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Enantiospecific and Diastereoselective Synthesis of *cis* Monobactams through Electrophilic Amination of Chiral 3-Hydroxyesters

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Abstract: A new efficient entry into *cis* monobactams starting from β-hydroxyesters is reported. This preparation is based on the stereoselective "electrophilic amination" of β-hydroxyester dianions and on Miller's biomimetic synthesis of the β-lactam nucleus. By this route, key intermediates for the preparation of pharmacologically important *cis* aztreonam **2** and carumonam **3** were prepared.

In 1981 the Squibb[1] and Takeda[2] groups announced the discovery of novel monocyclic β-lactam antibiotics characterized by the presence of an SO_3^- group bonded to the azetidinone nitrogen.[3] These compounds, called monobactams[1] or sulfazecins,[2] showed interesting β-lactamase stability. After thorough structure-activity relationship studies,[4] aztreonam **1** and carumonam **3** were selected for further development (Scheme 1). They possess a specific activity against gram-negative bacteria coupled with a high β-lactamase stability. These properties allowed these compounds to be brought into clinical use.

Since 4-substituted monobactams are not accessible through microbiological methods, their preparation requires the development of total syntheses of the corresponding 3-amino monobactamic acids (3-AMA) derivatives, like **4-6**.[5-8] One of the most efficient methodologies for the general preparation of 3-AMA derivatives involves the biomimetic cyclization of suitably derivatized 2-amino-3-hydroxyacids (Scheme 2).[9] For example **1** is efficiently synthesized from easily available L-threonine.[6] In other cases, however, this strategy is limited by the troublesome availability of the requisite starting 2-amino-3-hydroxyacid. For example, although it has been demonstrated that the *cis* 4-methyl monobactam **2** is even more active and β-lactamase resistant than its *trans* counterpart,[4a,10] its clinical development was prevented by the fact that the only preparation of *cis* zwitterion **5** reported to date[6d] requires the quite expensive L-*allo*-threonine **7** (R^1 = Me, R^2, R^3, R^4 = H) as starting material. Accordingly, the possible preparation of carumonam **3** by this strategy is hampered by the difficult availability of requisite starting *anti* (*allo*) 2-amino-3,4-dihydroxybutanoic acids derivatives **7** ($R^1 = CH_2OH$).

We have previously reported[11,12] the diastereoselective condensation of ethyl 3-hydroxybutyrate[11] as

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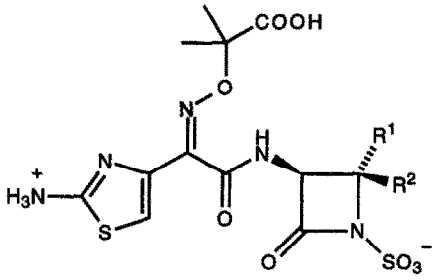
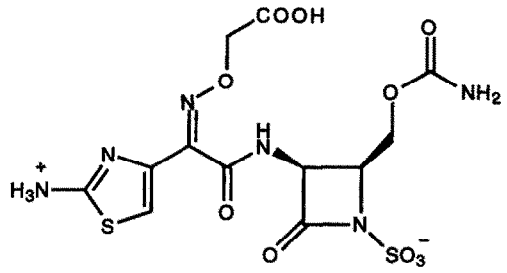
Scheme 1

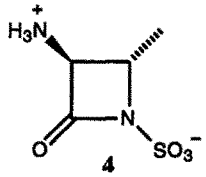


1 Aztreonam $R^1 = Me, R^2 = H$

2 SQ 26,917 $R^1 = H, R^2 = Me$

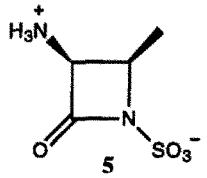


3 Carumonam



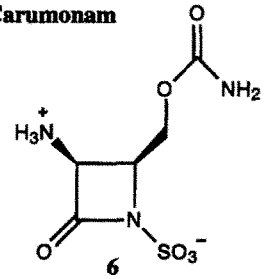
4

***trans* 4-Methyl-3-AMA**



5

***cis* 4-Methyl-3-AMA**



6

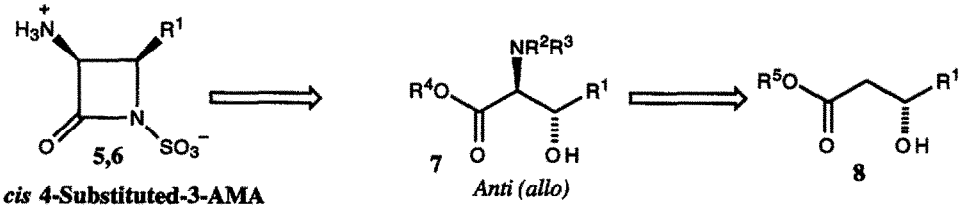
***cis* 4-Carbamoyloxymethyl-3-AMA**

well as of 4-alkoxy-3-hydroxyesters derived from malic acid,[12] with di-*t*-butyl azodicarboxylate.[13] These condensations furnished, as major products, the corresponding protected 2-hydrazino-3-hydroxyesters **7** [R^2= Boc, R^3=NH(Boc)] with *anti* relative configuration. Since the above mentioned biomimetic cyclizations take place with inversion of configuration at C-4 (β-lactam numbering), we envisioned that these *anti* adducts could be ideal building blocks for the construction of *cis* 4-substituted-3-aminomonobactamic acids, like **5** and **6** (Schemes 1, 2). As a continuation of our continuing efforts toward the synthesis of pharmacologically important β-lactams,[14] we report now the successful synthesis of **5** and of a known precursor of **6** and **3** through this strategy.

Synthesis of cis Aztreonam precursors

As previously reported,[11] "electrophilic amination" of the dianion of (*S*) ethyl β-hydroxybutyrate[15] with di-*tert*-butyl azodicarboxylate[13] furnished in good yield the *anti* protected 2-hydrazino-3-hydroxyester **10** (Scheme 3). We argued that **10** could be regarded as a very useful chiral building block; indeed, it has not only the hardly achievable configuration of *allo* -threonine, but it also possesses the aminic and carboxylic

Scheme 2



5,6

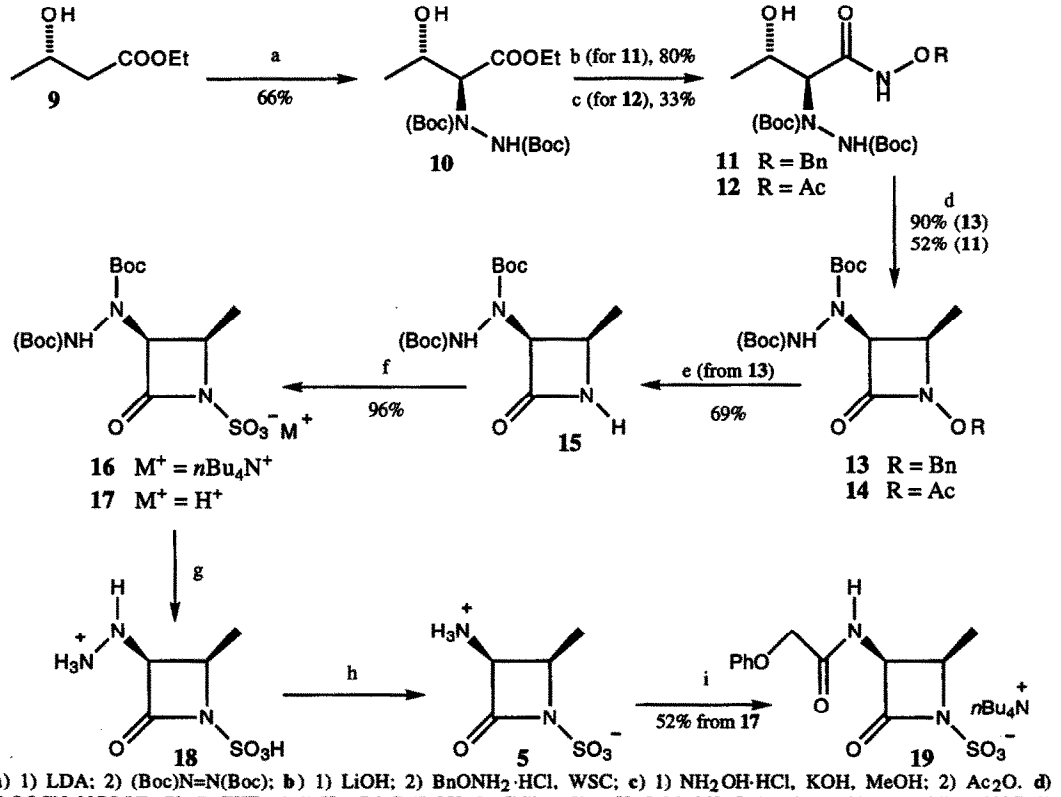
***cis* 4-Substituted-3-AMA**

7

Anti (allo)

8

Scheme 3



a) 1) LDA; 2) (Boc)N=N(Boc); **b**) 1) LiOH; 2) $BnONH_2 \cdot HCl$, WSC; **c**) 1) $NH_2OH \cdot HCl$, KOH, MeOH; 2) Ac_2O. **d**) EtOOCN=NCOOEt, Ph_3P, THF; **e**) 1) H_2, Pd-C, EtOH; 2) $TiCl_3$, pH 7, H_2O-MeOH. **f**) 1) SO_3·pyridine, pyridine, 80°C; 2) *n*-Bu_4NHSO_4; 3) silica gel chromatography; **g**) CF_3COOH, CH_2Cl_2, 0°C → r.t.; **h**) H_2, PtO_2, EtOH, r.t.; **i**) $PhOCH_2COCl$, Et_3N, DMF, r.t..

functions in a protected form, which is a prerequisite for most synthetic applications.[16] It is well known that a hydrazinic group is easily transformable into an amine by hydrogenolysis over platinum[13c] or nickel[13a] catalysts.

