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AN IMPROVED SYNTHESIS OF GLYCINAMIDE RIBONUCLEOTIDE

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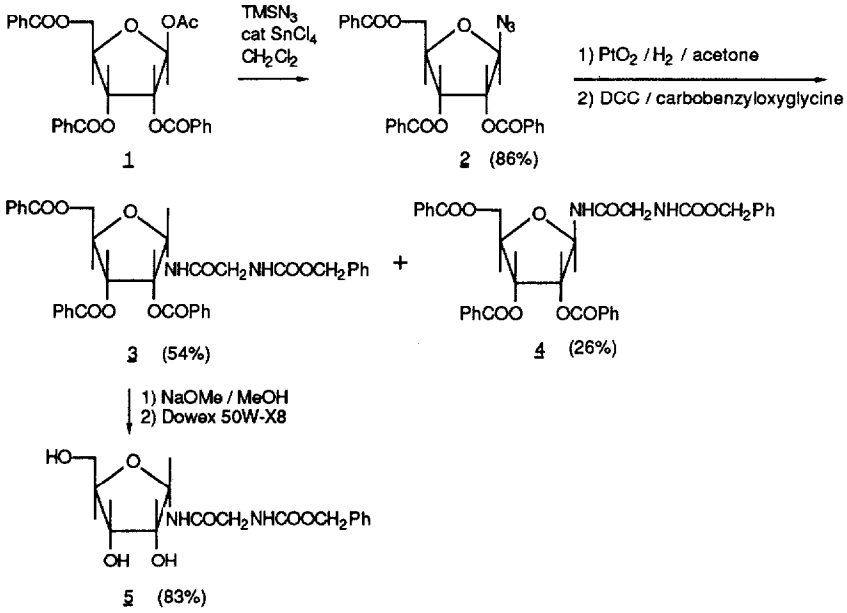
Abstract: Glycinamide ribonucleotide (GAR) was obtained in 7 steps in 15% yield from a commercially available ribose derivative.

Glycinamide ribonucleotide transformylase (GAR-Tfase) catalyzes the transfer of a formyl group from 10-formyl tetrahydrofolic acid to glycinamide ribonucleotide (GAR) producing N-formyl glycinamide ribonucleotide. This transformation is the first of two folate mediated one-carbon transfer reactions in the *de novo* biosynthesis of purines. The syntheses of GAR reported in the literature involve isolation of the barium or sodium salt of GAR. The drawback to these approaches is that purification of the prerequisite free phosphate is difficult.[2,3] Our synthesis of GAR avoids this problem and is presented here.

