CHIRAL β-LACTAMS AS SYNTHONS. STEREOSPECIFIC SYNTHESIS OF A 6-EPI-LINCOSAMINE DERIVATIVE[1] 祝古稀

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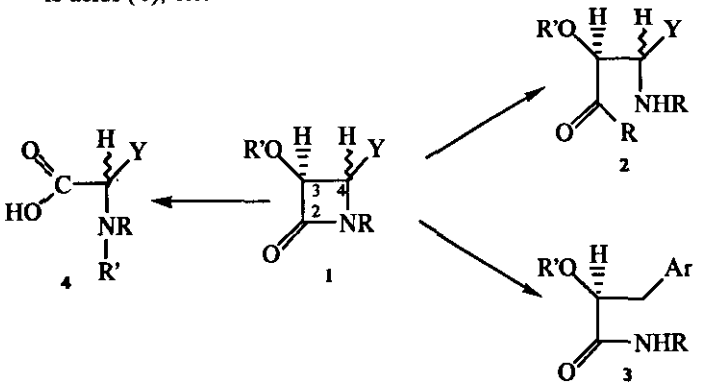
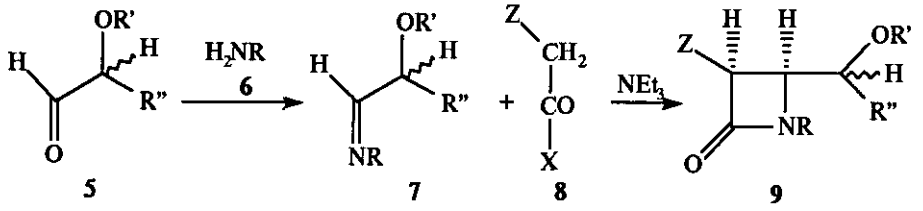
Abstract - A derivative of 6-epi-lincosamine has been prepared by a sequence of stereospecific steps from an optically active, *cis*-α-hydroxy-β-lactam. This β-lactam was obtained by an enantiospecific cycloaddition reaction between methoxyacetyl chloride, triethylamine and a Schiff base derived from benzylamine and an optically active aldehyde derived from D-galactopyranose.

祝古稀 Dedicated to Prof. Arnold Brossi on the happy occasion of his seventieth birthday.

A substituted β-lactam (e.g. **1**) constitutes a densely functionalized molecule that can undergo a variety of stereospecific reactions including molecular rearrangements.[2] Additionally, the four-membered heterocyclic ring can be cleaved in several ways to produce various types of compounds such as derivatives of β-amino acids (**2**), α-hydroxyacids (**3**), α-amino acids (**4**), etc.[3]



In recent years we[4] have studied different approaches to optically pure β-lactams of predictable absolute configuration. Independent work from Hoffmann-La Roche laboratories[5] and our research group [6] has indicated that the reaction of an acid chloride (or equivalent) (**8**) with a Schiff base (**7**) in presence of triethylamine (or other tertiary amines) leads to a single, optically pure, cis stereoisomer of a β-lactam (**9**) if the Schiff base is derived



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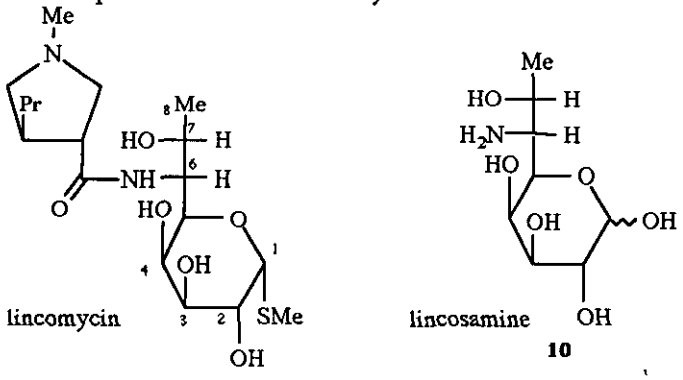
from an optically active aldehyde of type (**5**) and an achiral amine (**6**).

We[7] initiated a study on the suitability of optically active β-lactams of type (**9**) as synthons for higher amino sugars found in nature. We wish to report here on our synthetic approach to isomers of lincosamine[8] (**10**), an eight carbon amino sugar that is a part of the antibiotic lincomycin.



