

CHIRAL β -LACTAMS AS SYNTHONS. STEREOSPECIFIC SYNTHESIS OF A 6-EPI-LINCOSAMINE DERIVATIVE¹ 祝古稀

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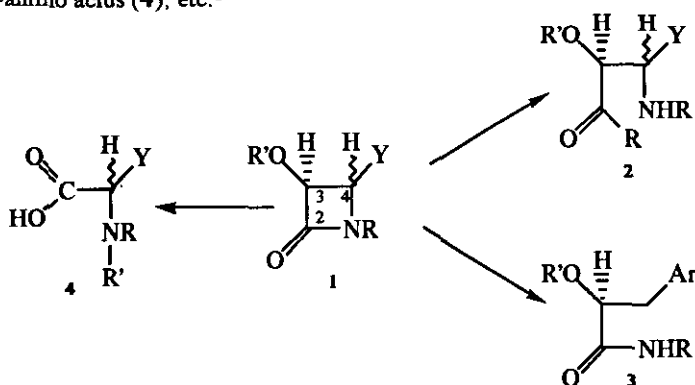
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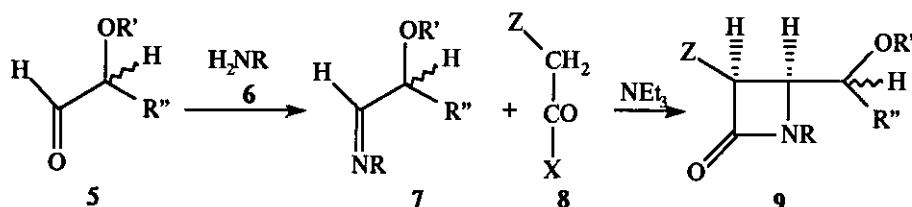
Abstract - A derivative of 6-epi-lincosamine has been prepared by a sequence of stereospecific steps from an optically active, *cis*- α -hydroxy- β -lactam. This β -lactam was obtained by an enantiospecific cycloaddition reaction between methoxyacetyl chloride, triethylamine and a Schiff base derived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

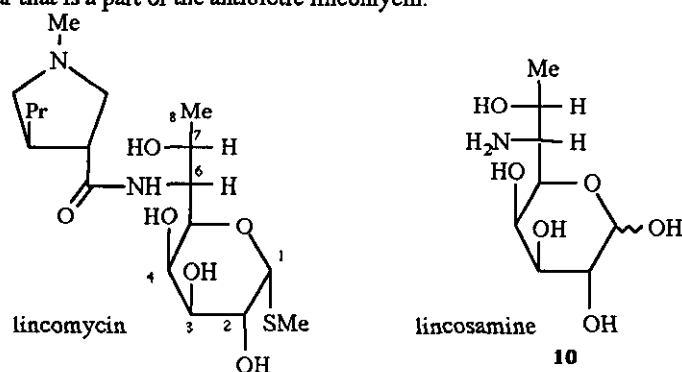


In recent years we⁴ have studied different approaches to optically pure β -lactams of predictable absolute configuration. Independent work from Hoffmann-La Roche laboratories⁵ and our research group⁶ has indicated that the reaction of an acid chloride (or equivalent) (**8**) with a Schiff base (**7**) 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



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

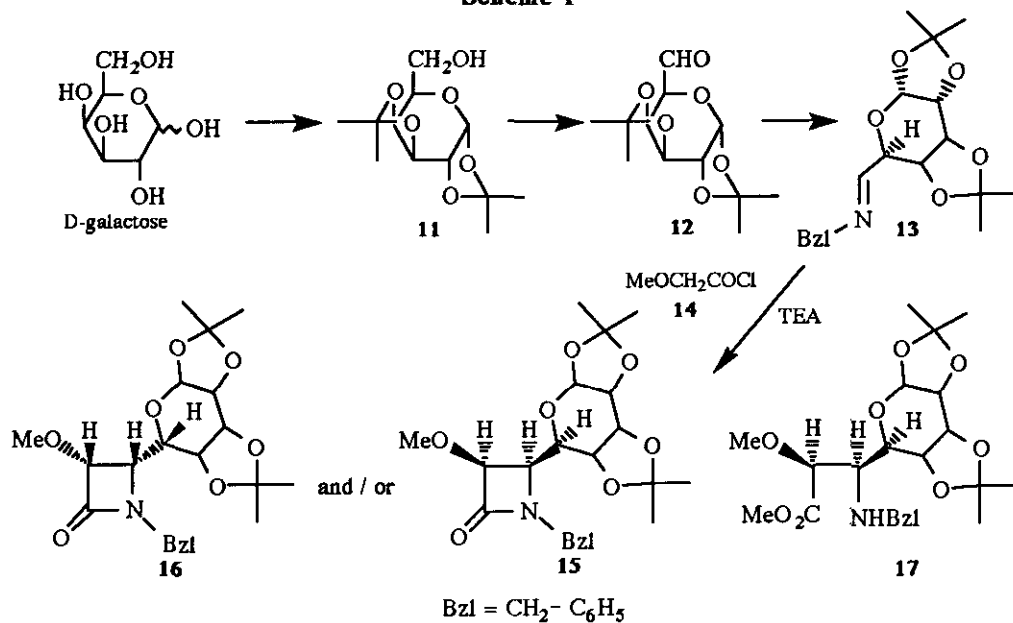
We⁷ initiated a study on the suitability of optically active β -lactams of type (**9**) as synthons for higher amino sugars found in nature. We wish to report here on our synthetic approach to isomers of lincosamine⁸ (**10**), an eight carbon amino sugar that is a part of the antibiotic lincomycin.



