Synthesis of Capuramycin

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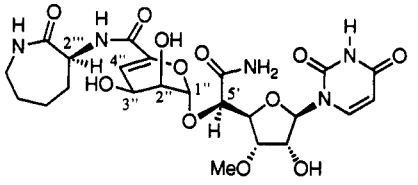
Received November 16, 1993®

Summary: The structure of capuramycin (1) is confirmed by an efficient synthesis that features glycosylation with a D-*manno*-pyranuronate donor **15** at the hindered C-5′ hydroxyl of L-*talo*-uridine **10**.

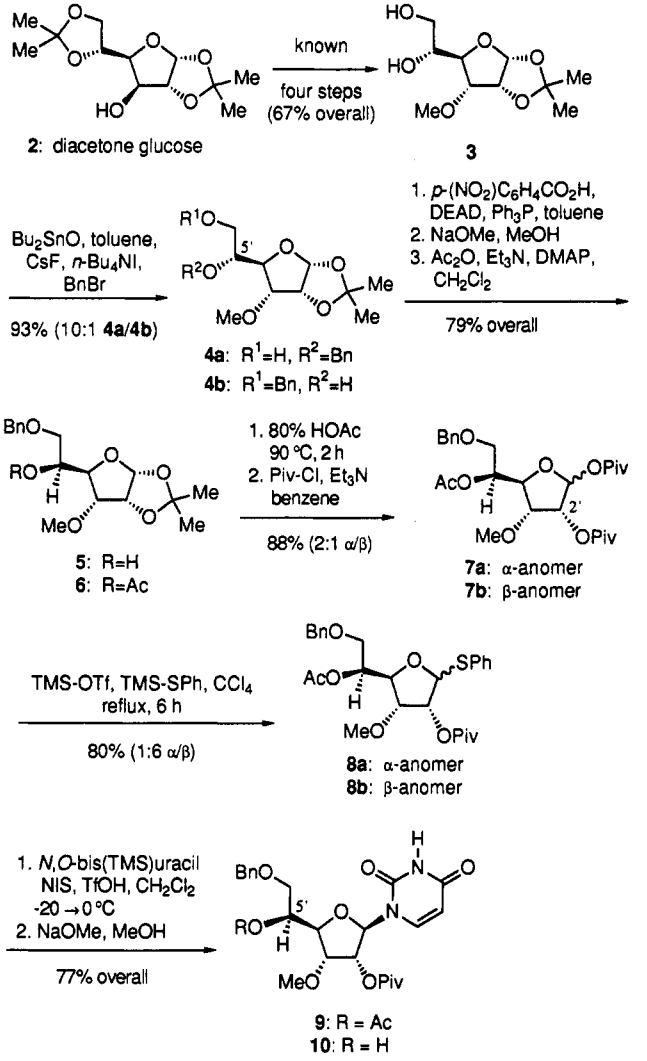
Capuramycin (1) is a complex nucleoside antibiotic[1] produced by *Streptomyces griseus* 446-S3 in culture broth. It exhibits activity against *Streptococcus pneumoniae* and *Mycobacterium smegmatis* ATCC 607, with very low toxicity in mice.[2] In 1988, Seto, Clardy, and co-workers assigned the structure **1** to capuramycin based on NMR spectroscopy, chemical degradation, and X-ray analysis of a derivatized fragment. The antibiotic consists of a 4-deoxy-4-hexenuronic acid joined to an L-taluronamide nucleoside by a glycosidic linkage and to 2(*S*)-aminocaprolactam by a peptide bond.[3] The absolute configuration of the pyranose portion (*S* at C-1″, C-2″, and C-3″) was assigned by the cuprous ammonium CD method applied to the 4″,5″-dihydro derivative of **1**.[3] Capuramycin presents some special challenges for synthesis, most notably the glycosylation required at the extremely hindered C-5′ hydroxyl of the *talo*-furanose. Here, we report a synthesis of **1** that solves the glycosylation problem and confirms the structure and absolute stereochemistry of the natural product.



1: capuramycin

Rather than elaborate a protected uridine to form the L-*talo*-furanosyl portion of **1**, we chose to transform diacetone glucose (**2**) into the more versatile donor (for N-glycosylation)/acceptor (for O-glycosylation) hybrid **8**. Scheme 1 shows the synthesis of **8** and its conversion to the L-*talo*-uridine **10**. Preparation of the 3-*O*-methyl-α-D-*allo*-furanose **3** followed the literature procedure.[4] Selective benzylation of the primary hydroxyl of **3** was achieved through the stannylene acetal.[5] The configuration at C-5′ (capuramycin numbering) was inverted under Mitsunobu conditions modified by using *p*-nitrobenzoic acid as the nucleophile.[6] The switch to acetate