Thus our synthetic strategy started from **10** and followed the biomimetic approach first developed by Miller[9] (Scheme 3). We converted ester **10** into both the O-benzyl hydroxamate **11** and the O-acyl hydroxamate **12**. The former compound was obtained in excellent yields through saponification followed by *in situ* WSC[17] mediated coupling with O-benzylhydroxylamine.[6b] On the contrary, preparation of the latter under the conditions described by Miller[6e] (hydroxylaminolysis with NH_2OH in MeOH followed by *in situ* acetylation) afforded **12** in only 33% yield.[18] Cyclization to the β-lactams under Mitsunobu conditions proceeded smoothly and in excellent yield (90%) in the case of O-benzylhydroxamate **11**, while O-acetyl derivative **12** afforded **14** in only moderate yield. Due to the higher yields achieved both in the hydroxamate formation and in the cyclization, we continued our synthesis on the O-benzyl derivative.

After removal of benzyl protecting group, reductive cleavage of N-OH bond with $TiCl_3$[6c] gave the 1-unsubstituted azetidinone **15**. Sulfonation of **15** was carried out with the pyridine-SO_3 complex in hot pyridine[6d] and the resulting azetidinesulfonic acid was first isolated through extraction of its tetra-

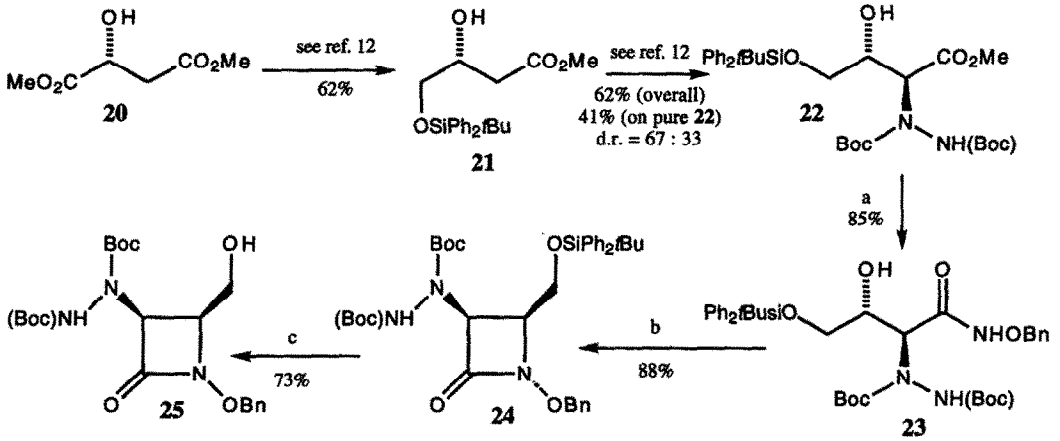
n-butylammonium salt **16**.[6d] A further purification *via* silica gel chromatography (AcOEt / MeOH) surprisingly afforded the azetidinesulfonic acid **17** instead than the expected *n*-Bu_4N^+ salt **16.** The structure of **17** was confirmed by ^1H n.m.r., I.r. and elemental analysis.[19] It should be noted that the yields of the above described steps (from **10** to **17**) are comparable or even better than those achieved with the (Boc) amino analogues, showing that the protected hydrazino group is perfectly compatible with these reaction conditions.

When the protected sulfonic acid **17** was subjected to acidic cleavage of *t*-butylurethanes with CF_3COOH, the hydrazinium salt **18** was obtained. ^1H n.m.r. of the crude product showed that it was essentially pure, but that a small quantity of open chain product derived from β-lactam hydrolysis was also present (the ratio of **18** vs. open chain byproduct was 82 : 18 by ^1H n.m.r.). The crude hydrazinium salt[21] was then hydrogenated over PtO_2 to give 4-β-methyl-3-AMA **5**. We experienced some difficulties in separating it from ammonium trifluoroacetate (which is a necessary by-product of hydrogenolysis) and from open chain products. Nevertheless the structure of **5** was demonstrated through ^1H n.m.r., ^{13}C n.m.r. and I.r., and by conversion of the crude product into phenoxyacetyl monobactam **19**, isolated and purified as its *n*-Bu_4N^+ salt.[22] Conversion of zwitterion **5** into SQ 26,917 as well as into other 4-β-methyl monobactams was already reported,[4a,23] and so the here presented method represents a new efficient entry into that valuable class of antibiotics. The overall yield of **5** from β-hydroxybutyrate **6** is at least 17%, thus comparable with that obtained in the previous synthesis starting from L-*allo*-threonine (19%).[6d] Since (*S*) β-hydroxybutyrate is more easily available[15] and considerably cheaper than L-*allo*-threonine, we think that the here presented procedure is one of the most efficient preparation of **5** to date.

Synthesis of carumonam precursors

In order to obtain intermediates useful for the synthesis of carumonam **3**, we had to start with (*R*) 3,4-dihydroxybutanoates selectively protected at the primary hydroxyl. These compounds can be prepared from commercially available (*R*) dimethyl malate **20**, *via* regioselective reduction at the C-1 carboxyl,[24] followed by regioselective protection.[12] In this way we have previously obtained compound **21**, whose condensation with di-*t*-butyl azodicarboxylate furnished *anti* adduct **22** in good yield, but with only moderate

Scheme 4

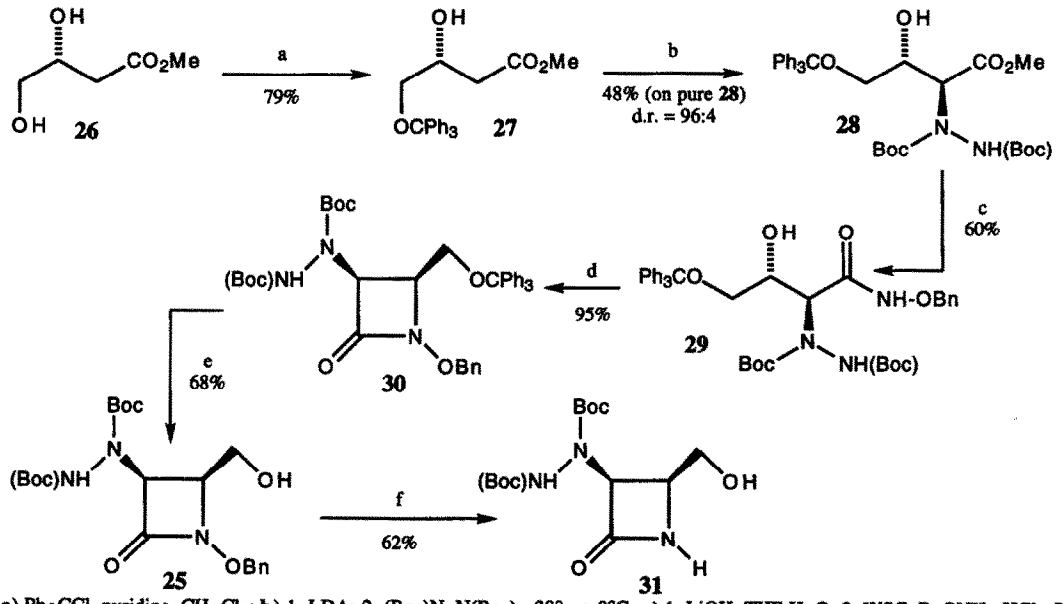


a) $BnONH_2 \cdot HCl$, Me_3Al, THF. b) Ph_3P, DEAD, THF; c) $nBu_4NF \cdot 3\,H_2O$, THF, -40°C.

diastereoselection (scheme 4). Attempts to improve this stereoselectivity by increasing the reaction temperature[11] failed, since at higher temperatures the yields dropped sharply, probably because of shifting of the silyl group on the secondary alcohol followed by easy elimination. However the two diastereoisomers could be separated by silica gel chromatography.[25] Conversion of methyl ester into O-benzyl hydroxamate **23** by the same methodology applied in the *cis* aztreonam synthesis turned out to be unfeasible. Actually all attempts to hydrolyze the ester group, either with LiOH, with the more nucleophilic LiOOH,[26] or with the aid of enzymes, failed. Also in this case, competitive silyl migration to the secondary alcohol followed by elimination took place preferentially. This problem was finally solved by employing Weinreb's method for direct conversion of esters into amides.[27] Cyclization under Miller's conditions[9] and silyl group removal by use of nBu$_4$NF at -40°C, furnished 4-hydroxymethyl β-lactam in high yield. It is worth noting that, carrying out the desilylation at higher temperatures, isomerization of **25** to give the corresponding δ-lactone took place.

