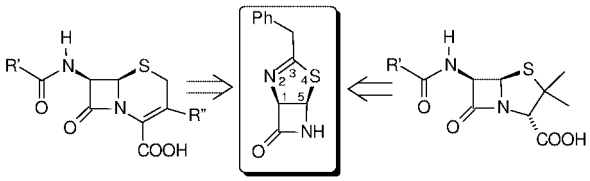
A Total Synthesis of (1*R*, 5*R*)-3-Phenylmethyl -4-thia-2,6-diazabicyclo [3.2.0]hept-2-en-7-one, a Useful Intermediate for the Preparation of Penem and Cepham Derivatives

Gianfranco Cainelli,* Daria Giacomini,* Paola Galletti

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, Via Selmi 2, 40126 BO, Italy
Fax +39(051)2099456; E-mail: cainelli@ciam.unibo.it; giacomin@ciam.unibo.it
Received 28 July 1999; revised 30 September 1999

Abstract: The preparation of the thiazoline (1*R*,5*R*)-3-phenylmethyl-4-thia-2,6-diazabicyclo [3.2.0]hept-2-en-7-one (**1**) is presented. This compound, which has been extensively used as an intermediate for the synthesis of penems and cephams, has been obtained starting from a C-4 unsubstituted azetidinone by means of facile processes while chirality has been obtained through enzymatic resolution.

Key words: antibiotics, β-lactams, cycloaddition, enzymes, kinetic resolution



Scheme 1

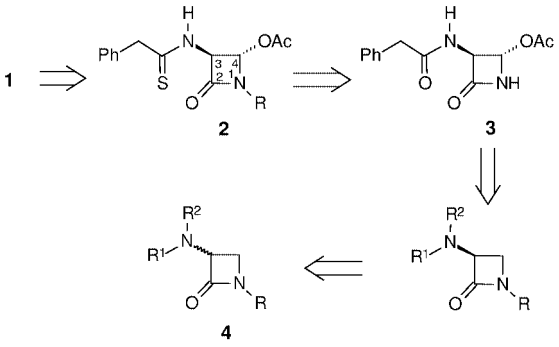
Penicillins and cephalosporins represent one of the most important groups of antibiotics. Even though many other antimicrobial agents have been isolated since their discovery, they are still the pharmaceutical of choice for a great variety of infectious diseases and new derivatives are being prepared continuously.[1]

Few total syntheses of β-lactam antibiotics have been reported in the literature.[2] Generally, β-lactam compounds are obtained through semisynthetic approaches that exploit the intermediate products obtained by the degradation of biosynthetic Penicillin G and V or Cephalosporin C. With this methodology, i.e. by opening and reconstructing the thiazolidine ring of penicillins or refunctionalizing the dihydrothiazine ring of cephalosporins, many important semisynthetic approaches to β-lactam antibiotics have been realized. Both the starting material and the target have bicyclic β-lactam structures, and the success of this approach rests on the low-cost and ready availability of the intermediates.

One of the synthons used is the thiazoline-azetidinone (1*R*,5*R*)-3-phenylmethyl-4-thia-2,6-diazabicyclo[3.2.0] hept-2-en-7-one (**1**), derived from penicillin G.[3] The chemical structure of **1** is particularly attractive because of the correct functionalization and natural stereochemistry at the C-1 and C-5 bonds. It has been used, together with its 3-phenoxymethyl-analog,[4] to prepare several penams, penems, oxopenams and cephams.[5] As an example, the thiazoline ring of **1** is readily opened to give the corresponding *cis* 4-mercaptoazetidin-2-one,[6] which easily undergoes base-induced 1,4-addition to α-halo-α,β-unsaturated esters affording penam derivatives.[7]

In the context of our ongoing interest in the field of β-lactams,[8] we decided to develop a total synthetic approach to penicillin and cephalosporin derivatives through the full chemical synthesis of compound **1**.

Our strategy for the total synthesis of **1** is shown in Scheme 2. The direct precursor has been identified as the thioamide **2,** which can furnish target **1** through nucleophilic attack of the sulfur atom, thus exploiting the good leaving ability of the acetoxy function at C-4. Thioamide **2** can in turn be obtained from the corresponding amide **3,** where the acetoxy group can be introduced starting from a 3-amino-β-lactam **4**. Even compound **3** is an interesting intermediate in the total synthesis of cephalosporins and penicillins.[9]

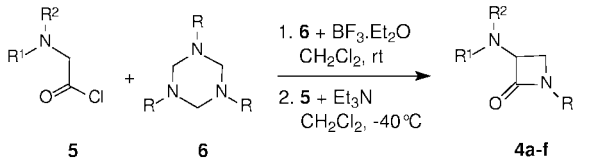


Scheme 2

The key step is to obtain the two stereogenic centers at C-1 and C-5 in the thiazolidine ring in high optical purity. Among the possible synthetic solutions, we decided to use facile racemic processes with inexpensive starting materials and to obtain the natural configuration through a kinetic enzymatic resolution. The required *cis* junction of the thiazoline ring will follow as a consequence of the steric ring tension in the bicyclic system.

