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Cyclization and rearrangement of 4-(2-methyloxiranyl)-β-lactams promoted by titanocene dichloride/Zn⁰

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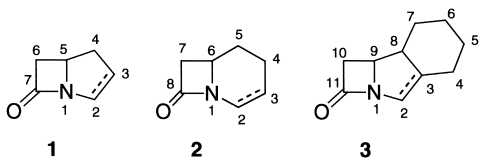
Dedicated in memory of the late Dr Benedicto del Rey

Abstract—Enantiopure epoxyalkene-2-azetidinones derived from D-glucosamine by Staudinger reaction gave on treatment for 2 h with titanoncene (III) monochloride generated in situ, bicyclic and tricyclic β-lactams with high regio and stereo-selectivity but with low conversion. For extended reaction times (15–22 h) a rearranged five-membered ring imide was the main reaction product together with the tribactam.

1. Introduction

The discovery of natural and synthetic β-lactam antibiotics of the carbapenem,[1] **1**, carbacephem,[2] **2**, and tribactam,[3] **3**, types (Fig. 1)[4] with improved biological activity and resistance to enzymes has provoked a continuing development of high level methodology to prepare these compounds.

The potent antibacterial properties of tribactam-type compounds have recently made these substances a major synthetic objective[5] in the β-lactam field. Most of the approaches to these compounds rest in a stepwise method starting by a functionalized 2-azetidinone, the central ring is then formed by methods that have been used for years in the preparation of bicyclic β-lactams[6] and then the third ring is closed. A different approach based on the azomethine ylide reactivity with dipolarophiles has been recently disclosed,[7] and this strategy led to the tricyclic [4.5.6] skeleton in a single step from 2-azetidinones.



1 **2** **3**

Figure 1. Bi- and tricyclic β-lactam skeletons.

The simultaneous formation of two of the three rings of a tricyclic β-lactam system on a preformed monocyclic 2-azetidinone appeared attractive and consequently, we have investigated the radical cyclizations from 4-oxyranyl-2-azetidinones using titanocene monochloride (Cp_2TiCl)[8] as a new route to the synthesis of this type of compounds.

2. Results and discussion

The synthesis of the epoxides necessary for our study, **4**, is illustrated in Scheme 1.

The starting *cis*-monobactams **6a** and **6b** were prepared as a 1:2.1 mixture by Staudinger reaction[9] between methoxyacetyl chloride and the imine obtained from methylacrolein and the glucosamine derivative **5**.[10] Column chromatography of the crude reaction mixture allowed isolation of the pure diastereomers **6a** and **6b**.

The relative configuration at C-3 and C-4 of both isomers were deduced from the ^1H NMR coupling constants $J_{3,4} > 4$ Hz[10] and the absolute configuration was assigned by comparison of their $[\alpha]_D$ data with those of 2-azetidinones of known absolute configuration established by X-ray crystallography.[10c,11]

Treatment of each monobactam **6** with $PhI(OCOCF_3)_2$ and $NaHCO_3$ in CH_3CN/H_2O 85:15[12] followed by Wittig reaction with $Ph_3P{=}CHCO_2Me$ afforded the respective

Keywords: epoxy-β-lactams; carbapenam; tribactam; titanocene; ring expansion.

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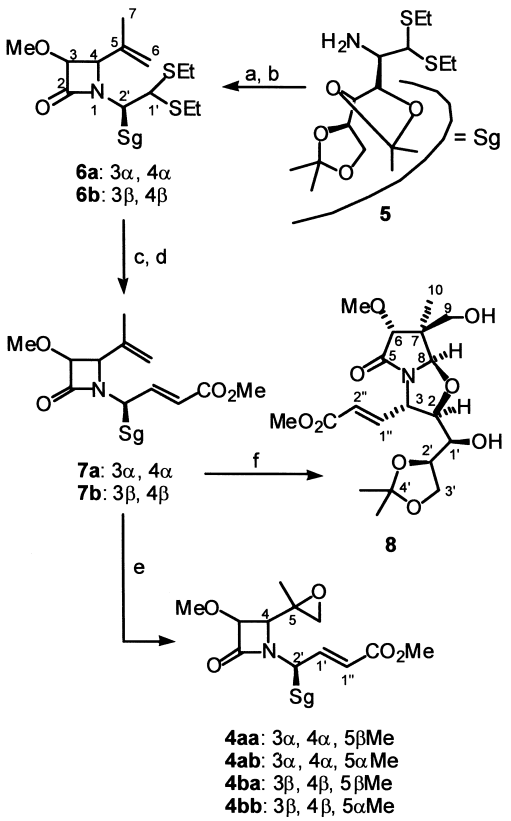


Scheme 1. *Reagents and conditions*: (a) $CH_2{=}C(CH_3){-}CHO$, CH_2Cl_2, rt, 3 days; (b) TEA, CH_3CH_2COCl, CH_2Cl_2, rt, 12 h; (c) $PhI(CF_3CO_2)_2$, $NaHCO_3$, CH_3CN/H_2O 85:15, rt; (d) $Ph_3P{=}CH{-}CO_2Me$, THF, rt; (e) *m*-CPBA, CH_2Cl_2, rt, 8 h; (f) *m*-CPBA, CH_2Cl_2, rt, 30 h.

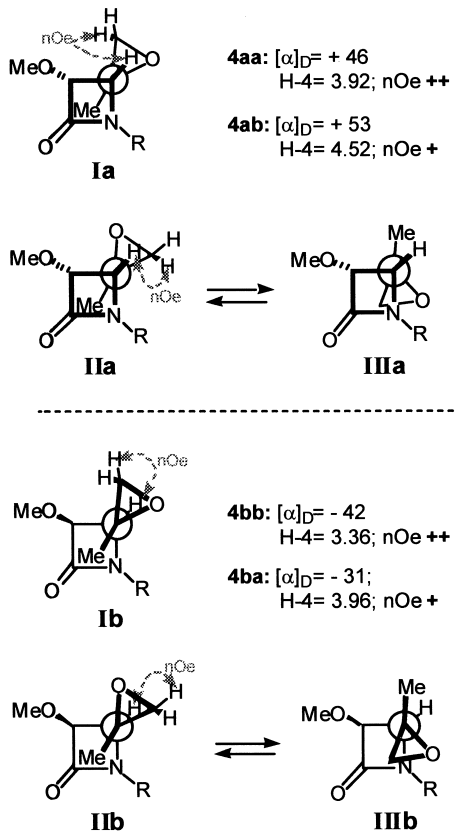


Figure 2. Minimum energy conformers of epoxides **4**.

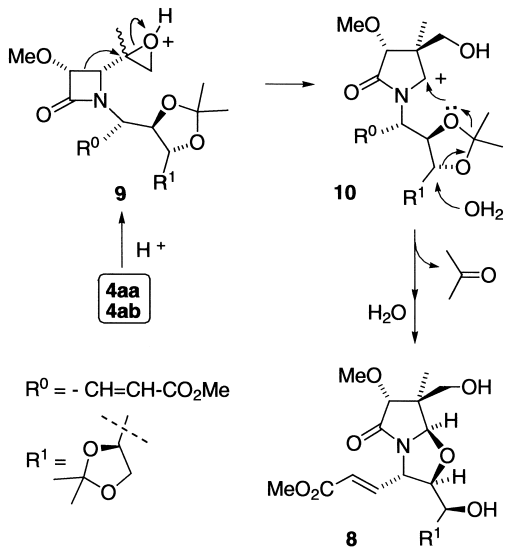
trans α,β-unsaturated esters **7a** and **7b** which on treatment with *m*-CPBA gave in 58 and 81% yield, respectively, the epoxides **4aa/4ab** in a 1.1:1 ratio and **4ba/4bb** as a 1.4:1 mixture. When the treatment of the monobactam **7a** with *m*-CPBA was continued for 30 h, a mixture of three products were obtained in 80% yield. The most abundant product was identified as the bicyclic γ-lactame **8** (45%) and the minor constituents were identified as the epoxides **4aa** (19%) and **4ab** (17%).

