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Synthesis of Gentamicin Minor Components: Gentamicin B1 and Gentamicin X2

Parasuraman Rajasekaran and David Crich*

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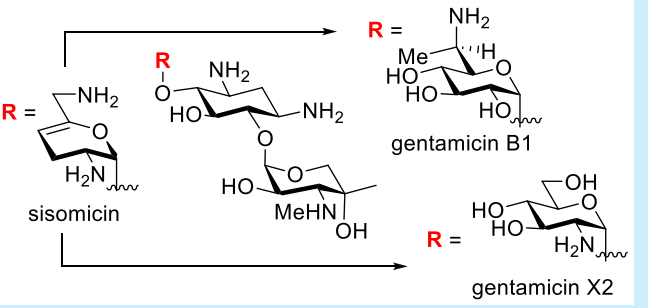
ABSTRACT: The clinical aminoglycoside antibiotic gentamicin is a mixture of several difficult-to-separate major and minor components. The relative inaccessibility of the minor components in particular complicates efforts to separate antibacterial activity from nephro- and/or ototoxicity and to clarify the origin of the potentially therapeutically important read-through activity. With a view to facilitating such studies, the synthesis of a fully and selectively protected garamine-based acceptor has been developed from readily available sisomicin. Glycosylation of this acceptor with a 6-azido-6,7-dideoxy-D-glycero-D-glucoheptopyranosyl donor affords gentamicin B1 after deprotection, whereas employment of a 2-azido-2-deoxy-D-glucopyranosyl donor under *N*,*N*-dimethylformamide-directed glycosylation conditions affords gentamicin X2 after deprotection.



Gentamicin is a clinically important aminoglycoside antibiotic used in the treatment of Gram-negative bacterial infections that figures on the WHO Essential Medicines List.[1] Produced by fermentation from *Micromonospora purpurea*, gentamicin is supplied as a mixture comprised mainly of gentamicin C1, gentamicin C1a, and gentamicin C2 and C2a together with minor amounts of sisomicin, gentamicins A, B, and B1, 2-deoxystreptamine, garamine, and garosamine (Figure 1).[2−5]

The antibacterial activity of aminoglycoside antibiotics stems from binding of the drugs to the decoding A site on helix 44 of the small subunit of the bacterial ribosome, whereas the important side effect of ototoxicity (drug induced hearing loss) is mainly the result of binding to the human mitochondrial and, in hypersusceptible patients, to the human A1555G mutant mitochondrial ribosome.[6−8] Aminoglycoside binding to the decoding A site of the human cytoplasmic ribosome on the other hand is expected to convey more systemic toxicity.[7] Fortunately, well-mapped differences in the decoding A sites of bacterial and human mitochondrial and cytoplasmic ribosomes can be exploited in the development of novel aminoglycosides with improved antibacterial activity and reduced toxicity.[9−11]

Somewhat paradoxically, because aminoglycoside binding to the human cytoplasmic ribosome results in misreading and consequently defective protein synthesis, aminoglycosides are also under intense investigation as potential therapeutics for genetic diseases arising from the mutation of an amino acid codon to a premature termination codon (PTC).[12] Variable results presented by gentamicin in clinical trials with patients suffering from Duchenne muscular dystrophy and cystic fibrosis[13−15] have resulted in efforts to develop structure−activity relationships among the various components of gentamicin and to identify the active principle for use in read-through therapy. Yet other efforts have focused on geneticin (G418) as an alternative lead for the development of compounds with improved read-through activity.[16−18] Unfortunately, these efforts are marred by the complexity of the mixture of gentamicins obtained by fermentation and the consequent difficulty of isolating pure components. For example, read-through activity originally assigned to gentamicin B1 was subsequently found to result from a mislabeled commercial sample of the closely related regioisomeric geneticin (G418), with purified gentamicin B1 itself showing no such activity.[19] More recently, gentamicin X2, a further minor component of gentamicin, was reported to have read-through activity surpassing that of geneticin.[20]

In view of the difficulty in obtaining authentic pure samples of minor gentamicin components, we embarked on the synthesis of gentamicins B1 and X2 and report here on the outcome of our studies.

