Tetrahedron Vol. 47, No. 43, pp. 9061-9070, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

β-LACTAMS FROM ESTER ENOLATES AND SILYLIMINES: AN ENANTIOSPECIFIC SYNTHESIS OF MONOCYCLIC β-LACTAMS.

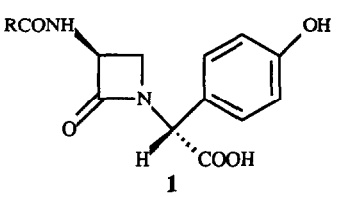
Patrizia Andreoli[a], Laura Billi[a], Gianfranco Cainelli[a]*, Mauro Panunzio[a]*, Elisa Bandini[b], Giorgio Martelli[b], Giuseppe Spunta[b]

a) Dipartimento Chimico G.Ciamician Università and C.S.F.M-C.N.R.
Via Selmi, 2 40126 BOLOGNA, ITALY
b) ICOCEA-C.N.R. Via della Chimica, 8 40064 OZZANO E. ITALY

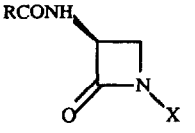
(*Received in UK* 1 *July* 1991)

Abstract: *Optically active 3,4-disubstituted azetidin-2-ones have been prepared by annelation of chiral silylimines derived from (S) or (R)-lactaldehyde with the ester enolate of the ethyl 2,2,5,5,-tetramethyl-1,2,5-azadisilolidin-1-acetate (STABASE). Oxidation of the hydroxyethyl side chain on the C-4 position of the β-lactam ring, followed by Baeyer-Villiger oxidation led to the optically active (3S, 4S) 3-amino-4-acetoxy-β-lactam. The absolute configuration of this compound was determined by elaboration of this substrate to a key intermediate in the synthesis of the antibiotic "Aztreonam". Nucleophilic displacement of the acetoxy group led to optically active 3-amino-4-alkyl (aryl)-azetidin-2-ones.*

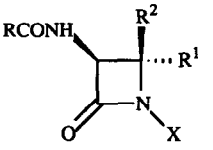
In view of the growing interest in the biological activity of naturally occurring monocyclic β-lactams such as the nocardicin **1** and the monobactam **2**, many synthetic analogues having more desirable biological properties have been developed[1].



1



2

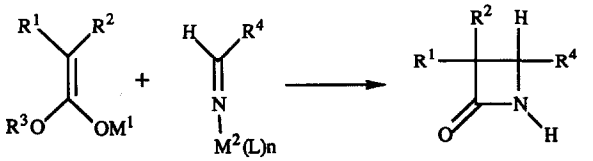


3

$X = SO_3^-$; OSO_3^-
R^1, R^2 = H, Me

These include monobactams alkylated at the 4-position **3**[2] which have been synthetized from 6-APA[3], by cyclization of β-hydroxyacyl sulfamates[4] or of β-hydroxy hydroxamic acid derivatives,[5] or by photolytic reaction of imines with pentacarbonyl[(dibenzylamino)carbene]chromium(0)[6].

Since the pioneering work by Gilman[7], many papers have appeared dealing with the construction of the azetidinone ring involving annelation of imines with ester enolates[8] (Eq.1). Particularly interesting and useful appears the cycloaddition reaction between *N* -metalloimines and ester enolates which furnishes directly *N*-unsubstituted β-lactam rings.



Eq. 1

M^1 = Na, Li, Zn, Al.

M^2 = Si, Al

Recently[9] we reported a new highly enantioselective synthesis of the carbapenem (+) PS-5 through the cycloaddition reaction between the *N* -trimethylsilylimine of the O-protected (*S*)-lactaldehyde, and the lithium enolate of *tert* -butyl butanoate. The application of this approach to the synthesis of monocyclic optically active 3-amino-4-alkyl (aryl) β-lactams is described in this paper. The stereochemical outcome in different conditions will also be described.

Results and discussion.

Lactaldehyde, in both enantiomeric form (*S*) or (*R*), is readily available by the reduction with diisobutylaluminum hydride (DIBAH) of the corresponding optically active ethyl ester, protected on the hydroxyl functionality as *tert* -butyldimethylsilylether[10] . This compound has been used as chiral building block, whereas the enolate of the ethyl 2,2,5,5,-tetramethyl-1,2,5-azadisilolidin-1-acetate (STABASE)[11] **6**, has been utilized as source of the necessary amino group in the 3-position of the forming β-lactam ring, in the syntheses of enantiomerically pure azetidinones we are going to describe.

Treatment of (2*R*)-2-*tert* -butyldimethylsilyloxy propanal **4** in THF with lithium bis(trimethysilyl)amide (LHMDSA) produces the *N* -trimethylsilyl imine[12] **5** (Scheme I). The resulting homogeneous solution was added at -78°C to an equimolar solution of the lithium enolate of STABASE **7**, prepared according to the standard procedure by treatment of the ester **6** with one equivalent of LDA in THF at -78°C. The mixture was stirred overnight leaving the temperature spontaneously reach r.t.. After quenching the reaction mixture as described in the experimental section, the β-lactams **8** and **9** were obtained as carbobenzoyloxy derivatives in 85% overall chemical yield and 98/2 ratio. No traces of the 3,4-cis isomers could be detected.The trans relationship of the C3H and C4H was established from the value[13] of $J_{3,4}$ at ^{1}H NMR. The absolute configuration of the C3 and C4 stereocenters was assigned through the chemical elaboration to a compound of known configuration (see below).