The structure of each epoxide **4** was deduced from 1D and 2D NMR data, including COSY and HMQC experiments for the compounds **4ba** and **4bb**. The C-5 configuration for the four isomeric epoxides were tentatively assigned on the basis of a conformational analyses of the C4–C5 rotational isomers[13] (Fig. 2).

From this study it emerges that the isomers **4aa** and **4bb** show only one rotational isomer of minimum energy, the conformers **Ia** and **Ib**, respectively. However, the isomers **4ab** and **4ba** show two rotational minima **IIa/IIIa** and **IIb/IIIb**, respectively. Accordingly, the shielding effect of the oxyrane ring on H-4 should be stronger for the isomers **4aa** and **4bb** (conformers **Ia** and **Ib**) than for the isomers **4ab** and **4ba** in which H-4 is out of the shielding zone in one of the conformers of low energy. The isomers of each pair with more shielded H-4, which also present strong nOes between H-4 and H-6, are the isomers with $[\alpha]_D{=}{+}46$ and $[\alpha]_D{=}{-}42$, for which we propose the configuration **4aa** (3*R*,4*R*,5*S*) and **4bb** (3*S*,4*S*,5*R*), respectively. This implies that the epimeric epoxides should have the configurations **4ab** (3*R*,4*R*,5*R*) and **4ba** (3*S*,4*S*,5*S*), respectively.

The spectroscopic data for the compound **8** were quite different from those expected for a β-lactam derivative. This compound showed IR bands which indicates the presence of hydroxyl groups and the absence of the β-lactam ring (3443, 1715 cm^{-1}) and the carbonyl carbon signal absorbed at lower fields than expected for the carbonyl absorption of 2-azetidinones (173.4 ppm vs. 165–170 ppm). In addition, the ^1H NMR spectrum showed signals for only one isopropylidene group and the characteristic signal for the proton geminal to the methoxy group in our 2-azetidinones, (δ 4.50–4.60, doublet), appeared in **8** as a singlet at 3.82 ppm, as was confirmed by 2D HMQC. These and the remaining spectral data are in good accordance with the structure of the bicyclic γ-lactam proposed for compound **8**. The stereochemistry of C-7 and C-8 was deduced from the nOe effects observed between H-8 with Me-10 and H-2 and between H-1″ with H-3 and H-2. These last hydrogen atoms keeps the α-configuration of the starting D-glucosamine, hence H-8 and Me-10 should also be α. The proposed stereochemistry for C-1′ is in agreement with the H-1′ vicinal coupling constants, the steric hinderance and the predicted cyclization mechanism.

The required acidic medium for the selective epoxidation of the propenyl group in β-lactam **7a** could be the responsible for the formation of the bicyclic γ-lactam **8**. The protonated epoxides **9** (Scheme 2) could rearrange by C3–C4 ring expansion to the stabilized five-membered-ring carbocation intermediate **10**[14] which could progress by elimination of



Scheme 2. Possible mechanism to explain the formation of **8**.

one molecule of acetone and simultaneous backwards addition of water molecule to give **8**.

To explore the reactivity of the isomeric C-5 epoxides **4** with titanocene(III) chloride (Table 1), a THF solution of the epoxide (1.0 mmol) was added at room temperature to a green solution of Cp_2TiCl in THF generated in situ from Cp_2TiCl_2 (2.2 mmol) and Zn^0 (6.6 mmol)[8f] (Eq. (1)):

$$2Cp_2TiCl_2 + Zn^0 \rightarrow 2Cp_2TiCl + ZnCl_2 \quad (1)$$

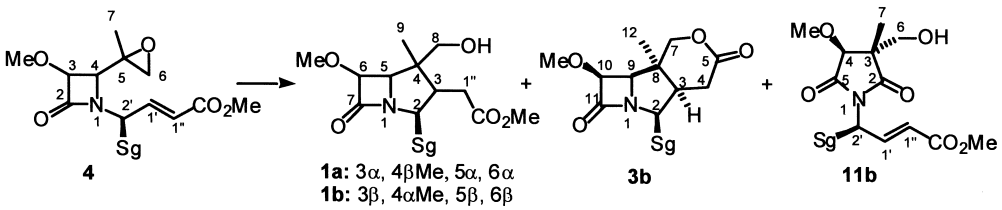
We first examined the cyclization of the mixtures of epoxides **4aa**+**4ab** and **4ba**+**4bb** separately, assuming that the reductive opening of epoxide ring with titanocene monochloride should promote the formation of the C-5 tertiary radical intermediate. Thus, treatment of the 1.7:1 mixture of the epimeric epoxides **4aa**+**4ab** with titanocene monochloride for 2 h followed by acidic workup afforded the expected bicyclic carbapenam **1a** (35%) together with a high proportion of the unreacted starting material **4aa**+**4ab** (55%) (entry 1, Table 1). Under the same conditions, different products were obtained for the reaction of the 2:1 isomeric mixture **4ba**+**4bb** (entry 3, Table 1). In this case, three reaction products were isolated (23%), the bicyclic diastereomer **1b**, the tribactam **3b** and the imide **11b**, also accompanied with a high amount (50%) of the starting material. To increase the conversion of the starting epoxides both mixtures **4aa**+**4ab** and **4ba**+**4bb** were reacted for 16 h. Under these conditions, the starting material disappeared in both cases. Unfortunately the epoxides **4aa**+**4ab** suffered an extensive decomposition to mixtures of unknown compounds, but the reaction of **4ba**+**4bb** afforded the tricyclic β-lactam **3b** and the imide **11b** in 84% yield (entries 2 and 4, Table 1).

In order to determine if the stereochemistry of the epoxides had any influence on the reactivity, the pure diastereomeric epoxides **4ba** and **4bb** were then separately treated with Cp_2TiCl in the same conditions than the mixture of both epimers. The product distribution and yield obtained for each epoxide after reacting either for 2 h or for 15–20 h was nearly identical to the results obtained from the mixture (entries 5–8, Table 1).

The proposed structures for the tribactam **3b** and the imide **11b** were deduced mainly from MS and NMR data, including 2D COSY, HMQC, HMBC and 1D nOe experiments. The bicyclic β-lactams **1a** and **1b** could not be isolated as pure substances so their structures were proposed according to the spectral data of enriched fractions.

The relative *cis*-configuration between H-2, H-3, Me-12, H-9 and H-10 in compound **3b** was deduced from the coupling constants and the observed nOes between H-2/H-3, H-2/H-4a, H-2/H-9, H-9/H-10 and H-9/Me-12. As the configuration of C-2, C-9 and C-10 was known, we proposed for tribactam **3b** the depicted absolute configuration and consequently, the absolute configuration 2*S*, 3*R*, 4*R*, 5*R*, 6*S* for its bicyclic precursor **1b**.

Table 1. Reaction of the epoxides **4** with Cp_2TiCl_2 and Zn^0



Entry	Epoxide	Time (h)	Epoxide (%)[a]	Products (yield, %)[b]		
1	**4aa**+**4ab** (1.7:1)	2	55	**1a** (35)[c]	–	–
2	**4aa**+**4ab** (1.7:1)	16	–	–	–	–
3	**4ba**+**4bb** (2:1)	2	50	**1b** (17)[c]	**3b** (3)	**11b** (3)
4	**4ba**+**4bb** (2:1)	16	–	–	**3b** (32)	**11b** (52)
5	**4ba**	2	50	**1b** (16)[c]	**3b** (8)	**11b** (8)
6	**4ba**	15	–	–	**3b** (28)	**11b** (53)
7	**4bb**	2	50	**1b** (18)[c]	–	–
8	**4bb**	22	–	–	**3b** (32)	**11b** (44)

[a] Recovered material after reaction.
[b] Isolated yield after column chromatography.
[c] Calculated yield from GC/MS and ^1H NMR data.