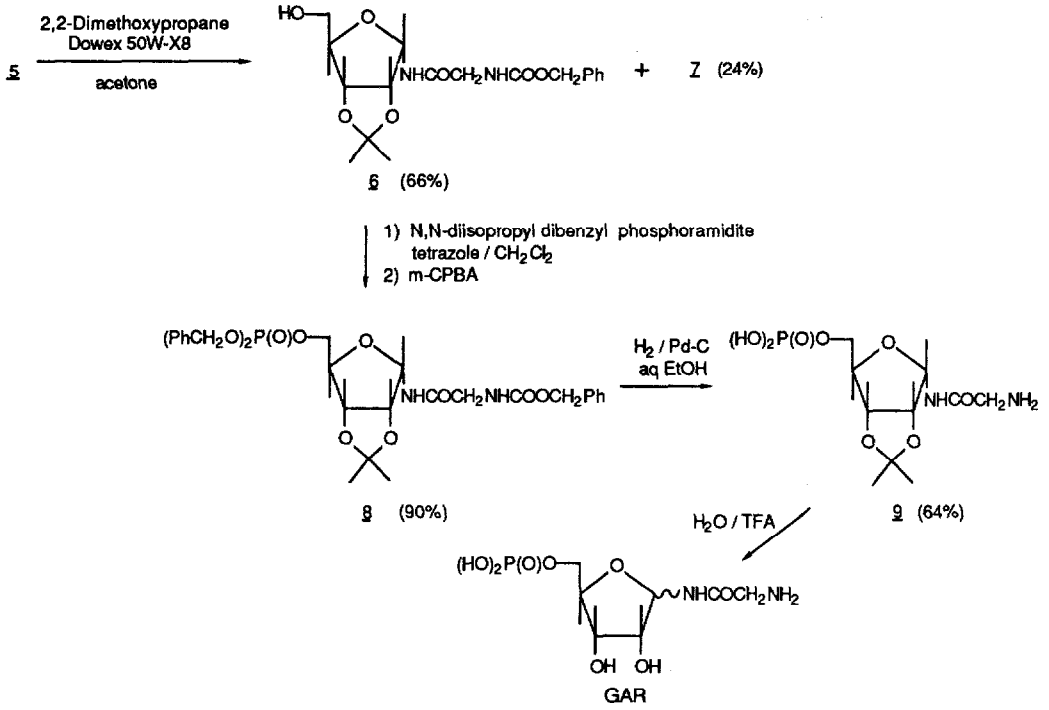
Treatment of commercially available 1-acetate-2,3,5-tribenzoate-β-D-ribose 1 with trimethylsilyl azide in methylene chloride in the presence of a catalytic amount of stannic chloride gave β-azide 2 as previously reported.[4] The azide was reduced to the corresponding amine via room pressure hydrogenation with platinum oxide in acetone.[3,5] The amine was not isolated but was treated directly with carbobenzyloxyglycine and dicyclohexylcarbodiimide to give a 2.5 : 1 mixture of 3 and 4.[2,3,5] The benzoate groups were removed from 3 (the α anomer) with a catalytic amount of sodium methoxide in methanol, followed by the addition of Dowex-H$^+$, providing triol 5.[3,5]



1 2 (86%) 3 (54%) 4 (26%) 5 (83%)

Treatment of 5 with 2,2-dimethoxypropane in acetone containing Dowex-H$^+$ gave a mixture of 6 and 7. The α isomer 6 was obtained in 66% yield and the β anomer 7 in 24% yield.[6] The phosphate ester 8 was obtained by reacting alcohol 6 with N,N-diisopropyl dibenzyl phosphoramidite and tetrazole in methylene chloride followed by the addition of m-CPBA.[7] Hydrogenation of 8 in aqueous ethanol using palladium on carbon gave a 64% yield of 9. Removal of the acetonide group was achieved by stirring an aqueous solution of 9 containing several drops of trifluoroacetic acid at room temperature for 24 hours.[8] Concentration *in vacuo* at room temperature provided GAR in

quantitative yield as a 1 : 1.2 mixture of α to β anomers.[9] Enzymatic assay showed that GAR prepared by this approach was twice as active as a sample of GAR prepared using Benkovic's approach.[2,10]



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5. Baddiley, J.; Buchanan, J. G.; Hodges, R.; Prescott, J. F. *J. Chem. Soc.*, **1957**, 4769 .
6. Both 6 and 7 were earlier prepared by a similar route, see reference 2.
7. Yu, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.*, **1988**, *29*, 979. Use of the benzyl protecting group is crucial. We were unable to cleanly remove the ethyl or phenyl phosphate protecting groups to give the required free phosphate.
8. Initally this deprotection was followed by 300 MHz ^{1}H-NMR. 9 was dissolved in D_2O and treated with deuterated trifluoroacetic acid. The disappearance of the doublet at 1.01 and 1.25 ppm (for the acetonide group) and the appearance of a singlet at 1.80 ppm (for acetone) was monitored.
9. The structure of GAR was confirmed by high resolution FAB mass spec and comparison of the ^{13}C-NMR and ^{1}H-NMR spectral data to that reported in the literature.[2,3] For complete characterization of intermediates, the α and β anomers were separated at two stages of this synthesis (3 and 4 ; 6 and 7). Since GAR is an anomeric mixture, these separations are not required.
10. The barium salt of GAR prepared following Benkovic's procedure is a 1:1 mixture of anomers. The β anomer of GAR is the active form.

Acknowledgements

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