The preparation of racemic 3-aminoazetidin-2-one **4**, which represents the first step in the synthesis, was real-

ized by means of the Staudinger reaction,[10] by treating the aminoketene derived from the acyl chloride **5** with the appropriate formaldimine obtained from hexahydrotriazine[11] **6** (Scheme 3). In the presence of the Lewis acid, the hexahydrotriazine might be in equilibrium with a boron trifluoride complex of the unstable monomeric formaldimine, which then reacts with the ketene in the presence of Et_3N to give C-4 unsubstituted azetidin-2-ones **4a-f** (Scheme 3).



a: R^1, R^2 = Pht; R = $CH_2CH{=}CH_2$ **d**: R^1 = R^2 = Cbz; R = $CH_2CH{=}CH_2$
b: R^1, R^2 = Pht; R = *p*-OMePhenyl **e**: R^1 = R^2 = Cbz; R = *p*-OMePhenyl
c: R^1, R^2 = Pht; R = CH_2Ph **f**: R^1 = R^2 = Cbz; R = CH_2Ph

Scheme 3

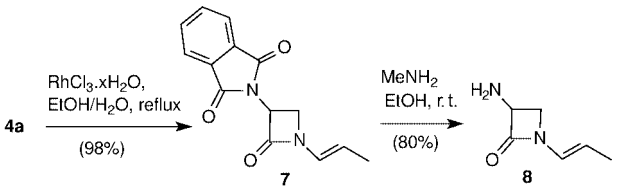
The choice of the protecting groups for the two nitrogen atoms was critical for the synthesis. Two kinds of protecting groups were tested for the amino group at C-3, while three were tested for N−1. In each case, the β-lactams were formed in good yields (Table).[12] The reactions were performed in dichloromethane at -40 °C by treating one equimolar amount of acid chloride with excess triethylamine, and then adding to a solution of the resulting unstable ketene a dichloromethane solution of hexahydrotriazine and $BF_3{\bullet}OEt_2$ at the same temperature. A simple trituration in CH_3OH was needed to obtain β-lactams **4a-c**.

For the reminder of the synthesis, the best results were obtained using phthalimidoacetyl chloride and *N*,*N*′,*N*″-triallylhexahydrotriazine (β-lactam **4a**). In all other cases, the protecting groups presented several compatibility problems with the other β-lactam functions in the deprotection phase. Compound **4a** was then converted to the corresponding propen-1-yl derivative **7** in good overall yield by isomerization of the *N*-allylic sidechain. This passage, which is the first step in the oxidative chain deprotection procedure,[13] could be performed at various stages of the synthesis. However, at this stage it was easy to recover the product from the reaction mixture by simple filtration, and no further purification was needed. The final removal of the phthalimide group with methylamine in ethanol[14] gave compound **8** as a racemic mixture (Scheme 4).

Table Synthesis of Azetidinones **4a-f**

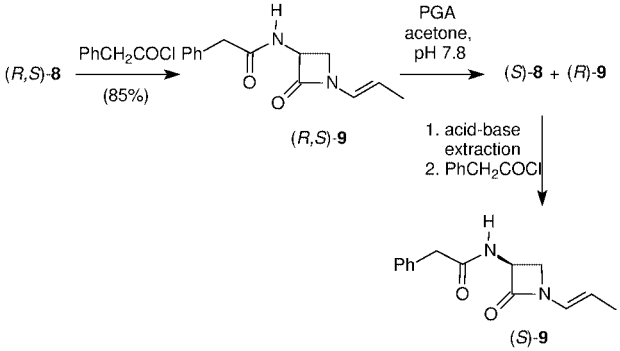
Entry	R^1, R^2	R	Product	Yield (%)[a]
1	R^1, R^2 = Pht	$CH_2CH{=}CH_2$	**4a**	75
2	"	*p*-OMePh	**4b**	80
3	"	CH_2Ph	**4c**	68
4	R^1=R^2=Cbz	$CH_2CH{=}CH_2$	**4d**	80
5	"	*p*-OMePh	**4e**	63
6	"	CH_2Ph	**4f**	57

[a]Isolated yields.



Scheme 4

The racemate was separated by enzymatic kinetic resolution using Penicillin G Acylase (PGA).[15] PGA is an enzyme produced by *E. Coli* that is capable of transferring a phenylacetyl group from esters, amides or acids to acceptor molecules such as alcohols, amines or water. It is used on an industrial scale for the production of 6-APA-, in peptide protective group chemistry and for the resolution of alcohols.[16] To be suitable for enzymatic hydrolysis, (*R*,*S*)-**8** was first converted to the racemic phenylacetamido derivative (*R*,*S*)-**9** by treatment with phenylacetylchloride under Schotten–Baumann conditions. The enzymatic kinetic enantioselective hydrolysis of (*R*,*S*)-**9** led to the *S*-enantiomer of **8,** while the *R*-enantiomer remained as such and the two species could be separated through a simple acid-base extraction (Scheme 5).



Scheme 5

The hydrolysis was carried out by incubating (*R*,*S*)-**9** in phosphate buffer (pH 7.8) and acetone as a cosolvent at r.t. with PGA immobilized on Eupergit C beads (10% w/w). These conditions were established through a detailed study[17] of the resolution of (*R*,*S*)-**9** performed by monitoring the course of the e.e.% in relation to the conversion at various pH values, temperatures and amount of enzyme. Since the pH of the reaction decreases during the hydrolysis, the rates of the reaction and conversion were monitored by the amount of 0.1N NaOH added to maintain the

initial value. At the desired conversion, the crude reaction mixture was extracted at pH 4.5 with ethyl acetate, and the (*S*)-3-amino-azetidin-2-one (*S*)-**8** was separated in the aqueous phase and directly rederivatized to (*S*)-3-phenylacetamido-azetidin-2-one (*S*)-**9**. The presence of the *N*-1 propenylic chain is important, in fact, a completely deprotected β-lactam would have been too hydrophilic and the extraction in the organic phase would have been more difficult.

