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THE ASYMMETRIC SYNTHESIS OF β-LACTAM ANTIBIOTICS - IV.[1]

A FORMAL SYNTHESIS OF THIENAMYCIN.

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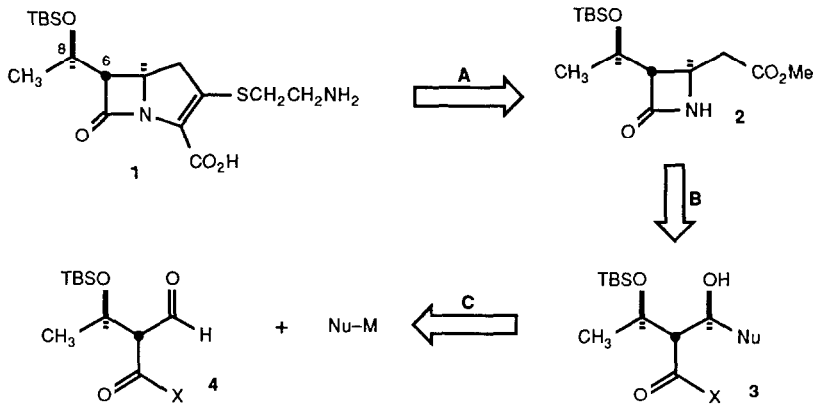
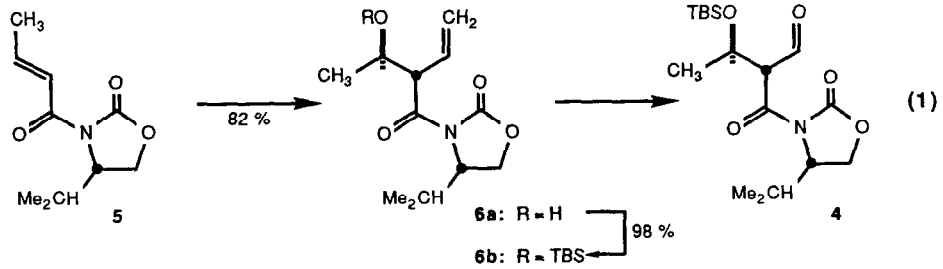
Abstract: Oxidative cleavage of crotonate imide aldol adduct **6b** provides the configurationally stable aldehyde **4**. Transformation of this aldehyde to enantiomerically pure β-lactams is described.

One of the unique structural features that differentiates the carbapenem antibiotic thienamycin **1** from the penicillins and cephalosporins is the hydroxyethyl side chain at C-6. In total syntheses directed toward this molecule, the stereocontrolled incorporation of this side chain has proven to be one of the major challenges.[2] One previously unexplored approach to the synthesis of thienamycin (**1**) is illustrated below. This projected route proceeds through the known lactam ester **2**[3] which might be constructed from a precursor such as **3** (X = NHR, Nu = CH_2CO_2Me) *via* intramolecular N-C_4 alkylation (Transform B). It was of particular interest in this study to determine whether α-formyl β-hydroxy carboxylic acid derivatives such as **4** could be constructed, and more importantly, to evaluate whether these intermediates might be suitable substrates for diastereoselective carbonyl addition (Transform C). This letter examines each of these issues and outlines an efficient enantioselective synthesis of the versatile thienamycin precursor **2**.



In initiating the above plan, the C-6 and C-8 stereocenters of thienamycin were established through aldol addition of the dibutylboryl enolate of imide **5** to acetaldehyde as described in the preceeding Letter (eq 1).[4] The hydroxyl group of the adduct **6a** was protected using tert-butyldimethylsilyltriflate[5] (2,6-lutidine, CH_2Cl_2, 0°C) to give **6b** in 98% yield. Oxidative cleavage to the aldehyde **4** was achieved in high yield as follows: To a 0.1*M*

solution of the silyl ether **6b** in 1:1 CH_2Cl_2:MeOH was added 0.5 equiv of 2,6-lutidine and a trace of Sudan III dye. The pink solution was cooled to –78°C and treated with a dilute stream of ozone in oxygen until the color of the dye faded. After the excess ozone was quenched with a few drops of 2,3-dimethyl-2-butene, dimethyl sulfide (10 equiv) was added and the solution stirred at room temperature for 45 min. The reaction was partitioned between hexane and water, the organic phase washed with saturated aqueous $CuSO_4$, water, and brine, and then dried (Na_2SO_4). Concentration afforded an oily solid, consisting of the aldehyde **4** and varying amounts of the the corresponding methyl hemiacetal. NMR analysis of this material revealed the aldehyde to be stereochemically homogeneous, with none of the enol tautomer or α-epimer detected. The configurational stability of **4** was not unexpected based on our earlier experience with related β-keto imides;[6] however, we have found this aldehyde to be labile to both chromatography and storage, and it is recommended that this material be used promptly without further purification.