Scheme 1. Synthesis of the L-*talo*-Uridine Acceptor



as the C-5′ protecting group was made necessary by the incompatibility of *p*-nitrobenzoate to subsequent transformations. Removal of the second acetonide[7] and pivaloylation (pivaloyl is an excellent C-2′ participating group[8]) gave L-*talo*-furanose derivative **7**, and exchange of the C-1′ pivaloyloxy for phenylthio[9] led to the donor/acceptor hybrid **8**. The use of benzene as the solvent for pivaloylation proved to be crucial, as more polar solvents led to incomplete reaction and much lower yields of **8**. Conversion of **8** to the corresponding L-*talo*-uridine **9** was carried out by using the method we had developed for N-glycosylation of silylated pyrimidines with thioglycoside donors.[10] The mild conditions (coupling occurs below 0 °C within 10 min) and high yield of nucleoside (85%) are

• Abstract published in *Advance ACS Abstracts*, January 1, 1994.

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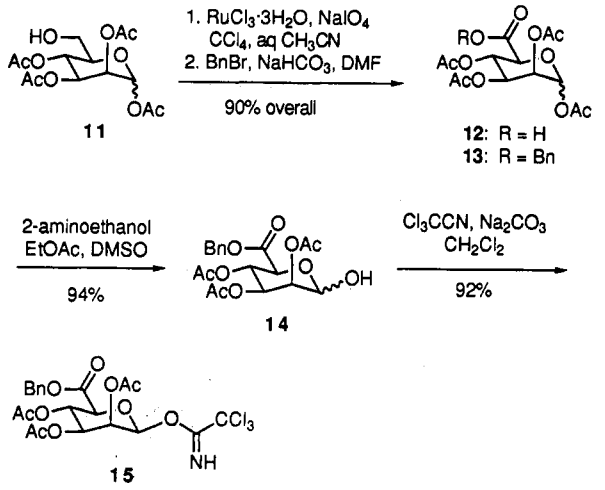
Scheme 2. Synthesis of the D-*manno*-Pyranuronate Donor



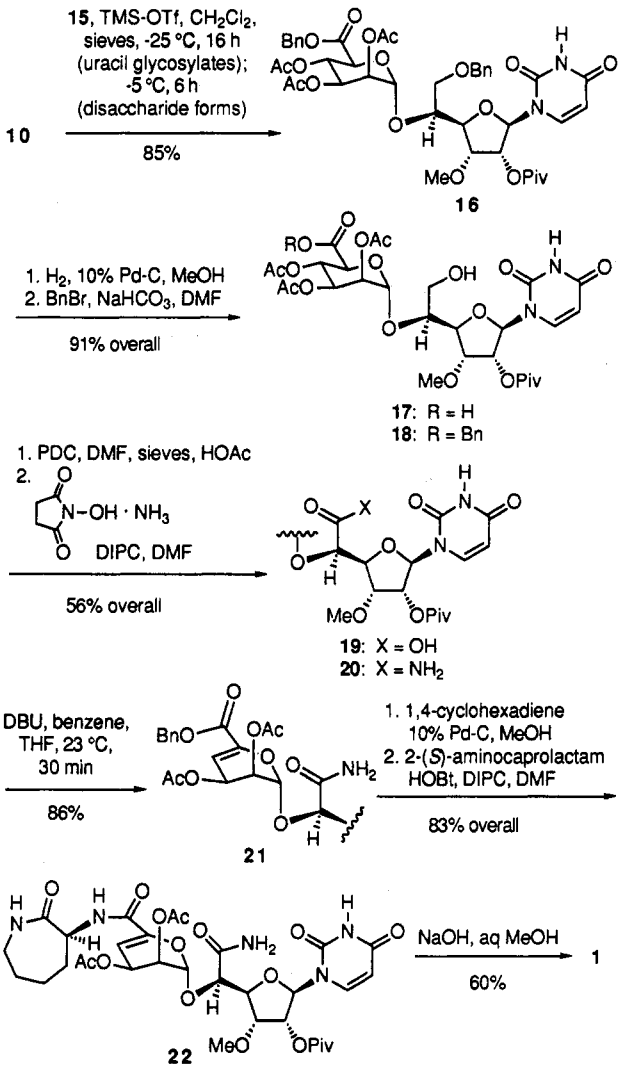
notable. Finally, selective deacetylation at C-5′ provided **10**. The 13-step sequence from diacetone glucose proceeds in about 27% overall yield.

Scheme 2 illustrates the preparation of a saturated D-*manno*-pyranuronate donor (**15**) suitable for coupling to the nucleoside acceptor **10**. Ruthenium(III)-catalyzed oxidation[11] of 1,2,3,4-tetra-*O*-acetyl-D-mannopyranose (**11**)[12] followed by esterification gave tetraacetate **13**, and selective removal of the anomeric acetate[13] and then activation of the anomeric center according to Schmidt[14] produced **15**.

