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A versatile route to 2,4,6-trideoxy-4-aminohexoses: Stereoselective syntheses of D-vicenisamine and its epimers via iodocyclization of carbamate

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ABSTRACT

Stereoselective syntheses of the 2,4,6-trideoxy-4-amino sugar D-vicenisamine and its epimers 3-*epi*- and 4-*epi*-D-vicenisamine were accomplished via stereoselective nitrogen functional group introduction and iodocyclization of carbamate. This versatile synthetic route started from the enantiomerically pure diol obtained from ethyl sorbate by Sharpless asymmetric dihydroxylation.

1. Introduction

Sugar components, especially deoxy and deoxyamino sugars, are found in clinically important antibiotics, such as antimicrobial macrolides and antitumor antibiotics.[1] In most cases, the sugar components of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not been investigated thus far.[2] We envisaged that modification of the sugar moieties of these antibiotics could serve as a tool for investigating the significance of the corresponding sugars and their structure–activity relationships and for elucidating the biosynthetic route for antibiotics.[3] For this purpose, a versatile synthetic route for deoxy and deoxyamino sugars is highly desirable. Thus far, we have been interested in developing new synthetic routes, especially for deoxyamino sugars[4] and branched-chain sugars, such as noviose,[5] from non-sugar materials.

Vicenistatin (**1**), an antitumor antibiotic isolated from *Streptomyces* sp. HC-34, has a unique structure that includes a 20-membered macrocyclic lactam aglycone and an unprecedented deoxyamino sugar, D-vicenisamine Fig. 1.[6] A major biological characteristic of this compound is its significant inhibitory activity, especially against HL-60 (human leukemia) and COLO205 (human colon carcinoma) *in vitro* and Co-3 (human colon carcinoma) *in vivo*.[6] The entire structure of vicenistatin, including its absolute configuration, was proposed from degradation studies[6,7] and was confirmed during the course of synthetic studies toward the first total synthesis.[8]

Vicenistatin has received considerable attention because of its potential as a new anticancer drug. Similarly, the biosynthetic pathway of vicenistatin has been extensively studied.[9] Vicenistatin was also recently identified as a biologically active molecule from the National Cancer Institute (NCI) libraries using a high-throughput yeast halo assay.[10] In addition, a novel macrolactam antibiotic, sannastatin, whose structure is closely related to that of vicenistatin Fig. 1, i.e. it has the same deoxyamino sugar vicenisamine, was newly isolated, together with vicenistatin, as a growth inhibitor against brine shrimp (*Artemia salina*) larvae.[11] Recently, a total synthesis of vicenistatin was newly reported, along with its structure–activity relationship, especially for the macrolactam skeleton.[12] In this study, the vicenisamine sugar moiety was synthesized as a protected glycosyl donor using an intramolecular epoxide opening reaction via the carbamate. Further, the Tsukuba group very recently suggested that vicenistatin is a novel

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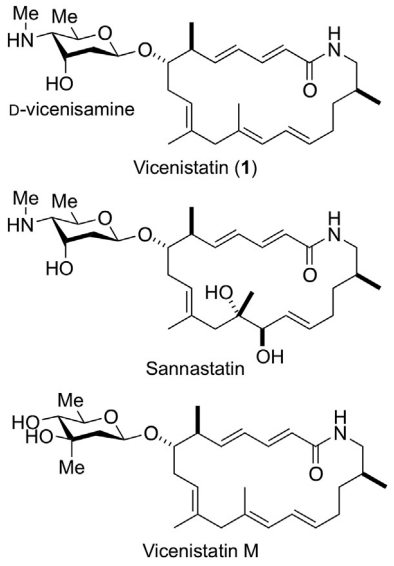


Fig. 1. Structures of vicenistatin and related compounds.

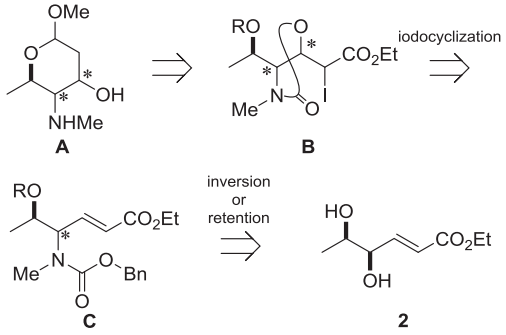
compound that induces the formation of early endosome-derived vacuole-like structures in cells by activating Rab5 and by increasing the fluidity of the membrane surface.[13]

Interestingly, instead of vicenisamine, a new congener, vicenistatin M, which contains a neutral sugar moiety, D-mycarose (2,6-dideoxy-3-*C*-methyl-D-*ribo*-hexose) Fig. 1 and shows no cytotoxicity, was isolated during the course of biosynthetic studies.[14] This finding strongly suggests that the vicenisamine amino sugar plays an important role in the cytotoxicity of vicenistatin.

