ORGANIC LETTERS

2000
Vol. 2, No. 10
1391−1393

Synthesis of the Ezomycin Nucleoside Disaccharide

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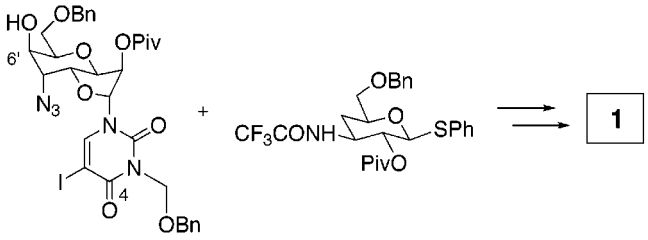
Received February 19, 2000

ABSTRACT



A protected ezomycin octosyl nucleoside was glycosylated at O-6′ with a protected ezoaminuroic acid donor to afford, following several functional group modifications, the title compound 1 (≡ 4-desamino-4-oxoezomycin A_2).

The ezomycins are a class of fermentation-derived complex nucleoside antibiotics[1] whose structures were elucidated in the 1970s.[2,3] They feature an unusual combination of parts: an octosyl nucleoside, a [1′′→6′]-*β*-glycosylating 3-amino-3,4-dideoxy-D-glucuronic acid ("ezoaminuroic acid"), and an N-linked pseudopeptide (L-cystathionine).

Three ezomycins containing the L-cystathionine component, A_1, B_1, and C_1 (the anomer of B_1 at C-1′), are active against certain species of phytopathogenic fungi such as *Sclerotinia* and *Botritus*, whereas those lacking this pseudopeptide (e. g., A_2 and B_2) are inactive. Some members (B, C, and D series) bear a C-5 glycosylated *pseudo*-uracil rather than the more usual N-1 linked pyrimidine nucleoside bases.

A number of synthetic routes to the ezoaminuroic acid portion have appeared,[4,5] and several groups have synthesized octosyl nucleosides that resemble the ezomycin component.[6,7] A method for glycosylating a model octose at C-6′ was reported from our lab in 1994.[5] In this paper we describe the first synthesis of the ezomycin nucleoside disaccharide **1** (≡ 4-desamino-4-oxoezomycin A_2).

Although we had previously developed a satisfactory route to the ezoaminuroic acid donor **6**,[5] the requirement of excess donor for the nucleoside glycosylation, and the difficulties associated with large-scale preparation of the Cerny epoxide precursor, prompted us to develop the shorter alternative route shown in Scheme 1. Selective hydrolysis[8] of 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **2**,[9]

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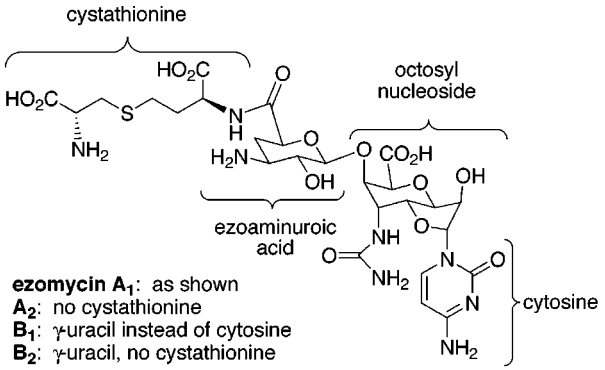
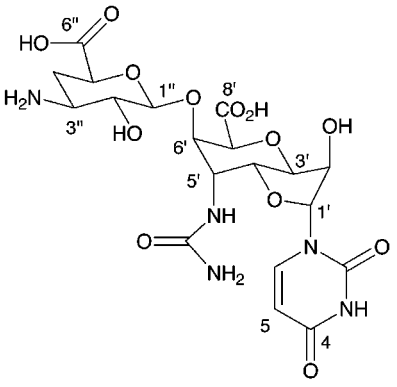
10.1021/ol005696f CCC: $19.00
Published on Web 04/18/2000