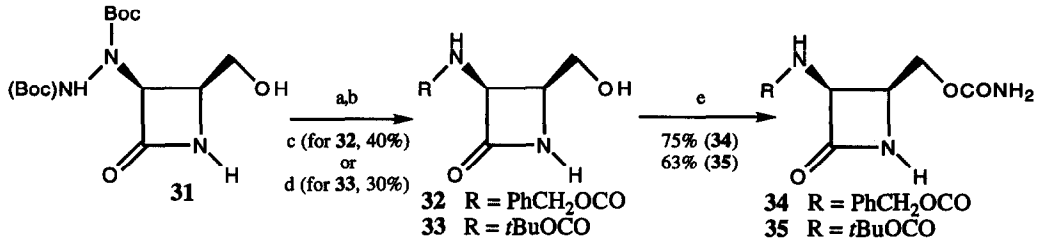
Although the synthesis of **25** through this route was satisfactory, the low stereoselectivity in the electrophilic amination step prompted us to search for alternative protecting groups to be introduced on malate derived diol **26**. After several attempts[28] we found out that the triphenylmethyl (trityl) group was well suited for our purposes (Scheme 5).[31] It was indeed easily introduced on **26** in a completely regioselective manner. Furthermore, its stability under basic conditions allowed the use of higher reaction temperatures in the dianion formation, as well as in the condensation with (Boc)N=N(Boc).[32] As previously reported,[11] in this type of reactions, the increase in reaction temperature brings about an increase of diastereoselecivity. In the present case it turned out to be excellent, although on the other hand the yield was only moderate. Contrary to what happened in the silyl protected compound, in this case conversion into the benzyl

Scheme 5



a) Ph_3CCl, pyridine, CH_2Cl_2; b) 1. LDA; 2. (Boc)N=N(Boc), -20° → 0°C; c) 1. LiOH, THF-H_2O; 2. WSC, $BnONH_2$·HCl; d) DEAD, PPh_3, THF; e) pTSA, MeOH; f) 1. H_2, Pd-C; 2. $TiCl_3$, H_2O-MeOH, pH 7.

Scheme 6



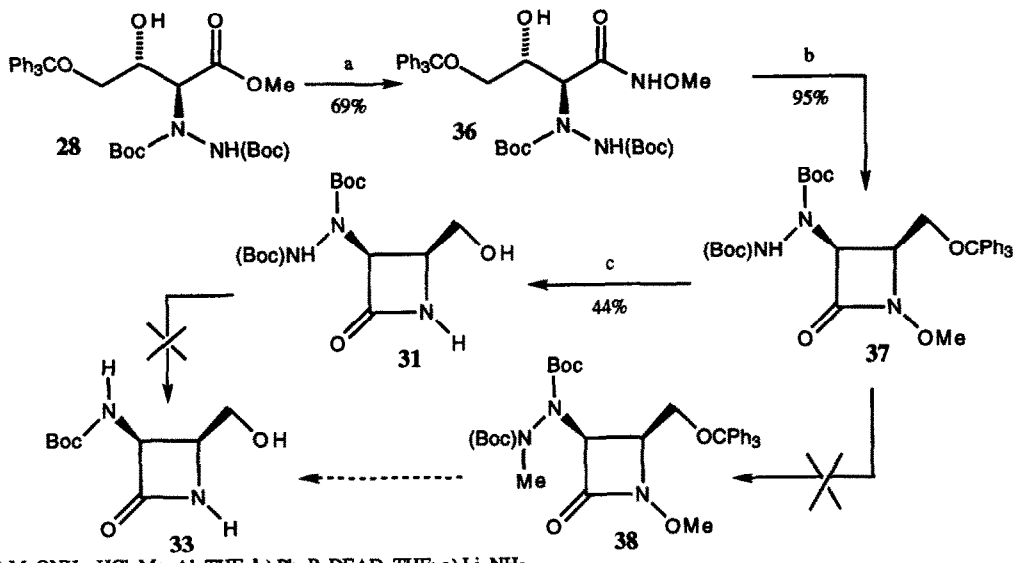
a) CF_3COOH, CH_2Cl_2; b) H_2, PtO_2; c) $PhCH_2OCOCl$, $NaHCO_3$, H_2O; d) $(tBuO)_2CO$, Et_3N, DMF; e) 1. $ClCH_2C(=O)$-NCO, CH_2Cl_2, DMF; 2. MeNH-C(=S)-SNa.

hydroxamate could be achieved by the usual, two step methodology, to give **29**, whose cyclization to β-lactam **30** proceeded once again in excellent yields. At this stage it was possible to selectively deprotect the trityl ether in the presence of the (Boc) groups by controlled acid catalyzed hydrolysis. The overall yield of **25** was comparable with that realized in Scheme 4. However the higher stereoselectivity makes purification of intermediate **28** easier than that of **22**. Finally, hydrogenolysis of the benzyl group and $TiCl_3$ reduction[6c] of the N-hydroxy bond gave protected hydrazino β-lactam **31**. Interestingly, when this two step protocol was applied to **30**, the $TiCl_3$ reduction did not take place, presumably because of the steric hindrance. On the contrary reduction of debenzylated **25** was considerably faster than usual (for example of debenzylated **13**), indicating a possible assistance by the free OH group.

Removal of *t*-butoxycarbonyl groups was carried out with CF_3COOH and the resulting hydrazine salt directly hydrogenated to give, after *in situ* protection, the known compounds **32** and **33**,[8m] which were in turn converted into the corresponding carbamates **34** and **35**. The former has already been transformed into carumonam **3** by a three step sequence.[8b,o]

We think that the moderate yield in the three step conversion of **31** into **32** was due to acid catalyzed opening of the β-lactam during the (Boc) deblocking or during the hydrogenolysis reaction. In order to improve this step we thus decided to look for an alternative method for converting the protected hydrazine into a protected amine without need to cleave the *t*-butyl urethanes. A literature survey showed that the N-N bond of doubly acylated hydrazines could be reductively cleaved by dissolving metal reductions, at least if the two nitrogen are fully substituted.[33] Since dissolving metals are capable also to N-demethoxylate N-methoxy β-lactams[6d] and to cleave trityl ethers, we decided to synthesize compound **37**, with the hope to convert it in one step into **33** (Scheme 7). Methyl hydroxamate **36** was readily produced from **28** by the above mentioned Weinreb's method,[27] and cyclized[9] in high yield to give **37**. Treatment of the latter with lithium in ammonia produced both trityl ether cleavage and demethoxylation at the β-lactam nitrogen. However the protected hydrazino group remained unchanged.[34] Supposing that the presence of an hydrogen atom on the terminal nitrogen was responsible for this lack of reactivity, we decided to N-methylate **37**. However, surprisingly,[35] we did not succeed in obtaining the desired product **38**. Actually, the use of a strong base (like NaH) to deprotonate the NH leads to rapid decomposition, while employing a mild base (like K_2CO_3) in aprotic dipolar solvents or under phase transfer conditions, the reaction did not take place, even with strong methylating agents.

Scheme 7



a) $MeONH_2$·HCl, Me_3Al, THF; b) Ph_3P, DEAD, THF; c) Li, NH_3.

Anyway, the preparation of alcohol **31** by the route shown in Scheme 7 is in our opinion, more convenient that the ones depicted in Schemes 4 and 5, thanks to the low number of steps, and of their operative simplicity.

Conclusion

We have demonstrated that the "electrophilic amination" of optically active 3-hydroxyesters with di-*t*-butyl azodicarboxylate, which gives preferentially *anti* protected 2-hydrazino-3-hydroxyesters, can be used for the preparation of *cis* azetidinone derivatives, useful precursors of *cis* monobactams, like SQ 26,917, and carumonam.

Acknowledgements

Part of this project was financially assisted by C.N.R. (Progetto finalizzato Chimica Fine).

EXPERIMENTAL

N.m.r. spectra were recorded on Varian FT 80 or Varian Gemini 200 spectrometers. Tetramethylsilane was used as internal standard for spectra in $CDCl_3$, d-6 DMSO and CD_3OD; 2,2,3,3-d_4 3-(trimethylsilyl)propanoic acid sodium salt (δ = 0.00 ppm) for ^1H, or dioxane (δ = 67.40) for ^{13}C spectra in D_2O; I.r. spectra were recorded on a Perkin-Elmer 881 instrument as $CHCl_3$ solutions. Mass spectra were obtained with a VG 70-70 EQ spectrometer with the FAB method at 6 KeV (Xe primary beam). Elemental analyses were performed with a Perkin-Elmer 240 instrument. Densitometric analyses were carried out with a CAMAG TLC-SCANNER instrument. The samples were deposed on 0.25 mm silica gel F 254 plates (Merck) with a CAMAG LINOMAT automatic deposer. Organic extracts were dried over Na_2SO_4 and filtered before removal of solvent under reduced pressure. All reactions employing dry solvents were run under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried over K/benzophenone; CH_2Cl_2, pyridine, and dimethylformamide (DMF) were doubly dried[36] over 4 Å molecular sieves. Chromatographies were carried

out on 220-400 mesh silica gel. Thin layer chromatographies were carried out on 0.25 mm silica gel F 254 plates (Merck). Spots were detected through immersion in the requisite solution [solution A: 21 g $(NH_4)_4MoO_4 \cdot 4\ H_2O$, 1 g $Ce(SO_4)_2 \cdot 4\ H_2O$, 469 ml H_2O, 31 ml conc. H_2SO_4. Solution B: 0.3 g ninhydrin, 100 ml *n* BuOH, 3 ml AcOH] followed by warming on a hot plate.

(*2S,3S*)-Ethyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino-3-hydroxybutanoate 10. It was prepared starting from a sample of (*S*) ethyl β-hydroxybutyrate **9** having $[\alpha]_D$ = + 40.2° (corresponding to a o.p. of 92.5%)[15a] essentially as described in ref. 11. For large scale preparations (10-20 g), however, we found more convenient to use 2.5 mol of LDA and 1.3 mol of di-*tert* -butylazodicarboxylate for each mol of **9.** In this way yields of 62-66% of diastereomerically pure **10** were routinely obtained and purification from di-*t*-butyl hydrazinodicarboxylate was easier.