Gentamicin B1 **7** has not been synthesized previously. Gentamicin X2 **8** was prepared in 1976 by Mallams and coworkers in 8 steps and 3.7% overall yield from penta-*N*-Cbz-

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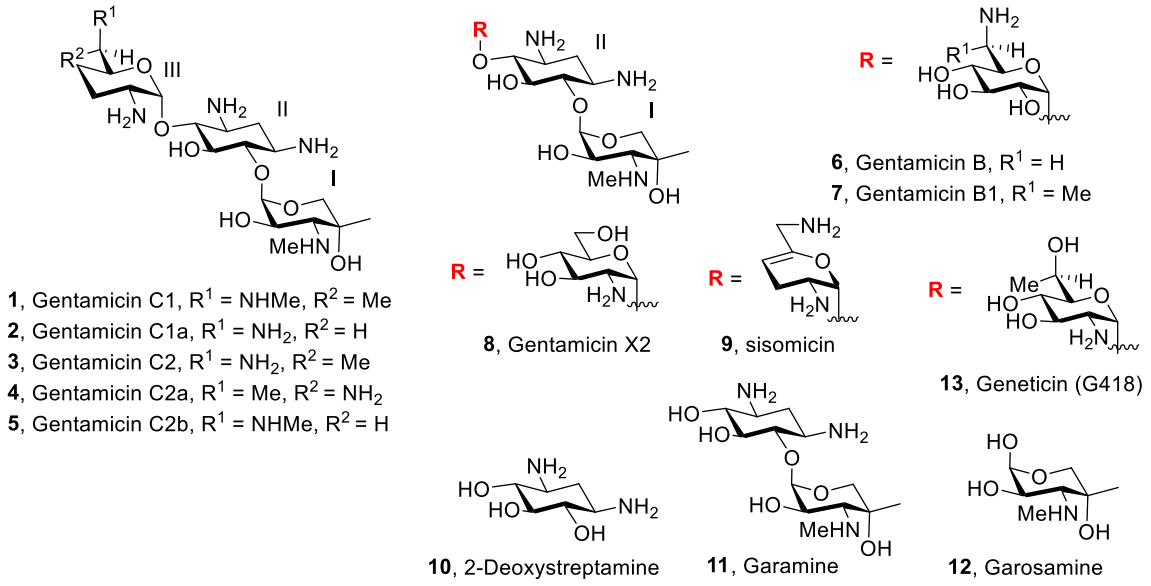
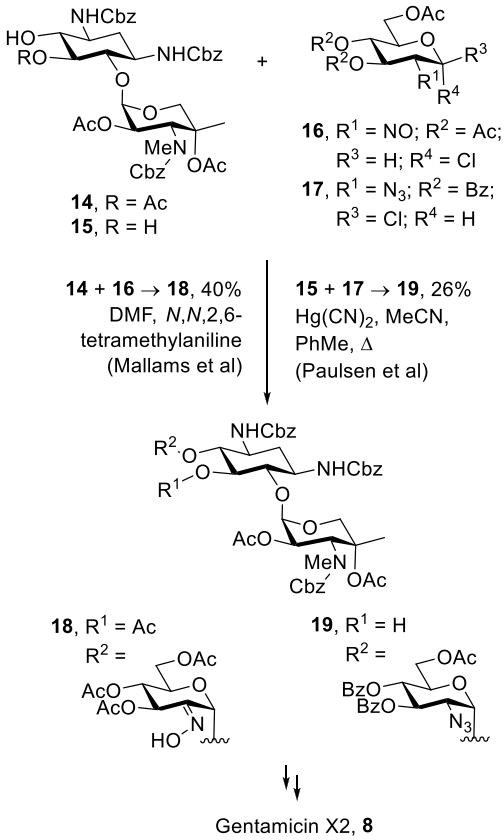
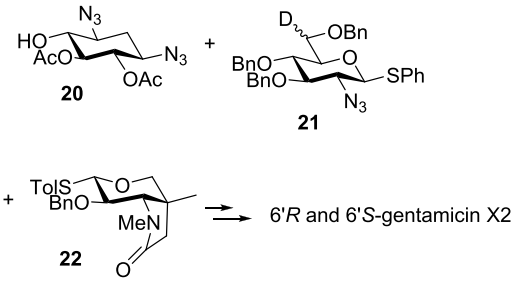


Figure 1. Major and minor components of gentamicin, and geneticin (G418).

