated could then be transformed to either (**10**) or (**12**). Thus, treatment of (**5**) with methyl formylchloroacetate (**6**)[11] in dimethylsulphoxide (DMSO) containing K_2CO_3 gave a mixture of the carboxylates (**7**) (m.p. >300 °C, 40%) and (**8**) (m.p. 283—285 °C, 25%) (Scheme 1).† However, heating an aqueous solution of (**5**) and (**6**) with NaOAc for 1 h increased the yield of the desired major product (**7**) to 50%. Although pure (**7**) and (**8**) could be separated from the mixture on a small scale (<100 mg) by fractional crystallization [the less soluble (**7**) crystallizes first from MeOH], attempted large scale separation resulted in co-crystallization of (**7**) and (**8**). The problem was, however, resolved by selective protection of the pyrrole ring NH-proton in (**7**) with di-t-butyl dicarbonate (DBDC) in dimethylformamide (DMF)–triethylamine (TEA) to give (**9**) (m.p. 250 °C, 65%), followed by filtration of (**9**) from the insoluble (**8**) in boiling EtOAc. The appearance of the vinyl proton in the ^{1}H n.m.r. spectrum of (**9**) as a singlet at δ 7.54

† All new compounds reported here exhibited spectra (u.v., i.r., ^{1}H and ^{13}C n.m.r.) in full accord with assigned structures and gave satisfactory elemental analyses.



Scheme 1

[*vs.* a doublet at δ 7.35 of (**7**)] indicated N-7 as the site of the t-butoxycarbonyl protecting group in (**9**).

The evidence that the minor product (**8**) is not the isomeric pyrrolo[2,3-*d*]pyrimidine was obtained by observing two sets of exchangeable protons (2H each for two NH_2 groups) at δ 6.53 and 7.31 in the ^{1}H n.m.r. spectrum, and appearance of a downfield singlet vinyl proton at δ 7.62 [compared to a doublet at δ 7.35 of (**7**)], which is characteristic of a furo[2,3-*d*]pyrimidine ring system.[12] Formation of such a substituted furo[2,3-*d*]pyrimidine in the reaction of (**5**) with α-halogeno ketones has been documented in the literature.[12] The position of the methoxycarbonyl group in (**8**) was assigned as C-6 on the basis of the ^{13}C n.m.r. spectrum.[12] The C-5 carbon peak at δ 114.09 splits into a doublet upon off-resonance decoupling, while C-6 (δ 136.31) remains as a singlet, thus placing the methoxycarbonyl group at C-6 in (**8**).

Heating of (**9**) with $POCl_3$ in the presence of *N*,*N*-diethylaniline (DEA) gave (**12**) (m.p. >280 °C, 20%). The low yield of (**12**) from (**9**) prompted us to investigate an alternative intermediate for the synthesis of (**3**). Reaction of (**9**) with MeOH/NH_3 (saturated at 0 °C) at 120 °C gave the amide (**11**) (m.p. >300 °C, 73%), which on treatment with $POCl_3$/DEA at reflux temperature gave (**10**) (m.p. >300 °C, 40%).

Using our sodium salt glycosylation method,[13] the sodium salt of (**10**), generated *in situ* by treatment with sodium hydride (60% in oil), was reacted with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**13**)[14] in anhydrous MeCN to give the protected nucleoside (**14**) (m.p. 169—171 °C, 75%). Deprotection of (**14**) with MeOH/NH_3 furnished the nitrile (**15**) (m.p. 246—248 °C, 88%). Treatment of (**15**) with NH_4OH/H_2O_2 provided (**16**) (m.p. 258—260 °C, 74%). The formation of (**16**) is of particular interest since the base treatment of (**15**) under mild conditions not only converted the nitrile function to the carboxamide group but also concomitantly hydrolysed the chloro group. Finally the synthesis of the target 2′-deoxycadeguomycin (**3**) (m.p. >310 °C, decomp., 64%)‡ was accomplished by heating (**16**) with 5 M KOH solution, followed by acidification.

A similar glycosylation of the sodium salt of (**12**) with (**13**) provided the protected nucleoside (**17**) (m.p. 191—193 °C, 87%), which on saponification with 2 M NaOH, followed by neutralization, afforded an alternative route to (**3**) (67%). The anomeric proton of (**3**) appeared as a triplet in the ^{1}H n.m.r. spectrum centred at δ 6.30 with a peak width of 14 Hz, which is similar to that observed for the anomeric proton of 2′-deoxy-7-deazaguanosine.[15] The glycosylation site was established as N-7 by comparison of the u.v. spectrum of (**3**) with that reported[2] for cadeguomycin, which were virtually identical.

In conclusion, a total and stereospecific synthesis of 2′-deoxycadeguomycin (**3**) and certain related nucleosides was achieved for the first time using the novel pyrrolo[2,3-*d*]pyrimidines (**10**) and (**12**). The aglycones (**10**) and (**12**) should prove to be useful for the synthesis of related natural 7-deazapurine nucleoside antibiotics.

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‡ ^{1}H n.m.r. (300 MHz, in CD_3SOCD_3) of (**3**): δ 6.30 (t, 1H, 1′-H, $w_{\frac{1}{2}}$ 14.0 Hz), 6.77 (br. s, 2H, NH_2), 7.80 (s, 1H, 6-H), 11.61 (br. s, 1H, N-3-H), 14.13 (s, 1H, CO_2H), and other sugar protons; u.v.: $\lambda_{max.}$ (pH 1 and 7) 232 nm (ε 25 700), 270 (8200), 297 (9300); $\lambda_{max.}$ (pH 11) 267 nm (ε 11 600); satisfactory elemental analyses were obtained.

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