Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 609-624, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00045-3

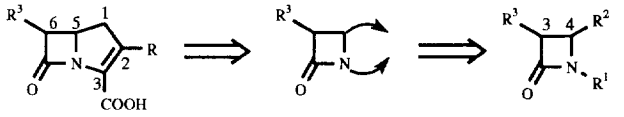
Different Approaches to the Asymmetric Synthesis of 1,3,6-Trisubstituted and 1,2,3,6-Tetrasubstituted Carbapenems[1] from *D*–Glucosamine

Josefa Anaya,* Derek H. R. Barton,[a] Stephane D. Gero,[b] Manuel Grande, José I. M. Hernando and Nieves M. Laso*

Departamento de Química Orgánica. Universidad de Salamanca, 37008 Salamanca, Spain.
[a]Department of Chemistry, Texas A&M University, College Station, Texas 77843, U.S.A.
[b]Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France.

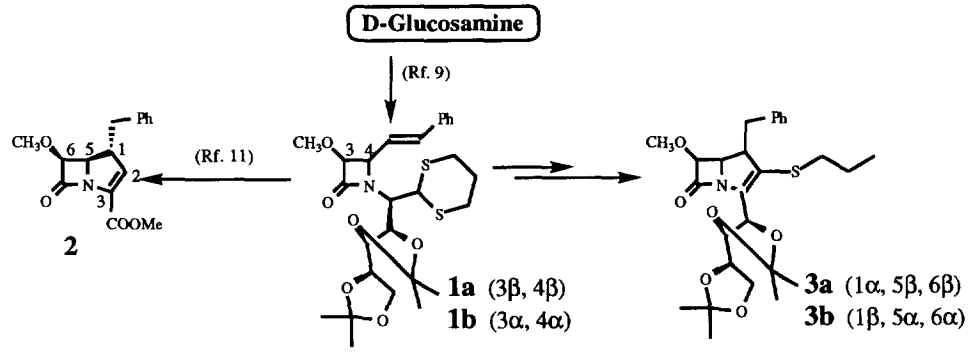
Abstract: Different stereocontrolled syntheses of optically active 1,3,6-trisubstituted and 1,2,3,6-tetrasubstituted carbapenems[1] are reported. *D*-glucosamine, as chiral auxiliary, *trans*-cinnamaldehyde and methoxyacetyl chloride were used as starting materials in the Staudinger ketene-imine monobactam formation. Radical cyclization and oxidation reactions led to the desired carbapenems.

The pharmaceutical importance of β–lactam antibiotics with resistance to β–lactamase, such as thienamycin and other related compounds,[2] as well as the inhibition of human leukocyte elastase (HLE) by cephalosporins,[3] penicillins,[4] penams[5] and monocyclic β–lactams,[6] have provided a continuing high level of interest in the chemical synthesis of β–lactams. Potent antibacterial properties and challenging chemical problems have made carbapenem-type compounds major synthetic objectives. The synthesis of carbapenem antibiotics usually begins with the construction of a monocyclic β–lactam leaving appropriate substituents for ring closure. The annelated second ring is then formed at a later stage in the synthesis and it is usually controlled by the chemical reactivity of the 2-azetidinone.

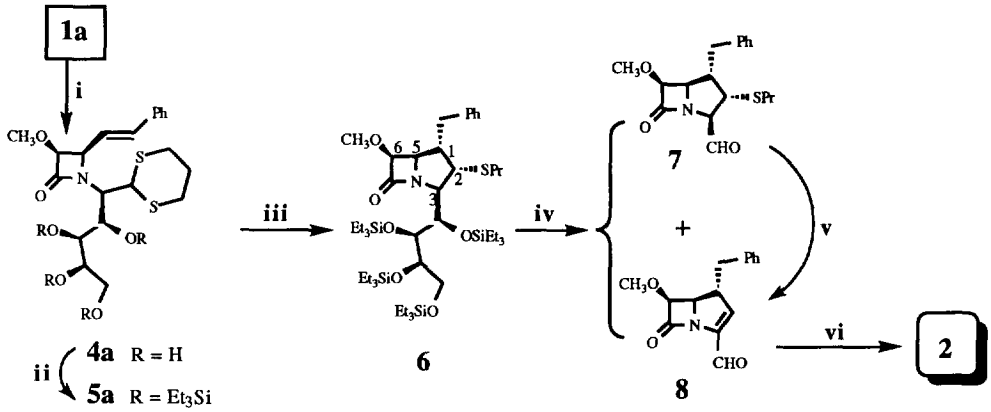


The most often used methods for the second ring closure rely either on an intramolecular Wittig-type reaction or on a diazo insertion reaction.[7] By contrast, there are numerous methods in the literature for the synthesis of monocyclic β–lactams but the formation of a suitably substituted 2-azetidinone usually requires many steps.[8] Consequently, the development of short and highly stereocontrolled methods for the synthesis of carbapenems retains a primary importance in β–lactam chemistry.

Our contributions in this field have been mainly addressed to the use of *D*-glucosamine[9] as chiral auxiliary in the Staudinger reaction.[10] In this paper we report the synthesis of the compounds **2**, **3a** and **3b** which show the synthetic utility of our methodology in the preparation of 1,3,6-trisubstituted and 1,2,3,6-tetrasubstituted carbapenems. Some preliminary results have been published.[11]



As we have previously reported,[11] the 1,3,4-trisubstituted-azetidin-2-ones **1a** and **1b** underwent ring closure by a radical cyclization. However, the desired 1,3,6-trisubstituted carbapenem **2** was not obtained. The transformation of monobactam **1a** into carbapenem **2** was nevertheless possible through its silylated derivative **5a** (Scheme 1).

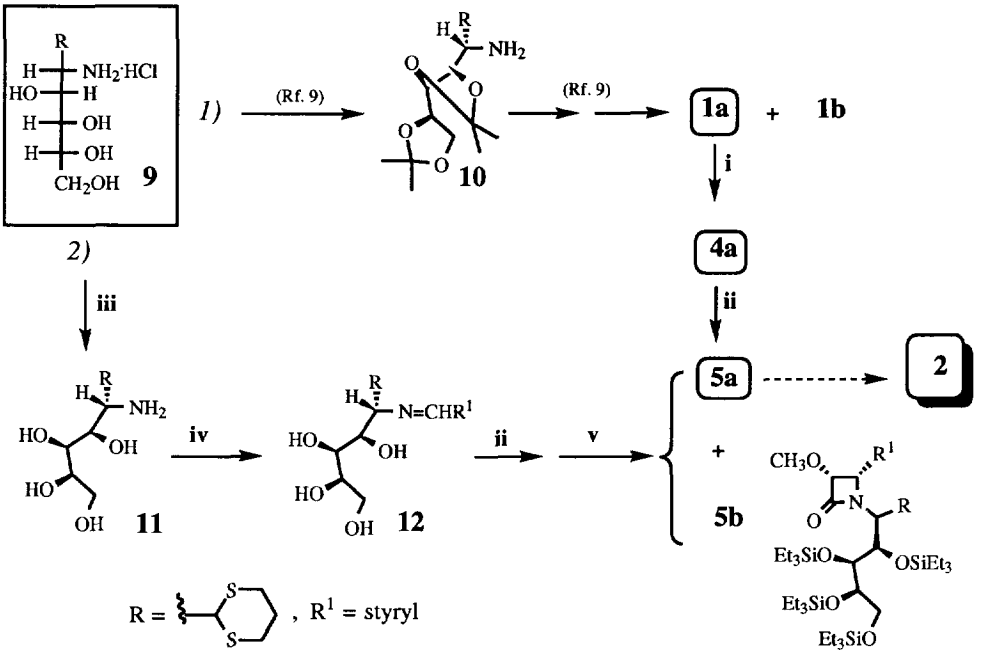


Scheme 1.- i: CF_3COOH / MeOH, 20°C. ii: Et_3SiCl-DMAP / pyridine, 20°C. iii: Bu_3SnH, AIBN / toluene, reflux. iv: a = Bu_4NF / THF, 0°C; b = Ph_3BiCO_3 / CH_3CN, reflux. v: a = *m*-CPBA / CH_2Cl_2, 20°C, b = toluene, reflux. vi: MnO_2-NaCN / MeOH, 20°C.

The silylated compound **5a** was obtained in 63% yield from monobactam **1a** by hydrolysis of the isopropylidene groups followed by silylation of the resulting tetrahydroxy monobactam **4a**. Treatment of the β–lactam **5a** with tri-(*n*-butyl)-stannane and 2,2'-azobisisobutyronitrile (AIBN) in refluxing toluene for 3h provided the carbapenam **6** through an *exo-Trig* process.[12] The *cis* arrangement of the C-1 and C-2 substituents for this compound was deduced from the ^{1}H-NMR data ($J_{2,1}$= $J_{5,1}$= 8Hz, $J_{2,3}$= 4Hz), which are in agreement with those reported for other carbapenams.[11,13]

Carbapenam **6** was converted into a mixture of aldehydes **7** and **8** in a one pot two steps process, by deprotection of the silyl groups with Bu_4NF, followed by treatment with triphenylbismuth carbonate.[14] The two aldehydes **7** and **8** could be easily separated by column chromatography. Then the compound **7** was transformed into carbapenem **8** by treatment with *m*-CPBA, followed by thermolysis of the resulting sulfoxide in refluxing toluene. Lastly, the aldehyde **8** was converted into the methyl ester **2** by Corey's oxidation method with manganese (IV) oxide and sodium cyanide in methanol.[15]

The key substance for this approach to the synthesis of the carbapenem **2**, the silyl derivative **5a,** was prepared in 29% yield (Scheme 2) from the hydrochloride of *D*-glucosamine-1,3-propanedithioacetal **9** in a five-step sequence,[9,13] i.e., preparation of the 3,4;5,6-di-*O*-isopropylidene derivative **10**, condensation with cinnamaldehyde, Staudinger reaction, hydrolysis of the isopropylidene groups and finally silylation of resulting monobactam **4a**. Trying to improve our results we have studied the preparation of monobactam **5a** using the silyl protecting groups in the first stages.



Scheme 2.- i: CF_3COOH / MeOH, 20°C. ii: Et_3SiCl-DMAP / pyridine, 20°C. iii: NaOH / H_2O, 20°C. iv: *trans*-cinnamaldehyde / *iso*BuOH, 70°C. v: TEA, CH_3OCH_2COCl / toluene, 20°C.

