Tetrahedron Vol. 47, No. 29, pp. 5379-5390, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

DIASTEREOSELECTIVE SYNTHESIS OF *bis*-beta-LACTAMS[1]

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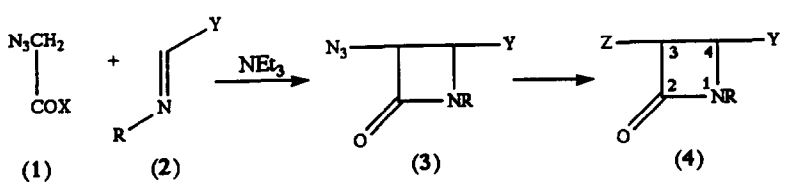
(*Received in USA* 8 *April* 1991)

Abstract: Schiff bases derived from (±)-4-aldehydo-2--azetidinones react with acid chlorides and triethylamine to produce (±)-*bis*-β-lactams in a diastereoselective fashion. The steric course of β-lactam formation was determined in one case by using chiral HPLC separation of enantiomers. Definitive evidence in support of this enantiospecific course of β-lactam formation was obtained from single crystal X-ray diffraction studies on a racemic *bis*-β-lactam.

Many important antibiotics are characterized by the presence of an α-amido-β-lactam (3-amido-2-azetidinone, **4b**) structural unit. A widely used method for the preparation of α-amino-β-lactams (**4a**) involves the cycloaddition reaction between an imino compound (e.g., **2**) and azidoacetyl chloride[2,3] (**1**) in presence of triethylamine and subsequent modification of the azido group of the 3-azido-2-azetidinone (**3**) so formed (Scheme 1).

Scheme 1



(1) (2) (3) (4)

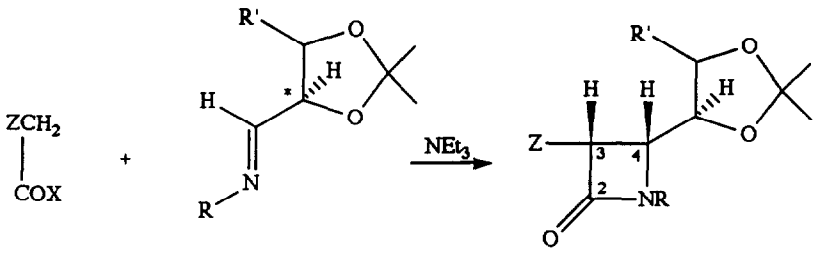
X = Cl or other leaving groups

(a) Z = NH_2
(b) Z = R'CONH

Independent work from two laboratories[4,5] has shown that the cyclization reaction between an acid chloride (e.g., **5**) and a Schiff base (**6**) derived from an achiral amine and an optically active aldehyde leads to the β-lactam (**7**) in a completely enantiospecific manner (Scheme 2).

We have found that the chirality of the carbinol carbon next to the imino group in (6) determines the absolute configuration at C4 of (7); the other chiral centers of the aldehyde from which (6) is derived do not seem to influence the induction of chirality.

Scheme 2

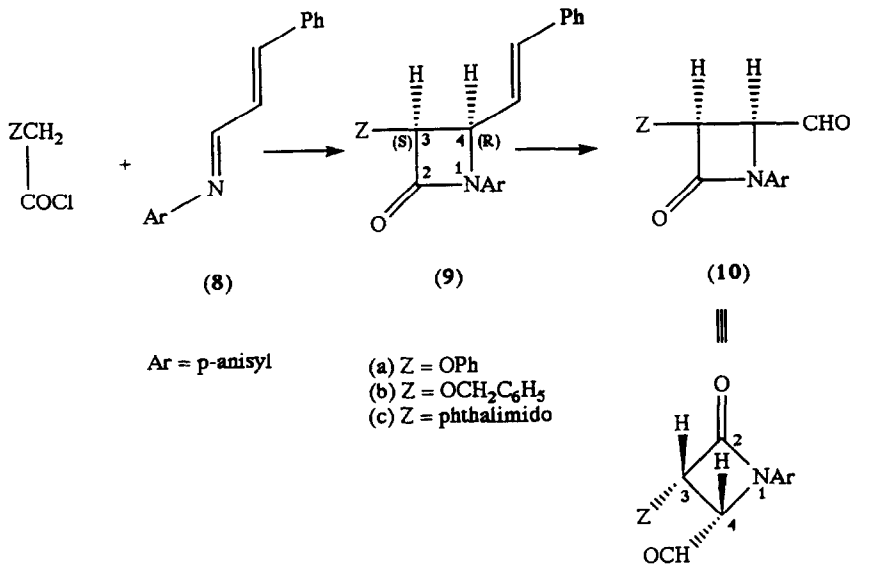


(5) (6) (7)