The structure of the carbapenam **1a** was similarly deduced from the spectral data and by comparison with **1b**. The observed proton coupling constant $J_{2,3}$=7.1 Hz was assigned in this case to a *trans*-orientation of the substituents at C-2 and C-3.[15]

The spectroscopic data for the imide **11b** are in good agreement with the proposed structure and the α configuration for Me-7 at C-3 was deduced from nOe experiments. By irradiation on H-4 a low nOe was observed with one of the H-6 protons while no nOe was observed between H-4 and the Me-7.

A possible mechanism to explain the formation of the reaction products is shown in the Scheme 3. The formation of **1a**, **1b** and **3b** can arise through path a, and involves the coordination of the titanium complex to the epoxy group of β-lactams **4** to yield the expected radical **12**. Conjugate addition on C-1′ affords the bicyclic intermediate **13**, which on hydrolysis leads to the final products **1a**, **1b** and **3b**.[8f]

The progress of the reaction through path b could explain the formation of the imide **11b**. The zinc chloride produced in the reduction of Cp_2TiCl_2, Eq. (1), could compete with Cp_2TiCl in the coordination to the oxyrane ring. The intermediate **15**, induces the four membered ring expansion (as in the case of the formation of **8**, Scheme 2) to form the stabilized carbocationic species **15** which under the hydrolytic workup gives the hydroxy γ-lactam **16**. This last substance should progress by oxidation to the imide **11b** but, at present, we have no evidence to rationalize this oxidation step. In addition, the different evolution of **10** and **15** is not easily explained but it could be caused by solvent effects or by coordination of $ZnCl_2$ to the oxygen atoms in this last experiment, which prevent the approach of the oxolane oxygen to the lactam ring.

In order to optimize the formation of the bicyclic and tricyclic β-lactams **1b** and **3b**, we carried out a new experiment with the major epoxy β-lactam **4ba** decreasing the concentration of the $ZnCl_2$. We added, in this case 2.0 mmol of Cp_2TiCl dropwise to a THF solution of the epoxide **4ba** but the green color due the titanium(III) species changed to the red color of the titanium(IV) species while the substrate remained unchanged.

It seems from the experimental behavior of diastereomers **4** that the epoxy groups in these β-lactams are slowly reduced by Cp_2TiCl, a reagent which under the experimental conditions slowly decomposes and then the epoxide can progress through the $ZnCl_2$ pathway to give the imide **11b**.

The present study shows that the cyclization and rearrangement of the 4-(2-methyloxiranyl)-β-lactams promoted by titanocene dichloride/Zn^0, are stereocontrolled processes and can be used to prepare new policyclic β-lactams as well as γ-lactams structurally related to pyrrolizidine alkaloids and nootropic drugs such as ethosuximide.[16]

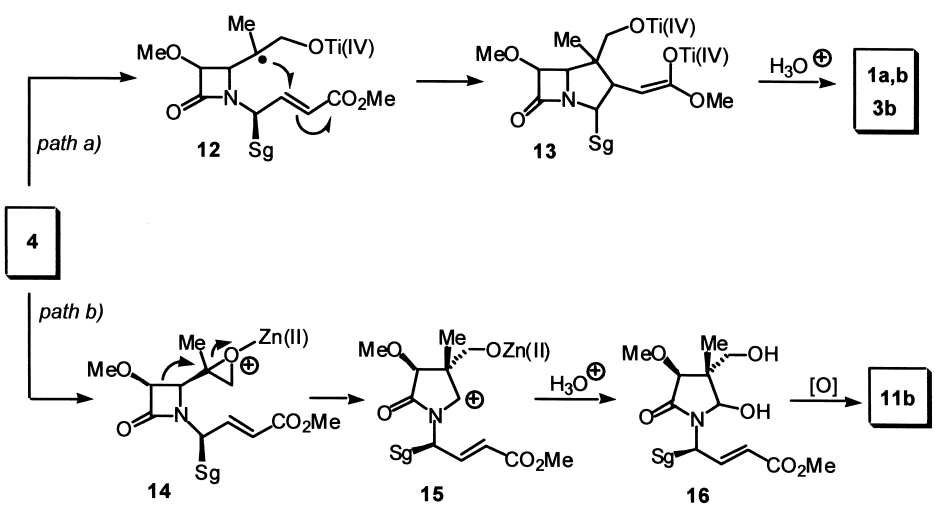
As far as we know, this is the first example of a rearrangement of the 2-azetidinone nucleus promoted by titanocene dichloride/Zn^0.

Efforts to extend the cyclization of 4-oxyranyl-β-lactams as an easy entry to other policyclic β-lactams and to overcome the limitations of our approach are currently being undertaken.

3. Experimental

3.1. 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). Mass spectra (MS), were recorded on a VG TS-250 spectrometer: EI at 70 eV; FAB with xenon as ionization gas; HRMS with *m*-nitrobenzyl alcohol matrix and 10 keV acceleration potential. Optical rotations were recorded in $CHCl_3$ solution in a 1 dm cell on a Perkin–Elmer 243 polarimeter. IR spectra were recorded as neat film on a Bomem MB-100 instrument. ^1H and ^{13}C NMR spectra were obtained on Bruker instruments WP200SY and Advance 400DRX (200



Scheme 3. Possible mechanism for the formation of compounds **1a**, **1b**, **3b** and **11b**.

and 400 MHz, respectively) in $CDCl_3$ solutions with tetramethylsilane as internal standard. Solvents and reagents were purified according to standard techniques.

3.2. In situ generation of Cp_2TiCl

To 548 mg (2.2 mmol) of titanocene dichloride in anhydrous THF (4.4 mL), 432 mg (6.6 mmol) of activated zinc granules was added. The mixture was then vigorously stirred for 30 min under nitrogen with rigorous exclusion of oxygen.

3.3. Monobactams 6

A solution of the amine **5** (1.9 g, 5.2 mmol) and methylacroleine (0.45 mL, 5.0 mmol) in CH_2Cl_2 (52 mL) was stirred for 3 days at room temperature, until the starting material disappeared in TLC. The imine was concentrated in Rotavapor and was used without further purification in the Staudinger reaction. To a solution of the crude imine and dry TEA (12.5 mmol) in CH_2Cl_2 (30 mL), a solution of methoxyacethyl chloride (7.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise under argon atmosphere. The reaction mixture was stirred for 12 h at rt until the starting material disappeared in TLC. The evolution of the reaction was also followed through IR, and once the imine band disappeared, the reaction mixture was poured into a cold ammonium chloride solution, neutralized to pH 7 by addition of acetic acid and extracted with dichloromethane. Removal of the solvent and further purification by silica gel column chromatography allowed the isolation of *cis* monobactams **6** in 79.5% yield.