To prevent the silylation of the amino group under the basic conditions employed to protect the alcohols with alkylsilyl chlorides we first carried out the protection of the amine group. The crystalline imine **12** was prepared in 49% yield from the hydrochloride **9** by basification with NaOH in ethanol and condensation of resulting amine **11** with *trans*-cinnamaldehyde. Silylation of compound **12** with triethylsilyl chloride gave its silyl derivative in a quantitative yield, which was used without further purification in the Staudinger reaction. The pure diastereomeric *cis* products **5a** and **5b** were obtained in 55% yield and 78:22 ratio after isolation by column chromatography on deactivated silica-gel with TEA. The *cis* configuration of the substituents at C-3 and C-4 in compounds **5a** and **5b** was evident from the ^{1}H-NMR ($J_{3,4}$= 5Hz) spectrum.[9,13] The spectral data of the major diastereoisomer **5a**, were identical to those of the sample obtained through the preceding procedure.

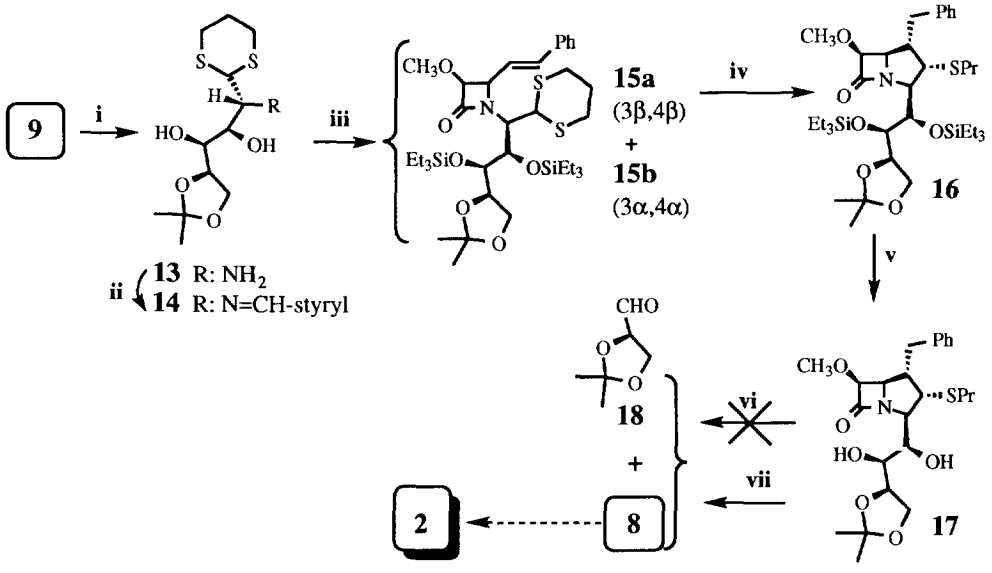
As it is shown in the Table 1, the global yields in the preparation of the tetrasilylated monobactam **5a** are better in the first procedure through the diisopropylidene derivative **10**, but an increase in diastereoselectivity was observed when the Staudinger reaction was carried out with the tetrasilylated imine **12**.

Table 1.- Chemical yield[a] and proportion of diasteroisomers for compounds showed in Scheme 2.

	Compound							
Path	**10**	**11**	**12**	**1a**	**4a**	**5a**	Global yield for **5a**	Diastereoisomeric proportions
1	85			54	90	70	29	64 : 36 (**1a** : **1b**)
2		70	70			43	21	78 : 22 (**5a** : **5b**)

[a]Yield in % of isolated pure products by crystallization or column chromatography.

Since the observed chemical yield in this later approach was lower than expected, we decided to investigate the synthesis of the dihydroxycarbapenam **17** from *D*-glucosamine-1,3-propanedithioacetal hydrochloride **9** (Scheme 3). Carbapenam **17** is an interesting intermediate in the synthesis of carbapenem **2** and related substances; the oxidative cleavage of the glycol moiety with Ph_3BiCO_3 would afford the desired compound **8** and 2,3-*O*-isopropylidene-*D*-glyceraldehyde **18**, an useful chiral building block in asymmetric synthesis.[16]



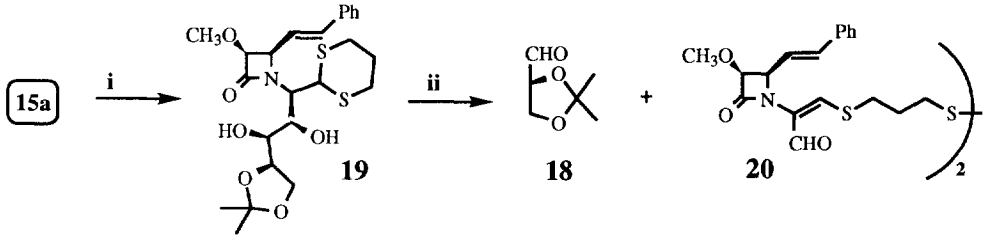
Scheme 3.- i: Methoxypropene-*p*-TsOH / DMF, 20°C. ii: *trans*-cinnamaldehyde / toluene, 70°C. iii: a= Et_3SiCl-DMAP / pyridine, 20°C. b = TEA, CH_3OCH_2COCl / toluene, 20°C. iv: Bu_3SnH, AIBN / toluene, reflux. v: Bu_4NF / THF, 0°C. vi: Ph_3BiCO_3 / CH_3CN, reflux. vii: a= $NaIO_4$ / MeOH; b= refluxing CH_3CN.

As it is shown in Scheme 3, the explored synthetic route to compound **2** begins with the preparation of the chiral Schiff base **14**. Treatment of *D*-glucosamine-1,3-propanedithioacetal hydrochloride **9** with 2-methoxypropene (1:1.1 mmol) in DMF and *p*-TsOH for 8h at room temperature[17] afforded the crystalline amine **13** in 75% yield. Condensation of this amine with cinnamaldehyde provided quantitatively the Schiff base **14** which was transformed into its disilylated derivative by treatment with triethylsilylchloride in DMAP-pyridine. The cycloaddition was accomplished by reaction of the disilyl derivative of imine **14** with methoxyacetylchloride and TEA. A 72:28 mixture of two *cis*-monobactams **15a** and **15b** was obtained in 55% yield. The structures of both *cis*-diastereoisomers were rigorously established from the coupling constants of

the H-3 and H-4 β–lactam protons ($J_{3,4}$ = 5Hz) and the absolute configuration of these compounds was unequivocally assigned from the $[\alpha]_D$ data[9] and the X-ray analysis of monobactam **1a**.[18] Treatment of monobactam **15a** with Bu_3SnH-AIBN in refluxing toluene over 3h afforded carbapenam **16** in 70% yield.

Unfortunately, the transformation of carbapenam **16** into 3-formylcarbapenem **8** by deprotection of the silyl groups and oxidative cleavage of the resulting glycol with Ph_3BiCO_3, was not possible. Treatment of carbapenam **16** with Bu_4NF in THF gave the expected dihydroxycarbapenam **17** in 65% yield but this compound was unchanged by the action of Ph_3BiCO_3 in refluxing MeCN.[14] Finally, the oxidative cleavage of diol in carbapenam **17** was carried out with $NaIO_4$ affording a mixture of the aldehyde **8** and 2,3-*O*-isopropyliden-*D*-glyceraldehyde **18** in low yield.

In contrast with these results, the oxidative cleavage of the dihydroxymonobactam **19** with Ph_3BiCO_3 (Scheme 4) gave the aldehydes **18** and **20**[11] with good yields (45% and 60%). Perhaps the free hydroxyl groups in carbapenam **17** are too crowded to be accessed by the voluminous bismuth salt.



Scheme 4.- i: Bu_4NF / THF, 0°C. ii: Ph_3BiCO_3 / CH_3CN, 60°C.

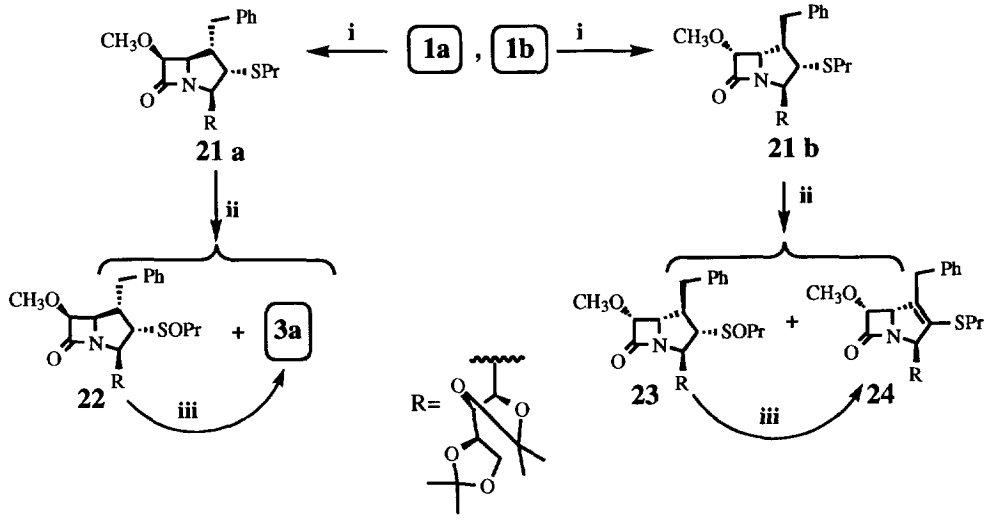
Incidentally, the formation of the disulfide **20** can be explained by nucleophilic attack of a sulfur lone pair onto Bi(V) assisted by the concomitant elimination of CO_2 and H_2O. According to the proposed mechanisms to explain the formation of disulfides by oxidation of thiols with Bi(V) salts,[19] the intermediate Bi(V) dithiolate derived from **19** must rearrange through a redox process to give **20** and Ph_3Bi.

We have also investigated the synthesis of 1,2,3,6-tetrasubstituted carbapenems **3a** and **3b** from the readily available monobactams **1a** and **1b** (Scheme 1).[9] We were interested in these substances to verify the potential biological activity as HLE inhibitors.[20] The carbapenem structure is even more active against bacteria than cephalosporins, penicillins and penams and these last bicyclic β-lactams are important HLE inhibitors.[3-5] The 1,2;3,4-di-*O*-isopropylidene tetrahydroxybutyl group at C-3 in carbapenems **3a** and **3b** could be an important group for HLE inhibition for these compounds because in monocyclic β–lactams with the 2-deoxy-2-dithianyl-3,4;5,6-di-*O*-isopropylidene-*D*-2-glucosyl group attached to the β–lactam nitrogen atom is related to the specificity against HLE.[21] The 1,2,3,6-tetrasubstituted carbapenems **3a** and **3b** were synthetised as follows (Scheme 5).