Hydrolysis of the silylimine of (*R*)-lactaldehyde obtained by standard procedure, furnished an aldehyde whose superposable IR and NMR spectra and the identical specific rotation values with that of authentic (*R*)-lactic aldehyde: $[\alpha]^{25}_D$=+11.5 (*c* 1.5, $CHCl_3$) [lit -12 for the (*S*) enantiomer[14]] proved that there has been no loss of optical purity. Moreover, a careful ^{1}H NMR analysis of the product **8** with Eu (tfc)$_3$ did not reveal the presence of its enantiomer thus showing a total enantioselectivity of the cycloaddition reaction.

The almost complete induction at the C(4) stereocenter resembles the cycloaddition of the cinnamyliden *N* -p-methoxy phenylimine with the lithium enolate of the ethyl-3-hydroxy butanoate we have described in previous papers[15]. In that case the driving effect was attributed to the formation of a cyclic structure of the nucleophilic partner with consequent attack of the electrophilic imine from the less hindered face of the diastereotopic plane. Analogously in the present case a cyclic structure can be postulated for the electrophilic partner, so that a preferred attack of the enolate from the less hindered diastereotopic face, once again, takes place[16].

A number of experiments based on the coordinating aptitude of the counter cations involved in the reaction, substantiate this hypothesis. Accordingly, when sodium hexamethyldisilylamide is used either in the preparation of the enolate or as source of the iminic nitrogen[17], the diastereoselectivity of the reaction drops dramatically because the sodium cation, being less coordinating, renders less stable the cyclic structure of the

imine (Table 1). The ratios of the diastereoisomers were determined on pure isolated products, since the complexity of the NMR signals due to the C(3), C(4), C(4') protons did not allow to assign the relative attributions and integrations on the diastereomeric mixtures. The stereorelationship of the substituents was assigned on the base of the previously discussed parameters[13].

SCHEME 1

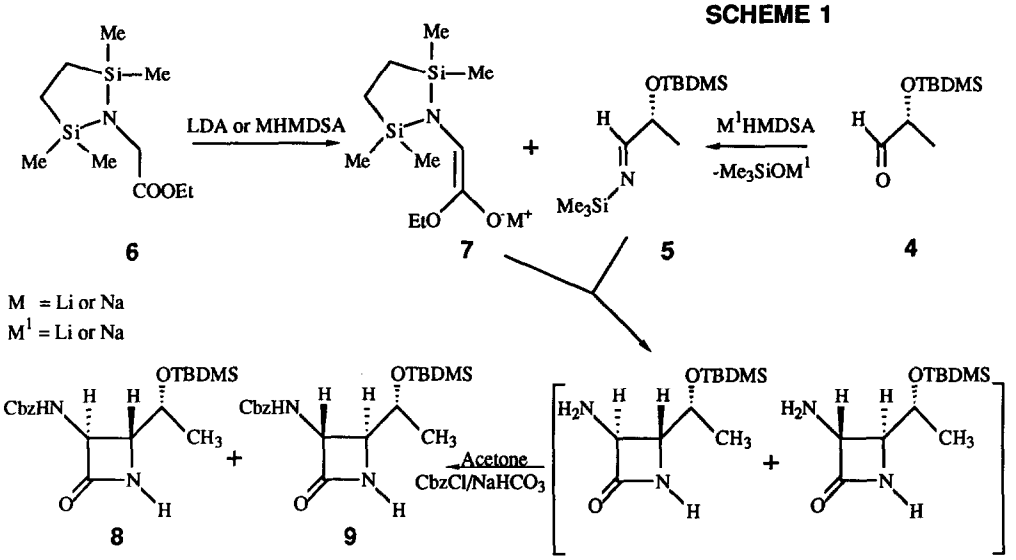
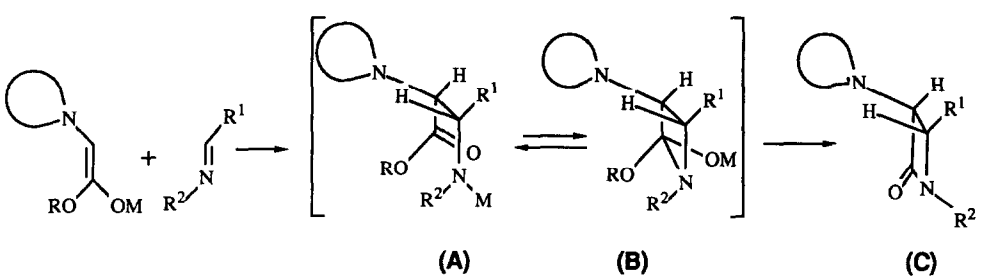


Table 1

Ex	M^1	M	Yield %	(8) / (9) Ratio
1	Li	Li	85	98/2
2	Li	Na	73	40/60
3	Na	Li	33	45/55
4	Na	Na	51	40/60

The formation of the β-lactam ring from the ester enolate and the imine is generally assumed to be a multistage process. In the first step the addition of the enolate to the imine gives rise to an acyclic amino ester intermediate (**A**) in equilibrium with the corresponding four membered cyclic structure (**B**). The elimination of the alkoxy group from the cyclic specie furnishes the end product. (**C**) (Chart 3).