Scheme 3 shows the successful glycosylation and completion of the synthesis. Excess Schmidt donor **15** reacted with the L-*talo*-uridine acceptor **10** under activation by TMS-OTf at −25 °C to consume **10** and give a new product with much higher R_f, according to TLC analysis. After bicarbonate quench, however, **10** was recovered in 86% yield. We infer that glycosylation occurs first on the uracil ring.[15] When the reaction was instead allowed to warm to −5 °C, a different product formed, and after quench and chromatography, the nucleoside disaccharide **16** was isolated in high yield. The use of fewer than 8 molar equiv of the donor **15** led to incomplete glycosylation and lower yield of **16**.

The remaining operations were carried out in an efficient sequence, but the sensitive and complex functionality present in the target did not tolerate variations in the order of the transformations. Hydrogenolytic removal of both benzyl groups gave the hydroxy acid **17**, which was reesterified under mild conditions to produce hydroxy ester **18**. PDC oxidation[16] to the carboxylic acid **19** was followed by conversion[17] to the corresponding primary amide **20**. Elimination of acetate from C-4″ (**20** → **21**) could be effected by DBU under conditions that did not damage the product when C-6″ was held as an ester, but not an amide. Selective deprotection of the benzyl ester without hydrogenation of the easily-reduced[3] C-4″ olefin was

Scheme 3. O-Glycosylation and Completion of the Synthesis



accomplished by transfer hydrogenolysis in methanol solution[18] and then coupling[19] of the resulting acid with commercially available 2-(*S*)-aminocaprolactam was carried out in high yield. Hydrolysis of the two acetates and the pivaloate under the action of dilute sodium hydroxide gave capuramycin **1** when the reaction was stopped after about 60% conversion (2.5 h). Further exposure to the same conditions, however, led to destruction of the product. Synthetic **1** was isolated by chromatography and was shown to be identical to the natural product by comparison of the well-resolved 400-MHz ^1H NMR spectra acquired under identical conditions.

Several variations on the featured glycosylation reaction were attempted, and although these were unsuccessful, they led to some interesting observations. Reaction of the C-6′ *ester* **23** with donor **15** under conditions that were successful for **10** gave apparent uracil ring glycosylation but no reaction at the C-5′ hydroxyl. This may be attributed to the electron-withdrawing nature of the ester group compared with the benzyloxy of **10** and possibly to increased steric hindrance at C-5′.

The C-4″-unsaturated thioglycoside **24** was prepared from 1,2,3,4-tetra-*O*-benzoyl-D-mannopyranose, but this

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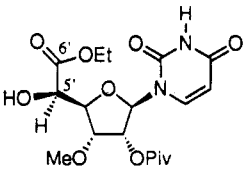

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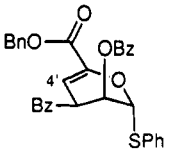

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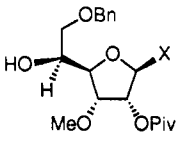
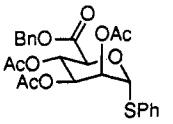


25: X = OPiv
26: X = SPh



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donor did not react with L-*talo*-furanoside **25** under activation by NIS/TfOH[20] to give any detectable disaccharide. Oxidation of **24** to a sulfoxide, followed by mixing with **26** and activation with either triflic anhydride or TfOH according to Kahne,[21] led to complete consumption of both donor and acceptor and the isolation of several donor-derived dibenzoates and the original thioglycoside **24** (13%, based on acceptor), but no products derived from **26**. A possible mechanism for the production of **24** in this reaction was provided by a separate experiment in which the acceptor **26** was treated with excess donor **15** under conditions that were successful for **10**. The phenyl 1-deoxy-1-thio-α-D-mannopyranoside **27** was isolated in 96% yield based on **26**, the result of an unusual intermolecular phenylthio transfer from the anomeric position of acceptor **26** to the donor **15**. Thioglycosides are occasionally employed as glycosyl *acceptors*; the low coupling yields in some reported cases,[21] especially those involving electron-poor donors,[22] might well have resulted in part from an unappreciated phenylthio transfer process analogous to this reaction of **26**.

Acknowledgment. We are grateful to the Charles and Johanna Busch Memorial Fund, Berlex Corp., and Hoffmann-La Roche for financial support of this work, to Prof. Haruo Seto for a sample of natural capuramycin, and to Mr. Rich Trilles and Mr. Chad Cohen for preparative assistance. S.K. thanks American Cyanamid for a Cyanamid Faculty Award.

Supplementary Material Available: Experimental procedures and spectral data for the preparation of **1** from **3** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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