As we have previously reported,[11] the 1,2,3,6-tetrasubstituted carbapenams **21a** and **21b** were prepared in 62 and 68% yield respectively by treatment of monobactams **1a** and **1b** with Bu_3SnH-AIBN in refluxing toluene.

The relative configuration at C-1 and C-2 for both carbapenams was deduced from the vicinal coupling constants of the hydrogen atoms H-1 and H-2 ($J_{1,2}$=$J_{1,5}$= 8Hz, $J_{2,3}$= 4Hz for **21a** and $J_{2,1}$= 10Hz, $J_{2,3}$= $J_{5,1}$= 8Hz for **21b**) and the absolute configuration at C-1 and C-2 for these compounds as (1*S*, 2*S*) and (1*R*, 2*S*) respectively was deduced from the X-ray crystal structure of compounds (2*R*, 3*S*, 4*S*, 5*R*, 6*S*,1'*R*, 2'*S*, 3'*R*)-3-

Ethylthio-4-(2-furanylmethyl)-6-methoxy-2-(1,2;3,4-di-*O*-isopropylidene-1,2;3,4-tetrahydroxy-butyl)-1-aza-bicyclo[3.2.0]-heptan-7-one[13,22] and the sulfone derivative of **21b**.[11,22]



Scheme 5.- i: Bu_3SnH, AIBN / toluene, reflux. ii: Cl_2IPh, pyridine / CH_2Cl_2, -40°C. iii: $(CF_3COO)_2$, TEA / CH_2Cl_2, 0°C.

A method widely used in β–lactam chemistry to reach the Δ^2 unsaturated carbapenems from 2-alkylthio derivatives is based in the preparation of an α-chlorosulfoxide followed by HCl elimination using iodobenzene dichloride as oxidant and TEA as base.[23] In our case when the carbapenams **21a** and **21b** were treated with iodobenzene dichloride in pyridine the sulfoxides **22** and **23** were obtained as major products of reaction and the unsaturated bicyclic systems **3a** and **24** were produced only in 10% and 7% yield respectively (neither the formation of α-chlorosulfoxides nor carbapenem **3b** were observed).

The sulfoxide **22** could be transformed into the carbapenem **3a** in 55% by treatment with $(CF_3COO)_2$ and TEA (Pummerer rearrangement).[24] The same reaction was carried out on the sulfoxide **23** but in this case the Δ^1 unsaturated compound **24** was obtained in 50 % yield. The formation of compounds **3a** and **24** is in agreement with a *syn* β–elimination of H-3 and H-1 protons respectively. The structures of compounds **3a** and **24** were deduced by comparison of their ^1H and ^{13}C-NMR with those of carbapenams **21a** and **21b** respectively (Table 2).

Table 2.- ^1H- and ^{13}C-NMR data[a] for compounds **21a**, **21b**, **3a** and **24** in the region of interest

Compound	H-1	H-2	H-3	C-1	C-2	C-3
21a	2.92 *(qnt)*	3.58 *(dd)*	3.81 *(t)*	42.6	55.8	69.3
21b	2.41 *(m)*	3.28 *(dd)*	3.86 *(dd)*	46.3	55.6	67.7
3a	3.69 *(m)*	-	-	48.5	140.5	137.3
24	-	-	4.82 *(d)*	136.1	147.2	68.0

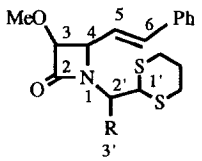
[a]Solvent: $CDCl_3$; δ in ppm. Multiplicity in parenthesis

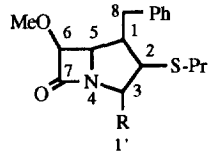
As shown in Table 2, the proton signals for H-2 and H-3 in compounds **3a** as well as those for H-1 and H-2 in **24** have disappeared. Also the ^{13}C-NMR data were in complete agreement with Δ^2 and Δ^1 unsaturations for **3a** and **24**, respectively.

Further studies on the synthesis of natural carbapenems using the preceding methodologies as well as testing for biological activity of our products are now in progress.

Experimental section.

General methods. Flash chromatographies were run on silica gel (Merck 60 230-400 mesh) and thin layer chromatographies (TLC) on commercial silica gel plates (Merck F-254). Experiments requiring an inert atmosphere were carried out under dry argon or nitrogen in a flame dried glass system. Hexane and EtOAc were purified by distillation. CH_2Cl_2, THF and toluene were distilled over P_2O_5 and Na/benzophenone respectively. Triethylamine and pyridine were distilled over KOH pellets. Ph_3BiCO_3[25] and $C_6H_5ICl_2$[26] were prepared according to literature methods from Ph_3Bi and C_6H_5I respectively. All the other starting materials used in this work were commercially available in 98% or higher purity and were used without further purification. "Usual workup" means washing the organic layers with brine or NH_4Cl solution, drying on anhydrous Na_2SO_4 and evaporating *in vacuo* with a rotatory evaporator at aspirator pressure. **Optical rotations** were recorded in $CHCl_3$ solution in a 1 dm cell on a Perkin-Elmer 243 polarimeter. **IR** spectra were recorded on a Beckman Acculab-8 or on a Nicolet 205 FTIR instrument, neat or in KBr pellets. Melting points are uncorrected. Microanalytical data were obtained in the laboratory of Microanalysis of ICSN-CNRS, Gif-sur-Yvette. Mass spectra (**MS**), were recorded on an GTS-250 instrument (70 eV, electron impact spectra, EI) are reported in the form: "m/z (intensity relative to base peak=100%)". **^{1}H-NMR** spectra were obtained on Bruker instruments WP200SY, AC250 or AM 400 (200 MHz, 250 MHz and 400 MHz respectively) in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS. The ^{1}H-NMR data are presented in the order: δ value of the signal, peak multiplicity, coupling constants in Hertz, integrated number of protons and proton assignation. ^{13}C spectra were measured at 62.5 and 50.3 MHz and the chemical shifts are reported relative to the $CDCl_3$ triplet centered at 77.00 ppm. The ^{13}C multiplicities were assigned by the DEPT[27] or SEPT[28] technique. Two dimensional homo and heteronuclear correlation experiments were performed with standard Bruker software. The numbering in monobactams and carbapenams used in the ^{1}H and ^{13}C NMR assignments are as follows:





General procedure for cycloaddition [2+2] of ketene-imines. (Reactions were carried out on a 2-5 mmol scale). To a solution of imine (1 mmol) and dry TEA (2.5 mmol) in dry toluene (10 ml), a solution of methoxyacetic chloride (1.5 mmol) in dry toluene (2 ml) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred for 30 min at room temperature, treated with ice NH_4Cl solution and extracted with CH_2Cl_2. The solution was neutralized to pH 7 by addition of acetic acid. Evaporation of solvent afforded two isomeric monobactams which were purified by silica gel column chromatography.

General procedure for radical cyclizations. (Reactions were carried out on a 2-7 mmol scale). A solution of monobactam (1 mmol), tributyltinhydride (3.2 mmol) and AIBN (3% in mol) in dry deaerated toluene (15 ml) was refluxed for 3 h. Evaporation of solvent and chromatography on silica gel afforded the carbapenams.

General procedure for oxidative cleavage of diols with Ph_3BiCO_3. (Reactions were carried out on a 0.5-1 mmol scale). A solution of glycol (1 mmol) and Ph_3BiCO_3 (1.2 mmol/glycol) in dry acetonitrile (10 ml) was refluxed for 5 h. Filtration of reaction mixture through celite, evaporation *in vacuo* of the solvent and column chromatography afforded the respective aldehydes.

General procedure for oxidation with iodobenzene dichloride. (Reactions were carried out on a 0.5 mmol scale). To a solution of the sulfur compound (1 mmol) in dry CH_2Cl_2 (2 ml) cooled to -40°C, a solution of iodobenzene dichloride (1.1 mmol) and dry pyridine (3.5 mmol) in dry CH_2Cl_2 (2 ml) was added. The reaction mixture was stirred for 1 h and brought to room temperature. The usual workup afforded in all cases a mixture of sulfoxides and elimination products which were purified by silica gel column chromatography.

General procedure for Pummerer rearrangement. (Reactions were carried out on a 0.5 mmol scale). To an ice cooled solution of sulfoxide (1 mmol) and dry TEA (3 mmol) in dry CH_2Cl_2 a solution of trifluoracetic anhydride (1.7 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise. The reaction mixture was warmed to room temperature and then stirred for 6h. The usual workup and silica gel column chromatography afforded the rearrangement products.

Monobactam 4a: *1-(1-[1,3]Dithian-2-yl-2,3,4,5-tetrahydroxy-pentyl)-3β-methoxy-4β-styryl-azetidin-2-one.* A solution of **1a** (1 mmol) and trifluoracetic acid (5 ml) in methanol (5 ml) was stirred for 4h. Methanol and trifluoracetic acid were evaporated *in vacuo* at room temperature. The residue was crystallized from MeOH affording **4a** in 90% yield. TLC, R_f: 0.3 (CH_2Cl_2-MeOH 9/1). Mp. : 174-176°C (MeOH). $[\alpha]_D$: -82 (c=1, MeOH). IR: 3465, 3350, 3032, 2295, 1738, 1655, 1490. ^{1}H-NMR (200 MHz, DMSO): 1.40-1.60 (m, 2H, $H_{8'}$); 1.60-1.81 (m, 2H, $H_{7'a}$); 2.21-2.30 (m, 2H, $H_{7'b}$); 3.04 (s, 3H, CH_3O); 2.92-3.20 (m, 4H, OH); 3.77 (m, 1H, $H_{4'}$); 4.10-4.25 (m, 5H, $H_{1'-2'}$, $H_{5'-6'}$); 4.34 (dd, $J_{3',2'}$=2 Hz, $J_{3',4'}$=10 Hz, 1H, $H_{3'}$); 4.37 (d, $J_{3,4}$=5Hz, 1H, H_3); 4.42 (dd, $J_{4,3}$=5Hz, $J_{4,5}$=9Hz, 1H, H_4); 5.98 (dd, $J_{5,4}$=9Hz, $J_{5,6}$=16 Hz, 1H, H_5); 6.50 (d, $J_{6,5}$=16Hz, 1H, H_6); 7.05-7.30 (m, 5H, H_{Ph}). ^{13}C-NMR (DMSO): 24.3 ($C_{8'}$), 27.6, 27.9 ($C_{7'}$), 46.3, 55.4 ($C_{1'}$, $C_{2'}$), 56.3 (CH_3O), 60.3 (C_4), 62.1 ($C_{6'}$), 66.3, 69.3, 70.2 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 83.3 (C_3), 124.6 (C_5), 125.2, 126.4, 127.2, 127.3 ($5CH_{Ph}$), 132.9 (C_6), 135.2 (C_{Ph}), 165.9 (C_2). EIMS: 455 (M^+, 8), 440 (12), 364 (5), 336 (30), 304 (6), 264 (15), 214 (15), 160 (90), 119 (100), 91 (55). Anal. Calcd. for $C_{21}H_{24}NO_6S_2$: C 55.37, H 6.41, N 3.07, S 14.05. Found: C 55.62, H 6.47, N 3.02, S 14.13.