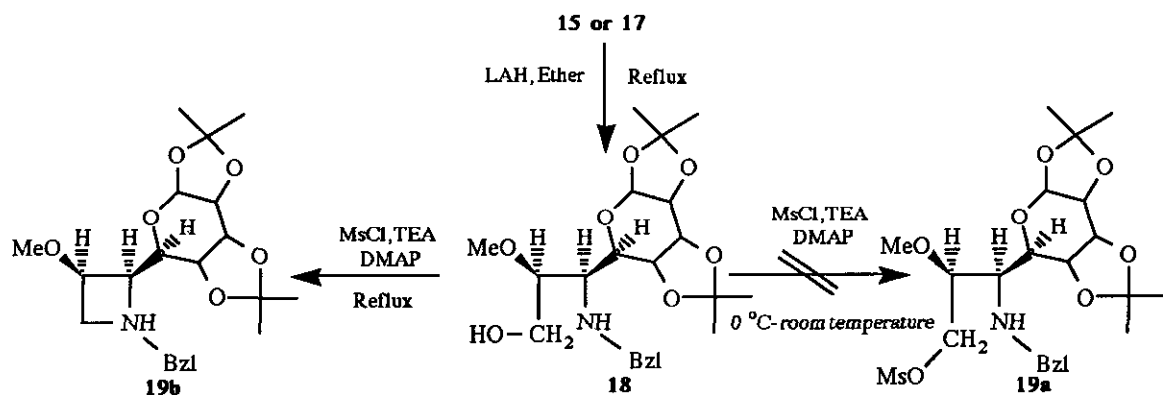
Our starting point was commercially available⁹ 1,2,3,4-di-*O*-isopropylidene- α -D-galactopyranose (**11**) which was oxidized with pyridinium chlorochromate to the known aldehyde¹⁰ (**12**). Condensation with benzylamine in presence of molecular sieves converted **12** to the Schiff base (**13**) which 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 obtained 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



