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Synthesis of paromomycin derivatives modified at C(5″) to selectively target bacterial rRNA

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—The furanosyl moiety (ring III) of C(6′)-deoxyparomomycin and paromomycin was modified in search of aminoglycoside antibiotics with altered selectivity. The key intermediates were the *N*-Boc-protected derivative of C(6′)-deoxyparomomycin and the benzylidene-protected paromomycin. Their $H_2C(5'')$–OH group was oxidised with trichlorocyanuric acid or [bis(acetoxy)iodo]-benzene in the presence of catalytic amounts of TEMPO to yield the corresponding aldehydes and acids, which were transformed into the protected alkoxy imines, amides and the amine. Standard deprotection gave the title compounds derived from C(6′)-deoxyparomomycin and derived from paromomycin that proved less active than paromomycin and its C(6′)-deoxy analogue.

Keywords: Aminoglycoside antibiotics; Paromomycin; Selectivity; Oxidation; Oxime; Carboxamide; Mycobacterium smegmatis

1. Introduction

Paromomycin, a broad-spectrum aminoglycoside antibiotic,[1,2] binds to the 16S rRNA at the tRNA acceptor A site and impairs the translation process by causing misreading and by hindering translocation.[3–6] The selectivity of paromomycin, that is the discrimination between prokaryotic and eukaryotic ribosomes, and of aminoglycoside antibiotics in general, is significantly limited by the cross-species conservation of the structure of the decoding site of prokaryotic and eukaryotic ribosomes[7,8] with the consequence of significant drug-associated toxicity.[9,10] Experimental results of the interactions between aminoglycosides and mutated A-sites indicate that rRNA sequence differences largely account for the selectivity of aminoglycosides with respect to bacterial and human ribosomes.[11–17] Modifications of strategic structural elements of aminoglycoside antibiotics, or structure based design of new drugs have thus been pursued to obtain antibiotics that discriminate between prokaryotic and eukaryotic rRNA,[18–24] and recent key insights into the crystal structure of the complex formed by paromomycin and the 16S rRNA A-site[25–29] allow for a rational approach to such modifications. Thus, bacterial ribosomes possess a guanine base (G) at position 1491 (numbered according to the *E. coli* sequence), while eukaryotic cytoplasmic ribosomes are characterised by 1491A and mitochondrial ones by 1491C.[11,12,28,30–32] The above mentioned crystal structure shows a distance between C(5″)–O and N(7) of 2.41 Å, indicating that C(5″)–OH of ring III of paromomycin forms a hydrogen bond to N(7) of G1491 in the bacterial ribosome. In eukaryotic cytoplasmic ribosomes, there may be a corresponding hydrogen bond between C(5″)–OH and N(7) of A1491. We planned to impair the (speculative) interaction of paromomycin with N(7) of A1491 by replacing C(5″)–OH by a substituent that cannot act as hydrogen bond donor, and to differentiate between G, A and C on the basis of their different charge density distribution.[33] Aromatic