Monobactam 5a: *1-[1-(1,2,3,4-tetra-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3β-methoxy-4β-styryl-azetidin-2-one.* A solution of **4a** (5 mmol) and triethylsilyl chloride (30 mmol) in dry pyridine (30 ml) was stirred at 35°C overnight. The reaction mixture was worked up as usual and purified by column chromatography on deactivated silica gel with 0.5% TEA (Hexane-EtOAc=19:1) affording **5a** in 70% yield. TLC, R_f: 0.4 (Hexane/EtOAc: 9/1). $[\alpha]_D$: -48 (c=1, $CHCl_3$). IR: 1755, 1461, 1112. ^{1}H-NMR (200 MHz): 0.50-0.78 (m, 36H, $SiCH_2\underline{CH_3}$); 0.80-1.10 (m, 24H, $Si\underline{CH_2}CH_3$); 1.90-2.10 (m, 2H, $H_{8'}$); 2.50-2.70 (m, 2H, $H_{7'a}$); 2.90-3.15 (m, 2H, $H_{7'b}$); 3.40 (s, 3H, CH_3O); 3.50 (dd, $J_{4',3'}$=10Hz, $J_{4',5'}$=6 Hz, 1H, $H_{4'}$); 3.70-3.80 (m, 3H, $H_{1'}$, $H_{5'}$, $H_{6'a}$); 3.87-4.00 (m, 2H, $H_{2'}$, $H_{6'b}$); 4.33 (dd, $J_{4,3}$=5Hz, $J_{4,5}$=9Hz, 1H, H_4); 3.35 (m, 1H, $H_{3'}$); 4.66 (d, $J_{3,4}$=5Hz, 1H, H_3); 6.45 (dd, $J_{5,4}$=9Hz, $J_{5,6}$=16Hz, 1H, H_5); 6.71 (d, $J_{6,5}$=16Hz, 1H, H_6); 7.30-7.60 (m, 5H, H_{Ph}). ^{13}C-NMR: 4.5 ($Si\underline{C}H_2CH_3$), 6.3 ($SiCH_2\underline{C}H_3$), 25.3 ($C_{8'}$), 28.3 ($C_{7'}$), 46.1, 54.2 ($C_{1'}$,$C_{2'}$), 58.0 (CH_3O), 61.3 (C_4), 63.2 ($C_{6'}$), 68.7, 74.9, 75.9 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 85.0 (C_3), 125.4

(C_5), 126.4, 127.4, 128.0 ($5CH_{Ph}$), 134.8 (C_6), 136.4 (C_{Ph}), 168.9 (C_2). EIMS : 912 (MH^+, 5), 911 (10), 882 (20), 792 (8), 722 (12), 660 (10), 474 (48), 275 (55), 160 (40), 115 (90), 87 (100).

Carbapenam 6: *4α-Benzyl-6β-methoxy-3α-propylthio-2-(1,2,3,4-tetra-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-aza-bicyclo[3.2.0]heptan-7-one.* This compound was obtained by radical cyclization of monobactam **5a** *via* the general procedure in 75% yield. TLC, R_f: 0.5 (Hexane-EtOAc 9/1). IR: 1774, 1600, 1500, 1465. ^{1}H-NMR (200 MHz): 0.50-0.80 (m, 36H, $SiCH_2\underline{C}H_3$); 0.82-1.15 (m, 27H, $Si\underline{C}H_2CH_3$, CH_{3Pr}); 1.60 (sex, J=7Hz, 2H, $SCH_2\underline{C}H_2$); 2.50 (t, J=7Hz, 2H, SCH_2); 2.55-2.80 (m, 1H, H_{8a}); 3.01-3.20 (m, 2H, H_1, H_{8b}); 3.28 (s, 3H, CH_3O); 3.35 (dd, $J_{2,1}$=8Hz, $J_{2,3}$=4 Hz, 1H, H_2); 3.48 (dd, $J_{3,2}$=4Hz, $J_{3,1'}$=2Hz, 1H, H_3); 3.55 (dd, $J_{5,6}$=4 Hz, $J_{5,1}$=8 Hz, 1H, H_5); 3.65 (dd, $J_{3',2'}$ =10 Hz, $J_{3',4'}$ =8 Hz, 1H, $H_{3'}$); 3.98-4.10 (m, 3H, $H_{2'}$, $H_{4'}$); 4.23 (d, $J_{6,5}$=4 Hz, 1H, H_6); 4.40 (dd, $J_{1',3}$=2Hz, $J_{1',2'}$=10Hz, 1H, $H_{1'}$); 7.10-7.30 (m, 5H, H_{Ph}). ^{13}C-NMR: 5.2 ($Si\underline{C}H_2CH_3$), 7.2 ($SiCH_2\underline{C}H_3$), 13.7 (CH_{3Pr}), 23.2 ($SCH_2\underline{C}H_2$), 36.1 (SCH_2), 37.8 (C_8), 43.2 (C_1), 52.7 (C_2), 58.7 (CH_3O), 61.8 (C_5), 63.8 ($C_{4'}$), 68.0 (C_3), 73.3, 77.8, 81.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$) 86.9 (C_6), 126.4, 126.6, 129.3 ($5CH_{Ph}$), 140.5 (C_{Ph}), 171.5 (C_7). EIMS : 882 (MH^+, 20), 881 (60), 852 (90), 825 (60), 708 (60), 592 (60), 403 (60), 115 (70), 87 (100).

Aldehydes 7 and 8: *4α-Benzyl-6β-methoxy-7-oxo-3-propylthio-1-aza-bicyclo[3.2.0]heptane-2-carbaldehyde* and *4α-Benzyl-6β-methoxy-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carbaldehyde.* An ice cooled solution of **6** (0.3 mmol) and Bu_4NF (1.6 mmol) in dry THF (10 ml) was stirred for 15 min, then aqueous methanol (5 ml) was added and the solvents were evaporated. The residue was treated with Ph_3BiCO_3 for oxidative cleavage *via* the general procedure above to give a mixture of the aldehydes **7** and **8** in 40% and 20% yield respectively, after chromatography.

Aldehyde **7:** TLC, R_f: 0.4 (Hexane-EtOAc 1/1). $[\alpha]_D$: -12 (c=1, $CHCl_3$). IR: 1742, 1705. ^{1}H-NMR (200 MHz): 0.96 (t, J=7Hz, 3H, CH_{3Pr}); 1.60-1.80 (m, 2H, $SCH_2\underline{C}H_2$); 2.72-2.99 (m, 2H, SCH_2); 3.10-3.50 (m, 4H, H_8, H_1, H_2); 3.60-3.80 (m, 1H, H_5); 4.19 (d, $J_{6,5}$=4Hz, 1H, H_6); 4.67 (m, 1H, H_3); 7.20-7.35 (m, 5H, H_{Ph}); 9.23 (d, J=1.8Hz, 1H, CHO).

Aldehyde **8:** TLC, R_f: 0.3 (Hexane-EtOAc 1/1). $[\alpha]_D$: -32 (c=0.8, $CHCl_3$). IR: 1745, 1666, 1600, 1410. ^{1}H-NMR (200 MHz): 2.71-2.90 (m, 2H, H_8); 3.32 (s, 3H, CH_3O); 3.45-3.60 (m, 1H, H_1); 3.65-3.80 (m, 1H, H_5); 4.40 (d, $J_{6,5}$=4 Hz, 1H, H_6); 6.21 (d, $J_{2,1}$=3Hz, 1H, H_2); 7.20-7.40 (m, 5H, H_{Ph}); 9.51 (s, 1H, CHO); EIMS: 258 (MH^+, 8), 228 (6), 214 (90), 166 (25), 151 (20), 123 (25), 103 (52), 91 (100).

Carbapenem 2: *4α-Benzyl-6β-methoxy-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylic acid methyl ester.* To a solution of **8** (0.3 mmol) in dry methanol (5 ml) under N_2 atmosphere, NaCN (1.5 mmol), acetic acid (0.45 mmol) and MnO_2 recently prepared (6.3 mmol) were added. The reaction mixture was stirred for 6 h at room temperature and filtered through Celite. Solvent was evaporated under reduced pressure and the residue purified by chromatography (Hexane/EtOAc=1:1) affording the ester **8** in 75% yield. TLC, R_f: 0.4 (Hexane-EtOAc 1/1). $[\alpha]_D$: -26 (c=0.5, $CHCl_3$). IR: 1745, 1695. ^{1}H-NMR (200 MHz): 2.80-3.10 (m, 2H, H_8); 3.41 (s, 3H, CH_3O); 3.40-3.55 (m, 1H, H_1); 3.72 (s, 3H, $COO\underline{C}H_3$); 4.30 (dd, $J_{5,1}$=6 Hz, $J_{5,6}$=4 Hz, 1H, H_5); 4.80 (d, $J_{6,5}$=4 Hz, 1H, H_6); 6.24 (d, $J_{2,1}$=3Hz, 1H, H_2); 7.30-7.50 (m, 5H, H_{Ph}). ^{13}C-NMR: 36.3 (C_8), 49.5 (C_1), 51.5 ($COO\underline{C}H_3$), 58.7 (CH_3O), 61.5 (C_5), 82.3 (C_6), 126.3, 127.5, 129.1 ($5CH_{Ph}$), 136.4 (C_2), 136.6 (C_{Ph}), 145.6 (C_3), 165.2 ($\underline{C}OOCH_3$), 172.2 (C_7). EIMS: 288 (MH^+, 10), 258 (25), 229 (15), 214 (70), 196 (30), 181 (20), 153 (18), 91 (100).

