0.66 cm^3 of hexane, 20 h, room temperature.

1,3,5-Trichlorobenzene: 129 mg (0.71 mmol) of substrate, 49.5 mg (0.146 mmol) of $(Bu)_4N^+HSO_4^-$, 392 mg of 60% NaOD/D_2O, 0.4 cm^3 of hexane, 20 h, room temperature.

4-Bromochlorobenzene: 53 mg (0.28 mmol) of substrate, 23.5 mg (0.069 mmol) of $(Bu)_4N^+HSO_4^-$, 177 mg of 60% NaOD/D_2O, 0.25 cm^3 of hexane, 20 h, room temperature.

Autoxidation Experiments. Reaction conditions: 1.5 mmol of substrate, 0.3 mmol of $(Bu)_4N^+HSO_4^-$, 450 mg of 50% NaOH, 1.5 cm^3 of benzene, air, room temperature.

The reaction was carried out in an open vial with magnetic stirring as described previously. A sample was taken, evaporated, and dissolved in an acetone-d_6/CCl_4 mixture. The ^1H NMR spectrum of this solution was recorded. PLC was run on Kieselgel 60 F 254 (Merck), the product was extracted with methylene chloride, and the solvents were evaporated.

Autoxidation of Diphenylmethane (DPM) (3). Kinetic Studies. The kinetic studies were performed in an open round-bottomed flask (25 mL) with vigorous magnetic stirring. The organic layer (20 μL) was sampled with a syringe. The solvent was evaporated, and the sample was dissolved in acetone-d_6/CCl_4 (0.3 mL, 1:3) for ^1H NMR estimations. In order to obtain the rate constants, at least two runs were taken.

Reaction conditions: 1.61 g (9.6 mmol) of DPM, 1 mmol of PTC catalyst, 3.2 g of 50% aqueous NaOH w/w, 10 mL of toluene, 25 °C. The effect of the catalyst was studied at the following concentrations: 0.5, 0.75, and 1.0 mmol. The effect of substrate concentration was studied at 9.6, 4.8, and 2.4 mmol. The temperature effect was studied in a thermostated bath (±0.5 °C). Bubbling of oxygen was performed in a 25-cm^3 flask with side arms, one of which was stoppered with a septum stopper and the other connected to an oil trap. The air was first removed by evacuation, the oxygen was then introduced, and the reaction was started. The effect of an additional amount of catalyst was studied as follows: the first amount of catalyst added was 0.5 mmol and reacted for 150 min. After this period of time, a second portion of catalyst (0.5 mmol) was added and the reaction parameters were studied.

NMR Spectra. NMR spectra were recorded at 200.133 MHz and 300.133 MHz (for protons) with the aid of WP-200 and WH-300 NMR spectrometers, respectively (Bruker Physik). The field/frequency regulations were maintained by ^2H locking to internal standard acetone-d_6. The free induction decay (FID) signals were digitized and accumulated on an Aspect-2000 computer. The extent of exchange was determined from the relevant peak areas relative to an internal standard before and after reactions. In order to avoid saturation, a relaxation delay (RD) of 5 s was programmed. The acetone peak is taken as standard at 2.04 ppm. For benzylic hydrogens, benzo[*b*]thiophene (**9**), and benzo[*b*]furan (**8**), the aromatic nonexchangeable protons were taken as internal standards, while mesitylene was taken as standard for thiophene (**10**) and hexamethylbenzene for halobenzenes.

Carbon-13 NMR spectra were recorded at 50.46 MHz. The position of the exchanged protons was deduced from proton-decoupled spectra. The $^1J_{C-D}$ (as well as $^2J_{H-D}$) coupling constants allowed the assignment of the particular carbon whose protons were exchanged as well as the estimation of the degree of exchange.

Mass Spectroscopy. Electron-impact mass spectra were recorded on a Varian MAT 311 mass spectrometer. In those cases where the mass spectra were performed at low energies (13–20 eV), the ratio between singly and doubly exchanged molecules could be estimated.

Supplementary Material Available: Table VII reporting the ^1H and ^{13}C NMR and mass spectral data of the exchanged and oxidized products (4 pages). Ordering information is given on any current masthead page.

Preparation of 4-Unsubstituted β-Lactams from 4-Acetoxyazetidin-2-ones. A Formal Approach to Monobactams and Nocardicins[1]

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The synthesis of 4-unsubstituted azetidin-2-ones is described. Treatment of Schiff bases derived from α-methylcinnamaldehyde and amines with acetic acids in the presence of phenyl dichlorophosphate and triethylamine followed by ozonolysis of the resulting β-lactams afforded *cis*-4-acetyl β-lactams in good yields. Baeyer–Villiger oxidation of the latter gave the corresponding 4-acetoxy β-lactams, which upon treatment with a sixfold excess of a hydrosilane in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst afforded 4-unsubstituted azetidin-2-ones. Application of this methodology to Schiff bases derived from α-methylcinnamaldehyde and phenylglycine as well as protected *p*-hydroxyphenylglycine for the synthesis of (±)-3-aminonocardicinic acid is also described.