(*2S,3S*) Benzyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxybutanohydroxamate 11. A solution of **10** (9.31 g, 25.69 mmol) in freshly distilled THF (100 ml) and water (90 ml) was cooled to 0°C and treated, during 5 minutes, with 1N aqueous LiOH (56.5 ml, 56.5 mmol). After stirring for 45 minutes at the same temperature, the solution was neutralized with 1N HCl and treated with O-benzylhydroxylamine hydrochloride (4.92 g, 30.8 mmol). The pH was adjusted to 4 and a solution of WSC[17] (9.85 g, 51.4 mmol) in water (100 ml) was added. After 5 minutes the suspension was allowed to reach room temperature and stirred for 2h. The pH was then increased to 5.5 by careful addition of 1N LiOH and the mixture stirred for 30 minutes. After rising the pH to 7 with 1N LiOH and further stirring for 30 min., the mixture was acidified to pH 4, saturated with NaCl and extracted with diethyl ether (twice) and ethyl acetate (once). The organic extracts were washed with saturated brine, and evaporated to dryness. Silica gel chromatography (250 g, eluant = petroleum ether / Et_2O 6:4→1:1) afforded pure **8** as a white foam (9.03 g, 80%). Found C, 57.15; H, 7.60; N, 9.40% (calc. for $C_{21}H_{33}N_3O_7$: C, 57.39; H, 7.57; N, 9.56%). R_f : 0.30 (petroleum ether / AcOEt 1:1; detection: A). $[\alpha]_D$ = -35.5° (c 1.5 $CHCl_3$). ^1H n.m.r. (80 MHz., DMSO d_6, 90°C):[37] δ 8.36 [1 H, broad s, N*H*]; 7.38 [5 H, s, aromatics]; 4.85 [2 H, s, CH_2Ph]; 4.30-3.80 [2 H, m, C*H*-N & C*H*-OH]; 1.43 & 1.42 [2 x 9 H, 2 s, (CH_3)$_3$C]; 1.18 [3 H, d, CH_3-CH, J 5.9 Hz.].

(*2S,3S*) O-Acetyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxybutanohydroxamate 12. A solution of **10** (500 mg, 1.380 mmol) in MeOH (6 ml) was cooled to 0°C and treated with a suspension obtained by mixing a solution of hydroxylamine hydrochloride (192 mg, 2.760 mmol) in MeOH (3 ml) and a 1.5 M solution of KOH in MeOH (3.22 ml, 4.83 mmol). After 2h the mixture was warmed to room temperature and stirred for 30 minutes. Acetic anhydride (2 x 195 μl, 2 x 2.07 mmol) was added in two portions spaced ten minutes. After stirring for 30 minutes more, the mixture was poured into 3M K_2CO_3 (20 ml) and extracted with Et_2O (30 ml). The organic phase was separated, washed with diluted K_2CO_3 and evaporated to dryness. This crude product furnished, upon silica gel chromatography (petroleum ether / Et_2O 40 : 60), mg 144 (30%) of *anti* (*2S,3S*) methyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxybutanoate and mg 71 (15%) of its *syn* (*2R,3S*) diastereoisomer. The reunited aqueous extracts were acidified to pH 4-5 with conc. HCl and extracted with AcOEt to give, after chromatography through silica gel (petroleum ether / AcOEt 1:1→1:2) pure **12** (mg 178, 33%). R_f : 0.28 (petroleum ether / AcOEt 1:1, detection A). ^1H n.m.r. (80 MHz., $CDCl_3$-D_2O, 28°C) : δ 6.85 [1 H, broad s, N*H*]; 4.65-3.70 [2 H, m, C*H*-N & C*H*-OH],[37] 2.21 [3 H, s, CH_3-C=O]; 1.49 & 1.47 [2 x 9 H, 2 s, (CH_3)$_3$C]; 1.24 [3 H, d, CH_3-CH, J 5.9 Hz.].

(*3S,4R*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-methylazetidin-2-one 13. A solution of hydroxamate **11** (7.88 g, 17.93 mmol) and triphenylphosphine (7.05 g, 26.9 mmol) in dry THF (100 ml) was cooled to 0°C and treated with diethyl azodicarboxylate (DEAD) (4.234 ml, 26.9 mmol). The cooling bath was removed and the solution stirred overnight at room temperature. The solvent was removed at reduced pressure (bath temp. < 30°C) and the residue chromatographed through 250 g of silica gel eluted with petroleum ether / AcOEt 8:2→65:35, to give 6.81 g of pure **13** as a foam (90%). Found C, 59.75; H, 7.40; N, 9.80%. Calculated for $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.41; N, 9.97%. R_f : 0.69 (petroleum ether / AcOEt 1:1; detection A). $[\alpha]_D$ = + 7.2° (c 2.75, $CHCl_3$). ^1H n.m.r. (80 MHz., d_6 DMSO, 95°C):[37] δ 8.79 [1 H, broad s, N*H*]; 7.41 [5 H, s, aromatics]; 4.95 [2 H, s, CH_2-Ph]; 4.80 [1 H, d, C*H*-N, J 5.2 Hz.]; 3.99 [1 H, dq, C*H*-CH_3,

J 5.2(d)[38] & 6.3 Hz (q).]; 1.43 & 1.42 [2 x 9 H, 2 s, $(CH_3)_3C$]; 1.18 [3 H, d, CH_3-CH, J 6.3 Hz.]; I.r. ($CHCl_3$): ν_{max} 1774, 1717 cm^{-1}.

(*3S,4R*) 1-(Acetoxy)-3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-methylazetidin-2-one 14. It was prepared with the same procedure used for **13** in 56% yield. R_f : 0.56 (petroleum ether / AcOEt 1:1; detection A). ^1H n.m.r. (80 MHz., $CDCl_3$, 28°C)[37]: δ 6.47 [1 H, broad s, N*H*], 5.50-5.00 [1 H, broad m, C*H*-N]; 4.60-4.00 [1 H, m, C*H*-OH]; 2.17 [3 H, s, CH_3-C=O]; 1.49 and 1.47 [2 x 9 H, 2s, $(CH_3)_3C$]; 1.25 [3 H, d, CH_3-CH, J 5.9 Hz.]. I.r. ($CHCl_3$): ν_{max} 1810, 1780, 1720 cm^{-1}

(*3S,4R*) 3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-methylazetidin-2-one 15. A solution of **13** (7.257 g, 17.22 mmol) in absolute MeOH (70 ml) was hydrogenated overnight over 10% palladium on carbon (400 mg). After filtration of the catalyst, the colourless solution was evaporated to dryness. The crude product was taken up in MeOH (20 ml) and added to a pH 7 (0.2M) phosphate buffer solution (150 ml). While this suspension was rapidly mechanically stirred and occasionally cooled with ice, a solution of $TiCl_3$ (30% in 2N HCl) (27.4 ml, 68.89 mmol) and a 3N solution of KOH in H_2O (≈ 100 ml) were simultaneously added over 30 minutes, in such a way to keep the pH in the range between 6 and 7.5. Then the suspension was further stirred for 2h (if necessary the pH was adjusted to 7) and then extracted thrice with AcOEt. The organic extracts were evaporated to dryness to give a crude product which was chromatographed through 150 g of silica gel eluted with Et_2O to give pure **15** (3.740 g, 69%) as a white solid. M.p. = 147-149°C. Found C, 53.19; H, 7.88; N, 13.08 %. Calculated for $C_{14}H_{25}N_3O_5$: C, 53.32; H, 7.99; N, 13.32%. R_f : 0.45 (petroleum ether / AcOEt 1:2; detection A). $[\alpha]_D$ = + 19.2° (c 1.8, $CHCl_3$). ^1H n.m.r. (80 MHz., d_6 DMSO, 95°C):[37] δ 8.81 [1 H, broad s, N*H*]; 7.90 [1 H, broad s, N*H*]; 4.81 [1 H, dd, C*H*-N, J 1.4 & 4.9 Hz. (becomes a doublet with J 4.9 Hz. when irradiated at 7.92 ppm)]; 3.71 [1 H, dq, C*H*-CH_3, J 4.9 (d)[38] & 6.3 (q) Hz.]; 1.42 [18 H, s, $(CH_3)_3C$]; 1.20 [3 H, d, CH_3-CH, J 6.3 Hz.]; I.r. ($CHCl_3$): ν_{max} 1766, 1713 cm^{-1}.

(*3S,4R*) 3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-methyl-2-oxoazetidine-1-sulfonic acid 17. A solution of β-lactam **15** (1.200 g, 3.805 mmol) in dry pyridine (8 ml) was treated with pyridine-sulfur trioxide complex (2.42 g, 15.22 mmol) and immediately warmed to 90°C. After stirring for 1h at this temperature, the mixture was allowed to cool to r.t. and poured into 1M aqueous KH_2PO_4 (100 ml). *n*-Bu_4NHSO_4 (1.356 g, 4.00 mmol) was added to the solution. Extraction with CH_2Cl_2 followed by evaporation of the solvent gave 2.587 g of a crude product as a white foam. ^1H n.m.r. showed that it was constituted essentially of tetra-*n*-butylammonium salt **16**. Chromatography through 110 g of silica gel eluted with AcOEt→AcOEt / MeOH 75:25 gave pure **17** as a white solid (1.438 g, 96%). M.p. > 280°C (a change of form of crystals was observed at 148-149°C). R_f : 0.28 (AcOEt / MeOH 9:1; detection A). $[\alpha]_D$ (c 2, $CHCl_3$)= + 8.5°. ^1H n.m.r. (80 MHz., d_6 DMSO, 95°C):[37] δ 8.81 [1 H, broad s, N*H*]; 4.78 [1 H, d, C*H*-N, J 5.4 Hz.]; 3.88 [1 H, quint., C*H*-CH_3, J 6.0 Hz.]; 1.43 [18 H, s, $(CH_3)_3C$]; 1.29 [3 H, d, CH_3, J 6.3 Hz.]. I.r. ($CHCl_3$): ν_{max} 1740 cm^{-1} (broad).