D-Glucosamine 1,3-propanedithioacetal **(11).** A solution of *D*-glucosamine 1,3-propanedithioacetal hydrochloride (20 mmol) and NaOH (20 mmol) in H_2O (40 ml) was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue dissolved in hot ethanol. After filtration, concentration and crystallization pure **11** was isolated in 70% yield. Mp.: 188-170°C (EtOH). ^{1}H-NMR (200 MHz, DMSO): 1.71-2.00 (m, 2H, H_8); 2.60-2.90 (m, 4H, H_7); 3.02 (dd, $J_{2,1}$=8Hz, $J_{2,3}$=2Hz, 1H, H_2); 3.10-3.63 (m, 9H, H_{3-6}, 4OH); 3.91 (d, $J_{1,2}$=8Hz, 2H, H_1); 4.35-4.55 (*br.* s, 2H, NH_2). ^{13}C-NMR (DMSO): 25.5 (C_8), 27.0, 27.6 (C_7), 51.6, 56.7 ((C_1,C_2), 63.4 (C_6), 67.3, 70.2, 74.7 (C_3, C_4, C_5). EIMS: 270 (MH^+, 8), 150 (100), 132 (68), 119 (78).

N,N-Phenylallylidene-D-glucosamine 1,3-propanedithioacetal **(12).** A solution of **11** (8mmol) and *trans*-cinnamaldehyde (8.5 mmol) in isobutanol (20 ml) was refluxed for 5 h. The reaction mixture was brought to room temperature obtaining **12** as a precipitate in 70% yield. Mp.: 136-138 °C (*iso*BuOH). $[\alpha]_D$: -37 (c=1, MeOH). ^{1}H-NMR (250 MHz, DMSO): 1.80-2.10 (m, 2H, H_8); 2.30-2.80 (m, 4H, H_7); 2.95-4.01 (m, 7H, H_{1-6}); 6.19 (dd, $J_{10,9}$=9Hz, $J_{10,11}$=16Hz, 1H, H_{10}); 6.40 (d, $J_{11,10}$=16 Hz, 1H, H_{11}); 6.50-6.70 (m, 5H, H_{Ph}); 7.21 (d, $J_{9,10}$=9 Hz, 1H, H_9). EIMS: 383 (M^+, 10), 264 (85), 188 (20), 144 (35), 132 (100).

Monobactams 5a and 5b: *1-[1-(1,2,3,4-tetra-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3β-methoxy-4β-styryl-azetidin-2-one* and *1-[1-(1,2,3,4-tetra-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3α-methoxy-4α-styryl-azetidin-2-one.* To a solution of imine **12** (5 mmol) in dry pyridine (30 ml) triethylsilyl chloride (30 mmol) was added. The reaction mixture was stirred at 35°C overnight and worked up as usual. The residue was used as such in the cycloaddition reaction *via* the general procedure above. Two isomeric monobactams **5a** (previously described) and **5b** were obtained in 78:22 ratio and 55% yield after isolation by column chromatography on deactivated silica gel with 0.5% TEA (Hexane- EtOAc=19:1).

Monobactam **5b:** TLC, R_f: 0.35 (Hexane/EtOAc: 9/1). $[\alpha]_D$: +103 (c=1, $CHCl_3$). IR: 1745, 1448, 1350, 995. ^{1}H-NMR (200 MHz): 0.50-0.80 (m, 36H, $SiCH_2\underline{CH_3}$); 0.80-1.10 (m, 24H, $Si\underline{CH_2}CH_3$); 1.90-2.15 (m, 2H, $H_{8'}$); 2.50-2.70 (m, 2H, $H_{7'a}$); 2.80-3.15 (m, 2H, $H_{7'b}$); 3.40-3.55 (m, 1H, $H_{4'}$); 3.46 (s, 3H, CH_3O); 3.68-3.90 (m, 3H, $H_{1'}$, $H_{5'}$, $H_{6'a}$); 4.10-4.25 (m, 2H, $H_{2'}$, $H_{6'b}$); 4.40-4.50 (m, 1H, H_4); 4.62 (d, $J_{3,4}$=5Hz, 1H, H_3); 4.60-4.70 (m, 1H, $H_{3'}$); 6.58 (dd, $J_{5,4}$=9Hz, $J_{5,6}$=16Hz, 1H, H_5); 6.75 (d, $J_{6,5}$=16Hz, 1H, H_6); 7.20-7.35 (m, 5H, H_{Ph}).

5,6-O-Isopropylidene-D-glucosamine 1,3-propanedithioacetal **(13).** A solution of *D*-glucosamine 1,3-dithioacetal hydrochloride (30 mmol), *p*-toluenesulfonic acid (100 mg) and 2-methoxypropene (35 mmol) in DMF (100 ml) was stirred at room temperature for 8 h. Usual workup and column chromatography (Hexane/EtOAc=2:8) afforded **13** in 75% yield. Mp.: 73-75°C (CH_2Cl_2-Hexane). $[\alpha]_D$: -6 (c=1, $CHCl_3$). ^{1}H-NMR (200 MHz): 1.37 (s, 3H, $C(\underline{CH_3})_2$); 1.42 (s, 3H, $C(\underline{CH_3})_2$); 1.90-2.10 (m, 2H, H_8); 2.15-2.60 (*br.* s, 4H, NH_2, 2OH); 2.65-3.00 (m, 4H, H_7); 3.28 (dd, $J_{2,1}$=8Hz, $J_{2,3}$=2Hz, 1H, H_2); 3.70-3.80 (m, 3H, H_5, H_6); 3.95 (d, $J_{1,2}$=8Hz, 1H, H_1); 4.04 (t, J=8Hz, 1H, H_4); 4.45 (dd, $J_{3,2}$=2Hz, $J_{3,4}$=8Hz, 1H, H_3). ^{13}C-NMR: 25.3 ($C(\underline{C}H_3)_2$), 25.7 (C_8), 26.8 ($C(\underline{C}H_3)_2$), 28.7, 29.1 (C_7), 51.5, 57.9 (C_1, C_2), 67.0 (C_6), 67.9, 75.3, 76.0 (C_3, C_4, C_5), 109.1 ($\underline{C}(CH_3)_2$). Anal. Calcd. for $C_{12}H_{23}O_4NS_2$: C 46.58, H 7.49, N 4.53, S, 20.72. Found C 46.58, H 7.26, N 4.40, S 20,50.

Monobactams 15a and 15b: *1-[1-(3,4-O-isopropylidene-1,2-di-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3β-methoxy-4β-styryl-azetidin-2-one* and *1-[1-(3,4-O-isopropylidene-1,2-di-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3α-methoxy-4α-styryl-azetidin-2-one.* A solution of amine **13** (8 mmol) and *trans*-cinnamaldehyde (9 mmol) in toluene (20 ml) was heated at 60°C in rotavapor under reduced pressure. Toluene was then added, the solution stirred for 3 h and finally the solvent was evaporated. The residue in dry pyridine (50 ml) was reacted with triethylsilyl chloride (24 mmol). The reaction mixture was stirred at 35°C overnight and worked up as usual. The residue obtained was used for subsequent transformation without further purification. Cycloaddition reaction of this imine *via* the general procedure afforded the two isomeric monobactams **15a** and **15b** in a ratio 72:28 and 55% yield after column chromatography on deactivated silica gel with 0.5% TEA (Hexane-EtOAc=9/1).

Monobactam **15a:** TLC, R_f: 0.35 (Hexane/EtOAc: 9/1). $[\alpha]_D$: -67 (c=1, $CHCl_3$). IR: 1760, 1461, 1370. ^{1}H- NMR (200 MHz): 0.62 (t, J=7 Hz, 18H, $SiCH_2\underline{CH_3}$); 0.80-1.08 (m, 12H, $Si\underline{CH_2}CH_3$); 1.33 (s, 3H, $C(\underline{CH_3})_2$); 1.36 (s, 3H, $C(\underline{CH_3})_2$); 1.90-2.11 (m, 2H, $H_{8'}$); 2.62-2.91 (m, 4H, $H_{7'}$); 3.46 (s, 3H, CH_3O); 3.71-4.20 (m, 5H, $H_{1'}$, $H_{4'\text{-}6'}$); 4.21-4.48 (m, 2H, $H_{2'\text{-}3'}$); 4.65 (dd, $J_{4,3}$=5Hz, $J_{4,5}$=9Hz, 1H, H_4); 4.69 (d, $J_{3,4}$=5Hz, 1H, H_3); 6.41 (dd, $J_{5,4}$ =9Hz, $J_{5,6}$=16 Hz, 1H, H_5); 6.74 (d, $J_{6,5}$=16Hz, 1H, H_6); 7.25-7.65 (m, 5H, H_{Ph}). ^{13}C-NMR: 4.9 ($Si\underline{C}H_2CH_3$), 6.9 ($SiCH_2\underline{C}H_3$), 23.2, 24.5 $C(\underline{C}H_3)_2$), 25.0 ($C_{8'}$), 26.6 ($C_{7'}$), 45.3, 51.5 ($C_{1'}$, $C_{2'}$), 58.6 (CH_3O), 61.5 (C_4), 64.3 ($C_{6'}$), 71.7, 73.6, 74.9, 76.5 (C_3, $C_{3'}$, $C_{4'}$, $C_{5'}$), 109.8 ($\underline{C}(CH_3)_2$), 125.0 (C_5), 126.6, 127.8, 128.0 ($5CH_{Ph}$), 135.8 (C_6), 137.2 (C_{Ph}), 168.1 (C_2).

Monobactam **15b:** TLC, R_f: 0.30 (Hexane/EtOAc: 9/1). $[\alpha]_D$: +42 (c=1, $CHCl_3$). IR: 1758, 1463, 1350. ^{1}H-NMR (200 MHz): 0.49 (t, J=7 Hz, 18H, $SiCH_2\underline{CH_3}$); 0.80-1.10 (m, 12H, $Si\underline{CH_2}CH_3$); 1.39 (s, 3H, $C(\underline{CH_3})_2$); 1.47 (s, 3H, $C(\underline{CH_3})_2$); 1.90-2.10 (m, 2H, $H_{8'}$); 2.50-2.70 (m, 2H, $H_{7'a}$); 2.80-3.10 (m, 2H, $H_{7'b}$); 3.44 (s, 3H, CH_3O); 3.80-4.05 (m, 5H, $H_{1'}$, $H_{4'\text{-}6'}$); 4.30-4.60 (m, 3H, H_4, $H_{2'\text{-}3'}$); 4.61 (d, $J_{3,4}$=5Hz, 1H, H_3); 6.45 (d, $J_{6,5}$=16Hz, 1H, H_6); 6.55 (dd, $J_{5,4}$ =9Hz, $J_{5,6}$=16 Hz, 1H, H_5); 7.30-7.50 (m, 5H, H_{Ph}).

