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SYNTHESIS OF CARBAPENEMS *via* METALLOIMINES-ESTER ENOLATES CONDENSATION: A NEW SYNTHESIS OF (+)-1β-METHYL PS-5

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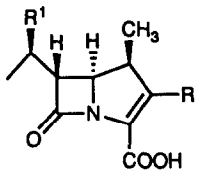
Abstract: The synthesis of the new β-lactam antibiotic, namely the (+)-1β-methyl PS-5, is described. The key step involves the ester enolate-metallo imine cycloaddition reaction.

Carbapenem antibiotics such as thienamycin[1] **1**, imipenem[2] **2**, the related 1β-methyl derivative[3] **3**, PS-5 and PS-6 **4**, **5**[4] and penem[5] **6** having unprecedented breath of spectrum and potency, have aroused a widespread interest and a variety of stereoselective syntheses of these significant compounds have been reported. The recent availability of the tribactam derivatives[6] **7** and of the monocyclic monobactam Aztreonam[7] **8** have increased the need of straightforward and versatile preparation methods for the synthesis of such compounds. One of the most versatile approach takes in account the synthesis of an azetidin-2-one ring variously substituted on the 3 and 4 positions followed by a final assembly to the bicyclic or tricyclic derivative as the last step of the strategic plan[4,5,6,8]. For this reason, over the last decade the literature in this field has witnessed the growing up of methodologies for the synthesis of the β-lactam ring.



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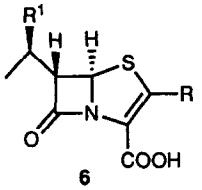

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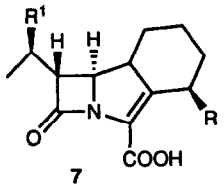
1: R=$SCH_2CH_2NH_2$, R^1=OH, R^2=H
2: R=$SCH_2C(NH)NH_2$, R^1=OH, R^2=H
3: R=$SCH_2CH_2NH_2$, R^1=OH, R^2=CH_3
4: R=$SCH_2CH_2NHCOCH_3$, R^1=H, R^2=H
5: R=$SCH_2CH_2NHCOCH_3$, R^1=CH_3, R^2=H
6: R=CH_2OCONH_2, R^1=OH, R^2=H
7: R=OCH_3, R^1=OH
8: R=AMT



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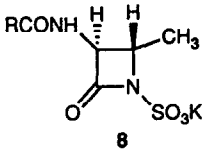

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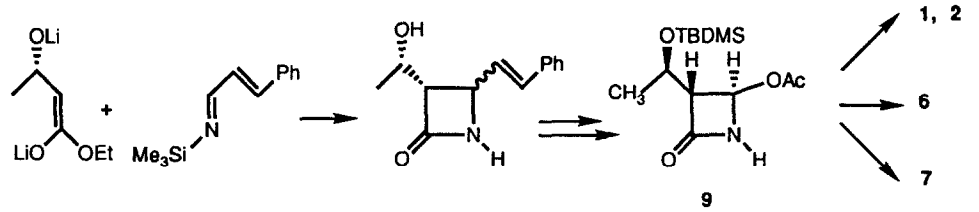
Among other methods, the condensation of metal ester enolates with imine has became one of the major routes by which the 2-azetidinone ring is constructed[9].

