

ENANTIOMERICALLY PURE β -LACTAMS WITH THE THIENAMYCIN SIDE CHAIN VIA GLYCOSYLATION¹

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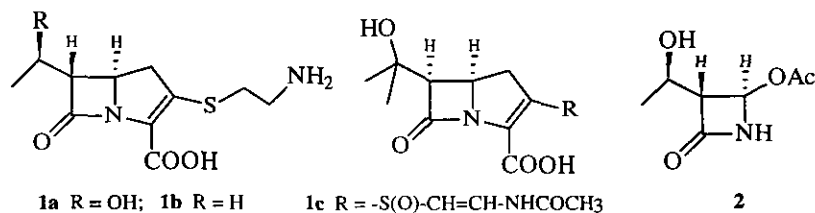
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Dedicated to the memory of Prof. Shun-ichi Yamada

Abstract - Easy access to both enantiomers of β -lactams with the thienamycin side chain was achieved via iodine catalyzed Ferrier reaction with commercially available tri-O-acetyl-D-glucal.

A new chapter in β -lactam chemistry was initiated in 1976 with the discovery of the β -lactam antibiotic thienamycin² (**1a**) with a carbon side chain in place of an amide side chain that characterizes penicillins and cephalosporins. This is also the first β -lactam antibiotic in clinical use to be manufactured by total synthesis³ rather than by fermentation. Other antibiotics of the thienamycin type include PS-5 (**1b**), carpenimycin (**1c**) and many synthetic carbapenems. Analogs of **1** are still being prepared by medicinal chemists. Several of the synthetic approaches require optically pure 3-(1'-hydroxyethyl)-4-acetoxy-2-azetidinone (**2**).⁴

We wish to present here a preliminary report on a convenient strategy involving reaction with commercially available glycal derivatives for obtaining both enantiomeric forms of racemic β -lactams with a 1-hydroxyethyl side chain (for example **8**). The availability of both antipodal forms of compounds is desirable for biological testing since enantiomers may differ in their pharmacological profiles.



The Ferrier Reaction

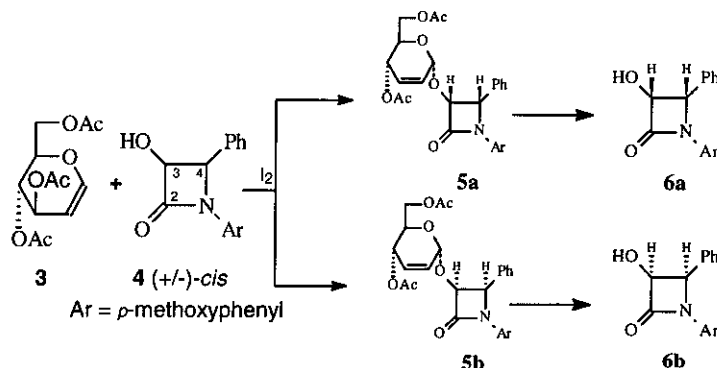
In the course of our continuing studies on β -lactams we have found variously substituted 3-hydroxy-2-azetidinones to be versatile synthons for compounds of different types (including antibiotics, alkaloids, amino acids, amino sugars, etc.).⁵ For an easy access to both the natural and the non-natural enantiomers of natural products we examined several approaches to both enantiomers of α -hydroxy- β -lactams.⁶ Recently⁷ we described the synthesis of the antipodal forms of a β -lactam (**6**) that is an intermediate for the side chain of Taxol.⁸ The strategy was to produce two easily separable diastereomers (**5a**) and (**5b**) by the Ferrier reaction⁸ on a racemic α -hydroxy- β -lactam which then led to the two enantiomeric forms (**6a**) and (**6b**) of this synthon (Scheme 1).

The Ferrier reaction involves an allylic rearrangement when a substituted glycal with a leaving group at C-3 reacts with a hydroxy compound. The products, under the influence of an acid catalyst, are 2,3-unsaturated pyranosides (usually a mixture of α - and β -anomeric forms with the thermodynamically more stable α -

anomer being favored in general). Koreeda *et al.*⁹ used iodine as a mild, neutral catalyst for reaction with several alcohols and reported the formation of both anomeric glycosides in varying ratios.

In our preliminary studies⁷ an optically pure *cis*- α -hydroxy- β -lactam was submitted to the Ferrier reaction catalyzed by iodine and the formation of only the α -anomeric glycoside was observed. This facilitated the separation of products from racemic alcohols since only two diastereomers instead of four were involved.

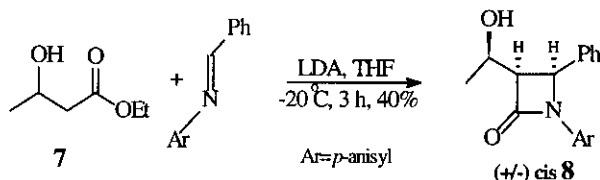
Scheme 1



Ferrier Reaction with Racemic 8

Our starting point was the racemic compound (**8**) prepared by a method described by Georg *et al.*¹⁰ Thus, reaction of the dianion of ($\pm$)-ethyl 3-hydroxybutyrate (**7**) and *N*-*p*-anisylbenzlideneamine using THF as solvent at -20°C afforded **8** as a single *cis*-isomer in 40% yield (Scheme 2).