Carbapenam 16: *4α-Benzyl-2-(3,4-O-isopropylidene-1,2-di-O-triethylsilyl-1,2,3,4-tetrahydroxybutyl)-6β-methoxy-3α-propylthio-1-aza-bicyclo[3.2.0]heptan-7-one.* This carbapenam was obtained by radical cyclization of monobactam **15a** *via* the general procedure above in 70% yield. TLC, R_f: 0.55 (Hexane-EtOAc 9/1). IR: 1770, 1600, 1500, 1463. ^{1}H-NMR (200 MHz): 0.50-0.80 (m, 18H, $SiCH_2\underline{CH_3}$), 0.90-1.20 (m, 15H, $Si\underline{CH_2}CH_3$, CH_{3Pr}); 1.32 (s, 3H, $C(\underline{CH_3})_2$); 1.43 (s, 3H, $C(\underline{CH_3})_2$); 1.80-2.00 (m, 2H, $SCH_2\underline{CH_2}$); 2.45-2.90 (m, 3H, SCH_2, H_{8a}); 3.15-3.23 (m, 2H, H_1, H_{8b}); 3.28 (s, 3H, CH_3O); 3.30-3.45 (m, 2H, H_2, H_5); 3.50-3.70 (m, 1H, H_3); 3.85 (d, $J_{6,5}$=5Hz, 1H, H_6); 4.10-4.30 (m, 5H, $H_{1'\text{-}4'}$); 7.20-7.35(m, 5H, H_{Ph}).

Carbapenam 17: *4α-Benzyl-2-(3,4-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-6β-methoxy-3α-propylthio-1-aza-bicyclo[3.2.0]heptan-7-one.* An ice cooled solution of **16** (0.3 mmol) and Bu_4NF (0.7 mmol) in dry THF (10 ml) was stirred for 15 min. Aqueous methanol (3 ml) was added to the solution and stirred for 5 min. The solvents were evaporated under reduce pressure and the residue was purified by column chromatography on fluorisil to give the monobactam **17** in 65% yield. TLC, R_f: 0.35 (EtOAc). $[\alpha]_D$: -21 (c=0.7, $CHCl_3$).IR: 3400, 1743, 1460, 1370, 1090. ^{1}H-NMR (200 MHz): 0.98 (t, J=7Hz, 3H, CH_{3Pr}); 1.34 (s, 3H, $C(\underline{CH_3})_2$); 1.37 (s, 3H, $C(\underline{CH_3})_2$); 1.45-1.70 (m, 2H, $SCH_2\underline{CH_2}$); 2.49 (t, J=7Hz, 2H, SCH_2); 2.55-2.65 (m, 1H, H_{8a}); 3.09-3.20 (m, 2H, H_1, H_{8b}); 3.21 (s, 3H, CH_3O); 3.30-3.40 (m, 3H, $H_{2\text{-}3}$, H_5); 3.42-3.70 (m, 3H, $H_{3'\text{-}4'}$); 3.90-4.15 (m, 2H, $H_{1'\text{-}2'}$); 4.10 (d, $J_{6,5}$=4Hz, H_6); 7.05-7.30 (m, 5H, H_{Ph}).

Oxidative cleavage of 17. A solution of **17** (1 mmol) and $NaIO_4$ (4 mmol) in methanol (10 ml) was stirred at 0°C for 1h. Solvent evaporation under reduced pressure left a residue which was taken in acetonitrile (10 ml) and refluxed. A difficult to purify mixture of **8** (see above) and 2,3-*O*-isopropylidene-*D*-glyceraldehyde **18** was obtained.

Monobactam 19: *1-[1-(3,4-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-1-[1,3]dithian-2-yl-1,1-dihydroxy-methyl]-3β-methoxy-4β-styryl-azetidin-2-one.* An ice cooled solution of **15a** (0.3 mmol) and Bu_4NF (0.6 mmol) in dry THF (10 ml) was stirred for 15 min. Aqueous methanol (3 ml) was added to the solution and stirred for 5 min. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on fluorisil to give the monobactam **19** in 80% yield. TLC, R_f: 0.50 (EtOAc). Mp.: 96-98°C (CH_2Cl_2-Hexane). $[\alpha]_D$: -111 (c=1, $CHCl_3$). IR (KBr): 3340, 2990, 1742, 1643, 1622, 1215, 756, 696. ^{1}H-NMR (200 MHz): 1.30 (s, 3H, C($\underline{CH_3}$)$_2$); 1.34 (s, 3H, C($\underline{CH_3}$)$_2$); 1.90-2.11 (m, 2H, $H_{8'}$); 2.80-2.95 (m, 4H, $H_{7'}$); 3.45 (s, 3H, CH_3O); 3.55-3.70 (m, 1H, $H_{4'}$); 3.90-4.12 (m, 4H, $H_{1'}$, $H_{5'\text{-}6'}$); 4.30-4.40 (m, 1H, H_4); 4.45 (d, J=8Hz, 1H, $H_{3'}$); 4.60-4.70 (m, 2H, H_3, $H_{2'}$); 6.44 (dd, $J_{5,4}$ =9Hz, $J_{5,6}$=15Hz, 1H, H_5); 6.80 (d, $J_{6,5}$=15Hz, 1H, H_6); 7.30-7.50 (m, 5H, H_{Ph}). ^{13}C-NMR (MeOH): 25.7 ($C_{8'}$), 26.8, 27.1 (C($\underline{C}H_3$)$_2$), 29.2, 29.4 ($C_{7'}$), 47.7. 50.2 ($C_{1'}$, $C_{2'}$), 58.8 (CH_3O), 64.8 (C_4), 67.9 ($C_{6'}$), 69.4 , 74.1, 77.5 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 85.9 (C_3), 110.4 ($\underline{C}(CH_3)_2$), 125.9 (C_5), 127.6, 129.0, 129.6 ($5CH_{Ph}$) , 136.0 (C_6), 136.8 (C_{Ph}), 170.5 (C_2).

Aldehydes 18 and 20: *2,3-O-Isopropyliden-D-glyceraldehyde* and *2-(3β-Methoxy-2-oxo-4β-styryl-azetidin-1-yl)-3-(3-[3-[2-(3β-methoxy-2-oxo-4β-styryl-azetidin-1-yl)-3-oxo-propenylthio]-propyldithio}-propylthio)-prop-2-enal.* These aldehydes were obtained by reaction of glycol **19** with Ph_3BiCO_3 *via* the above general procedure in 45% and 60% yield respectively.

Dimeric aldehyde **20**: TLC, R_f: 0.4 (Hexane-EtOAc 2/8). IR: 3100, 1760, 1672. ^{1}H-NMR (200 MHz): 2.10 (q, J=7Hz, 4H, $SCH_2\underline{CH_2}CH_2S_2$); 2.75 (t, J=7Hz, 4H, $S\underline{CH_2}CH_2CH_2S_2$); 3.05 (t, J=7Hz, 4H, $SCH_2CH_2\underline{CH_2}S_2$); 3.47 (s, 6H, OCH_3); 4.71 (d, $J_{3,4}$=5Hz, 2H, H_3); 5.13 (dd, $J_{4,3}$ =5Hz, $J_{4,6}$=9Hz, 2H, H_4); 6.25 (dd, $J_{5,4}$ =9Hz, $J_{5,6}$=16Hz, 2H, H_5); 6.67 (d, $J_{6,5}$=16Hz, 2H, H_6); 7.14-7.40 (m, 12H, H_{Ph}, $H_{1'}$); 9.17 (s, 2H, CHO). ^{13}C-NMR: 28.8 ($SCH_2\underline{CH_2}CH_2S_2$), 33.7, 35.9 ($S\underline{CH_2}CH_2\underline{CH_2}S_2$), 58.7 ($OCH_3$), 61.7 ($C_4$), 85.4 ($C_3$), 122.6 ($C_5$), 126.6 ($CH_{Ph}$), 128.2 ($CH_{Ph}$), 130.4 ($C_{2'}$), 135.9 ($C_{Ph}$), 136.5 ($C_6$), 151.3 ($C_{1'}$), 164.3 ($C_2$), 184.3 (CHO). *2,4-Dinitophenylhidrazone*: Mp.: 183-185°C (EtOH). IR: 2254, 1760, 1626. RMN ^{1}H (200 MHz,): 2.16 (q, J=7Hz, 4H, $SCH_2\underline{CH_2}CH_2S_2$); 2.68 (t, J=7Hz, 4H, $S\underline{CH_2}CH_2CH_2S_2$); 3.12 (t, J=7Hz, 4H, $SCH_2CH_2\underline{CH_2}S_2$); 3.55 (s, 6H, OCH_3); 4.68 (d, $J_{3,4}$=4,7Hz, 2H, H_3); 5.09 (dd, $J_{4,3}$=4,7Hz, $J_{4,6}$=9Hz, 2H, H_4); 6.32 (dd, $J_{5,4}$=9Hz, $J_{5,6}$=16Hz, 2H, H_5); 6.60 (d, $J_{6,5}$=16Hz, 2H, H_6); 6.80 (s, 2H, NH); 7.20-7.40 (m, 12H, H_{Ph}, $H_{1'}$); 7.65 (s, 2H, $H_{3'}$), 7.80 (d, $J_{6'',5''}$=10Hz, 2H, $H_{6''}$); 8.36 (dd, $J_{5'',3''}$=1Hz, $J_{5'',6''}$= 10Hz, 2H, $H_{5''}$); 9.01 (d, $J_{3'',5''}$=1Hz, 2H, $H_{3''}$).