3.3.1. (3α,4α)- and (3β,4β)-(1-(1′,2′-Dideoxy-1′,1′-diethylthio-3′,4′;5′,6′-di-*O*-sopropylidene-2′-D-glucosyl)-3-methoxy-4-(1-methylethenyl)-2-azetidinone (6a and 6b). Compound **6a**. (662 mg, 26%). $[\alpha]_D$=+18 (c=1, $CHCl_3$). IR: 1761, 1454, 1379, 1215, 1065, 914, 733 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.19, 1.20 (2t, J=7.4 Hz, 6H, CH_2CH_3); 1.27, 1.31, 1.35, 1.39 (4s, 12H, $C(CH_3)_2$); 1.87 (s, 3H, H-7); 2.64, 2.67 (2q, J=7.4 Hz, 4H, CH_2CH_3); 3.39 (s, 3H, OCH_3); 3.57 (dd, $J_{4',3'}$=7.6 Hz, $J_{4',5'}$=7.8 Hz, 1H, H-4′); 3.78–3.86 (m, 2H, H-2′, H-6′a); 3.97–4.14 (m, 2H, H-5′, H-6′b); 4.20 (d, $J_{1',2'}$=7.2 Hz, 1H, H-1′); 4.50 (d, $J_{4,3}$=5.2 Hz, 1H, H-4); 4.57 (d, $J_{3,4}$=5.2 Hz, 1H, H-3); 4.84 (dd, $J_{3',2'}$=3.9 Hz, $J_{3',4'}$=7.6 Hz, 1H, H-3′); 5.10, 5.20 (2s, 2H, H-6). ^{13}C NMR (50.3 MHz), δ (ppm): 14.1, 14.2 (2C, CH_2CH_3); 19.7 (C-7); 24.9, 25.6 (2C, CH_2CH_3); 25.4, 26.5, 26.6, 27.2 (4C, $C(CH_3)_2$); 52.8 (C-2′); 58.0 (C-1′); 58.7 (OCH_3); 66.2 (C-4); 68.0 (C-6′); 77.4, 78.8, 79.5 (3C, C-3′-5′); 84.7 (C-3); 109.7, 110.0 (2C, $C(CH_3)_2$); 117.1 (C-6); 141.1 (C-5); 168.6 (C-2). MS (FAB) *m/z* (rel. int.): 490 (18), 370 (12), 326 (22), 216 (24), 143 (100), 101 (85). HRMS (FAB): calcd for $C_{23}H_{40}NO_6S_2$ (M^++1) 490.2297; found 490.2302.

Compound **6b**. (1375 mg, 54%): $[\alpha]_D$=−114 (c=1, $CHCl_3$). IR: 1763, 1456, 1381, 1262, 1213, 1067, 887, 847 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.27, 1.28 (2t, J=7.6 Hz, 6H, CH_2CH_3); 1.32, 1.39, 1.45 (3s, 12H, $C(CH_3)_2$); 1.91 (s, 3H, H-7); 2.18, 2.20 (2q, J=7.6 Hz, 4H, CH_2CH_3); 3.40 (s, 3H, OCH_3); 3.72 (dd, $J_{4',3'}$=7.8 Hz, $J_{4',5'}$=7.6 Hz, 1H, H-4′); 4.01–4.23 (m, 5H, H-1′, H-2′, H-5′, H-6′); 4.45 (d, $J_{4,3}$=5.4 Hz, 1H, H-4); 4.70 (d, $J_{3,4}$=5.4 Hz, 1H, H-3); 4.75 (dd, $J_{3',2'}$=2.8 Hz, $J_{3',4'}$=7.8 Hz, 1H, H-3′); 5.01, 5.13 (2s, 2H, H-6). ^{13}C NMR (50.3 MHz), δ (ppm): 14.1, 14.3 (2C, CH_2CH_3); 19.9 (C-7); 24.4, 25.2 (2C, CH_2CH_3); 25.2, 25.4, 26.4, 26.5 (4C, $C(CH_3)_2$); 52.4 (C-2′); 55.6 (C-1′); 58.9 (OCH_3); 64.7 (C-4); 67.7 (C-6′); 77.1, 77.3, 79.0 (3C, C-3′-5′); 84.7 (C-3); 109.4, 110.1 (2C, $C(CH_3)_2$); 116.8 (C-6); 141.5 (C-5); 170.7 (C-2). MS (FAB) *m/z* (rel. int.): 490 (10), 326 (8), 228 (22), 143 (100), 101 (35). HRMS (FAB): calcd for $C_{23}H_{40}NO_6S_2$ (M^++1) 490.2297; found 490.2317.

3.4. Conversion of 6a and 6b to 7a and 7b

To a solution of each monobactam **6** (490 mg, 1.0 mmol) and $NaHCO_3$ (336 mg, 4.0 mmol) in 85:15 CH_3CN/H_2O (10.0 mL), [bis(trifluoroacetoxy)iodo]benzene (645 mg, 1.5 mmol) was added and the solution stirred at room temperature until the starting material disappeared. The reaction product was then concentrated to dryness, the residue was solved in ethyl acetate, washed successively with a saturated ammonium chloride solution and water and then dried on Na_2SO_4. After solvent distillation the unprotected aldehydes were used without further purification in the Wittig reaction.

To a solution of the crude aldehyde (383 mg, 1.0 mmol) in dry THF (7.5 mL), was added dropwise under argon atmosphere a solution of (methoxycarbonylmethylene)-triphenylphosphorane (386 mg, 1.1 mmol) in dry THF (5.0 mL). The reaction mixture was stirred at room temperature until the starting material disappeared in TLC and then was poured into a cold ammonium chloride solution. The aqueous layer was extracted twice with ethyl acetate and washed with water. After removal of the solvent, the crude product was purified by chromatography on silica gel using hexane:ethyl acetate mixtures as the eluent.

3.4.1. (3α,4α)- and (3β,4β)-1-(1′,2′-Dideoxy-1′-methoxycarbonylmethylidene-3′,4′;5′,6′-di-*O*-isopropyl-idene-2′-D-glucosyl)-3-methoxy-4-(1-methylethenyl)-2-azetidinone (7a and 7b). Compound **7a**. Isolated in 83% yield from the free aldehyde (713 mg, 1.86 mmol) after 7 h stirring. $[\alpha]_D$=+52 (c=1, $CHCl_3$). IR: 1761, 1730, 1658, 1454, 1383, 1215, 1152, 1075, 916, 733 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.30, 1.33, 1.36, 1.40 (4s, 12H, $C(CH_3)_2$); 1.76 (s, 3H, H-7); 3.44 (s, 3H, OCH_3); 3.67 (dd, $J_{4',3'}$=7.9 Hz, $J_{4',5'}$=5.7 Hz, 1H, H-4′); 3.72 (s, 3H, CO_2CH_3); 3.87–4.03 (m, 2H, H-6′a, H-5′); 4.10 (dd, $J_{6'b,5'}$=5.6 Hz, $J_{6'b,6'a}$=7.6 Hz, 1H, H-6′b); 4.21 (dd, $J_{2',1'}$=8.3 Hz, $J_{2',3'}$=6.0 Hz, 1H, H-2′); 4.50 (d, $J_{4,3}$=4.2 Hz, 1H, H-4); 4.52–4.59 (m, 2H, H-3′, H-3); 5.10 (s, 1H, H-6a); 5.12 (s, 1H, H-6b); 6.09 (d, $J_{1'',1'}$=15.8 Hz, 1H, H-1″); 6.81 (dd, $J_{1',2'}$=8.3 Hz, $J_{1',1''}$=15.8 Hz, 1H, H-1′). ^{13}C NMR (50 MHz) δ (ppm): 18.9 (C-7); 25.2, 26.3, 27.4, 27.6 (4C, $C(CH_3)_2$); 51.6 (CO_2CH_3); 55.4 (C-2′); 58.8 (OCH_3); 64.2 (C-4); 67.6 (C-6′); 76.9 (C-5′); 79.4, 80.3 (3C, C-3′, C-4′); 84.9 (C-3); 110.1, 110.6 ($C(CH_3)_2$); 117.4 (C-6); 124.9 (C-1″); 141.0, 141.1 (C-5, C-1′); 165.8 (CO_2CH_3); 167.6 (C-2). MS (FAB) *m/z* (rel.int.): 440 (54), 382 (48), 143 (74), 98 (100). HRMS (FAB): calcd for $C_{22}H_{34}NO_8$ (M^++1) 440.2284; found 440.2301.