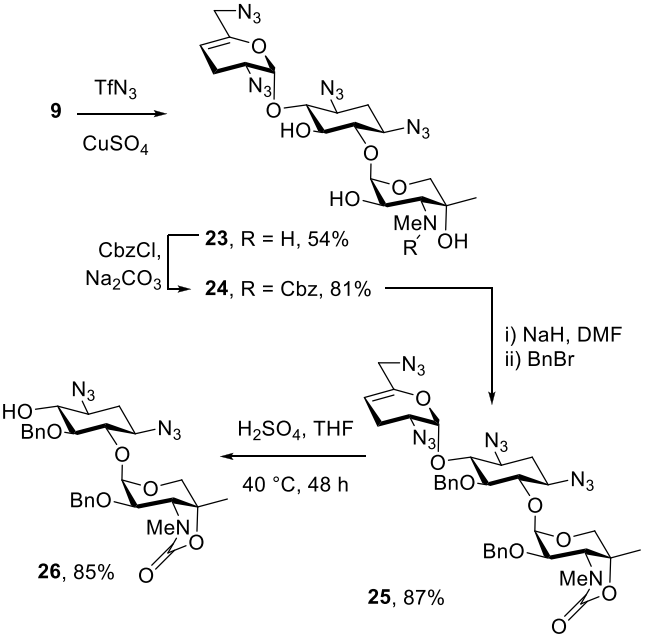
Scheme 1. Key Steps in the Mallams and Paulsen Syntheses of Gentamicin X2



Scheme 2. Key Elements of the Liu Synthesis of 6′*R*- and 6′*S*-Gentamicin X2



Scheme 3. Synthesis of a Garamine-Based Acceptor from Sisomycin



sisomicin. In the key step, the garamine derivative **14**,[21] obtained from sisomicin **9**, was glycosylated with a per-*O*-acetyl-2-deoxy-2-nitroso-α-D-glucopyranosyl chloride **16** under Koenigs–Knorr conditions to obtain the pseudo disaccharide **18** in 40% yield (Scheme 1).[22] A second synthesis of gentamicin X2 was achieved in 1981 by Paulsen and co-workers in 4 steps and 3.4% overall yield from a penta-*N*-Cbz-gentamicin C complex.[23] The core of this synthesis was glycosylation of garamine derivative **15**, obtained by degradation of gentamicin C complex,[24] with

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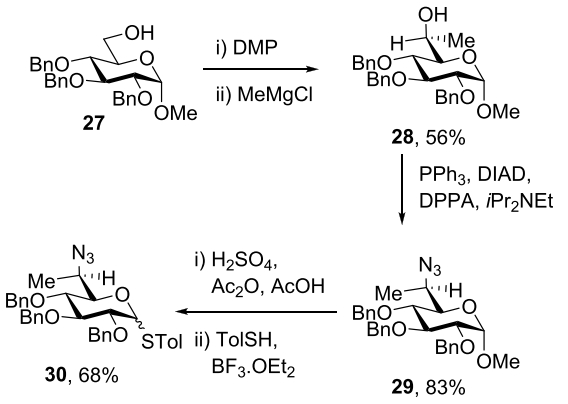
Scheme 4. Synthesis of 6-Azido-6,7-dideoxy-D-glycero-D-glucoheptopyranosyl Donor 30



the 2-azido-2-deoxyglucosyl chloride **17** and mercuric cyanide as promoter giving pseudo disaccharide **19** in 26% yield (Scheme 1).