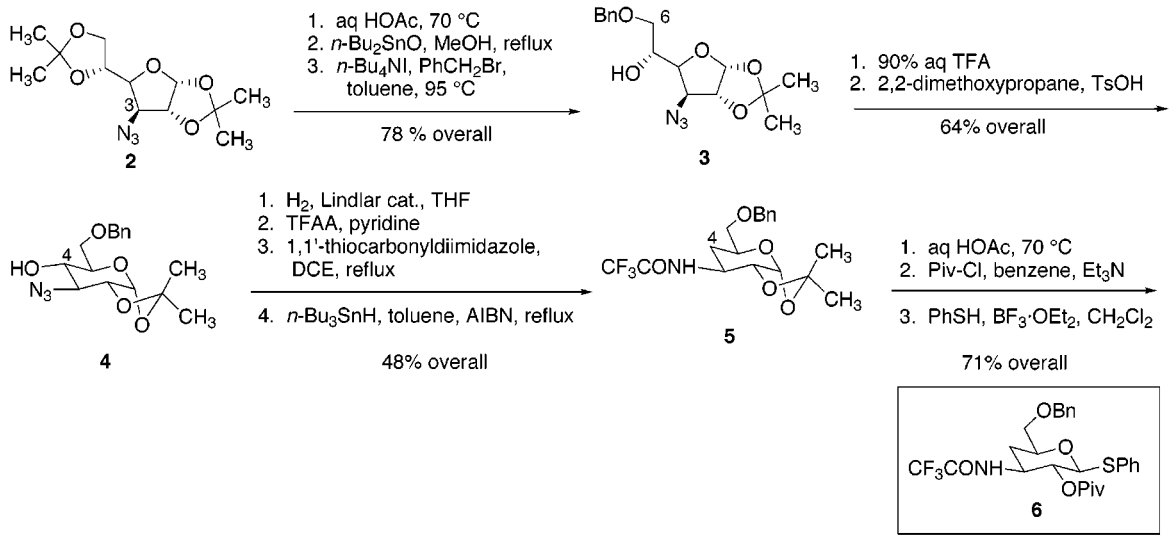
1: ezomycin nucleoside disaccharide (4-desamino-4-oxo-ezomycin A_2)

and then selective benzylation at O-6 by way of the 5,6-*O*-stannyleneacetal,[10] afforded the mono-benzyl ether **3**. Hydrolysis of the second isopropylidene ketal and reformulation of the resulting triol as the pyranose 1,2-ketal **4** was followed by reduction of the azide and protection of the amino as its trifluoroacetyl derivative. Radical deoxygenation[11] at C-4 led to the pyranose **5**. Attempted deoxygenation prior to the reduction of the azido function was unsuccessful owing to the reactivity of azido under the reducing conditions.[12] Hydrolysis of **5** to the diol, *O*-pivaloylation in the nonpolar solvent benzene,[13] and then exchange of pivaloate for phenylthio at C-1 furnished the donor **6**, identical to that prepared previously.[5]