Carbapenam 21a: *4α-Benzyl-6β-methoxy-3α-propylthio-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-1-aza-bicyclo[3.2.0]heptan-7-one.* The compound **21a** was obtained by radical cyclization of monobactam **1a** *via* the general procedure above in 62% yield. TLC, R_f: 0.4 (Hexane-EtOAc: 9/1). $[\alpha]_D$: -13 (c=0.8, $CHCl_3$). IR: 1767, 1435, 1390, 1385. ^{1}H-RMN (400 MHz): 0.96 (t, J=7Hz, 3H, CH_{3Pr}); 1.22 (s, 3H, C($\underline{CH_3}$)$_2$); 1.28 (s, 3H, C($\underline{CH_3}$)$_2$); 1.43 (s, 3H, C($\underline{CH_3}$)$_2$); 1.60 (s, 3H, C($\underline{CH_3}$)$_2$); 1.82 (m, 2H, $CH_3\underline{CH_2}$); 2.55 (m, 2H, SCH_2); 2.65 (dd, $J_{8a,1}$=8 Hz, $J_{8a,8b}$=18 Hz, 1H, H_{8a}); 2.92 (quintet, J=8 Hz, 1H, H_1); 3.05 (dd, $J_{8b,1}$=8 Hz, $J_{8b,8a}$=18 Hz, 1H, H_{8b}); 3.28 (s, 3H, CH_3O); 3.58 (dd, $J_{2,1}$=8 Hz, $J_{2,3}$=4 Hz, 1H, H_2); 3.68 (dd, $J_{5,1}$=8 Hz,

$J_{5,6}$=4 Hz, 1H, H_5); 3.81 (t, J=4Hz, 1H, H_3); 3.80-4.00 (m, 2H, $H_{3'}$, $H_{4'a}$); 4.13 (dd, $J_{4'b,3'}$=8 Hz, $J_{4'b,4'a}$=12 Hz, 1H, $H_{4'b}$); 4.24 (dd, $J_{1',3}$=4 Hz, $J_{1',2'}$=12 Hz, 1H, $H_{1'}$); 4.34 (dd, $J_{2',1'}$=12 Hz, $J_{2',3'}$=8 Hz, 1H, $H_{2'}$); 4.35 (d, $J_{6,5}$=4 Hz, 1H, H_6); 7.10-7.30 (m, 5H, H_{Ph}). ^{13}C-RMN: 13.5 ($\underline{C}H_{3Pr}$), 23.0 ($CH_3\underline{C}H_2$), 25.4, 26.6, 26.7, 27.2 ($C(\underline{C}H_3)_2$), 34.3 (SCH_2), 34.9 (C_8), 42.6, 55.8 (C_1, C_2), 58.7 (CH_3O), 62.6 (C_5), 68.1 ($C_{4'}$), 69.3 (C_3), 77.8, 79.1 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 82.1 (C_6), 109.7, 110.0 ($\underline{C}(CH_3)_2$), 126.2, 128.4, 129.1 ($5CH_{Ph}$), 140.1 (C_{Ph}), 171.3 (C_7). EIMS: 506 (MH^+, 2), 505 (4), 490 (8), 478 (4), 434 (5), 336 (10), 269 (60), 161 (70), 91 (40), 74 (100). Anal. Calcd. for $C_{27}H_{39}NO_6S$: C 64.13, H 7.77, N 2.77, S 6.34. Found: C 64.22, H 8.02, N 3.01, S 6.13.

Carbapenam 21b: *4β-Benzyl-6α-methoxy-3α-propylthio-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-1-aza-bicyclo[3.2.0]heptan-7-one.* The compound **21b** was obtained by radical cyclization of monobactam **1b** *via* the general procedure above in 68% yield. TLC, R_f: 0.38 (hexano-EtOAc: 9/1). $[\alpha]_D$: +3.4 (c=1, $CHCl_3$). IR: 1780, 1440, 1390. ^{1}H-RMN (400 MHz): 1.01 (t, J=7Hz, 3H, CH_{3Pr}); 1.31 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.36 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.50 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.65 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.40-1.70 (m, 2H, $SCH_2\underline{CH}_2$); 2.40-2.45 (m, 1H, H_1); 2.50-2.70 (m, 2H, SCH_2); 2.65 (dd, $J_{8a,1}$=10 Hz, $J_{8a,8b}$=14 Hz, 1H, H_{8a}); 2.83 (s, 3H, CH_3O); 3.25 (dd, $J_{8b,1}$=4 Hz, $J_{8b,8a}$=14 Hz, 1H, H_{8b}); 3.28 (dd, $J_{2,1}$=10 Hz, $J_{2,3}$=8 Hz, 1H, H_2); 3.61 (dd, $J_{5,1}$=8 Hz, $J_{5,6}$=4 Hz, 1H, H_5); 3.81 (t, J=7Hz, 1H, $H_{4'a}$); 3.86 (dd, $J_{3,2}$=8 Hz, $J_{3,1'}$=2 Hz, 1H, H_3); 4.15-4.20 (m, 4H, $H_{1'-3'}$, $H_{4'b}$); 4.38 (d, $J_{6,5}$=4 Hz, 1H, H_6); 7.15-7.40 (m, 5H, H_{Ph}). ^{13}C-RMN: 13.6 (CH_{3Pr}), 23.2 ($CH_3\underline{C}H_2$), 25.4, 26.4, 26.8, 27.4 ($C(\underline{C}H_3)_2$), 32.0 (SCH_2), 37.3 (C_8), 46.3 (C_1), 55.6 (C_2), 58.9 (CH_3O), 63.4 (C_5), 65.2 ($C_{4'}$), 67.7 (C_3), 77.3, 79.1, 79.4 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 83.7 (C_6), 109.6, 110.1 ($\underline{C}(CH_3)_2$), 126.3, 128.4, 129.4 ($5CH_{Ph}$), 140.1 (C_{Ph}), 176.9 (C_7). EIMS: 506 (MH^+, 10), 478 (15), 463 (12), 403 (8), 372 (20), 268 (80), 161 (60), 91 (50), 75 (100). Anal. Calcd. for $C_{27}H_{39}NO_6S$: C 64.13, H 7.77, N 2.77, S 6.34. Found: C 64.24, H 7.95, N 2.99, S 6.32.

Compounds 22 and 3a: *4α-Benzyl-6β-methoxy-3α-(propyl-1-sulfinyl)-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybut-yl)-1-aza-bicyclo[3.2.0]heptan-7-one* and *4α-Benzyl-6β-methoxy-3α-propylthio-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-1-aza-bicyclo[3.2.0]hept-2-en-7-one.* These compounds were obtained by oxidation of **21a** with Cl_2IPh *via* the general procedure in a yield of 50% and 10% respectively. Carbapenem **3a** was also obtained from **22** by Pummerer rearrangement *via* the general procedure in 55% yield.

Carbapenam **22:** TLC, R_f: 0.3 (Hexane-EtOAc 1/1). IR: 1764, 1385, 1205, 1057. ^{1}H-NMR (200 MHz): 0.98 (t, J=7Hz, 3H, CH_{3Pr}); 1.29 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.31 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.36 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.46 (s, 3H, $(C(\underline{CH}_3)_2)$; 2.15-2.35 (m, 2H, $SOCH_2\underline{CH}_2$); 3.02-3.25 (m, 5H, $SOCH_2$, H_8, H_1); 3.35 (s, 3H, CH_3O); 3.75-4.50 (m, 8H, H_{2-3}, H_5, $H_{1'-4'}$); 4.55 (d, $J_{6,5}$=4Hz, H_6), 7.15-7.30 (m, 5H, H_{Ph}). ^{13}C-NMR: 13.2 (CH_{3Pr}), 16.6 ($SOCH_2\underline{C}H_2$), 25.2, 26.3, 26.6, 26.9 ($C(\underline{C}H_3)_2$), 33.5 (C_8), 43.3 (C_1), 51.8 ($SOCH_2$), 57.9 (C_3), 58.6 (OCH_3), 62.6 (C_5), 67.9 ($C_{4'}$), 68.4 (C_2), 77.9, 79.0, 80.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 80.8 (C_6), 109.5, 109.6 ($C(\underline{C}H_3)_2$), 126.3, 128.3, 128.4, 128.8 ($5CH_{Ph}$), 139.0 (C_{Ph}), 172.0 (C_7).

Carbapenem **3a:** TLC, R_f: 0.5 (Hexane-EtOAc 8/2). $[\alpha]_D$: -101 (c=0.4, $CHCl_3$). IR: 1780, 1375, 1190, 1060. ^{1}H-NMR (200 MHz): 0.98 (t, J=7Hz, 3H, CH_{3Pr}); 1.31 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.35 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.41 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.47 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.70-1.90 (m, 2H, $SCH_2\underline{CH}_2$); 2.30-2.80 (m, 2H, SCH_2); 3.10-3.35 (m, 3H, H_8, H_5); 3.40 (s, 3H, CH_3O); 3.60-3.80 (m, 1H, H_1); 3.89-4.40 (m, 6H, H_6, $H_{1'-4'}$); 7.21-7.50 (m, 5H, H_{Ph}). ^{13}C-NMR: 11.1 (CH_{3Pr}), 22.9 ($SCH_2\underline{CH}_2$), 23.9, 25.4, 26.0, 26.6 ($C(\underline{CH}_3)_2$), 33.6 (SCH_2), 37.3 (C_8),

48.5 (C_1), 57.9 (CH_3O), 62.9 (C_5), 67.9 ($C_{4'}$), 76.3, 77.0, 77.6 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 82.2 (C_6), 109.4, 109.8 ($\underline{C}(CH_3)_2$), 126.6, 128.6, 130.0 ($5CH_{Ph}$), 137.3 (C_3), 138.5 (C_{Ph}), 140.5 (C_2), 174.4 (C_7). EIMS: 503 (M^+, 12), 488 (8), 429 (10), 414 (8), 397 (25), 145 (60), 91 (100), 75 (70).

Compounds 23 and 24: *4β-Benzyl-6α-methoxy-3α-(propyl-1-sulfinyl)-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybut-yl)-1-aza-bicyclo[3.2.0]heptan-7-one* and *4-Benzyl-6α-methoxy-3-propylthio-2-(1,2;3,4-di-O-isopropylidene-1,2,3,4-tetrahydroxybutyl)-1-aza-bicyclo[3.2.0]hept-3-en-7-one.* These compounds were obtained by oxidation of **21b** with Cl_2IPh *via* the above general procedure in a 50% and 7% yield respectively. Carbapenem **24** was also obtained from **23** by Pummerer rearrangement *via* the general procedure in 50% yield.

Carbapenam **23:** TLC, R_f: 0.3 (Hexane-EtOAc 1/1). $[\alpha]_D$: +15 (c=1, $CHCl_3$). IR: 1780, 1375, 1205, 1060. ^{1}H-NMR (200 MHz): 1.09 (t, J=7Hz, 3H, CH_{3Pr}); 1.31 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.39 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.47 (s, 3H, $C(\underline{CH}_3)_2$); 1.60-1.90 (m, 2H, $SOCH_2\underline{CH}_2$), 2.61 (t, J=7Hz, 2H, $SOCH_2$); 2.83 (dd, $J_{8a,1}$=8Hz, $J_{8a,8b}$=14Hz, 1H, H_{8a}); 2.96 (s, 3H, CH_3O); 3.20-3.40 (m, 2H, H_1, H_{8b}); 3.52 (dd, $J_{5,6}$=4Hz, $J_{5,1}$=8Hz, 1H, H_5); 3.75 (t, J=8Hz, 1H, H_2); 3.80-4.20 (m, 6H, H_3, $H_{1'-4'}$); 4.96 (d, $J_{6,5}$=4Hz, 1H, H_6); 7.20-7.40 (m, 5H, H_{Ph}). ^{13}C-NMR: 13.1 (CH_{3Pr}), 16.4 ($SOCH_2\underline{CH}_2$), 24.9, 26.3, 26.4, 26.9 ($C(\underline{C}H_3)_2$), 39.7 (C_8), 41.7 (C_1), 52.4 ($SOCH_2$), 58.4 (C_3), 58.8 (CH_3O), 65.0 (C_5), 67.8 ($C_{4'}$), 72.8 (C_2), 76.2, 77.5, 82.3 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 83.9 (C_6), 109.8, 109.9 ($\underline{C}(CH_3)_2$), 126.4, 128.3, 129.0 ($5CH_{Ph}$), 136.9 (C_{Ph}), 175.0 (C_7).