(*3'S,4'R*) 2-(4-methyl-2-oxo-1-sulfoazetidin-3-yl)hydrazinium trifluoroacetate 18.- A solution of **17** (372 mg, 0.941 mmol) in dry CH_2Cl_2 (1.5 ml) was cooled to 0°C and treated with trifluoroacetic acid (1.5 ml). After 20 minutes, the cooling bath was removed and the solution stirred for 50 minutes at room temperature. The solvent was removed at reduced pressure (bath temperature < 30°C) and the white solid residue stripped for 5h at 10^{-2} mbar to give crude **18** (297 mg). ^1H n.m.r. showed that it was a 82:18 mixture of **15** and and the open chain product deriving from β-lactam hydrolysis. This crude product was used as such for next reactions. R_f : 0.53 (*n*-BuOH / AcOH / H_2O 3:1:1; detection B). ^1H n.m.r. (200 MHz., D_2O, 25°C): δ 4.63 [1 H, d, C*H*-N, J 5.5 Hz.]; 4.41 [1 H, quint., C*H*-CH_3, J 6.2 Hz.]; 1.45 [3 H, d, CH_3-CH, J 6.2 Hz.].

(*3S,4R*) 3-ammonio-4-methyl-2-oxoazetidine-1-sulfonate 5.- A solution of crude **18** (obtained as described above) in H_2O (7 ml) was hydrogenated overnight over PtO_2 (85 mg). After filtration of the catalyst and evaporation to dryness, a white solid (249 mg) was obtained. ^1H n.m.r. in presence of CH_3COONa as internal standard showed that the yield of **5** from **17** was 56%. R_f : 0.44 (*n*-BuOH / AcOH / H_2O 3:1:1; detection B). ^1H n.m.r. (200 MHz., D_2O, 25°C) : δ 4.51 [1 H, d, C*H*-N, J 5.9 Hz.]; 4.39 [1 H,

quint., C*H*-CH_3, J 6.2 Hz.]; 1.46 [3 H, d, CH_3-CH, J 6.4 Hz.]. ^{13}C (50 MHz., D_2O , 25°C): δ 163.51 [*C*=O]; 58.98 & 56.47 [*C*H–N & *C*H-CH_3]; 13.46 [CH_3].

(*3S,4R*) Tetra-*n*-butylammonium 4-methyl-2-oxo-3-(phenoxyacetylamino)azetidine-1-sulfonate 19.- A solution of crude zwitterion **5** (49.6 mg, derived from 0.187 mmol of **17**) in dry DMF (1 ml) was treated with triethylamine (108 µl, 0.774 mmol) and with phenoxyacetyl chloride (53.5 µl, 0.387 mmol) and stirred overnight at room temperature. After quenching with 0.45 N aqueous $(NH_4)H_2PO_4$ (10 ml), the aqueous phase was washed with CH_2Cl_2, treated with *n*-Bu_4NHSO_4 (131 mg, 0.387 mmol) and extracted with CH_2Cl_2. Evaporation to dryness, followed by preparative t.l.c. on silica gel (AcOEt / MeOH 80 : 20), gave pure **19** (54 mg, 52% from **17**). R_f : 0.51 (AcOEt / MeOH 85:15; detection : U.V.). $[\alpha]_D$ = + 12.9° (c 2, MeOH). ^1H n.m.r. (200 MHz., CD_3OD, 25°C): δ 7.39-6.91 [5 H, m, aromatics]; 5.21 [1 H, d, C*H*-NH, J 5.7 Hz.]; 4.61 [2 H, s, OCH_2]; 4.25 [1 H, quint., C*H*-CH_3, J 6.0 Hz.]; 3.40-3.15 [8 H, m, CH_2-N]; 1.76-1.53 [8 H, m, CH_2-CH_2-N]; 1.41 [8 H, sextuplet, CH_2-CH_3, J 7.3 Hz.]; 1.28 [3 H, d, CH_3-CH, J 6.3 Hz.]; 1.02 [12 H, t, CH_3-CH_2, J 7.2 Hz.]. ^{13}C n.m.r. (50 MHz., CD_3OD, 25°C): δ 171.79 [NH-*C*=O]; 165.39 [SO_3N-*C*=O]; 159.12, 130.60 (2 C), 122.84 & 115.85 (2 C) (aromatics); 68.04 (CH_2-O); 59.47 (CH_2-N); 58.20 & 57.27 (*C*H-N); 24.81 (CH_2-CH_2-N); 20.73 (CH_2-CH_3); 14.20 (CH_3CH); 14.26 (CH_3-CH_2). I.r. ($CHCl_3$): ν_{max} 1760, 1685 cm^{-1}.

(*R*) Methyl 4-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxybutanoate 21. A solution of **26** (5.00 g, 37.3 mmol) in dry DMF (20 ml) was treated, at room temperature, with imidazole (5.7 g, 83.7 mmol) and *tert*-butylchlorodiphenylsilane (10.7 ml, 41.1 mmol). The resulting solution was stirred at r.t. for 4h, diluted with H_2O, extracted with Et_2O, and evaporated to dryness. Silica gel chromatography (petroleum ether / Et_2O 7:3 → 55:45) gave pure **21** as a viscous oil (9.84 g, 71%). Found C, 67.9; H, 7.65 %. Calculated for $C_{21}H_{28}O_4Si$: C, 67.71; H, 7.58 %. R_f : 0.43 (petroleum ether / Et_2O 6:4; detection : U.V.). $[\alpha]_D$ = + 7.45° (c 2.1, $CHCl_3$). ^1H n.m.r. (200 MHz., $CDCl_3$, 25°C): δ 7.63-7.68.[4 H, m, aromatics]; 7.35-7.49 [6H, m, aromatics]; 4.10-4.23 [1H, m, C*H*-OH]; 3.69 [3 H, s, OCH_3]; 3.63-3.67 [2 H, m, CH_2-O]; 2.88 [1 H, d, O*H*]; 2.56 and 2.54 [2 H, AB part of an ABX system, CH_2CO_2Me, J_{AB}= 9.5, J_{AX} and J_{BX} = 3.4 and 9.1 Hz.]; 1.05 [9 H, s, $(CH_3)_3C$].

(*2S,3R*) Methyl 4-[(*tert*-butyldiphenylsilyl)oxy]-2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxybutanoate 22. A solution of ester **21** (8.10 g, 21.7 mmol) in dry THF (20 ml) was added, at -60°C, to a 0.5 N solution of lithium di-*iso*-propylamide in THF-hexane 2:1 (122 ml, 61 mmol). The temperature was allowed to rise to -30°C during 80 min. The solution was then recooled to -60°C, and treated with a solution of di-*tert*-butyl azodicarboxylate (9.04 g, 39.2 mmol) in THF (6 ml). After 20 min. at -60°C, the reaction was quenched with AcOH (6.0 ml, 104.6 mmol), diluted with H_2O / saturated brine 1:1, and extracted with Et_2O. Densitometric analysis of the crude product indicated a diastereoisomeric ratio of 68 : 32. Silica gel chromatography (petroleum ether / Et_2O 7:3 → 65 : 35) furnished pure **22** as a viscous oil (5.38 g, 41%), as well as 2.63 g of a mixture of starting **21** and the *syn* (*2R,3R*) isomer of **22**. A second chromatography with petroleum ether / AcOEt 9:1 → 85 : 15 furnished a pure sample of the *syn* adduct (1.91 g, 14%). **22** : Found C, 61.5; H, 7.65; N, 4.8 %. Calculated for $C_{31}H_{46}N_2O_8Si$: C, 61.77; H, 7.69; N, 4.65 %. R_f : 0.31 (petroleum ether / Et_2O 6:4; detection : A). $[\alpha]_D$ = + 13.5° (c 1.7, $CHCl_3$). ^1H n.m.r. (80 MHz., DMSO, 120°C):[37] δ 8.10 [1 H, broad s, N*H*]; 7.55-7.68 [4 H, m, aromatics]; 7.30-7.46 [6 H, m, aromatics]; 4.86 [1 H, d, C*H*-N, J 6.5 Hz.]; 4.09 (mc) [1 H, m, C*H*-OH]; 3.77-3.83 [2 H, m, CH_2O]; 3.64 [3 H, s, OCH_3]; 1.42 and 1.40 [2 x 9 H, 2s, $(CH_3)_3$C-O]; 1.06 [9 H, s, $(CH_3)_3$C-Si]. I.r. ($CHCl_3$): ν_{max} 3620-3335 (OH str.), 1741, 1600, 1530, 1430, 1250 cm^{-1}.