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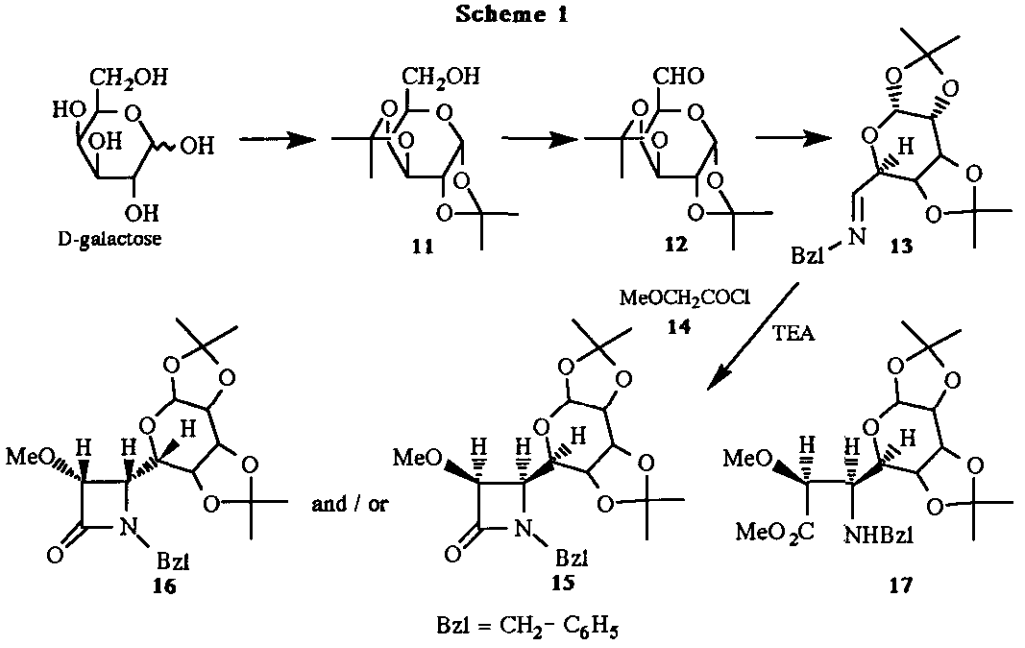
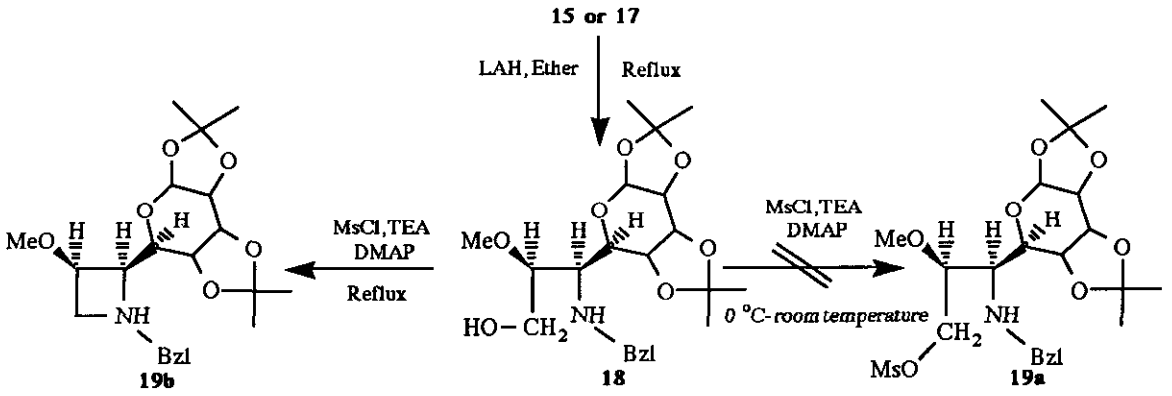
Our starting point was commercially available[9] 1,2,3,4-di-*O* -isopropylidene-α-D-galactopyranose (**11**) which was oxidized with pyridinium chlorochromate to the known aldehyde[10] (**12**). Condensation with benzylamine in presence of molecular sieves converted **12** to the Schiff base (**13**) which was characterized by ir and mass spectral data and then used without further purification for β-lactam formation.