Diastereoselective Synthesis of β-lactams

In continuation of these studies[6] on the asymmetric synthesis of β-lactams, we have now examined Schiff bases (e.g., **11**) derived from aldehydes (**10**) in which the chiral center next to the imino group carries a nitrogen function in place of an oxygen function (Scheme 3). Several β-lactams of type (**9**) prepared from cinnamaldehyde - derived Schiff bases

Scheme 3



(8) (9) (10)

Ar = p-anisyl

(a) Z = OPh
(b) Z = $OCH_2C_6H_5$
(c) Z = phthalimido

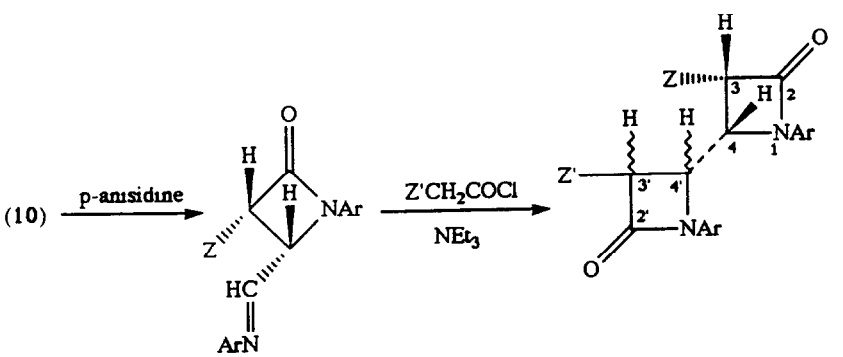
(**8**) were available in our laboratory in their racemic form. They were ozonized to aldehydes (**10**) and converted to racemic Schiff bases (**11**).

The reaction of (dl)-(**11**) with (**5**) and triethylamine led to the isolation of a single cis-*bis*-β-lactam (**12**) in each case that was investigated (Scheme 4). This β-lactam forming reaction, therefore, was highly diastereoselective. For establishing the nature of the new chiral center induced, a special strategy was developed.

Chiral HPLC Studies

By selecting Z=OPh for reactions in Schemes 3 and 4, (**12a**) was synthesized. This compund which could be meso or racemic in nature depending on the relative configuration of the hydrogen atoms at C-4 and C-4'. We hoped to determine whether (**12a**) was a meso (**14**) or a racemic compound (**13**) by high performance liquid chromatography (HPLC) using commercially available chiral columns. Separation of (**12a**) over such a column into two peaks of equal area would indicate that the analyte was a racemate. On the other hand, the failure to obtain two separate peaks could be ambiguous since it could indicate a meso compound or a racemate that was not resolved under the condition used.

Scheme 4



(a) Z = Z' = OPh
(b) Z = OCH_2Ph, Z' = OPh
(c) Z = Phthalimido, Z' = OCH_2Ph

The high degree of internal symmetry of (**12a**) is reflected in its spectral data. The ^{13}C NMR spectra shows peaks for only half the number of carbons in (**12**). The ^{1}H NMR spectra in $CDCl_3$ has a sharp singlet at 3.71 ppm integrating for 6 protons and two multiplets each corresponding

to 2 protons at 5.05 and 5.55 ppm. A decoupling of the peaks at 5.05 ppm causes the multiplet at 5.55 ppm to collapse to a sharp singlet with no other detectable effects on the spectrum. This indicates that the two sets of proton signals, one at 5.05 and the other at 5.55 ppm, are in fact C3, C3′ and C4, C4′, respectively. The infrared spectrum in chloroform solution shows a single carbonyl absorption at 1735 cm^{-1}. It was noted that this band showed low intensity inspite of the presence of two carbonyl groups.