(*2S,3R*) Benzyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxybutanohydroxamate 23. A suspension of O-benzyl hydroxylamine hydrochloride (2.425 g, 15.04 mmol) in dry THF (15 ml) was cooled to 0°C and treated slowly with a 2M solution of Me_3Al in toluene (7.52 ml, 15.04 mmol). During this addition, a strong gas evolution was observed. The cooling bath was removed, and the mixture stirred for 1h, until a solution was formed. This solution was added, at 0°C, to solution of **2** (2.935 g, 4.87 mmol) in THF (10 ml). The resulting suspension was stirred for 1h at r.t.. A clear solution was formed. The reaction was quenched with caution with saturated brine, diluted with AcOEt, and

filtered through a celite cake. The phases were separated, and the organic phase gave, after evaporation, a crude product, which was chromatographed on silica gel (petroleum ether / Et_2O 7:3) to give a 78 : 22 (w/w) mixture (^1H n.m.r.) of **23** and O-benzyl hydroxylamine, which were very difficult to separate (3.663 g, corresponding to 2.857 g of **23**, 85%). R_f : 0.36 (petroleum ether / Et_2O 1:1; detection : A). ^1H n.m.r. (200 MHz., DMSO, 120°C):[37] δ 8.20 [1 H, broad s, N*H*(Boc)]; 7.77-7.67 [4 H, m, aromatics of Ph_2Si]; 7.50-7.25 [11 H, m, aromatics of Ph_2Si and $PhCH_2$]; 4.85 [2 H, s, CH_2Ph]; 4.59 [1 H, d, C*H*-N(Boc), J= 6.3 Hz.]; 4.25-4.08 [1 H, m, C*H*OH, mc: 4.17]; 3.92 and 3.78 [2 H, AB part of an ABX system, CH_2O, J_{AB} = 10.3; J_{AX} and J_{BX}= 4.7 and 5.8 Hz.]; 1.42 and 1.40 [2 x 9 H, 2 s, (CH_3)$_3$C-O]; 1.06 [9 H, s, (CH_3)$_3$C-Si]. I.r. ($CHCl_3$): ν_{max} 3340, 1718, 1670, 1368, 1310, 1145 cm^{-1}.

(*3S,4S*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-[(*tert*-butyldiphenylsilyl-oxy)methyl]-2-azetidinone 24. A solution of **23** (2.967 g of the 78:22 mixture with $BnONH_2$ obtained above, 3.335 mmol) in dry THF (25 ml) was treated, at 0°C, with triphenylphosphine (1.31 g, 4.99 mmol) and diethyl azodicarboxylate (DEAD)(0.787 ml, 4.99 mmol). The resulting solution was stirred at r.t. for 40h, concentrated, and chromatographed through silica gel (petroleum ether / Et_2O 8:2 → 5:5) to give a 94:6 mixture (w/w) of **24** and $BnONH_2$ (g 2.27). Repeated chromatography furnished pure **24** (1.98 g, 88%) as a white, low melting, solid. Found: C, 65.4; H, 7.3; N, 6.4. Calculated for $C_{37}H_{49}N_3O_7Si$: C, 65.75; H, 7.31; N, 6.22%. $[\alpha]_D$ = + 16.6° (c 2, $CHCl_3$). R_f : 0.36 (petroleum ether / Et_2O 1:1; detection : A). ^1H n.m.r. (200 MHz., DMSO, 110°C):[37] δ 8.57 [1 H, broad s, N*H*(Boc)]; 7.72-7.62 [4 H, m, aromatics of Ph_2Si]; 7.50-7.30 [11 H, m, aromatics of Ph_2Si and $PhCH_2$]; 5.01 [2 H, s, CH_2Ph]; 4.94 [1 H, d, C*H*-N(Boc), J= 5.4 Hz.]; 4.19 [1 H, q, C*H*-CH_2O, J= 5.3 Hz.]; 4.05 [2 H, CH_2OSi, d, J= 5.5 Hz.]; 1.38 and 1.30 [2 x 9 H, 2 s, (CH_3)$_3$C-O]; 1.05 [9 H, s, (CH_3)$_3$-Si]. I.r. ($CHCl_3$): ν_{max} 1780, 1720, 1370, 1145 cm^{-1}.

(*3S,4S*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-hydroxymethyl-2-azetidin-one 25.

A) From compound **24**. A solution of **24** (37.5 mg, 46.5 μmol) in dry THF (1 ml) was cooled to -40°C, and treated with 1 M nBu_4NF•3 H_2O in THF (80 μl, 80 μmol). After 1 h the reaction was complete and it was quenched with H_2O, extracted with Et_2O, evaporated to dryness and chromatographed by preparative tlc (petroleum ether / Et_2O 23:77) to give pure **25** (14.8 mg, 73%).

B) From compound **30**. A solution of **30** (1.045 g, 1.54 mmol) in dry MeOH (20 ml) was cooled to 0°C and treated with *p*-toluenesulfonic acid hydrate (292 mg, 1.54 mmol). After 5 min. the cooling bath was removed and the mixture stirred at r.t. for 2.5 h. After neutralization with solid $NaHCO_3$, the mixture was concentrated to a small volume, diluted with saturated brine, and extracted with AcOEt to give, after silica gel chromatography (petroleum ether / Et_2O 1:1 → 3:7), pure **25** (458 mg, 68%) as a white foam.

Found C, 57.28; H, 6.96; N, 9.48%. Calculated for $C_{21}H_{31}N_3O_7$: C, 57.65; H, 7.14; N, 9.60%. $[\alpha]_D$ = + 7.65° (c 2, $CHCl_3$). R_f : 0.14 (petroleum ether / Et_2O 1:1; detection: A). ^1H n.m.r. (200 MHz., d-6 DMSO, 110°C)[37]: δ 8.61 [1 H, broad s, N*H*]; 7.50-7.30 [5 H, m, aromatics]; 5.01 and 4.98 [2 H, AB system, CH_2Ph, J= 11.3 Hz.]; 4.92 [1 H, d, C*H*-N(Boc), J= 4.7 Hz.]; 4.77-4.60 [1 H, m, O*H*]; 4.03 [1 H, q, C*H*-CH_2OH, J= 5.5 Hz.]; 3.84-3.56 [2 H, m, CH_2OH]; 1.42 [18 H, s, (CH_3)$_3$C]. MS (FAB): m/z 438 $[M-H]^+$ (10%); 424 (4%); 396 (7.5%); 382 (13%); 366 (2.5%); 348 (4%); 332 (13%); 326 (100%); 306 (13%); 292 (16%); 276 (30%); 236 (44%); 220 (65%); 177 (43%); 91 (82%).

(*R*) Methyl 3-hydroxy-4-(triphenylmethoxy)butanoate 27.[31] A solution of **26** (12.96 g, 96.62 mmol) in dry CH_2Cl_2 (200 ml) was cooled to 0°C and treated with dry pyridine (11.72 ml, 144.93 mmol) and with chlorotriphenylmethane (32.32 g, 115.92 mmol). After 15 min. the solution was allowed to stir for 20 h at r.t. A further addition of pyridine (3 ml, 3.71 mmol) and chlorotriphenylmethane (0.8g, 2.87 mmol) was made, and the solution stirred for 3 h more. Dilution with saturated brine, extraction with Et_2O (thrice), and evaporation to dryness, gave a crude product, which was chromatographed on silica gel (petroleum ether / Et_2O / Et_3N 8:2:0.1 → 3:7:0.1) to give pure **27** as a solid (28.69 g, 79%), which may be recrystallized from *i*-Pr_2O / pentane. M. p. 71.8°-72.6°C (lit.[31] 80-82°C). Found C, 76.5; H, 6.25%. Calculated for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43%. $[\alpha]_D$ = + 5.48° (c 2, $CHCl_3$)(lit.[31] -5.52°, c 2, CH_2Cl_2 for the (*S*) enantiomer). R_f : 0.43 (petroleum ether / Et_2O 6:4, detection: U.V.). ^1H n.m.r. (200 MHz., $CDCl_3$, 25°C): δ 7.46-7.23 [15 H, m, aromatics]; 4.23 (mc) [1 H, m, C*H*-OH]; 3.68 [3 H, s, OCH_3]; 3.17 [2 H, d, CH_2-O, J= 5.4 Hz.]; 2.90 [1 H, d,

O*H*, J= 4.7 Hz.]; 2.57 and 2.53 [2H, AB part of an ABX system, CH_2CO$_2$Me, J_{AB}= 14.7; J_{AX} and J_{BX}= 3.6 and 9.2 Hz.]. I.r. ($CHCl_3$): ν_{max} 1728 cm^{-1}.

(*2S,3R*) Methyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxy-4-(triphenylmethoxy)-butanoate 28. A solution of ester **27** (7.69 g, 20.4 mmol) in dry THF (20 ml) was added, at -40°C, to a 0.5 N solution of lithium di-*iso*-propylamide in THF-hexane 2:1 (122 ml, 61 mmol). After 5 min. the flask was put in a 0°C cooling bath and stirred for 30 min. The solution was then recooled to -20°C, and treated with a solution of di-*tert*-butyl azodicarboxylate (9.39 g, 40.8 mmol) in THF (20 ml). The temperature was allowed to rise gradually to 0°C, and then the reaction was quenched with AcOH (7.5 ml, 130.7 mmol), diluted with H_2O / saturated brine 1:1, and extracted with Et_2O. Densitometric analysis of the crude product indicated a diastereoisomeric ratio of 96 : 4. Silica gel chromatography (petroleum ether / Et_2O / Et_3N 8:2:0.03 → 5:5:0.03) furnished pure **28** (5.95 g, 48%). Found C, 67.0; H, 6.9; N, 4.7%. Calculated for $C_{34}H_{42}N_2O_8$: C, 67.31; H, 6.98; N, 4.62%. $[\alpha]_D$ = + 18.73° (c 2, $CHCl_3$). R_f : 0.54 (petroleum ether / Et_2O 1:1, detection: A, U.V.). ^{1}H n.m.r. (80 MHz., d-6 DMSO, 130°C): δ 8.07 [1 H, broad s, N*H*]; 7.67-7.03 [15 H, m, aromatics]; 4.86 [1 H, d, C*H*-N, J= 6.5 Hz.]; 4.35-4.00 [1 H, m, C*H*-OH]; 3.61 [3 H, s, OCH_3]; 3.22 [2 H, d, CH_2-O, J= 5.3 Hz.]; 1.44 and 1.40 [2 x 9 H, 2 s, (CH_3)$_3$C]. MS (FAB): m/z 607 $[M-H]^+$ (8%); 465 (10%); 447 (21%); 429 (23%); 405 (12%); 382 (19%); 365 (25%); 326 (95%); 307 (65%); 289 (32%); 283 (52%); 276 (36%); 259 (40%); 253 (100%). I.r. ($CHCl_3$): ν_{max} 1731 cm^{-1}.