CHART 3

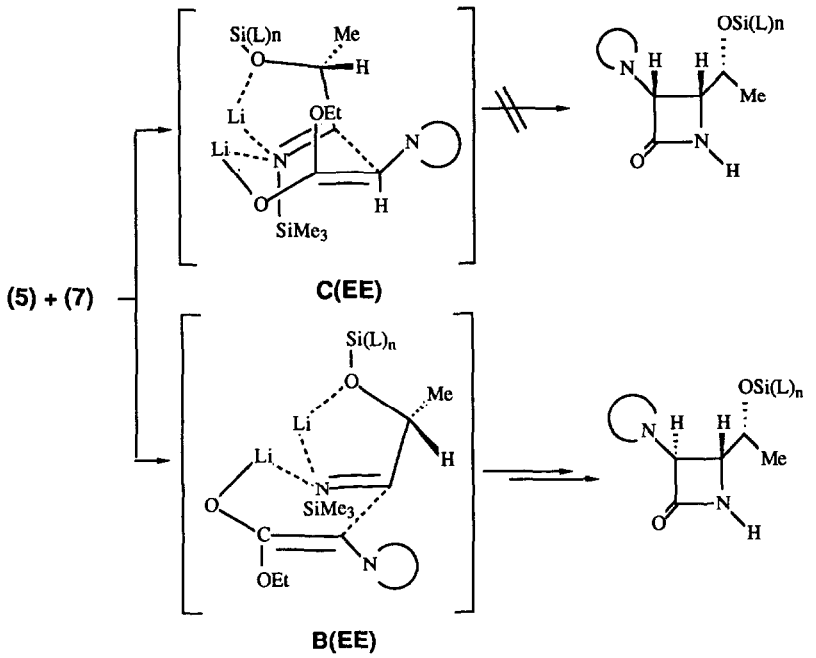


One very interesting feature of this reaction is the trans diastereoselectivity observed in the formation of the C3-C4 bond. Recent studies from our and other research groups on the ester enolate- aldimine cycloaddition reaction show that a predominant cis-diastereoselectivity is observed when the α-imine substituent is not

sterically demanding, whereas when a bulky branched substituent is present in the α-position of the azomethine carbon, the trans diastereoselectivity becomes predominant[18].

The lithium enolate **7** would be expected to be (E) enolate[19], because it is generated under kinetic conditions and because the tetramethyldazadisilolidin group has been shown to behave as a large substituent[20, 21]. Moreover, the imine should exist predominantly as the trans geometric isomer. Keeping fixed the structure of the imine and that of the enolate and using the Evans transition state descriptors[22], two possible transition state models, chair like transition state **C(EE)** and boat like transition state **B(EE)**, can be invoked to rationalize the stereochemical outcome of the cycloaddition (Chart 4).

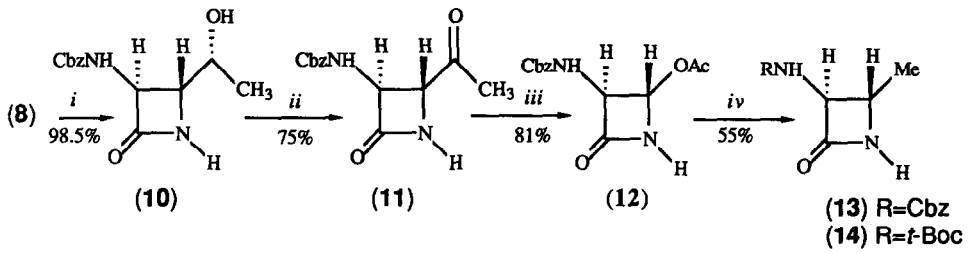
CHART 4



In the chair like transition state **C(EE)**, leading to the cis β-lactam, an important 1:3 diaxial non bonded interaction between the ethoxy group of the enolate and the imine side chain can be observed. In the boat like transition state **B(EE)**, leading to the trans β-lactam, the ethoxy group and the imine substituent are remote from each other. Moreover the 1:4 apical interaction between the ethoxy group of the ester and the trimethylsilyl group appears to be of moderate degree since the two groups are far away because the of the N-Si bond length. All these speculations suggest that the boat like transition state **B(EE)** should be predominant, leading to the formation of the trans azetidinones **8** and **9**.

Since the best results, from the chemical and stereochemical point of view[23], were obtained with experiment 1 (Table 1), we decided to carry out the synthesis of chiral 3-amino-4-substituted azetidin-2-ones, as well as to attribute of the absolute configuration of the chiral centers C(3), C(4) and C(4'), utilizing the azetidinone arising from this experiment. Treatment of **8** with HF in aqueous acetonitrile[24] afforded **10** (98.5%) which, upon oxidation by Jones reagent[25], gave **11** in 75% yield. Finally, Baeyer-Villiger oxidation[26] of **11** furnished the optical active acetoxy derivative **12** (81%) which constitutes an useful intermediate in the preparation of β-lactam antibiotics.

SCHEME 2



i: HF/CH_3CN/H_2O; *ii*: Jones Reagent/ Acetone; *iii*: MCPBA/$CHCl_3$; *iv*: CuCN/MeLi/THF.

The utility of this approach is illustrated by the conversion of the trans acetoxy azetidinone **12** to **13**, a key intermediate in the synthesis of the antibiotic Aztreonam. This goal was achieved *via* carbon extension at C-4 position of the β-lactam ring by means of methyl copper reagent. By the same procedure a number of related optically active 3-amino-4-substituted azetidin-2-ones (TABLE 2) was prepared[27].

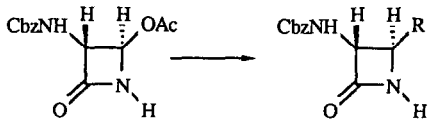


TABLE 2

R	Product	Yield %
Methyl	**16**	55
Butyl	**17**	57
Allyl	**18**	27[a], 40[b]
Phenyl	**19**	68
Furyl	**20**	25

[a]Yields obtained using copper reagent.