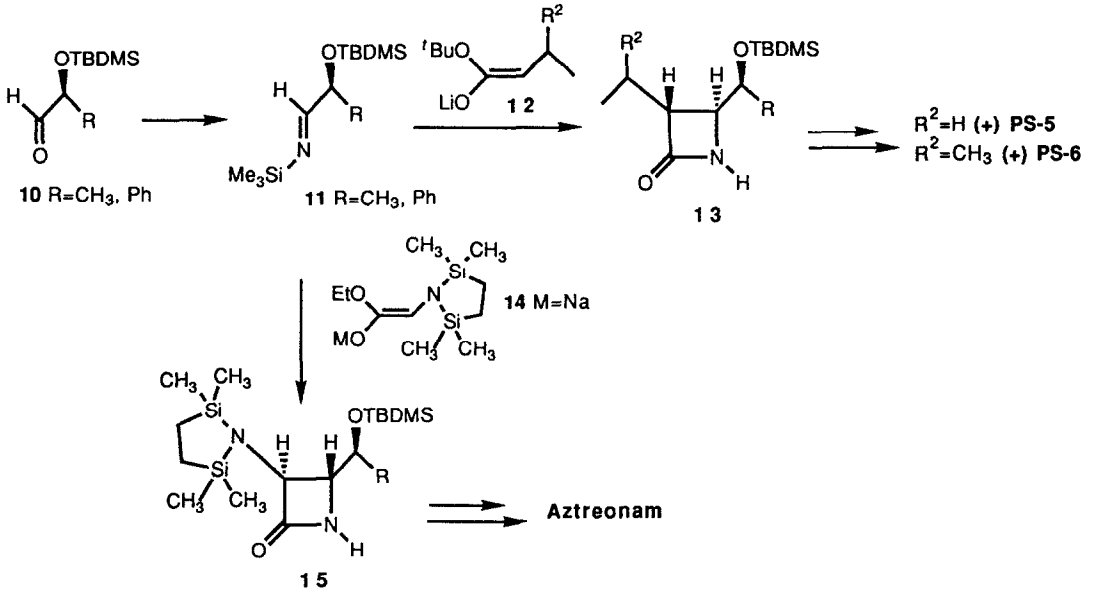
Our contributions in this field have been mainly addressed to the use of *N*-metallo imines as electrophilic partners in the condensation with ester enolates[10]. As a matter of fact our earlier papers[11] in this field have been concerned with the preparation of scalenic 4-acetoxy-3-hydroxyethyl azetidin-2-one **9**, a chiral building block for the preparation of thienamycin[12], penems and tribactams (Scheme 1).

Scheme 1



More recently, we succeeded in developing a highly stereocontrolled route to enantiomerically pure azetidinones *via* ester enolate-imine approach using a chiral imine as electrophilic partner in the cycloaddition reaction. By this methodology we have been able to prepare the naturally occurring carbapenem (+) PS-5 and (+) PS-6[13] and the synthetic monobactam Aztreonam[14]. Due to its complete diastereoselectivity, high overall yields, mild reaction conditions and use of inexpensive reagents such as ethyl lactate, the explored synthetic route constitutes one of the most practical method for preparing enantiomerically pure 3,4-disubstituted trans azetidinones bearing an achiral C3 side chain (Scheme 2)

Scheme 2



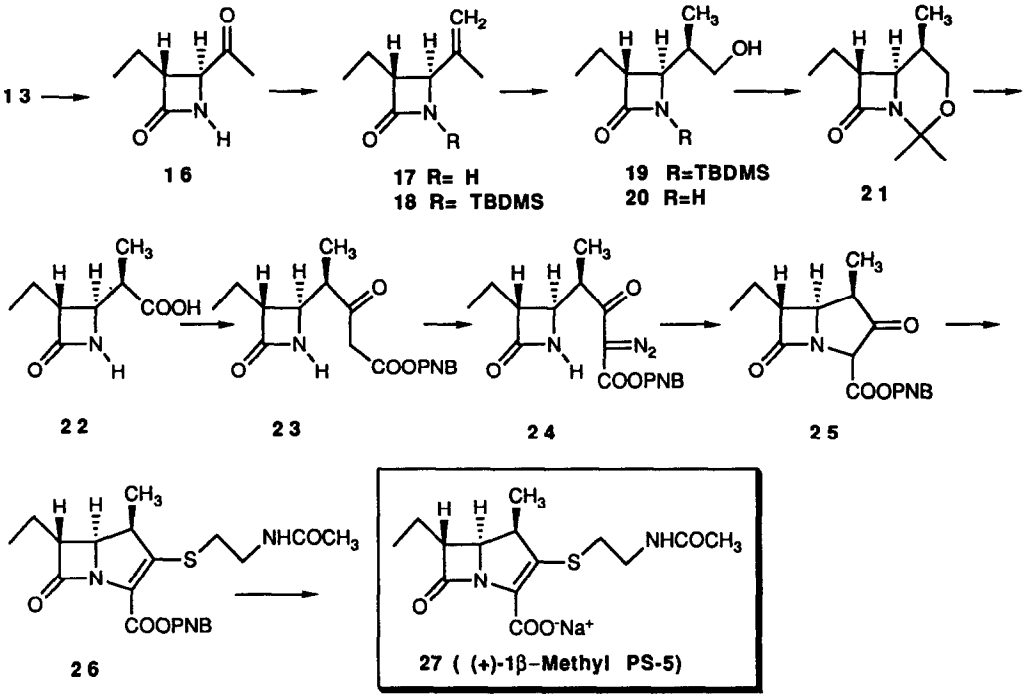
Aiming to further apply our method to the synthesis of other β-lactam antibiotics, the azetidinone **16** was sought to produce the new carbapenem (+) 1β-methyl PS-5 (Scheme 3).