An HPLC column with L-phenylglycine (obtained from Alltech. Associates Inc., Deerfield, IL) as the chiral stationary phase was selected on the basis of prior work by Pirkle et al.[7] This is a reverse phase column which requires the mobile phase to be nonaqueous and uses a Perkin-Elmer TriDet detector.

Our test sample (**12a**) was soluble in methylene chloride. Therefore, a modified methylene chloride phase was selected. Acetonitrile, methanol and heptane were investigated as potential modifiers. It was found that heptane produced higher resolution than acetonitrile but also had a longer retention time for the analyte. The optimum solvent system proved to be a 95:4:1 methylene chloride/heptane/methanol mixture which had a chromatographic resolution of 2.35 with retention time of less than four minutes. Temperature increase resulted in higher resolution but lower selectivity. The temperature of 24°C was found to be optimum. With a reasonably slow rate of flow, near baseline resolution of two peaks of equal area was consistently observed. The compound (**12a**) was therefore a racemate corresponding to the stereostructure (**13**).

X-ray Diffraction Studies

The stereochemistry assigned to (**12a**) was confirmed by single crystal X-ray diffraction analysis.

Figure 1 shows conformation of the molecule and the numbering scheme adopted for the X-ray studies, and clearly confirms that **12a** is not meso but is an asymmetric molecule (**13**).

Crystal data for compound **12a**: $C_{32}H_{28}N_2O_6$, monoclinic space group $P2_1/c$ (no. 14), a=12.338(3), b=8.683(1), c=25.822(4)Å, β=97.99(2)°, V=2739(2) $Å^3$, Z=4, D_x=1.209 gcm^{-1}, μ(MoKα)=0.750 cm^{-1}. The crystal used for measurement was obtained from CH_2Cl_2 solution; size 0.5x0.4x0.2 mm^3 (cut from a larger plate). Atomic coordinates for compound (**12a**) have been deposited with the Cambridge Crystallographic Data Centre,

University Chemical Laboratory, Cambridge CB2 1EW, UK.

Structural Features: The molecule consists of two disubstituted planar β-lactam units bonded *via* the C4-C4′ bond and parallel to each other. Their N-atoms are substituted by p-anisyl groups which are twisted 32.3(4) and 25.4(4)° from the least-squares plane of the appropriate β-lactam ring. These phenyl rings are almost coplanar, with the angle between their least-squares planes equal to 13.6(7)°. The OPh groups located at C3 and C3′ atoms are turned in opposite directions with respect to the β-lactam ring planes. The phenyl rings are almost coplanar and are twisted by 130.6(2) and 135.4(2)° from the appropriate 4-membered ring planes. Although oxygen atoms in the above groups are *trans* located, their interatomic distance of 3.050(8)Å remains one of the shortest nonbonding distances in the whole molecule.

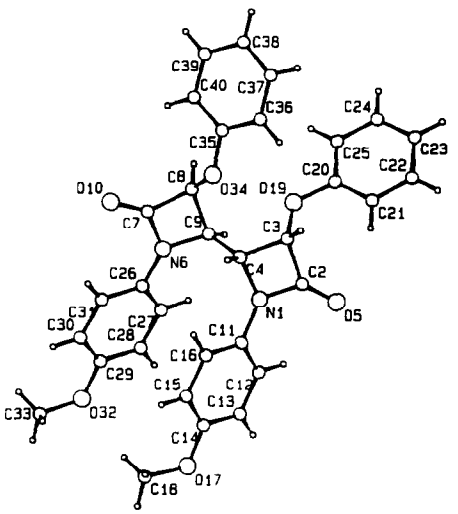


Fig. 1. PLUTO-diagram of **12a**.

The H-atoms on the β-lactam ring were shown to be located *cis* within each ring but *trans* with respect to the C4-C4′ bond. *Cis* configuration at the C3-C4 bond is confirmed by the values of O19-C3-C4-C9 and O34-C8-C9-C4 torsion angles which are 2.3(7) and 8.6(6)°, respectively.

No particular differences were found between the geometry of the compound under study and the geometry of the other molecules containing the β-lactam moiety as described in the published literature.

The PLUTO diagram shows that the carbonyl groups of the two β-lactam rings in (**12a**) are aligned with their dipoles opposing each other.