Scheme 2



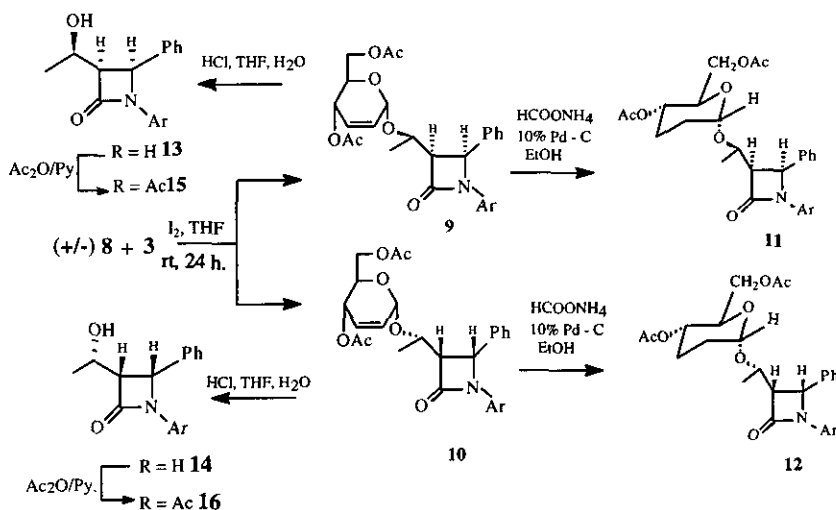
The Ferrier reaction⁸ was conducted by mixing a solution of **8** and commercially available tri-*O*-acetyl-D-glucal (**3**) in THF solution in the presence of iodine^{7, 11} as catalyst for 40 h. After the usual work-up, two products (**9**) and (**10**) were isolated in 60% yield (Scheme 3).

To establish the steric course of this reaction both the products (**9**) and (**10**) were reduced¹² by catalytic transfer hydrogenation (ammonium formate in the presence of Pd/C catalyst). The ¹H NMR spectra of the 2,3-dideoxy sugar derivatives (**11**) and (**12**) so obtained showed only small couplings ($J=1\text{Hz}$) of the anomeric proton indicating an axial linkage (α -glycoside)¹³ for the glycoside bond (Scheme 3).

The diastereomers (**9**) and (**10**) were separated by silica gel chromatography and hydrolyzed individually under mild acid conditions to give the enantiomers (**13**) and (**14**). These were converted to their respective acetates (**15**) and (**16**) (Scheme 3). The β -lactam (**15**) was shown to be enantiomerically pure by ¹H NMR spectroscopy using an optically active shift reagent.¹⁴ A similar NMR study showed **16** to have 85% ee (probably because of incomplete separation of **9** from **10**). This NMR study further indicated that the β -lactams (**13**) and (**14**) were antipodal. The partially racemic sample of **14** was resubmitted to the Ferrier reaction with **3** and the new sample of **16** so obtained was found to be optically pure.

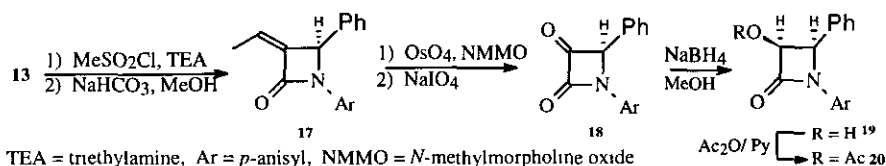
For determining the absolute configuration of **13** and **14**, oxidation of **13** was conducted with pyridine chlorochromate (PCC) to a ketone which was subjected to Baeyer-Villiger oxidation under a variety of conditions. Unfortunately, the desired acetate - for comparison with the acetates of **6a** and **6b** - could not be obtained. Hence, an alternative approach based on some of our previous work¹⁵ was attempted.

Scheme 3



The hydroxy- β -lactam (**13**) was converted to the olefin (**17**)¹⁵ in good yield by a two step sequence of mesylation followed by elimination.¹⁶ Osmium tetroxide catalyzed oxidation of **17** to a diol and subsequent cleavage with sodium periodate gave the α -keto- β -lactam (azetidine-2,3-dione) (**18**) in 80% yield. This optically active compound was reduced to a *cis*-3-hydroxy-2-azetidinone (**19**) following the method described by Palomo *et al.*¹⁷ The NMR spectra of the corresponding acetate (**20**) (Scheme 4) in presence of a chiral shift reagent showed it to be optically pure and with the same absolute configuration as **6b** described earlier (Scheme 1). Therefore, the stereostructures of **13**, **14**, **15** and **16** indicate their absolute configuration.

Scheme 4



Concluding Remarks:

The extensive research conducted in industrial and academic laboratories has established various approaches to thienamycin,¹⁸ its analogs and related antibiotics.⁴ The phenyl (or substituted phenyl) group at C-4 of β -lactams has been oxidized to a carboxy group¹⁹ which has been replaced by a *trans* acetoxy group by reaction with lead tetraacetate.²⁰ The *N*-*p*-methoxyphenyl group of β -lactams can be replaced by a hydrogen by cerium(IV) ammonium nitrate (CAN) oxidation.²¹ Thus, optically active *cis* **14** is in a formal sense an intermediate for thienamycin and its diastereomers such as epi-thienamycin and analogs. Standard chemical transformations of the hydroxyethyl side chain of **8** would lead to the side chain of PS-5, carpetimycin and asparenomycons.

In brief, a convenient access to antipodal forms of various types of hydroxy- β -lactams has been developed using iodine catalyzed Ferrier reaction with commercially available glycals.

ACKNOWLEDGMENT

We are grateful to the Stevens Institute of Technology for research facilities and the National Science Foundation (INT-9116107) for financial support to Olivia Zegrocka of the Institute of Organic Chemistry, Warsaw, Poland.

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