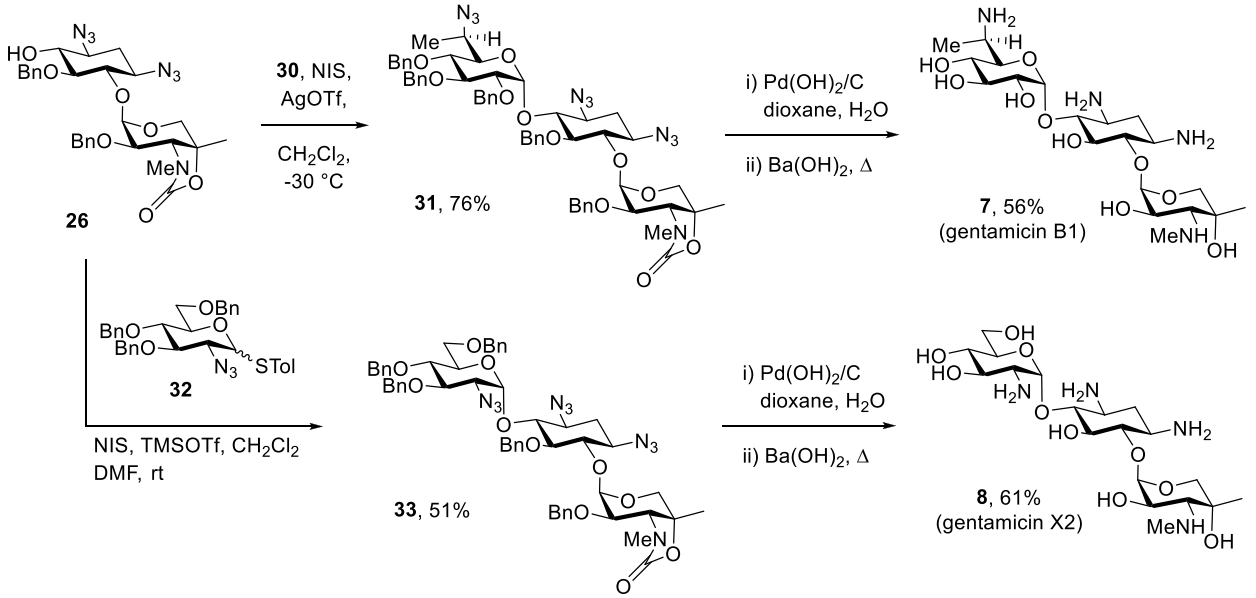
The Mallams synthesis was prescient in that it employed DMF as solvent resulting in the selective formation of the axial glycoside,[25−27] but it required several steps for the selective acetylation of tris-*N*-(Cbz)-garamine to obtain acceptor **14**, and reduction of the oxime **16** subsequent to glycosylation. The Paulsen synthesis relied on regioselctive glycosylation of the gaaramine diol **15**, but consequently only gave a moderate yield of 26%, and employed mercuric cyanide as promoter. More recently, Liu and co-workers prepared 6′*R*- and 6′*S*-monodeuterio gentamicin X2 (Scheme 2)[28] by an initial glycosylation of the deoxystreptamine derivative **20**, itself obtained by enzymatic desymmetrization of 2-deoxystreptamine according to Wong,[29] with thioglycoside **21**. This step was followed, after deacetylation, by a second regioselective glycosylation with the garosamine donor **22** that was prepared by degradation of gentamicin and subsequent derivatization.

We envisaged that both gentamicins B1 and X2 would be readily prepared from a common pseudo disaccharyl garamine-based acceptor, and that this acceptor would in turn be readily accessible from sisomicin **9**. Thus, by adapting literature methods, sisomicin **9** was converted to the known tetraazide **23**[30] in 54% yield by treatment with triflyl azide,[31,32] and then to the known tertiary carbamate **24**[33] in 81% yield by standard means. Treatment of **24** with excess sodium hydride in DMF at 0 °C to effect conversion of the carbamate to the oxazolidinone was followed by addition of benzyl bromide and stirring at room temperature to afford the fully protected sisomicin derivative **25** in 87% yield. Attempted cleavage of the unsaturated ring from **25** with Amberlite IR120 H^+ resin or with 4 N HCl, according to literature protocols for related compounds,[21,34] was not effective, but stirring with sulfuric acid in THF at 40 °C for 48 h[21] brought about the desired transformation and afforded the selectively protected glycosyl acceptor **26** in 85% yield (Scheme 3).