Steric Course of Cycloaddition

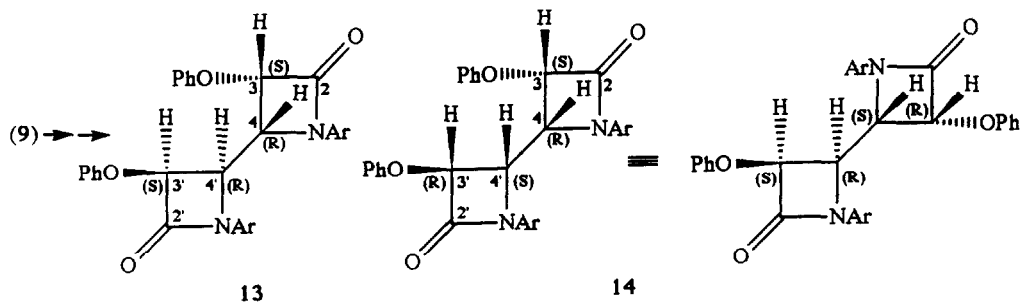
During the reactions that transform the starting cis mono-β-lactam (**9**) to the *bis*-β-lactam (**12**) (with *cis* stereochemistry), there is no opportunity for C-3 of the mono-β-lactam to undergo any modification. C-3 can therefore serve as a point of reference for correlating the configuration of the related molecules (**9a**) and (**12a**). The cis stereochemistry of both β-lactam moieties of (**12**) indicates the absence of epimerization either at the aldehyde stage or the imino stage or later, because epimerization would favor the thermodynamically more stable trans structures.

The chirality induced during the formation of the second β-lactam can now be deduced unequivocally even though the PLUTO diagram provides only the relative configuration of various substituents in (**12a**). By selecting the enantiomer of (**9a**) with the S absolute configuration at C-3 we arrive at the absolute configuration shown by (**13**) for the *bis*-β-lactam on the basis of information from the PLUTO diagram. Now we are in a position to predict the absolute configuration of the other *bis*-β-lactams based on the absolute configuration of the starting mono β-lactam.

Conclusions

The mechanism of β-lactam formation by the acid chloride-imine--triethylamine method is far from established. Nevertheless, an empirical relationship based on experimental observations can be stated in terms of the stereostructures shown in Scheme 5.

Scheme 5



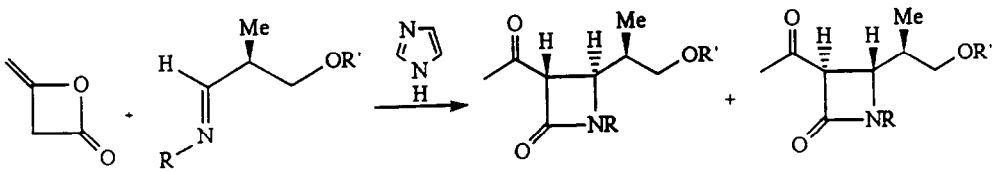
13 14

Ar = p-amsyl

The heteroatom on the chiral carbon next to the imino group appears to play a key role in selecting the steric course of formation of (7) and (12). It is important to note that this relationship is the same whether this chiral carbon carries an oxygen function (Scheme 2) or a nitrogen function (Scheme 5).

Ito and coworkers[8] have reported that the imine which lacks such a hetero atom produces β-lactams with variable diastereoselectivity (Scheme 6).

Scheme 6



Variously substituted β-lactams can serve as synthons for optically active sugars, alkaloids and other types of heterocycles.[9] Enantiospecific methods, such as the present one, for the formation of β-lactams with predictable absolute configuration are therefore of far-reaching importance.

EXPERIMENTAL SECTION

MATERIALS. All the chemicals used were reagent grade. The methylene chloride was distilled in the presence of phosphorous pentoxide and kept over molecular sieves. Flash chromatographic solvents were undistilled and reagent grade. High Performance Liquid Chromatographic solvents were HPLC grade. Spectroscopic data were obtained using a Bruker NR/200 FTNMR, Perkin-Elmer 1310 Infrared Spectrometer, a Perkin-Elmer 1760 Infrared Fourier Transform Spectrometer, Scientific Research Instruments Biospect and Kratos MS25 mass spectrometers.