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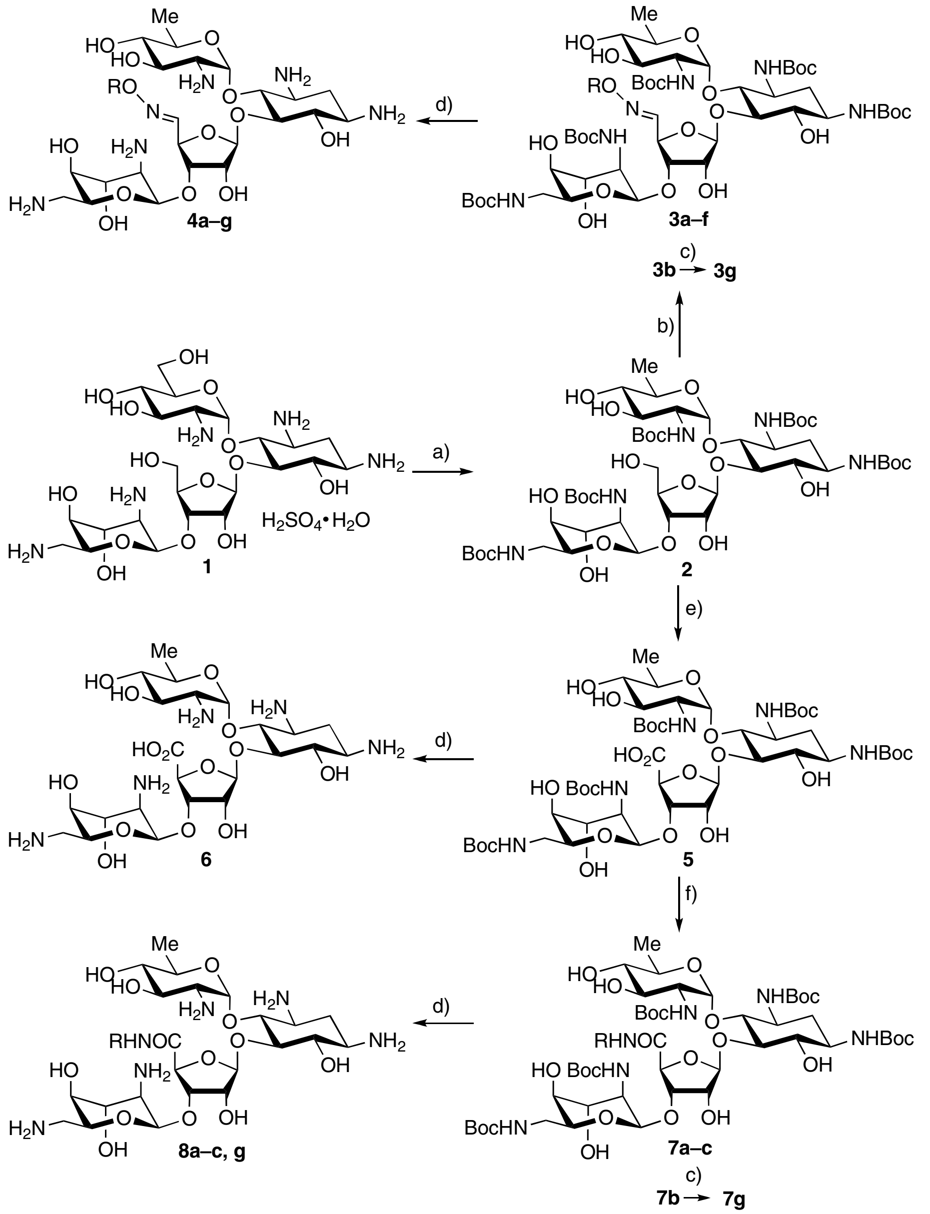
intermolecular interactions (π–π or CH–π interactions[34]) appeared promising, and we speculated that they may also compensate for the partial loss of activity resulting from deoxygenation of C(6′) of paromomycin.[35] Based on similar assumptions, Foloppe et al. screened a library of small molecules to find compounds with good stacking interactions with G1491.[21] We report on the preparation of paromomycin and C(6′)-deoxyparomomycin derivatives bearing either a C(5″)-hydroximo-, *O*-substituted C(5″)-hydroximo-, anilino or a corresponding carboxyl, or aminocarbonyl function and on the influence of these modifications at position C(5″) on the antibiotic activity. This position was already modified by a few research groups. Thus, Baasov et al. prepared a series of branched neomycin (C(6′)=NH_2) derivatives possessing an additional glycosyl moiety at *O*–C(5″)[36,37] to obtain antibiotics resistant towards aminoglycoside phosphotransferase APH(3′) that phosphorylates the C(5″)–OH group. Hanessian et al. prepared C(5″)–NH_2 derivatives of paromomycin and neomycin for the same purpose.[38] The same hydroxymethyl group was also modified to obtain conformationally biased



a: R = Bn, **b**: R = $CH_2C_6H_4(4\text{-}NO_2)$, **c**: R = Ph, **d**: R = Me,
e: R = $CH_2C_6F_4$, **f**: R = Tr, **g**: R = $CH_2C_6H_4(4\text{-}NH_2)$,

Scheme 1. Reagents and conditions: (a) six steps, 18% overall yield; (b) TCCA, TEMPO, EtOAc, 25 °C; then $RONH_2$·HCl, 1:1 pyridine–MeOH, 25 °C; 44–72% from **2**; (c) H_2, Pd/C, MeOH or 80% aq AcOH, 25 °C, 72–88%; (d) 97:3, CF_3 COOH/anisole, 25 °C, 56–91%; (e) BAIB, TEMPO, 1:1 MeCN–water, 23 °C; 54%; (f) EDAC, HOBt, DMF, 0 °C; then DIPEA, RNH_2, 25 °C, 40–45%.