During the initial stage of the reaction, enantiomerically pure *(S)*-**8** was found to be the product of the hydrolysis and a good kinetic resolution was achieved for conversions of 30% (e.e. > 94%) and 40% (e.e. >86%). At 60% conversion, the remaining substrate fraction *(R)*-**9** resulted in e.e. = 89%, so that both enantiomers could be obtained with a good degree of purity depending on the rate of conversion.

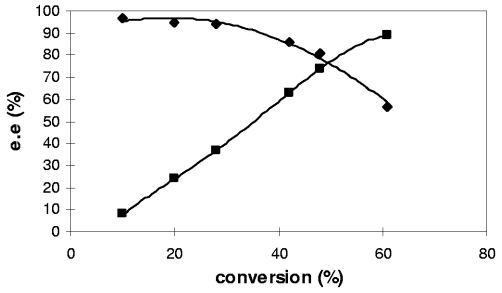
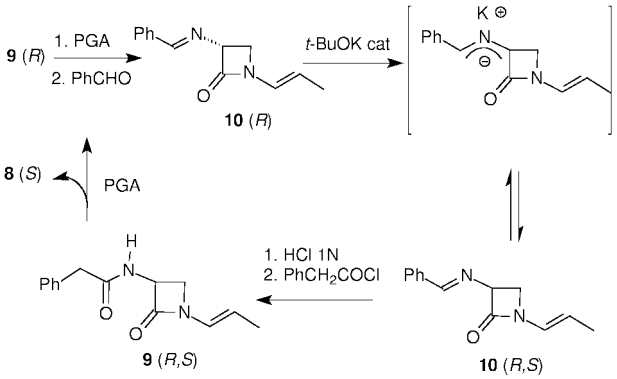


Figure Dependence of ee% of (*S*)-9 (♦) and of (*R*)-9 (■) on the % conversion during enzymatic resolution. Experimental conditions: phosphate buffer/acetone 2:1; 25°C; pH 7.8; PGA (10% w/w).

The enantiomer (*S*)-**9** was used for the following synthesis; the enantiomer(*R*)-**9** can be used in the same way and with an identical procedure to obtain specular thiazoline and enantiomers of β-lactam antibiotics.

To increase the yield of resolution from 40% to completeness, product (*R*)-**9** was racemized through a simple procedure and recycled, as shown in Scheme 6. To achieve racemization, the (*R*) enantiomer of β-lactam **9** was hydrolyzed with PGA to give (*R*)-**8** and then reacted with benzaldehyde to furnish the corresponding phenyl imine **10**. This compound is quite acidic at the C-3 position and treatment with a catalytic amount of *t*-BuOK was sufficient to establish an equilibrium with the planar 1,3 azaallylanion. After refunctionalization, racemic **9** (*R*,*S*) is obtained and the product can be submitted again to the enzymatic resolution.

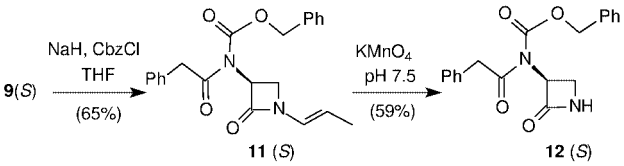
The 4-acetoxy group was introduced by ruthenium-catalyzed oxidation with peracetic acid following the Murahashi procedure.[18] However, preliminary experiments[19] showed that the oxidation failed when the β-lactam nitrogen was protected; for example, the reaction did not take place when it was carried out on N-1-substituted compounds such as **7**. Moreover, the substituent on the C-3 amino group played an important role: when a mono-substituted amide was tested, we observed a complex mixture



Scheme 6

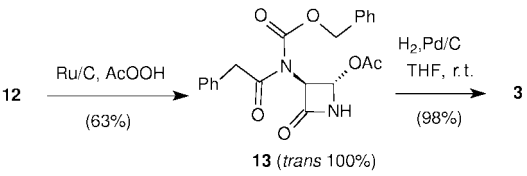
from which traces of the 3-acetoxy derivative could be recovered.

These difficulties could be overcome by oxidizing an azetidinone derivative with an N-1-unsubstituted β-lactam ring and double-protected C-3 nitrogen. For this purpose, (*S*)-**9** was converted to (*S*)-**11** with sodium hydride and carbobenzoxy chloride in THF at room temperature. The resulting β-lactam was then deprotected by oxidation with potassium permanganate to afford **12** (Scheme 7).