Data Collection: 4802 intensities were collected on an Enraf-Nonius CAD4 difractometer in $\theta/2\theta$ mode using monochromatized MoKα radiation. Intensities were corrected for fluctuation of intensity of standard reflections, polarization, and semiempirical spherical absorption factors; 1737 unique reflections with $F>2\sigma(F)$ were used for structure solution and refinement.

Structure solution and refinement: The structure was solved by direct methods (MULTAN) and subsequent Fourier series. H-atom positions were calculated or found from the $\Delta\rho$ maps, and included into structure factor calculations. The refinement converged for all non-H atoms with an isotropic temperature factors and the four β-lactam ring H-atoms with R-factor 0.0516 and R_w =0.0601 [weight w = $1/[\sigma(F)^2 + (0.02F)^2 + 1]$, where σ is derived from counting statistics. Final shift/error < 0.10. No electron density fluctuation above 0.27 e/Å^3 was found on the final $\Delta\rho$ maps. All calculations were done using the SDP system implemented on a Microvax II computer. The refined atomic coordinates bond lengths and selected bond angles have been deposited at the Cambridge Data Centre.

N-Cinnamylidene-p-anisidine (8):

Cinnamaldehyde (31 ml, 0.22 mol) was added to a mixture of p-anisidine (24 g, 0.2 mol) and molecular sieves in dry chloroform and stirred for 6 hr at room temperature. After filtration and removal of the solvent under reduced pressure N-cinnamylidene- p-anisidine (8) was obtained as a yellowish solid, mp 116-119°; IR(nujol): 1610, 1580, 1510 cm^{-1}.

General Synthesis of β-Lactams

The Schiff base (0.045 mol) was dissolved in dry methylene chloride and triethylamine (0.135 mol) was added to it and the solution was cooled to 0°C . A solution of the acid chloride (0.045 mol) in methylene chloride was added dropwise with constant stirring over a period of 1 hr. The reaction mixture was then allowed to come to room temperature and stirred overnight. It was then successively washed with water, cold 1N HCl, water, dried (Na_2SO_4) and concentrated under reduced pressure. Filtration of the concentrated solution over Florisil followed by crystallization with an appropriate solvent gave the pure β-lactam.

Cis-1-(p-anisyl)-3-phenoxy-4-styrylazetidin-2-one (9a):

This β-lactam was prepared from phenoxyacetyl chloride and the Schiff base derived from cinnamaldehyde and p-anisidine in 82% yield, m.p. 174-175°.

IR(nujol): 1740, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ: 7.5-6.8(m, 14H), 6.3(dd, J_1 = 7.7 and J_2 = 16 Hz, 1H), 5.9(d, J = 4.9 Hz, 1H), 4.9(dd, J_1 = 4.9 Hz and J_2 = 5.7 Hz, 1H), 3.8(s, 3H); ^{13}C-NMR($CDCl_3$)ppm: 162, 157, 156, 136.9, 135.8, 130.9, 129.5, 128.6, 128.3; CIMS (NH_3 reagent gas) m/z:

397$(M + NH_4)^+$.

Cis-1-p-methoxyphenyl-3-benzyloxy-4-styrylazetidin-2-one (**9b**):

The title compound (4.44g, 27%) was obtained from 10g of the Schiff base (**8**) and 5.78 ml of benzyloxyacetyl chloride, mp 153-155°: IR($CHCl_3$): 3000, 2720, 1730, 1500, 1210, 760cm^{-1}; ^{1}H-NMR ($CDCl_3$)δ :3.75(s, 3H), 4.75(m, 3H), 4.93(d, 1H, J = 4.88 Hz), 6.34(dd, 1H), 6.82(m, 3H), 7.45(m, 12H); CIMS (CH_4, NH_3, 150°C): 386 $(M+H)^+$, 403 $(M+NH_4)^+$.

Cis-1-p-methoxyphenyl-3-phthalimido-4-styrylazetidin-2-one (**9c**):

This β-lactam was obtained from phthalimidoacetyl chloride and (**8**), mp 182-185°C, IR (Nujol): 2840, 1690, 1435, 1360 cm^{-1}: ^{1}H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 5.03(dd, 1H), 5.70(d, 1H, J = 5.37 Hz), 6.32 (dd, 1H), 6.70 -8.10(m, 13H); CIMS(Isobutane, 275-300°C): 425 $(M+H)^+$, 276, 238, 148, 129.

