ENANTIOMERICALLY PURE β-LACTAMS WITH THE THIENAMYCIN SIDE CHAIN *VIA* GLYCOSYLATION[1]

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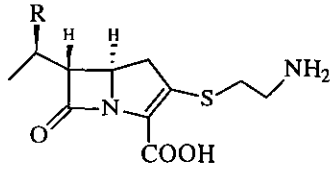
Dedicated to the memory of Prof. Shun-ichi Yamada

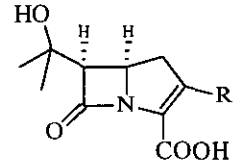
Abstract - Easy access to both enantiomers of β-lactams with the thienamycin side chain was achieved via iodine catalyzed Ferrier reaction with commercially available tri-O-acetyl-D-glucal.

A new chapter in β-lactam chemistry was initiated in 1976 with the discovery of the β-lactam antibiotic thienamycin[2] (**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 synthesis[3] rather than by fermentation. Other antibiotics of the thienamycin type include PS-5 (**1b**), carpetimycin (**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]

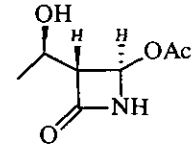
We wish to present here a preliminary report on a convenient strategy involving reaction with commercially available glycal derivatives for obtaining both enantiomeric forms of racemic β-lactams with a 1-hydroxyethyl side chain (for example **8**). The availability of both antipodal forms of compounds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



1a R = OH; **1b** R = H



1c R = -S(O)-CH=CH-NHCOCH3



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The Ferrier Reaction

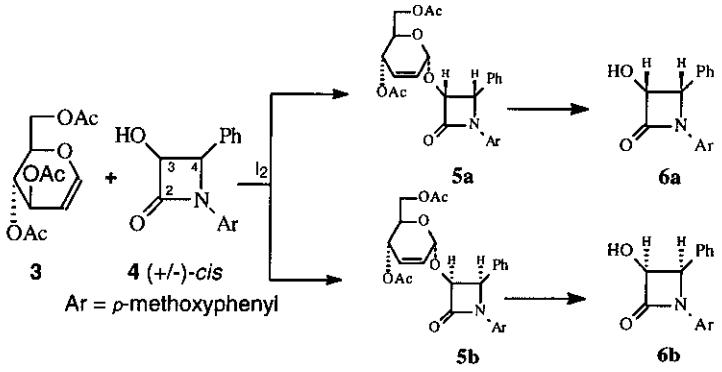
In the course of our continuing studies on β-lactams we have found variously substituted 3-hydroxy-2-azetidinones to be versatile synthons for compounds of different types (including antibiotics, alkaloids, amino acids, amino sugars, etc.).[5] For an easy access to both the natural and the non-natural enantiomers of natural products we examined several approaches to both enantiomers of α-hydroxy-β-lactams.[6] Recently[7] we described the synthesis of the antipodal forms of a β-lactam (**6**) that is an intermediate for the side chain of Taxol.® The strategy was to produce two easily separable diastereomers (**5a**) and (**5b**) by the Ferrier reaction[8] 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 studies[7] 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.

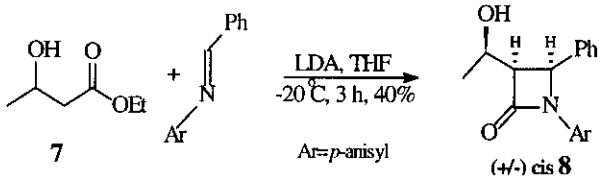
Scheme 1



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 (±)-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



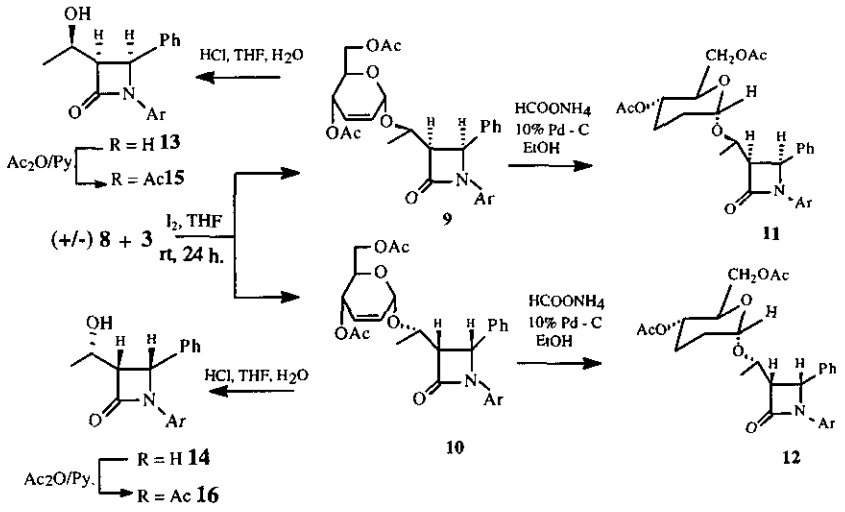
The Ferrier reaction[8] was conducted by mixing a solution of **8** and commercially available tri-*O*-acetyl-D-glucal (**3**) in THF solution in the presence of iodine[7, 11] as catalyst for 40 h. After the usual work-up, two products (**9**) and (**10**) were isolated in 60% yield (**Scheme 3**).

To establish the steric course of this reaction both the products (**9**) and (**10**) were reduced[12] by catalytic transfer hydrogenation (ammonium formate in the presence of Pd/C catalyst). The ^{1}H NMR spectra of the 2,3-dideoxy sugar derivatives (**11**) and (**12**) so obtained showed only small couplings (J=1Hz) 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 ^{1}H 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.

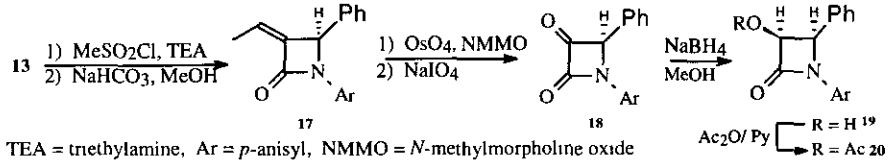
For determining the absolute configuration of **13** and **14**, oxidation of **13** was conducted with pyridine chlorochromate (PCC) to a ketone which was subjected to Baeyer-Villiger oxidation under a variety of conditions. Unfortunately, the desired acetate - for comparison with the acetates of **6a** and **6b** - could not be obtained. Hence, an alternative approach based on some of our previous work[15] 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 group[19] 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 asparenomycins.

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

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