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THE ASYMMETRIC SYNTHESIS OF β-LACTAM ANTIBIOTICS - III[1]. ENANTIOSELECTIVE SYNTHESIS OF (+) PS-5

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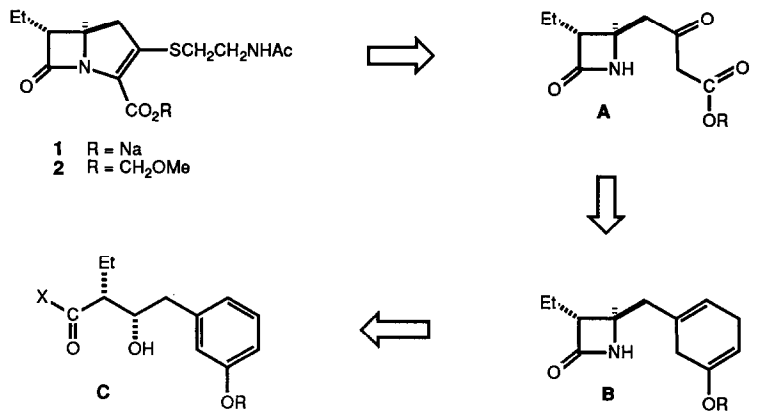
Abstract: An asymmetric synthesis of the carbapenem PS-5 is described.

Recently, we described an enantioselective synthesis of 1-carbacephalosporins, β-lactam antibiotics which are nuclear analogs of the natural cephalosporins.[1] An essential feature of this successful synthesis involved the utilization of 3-substituted anisoles as masked β-keto ester synthons. This synthon equivalency was established via dissolving metal reduction and subsequent ozonolytic degradation of the derived dihydroanisole. The purpose of this Letter is to report that this concept may be extended to the synthesis of carbapenems such as PS-5 (1).[2,3] The synthesis plan for this antibiotic is illustrated below.

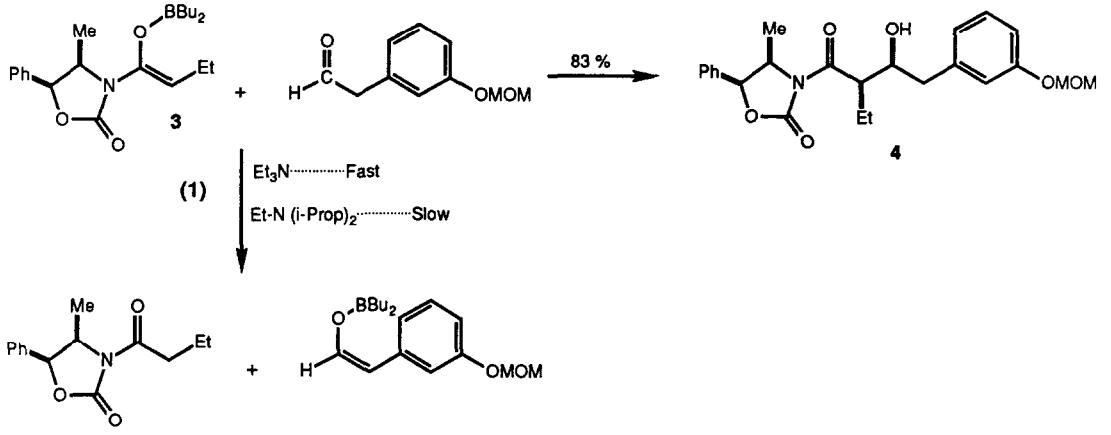
One of the self-imposed constraints that was placed on the synthesis plan involved the efficient use of protecting groups. In all reported syntheses of PS-5,[3] and related structures such as thienamycin,[4] the hydrolytic instability of the carbapenem nucleus places significant boundary conditions on the selection of an appropriate carboxyl protecting group R. In the synthesis plan outlined in Scheme I, we have found that the methoxymethyl (MOM) protecting group is fully compatible with all of the individual steps in the

Scheme 1



synthesis and may be successfully removed from the carbapenem nucleus. The ensuing discussion describes the specific details of this study.