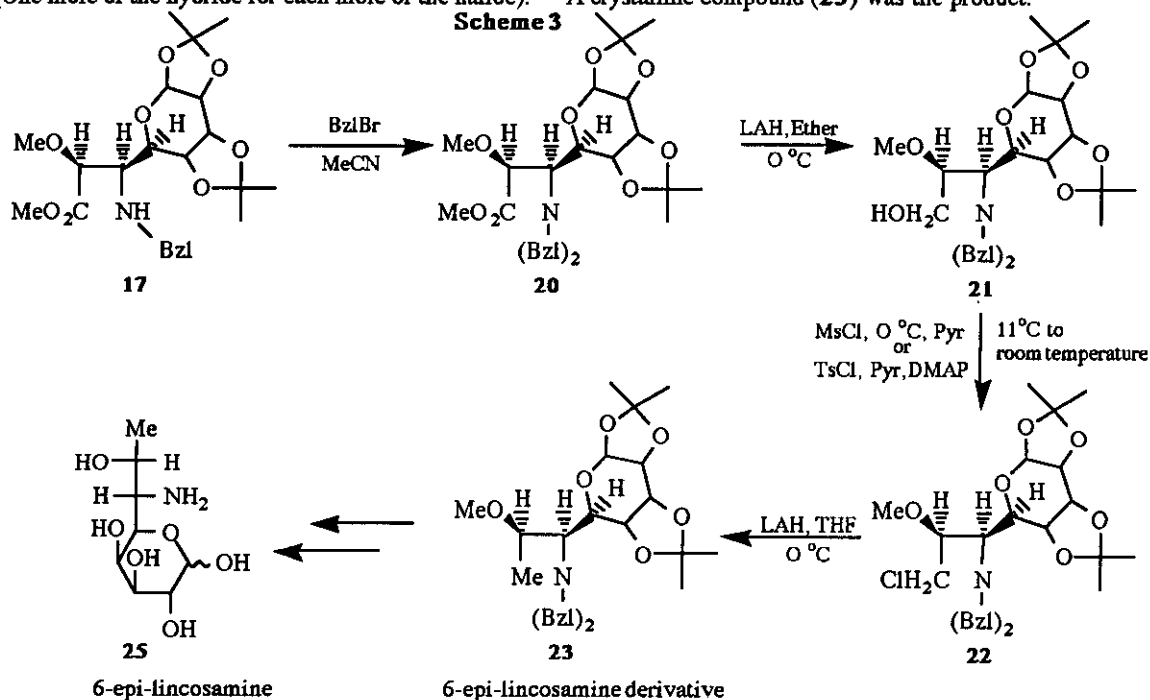
Scheme 2



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.



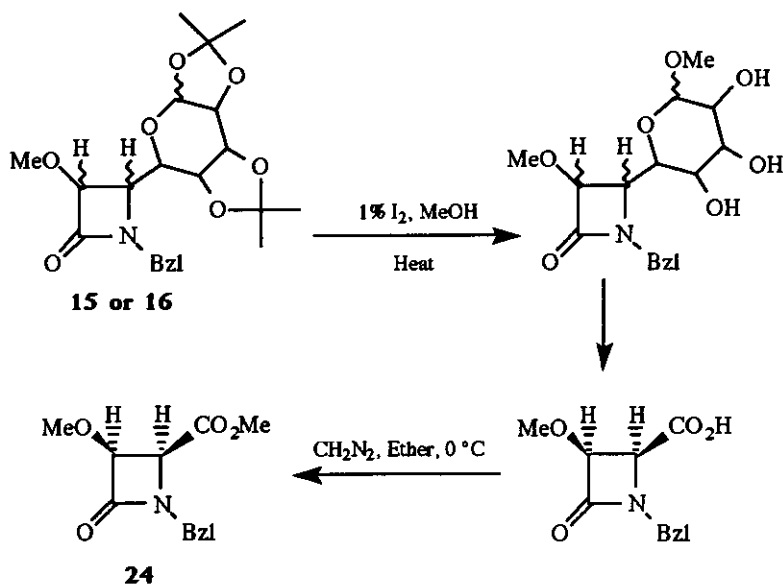
While the above chemical transformations were in progress, experiments were performed to determine the chirality induced during β -lactam formation. Following a published procedure¹³ (**15** or **16**) was heated under reflux with iodine and methanol to remove the isopropylidene protective groups. Subsequent oxidation with ruthenium tetroxide ($\text{RuCl}_3 + \text{NaIO}_4$) according to a literature method¹⁴ 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**.

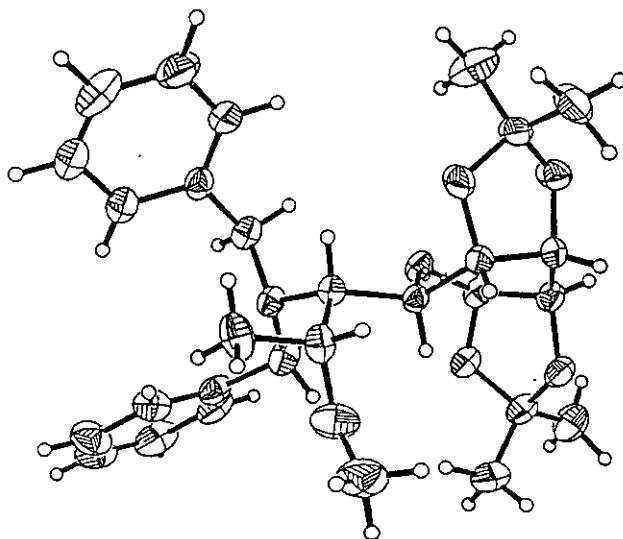
In summary, we have developed a short and stereospecific synthesis of an optically active stereoisomer of lincosamine and indicated pathways to other isomers and analogs. Comparison with the substituted β -lactam of known absolute configuration that was available in our laboratory¹⁶ established that the stereostructure (**15**) rather

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

Scheme 4



was noted that the correct configuration at C-4 of 15 can be predicted¹⁷ on the basis of the absolute configuration of the asymmetric carbon next to the amino group in 13.



ACKNOWLEDGMENT

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