A glycosyl donor suitable for construction of gentamicin B1 was prepared from methyl α-D-glucopyranoside, which was converted to the known alcohol **27**[35] in 68% yield by three straighforward steps as described in the Supporting Information. Oxidation with the Dess Martin periodinaine[36] gave an aldehyde, which on immediate treatment with methylmagnesium chloride at −78 °C gave the known heptose derivative **28**[37] in 56% overall yield (Scheme 4). Consistent with the literature, **28** was obtained predominantly in the form of the L-glycero-D-gluco-isomer as verified by conversion to a 4,6-*O*-benzylidene acetal derivative in which the newly introduced methyl group occupied the axial site at C6 (Supporting Information). Triflation of **28** followed by displacement with sodium azide was complicated by significant elimination, but reaction with diphenylphosphoryl azide[38] gave the desired D-glycero-D-gluco-configured azide **29** in 83% yield. Finally, acetolysis of the methyl glycoside followed by treatment with 4-methylbenzenethiol in the presence of BF_3-etherate afforded the requisite donor **30** in 68% yield.

Coupling of acceptor **26** with donor **30** was accomplished with *N*-iodosuccinimide and silver triflate in dichloromethane

Scheme 5. Synthesis of Gentamicin B1 and Gentamicin X2



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at −30 °C in the presence of 4 Å molecular sieves. This reaction afforded the desired glycoside **31** in 76% yield as the pure α-anomer, with the high selectivity seemingly a function of the extra substitution at the 6-position of the donor (Scheme 5). Coupling of acceptor **26** with *p*-tolyl 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α,β-D-thiogluopyranoside **32**, prepared according to the literature method,[39] under the same conditions gave the glycoside **33** in 62% yield as a 3:1 α,β-mixture, but activation with NIS and TMS triflate in dichloromethane in the presence of DMF[25−27,40] afforded the pure α-anomer of **33** in 51% yield together with 13% of the recovered glycosyl acceptor **23** (Scheme 5). Deprotection of both **31** and **33** was accomplished by hydrogenolysis over palladium hydroxide on charcoal followed by heating to 60 °C with aqueous barium hydroxide, with final purification by filtration on Sephadex C25 and lyophilization from aqueous acetic acid. In this manner gentamicin B1 **7** and gentamicin X2 **8** were obtained in 56% and 61% yield from **31** and **33**, respectively, in the form of their peracetate salts (Scheme 5).

Overall the synthesis of gentamicin B1 was accomplished from sisomicin **9** in 6 steps and 13.8% yield. The synthesis of gentamicin X2 was achieved from sisomicin **9** in 6 steps and 10.1% yield, which compares favorably with the precedent (Schemes 1 and 2). The straightforward syntheses of the common acceptor **26** and of the two donors **30** and **32**, together with the relatively high yields and excellent selectivities of the coupling reactions, suggest that these syntheses are potentially scalable should the need for larger quantities of material arise. We anticipate that other minor components of gentamicin should be similarly readily available by glycosylation of **23** should the need arise.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01107.

Complete experimental and characterization details and copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

David Crich − *Department of Pharmaceutical and Biomedical Sciences, Complex Carbohydrate Research Center, and Department of Chemistry, University of Georgia, Athens, Georgia 30602, United States;* orcid.org/0000-0003-2400-0083; Email: david.crich@uga.edu

Author

Parasuraman Rajasekaran − *Department of Pharmaceutical and Biomedical Sciences and Complex Carbohydrate Research Center, University of Georgia, Athens, Georgia 30602, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01107

Notes

The authors declare the following competing financial interest(s): D.C. is a cofounder of and an equity holder in Juvabis AG, a biotech company developing novel aminoglycoside antibiotics.

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