[b]Yields obtained using allyltributyltin/BF_3/Et_2O mixture as alkylating agent[28]

The synthesis of (3*S*, 4*S*)-3-(benzyloxycarbonyl)-amino-4-methyl-azetidin-2-one **13** is reported as typical procedure: to a suspension of previously dried CuCN[29] in anhydrous THF, MeLi (solution in ether) is added at -78°C. The heterogeneous mixture is allowed to warm to 0°C (homogeneous solution) at which temperature it is stirred for a further 1-2 min. and then recooled to -78°C. To this solution acetoxy derivative **12** is added by side arm. The solution is stirred overnight, while the temperature is allowed to reach -10°C. The reaction mixture is decomposed in buffer (NH_4Cl/NH_4OH) and extracted with ethyl acetate. After chromatographic purification on column, the optically active azetidinone **13** is isolated in 55% yield. Finally **13** is elaborated into the derivative **14** following standard procedure (see Ex.part) Since this β–lactam has already been transformed to the monobactam Aztreonam[30], this synthesis constitutes a formal synthesis of this β–lactam antibiotic.

Recently a few syntheses of optically active β-lactams have been reported[31]. The method described here allows the preparation of a variety of 3-amino-4-(1'-hydroxy)-substituted monocyclic β-lactams in optically active form starting from an optically active aldehyde precursor and an achiral ester enolate. The preparation of optically active β-lactams using different chiral precursor of the metallo-imine is currently under investigation.

EXPERIMENTAL SECTION.

General procedure. Melting points are uncorrected. NMR spectra were recorded, if not otherwise specified, in $CDCl_3$ and chemical shifts are given in ppm relative to Me_4Si (=0 ppm; ^1H) or $CDCl_3$ (=77 ppm; ^{13}C). I.R. spectra are reported in cm^{-1}. Mass spectra were recorded at an ionization energy of 70 ev. Flash chromatography was performed over silica gel (230-400 Mesh). All reactions were carried out under a blanket of argon in flame dried apparatus. THF was obtained anhydrous and oxygen free by distillation over sodium ketyl under argon. Methylene chloride was distilled over P_2O_5.

(2*R*)-2-(*tert* -Butyldimethylsilyloxy)-N-Trimethylsilyl-Propane Imine (5).

To a 10 ml of 1 M THF solution of lithium bis(trimethylsilyl)amide (ALDRICH) at -40 °C was added a solution of (2*R*)-(*tert* -butyldimethylsilyloxy)-propanal (1.88 g, 10 mmol) in anhydrous THF (15 ml). The mixture was stirred at -40 °C for 30 min and the resulting solution was used directly in the following reaction.
This imine was obtained by the same procedure substituting the sodium bis(trimethylsilyl)-amide to the lithium one and leaving to react for 12 h at -30°C.

(1'*R*,3*S*,4*R*) and (1'*R*,3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(1'-*tert*-Butyldimethylsilyloxy-Ethyl)-Azetidin-2-ones (8) and (9).

To a solution of 1.01 g (10 mmol) of diisopropylamine in 20 ml of anhydrous THF, was added butyllithium (4 ml of 2.5 M solution in hexane) at 0°C. The mixture was stirred for 15 min and then a solution of ethyl 2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-acetate (STABASE, Fluka) (2.45g, 10 mmol) in 10 ml of THF was added at -78°C. The mixture was stirred for 2 h, followed by the addition of (5) (10 mmol) prepared as previously described. The resulting solution was stirred overnight, during which time the mixture was allowed to reach r.t.. To this brown solution, at 0°C, 10 ml of saturated NH_4Cl was added and the pH was adjusted to 7 by addition of 1 N solution of HCl, followed by the addition of 1.51g (18 mmol) of $NaHCO_3$. Benzyloxychloroformate (2.05g, 12 mmol), dissolved in acetone (10 ml), was added dropwise. After 3h stirring at room temperature, the reaction mixture was decomposed in water and extracted with ethyl acetate (400 ml). The organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was cromatographed over silica gel by flash chromatography with hexane/ethyl acetate 80/20 to give 2.82g of (8) and 0.06 g of (9) (85 % overall yield).

Compound (8)

$[\alpha]^{25}_D$= - 25.2 (c 2.46, $CHCl_3$) I.R. (neat) 3410, 1770, 1730, 1250, 1050. ^1H NMR (200 MHz) 7.4 (m, 5 H); 6.8 (s, 1 H); 6.1 (d, J = 8.4 Hz, 1 H); 5.1 (s, 2 H); 4.6 (dd, J_1=8.4 Hz; J_2=1.9 Hz, 1 H); 3.9 (quintet J = 7 Hz, 1 H); 3.5 (dd, J_1=7 Hz, J_2= 1.9 Hz, 1 H); 1.2 (d, J= 7Hz, 3 H); 0.9 (s, 9 H); 0.1 (s, 6 H). ^{13}C NMR (80 MHz) 168.18, 155.54, 135.96, 128.31, 128.00, 127.93, 69.71, 66.87, 63.57, 60.37, 25.55, 19.90, 17.69, -3.93. Anal. Calcd for $C_{19}H_{30}N_2O_4Si$: C, 60.29; H, 7.99; N, 7.40. Found: C, 60.16; H, 7.98, N, 7.41. Mass Spectra 378.1974698.

Compound (9)

$[\alpha]^{25}_D$= +12.12 (c, 10.39, $CHCl_3$). I.R. (neat): 3410, 1770, 1730, 1250, 1050 . ^1H NMR (200 MHz) 7.4 (m, 5 H); 6.4 (bs, 1 H); 5.7 (d, J= 8.4 Hz, 1 H); 5.1 (s, 2 H); 4.8 (dd, J_1= 8.4 Hz, J_2= 2.4 Hz, 1 H); 4.0 (dq, J_1= 6.2 Hz, J_2= 2.4 Hz, 1 H); 3.6 (m, 1 H); 1.2 (d, J= 6,2 Hz, 3 H); 0.9 (s, 9H); 0.1 (s, 6 H). ^{13}C NMR (200 MHz) 168.50, 155.79, 136.26, 128.59, 128.22, 128.14, 66.97, 66.50, 62.02, 58.56, 25.53, 19.87, 17.71, -3.81.