Our approach starts from the readily available azetidinone **13** (R^2=H) obtained from (*S*) lactic aldehyde **10** in two high yielding steps[13] (Scheme 2). Oxidation of **13** (R^2=H) furnished its parent acetyl derivative (Chromic acid solution in Et_2O[13]) **16** which upon Witting olefination (NaH, DMSO/ methyltriphenylphosphonium bromide) yielded (60%) the expected 4-isopropenyl derivative **17** ($[\alpha]_D^{25}$=-73.6 (c 2.16, $CHCl_3$)) with the correct configuration at the C3 and C4 side chains. At this stage it was gratifying to find out that the hydroboration-oxidation of this material, previous protection of the N-H as TBDMS derivative **18** (TBDMSCl, DMAP, CH_2Cl_2 r.t. 92%) ($[\alpha]_D^{25}$= -22.8 (c 5.12, $CHCl_3$)), with dimethylsulfide-borane complex, followed by oxidation with H_2O_2[15] gave rise in 46% yield the azetidinone **19** ($[\alpha]_D^{25}$= -49.7 (c 6.15, $CHCl_3$)).

Having thus established the necessary stereocenters on the azetidinone ring, our synthetic plan called for the cleavage of the silyl group, followed by oxidation of the hydroxyl functionality and thereafter five membered ring assembly. Insofar cleavage of the silyl group was performed in quantitative yield by means of 1 N solution

of HCl in methanol. The so obtained alcohol **20** ($[\alpha]_D^{25}$=+8.1 (c 3.33 $CHCl_3$)) was converted in 70% yield to the acetonide **21** ($[\alpha]_D^{25}$=+27.8 (c 2.54 $CHCl_3$)) by treatment with dimethoxy propane in the presence of BF_3 Et_2O (Y%=69). Oxidation of **21** with Jones reagent[16] afforded in 74% yield the corresponding acid **22** (m.p. 107-108°C; $[\alpha]_D^{25}$=-8.4 (c 1.19 $CHCl_3$)).

Scheme 3



Treatment of the acid **22** under Masamune's conditions[17] yielded the chain extended β-keto ester **23** (64 % yield) ($[\alpha]_D^{25}$=-9.7 (c 1.85 $CHCl_3$)). The diazoester **24** ($[\alpha]_D^{25}$=-16.4 (c 3.0 $CHCl_3$)) was obtained with tosyl azide in CH_3CN (94%). The last step of our synthetic scheme was accomplished by the well known Merck procedure[3a] (52% overall yield) to give the bicyclic intermediate **26** ($[\alpha]_D^{25}$=+76 (c 0.38 $CHCl_3$)).

Hydrogenolysis of this material (H_2/Pd 10% on coal) furnished the unknown (+)-1β-methyl (+) PS-5 **27** ($[\alpha]_D^{25}$=+58 (c 1.55 H_2O)) in 30% yield.

Work is in progress to evaluate the biological activity of this and related compounds.

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