Scheme 7

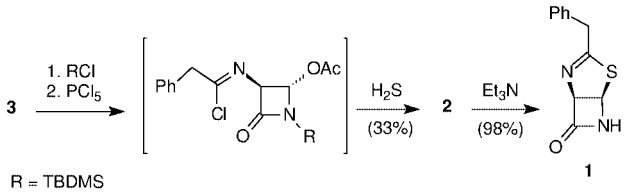
Oxidation of **12** with the Murahashi procedure finally led to **13** in good overall yield and with complete diastereoselective induction. The final step in the synthesis involved removal of the carbobenzoxy group by hydrogenolysis under mild conditions in THF using Pd on activated charcoal as a catalyst to give **3** (Scheme 8).[20]



Scheme 8

Compound **3** was then converted into the corresponding thioamide by means of phosphorus pentachloride and treatment of the resulting chloroimine with hydrogen sulfide. Formation of the unstable chloroimine is industrially exploited to deprotect a phenylacetamide chain by quenching with excess alcohol,[21] whereas in this case quenching with H_2S furnished compound **2,** the yield of which is not yet optimized. Upon treatment with TEA,

(3*S*)-phenylthioacetamido-(4*S*)-acetoxyazetidin-2-one **2** easily and quantitatively underwent cyclization to give the target compound **1**.



Scheme 9

In conclusion, we realized a total synthesis of homochiral thiazoline **1**, a useful intermediate for the synthesis of penicillin and cephalosporin derivatives. This synthesis involves facile processes using inexpensive and readily available starting materials, while chirality is introduced through enzymatic resolution followed by recycling of the undesired enantiomer.

Penicillin G Amidase (PGA), used for the enzymatic resolution, was kindly supplied by Recordati (Italy). The enantiomeric excess was determined by HPLC: HP1900, direct phase, chiral column *S,S*-DACH.DNB Lichosorb si.100, 5 micron 25cm x 4mm, kindly provided by Prof. Gasparrini, University of Rome (Italy). Hexahydrotriazines **6** were prepared following the procedure reported in the literature[9] using EtOAc as a solvent instead of benzene.

Azetidinones 4 a-c; General Procedure

To a solution of phthalimidoacetyl chloride (30 mmol, 6.7 g) cooled at -40 °C in anhyd CH_2Cl_2 (80 mL), Et_3N (60 mmol, 8.4 mL) was added dropwise. The solution became yellow and then orange to confirm that the ketene was formed. After 30 min at -40 °C, a solution of the appropriate hexahydrotriazine **6** (10 mmol) and BF_3•OEt_2 (30 mmol, 3.68 mL) in CH_2Cl_2 (80 mL), previously mixed at r.t., was added dropwise. After 4 h at -40 °C, the solution was quenched with HCl (1 M, 40 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic phase was washed with aq $NaHCO_3$ (5%, 40 mL), brine (40 mL), dried (Na_2SO_4) and concentrated in vacuo. The products **4a-c** were obtained as white solids after careful trituration in CH_3OH.

4a: mp 87 °C.

IR (nujol): 1759, 1717 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.63 (dd, 1H, *J* = 5.4, 5.4 Hz), 3.70 (dd, 1H, *J* = 5.4, 2.9 Hz), 3.85 (dd, 1H, *J* = 5.5, 15.7 Hz), 4.10 (dd, 1H, *J* = 5.5, 15.7 Hz), 5.25–5.42 (m, 2H), 5.45 (dd, 1H, *J* = 2.9, 5.4 Hz), 5.90 (m, 1H), 7.80 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.0, 164.7, 134.4, 131.7, 131.1, 123.6, 118.8, 53.6, 45.5, 44.7.

HRMS: *m/z* calc for $C_{14}H_{12}N_2O_3$ (M^+) 256.0848. Found: 256.0849.

4b: mp 192 °C.

IR (nujol): 1750, 1710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 4.00 (m, 2H), 5.56 (dd, 1H, *J* = 5.4, 3.4 Hz), 6.90–7.35 (m, 4H), 7.75–7.85 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.9, 160.9, 156.4, 134.5, 131.6, 131.3, 123.7, 118.0, 114.4, 55.5, 52.8, 45.3.

HRMS: *m/z* calc for $C_{18}H_{14}N_2O_4$ (M^+) 322.0954. Found: 322.0950.

4c: mp 119 °C.

IR (nujol): 1760, 1720 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.53 (dd, 1H, *J* = 5.4, 5.4 Hz), 3.58 (dd, 1H, *J* = 5.4, 3.2 Hz), 4.45 (d, 1H, *J* = 15.3 Hz), 4.68 (d, 1H, *J* = 15.3 Hz), 5.48 (dd, 1H, *J* = 5.4, 3.2 Hz), 7.3 (m, 5H), 7.8 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.8, 164.7, 134.6, 134,4, 134.3, 133.9, 131.5, 128.7, 128.6, 128.5, 123.8, 123.5, 53.5, 46.1, 45.4.

HRMS: *m/z* calc for $C_{18}H_{14}N_2O_3$ (M^+) 306.1004. Found: 306.1001.

Azetidinones 4d-f; General Procedure

To a solution of *N,N*-dicarbobenzyloxyglycine (343 mg, 1 mmol) in CH_2Cl_2 (10 mL) at r.t., oxalyl chloride (1.5 mmol, 0.13 mL) was added to form the corresponding acyl chloride. After the mixture was stirred for 3 h, the temperature was brought to -40 °C and the same procedure for β-lactams **4a-c** was used. The products were purified by chromatography over silica gel (cyclohexane/ EtOAc 8:2).

4d: mp 75 °C.

IR ($CHCl_3$): 1760, 1700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.34 (dd, 1H, *J* = 5.1, 2.9 Hz), 3.44 (dd, 1,H, *J* = 5.2, 5.1 Hz), 3.54 (dd, 1H, *J* = 5.2, 15.6 Hz), 3.76 (dd, 1H, *J* = 5.2, 15.6 Hz), 5.11–5.27 (m, 6H), 5.48–5.68 (m, 2H), 7.35 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.8, 152.5, 134.5, 131.3, 128.6, 128.5, 128.4, 118.6, 69.5, 59.8, 45.9, 44.3.