Compound **7b**. Isolated in 92% yield from the free aldehyde

(747 mg, 1.95 mmol) after 2 h stirring. $[\alpha]_D$=−41 (c=1, $CHCl_3$). IR: 1750, 1735, 1665, 1456, 1373, 1213, 1072, 847 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.23, 1.25, 1.27, 1.31 (4s, 12H, $C(CH_3)_2$); 1.72 (s, 3H, H_7); 3.38 (s, 3H, OCH_3); 3.64 (s, 3H, CO_2CH_3); 3.61 (dd, $J_{4',3'}$=8.1 Hz, $J_{4',5'}$=5.2 Hz, 1H, H-4′); 3.77 (dd, $J_{6'a,5'}$=5.0 Hz, $J_{6'a,6'b}$=8.0 Hz, 1H, H-6′a); 3.78–4.07 (m, 3H, H-5′, H-6′b, H-2′); 4.26 (d, $J_{4,3}$=4.9 Hz, 1H, H-4); 4.29 (dd, $J_{3',2'}$=5.7 Hz, $J_{3',4'}$=7.9 Hz, 1H, H-3′); 4.50 (d, $J_{3,4}$=4.9 Hz, 1H, H-3); 4.98 (s, 1H, H-6a); 5.04 (s, 1H, H-6b); 6.01 (d, $J_{1'',1'}$=15.8 Hz, 1H, H-1″); 7.10 (dd, $J_{1',2'}$=8.4 Hz, $J_{1',1''}$=15.8 Hz, 1H, H-1′). ^{13}C NMR (50 MHz) δ (ppm): 19.2 (C-7); 25.0, 26.1, 27.6 (4C, $C(CH_3)_2$); 51.4 (CO_2CH_3); 58.6 (OCH_3); 58.9 (C-2′); 64.9 (C-4); 67.4 (C-6′); 76.6, 79.7, 80.5 (3C, C-3′-5′); 84.8 (C-3); 109.8, 110.4 ($C(CH_3)_2$); 116.3 (C-6); 125.0 (C-1″); 140.2 (C-5); 140.4 (C-1′); 165.6 (CO_2CH_3); 166.7 (C-2). MS (FAB) m/z (rel. int.): 440 (50), 382 (14), 143 (98), 98 (100). HRMS (FAB): calcd for $C_{22}H_{34}NO_8$ (M^++1) 440.2284; found 440.2302.

3.5. Epoxyolefins 4

A solution of **7** (439 mg, 1.0 mmol) and *m*-CPBA (207 mg, 1.2 mmol) in dry dichloromethane (10.0 mL) was stirred under argon atmosphere at room temperature overnight. The reaction mixture was diluted in dichloromethane, washed with a solution of sodium bicarbonate and water, dried (Na_2SO_4) and evaporated to dryness. The crude products were purified by chromatography on silica gel with hexane:ethyl acetate mixtures as the eluent.

3.5.1. 4α-(1β)- and 4α-(1α)-1-(1′,2′-Dideoxy-1′-methoxycarbonyl-methylidene-3′,4′;5′,6′-di-*O*-isopropylidene-2-D-glucosyl)-3α-methoxy-4-(1,2-epoxy-1-methylethyl)-2-azetidinone (4aa and 4ab); 2β-[(2′,3′-*O*-isopropyliden)-D-*eritro*-1′,2′,3′-trihidroxy-propyl]-3β-[(*E*)-methoxycarbonylethenyl]-7β-hidroxy-methyl-6β-methoxy-7α-methyl-1-oxapirrolizidin-5-one (8). The epoxidation of **7a** (678 mg, 1.54 mmol) for 15 h gave the epoxyolefins **4aa** (210 mg, 30%) and **4ab** (196 mg, 28%). When the peroxyacid treatment was extended for 30 h, the reaction product was a mixture of the epoxides **4aa** and **4ab** (256 mg, 36%) and the γ-lactam **8** (287 mg, 45%).

Compound **4aa**. $[\alpha]_D$=+46 (c=1.1, $CHCl_3$). IR: 1759, 1732, 1437, 1375, 1217, 1152, 1071, 847 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.29, 1.33, 1.34, 1.36 (4s, 12H, $C(CH_3)_2$); 1.36 (s, 3H, H-7); 2.62 (d, $J_{6a,6b}$=4.5 Hz, 1H, H-6a); 2.87 (d, $J_{6b,6a}$=4.5 Hz, 1H, H-6b); 3.54 (s, 3H, OCH_3); 3.66 (dd, $J_{4',3'}$=8.1 Hz, $J_{4',5'}$=4.9 Hz, 1H, H-4′); 3.72 (s, 3H, CO_2CH_3); 3.87 (dd, $J_{6'a,5'}$=4.7 Hz, $J_{6'a,6'b}$=7.9 Hz, 1H, H-6′a); 3.92 (d, $J_{4,3}$=5.0 Hz, 1H, H-4); 3.93–4.01 (m, 2H, H-5′, H-2′); 4.10 (dd, $J_{6'b,5'}$=5.9 Hz, $J_{6'b,6'a}$=7.9 Hz, 1H, H-6′b); 4.40 (dd, $J_{3',2'}$=5.5 Hz, $J_{3',4'}$=8.1 Hz, 1H, H-3′); 4.57 (d, $J_{3,4}$=5.0 Hz, 1H, H-3); 6.10 (d, $J_{1'',1'}$=15.8 Hz, 1H, H-1″); 6.85 (dd, $J_{1',2'}$=8.4 Hz, $J_{1',1''}$=15.8 Hz, 1H, H-1′). ^{13}C NMR (50 MHz), δ (ppm): 18.2 (C-7); 25.0, 26.1, 27.5, 27.6 (4C, $C(CH_3)_2$); 51.6 (CO_2CH_3, C-6); 55.6 (C-5); 56.1 (C-2′); 59.1 (OCH_3); 61.4 (C-4); 67.3 (C-6′); 76.5 (C-5′); 78.9 (C-4′); 79.7 (C-3′); 83.4 (C-3); 109.9, 110.7 (2C, $C(CH_3)_2$); 125.1 (C-1″); 141.2 (C-1′); 165.6 (CO_2CH_3); 167.9 (C-2). HRMS (FAB): calcd for $C_{22}H_{34}NO_9$ (M^++1); 456.2234; found 456.2197.

Compound **4ab**. $[\alpha]_D$=+53 (c=1.2, $CHCl_3$). IR: 1759, 1730, 1437, 1383, 1219, 1155, 1071, 847 cm^{-1}. ^1H NMR (200 MHz), δ (ppm): 1.30, 1.33, 1.34, 1.36 (4s, 12H, $C(CH_3)_2$); 1.36 (s, 3H, H-7); 2.66 (d, $J_{6a,6b}$=4.5 Hz, 1H, H-6a); 2.79 (d, $J_{6b,6a}$=4.5 Hz, 1H, H-6b); 3.51 (s, 3H, OCH_3); 3.73 (dd, $J_{4',3'}$=7.6 Hz, $J_{4',5'}$=4.9 Hz, 1H, H-4′); 3.73 (s, 3H, CO_2CH_3); 3.89 (dd, $J_{6'a,5'}$=4.7 Hz, $J_{6'a,6'b}$=7.7 Hz, 1H, H-6′a); 3.92–4.10 (m, 2H, H-5′, H-2′); 4.32 (dd, $J_{3',2'}$=4.9 Hz, $J_{3',4'}$=7.6 Hz, 1H, H-3′); 4.41 (dd, $J_{6'b,5'}$=5.7 Hz, $J_{6'a,6'b}$=7.7 Hz, 1H, H-6′b); 4.52 (d, $J_{4,3}$=4.3 Hz, 1H, H-4); 4.58 (d, $J_{3,4}$=4.3 Hz, 1H, H-3); 6.15 (d, $J_{1'',1'}$=15.9 Hz, 1H, H-1″); 6.95 (dd, $J_{1',2'}$=7.9 Hz, $J_{1',1''}$=15.9 Hz, 1H, H-1′). ^{13}C NMR (50 MHz), δ (ppm): 17.6 (C-7); 25.2, 26.3, 27.4, 27.8 (4C, $C(CH_3)_2$); 51.6 (CO_2CH_3, C-6); 55.2 (C-5); 56.1 (C-2′); 59.1 (OCH_3); 65.0 (C-4); 67.5 (C-6′); 76.4 (C-5′); 79.3 (C-4′); 80.0 (C-3′); 83.4 (C-3); 110.0, 110.9 (2C, $C(CH_3)_2$); 125.7 (C-1″); 141.0 (C-1′); 165.8 (CO_2CH_3); 167.6 (C-2).