(1'*R*, 3*S*, 4*R*)-3-(Benzyloxycarbonylamino)-4-(1'Hydroxyethyl)-Azetidin-2-one (10).

3.78g (10 mmol) of (8) were dissolved in 60 ml of acetonitrile containing 3 ml of a 40% solution of HF in H_2O. The reaction was monitored by t.l.c..
When the deprotection was complete, saturated $NaHCO_3$ was added until pH 7 was reached. The reaction mixture was stirred for 30 min. and then extracted with 100 ml portions of ethyl acetate. The organic layers

were washed with brine, dried over $MgSO_4$, and the solvent removed at reduced pressure. (**10**) was obtained as a white solid (2.6g , 98.5%).
m.p.= 138-140°C. $[\alpha]^{25}_D$= - 44.74 (c 5.28, MeOH) I.R. ($CHCl_3$) 3420, 1780, 1730. ^1H NMR (90 MHz, CD_3COCD_3) 7.3 (m, 7 H); 5.1 (s, 2 H); 4.6 (dq, J_1= 2.5 Hz, J_2= 7.5 Hz, 1 H); 3.8 (quintet J=6 Hz, 1 H); 3.5 (dd, J_1=2.5 Hz, J_2= 6 Hz, 1 H); 3.0 (bs, 1 H); 1.2 (d, J=6Hz, 3H). ^{13}C NMR (CD_3COCD_3) 167.89; 159.69; 137.89, 129.19, 128.95, 128.69, 68.57; 67.04; 63.01; 61.31; 20.12. Anal.Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.1; N, 10.6. Found: C, 59.15; H, 6.09; N, 10.59.

(3*S*,4*R*)-3-(Benzyloxycarbonylamino)-4-(1'-oxo-ethyl)-Azetidin-2-one (11).
To a solution of the azetidinone (**10**) (2.11g, 8 mmol), in acetone (30 ml), 2.5 ml of Jones reagent 8N was added at 0°C. The mixture was stirred for 3 h, neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel eluting with cyclohexane/ethyl acetate 50/50 to give (**11**) as a white solid (1.32g, 73%).
m.p.= 94-96°C. $[\alpha]^{25}_D$=-37.74 (c 3.82, $CHCl_3$). I.R. ($CHCl_3$) 3430, 1780, 1730 .^1H NMR (90 MHz) 7.3 (m, 6 H); 6.6 (d, J=7 Hz, 1 H); 5.1 (s, 2 H); 4.6 (dd, J_1=7 Hz, J_2= 2.5 Hz, 1 H); 4.2 (d, J=2.5 Hz, 1 H); 2.2 (s, 3H). ^{13}C NMR (80 MHz): 205.02; 166.71; 155.54; 135.45; 128.17; 127.82; 127.77; 66.98; 62.73; 25.97. Anal Calc for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.43; H, 5.39; N, 10.70.

(3*S*, 4*S*)-3-(Benzyloxycarbonylamino)-4-Acetoxy-Azetidin-2-one (12).
To a stirred solution of (**11**) (1.31g, 5 mmol) in $CHCl_3$ (70 ml), was added m-chloro perbenzoic acid (4.31g, 25 mmol) at room temperature. The solution was stirred overnight and then poured into a cold solution of saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was chromatographed by flash chromatography with hexane/ethyl acetate 60/40 over silica gel. 1.13g of (**12**) were obtained (81%).
m.p. = 89°C. $[\alpha]^{25}_D$= -59.48 (c 1.35, $CHCl_3$). I.R. ($CHCl_3$) 3420, 1800, 1740. ^1H NMR (90 MHz) 7.3 (m, 6 H); 6.2 (d, J=7.5 Hz, 1 H); 5.8 (d, J=1.5 Hz, 1 H); 5.1 (s, 2 H); 4.7 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 1 H); 2.1 (s, 3 H). ^{13}C NMR (80 MHz): 170.85; 165.26; 155.56; 135.49; 128.32; 128.15; 127.98; 78.87; 67.32; 64.36; 20.46. Anal Calc for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5..07; N, 10.07. Found: C, 56.19; H, 5.08; N, 10.08.

(3*S*, 4*S*)-3-(Benzyloxycarbonylamino)-4-Methyl-Azetidin-2-one (13).
CuCN (O.896g, 10 mmol) was placed in a dry two necked flask and azeotroped with toluene (10 ml) at room temperature under vacuum. The powder was placed under argon and 10 ml of anhydrous THF were added; to the resulting suspension, 12.5 ml (20 mmol) of 1.6 M methyl lithium in ether (Aldrich) were added at -78°C. The mixture was allowed to reach 0°C and was stirred for 1-2 minutes at this temperature: the solution became homogeneous and was then cooled again to -78°C. β-lactam (**12**) (0.278, 1 mmol) in THF (5 ml) was introduced by side arm and the solution was stirred overnight allowing it to warm to r.t.. The solution was poured into a NH_4Cl/NH_3 buffer and extracted with ethyl acetate. The solvent was dried over Na_2SO_4 and evaporated under vacuum to give a residue which was chromatographed eluting with hexane/ethyl acetate 40/60 to give (**13**) (0.129g, 55%).
m.p. 78-80 °C. $[\alpha]^{25}_D$=-18.02 (c 4.01, $CHCl_3$). I.R. ($CHCl_3$) 3430, 1770, 1730. ^1H NMR (200 MHz) 7.3 (m, 5 H); 6.8 (s, 1 H); 6.3 (d, J=7.8 Hz, 1 H); 5.1 (s, 2 H); 4.3 (dd, J_1=7.8 Hz, J_2=2.0 Hz, 1 H); 3.7 (dq, J_1=6.0 Hz, J_2=2.0 Hz, 1 H); 1.3 (d, J=6 Hz, 3 H). ^{13}C NMR (200 MHz): 168.05; 156.30; 136.40; 128.89, 128.61; 128.53; 67.28; 64.79; 54.01, 19.15. m/z 191 (M^+- 43), 147, 132. Anal Calc for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found C, 61.45; H, 6.04; N, 11.94.