Methyl D-vicenisaminide has been previously synthesized from a sugar material,[15] a chiral epoxy alcohol,[8b] ethyl sorbate,[4a] and methyl sorbate.[16] However, practical and generic approaches for obtaining vicenisamine and its isomers are still desirable from the viewpoint of producing vicenistatin derivatives or biosynthetic tools. In our opinion, the previously reported synthetic routes are not fully satisfactory in all these respects. In this paper, we describe a versatile strategy for the synthesis of D-vicenisamine and its epimers (3-*epi*- and 4-*epi*-D-vicenisamine) starting from a chiral diol (**2**). The diol is afforded in both enantiomers by Sharpless asymmetric dihydroxylation (AD) of commercially available ethyl sorbate.

2. Results/discussion

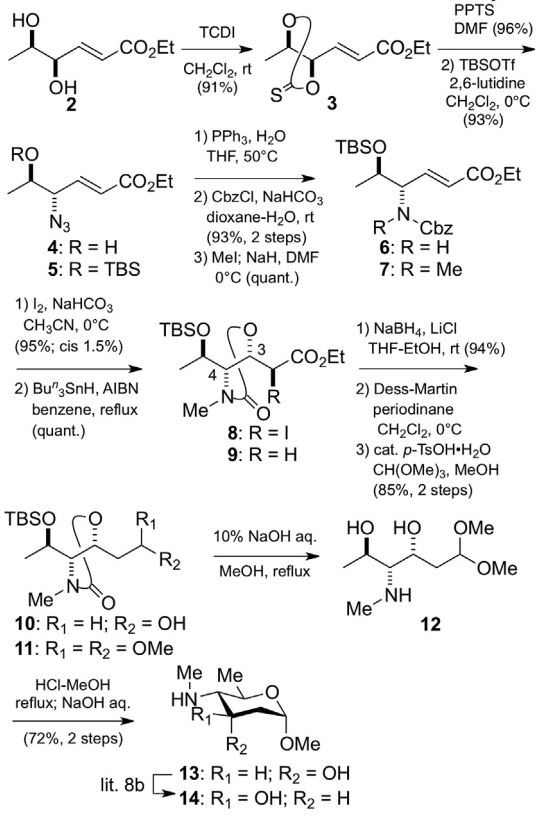
From the retrosynthetic analysis of vicenisamine and its isomers **A** Scheme 1, we assumed that oxazolidinones **B** would be a suitable precursor for deoxyamino sugars with a 3,4-aminoalcohol moiety, especially vicenisamine. Notably, oxazolidinone derivatives **B** could be prepared by iodocyclization of the carbamate based on the (*E*)-α,β-unsaturated ester moiety indigenous to the starting materials expectantly with 1,2-asymmetric induction. Moreover, carbamates **C** could be prepared, in turn, from chiral diol **2** via regioselective introduction of a nitrogen functional group with inversion or retention of the stereochemistry of the 4-hydroxy group. Evidently, both enantiomers of the starting chiral diol **2** are easily obtained by Sharpless AD.



Scheme 1. Retrosynthetic analysis of vicenisamine and its isomers.

Starting chiral diol **2**[17] was acquired in 88% yield from commercially available ethyl sorbate[18] by Sharpless AD (AD-mix β) using $(DHQD)_2PHAL$ (dihydroquinidine phthalazine) as a chiral ligand.[19] A similar chiral diol obtained from *tert*-butyl sorbate and its epimer were reported by the Kitasato group as chiral starting materials for macrosphelides.[20]

The first stage in this synthesis involved the introduction of the nitrogen functional group with inversion of the stereochemistry of the 4-hydroxy group of diol **2**. In our preliminary report,[4a] we conducted this transformation in 51% yield (three steps). Protection of the 5-hydroxy group of diol **2** with a *tert*-butyldimethylsilyl (TBS) group furnished the corresponding ether with moderate selectivity and 64% yield, along with substantial amounts of the starting diol (7%), its regioisomer (8%), and di-TBS ether (20%). Subsequent sulfonylation of the 4-hydroxy group was followed by azide ion nucleophilic displacement (80%, two steps). The enantiomeric purity of diol **2** was estimated as 93% ee by ^1H NMR analysis of the thus-obtained 5-OH mono-TBS-protected alcohol as its (+)/(−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) ester, as described previously.[4a,4b] In this report, we successfully conducted selective transformation via a cyclic thionocarbonate in



Scheme 2. Synthesis of vicenisamine and 3-epimer from chiral diol **2**.