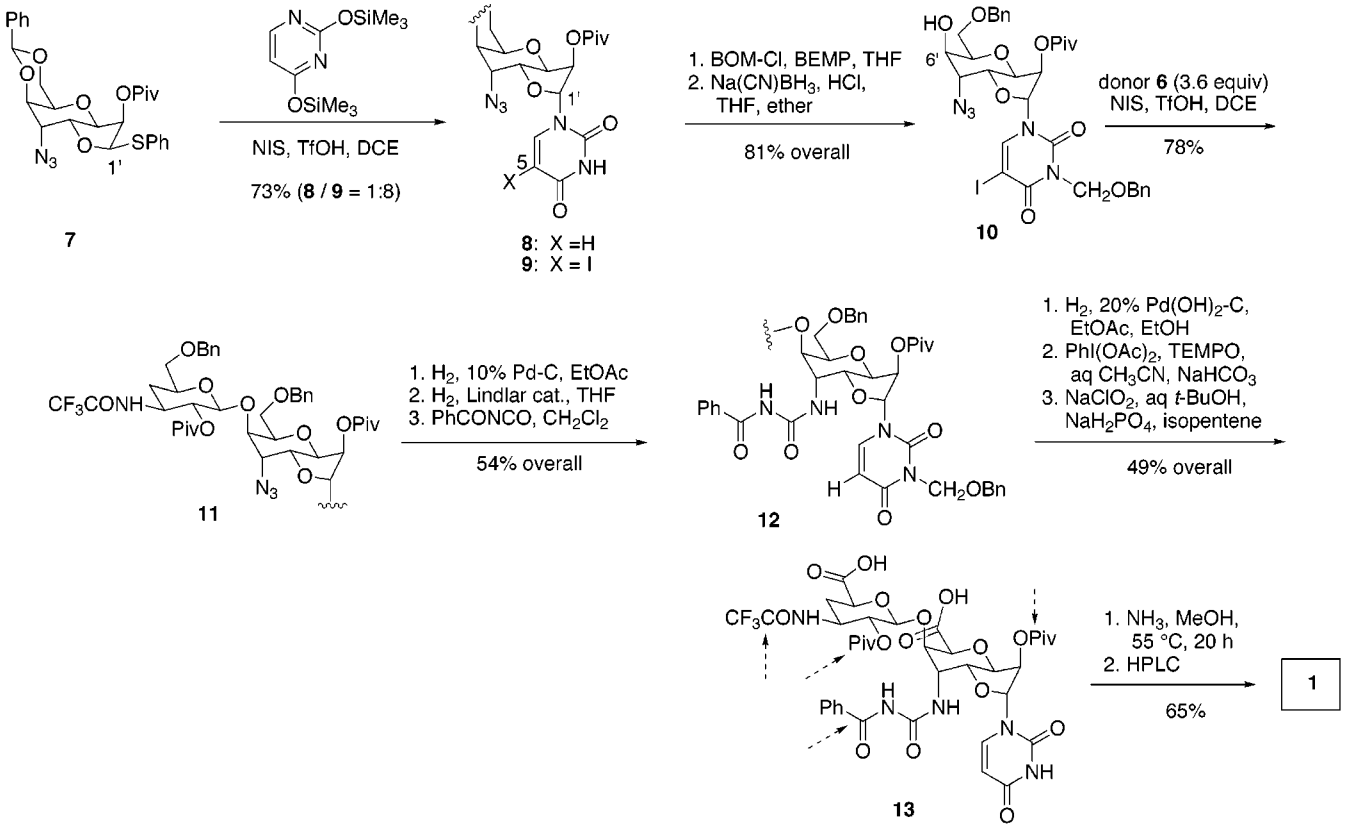
The octosyl nucleoside acceptor **10** was constructed from thioglycoside donor **7**[7] by N-1 glycosylation of *O*,*O*′-bis-(trimethylsilyl)uracil under conditions previously developed for this purpose (Scheme 2).[7,13,14] The resulting nucleoside **8** was accompanied by varying amounts of the 5-iodinated product **9**.[14] A more efficient overall glycosylation was obtained by driving the reaction further toward **9** with additional *N*-iodosuccinimide, and **9** proved to be superior in subsequent transformations anyway. The uracil was efficiently N-3-protected by using benzyloxymethyl chloride and BEMP,[15] and then the benzylidene was cleaved with HCl under reducing conditions[16] to give the required acceptor **10** possessing a free C-6′ hydroxyl.

Glycosylation of **10** with no less than 3.6 equiv of donor **6** gave the nucleoside disaccharide **11** in excellent yield considering the complexity and multisite Lewis basicity[17] of the acceptor. A series of highly selective functional group transformations was then carried out to convert **11** to the target ezomycin nucleoside disaccharide **1**. Clean hydrogenolysis of the C-5 iodide was followed by selective hydrogenolysis of the azido to amino[18] and then protection of the amino as its *N*-benzoylcarbamoyl derivative **12**. Hydrogenolysis of the three benzyl protecting groups exposed primary hydroxyls at C-8′ and C-6″. These were oxidized under Widlanski conditions[19] to afford dicarboxylic acid **13** (for complete conversion, a followup treatment with sodium chlorite was required). Ammonolysis in methanol solution removed the four acyl protecting groups (indicated by dashed arrows) and provided **1** directly. The nucleoside disaccharide was purified by HPLC and characterized by HRMS and COSY-assisted ^{1}H NMR analysis, which confirmed the full deprotection and the close similarity of **1** to ezomycin A_2.

Scheme 1



Scheme 2



We envision modifying this synthetic route to include conversion of the pyrimidine base from uracil to cytosine and site-selective attachment of the cystathionine to afford ezomycin A_1.

Acknowledgment. We thank Hoffmann-La Roche for financial support, Silvano DeBernardo and Theodore Lambros for helpful suggestions for the synthesis of **6** and the purification of **1**, respectively, and Gino Sasso, Vance Bell, Richard Szypula, and Theresa Burchfield of the Physical Chemistry Department at Hoffmann-La Roche for obtaining NMR and mass spectra.

Supporting Information Available: Experimental procedures and spectroscopic characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005696F

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