(3*S*, 4*S*)-3-(*tert* -Butyloxycarbonylamino)-4-Methyl-Azetidin-2-one (14).
β-lactam (**13**) (O.936g, 4 mmol) was dissolved in methanol (40 ml) and hydrogenated at 50 p.s.i. with Pd/C 10% as catalyst. After 4 h the solution was filtered and the solvent was removed under vacuum to give (3*S*,

4*S*)-3-amino)-4-methyl-azetidin-2-one as an oil which was directly used in the next step, in quantitative yield. This product was was dissolved in DMF (15 ml) and THF (25 ml).Triethylamine (1.12 ml, 8 mmol) was added, followed by di-tert-butyl dicarbonate (1.746g, 8 mmol) at r.t.. The solution was stirred overnight and then poured in H_2O and extracted with ether. The organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by crystallization (Ethyl acetate 2 ml, Hexane 5ml) to give (**14**) (0.640g, 80%) identical in all respect to authentic material[31].

(3*R*, 4*R*)-3-(Benzyloxycarbonylamino)-4-Acetoxy-Azetidin-2-one (15).
This product was obtained, following the same procedure and in the same overall yield, as for the corresponding enantiomer (**12**), starting from enantiomerically pure (*S*) ethyl lactate as chiral building block.

(3*R*, 4*R*)-3-(Benzyloxycarbonylamino)-4-Methyl-Azetidin-2-one (16).
This product was obtained in 59 % yield from (**15**) following the procedure described for the enantiomer (**13**).

(3*R*, 4*R*)-3-(Benzyloxycarbonylamino)-4-Butyl-Azetidin-2-one (17).
This product was obtained in 57% yield from (**15**) following the procedure described for (**13**).
m.p.= 35°C. $[\alpha]^{25}_D$=+15.55 (c 4.25, $CHCl_3$). I.R. ($CHCl_3$) 3440, 1770, 1730 .^{1}H NMR (200 MHz) 7.3 (m, 5 H); 6.9 (s, 1 H); 6.2 (d, J=7.8 Hz, 1 H); 5.1 (s, 2 H); 4.4 (dd, J_1=7.8 Hz, J_2=2.0 Hz, 1 H); 3.5 (dt, J_1=6.0 Hz, J_2=2.0 Hz, 1 H); 1.8-0.8 (complex pattern, 9 H). ^{13}C NMR (200 MHz): 168.09; 155.89; 136.22; 128.65; 128.48; 128.34, 67.08; 63.47; 58.29, 33.12; 28.87; 22.24; 13.67. m/z 233 (M^+- 43). Anal Calc for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found C, 65.07; H, 7.30; N, 10.13.

(3*R*,4*R*)-3-(Benzyloxycarbonylamino)-4-Allyl-Azetidin-2-one (18).
Obtained as for (**13**) in 27% yield starting from (**15**). A higher yield procedure was achieved using the tributyltinallyl/BF_3 procedure[29]. Thus to a solution of (56mg, 0.2 mmol)) of (**15**) in 6 ml of anhydrous CH_2Cl_2 was added 200 mg (0.6 mmol) of allyltributyltin and 10 mg (0.07 mmol) of boron trifluoride etherate under a nitrogen atmosphere. The resulting yellow solution was stirred at rt for 16 h. Dichloromethane was added and the mixture was washed three times with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 1/1) to give the desidered product (20.8 mg, 40%), identical in all respects to that arising from copper/mediated alkylation.
$[\alpha]^{25}_D$=+3.86 (c 3.11, $CHCl_3$). I.R. ($CHCl_3$) 3430, 1770, 1730 .^{1}H NMR (200 MHz) 7.3 (m, 5 H); 6.6 (s, 1 H); 6.0 (d, J=7.8 Hz, 1 H); 5.7 (m, 1 H); 5.1 (m, 4 H); 4.4 (dd, J_1=7.8 Hz, J_2=1.4 Hz, 1 H); 3.6 (dt, J_1=6.0 Hz, J_2=1.4 Hz, 1 H); 2.4 (m, 2 H). ^{13}C NMR (80 MHz): 166.59; 155.59; 135.98; 132.70; 128.60; 128.34, 128.23; 118.56; 67.38; 63.18; 56.99, 37.82. m/z 217 (M^+- 43), 126. Anal Calc for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found C, 64.69; H, 6.19; N, 10.75.

(3*R*, 4*R*)-3-(Benzyloxycarbonylamino)-4-Phenyl-Azetidin-2-one (19).
Obtained as (**13**) in 68% yield starting from (**15**)
m.p. 160-162 °C. $[\alpha]^{25}_D$=+35.26 (c 3.72, $CHCl_3$). I.R. ($CHCl_3$) 3430, 1780, 1730.^{1}H NMR (200 MHz) 7.3 (m, 10 H); 7.0 (s, 1 H); 6.3 (d, J=8 Hz, 1 H); 5.1 (s, 2 H); 4.7 (d, J=2 Hz, 1 H); 4.4 (dd, J_1=8.0 Hz, J_2=2.0 Hz, 1 H). ^{13}C NMR (80 MHz): 168.09; 155.74; 138.32; 135.83; 128.99; 128.69, 128.56; 128.44; 128.37; 128.18; 125.85; 67.68; 67.33; 59.59. m/z 296, 253, 209. Anal Calc for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found C, 68.78; H, 5.45; N, 9.46.