(*2S,3R*) Benzyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxy-4-(triphenylmethoxy)-butanohydroxamate 29. A solution of **28** (2.90 g, 4.78 mmol) in THF (20 ml) was diluted with H_2O (30 ml), cooled at 0°C, and treated, during 15 min., with a 0.5 N aqueous LiOH solution (31 ml, 15.3 mmol). The resulting suspension was vigorously stirred for 7 h at r.t. The pH was then brought to 6, by adding, with cooling, 1N HCl. O-Benzyl hydroxylamine hydrochloride (915 mg, 5.74 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) (1.833 g, 9.56 mmol) were added, and the pH adjusted to 6 by addition of 0.5 N LiOH. After stirring for 20 h at r.t., the solution was saturated with NaCl, and extracted with AcOEt, to give, after evaporation and silica gel chromatography (petroleum ether / Et_2O / Et_3N 6:4:0.03 → 4:6:0.03), **29** as a foam (1.994 g, 60%), slightly impure for the presence of $BnONH_2$. $[\alpha]_D$ = -6.3° (c 2.4 $CHCl_3$). R_f : 0.26 (petroleum ether / Et_2O 6:4, detection: A). ^{1}H n.m.r. (80 MHz., d-6 DMSO, 130°C)[37]: δ 7.24-7.47 [20 H, m, aromatics]; 4.79 [2 H, s, CH_2Ph]; 4.55 [1 H, d, C*H*-N(Boc), J= 6.2 Hz.]; 4.31-4.11 [1 H, m, C*H*OH]; 3.26-3.19 [2 H, m, CH_2O]; 1.40 and 1.37 [2 x 9 H, 2s, (CH_3)$_3$C]. I.r. ($CHCl_3$): ν_{max} 1719, 1685, 1673 cm^{-1}.

(*3S,4S*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-[(triphenylmethoxy)-methyl]-2-azetidinone 30. A solution of **29** (2.950 g, 4.67 mmol) in dry THF (25 ml) was treated at r.t. with triphenylphosphine (1.837 g, 7.01 mmol), and diethyl azodicarboxylate (DEAD) (1.10 ml, 6.99 mmol). The yellow solution was stirred for 15h, concentrated, and directly chromatographed through silica gel (petroleum ether / Et_2O 7:3 1:1) to give pure **30** as a foam (2.730 g, 95%). Found: C, 69.95; H, 6.75; N, 6.31%. Calculated for $C_{40}H_{45}N_3O_7$: C, 70.67; H, 6.67; N, 6.18%. $[\alpha]_D$ = + 5.07° (c 1.96, $CHCl_3$). R_f : 0.24 (petroleum ether / Et_2O 6:4; detection: A, U.V.). ^{1}H n.m.r. (80 MHz., d-6 DMSO, 130°C)[37]: δ 8.45 [1 H, broad s, N*H*(Boc)]; 7.50-7.24 [20 H, m, aromatics]; 4.99 [2 H, s, CH_2Ph]; 4.84 [1 H, d, C*H*-N(Boc), J= 5.6 Hz.]; 4.16 (mc) [1 H, m, C*H*-CH$_2$O]; 3.62-3.45 [2 H, m, CH$_2$O]; 1.37 and 1.27 [2 x 9 H, 2s, (CH_3)$_3$C]. I.r. ($CHCl_3$): ν_{max} 1783, 1722 cm^{-1}.

(*3S,4S*) 3-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-4-hydroxymethyl-2-azetidinone 31.
A) From compound **25**: A solution of **25** (746 mg, 1.71 mmol) was hydrogenated on 10% Pd/C (175 mg) for 1h at r.t. under the slight pressure of an inflated balloon. After removal of the catalyst by filtration and evaporation to dryness, the resulting colorless oil was immediately dissolved in MeOH (8 ml), and diluted with 0.1 M pH 7 buffer solution (KH_2PO_4-K_2HPO_4) (30 ml). To this mixture, kept under vigorous stirring, a 30% solution of $TiCl_3$ in 2N HCl (3.5 ml, 8.55 mmol) was slowly added, during 15 min.. During this addition the pH was controlled by a pHmeter and kept constant to about 7 by continuous addition of 3N NaOH (approximately 11 ml). At the end of the addition the mixture was stirred for 2 h at r.t., saturated with NaCl, brought to pH 8.5 by addition of 3N NaOH, and further stirred for 1 day in order to favour hydrolysis of the

titanium (IV) alcoholate formed. The suspension was filtered through a celite cake, and the phases separated. The organic extracts gave, after evaporation and silica gel chromatography (petroleum ether / AcOEt 2 : 8) pure **31** as a white solid (348 mg, 62%).
B) From compound **37**: To liquid NH_3 (10 ml), cooled to -78°C, lithium wire (low Na content) (50 mg, 7.2 mmol) was added. The resulting blue solution was treated with a solution of **37** (435 mg, 0.72 mmol) in dry THF (6 ml). The solution became colorless and thus 90 mg of lithium (12.96 mmol) were added. The solution turned to blue and, after a while, to red. The mixture was stirred at the temperature of NH_3 reflux for 1 h, and then quenched with solid NH_4Cl (535 mg, 10 mmol). The mixture became colorless. After evaporation of most NH_3, the residue was taken up with saturated brine and AcOEt, and the phases separated. The organic extracts were washed with saturated brine / 5% $(NH_4)H_2PO_4$ 5:1, evaporated to dryness, and chromatographed on silica gel (petroleum ether / Et_2O 7:3 → 0:100) to give pure **31** (105 mg, 44%).
Found: C, 50.6; H, 7.4; N, 12.7 %. Calculated for $C_{14}H_{25}N_3O_6$: C, 50.75%; H, 7.60; N, 12.68%. $[\alpha]_D$: + 16.4° (c 1.52, $CHCl_3$). R_f : 0.30 (AcOEt; detection: A). ^1H n.m.r. (80 MHz., d-6 DMSO + 5% D_2O, 130°C)[37]: δ 4.90 (mc) [1 H, m, C*H*-N(Boc)]; 3.79-3.52 [3 H, m, C*H*-CH_2OH]; 1.44 [18 H, s, $(CH_3)_3C$]. I.r. ($CHCl_3$): ν_{max} 1770, 1722 cm^{-1}.

(*3S,4S*) 3-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)-2-azetidinone 32. A suspension of **31** (95.6 mg, 288.5 μmol) in dry CH_2Cl_2 (1 ml) was cooled to 0°C, and treated with trifluoroacetic acid (0.5 ml). The mixture became soon a solution. After stirring for 45 min at 0°C and for 1 h at r.t. the solvent was evaporated at reduced pressure and stripped at 10^{-2} mmbar for 24 h. The resulting yellow oil was taken up in H_2O (5 ml), and hydrogenated over PtO_2 (50 mg) for 30 h at r.t. and under a small positive pressure given by an inflated balloon. The catalyst was removed and the solvent evaporated to dryness. It was taken up in 1N aqueous $NaHCO_3$ (3 ml), treated with benzyl chloroformate (64 μl, 403 μmol) and stirred at r.t. for 6 h. The mixture was diluted with saturated brine, extracted with AcOEt, and evaporated to dryness to give, after silica gel chromatography (petroleum ether / AcOEt 5 : 95), pure **32** as a white solid (36.1 mg, 40%). This compound had the same spectroscopic, chromatographic, and physical properties as an authentic sample prepared according to Thomas, *et al.*[8m] (see also refs. 8b,e,i,j) R_f : 0.27 (AcOEt / MeOH 95:5; detection: U.V.). ^1H n.m.r. (200 MHz., $CDCl_3$, 25°C): δ 7.33 [5 H, broad s, aromatics]; 6.81 [1 H, broad s, β-lactam N*H*]; 6.27 [1 H, d, N*H*(Z), J= 9.9 Hz.]; 5.14 [1 H, dd, C*H*-NH(Z), J= 4.8 and 9.9 Hz.]; 5.09 [2 H, s, CH_2Ph]; 3.88-3.80 [2 H, m, CH_2OH]; 3.68-3.62 [2 H, m, O*H* and C*H*-CH_2OH].