Reaction of methoxyacetyl chloride (**14**) with **13** in presence of triethylamine (TEA) in methylene chloride at low temperature led to a single *cis*-β-lactam in 50% yield which should correspond to **15** or **16** (Scheme 1). The strategy (Scheme 2) at this point was to hydrolyze the amide bond in the β-lactam and reduce the carboxy group to the desired methyl group (C-8) of lincosamine without affecting the stereochemistry of the methoxy group bearing carbon. Basic hydrolysis of **15** with sodium methoxide in methanol led to the desired β-lactam cleavage and produced the expected methyl ester (**17**) which was contaminated with the corresponding ethyl ester.[11] This impurity was no hindrance in the next step which was the lithium aluminum hydride reduction to the primary alcohol (**18**) which could also be abtained directly from the β-lactam (**15**). The next step was to be the standard conversion of primary alcohol to its mesylate (**19a**). The density of functional groups in **18**, however, favored the formation of the azetidine (**19b**) which was of no value to the proposed synthesis.

Scheme 1



Scheme 2

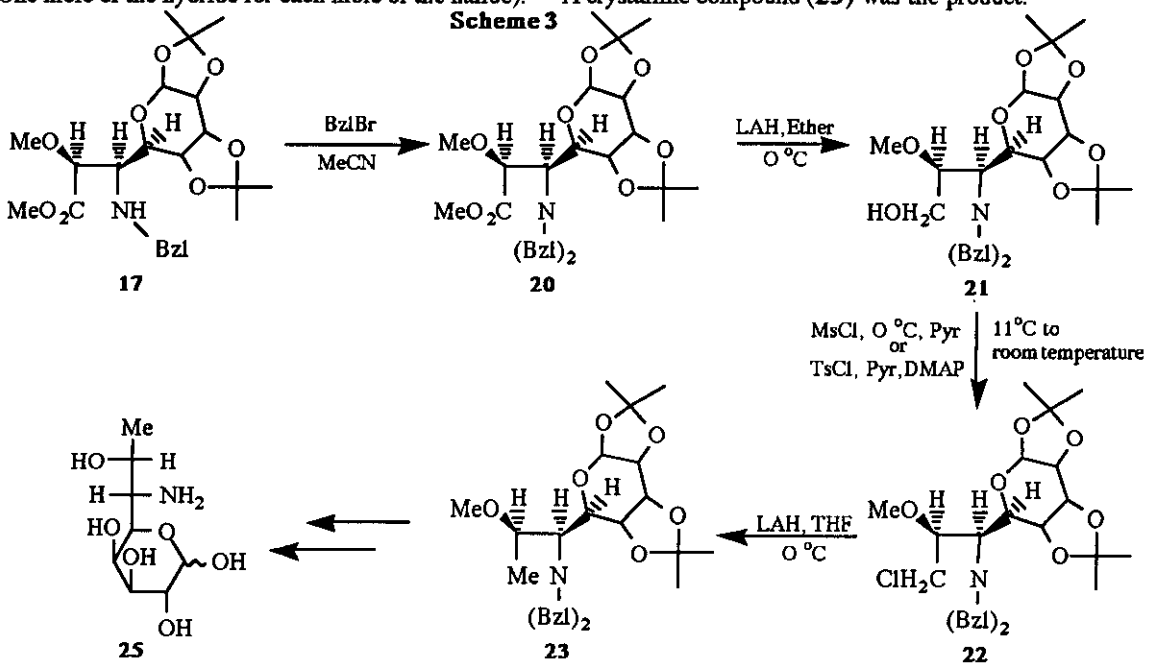


To prevent azetidine formation, it was planned to prepare an *N,N* -dibenzyl version of **18**. After some experimentation suitable conditions were found for benzylating (**17**) with benzyl bromide and obtain a crystalline product (**20**). Upon reduction with lithium aluminum hydride at 0 °C, the primary alcohol (**21**) could be obtained in good yield.

Treatment of **21** with mesyl chloride in pyridine at 0 °C, failed to produce the desired mesylate. The product of this reaction was found to be the primary chloride (**22**) (Scheme 3). Reduction of the chloromethyl group to a methyl group proved unexpectedly difficult. After many trial experiments it was found that the alkyl chloride

could be reduced in very good yield if a *clear solution* of lithium aluminum hydride in THF was used *in excess* (One mole of the hydride for each mole of the halide).[12] A crystalline compound (**23**) was the product.