(3R, 4S)-3-(Benzyloxycarbonyl amino)-4-Furyl-Azetidin-2-one (20).
Obtained as (**13**) in 25% yield starting from (**15**).
$[\alpha]^{25}_D$=+49.27 (c 4.81, $CHCl_3$). I.R. ($CHCl_3$) 3430, 1780, 1730 .^{1}H NMR (200 MHz) 7.3 (m, 6 H); 6.6 (s, 1 H); 6.3 (m, 2 H); 5.9 (d, J=8 Hz, 1 H); 5.1 (s, 2 H); 4.7 (m, 2 H). ^{13}C NMR (200 MHz): 167.86;

155.79; 150.82; 143.23; 135.96; 128.41; 128.32; 128.20; 110.70; 108.72; 67.39; 64.92; 52.56. m/z 286, 242. Anal Calc for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found C, 62.99; H, 4.94; N, 9.80.

Acknowledgement: We gratefully acknowledge the "Progetto Finalizzato Chimica Fine e Secondaria II" and Ministero Pubblica Istruzione (Fondi 40% and 60%) for generous support .

References and notes

1 For a recent review on β-lactams see: Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K.H. *Angew. Chem., Int. Ed. Engl.*, **1985**, *24* , 180.

2 (a) Cimarusti, C.M.; Bonner, D.P.; Breuer, H.; Chang, H.W.; Fritz, A.W.; Floyd, D.M.; Kissick, T.P.; Koster, W.H.; Kronenthal, D.; Massa, F.; Mueller, R.H.; Pluscec, J.; Slusarchyk, W.A.; Sykes, R.B.; Taylor, M.; Weaver, E.R.; *Tetrahedron* **1983**, *39*, 2577. (b) Yoshida C.; Hori, T.; Momoni, K.; Nagumo, K.; Nakamo, J.; Kitani, T.; Fukuoaka, Y.; Saikawa, I. *J. Antibiot.* **1985**, *38*, 1536. For recent reviews on the synthesis of monobactam antibiotics see: (a) *Chemistry and Biology of β-Lactam Antibiotics:;* Morin R.B.; Gorman, M. Eds.; Academic; New York, **1982**; Vol. 3; (c) Sykes, R.B.;Bonner, D.P.; Bush, K.; Georgopapadakou N.H. *Antimicrob. Agents Chemoter.* **1982**, *21*, 85. (d) Thomas, C.R. Synthetic aspect of monocyclic β–lactam antibiotics . In *Recent Progress in the Chemical Synthesis of Antibiotics* , Lukacs, G.; Ohno, M. Eds.; Springer Verlag Berlin, 1990; pp 534-564.

3 Cimarusti, C.M.; Applegate, H.E.; Chang, H.W.; Floyd, D.M.; Koster, W.H.; Slusarchyk, W.A.; Young, M.G. *J. Org. Chem.* **1982**,*47*, 180.Floyd, D.M.; Fritz, A.W.; Cimarusti, C.M. *J. Org. Chem.* **1982**, *47*, 176.

4 Floyd, D.M.; Fritz, A.W.; Cimarusti, C.M. *J. Org. Chem.* **1982**, *47*, 176.

5 Miller, M.J.; Biswas, A.; Krook, M.A. *Tetrahedron* **1983**, *39*, 2571. (b) Miller, M.J. *Acc. Chem. Res.*,**1986**, *19*, 49.

6 Hegedus, L.S.; D'Andrea, S. *J. Org. Chem.* **1988**, *53*, 3113. Hegedus, L.S.; Imwinkelried, R.; Alarid-Saegent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.

7 Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* , **1943**, *65* , *2255*. For reviews see: (a) Koppel, G.A. In "Small ring Heterocycles - Azetidines, β - lactams, Diazetidine and Diaziridines" Hasman, A., Ed.; Wiley; New York, **1983**, pp 337-359. (b) Gaudeman, M. *Organometallics Chemistry Rev.* **1972**, *8* , 183.

8 For a recent reviews on the ester-enolate-imine condensation see: (a) Hart., D. J.; Ha, D.-C. *Chem. Rev.*, **1989**, *89*, 1447. (b) Brown, M.J. *Heterocycles* **1989**, *29*, 2225. (c) Georg, G.I. In *Studies in Natural Product Chemistry* ; Rahman, A-ur, Ed.; Elsevier Science: Amsterdam; 1988, Vol. 2.

9 Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* 1988;*110*, 6879.

10 Hirama M.; Nishizaki, I.; Shigemoto, T.; Ito, S.I. *J. Chem. Soc., Chem. Commun.* 1986, 393.

11 Djaric, S.; Vernit,J.; Magnus, P.; *Tetrahedron Lett.*, 1981, *22*, 1787.

12 Andreoli,P.; Cainelli,G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.***1991**,*56*, 000.

13 Bouffard, F. A.; Christensen, B.G. *J. Org. Chem.* , 1981, 46, 2208..

14 Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. *J. Chem. Soc. Chem. Comm.* **1986**, 393.

15 (a) Cainelli, G.; Panunzio, M. *Il Farmaco*, **1991**, *46*, 177. (b) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc. Perkin Trans. I* , **1987**, 2637. (c) Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D. *Tetrahedron Lett.* **1985**, *26*, 937. See also Referece 7.

16 Cainelli, G.; Panunzio, M.; Andreoli, P.; Bandini, E.; Martelli, G.; Spunta, G. Giacomini, D.; *Pure and Appl Chem.* **1990**, *62*, 605.