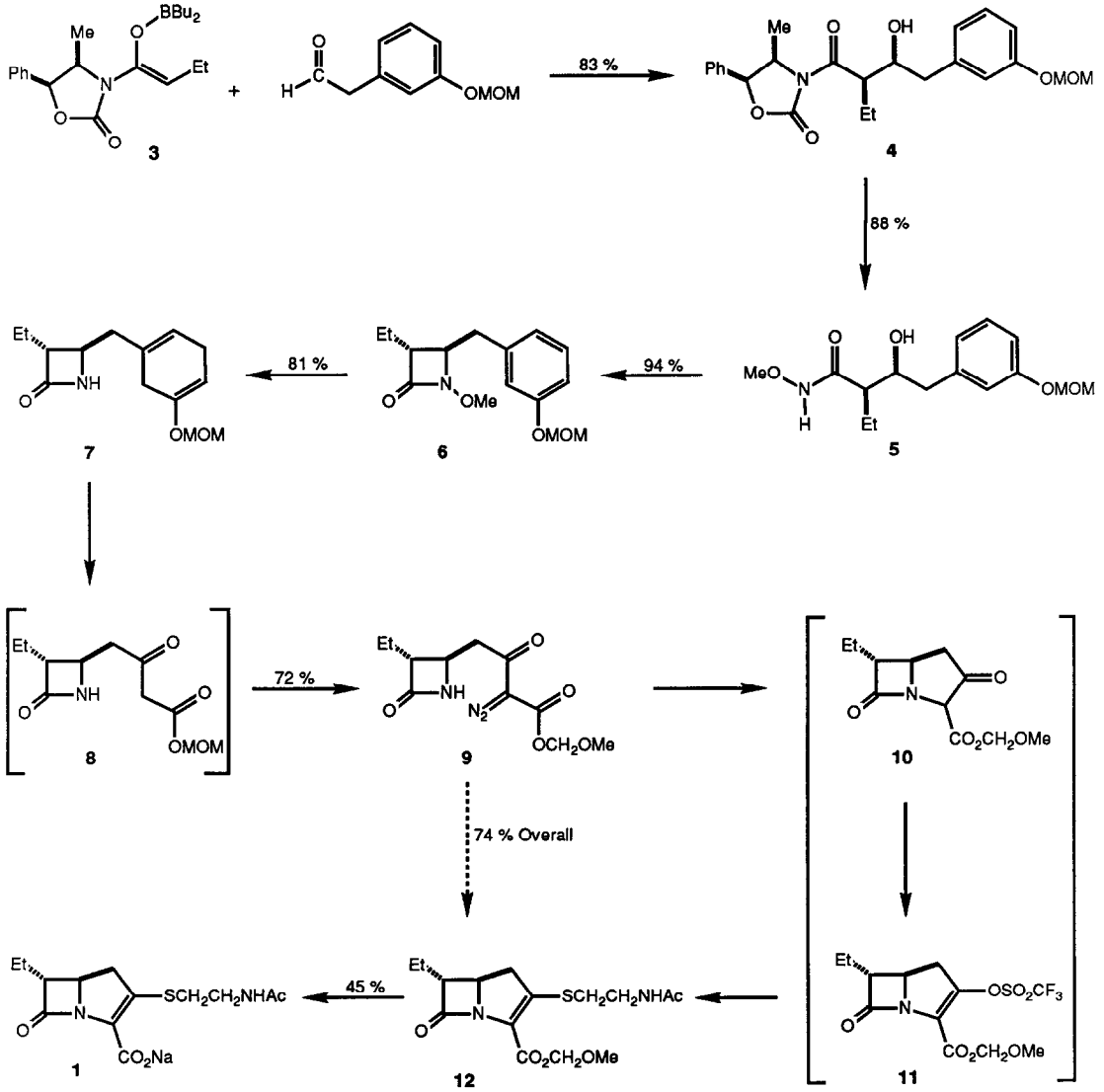
The two stereocenters of PS-5 were efficiently established via the asymmetric aldol addition reactions previously reported by us (Eq 1).[5] In this reaction, the boron enolate **3**, generated from the butyrimide precursor (1.0 equiv) with dibutylboron triflate (1.0 equiv) and diisopropylethylamine (1.1 equiv) under the following conditions (CH_2Cl_2, -78° to 0°C), was allowed to react with the illustrated phenylacetaldehyde derivative (0.7 equiv)[6] (-78° to 0°) to give the desired aldol adduct **4** in 83% yield. Quite surprisingly, the success of this reaction was critically dependent upon the structure of the amine base employed in the enolization step. While the more commonly used triethylamine as well as diisopropylethylamine were both successful in substrate enolization, it was found that triethylamine also effectively catalyzed the transfer of the dibutylboryl moiety to the readily enolizable phenylacetaldehyde, effectively aborting the aldol process. Fortunately, this transfer enolization process could be suppressed through the selection of a more sterically demanding enolization base, so that good yields of the aldol adduct could be realized.