HRMS: *m/z* calc for $C_{22}H_{22}N_2O_5$ (M^+) 394.1529). Found: 394.1527.

4e: mp 73 °C.

IR ($CHCl_3$): 1744, 1703 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.65 (dd, 1H, *J* = 5.4, 3.1 Hz), 3.81 (s, 3H), 3.82 (dd, 1H, *J* = 5.4, 5.5 Hz), 5.24 (m, 4H), 5.69 (dd, 1H, *J* = 5.5, 3.1 Hz), 6.84 (m, 2H), 7.18 (m, 2H), 7.27 (m, 10H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0, 156.1, 152.3, 134.2, 131.5, 128.5, 128.4, 117.7, 114.3, 69.6, 59.2, 55.5, 45.7.

HRMS: *m/z* calc for $C_{26}H_{24}N_2O_6$ (M^+) 460.1634. Found: 460.1637.

4f: IR ($CHCl_3$): 1759, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.29 (dd, 1H, *J* = 5.1, 3.0 Hz), 3.35 (dd, 1H, *J* = 5.4, 5.1 Hz), 4.02 (d, 1H, *J* = 15.0 Hz), 4.44 (d, 1H, *J* = 15.0 Hz), 5.1 (m, 4H), 5.55 (dd, 1H, *J* = 5.4, 3.0 Hz), 7.2–7.4 (m, 15H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.7, 152.4, 135.0, 134.5, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 69.4, 59.9, 45.8, 45.7.

HRMS: *m/z* calc for $C_{26}H_{24}N_2O_5$ (M^+) 444.1685. Found: 444.1683.

3-*N*-(Phthalimido)-1-*N*-(propen-1-yl)azetidin-2-one (7)

Azetidin-2-one **4a** (10.24 g, 40 mmol) was suspended in 90 mL of EtOH and 10 mL of H_2O; 150 mg of $RhCl_3.nH_2O$ were added and the solution was heated to reflux. After consumption of the starting material (30 min), the solution was poured into cold water (40 mL) causing product precipitation. After separation by filtration, to eliminate the dark color, the β-lactam was dissolved in CH_2Cl_2 and treated with carbon, filtered, dried and concentrated, to give **7** in 98% yield. mp 173 °C.

IR (nujol): 1775, 1745, 1720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.74 (dd, 3H, *J* = 7.1, 1.6 Hz), 3.82 (m, 2H), 5.17 (dq, 1H, *J* = 7.1, 14.2 Hz), 5.5 (dd, 1H, *J* = 3.2, 5.5 Hz), 6.66 (dd, 1H, *J* = 1.6, 14.2 Hz), 7.8 (m, 4H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.7, 160.5, 134.3, 131.5, 123.5, 121.9, 108.5, 52.7, 45.1, 14.6.

HRMS: *m/z* calc for $C_{14}H_{12}N_2O_3$ (M^+) 256.0848. Found: 256.0850.

3-Amino-1-*N*-(propen-1-yl)azetidin-2-one (8)
To a suspension of **7** (10 mmol, 2.56 g) in EtOH (15 mL), was added $MeNH_2$ (10 mL, 33% in EtOH, 8.32 M). The solution became clear but, after 3h at r.t., the phthalimido derivative began to precipitate whereas, product **8** remained in solution and was recovered after filtration in 80% yield.

IR ($CHCl_3$): 3300, 1750 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.67 (dd, 3H, *J* = 1.6, 6.8 Hz), 2.53 (br s, 2H), 3.11 (dd, 1H, *J* = 6.4, 2.6 Hz), 3.64 (dd, 1H, *J* = 5.9, 6.3 Hz), 4.20 (dd, 1H, *J* = 2.6, 5.9 Hz), 5.1 (dq, 1H, *J* = 14.8, 6.8 Hz), 6.5 (dd, 1H, *J* = 14.8, 1.6 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0, 122.2, 122.1, 107.6, 65.3, 47.9, 24.3.

HRMS: *m/z* calc for $C_6H_{10}N_2O$ (M^+) 126.0793. Found: 126.0790.

3-*N*-(Phenylacetyloxy)-1-*N*-(propen-1-yl)aminoazetidin-2-one (9)
To a solution of **8** (1.26 g, 10 mmol) and Na_2CO_3 (20 mmol) in acetone (15 mL) and H_2O (20 mL), at 0 °C, phenylacetyl chloride (12 mmol, 1.59 mL) was added dropwise. After 12 h at r.t., acetone was concentrated and the mixture was extracted with EtOAc (2 × 20 mL). The organic phase was washed with brine, dried and concentrated to directly obtain the product as a white solid in 85% yield; mp 102 °C.

IR ($CHCl_3$): 3300, 1752, 1655 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (d, 3H, *J* = 6.6 Hz), 3.25 (dd, 1H, *J* = 2.6, 6.1 Hz), 3.56 (s, 2H), 3.65 (dd, 1H, *J* = 6.1, 6.5 Hz), 4.9 (m, 1H), 5.06 (dq, 1H, *J* = 14.2, 6.9 Hz), 6.42 (d, 1H, *J* = 14.2), 7.08 (d, 1H, *J* = 7.41 Hz), 7.2–7.4 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.5, 162.8, 134.3, 129.2, 128.8, 128.7, 127.7, 127.1, 121.8, 108.5, 55.2, 47.4, 43.0, 14.6.