1-p-Methoxyphenyl-3-phenoxy-4-[1'-p-methoxyphenyl-3'-phenoxyazetidin--2'-one-4'-yl]-azetidin-2-one (**12a**):

1-p-Methoxyphenyl-3-phenoxy-4-styrylazetidin-2-one (**9a**) (1.0 g, 0.0027 mol) was dissolved in 125 ml of dry methylene chloride and cooled to -78°C. Ozone was bubbled through this solution for approximately 15 min, until a faint blue color appeared. The reaction mixture was subsequently saturated with oxygen followed by the addition of dimethyl sulfide (0.23 ml, 0.0041 mol), allowed to warm to room temperature and washed with water. The organic layer was dried (Na_2SO_4) filtered and concentrated under vacuum which gave the aldehyde (**10a**) as a brown-yellow oil.Without further purification the β-lactam adelhyde (**10a**) (0.80 g, 0.0027 mol) was dissolved in dry methylene chloride (100 mL), p-anisidine (0.58 g, 0.0052 mol) and molecular sieves were added and the reaction mixture was stirred at room temperature for 6 hr. The reactants were filtered and the filtrate concentrated under vacuum to afford the β-lactam Schiff base (**11a**) which was used for the next operation without further purification.

The β-lactam Schiff base (**11a**) (1.1 g, 0.0027 mol) was redissolved in dry methylene chloride with triethylamine (2.13 ml, 0.0162 mol) under nitrogen and cooled to 0°C. A 10 ml solution of phenoxyacetyl chloride (0.75 ml, 0.0054 mol) in dry methylene chloride was added dropwise over a 1 hr period . The reaction was then allowed to slowly come to room temperature and stirred overnight. It was then washed with water, cold 1N hydrochloric acid, water, dried (Na_2SO_4), filtered and concentrated under vacuum to get the cis-cis-*bis*-β-lactam (**12a**) in about 4% yeld which

was crystallized out of ethyl acetate and hexane, mp 245-246°C, IR (Nujol): 2870, 1735, 1450, 1370 cm^{-1}; ^1H-NMR ($CDCl_3$) δ:3.71 (s, 6H), 5.05(m, 2H), 5.55 (m, 2H), 6.22 (m, 4H), 7.10 (m, 10H), 7.34 (dd, 4H): ^{13}C NMR ($CDCl_3$) δ:-0.106, 55.280, 56.156, 76.276, 76.912, 77.547, 80.496, 113.825, 115.965, 119.186, 122.863, 129.674, 129.900, 156.583, 157.141, 162.826; CIMS (CH_4, NH_3, 175°C): 554$(M+NH_4)^+$, 535$(M-H)^-$, 571$(M+Cl)^-$.

Anal. Calc. for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.22; N, 5.22. Found C, 71.42; H, 5.39; N, 5.17.

1-p-Methoxyphenyl-3-benzyloxy-4-[1'-p-methoxyphenyl-3'-phenoxyazetidin--2'-one-4'-yl]-azetidin-2-one (**12b**):

The β-lactam (**9b**) (1.0 g, 0.0026 mol) was dissolved in dry methylene chloride and cooled to -78°C. Ozone was bubbled through this solution for 15 min until a faint blue color appeared. The solution was then purged with oxygen followed by the slow dropwise addition of dimethyl sulfide (0.15 ml, 0.0026 mol). This solution was allowed to warm to room temperature, washed with water and concentrated under vacuum. The β-lactam aldehyde (**10b**) was recovered as an oil and used without further purification.

This aldehyde (0.0026 mol) was dissolved in dry methylene chloride (100 ml) and added directly to a solution of p-anisidine (0.0048 mol, 0.59g) and molecular sieves in dry methylene chloride (125 ml) and stirred for 4 hr. The reaction mixture was filtered and concentrated under vacuum. The β-lactam Schiff base (**11b**) was used in the following reaction without further purification.