Compound **8**. $[\alpha]_D$=+37 (c=1.0, $CHCl_3$). IR: 3443, 1730, 1715, 1663, 1435, 1375, 1240, 883 cm^{-1}. ^1H (400 MHz), δ (ppm): 1.18 (s, 3H, H-10); 1.42, 1.43 (2s, 6H, $C(CH_3)_2$); 3.63 (s, 3H, OCH_3); 3.68 (d, $J_{9a,9b}$=10.6 Hz, 1H, H-9a); 3.74 (s, 3H, CO_2CH_3); 3.71–3.77 (m, 2H, H-2′, H-3′a); 3.82 (s, 1H, H-6); 3.81–3.85 (m, 1H, H-3′b); 3.92 (dd, $J_{2,3}$=8.9 Hz, $J_{2,1'}$=9.3 Hz, 1H, H-2); 4.10 (d, $J_{9b,9a}$= 4.3 Hz, 1H, H-9b); 4.08–4.12 (dd, $J_{1',2}$=9.3 Hz, $J_{1',2'}$= 5.3 Hz, 1H, H-1′); 4.84 (s, 1H, H-8); 5.31–5.34 (m, 1H, H-3′); 5.91 (dd, $J_{2'',1''}$=16.1 Hz, $J_{2'',3}$=2.3 Hz, 1H, H-2″); 7.14 (dd, $J_{1'',3}$=3.7 Hz, $J_{1'',2''}$=16.1 Hz, 1H, H-1″). ^{13}C NMR (100 MHz), δ (ppm): 16.0 (C-10); 26.7, 27.0 (2C, $C(CH_3)_2$); 47.4 (C-7); 49.2 (C-3′); 51.8 (CO_2CH_3); 60.0 (OCH_3); 62.3 (C-3′); 65.7 (C-9); 74.0 (C-2); 77.5 (C-2′); 77.7 (C-1′); 80.5 (C-6); 85.7 (C-8); 111.9 ($C(CH_3)_2$); 123.4 (C-2″); 140.6 (C-1″); 165.9 (CO_2CH_3); 173.4 (C-5). MS (FAB) m/z (rel. int.): 416 (M^++2, 8), 307 (11), 154 (100), 105 (41).

3.5.2. 4β-(1β) and 4β-(1α)-1-(1′,2′-Dideoxy-1-methoxycarbonylmethylidene-3′,4′;5′,6′-di-*O*-isopropylidene-2-D-glucosyl)-4-(1α,2-epoxy-1β-methylethyl)-3β-methoxy-2-azetidinone (4ba and 4bb). The epoxidation of **7b** (1300 mg, 3.0 mmol) for 15 h gave **4ba** (656 mg, 48%) and **4bb** (478 mg, 35%).

Compound **4ba**. $[\alpha]_D$=−31 (c=1.2, $CHCl_3$). IR: 1759, 1730, 1663, 1454, 1373, 1215, 1071, 847 cm^{-1}. ^1H NMR (400 MHz), δ (ppm): 1.30, 1.31, 1.34, 1.35 (4s, 12H, $C(CH_3)_2$); 1.41 (s, 3H, H-7); 2.62 (d, $J_{6a,6b}$=4.3 Hz, 1H, H-6a); 2.91 (d, $J_{6b,6a}$=4.3 Hz, 1H, H-6b); 3.55 (s, 3H, OCH_3); 3.63 (dd, $J_{4',3'}$=5.4 Hz, $J_{4',5'}$=8.4 Hz, 1H, H-4′); 3.72 (s, 3H, CO_2CH_3); 3.84 (dd, $J_{6'a,5'}$=5.7 Hz, $J_{6'a,6'b}$=8.5 Hz, 1H, H-6′a); 3.96 (d, $J_{4,3}$=5.1 Hz, 1H, H-4); 3.97 (ddd, $J_{5',4'}$=8.4 Hz, $J_{5',6'a}$=5.7 Hz, $J_{5',6'b}$=6.3 Hz, 1H, H-5′); 4.06 (ddd, $J_{2',1'}$=8.7 Hz, $J_{2',3'}$=8.8 Hz, $J_{2',1''}$=0.8 Hz, H, H-2′); 4.09 (dd, $J_{6'b,5'}$=6.3 Hz, $J_{6'b,6'a}$=8.4 Hz, 1H, H-6′b); 4.41 (dd, $J_{3',2'}$=8.8 Hz, $J_{3',4'}$=5.4 Hz, 1H, H-3′); 4.54 (d, $J_{3,4}$=5.1 Hz, 1H, H-3); 6.05 (d, $J_{1'',1'}$=15.8 Hz, 1H, H-1″); 7.05 (dd, $J_{1',2'}$=8.7 Hz, $J_{1',1''}$=15.8 Hz, 1H, H-1′). ^{13}C NMR (100 MHz), δ (ppm): 19.0 (C-7); 25.1, 26.2, 27.8 (4C, $C(CH_3)_2$); 50.6 (C-6); 51.6 (CO_2CH_3); 56.5 (C-5); 59.1 (OCH_3); 59.5 (C-2′); 61.1 (C-4); 67.4 (C-6′); 76.5 (C-5′); 79.9 (C-4′); 80.2 (C-3′); 82.9 (C-3); 109.9, 110.6 (2C,

$C(CH_3)_2$); 125.3 (C-1″); 140.3 (C-1′); 165.8 (CO_2CH_3); 167.2 (C-2). MS (FAB) *m/z* (rel. int.): 456 (28), 398 (22), 307 (24), 154 (100), 83 (70). HRMS (FAB): calcd for $C_{22}H_{34}NO_9$ (M^++1): 456.2234; found 456.2253.