HRMS: *m/z* calc for $C_{14}H_{16}N_2O_2$ (M^+) 244.1212. Found: 244.1213.

Enzymatic Hydrolysis
Compound **9** (100 mg, 0.41 mmol) was dissolved in acetone (2 mL) and diluted with 0.1 M phosphate buffer (4 mL) at pH 7.8. The enzyme (40 IU, 10% w/w) was added and the mixture stirred at 1000 rpm. The pH was maintained to its initial value with the automatic addition of NaOH (0.1N). At the desired conversion (30%), the supported enzyme was filtered off, acetone was eliminated in vacuo, the pH of the aq phase was adjusted to 4.5 with dilute HCl and extracted with EtOAc (3 × 10 mL). The organic phase (*R*)-**9** was collected. The aq phase containing (*S*)-**8** was treated with Na_2CO_3 (to pH 8) and phenylacetyl chloride (1.5 equiv) in acetone (10 mL) to obtain, after removal of acetone in vacuo and extraction with EtOAc (3 × 10 mL), compound (*S*)-**9**: $[\alpha]^{25}_D$ -30 (*c* = 0.9, $CHCl_3$); e.e. = 94% (HPLC).

Racemization Process
β-Lactam (*R*)-**9** was completely transformed into (*R*)-**8** by means of PGA in the same conditions of enzymatic hydrolysis with longer reaction times. After recovering by extraction with CH_2Cl_2 at pH 8, (*R*)-**8** (126 mg, 1 mmol) was dissolved in CH_2Cl_2 (5 mL) at r.t. and treated with benzaldehyde (0.1 mL, 1 mmol) and $MgSO_4$ (2 mmol) to give quantitatively imine (*R*)-**10**. The product was recovered by filtration and the solvent evaporated.

$[\alpha]^{25}_D$ +162 (*c* = 1.1, CH_2Cl_2).

IR ($CHCl_3$): 1769, 1638 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.72 (dd, 3H, *J* = 6.8, 1.5 Hz), 3.63 (dd, 1H, *J* = 2.3, 6.1 Hz), 3.82 (dd, 1,H, *J* = 6.1, 5.1 Hz), 4.88 (m, 1H), 5.15 (dq, 1H, *J* = 6.8, 14.2 Hz), 6.59 (dd, 1H, *J* = 1.5, 14.2 Hz), 7.2–7.8 (m, 5H), 8.48 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.2, 164.0, 135.5, 131.3, 128.6, 128.4, 122.2, 108.2, 72.7, 47.4, 14.7.

HRMS: *m/z* calc for $C_{13}H_{14}N_2O$ (M^+) 214.1106. Found: 214.1105.

Regeneration of (*R,S*)-9
Imine (*R*)-**10** was dissolved in THF (5 mL) and treated at 0 °C with a catalytic amount of *t*-BuOK (0.1 mL, 1M solution in THF). After 3 h at r.t., HCl (1N, 0.5 mL) was added. After 1 h, Na_2CO_3 (216 mg, 2 mmol) and phenylacetylchloride (0.16 mL, 1.2 mmol) were added to the mixture to give (*R,S*)-**9** in 90% yields. $[\alpha]^{25}_D$ 0 (*c* = 4, CH_2Cl_2); e.e.% = 0 confirmed by HPLC (chiral column).

(3*S*)-3-*N*-(Benzyloxycarbonyl)-3-*N*-(phenylacetyloxy)-1-*N*-(propen-1-yl)aminoazetidin-2-one (11)
β-lactam (*S*)-**9** (256 mg, 1 mmol) was slowly dropped into a suspension of NaH (42 mg, 1.9 mmol) in THF (5 mL) at 0 °C. After 10 min, benzyl chloroformate (0.27 mL, 1.9 mmol) was added. After 20 min at r.t., the reaction was quenched with NH_4Cl, extracted with EtOAc, washed with brine, dried and concentrated. After purification by flash chromatography (cyclohexane/EtOAc 8:2), the product was obtained in 65% yield; mp: 85 °C; $[\alpha]^{25}_D$ -56.6 (*c* = 0.514, $CHCl_3$).

IR ($CHCl_3$): 1760, 1700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.61 (dd, 3H, *J* = 6.8, 1.6 Hz), 3.36 (dd, 1H, *J* = 3.2, 5.6 Hz), 3.57 (dd, 1H, *J* = 5.8, 5.6 Hz), 4.26 (s, 2H), 4.86 (dq, 1H, *J* = 7.0, 14.2 Hz), 5.16 (d, 1H, *J* = 11.0 Hz), 5.28 (d, 1H, *J* = 11.0 Hz), 5.75 (dd, 1H, *J* = 3.2, 5.8 Hz), 6.36 (dd, 1H, *J* = 1.6, 14.2 Hz), 7.2–7.4 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5, 162.1, 152.9, 133.8, 133.7, 129.5, 129.4, 129.3, 129.0, 128.9, 128.7, 127.0, 133.8, 133.7, 121.9, 107.2, 69.7, 57.2, 45.2, 44.3, 14.6.