The Schiff base β-lactam (**11b**) was redissolved in dry methylene chloride (200 ml). Triethylamine (0.0156 mol, 2.06 ml) was added to this solution followed by cooling under nitrogen to 0°C. A solution of phenoxyacetyl chloride (0.0052 mol 0.72 ml) in methylene chloride (50 ml) was added dropwise, under anhydrous conditions, to the β-lactam Schiff base solution over a 1 hr period. The reactants were stirred overnight, filtered, washed with water, cold 1N HCl, and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum. The *bis* β-lactam (**12b**) obtained in about 20% yield, was purified by flash chromatorgraphy using a silica gel column with hexane and ethyl acetate (4:1 hexane/ethyl acetate): mp. 151°C: IR (Nujol) 2880, 1730, 1450, 1370, 1245 cm^{-1}; ^1H NMR($CDCl_3$) δ:3.68(s, 3H), 3.69(s, 3H), 4.72(d, 1H, J = 11.43 Hz), 4.78-5.50 (m, 4H), 5.46 (d, 1H, J = 4.90 Hz), 6.53 (d, 4H, J = 8.98 Hz), 6.97-7.42 (m, 14H); ^{13}C NMR ($CDCl_3$) δ: 55.6, 56.5 , 56.8, 74.1, δ 76.4, 77.0, 77.8, 80.4, 81.6, 113.9, 115.8, 119.2, 119.4, 123.0, 128.2,

128.4, 129.0, 130.0, 130.1, 130.2, 136.8, 156.5, 156.7, 157.5 , 163.0, 165.0; CIMS (NH_3, 170°C, PCI): 568; CIMS (NH_3, 170°C, NCI): 585.

Anal. Calc. for $C_{33}H_{30}N_2O_6$: C, 72.00; H, 5.45; N, 5.09. Found: C, 71.75; H, 6.61; N, 5.06.

1-p-Methoxyphenyl-3-phthalimido-4-[1'-p-methoxyphenyl-3'-phenyl-azetidin-2'-one-4'-yl]-azetidin-2-one (**12c**):

The β-lactam (**9c**) (4 g, 0.0094 mol) was ozonized in three batches by dissolving in dry methylene chloride (50 ml) and cooling to -78°C. In each case after passing ozone the solution was saturated with oxygen. Methyl sulfide (2.9 mls, 0.05 mols) was added to each solution followed by gradual warming to room temperature. At this stage the three batches were combined. This reaction mixture was washed with water, dried (Na_2SO_4) and concentrated to a pale yellow oil under vacuum. The β-lactam aldehyde (**10c**) so obtained was used without further purification.

This β-lactam aldehyde (3.29 g, 0.0094 mol) was dissolved in a stirred solution of p-anisidine (2.31 g, 0.19 mol) in methylene chloride (200 ml) containing molecular sieves. After 4 hr the reactants were filtered and concentrated under vacuum to afford the Schiff Base (**11c**).

This β-lactam Schiff base (**11c**) (4.16 g, 0.0094 mol) was dissolved in methylene chloride (200 ml) containing triethylamine (7.5 ml, 0.056 mol) and cooled to 0°C under nitrogen. To this was added a solution of benzyloxyacetyl chloride (3 ml, 0.019 mol) in methylene chloride (50 ml). The addition was carried out with continuous stirring over a 1 hr period followed by a gradual warming of the reaction mixture to room temperature and stirred overnight, washed with water, cold 1N HCl, water, dried (Na_2SO_4), filtered and concentrated under vacuum. Flash chromatography with 3:1 hexane/ethyl acetate was used to recover the *bis* β-lactam (**12c** in about 45% yield). It was further purified by recrystallization from methylene chloride - hexane, mp 240°C; IR (Nujol) 2860, 1695, 1440, 1370, 1245 cm^{-1}: ^1H NMR ($CDCl_3$) δ: 3.68 (s, 6H), δ 4.58 (d, 1H, J = 6.3 Hz), 4.75-5.04 (m. 4H), 5.83 (d, 1H. J = 5.3 Hz), 6.44 -8.06 (17H); CIMS (NH_3, 160°C, PCI)m/z: 377: 360, 352, 335, 245, 228; (NH_3, 160°C, NCI) 436, 310, 262.

Anal. Calcd. for $C_{35}H_{29}N_3O_7$: C, 69.65; H, 4.80, N, 6.96. Found: C, 69.55; H, 4.68; N, 7.04.

Acknowledgement

We are grateful to the Stevens Institute of Technology and the Howard Hughes Medical Institute for the support of this research. We thank Dr. Z. Kaluza and K. Barakat for preparing one of the intermediates and Ashok Krishnaswami and Keiko Tabei for spectral data.

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