Compound **4bb**. $[\alpha]_D$=−42 (*c*=1.2, $CHCl_3$). IR: 1761, 1728, 1440, 1373, 1217, 1152, 1071, 847 cm^{-1}. ^1H NMR (400 MHz), δ (ppm): 1.31, 1.33, 1.35 (3s, 12H, $C(CH_3)_2$); 1.43 (s, 3H, H-7); 2.61 (d, $J_{6a,6b}$=4.3 Hz, 1H, H-6a); 2.75 (d, $J_{6b,6a}$=4.3 Hz, 1H, H-6b); 3.36 (d, $J_{4,3}$=5.2 Hz, 1H, H-4); 3.51 (s, 3H, OCH_3); 3.71 (dd, $J_{4',3'}$=5.2 Hz, $J_{4',5'}$=8.4 Hz, 1H, $H_{4'}$); 3.72 (s, 3H, CO_2CH_3); 3.87 (dd, $J_{6'a,5'}$=5.6 Hz, $J_{6'a,6'b}$=8.4 Hz, 1H, H-6′a); 4.02 (dt, $J_{5',6'a}$=$J_{5',6'b}$=5.6 Hz, $J_{5',4'}$=8.4 Hz, 1H, H-5′); 4.11 (dd, $J_{6'b,5'}$=5.6 Hz, $J_{6'b,6'a}$=8.4 Hz, 1H, H-6′b); 4.16 (ddd, $J_{2',1'}$=8.4 Hz, $J_{2',3'}$=8.8 Hz, $J_{2',1''}$=0.8 Hz, 1H, H-2′); 4.46 (dd, $J_{3',2'}$= 8.8 Hz, $J_{3',4'}$=5.2 Hz, 1H, H-3′); 4.51 (d, $J_{3,4}$=5.2 Hz, 1H, H-3); 6.10 (dd, $J_{1'',1'}$=15.8 Hz, $J_{1'',2'}$=0.8 Hz, 1H, H-1″); 7.10 (dd, $J_{1',2'}$=8.4 Hz, $J_{1',1''}$=15.8 Hz, 1H, H-1′). ^{13}C (100 MHz), δ (ppm): 17.5 (C-7); 25.1, 26.2, 27.7, 27.8 (4C, $C(CH_3)_2$); 51.0 (C-6); 51.6 (CO_2CH_3); 55.3 (C-5); 59.1 (C-2′); 59.2 (OCH_3); 65.5 (C-4); 67.4 (C-6′); 77.0 (C-5′); 79.8 (C-3′); 80.0 (C-4′); 83.2 (C-3); 109.9, 110.7 (2C, $C(CH_3)_2$); 125.5 (C-1″); 140.1 (C-1′); 165.8 (CO_2CH_3); 166.9 (C-2). HRMS (FAB): calcd for $C_{22}H_{34}NO_9$ (M^++1): 456.2234; found 456.2237.

3.6. Reductive cyclization of the epoxides 4

A solution of epoxide (455 mg, 1.0 mmol) in THF (10.0 mL) was added dropwise to a solution of bis(cyclopentadienyl) titanium monochloride (548 mg, 2.2 mmol) in dry THF (22.0 mL). The reaction was quenched after the suitable reaction time with KH_2PO_4 (30.0 mL) and worked up as usual. The reaction products (Table 1) were purified by column chromatography on silica gel with hexane:ethyl acetate mixtures as the eluent.

3.6.1. β-[(1′,2′;3′,4′-Di-*O*-isopropyliden)-D-arabino-1′,2′,3′,4′-tetrahidroxybutyl]-4-hidroxymethyl-6α-methoxy-3-methoxycarbonylmethyl-4-methyl-5βH-carbapenam (1a). Isolated in 35% yield after reaction for 2 h from a 1.7:1 mixture of **4aa**+**4ab** (210 mg, 0.46 mmol). IR: 3488, 1740, 1439, 1373, 1213, 1159, 1067, 847 cm^{-1}. ^1H NMR (400 MHz), δ (ppm): 0.93 (s, 3H, H-9); 1.33, 1.34, 1.35, 1.37 (4s, 12H, $C(CH_3)_2$); 2.41 (dd, $J_{1''a,1''b}$=15.4 Hz, $J_{1''a,3}$=4.0 Hz, 1H, H-1″a); 2.52 (dd, $J_{1''b,1''a}$=15.4 Hz, $J_{1''b,3}$=7.1 Hz, 1H, H-1″b); 3.10 (dt, $J_{3,2}$=$J_{3,1''b}$=7.1 Hz, $J_{3,1''a}$=4.0 Hz, 1H, H-3); 3.50 (s, 3H, CO_2CH_3); 3.71 (s, 3H, OCH_3); 3.70–4.24 (m, 8H, H-2, H-5, H-9, H-2′, H-3′, H-4′); 4.65 (d, $J_{6,5}$=4.6 Hz, 1H, H-6).

3.6.2. β-[(1′,2′;3′,4′-Di-*O*-isopropylidene)-D-arabino-1′,2′,3′,4′-tetrahidroxybutyl]-4β-hidroxymethyl-6β-methoxy-3β-methoxycarbonylmethyl-4α-methyl-5αH-carbapenam (1b). Isolated in 18% yield after reaction for 2 h from a 2:1 mixture of **4ba**+**4bb** (300 mg, 0.66 mmol) and also in 17% yield, from pure **4ba** (340 mg, 0.75%) and in 16% yield from **4bb** (220 mg, 0.48 mmol). IR: 3486, 1745, 1439, 1373, 1213, 1159, 1067, 847 cm^{-1}. ^1H NMR (200 Hz), δ (ppm): 1.03 (s, 3H, H-9); 1.32, 1.36, 1.40 (3s, 12H, $C(CH_3)_2$); 2.31 (dd, $J_{1''a,1''b}$=15.5 Hz, $J_{1''a,3}$=3.9 Hz, 1H, H-1″a); 2.47 (dd, $J_{1''b,1''a}$=15.5 Hz, $J_{1'',3}$=7.0 Hz, 1H, H-1″b); 2.95–3.10 (m, 1H, H-3); 3.56 (s, 3H, CO_2CH_3); 3.68 (s, 3H, OCH_3); 3.68–3.82 (m, 3H, H-2′, H-5, H-2); 3.88–4.19 (m, 5H, H-8, H-3′, H-4′); 4.21–4.34 (m, 2H, H-1′, H-6).

3.6.3. β-[(1′,2′;3′,4′-Di-*O*-isopropyliden)-D-arabino-1′,2′,3′,4′-tetrahidroxybutyl]-10β-methoxy-8α-methyl-6-oxa-5-oxo-3αH-9αH-tribactam (3b). Isolated in 3 and 32% yield after a reaction time of 2 and 16 h, respectively, from a 2:1 mixture of **4ba**+**4bb** (300 mg, 0.66 mmol). Also isolated in 8% yield from **4ba** (340 mg, 0.75 mmol) after a reaction time of 2 h, in 28% yield from **4ba**, (200 mg, 0.44 mmol) after 15 h, and in 32% yield from **4bb** (90 mg, 0.22 mmol) after a reaction time of 22 h. $[\alpha]_D$=−19 (*c*=0.5, $CHCl_3$). IR: 1755, 1454, 13811219, 1155, 1067, 845 cm^{-1}. ^1H NMR (400 MHz), δ (ppm): 1.32 (s, 3H, H-12); 1.32, 1.35, 1.37 (3s, 12H, $C(CH_3)_2$); 2.46 (dd, $J_{4a,4b}$=15.6 Hz, $J_{4a,3}$=4.2 Hz, 1H, H-4a); 2.66 (dd, $J_{4b,4a}$=15.6 Hz, $J_{4b,3}$=7.3 Hz, 1H, H-8b); 2.82–2.87 (m, 1H, H-3); 3.41 (dd, $J_{2,3}$=5.8 Hz, $J_{2,1'}$=6.5 Hz, 1H, H-2); 3.50 (s, 3H, OCH_3); 3.76 (d, $J_{9,10}$=4.5 Hz, 1H, H-9); 3.93 (dd, $J_{4'a,3'}$=4.9 Hz, $J_{4'a,4'b}$=8.5 Hz, 1H, H-4′a); 3.98–4.04 (m, 2H, H-2′, H-3′); 4.07 (d, $J_{7a,7b}$=11.8 Hz, 1H, H-7a); 4.15 (dd, $J_{4'b,3'}$=5.6 Hz, $J_{4'b,4'a}$=8.5 Hz, 1H, H-4′b); 4.22 (d, $J_{7b,7a}$=11.8 Hz, 1H, H-7b); 4.32 (dd, $J_{1',2'}$=5.7 Hz, $J_{1',2}$=6.5 Hz, 1H, H-1′); 4.67 (d, $J_{10,9}$=4.5 Hz, 1H, H-10). ^{13}C NMR (100 MHz), δ (ppm): 20.3 (C-12); 25.2, 26.4, 26.8, 26.9 (4C, $C(CH_3)_2$); 32.6 (C-4); 45.4 (C-8); 52.7 (C-3); 59.2 (OCH_3); 61.0 (C-9); 68.1 (C-4′); 68.2 (C-2); 73.7 (C-7); 77.4 (C-3′); 78.1 (C-1′); 79.2 (C-2′); 83.7 (C-10); 109.8 (2C, $C(CH_3)_2$); 169.1 (C-11); 171.2 (C-5). MS (FAB) *m/z* (rel. int.): 426 (M^+, 72), 340 (50), 256 (46), 136 (100), 77 (68). HRMS (FAB): calcd for $C_{21}H_{31}NO_8$ (M^+): 426.2128; found 426.2106.