HRMS: *m/z* calc for $C_{22}H_{22}N_2O_4$ (M^+) 378.1579. Found: 378.1577.

(3*S*)-3-*N*-(Benzyloxycarbonyl)-3-*N*-(phenylacetyloxy) aminoazetidin-2-one (12)
To a solution of **13** (10 mmol, 3.78 g) in acetone (40 mL) and phosphate buffer (20 mL, pH 7.5), $KMnO_4$ (12 mmol, 1.740 g) dissolved in 5 mL of buffer was slowly added dropwise at a rate such that the passage from purple (MnO_4^-) to brown (MnO_2) was observed. This change indicated that the oxidation was going on. After consumption of the last drop, MnO_2 was filtered off, the solution was concentrated to eliminate acetone, extracted with CH_2Cl_2, washed with brine, dried and concentrated. The product was obtained in 59% yield after purification by flash chromatography (cyclohexane/EtOAc 1:1), $[\alpha]^{25}_D$ -32.2 (*c* = 4.12, $CHCl_3$).

IR (neat): 3300, 1760, 1748, 1670 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.40 (dd, 1H, *J* = 3.2, 5.4 Hz), 3.48 (dd, 1H, *J* = 5.4, 5.5 Hz), 4.24 (s, 2H), 5.20 (d, 1H, *J* = 11.7 Hz), 5.29 (d, 1H, *J* = 11.7 Hz), 5.69 (dd, 1H, *J* = 3.2, 5.5 Hz), 5.84 (br s, 1H), 7.21–7.38 (m, 10H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.6, 167.4, 153.0, 134.1, 133.9, 129.9, 129.1, 129.0, 128.9, 128.8, 128.7, 127.0, 69.6, 59.8, 44.4, 42.2.

HRMS: *m/z* calc for $C_{19}H_{18}N_2O_4$ (M^+) 338.1266. Found: 338.1268.

(3*S*,4*R*)-3-*N*-(Benzyloxycarbonyl)-3-*N*-(phenylacetyloxy) amino-4-acetoxyazetidin-2-one (13)
A mixture of Ru (5%) on carbon (80 mg, 0.04 mmol), anhyd sodium acetate (82 mg, 1 mmol), HOAc (1 mL), β-lactam **12** (1 mmol) and CH_2Cl_2 (3 mL) was charged into a 25 mL flask at r.t. To the above mixture, a 32% solution of AcOOH in HOAc (0.46 mL, 2.2 mmol)

was added dropwise over a period of 1 h at r.t., and stirred for 2 h. The mixture was poured into cold water, filtered and extracted with CH_2Cl_2 (3 × 15 mL). The organic solution was washed with 10% Na_2SO_3 (20 mL), brine and dried (Na_2SO_4). Evaporation, followed by column chromatography on silica gel (cyclohexane/EtOAc 6:4) gave **13** in 63% yield as a single *trans* diastereoisomer, $[\alpha]^{25}_D$ -33.9 (*c* = 1.65, $CHCl_3$).

IR ($CHCl_3$): 3300, 1800, 1750, 1700, 1257 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 4.26 (m, 2H), 5.25 (s, 2H), 5.6 (d, 1H, *J* = 0.8 Hz), 5.9 (d, 1H, *J* = 0.8 Hz), 6.42 (br s, 1H); 7.2–7.5 (m, 10H).).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.8, 170.0, 163.3, 152.5, 133.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.5, 127.2, 78.0, 69.9, 65.6, 44.3, 20.6.

HRMS: *m/z* calc for $C_{21}H_{20}N_2O_6$ (M^+) 396.1321. Found: 396.1320.

(3*S*, 4*R*)-3-*N*-(Phenylacetyloxy)amino-4-acetoxyazetidin-2-one (3)

To a solution of **13** (396 mg, 1 mmol) in THF (10 mL), Pd (10%) on activated charcoal (20 mg) were added. The reaction funnel was connected with a plastic balloon containing H_2 at the pressure of 1 atm and the reaction was monitored by TLC. After total consumption of the starting material (30–60 min), the Pd was filtered off and the THF was concentrated in vacuo affording **3** in 98% yield, $[\alpha]^{25}_D$ -50 (*c* = 0.4, $CHCl_3$).

IR ($CHCl_3$): 1793, 1750, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 3.65 (s, 2H), 4.65 (d, 1H, *J* = 6.4 Hz), 5.84 (s, 1H), 6.13 (d, 1H, *J* = 6.4 Hz), 6.77 (br s, 1H), 7.27 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.7, 170.8, 164.1, 133.8, 129.5, 129.2, 127.7, 78.6, 63.9, 43.2, 20.7.

HRMS: *m/z* calc for $C_{13}H_{14}N_2O_4$ (M^+) 262.0953. Found: 262.0955.

(1*R*, 5*R*)-3-Phenylmethyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (1)

To a solution of **3** (262 mg, 1 mmol) in CH_2Cl_2 (10 mL) at r.t., *t*-$BuMe_2SiCl$ (225mg, 1.5 mmol) and 4-dimethylaminopyridine (245 mg, 2 mmol) were added. After 12h, the temperature was brought to -50 °C, dimethylaniline (0.313 mL, 2.5 mmol) and PCl_5 (230 mg, 1.1 mmol) were added and, after 3h at low temperature, H_2S was bubbled inside the reaction funnel for 30 min. The mixture was allowed to reach r.t., quenched with $NaHCO_3$ (10%, 20 mL), extracted with CH_2Cl_2 (2 × 20 mL), washed with brine, dried and concentrated. The intermediate thioamide **2** thus obtained was directly converted into **1** by refluxing for 1h in toluene (10 mL) in the presence of Et_3N (0.125 mL, 1 mmol) and then stirring overnight at r.t. After quenching with H_2O (5 mL) and extraction with EtOAc (2 × 10 mL), the product was obtained in 98% yield after purification with flash chromatography (cyclohexane/EtOAc 1:1); mp 178 °C, $[\alpha]^{25}_D$ +91.8 (*c* = 1.23, $CHCl_3$).