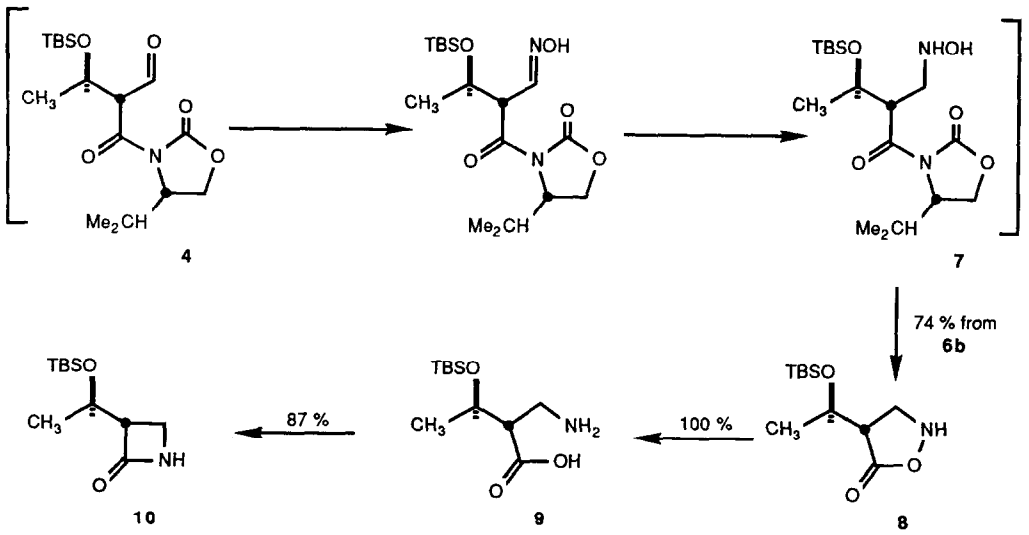
(1)

The initial plan to prepare **2** was envisioned to proceed via the 4-unsubstituted azetidinone **10**. The preparation of **10** is outlined in Scheme 1. Oxime formation under carefully defined conditions (10 equiv. hydroxylamine hydrochloride, 3 equiv pyridine, dichloromethane, 0°, 5h) afforded the derived oxime as mixture of syn and anti isomers. In analogy to the aldehyde **4**, best results were obtained when this material was used directly after a simple aqueous workup. Reduction of the crude oxime mixture with sodium cyanoborohydride (2 equiv, 0.5*M* in 2:1 HOAc:THF, 0°C) afforded the hydroxylamine **7** which, upon treatment with triethylamine in dichloromethane, underwent cyclization to give isoxazolidinone **8**. The overall yield from **6b** for the four steps was 74%. An important feature of this sequence is the intramolecular cyclization to **8**, which serves to both cleanly remove the chiral auxiliary and to activate the N-O bond. Hydrogenation (1 atm) over palladium on carbon in ethanol rapidly cleaved this weak N-O bond to generate the β-amino acid **9** in quantitative yield. Finally, treatment of **9** with 2,2'–dipyridyl disulfide and triphenylphosphine according to literature precedent[7] afforded azetidinone **10**, mp 67-68°C, $[\alpha]_D$ -74.4° (*c* 1.05, $CHCl_3$), in 87% yield.

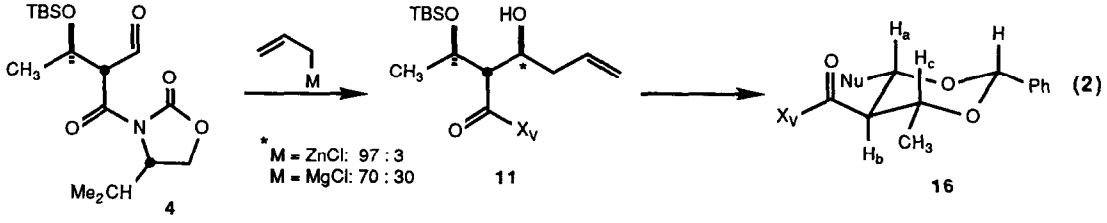
Conversion of **10** to the thienamycin intermediate **2** required oxidation followed by introduction of the carboxymethyl substituent. Electrochemical oxidation has been extensively used to effect oxidation α to the nitrogen of amides,[8] and 4-methoxy-2-azetidinone has been prepared in 51% yield from 2-azetidinone by this method.[9] However, we were unable to effect clean α-methoxylation with azetidinone **10** or simple derivatives thereof. In a simple cell using platinum electrodes (1 *M* solution in MeOH, Me_4N^+ BF_4^- electrolyte) oxidation of the solvent was the primary reaction, leading to low current yields. In addition, attempts to drive the reaction to completion led to a variety of byproducts, presumably resulting from over-oxidation and/or oxidation of the hydroxyethyl side chain.