Carbapenem **24:** TLC, R_f: 0.45 (Hexane-EtOAc 8/2). $[\alpha]_D$: +20 (c=0.8, $CHCl_3$). IR: 1780, 1352, 1210, 1063.^{1}H-NMR (200 MHz): 0.99 (t, J=7Hz, CH_{3Pr}); 1.25 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.37 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.53 (s, 3H, $(C(\underline{CH}_3)_2)$; 1.55 (s, 3H, $C(\underline{CH}_3)_2$); 1.40-1.62 (m, 2H, $SCH_2\underline{CH}_2$); 2.40-2.70 (m, 2H, SCH_2); 2.90-3.12 (m, 1H, H_{8a}); 3.48 (d, $J_{8b,8a}$=16 Hz, 1H, H_{8b}); 3.51 (s, 3H, CH_3O); 3.75-4.42 (m, 6H, H_5, $H_{1'-4'}$); 4.67 (d, $J_{6,5}$=5 Hz, 1H, H_6); 4.82 (d, $J_{3,1'}$=3Hz, 1H, H_3); 7.15-7.35 (m, 5H, H_{Ph}). ^{13}C-NMR: 13.1 (CH_{3Pr}), 23.2 ($SCH_2\underline{CH}_2$), 26.4. 26.6. 27.2. 29.6 ($C(\underline{C}H_3)_2$), 33.4 (SCH_2), 34.6 (C_8), 59.1 (CH_3O), 65.7 (C_5), 68.0 (C_3), 68.4 ($C_{4'}$), 77.0, 77.6, 78.3 ($C_{1'}$, $C_{2'}$, $C_{3'}$), 89.4 (C_6), 109.5, 109.6 ($\underline{C}(CH_3)_2$), 126.1, 128.3, 128.6 ($5CH_{Ph}$), 136.1 (C_1), 138.3 (C_{Ph}), 147.2 (C_2), 180.7 (C_7). EIMS: 503 (M^+, 8), 488 (8), 432 (10), 334 (10), 303 (85), 143 (100), 91 (65).

Acknowledgments.

We thank the Dirección General de Investigación Científica y Técnica (DGICYT) and the Junta de Castilla y León for financial support (Proj.: PB92-0286 and SA-49/12/92) as well as the Ministerio de Educación y Ciencia (MEC) and Universidad de Salamanca for the grants to two of us (J.I.M. H. and N. M. L).

References and notes.

1.- Carbapenem is an abbreviation for the basic system 1-azabicyclo[3.2.0]hept-2-en-7-one.

2.- Kahan, J. S.; Kahan, Goegelman, F.; R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, A. K.; Hendin, D.; Mochales, S.; Hernández, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979,** *32,* 1; Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T.*ibid.* **1980,** *33,* 796.

3.- Doherty, J. B.; Ashe, B. M.; Argenbright, L. W.; Barker, P. L.; Bonney, R. J.; Chandler, G. O.; Dahlgren, Mary E.; Dorn Jr., C. P.; Finke, P. E.; Firestone, R. A.; Fletcher, D.; Hagmann, W. K.; Mumford, R.; O'Grady, L.; Maycock, A. L.; Pisano, J. M.; Shah, S. K.; Thompson, K. R.; Zimmerman, M. *Nature*, **1986**, *322*, 192. Finke, P. E.; Shah, S. K.; Ashe, B. M.; Ball, R. G.; Blacklock, T. J.; Bonney, R. J.; Brause, K.A.;

Chandler, G. O.; Cotton, M.; Davies, P.; Dellea, P. S.; Dorn Jr., C. P.; Fletcher, D. S.; O'Grady, L.; Hagmann, W. K.; Hand, K. M.; Knight, W. B.; Maycock, A. L.; Mumford, R. A.; Osinga, D. G.; Sohar, P.; Thompson, K. R.; Weston, H.; Doherty, J. B. *J. Med. Chem.*, **1992**, *35*, 3731.

4.- Thompson, R. A.; Finke, P. E.; Shah, S. K.; Ashe, B. M.; Dahlgren, M. E.; Maycock, A. L.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2283. Thompson, R. A.; Finke, P. E.; Shah, S. K.; Ashe, B. M.; Dahlgren, M. E.; Dellea, P. S.; Fletcher, D. S.; Hand, K. M.; Maycock, A. L.; Doherty, J. B. *ibid.* **1993**, *3*, 2289.

5.- Finke, P. E.; Dahlgren, M. E.; Weston, H.; Maycock, A. L.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2277.

6.- Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M. and Dahlgren, Mary E.; *Tetrahedron*, **1990**, *46*, 2255. Maillard, J. L.; Favreau, C.; Reboud-Ravaux, M.; Kobaiter, R.; Joyeau, R.; Wakselman, M. *Eur. J. Cell. Biology*, **1990**, 213. Hagmann, W. K.; Shah, S. K.; Dorn, C. P.; O'Grady, L.; Hale, J. J.; Finke, P. E.; Thompson, K. R.; Brause, K.A.; Ashe, B. M.; Weston, H.; Dahlgren, Mary E.; Maycock, A. L.; Dellea, P. S.; Hand, K. M.; Osinga, D. G.; Bonney, R. J.; Davies, P.; Fletcher, D. S.; Doherty, J. B. *Bioorg. Med. Chem. Lett.*, **1991**, *1*, 545. Hagmann, W. K.; Thompson, K. R.; Shah, S. K.; Finke, P. E.; Ashe, B. M.; Weston, H.; Maycock, A. L.; Doherty, J. B. *ibid*, **1992**, *2*, 681.

7.- For some recent reviews, see: Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729; Georg G.I. in *Studies in Natural Product Chemistry, Vol.4* , Rahman, Atta-Ur, Ed.; Elsevier, Amsterdam, **1989**, p. 431; Palomo, C. in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G.; Ohno, M. Eds; Springer-Verlag, Berlin, **1990**, p. 565. Kant, J.; Walker, D.G. in *The organic Chemistry of β–lactams* , Georg G.I. Ed; VCH; New York, **1993**, p. 121.

8.- For some recent reviews, see: Thomas, R. C. in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G.; Ohno, M. Eds; Springer-Verlag, Berlin, **1990**, p. 533. Ternansky, R. J.; Morin, Jr., J. M.. in *The Organic Chemistry of β–Lactams* , Georg G.I. Ed; VCH; New York, **1993**, p. 257.

9.- Barton, D. H. R.; Gateau-Olesker, A.; Anaya-Mateos, J.; Cléophax, J.; Gero, S. D.; Chiaroni, A.; Riche, C. *J. Chem. Soc., Perkin Trans. 1*, **1990**, *11*, 3211.

10.- Georg, G. I.; Ravikumar, V. T. in *The Organic Chemistry of β–Lactams*, Georg G.I. Ed; VCH; New York, **1993**, p. 295.

11.- Anaya, J.; Barton, D. H. R.; Gero, S. D.; Grande, M.; Martín, N.; Tachdjian C. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 867.

12.- Clive, D. L. J.; Chittattu, G. J.; Farina, V.; Kiel, W. A.; Menchen, S. M.; Russell, C. G.; Singh, A.; Wong, C. K.; Curtis, N. J. *J. Am. Chem. Soc.* **1980**, *102*, 4438. Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 1541.

13.- An article describing the synthesis of β–lactams and carbapenams from *D*-glucosamine is in preparation.

14.- Barton, D.H.R.; Finet, J.P.; Motherwell, W.B.; Pichon, C. *Tetrahedron* **1986**, *42*, 5627.

15.- Corey, E.J.; Gilman, N.W.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

16.- Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron*, **1986**, *42*, 488.

17.- Wolfrom, M. L.; Diwadkar, A. B.;Gelas, J.; Horton, D. *Carbohydr. Res.*, **1974**, *35*, 87.

18.- Chiaroni, A.; Riche, C.; Anaya, J.; Gateau-Olesker, A.; Gero, S. D.; Hernando, J. I. M. *Acta Crys., Sect. C*, **1994**, *C50*, 1474.

19.- Barton, D.H.R.; Jonathan, P.K.; Lester, D.J.; Motherwell, W.B.; Papoula, T.B. *Tetrahedron*, **1981**, *37*, 73.

20.- For a review of sinthetic inhibitors see: Trainor, D. A. *Trends Pharmacol. Sci.* **1987**, *8*, 303.

21.- Adonias, M; Anaya, J.; Cámara, J.; Canet, E.; Gateau-Olesker, A.; Gero, S. D.; Grande, M.; Hernando, J. I.M. *Bioorg. Med. Chem. Lett.*,**1993**, *3*, 2547.

22.- Chiaroni, A.; Riche, C.; Adonias, M.; Anaya, J.; Gero, S. D.; Tachdjian C. *Acta Crys., Sect. C*, **1995**, *C51*, in press.

23.- Yoshioka, T.; Watanabe, A.; Issiki, K.; Fukagawa, Y.; Ishikura, T. *Tetrahedron Lett.*, **1986**, *36*, 4335. Cinquini, M.; Colonna, S. *J. Chem. Soc. Perkin 1*, **1972**, 1883.

24.- Bakuzis, P.; Bakuzis, M.L.F. *J. Org. Chem.*, **1985**, *50*, 2569.

25.- Goel, R.G.; Prasad, H.S. *Can. J. Chem.*, **1971**, *49*, 2529.

26.- Lucas, H. J.; Kenedy, E. R. *Org. Synth. Coll. Vol. III*, **1955**, 482.

27.- Bendall, M.R.; Pegg, D.T. *J. Magn. Res.*, **1983**, *53*, 144.

28.- Le Coq, C.; Lallemand, J.Y. *Chem. Commun.*, **1981**, 150.

(*Received in UK* 26 *December* 1994)