The subsequent transformations of the aldol adduct **4** to PS-5 are illustrated in Scheme 2. Displacement of the chiral auxiliary from **4** to give the crystalline hydroxamic acid **5**, mp 112-113°C, was achieved in good yield (88%) without detectable epimerization using the aluminum amide reagent derived from methoxyamine hydrochloride and trimethylaluminum (3.0 equiv of each, 0°C, THF).[9] We have found this transamination to be quite general for a wide variety of related aldol adducts. The presence of the unprotected hydroxyl group in this substrate appears to be essential for the transamination process. This reaction is projected to proceed via the aluminum aldolate which presumably assists in exocyclic carboxyl activation. Formation of the azetidinone **6** was accomplished in 94% yield through methanesulfonylation ($MeSO_2Cl$, pyridine, 0°C) of **5** and subsequent base treatment (K_2CO_3, refluxing acetone) according to literature precedent.[10] In the next step, the dissolving metal reduction successfully accomplished both aromatic ring reduction and N-O bond cleavage. In this reaction, azetidinone **6** was reduced under the designated conditions (0.07M substrate in 3:1:1 NH_3:THF:t-BuOH, 5.0 equiv of lithium, 78°C, 1 h) to give the desired azetidinone **7** in 81% yield. This dihydroanisole derivative was then subjected to ozonolysis at

-78°C (1:1 MeOH:CH_2Cl_2, 0.5 equiv pyridine, Sudan III dye indicator) and reductive workup with dimethyl sulfide to give the labile β-keto ester **8** which was treated directly with β-naphthylsulfonylazide (diisopropylethylamine, MeCN, 0°C) to afford the crystalline diazo ester **9**, mp 75-76°C, in 72% overall yield for the two steps. Careful analysis of the unpurified ester **8** revealed that no methyl ester had been produced in conjunction with the ozonolysis. Presumably, this result reflects the strong preference for the enol ether-derived primary ozonide to fragment to give the aldehyde rather than the ester carbonyl

Scheme 2



oxide.[11] Formation of the carbapenem ring proceeded efficiently using the Merck carbene insertion reaction.[12] Treatment of diazo ester **9** with rhodium (II) octanoate in refluxing alcohol-free chloroform (15 min) afforded a solution of β-keto ester **10** which was immediately derivatized without isolation. The above reaction mixture was cooled to -15°C and treated sequentially with diisopropyl-ethylamine (3.0 equiv) and triflic anhydride (1.0 equiv). After 15 min, N-acetylcysteamine (1.5 equiv) was added (0°C 1.0 h) and the desired carbapenem **12** was isolated, after flash chromatography, in 74% overall yield from **9** for the three steps. The final step of the synthesis, cleavage of the MOM ester, was initially attempted under hydrolytic conditions. However, it quickly became apparent that the carbapenem nucleus was more sensitive towards aqueous acid (aqueous pH 4 buffer) than the MOM ester. Better results were obtained with anhydrous Lewis acids. Treatment of **12** with anhydrous aluminum trichloride in anisole[13] (4.0 equiv, -50°C, 1 h) followed by an aqueous bicarbonate quench afforded a 45% yield of the (+)PS-5 sodium salt **1** after preparative reverse-phase HPLC and lyophylization.

Despite the moderate yield of the final carboxyl deprotection step, this route affords enantionmerically pure (+)PS-5 in 13% overall yield from 3-methoxymethylphenylacetaldehyde. In addition, the transamination-ring closure sequence represents an efficient preparation of trans dialkyl β-lactams from syn aldol adducts.[15]

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