The alternative to this route involved the incorporation of the C_4 side chain before closure of the β-lactam ring (eq 2). The desired synthon, alcohol **11**, is a bis aldol adduct which is conceptually available from two successive aldol addition reactions. In practice, though, this method failed due to rapid elimination of the

Scheme 1

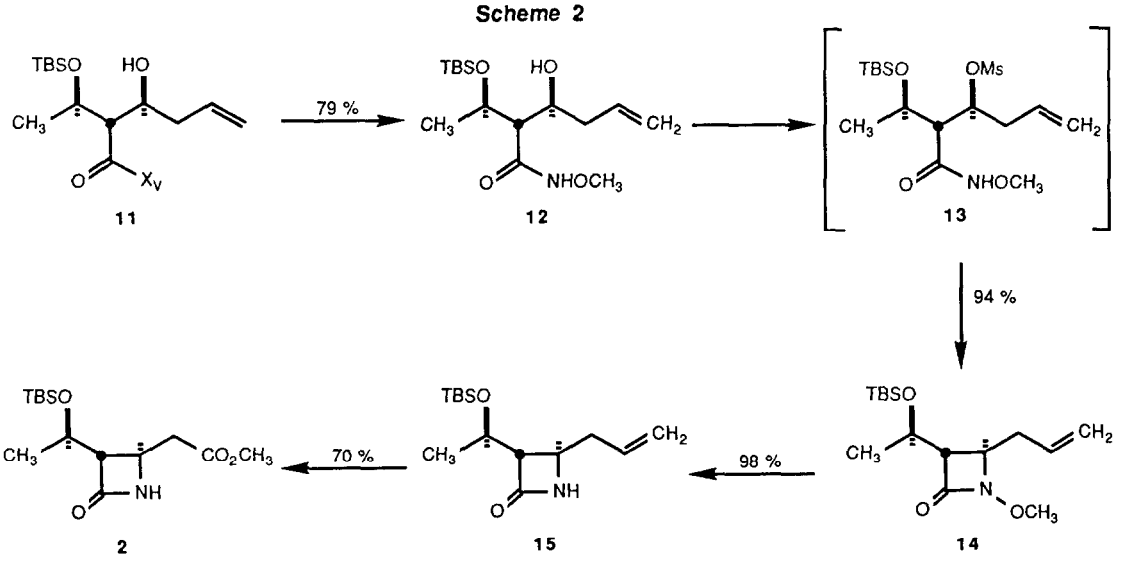


β–hydroxy (or β-alkoxy) group upon attempted enolization of aldol adducts with dibutlyboron triflate. The unique features of the 1,3 dicarbonyl system present in **4**, however, allow this synthon to be prepared by direct addition of carbon nucleophiles. After surveying a variety of conditions,[11] allylzinc was found to give both the highest stereoselection and the best overall yield. Addition of **4** to a mixture of allylmagnesium chloride (2.3 equiv.) and zinc chloride (1.5 equiv) in THF (-50°C, 3h) gave **11** and its epimer in a ratio of 97:3 (eq 2). Chromatography afforded pure **11**, mp 84-85°C, in 84% overall yield from **6b**. The configuration of the newly formed center was determined by desilylation (HF, acetonitrile) of **11** followed by acetal formation ($PhCH(OMe)_2$, PPTS) to give the dioxolane **16**. In this compound, H_b appears as a triplet with J = 9.6 Hz, which establishes the allyl group to be equatorial as shown.



Conversion of **11** to the thienamycin intermediate **2** utilized a series of reactions that we recently employed in the synthesis of PS-5 (Scheme 2).[1] Transamination of **11** with the reagent derived from trimethylaluminium and methoxyamine hydrochloride (3 equiv each, THF, 0°C, 8h)[12] afforded the N-methoxyamide **12** in 79% yield. Treatment of **12** with methanesulfonyl chloride (pyridine, 0°C) gave the mesylate **13** which was directly cyclized[13] (K_2CO_3, acetone, reflux) to give the N-methoxyazetidinone **14** in 94% overall yield from **12**. The 2.1 Hz coupling between H_3 and H_4 of this azetidinone confirms the trans orientation expected from cyclization of **13**. Dissolving metal reduction (THF, NH_3, 3 equiv Li, -78°C, 1 min) cleanly effected N-O bond cleavage to afford **15** in 98% yield. The synthesis was completed by oxidative cleavage of the olefin using RuO_4[14] followed by treatment of the unpurified acid with diazomethane to give **2**, mp 95.5-97.0°C, in 70% yield. This material proved identical in all respects to an authentic sample of **2**.

Scheme 2



The sequence described above provides the enantiomerically pure azetidinone **2** in 34% overall yield from the crotonate imide **5**. The principal virtue of the formal synthesis of thienamycin presented in the preceeding paragraphs lies in the flexibility for both analog production and future refinement. The present study clearly demonstrates that α-formyl carboximides such as **4** may be readily prepared with full control of all absolute stereochemical relationships. Further, one might project that other diastereoselective nucleophilic addition reactions could lead to even more efficient approaches to the thienamycin nucleus and related congeners.

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