17 The preparation of *N*-trimethylsilylimine of lactaldehyde from the sodium hexamethyldisilylamide was performed following the procedure described for the preparation of the same imine from the lithium hexamethyldisilylamide. Using NaHMDSA, however, the elimination reaction, which affords the final imine, is not complete since a certain amoun of the addition product is retained in the reaction mixture. Results on this topic will be discussed elsewhere: Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. Unpublished results.

18 It has been reported that the addition of lithium chloride (15 eq) to the reaction mixture increased the trans/cis ratio to a 87/13. No rationalization of the effect of lithium chloride has been reported. Hatanaka, M.; Park, Oee-S.; Ueda, I. *Tetrahedron Lett.* **1990**, *31*, 7631.

19 Overman, E.L.; Osawa, T. *J. Am. Chem. Soc.* 1985, *107*, 1698.

20 Diagnostic NOE experiments, after quenching the lithium enolate with TBDMSCl showed the formation of the E enolate.Duthaler, R.; Marti, R.; Hafner, A. Unpublished results, private commmunication.

21 The reaction of the corresponding zinc and aluminum enolate has been extensively studied by van Koten et al., e.g. (a) van der Steen, F.H.; Jastrzebski, J.T.B.H.; Van Koten, G. *Tetrahedron Lett.*, **1989**, *30*, 765. (b) Jastrzebski, J.T.B.H.; Van Koten, G.. *ibid.* **1988**, *29*, 2467. (c) Jastrzebski, J.T.B.H.; Van Koten, G. *Rec. Trav. Chim. Pays-Bas*, **1987**, *106*, 516. See also Ref. 7d.

22 Evans, D.A.; Nelson, J.V.; Taber, T.R. "*Topics in Stereochemistry* " Allinger, N.L.; Eliel, E.L.; Wilm, S.H.; Eds., Wiley, New York, **1982**, Vol. 13, pp1-117.

23 The use of the NaHMDSA , however, allows the large scale preparation of the azetidinone (8), with the natural (3 *R*) configuration of the C-3 aminic group, starting from the less expensive (*S*) ethyl lactate. Cainelli, G.; Panunzio, M.; Da Col , M. Dall'Asta, L. Unpublished results.

24 Newton, R.F.; Reynolds, D.P.; Finch, M.A.W.; Kelly, D.R.; Roberts, S.M. *Tetrahedron Lett.* 1979, 3981.

25 For a general review, see *Chromiun Oxidations in Organic Chemistry;* Cainelli, G.; Cardillo, G., Eds.; Springer: Berlin, 1984.

26 For comprehensive reviews on the use of the 4-acetoxy-azetidinone in the synthesis of β-lactam antibiotics see: (a) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles*, **1982**, *17*, 463. (b) Nagara, T.; Kametani, T.; *Heterocycles* **1987**, *25*, 729. (c) Davies, D.E.; Storr, R.C. In Lwowski, W. (Ed) "*Comprehensive Heterocyclic Chemistry*" Pergamon, New York, **1984**, Vol. 7 pag. 237. (d) Nagao, Y. In: Zwanenburg, B.; Klunder, A.J.H. (eds) "*Perspective in the Organic Chemistry of Sulfur*" Elsevier, New York, **1987**, p. 57. For the synthesis of thienamycin see: (e) Reider, P.J.; Grabowski, E.J.J. *Tetrahedron Lett.* **1982**, *23*, 2293. (f) Karaday S.; Amato, J.S.; Reamer, R.A.; Weinstock, L.M. *J. Am. Chem. Soc.* **1981**, *103* , 6765. (g) Attrill, R.P.; Barrett, A.G.M.; Quayle, P.; Van der Westhuizen, J. *J. Org. Chem.* , **1984**, *49* , 1679. (h) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.*, **1984**, *62* , 2936. For the synthesis of β-methyl-carbapenem: (i) Kim, C.U.; Luh, B.; Partyka, R.A. *Tetrahedron Lett.* **1987**, *28*, 507. (j) Shirai, F.; Nakai, T. *J. Org. Chem.* , **1987**, *52*, 5492. (k) Endo, M.; Droghini, R. *Can. J. Chem.* **1988**, *66*, 1400. For the synthesis of penems: (m) Miyadera, T. *J. Synth. Org. Chem Jpn.* **1983**, *41*, 1168. (n) Alpeggiani, M.; Battistini, C.; Bedeschi, A.; Franceschi, G.; Perrone, E.; Zarini, F. *Pure App. Chem.* **1987**, *59* , 467. Sheppard, A.; (o) Miller, M.J. *J. Chem. Soc. Perkin Trans. I* **1990**, 2519.

27 In these cases (*S*) lactaldeyde, protected as tert-butyldimethylsilylether, was used as starting material instead of the corresponding (*R*) lactaldeyde.

28 Fujimoto, K, Iwano, Y.; Hirai, K. *Bull. Chem. Soc. Jpn* **1986**, *59*, 1363.

29 (a) Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron*, **1984**, *40*, 5005. (b) Lipshutz, B.H.; Wilhelm, R.S. *J. Am. Chem. Soc.* **1981**, *103*, 7672. Lipshutz, B.H. *Synthesis* **1987**, 325.

30 Floyd, D.M.; Fritz, A.W.; Pluscec, J.; Weaver, E.R.; Cimarusti, C.M. *J. Org. Chem.*, **1982**, *47*, 5160.

31 Brown, J. M.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933. Ojma, I.; Habus, I. *Tetrahedron Lett.* **1990**, 4289. (d) See also Var der Steen, F. Application of the Zinc- and Aluminum Ester enolates in the Stereoselective Synthesis of beta-Lactam Antibiotics. University of Utrecht 1991.