(*3S,4S*) 3-[(*tert*-Butoxycarbonyl)amino]-4-(hydroxymethyl)-2-azetidinone 33. The first two steps of this preparation were the same as for the synthesis of **32**. The crude product deriving from hydrogenolysis was taken up in dry DMF (2 ml) and treated with triethylamine (115 μl, 810 μmol) and di-*tert*-butyl dicarbonate (320 μl, 1.35 mmol). The solution was stirred at r.t. for 3 days, diluted with saturated brine, extracted with AcOEt, and chromatographed (AcOEt / MeOH 95 : 5) to give pure **33** as a white solid (17.3 mg, 30% from **31**). This compound had the same spectroscopic, chromatographic, and physical properties as an authentic sample prepared according to Thomas, *et al.*[8m] R_f : 0.16 [AcOEt; detection: A (slightly visible)] ^1H n.m.r. (200 MHz., $CDCl_3$, 25°C): δ 8.21 [1 H, s, β-lactam N*H*]; 7.31 [1 H, d, N*H*(Boc), J= 9.8 Hz.]; 4.81 [1 H, dd, C*H*-NH(Boc), J= 4.1 and 9.8 Hz.]; 3.67-3.32 [3 H, m, CH_2OH and C*H*-CH_2OH]; 1.39 [9H, s, $(CH_3)_3C$].

(*3S,4S*) 3-[(Benzyloxycarbonyl)amino]-4-[(carbamoyloxy)methyl]-2-azetidinone 34. A solution of **32** (77.4 mg, 309 μmol) in dry CH_2Cl_2-DMF 6:1 (3.5 ml) was cooled to 0°C, and treated with chloroacetylisocyanate (53 μl, 619 μmol). After 1.5 h a solution of sodium N-methyldithiocarbamate[39] (239 mg, 1.85 mmol) in H_2O (2 ml) was added. The mixture was vigorously stirred at r.t. for 4 h, and then saturated with NaCl, and extracted with $CHCl_3$ / MeOH 85 : 15. The organic extracts gave, after evaporation and silica gel chromatography (AcOEt / MeOH 95 : 5), pure **34** as a white solid (67.9 mg, 75%), whose spectroscopic and physical data were in agreement with the reported ones.[8b,8f,32] R_f: 0.36 (AcOEt / MeOH 95 : 5; detection: U.V.).

(*3S,4S*) 3-[(*tert*-Butoxycarbonyl)amino]-4-[(carbamoyloxy)methyl]-2-azetidinone 35. It was prepared, starting from **33**, by the same method employed for **34** (yield 63%). Found C, 46.55; H, 6.8; N,

16.1%. Calculated for $C_{10}H_{17}N_3O_5$: C, 46.33; H, 6.61; N, 16.21%. $[\alpha]_D$ = +56.5° (c 0.75, MeOH). R_f: 0.45 (AcOEt / MeOH 95:5; detection: sprayed with 40% aqueous HBr, warmed, and then immeresed in solution B). ^{1}H n.m.r. (d-6 DMSO, 200 MHz, 25°C): δ 8.34 [1 H, s, β-lactam N*H*]; 7.56 [1 H, d, N*H*(Boc), J= 9.7 Hz.]; 6.55 [2 H, broad s, NH_2]; 4.90 [1 H, dd, C*H*-NH(Boc), J= 5.3 and 9.7 Hz.]; 4.12-3.91 [2 H, m, CH_2O]; 3.87-3.76 [1 H, m, C*H*-CH_2O]; 1.40 [9 H, s, $(CH_3)_3C$].

(*2S,3S*) Methyl 2-[N,N'-*bis*(*tert*-butyloxycarbonyl)hydrazino]-3-hydroxy-4-(triphenylmethoxy)-butanohydroxamate 36. It was prepared from **28** (4.545 g, 7.49 mmol), O-methyl hydroxylamine hydrochloride (1.914 g, 22.9 mmol) and Me_3Al (2M in toluene)(11.45 ml, 22.9 mmol) by following the same procedure employed for **23** (but this time the reaction time was 4 h). Silica gel chromatography (petroleum ether / Et_2O 4:6 → 0:100 → Et_2O / MeOH 99:1) gave pure **36** as a white foam (3.206 g, 69%). Found: C, 65.7; H, 7.05; N, 6.6%. Calculated for $C_{34}H_{43}N_3O_8$: C, 65.68; H, 6.97; N, 6.76%. $[\alpha]_D$ = + 0.47 (c 2, $CHCl_3$). ^{1}H n.m.r. (80 MHz., DMSO, 130°C):[37] δ 8.06 [1 H, broad s, N*H*(Boc)]; 7.60-7.10 [15 H, m, aromatics]; 4.52 [1 H, d, C*H*-N(Boc), J= 6.2 Hz.]; 4.21 [1 H, q, C*H*-OH, J= 5.6 Hz.]; 3.58 [3 H, s, OCH_3]; 3.22 [2 H, d, CH_2O, J= 5.1 Hz.]; 1.41 and 1.38 [2 x 9 H, 2s, $(CH_3)_3C$]. I.r. ($CHCl_3$): ν_{max} 1715, 1680, 1475, 1450, 1395, 1370, 1195, 1150 cm^{-1}.

(*3S,4S*) 3-[N,N'-*Bis*(*tert*-butyloxycarbonyl)hydrazino]-1-(methoxy)-4-[(triphenylmethoxy)methyl]-2-azetidinone 37. It was prepared from **36** using the same procedure employed for **30**. Yield: 95%. Found: C, 67.4; H, 6.8; N, 7.1%. Calculated for $C_{34}H_{41}N_3O_7$: C, 67.64; H, 6.85; N, 6.96%. $[\alpha]_D$ = -1.18° (c 2.5, $CHCl_3$). R_f: 0.26 (petroleum ether / Et_2O 4:6; detection: A). ^{1}H n.m.r. (200 MHz., DMSO, 110°C):[37] δ 8.46 [1 H, broad s, N*H*]; 7.45-7.20 [15 H, m, aromatics]; 4.84 [1 H, d, C*H*-N(Boc), J= 5.6 Hz.]; 4.30-4.10 [1 H, m, C*H*-CH_2]; 3.77 [3 H, s, OCH_3]; 3.57 and 3.48 [2 H, AB part of an ABX system, CH_2O, J_{AB}= 10.7; J_{AX} and J_{BX}= 3.0 and 8.3 Hz.]; 1.37 and 1.27 [2 x 9 H, 2s, $(CH_3)_3C$]. I.r. ($CHCl_3$): ν_{max} 1785, 1728, 1370, 1195, 1150 cm^{-1}.

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17. WSC (water soluble carbodiimide) = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
18. We found that the hydroxylaminolysis reaction was slower than in the case of (Z) serine esters (ref. 6d). Moreover, this reaction was accompanied by fast transesterification to give the methyl ester analogue of **10** and also by a slower epimerization of this methyl ester to give the *syn* diastereoisomer. So, if the reaction was carried out under harder conditions in order to bring it to completion, extensive epimerization took also place.

19. We could find in the literature only one example of silica gel chromatography of a related compound, that is 3-(benzyloxycarbonylamino)-4-fluoromethyl-2-oxo-1-azetidinesulfonic acid tetra-*n*-butyl-ammonium salt (see ref. 20). Contrary to our case, however, the chromatography furnished the expected *n*-Bu_4N^+ salt. A possible explanation of this anomalous behaviour can be a stabilization of the azetidinesulfonic acid through hydrogen bonding with the NH(Boc) group. Molecular models show that this hydrogen bond is indeed possible, while in the corresponding (Boc) amino derivatives it is not so likely.
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21. The intermediate hydrazinium salt **18** was also used for preparing novel monobactams having a 2-acylhydrazino (instead than an acylamino) side chain at position 3: Guanti, G.; Banfi, L.; Narisano, E.; Cevasco, G. *Brevetto Italiano*, N. 21427A/89 (august 2, 1989).
22. In this case preparative t.l.c. on silica gel furnished the expected *n* -Bu_4N^+ salt.
23. **a)** *U.S. Appl.* 119,276 (2-7-1980); *Chem. Abs.*, *96* , 181062x. **b)** *Eur. Pat. Appl.*, EP 48,953; *Chem. Abs.*, *97* , 92116w.
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25. On the contrary, more problematic resulted the separation of **22** from unreacted **21**.
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27. **a)** Levin, J. I.; Toros, E.; Weinreb, M. *Synth. Commun.* **1982**, *13*, 989-993. **b)** Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961-4964.
28. Attempted regioselective benzylation of **26** via the dibutylstannylene derivative (ref. 29) gave only poor yields. Attempted formation of the 4-O-*p*-anisyl derivative (ref. 30) by Mitsunobu reaction, or *via* the tosylate, furnished mainly elimination products.
29. **a)** David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans 1* **1981**, 1796-1801. **b)** Alais, J.; Veyrières, A. *J. Chem. Soc., Perkin Trans 1* **1981**, 377-381.
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31. The synthesis of the enantiomer of **27** was recently reported: Prasad, K.; Chen, K.-H.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 307-310.
32. When the enolization and the condensation were carried out at low temperatures, the reaction turned out to be largely incomplete, and the diastereoselection was lower.
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34. This result was not unexpected: see ref. 13a.
35. On the contrary, methylation of compound **13** with K_2CO_3 and MeI in DMF at 90°C took place in good yield (70%, unoptimized). The low reactivity of **37** is most likely a consequence of the high steric hindrance of triphenylmethyl group.
36. **a)** Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43* , 3966-3970. **b)** Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42* , 3060-3065.
37. At room temperature compounds **11-17**, **22-25**, **28-31**, and **36-37** gave unresolved n.m.r. spectra probably due to restricted rotation around the amidic bonds. When ^1H n.m.r. were taken in deuterated DMSO at 90-100°C, well resolved spectra could be obtained.
38. Determined with the aid of double resonance experiments.
39. Moore, M. L.; Crossley, F. S. *Org. Synth. Coll. Vol. 3* 599-600.

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