3.6.4. *N*-[(1′,2′-Dideoxy-3′,4′;5′,6′-di-*O*-isopropylidene-1′-methoxycarbonylmethylidene)-D-2′-glucosyl]-3α-hidroxymethyl-4β-methoxy-3β-methylsuccinimide (11b). Isolated in 3 and 52% yield after a reaction time of 2 h and 16 h respectively from a 2:1 mixture of **4ba**+**4bb** (300 mg, 0.66 mmol). Also isolated in 8% yield from **4ba** (340 mg, 0.75 mmol) after a reaction time of 2 h, in 53% yield from **4ba** (200 mg, 0.44 mmol) after 15 h, and in 44% yield from **4bb** (90 mg, 0.22 mmol) after a reaction time of 22 h. $[\alpha]_D$=−31 (*c*=0.9, $CHCl_3$). IR: 3486, 1715, 1456, 1373, 1211, 1154, 1071, 847 cm^{-1}. ^1H NMR (400 MHz), δ (ppm): 1.13 (s, 3H, H-7); 1.33, 1.38 (2s, 12H, $C(CH_3)_2$); 2.38 (bs, 1H, O*H*); 3.53–3.59 (m, 1H, H-6a); 3.68 (s, 3H, OCH_3); 3.71 (s, 3H, CO_2CH_3); 3.79–3.84 (m, 1H, H-4′); 3.92 (dd, $J_{6'a,5'}$=5.2 Hz, $J_{6'a,6'b}$=8.5 Hz, 1H, $H_{6'a}$); 3.93–3.96 (m, 1H, H-6b); 4.05 (ddd, $J_{5',4'}$=8.5 Hz, $J_{5',6'a}$=5.2 Hz, $J_{5',6'b}$=6.3 Hz, 1H, H-5′); 4.13 (dd, $J_{6'b,5'}$=6.3 Hz, $J_{6'b,6'a}$=8.5 Hz, 1H, H-6′b); 4.21 (s, 1H, H-4); 4.79–4.81 (m, 2H, H-2′, H-3′); 5.98 (d, $J_{1'',1'}$=15.9 Hz, 1H, H-1″); 7.15 (ddd, $J_{1',2'}$=3.8 Hz, $J_{1',3'}$=3.0 Hz, $J_{1',1''}$=15.9 Hz, 1H, H-1′). ^{13}C NMR (100 MHz), δ (ppm): 13.6 (C-7); 25.1, 26.3, 27.6, 28.1 (4C, $C(CH_3)_2$); 51.3 (C-3); 51.6 (CO_2CH_3); 55.6 (C-2′); 60.1 (OCH_3); 65.9 (C-6); 67.4 (C-6′); 76.3 (C-5′); 76.9 (C-3′); 78.5 (C-4); 81.3 (C-4′); 110.0, 111.1 (2C, $C(CH_3)_2$); 125.1 (C-1″); 139.5 (C-1′); 165.7 (CO_2CH_3); 174.7 (C-2); 178.9 (C-5). MS (FAB) *m/z* (rel. int.): 471 (M^+, 9), 414 (40), 391 (20), 318 (18), 149 (90), 110 (68), 62 (100).

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References

1. (a) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Curie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernández, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1–12. (b) Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Patel, G. S.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491–6499.
2. (a) Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551–556. (b) Guthikonda, R. N.; Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7584–7585.
3. Tamburini, B.; Perboni, A.; Rossi, T.; Donati, D.; Andreotti, D.; Gaviraghi, G.; Carlesso R.; Bismara, C. Eur. Pat. Appl. EP0416953 (cl. C07D477/00), March 13, 1991; *Chem. Abstr.* **1992**, *116*, 235337t.
4. The numbering of the bi- and tricyclic β-lactams is given according to the I.U.P.A.C. rules (*Pure Appl. Chem.* **1995**, *67*, 1307).
5. Recent examples: (a) Hanessian, S.; Reddy, B. *Tetrahedron* **1999**, *55*, 3427–3443. (b) Alcaide, B.; Almendros, P. *Tetrahedron Lett.* **1999**, *40*, 1015–1018. (c) Alcaide, B.; Polanco, C.; Sierra, M.-A. *J. Org. Chem.* **1998**, *63*, 6786–6796. (d) Annibale, A. D.; Pesce, A.; Resta, S.; Trogolo, C. T. *Tetrahedron* **1997**, *53*, 13129–13138. (e) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M.-A. *J. Org. Chem.* **1996**, *61*, 7125–7132.
6. For a review on cyclization methodologies to prepare bicyclic (β-lactams, see: (a) Kant, J.; Walker, D. G.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*. Georg, G. I., Ed. Strategies for the Synthesis of Bicyclic β-Lactams; VCH: New York, 1993; pp 121–196. Recent examples to the synthesis of trinem derivatives: (b) Di Fabio, R.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *38*, 3587–3590. (c) Marchioro, C.; Pentassuglia, G.; Perboni, A.; Donati, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 463–468. (d) Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 9884–9891.
7. Martell, S. R.; Wisedale, R.; Gallager, T.; Hall, L. D.; Mahon, M. F.; Bradbury, R. H.; Hales, N. J. *J. Am. Chem. Soc.* **1997**, *119*, 2309–2310.
8. (a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, *16*, 2500–2520. (b) Li, J. J. *Tetrahedron* **2001**, *57*, 1–24. (c) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2778. (d) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607–609. (e) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859. (f) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
9. For reviews on [2+2] cycloaddition of imines and ketenes, see: (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *64*, 3223–3235. (b) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed. Estereocontrolled Ketene–Imine Cycloaddition Reactions. VCH: New York, 1993; pp 295–368.
10. (a) Anaya, J.; Gero, S. D.; Grande, M.; Hernando, J. I. M.; Laso, N. M. *Bioorg. Med. Chem.* **1999**, *7*, 837–850. (b) Anaya, J.; Barton, D. H. R.; Gero, S. D.; Grande, M.; Hernando, J. I. M.; Laso, N. M. *Tetrahedron: Asymmetry* **1995**, *6*, 609–624. (c) 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**, 3211–3212.
11. Chiaroni, A.; Riche, C.; Anaya, J.; Gateau-Olesker, A.; Gero, S. D.; Hernando, J. I. M. *Acta Crystallogr.* **1994**, *C50*, 1474–1480.
12. (a) Ruano, G. Ph.D. Thesis, Universidad de Salamanca, 2002. (b) Ruano, G.; Anaya, J.; Grande, M. *Synlett* **1999**, 1441–1443.
13. The preferred conformations for epoxides **4** were derived from the CS Chem3D Pro software (CambridgeSoft Corporation) using MM2 calculations.
14. For a similar rearrangement from 4-formyl-2-azetidinones reacting with concentrated sulfuric acid see: Alcaide, B.; Martín-Cantalejo, Y.; Rodríguez-López, J.; Sierra, M.-A. *J. Org. Chem.* **1993**, *58*, 4767–4770.
15. Anaya, J.; Barton, D. H. R.; Gero, S. D.; Grande, M.; Martín, N.; Tachdjian, C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 867–869.
16. Millership, J. S.; Collier, P. S.; Hamilton, J. T.; Mc Roberts, G. W. C; Mifsud, J. *Chirality* **1995**, *7*, 173–180.