IR ($CHCl_3$): 3200, 1741, 1720, 1710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (d, 1H, *J* = 15.3 Hz), 4.0 (d, 1H, *J* = 15.3 Hz), 5.50 (d, 1H, *J* = 3.9 Hz), 6.01 (m, 1H), 6.58 (br s, 1H), 7.26–7.36 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.5, 164.8, 135.0, 129.1, 128.7, 127.4, 94.8, 64.3, 41.5.

HRMS: *m/z* calc for $C_{11}H_{10}N_2OS$ (M^+) 218.0514. Found: 218.0514.

Acknowledgement

This work was financially supported by MURST (40 and 60%), CNR, University of Bologna (fund for selected topics).

References

(1) Niccolai, D.; Tarsi, L.; Thomas, R. J. *J. Chem. Soc., Chem. Comm.* **1997**, 2333.
Berks, A. H. *Tetrahedron* **1996,** *52*, 331.
The Organic Chemistry of β-*Lactams*; Georg, G. I., Ed.; VCH: New York, 1993.
(2) Bucourt, R. In *Recent Advances in the Chemistry of* β-*Lactam Antibiotics*; Gregory G. I. Ed., Second International Symposium; London, 1980; and references cited therein.
(3) Cooper, R. D. G. *J. Am. Chem. Soc.* **1970**, *92*, 2575.
Brain, E. G.; Eglinton, A. J.; Nayler, J. H. C.; Pearson, M. J.; Southgate, R. *J. Chem. Soc., Perkin I trans.* **1976**, 447.
(4) Cooper, R. D. G.; José, L. F. *J. Am. Chem. Soc.* **1972,** *94*, 1021.
(5) Cooper, R. D. G. *J. Am. Chem. Soc.* **1972,** *94*, 1018.
Foglio, M.; Franceschi, G.; Lombardi, P.; Scarafile, C.; Arcamone, F. *J. Chem. Soc., Chem. Comm.* **1978**, 1101.
Marchand-Brynaert, J.; Ghosez, L. *Tetrahedron Lett*. **1980**, *21*, 3085.
Ghosez, L.; Marchand-Brynaert, J.; Vekemans, J.; Bodgan, S. *Tetrahedron* **1983,** *39*, 2493.
(6) Narisada, M.; Onoue, H.; Ohtani, M.; Watanabe, F.; Okada, T.; Nagata, W. *Tetrahedron Lett*. **1978**, *20*, 1755.
(7) Osborne, N. F. *J. Chem. Soc., Perkin Trans. I* **1982**, 1435.
(8) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G.; Bandini, E. In *Chemical Synthesis: Gnosis to Prognosis*; Chatgilialoglu, C; Snieckus,V. Eds.; NATO ASI, 1996.
(9) Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685.
(10) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979,** *35*, 323.
(11) Reynolds, D.; Cossar, B. *J. Heterocycl. Chem*. **1971**, *8*, 567.
(12) Cainelli, G.; Giacomini, D.; Galletti P. *Synlett* **1998**, *6*, 611.
(13) Georg, G. I.; He, P.;Kant, J.; Mudd, J. *Tetrahedron Lett*. **1990**, *31*, 451.
(14) Motawia, H. S.; Wengel, J.; Abdel-Megid, A. E. S., Pedersen, E. B. *Synthesis* **1989**, 384.
(15) Duggleby, H. J.; Tolley, S. P.; Hill, C. P.; Dodson, E. J.; Dodson, G.; Moody, P. C. E. *Nature* **1995**, *373*, 264.
(16) See for example: Baldaro, E.; Fuganti, C.; Servi, S.; Tagliani, A.; Terreni, M. In *Microbial Reagents in Organic Synthesis*; Kluwer Academic: 1992; p 175.
(17) Cainelli, G.; Giacomini, D.; Galletti P.; DaCol, M. *Tetrahedron Asymmetry* **1997**, *8*, 3231.
(18) Murahashi, *S*-I; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett*. **1991**, *32*, 2145.
Murahashi, *S*-I; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990,** *112*, 7820.
(19) Cainelli, G.; DaCol, M.; Galletti P.; Giacomini, D. *Synlett* **1997**, *8*, 923.
(20) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Chemistry*; J. Wiley Eds., New York, 1991.
(21) Hatfield, L. D.; Lunn, W. H.; Jackson, B. G.; Peters, L. R.; BlaszczaK, L. C.; Fisher, J. W.; Gardner, J. P.; Dunigan, J. M. In *Recent Advances in the Chemistry of* β-*Lactams Antibiotics*; Second International Symposium, Gregory, G. I. Ed., R. S. C.: London, 1980.

Article Identifier:
1437-210X,E;2000,0,02,0289,0294,ftx,en;Z05999SS.pdf