Scheme 3



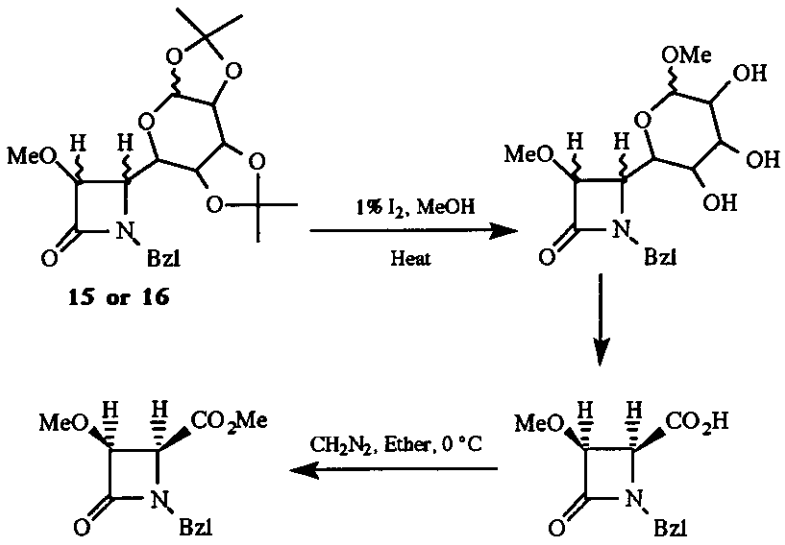
While the above chemical transformations were in progress, experiments were performed to determine the chirality induced during β-lactam formation. Following a published procedure[13] (**15** or **16**) was heated under reflux with iodine and methanol to remove the isopropylidene protective groups. Subsequent oxidation with ruthenium tetroxide ($RuCl_3$ + $NaIO_4$) according to a literature method[14] converted the sugar moiety to a carboxy function. Treatment with diazomethane provided a *cis*-β-lactam methyl ester (**24**) (Scheme 4).

Based on the stereospecific transformations conducted on **15** our final product should have the stereostructure (**23**) which corresponds to **25**, a 6-epi-lincosamine derivative. To remove all doubts about the structure of this compound single crystal X-ray diffraction studies were conducted on two compounds : **21** and **23**. The former proved unsuitable but the latter gave a structure (see the Pluto diagram **26**)[15] that was fully in agreement with the stereostructure and absolute configuration of **23**.

In summary, we have developed a short and stereospecific synthesis of an optically active stereoisomer of lincosamine and indicated pathways to other isomers and analogs. Comparison with the substituted β-lactam of known absolute configuration that was available in our laboratory[16] established that the stereostructure (**15**) rather

than **16**) was the correct designation of the enantiopure β-lactam obtained from the Schiff base (**13**). It

Scheme 4



15 or 16

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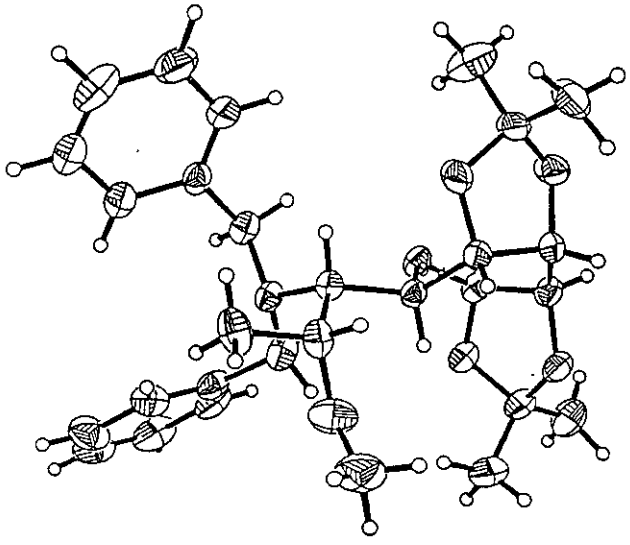
was noted that the correct configuration at C-4 of **15** can be predicted[17] on the basis of the absolute configuration of the asymmetric carbon next to the amino group in **13**.



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ACKNOWLEDGMENT

This research was supported by Stevens Institute of Technology and the National Science Foundation (INT-9116107).

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Received, 4th April, 1994