Since the discovery of the monobactam family **1** (Chart I) of monocyclic β-lactam antibiotics,[2] intense effort has been made to achieve their total synthesis.[3] Nocardicins **2**, discovered in 1976 by a group at Fujisawa laboratories,[4] are the first example of monocyclic β-lactams to exhibit high antibacterial activity.[5] The structural features of this

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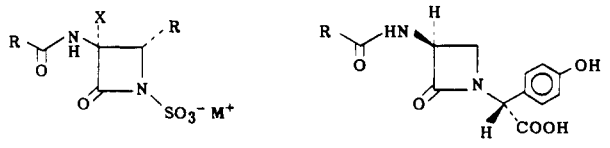
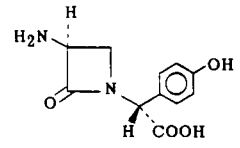
0022-3263/88/1953-3784$01.50/0

Chart I

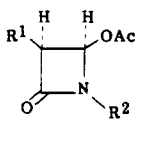


MONOBACTAMS 1

NOCARDICINS 2



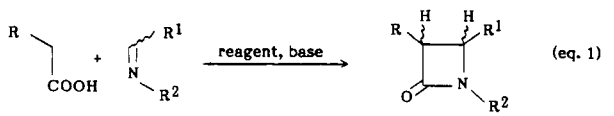
AMINO NOCARDICINIC ACID
3-ANA, 4



3

new type of β-lactams are (a) the absence of substituents at the C_4 position of the β-lactam ring, (b) the presence of diverse acylamino units at C_3, (c) the presence of the D-(−)*p*-hydroxyphenylacetic acid moiety at N_1, and (d) the relative stereochemistry at the C_3 and C′-N_1 positions.

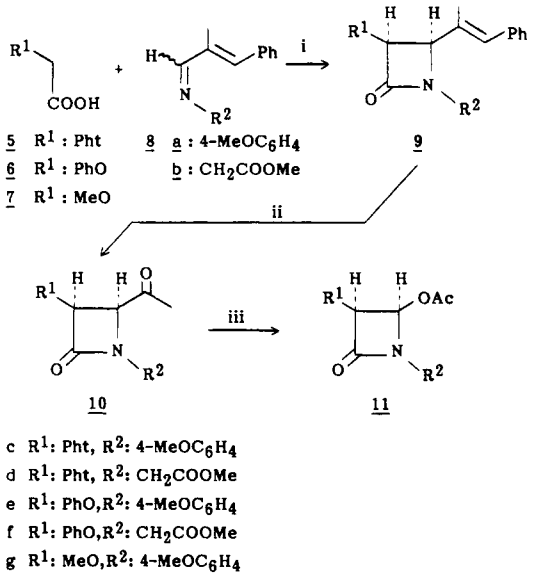
Among numerous methods for the synthesis of substituted monocyclic β-lactams,[6] the annelation of acid chlorides or equivalents with imines (a variant of the Staudinger reaction[7]) has proved to be a convenient procedure for the construction of the 2-azetidinone ring (eq 1). This



(eq. 1)

strategy is potentially quite versatile since the needed substrates, acetic acids and Schiff bases, are easily accessible, and therefore a number of β-lactams with latent functional groups at the three positions can be prepared. Although from this method the steric course of the β-lactam formation does not appear to be predictable, it can be controlled by the experimental conditions used[8] and by the choice of Schiff bases with bulky substituents.[9] The Fujisawa group[10] was the first to accomplish the total synthesis of nocardicins by this approach, but due to the inaccessibility of monomeric formaldehyde imines,[11] it has been necessary to develop new strategies for the preparation of monocyclic 4-unsubstituted-β-lactams.[12,13]

Scheme I[a]



5 R^1 : Pht
6 R^1 : PhO
7 R^1 : MeO

8 a : 4-$MeOC_6H_4$
b : CH_2COOMe

c R^1: Pht, R^2: 4-$MeOC_6H_4$
d R^1: Pht, R^2: CH_2COOMe
e R^1: PhO, R^2: 4-$MeOC_6H_4$
f R^1: PhO, R^2: CH_2COOMe
g R^1: MeO, R^2: 4-$MeOC_6H_4$

[a] Reagents and conditions: (i) $PhOP(O)Cl_2$, NEt_3, CH_2Cl_2, room temperature, 20–24 h; (ii) O_3, −78 °C, CH_2Cl_2, then Me_2S; (iii) *m*-chloroperbenzoic acid, C_6H_6, reflux.

4-Acetoxyazetidin-2-ones (**3**) are recognized as the most useful starting materials for synthetic work in β-lactam chemistry, because the acetoxy group can be replaced by a variety of nucleophiles.[14] Recently, we reported[15] a new methodology to convert 4-acetoxy β-lactams into 4-unsubstituted β-lactams by means of 1,1,3,3-tetramethyldisiloxane as hydride transfer agent and trimethylsilyl trifluoromethanesulfonate as catalyst. Herein we report experimental details that demonstrate the realization of this methodolgy as well as its application to the synthesis of (±)-3-aminonocardicinic acid (3-ANA (**4**)), which appears to be the general key intermediate in the synthesis of nocardicins.

Results and Discussion

Our intended strategy (Scheme I) involved first the synthesis of a precursor of type **9** with a 4-alkenyl substitutent as the latent carbonyl functionality and second, an ozonolysis–Baeyer–Villiger sequence to generate the required 4-acetoxy group. As a model for our work the synthesis of **10c** and **10d** was studied first. The starting materials, Schiff bases **8a,b**, were prepared by reaction of the corresponding amine and 2-methylcinnamaldehyde in refluxing methylene chloride. Compound **8a** was then treated with phthalimidoacetic acid and triethylamine followed by phenyl dichlorophosphate[16] to yield **9c** in 80%

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(12) For reviews, see: (a) Kamiya, T.; Aoki, H.; Mine, Y. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2, pp 165–226. (b) Cooper, R. D. G. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, 1980; Vol. 3, p 139. (c) Miller, M. *J. Acc. Chem. Res.* **1986**, *19*, 49. (d) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103.

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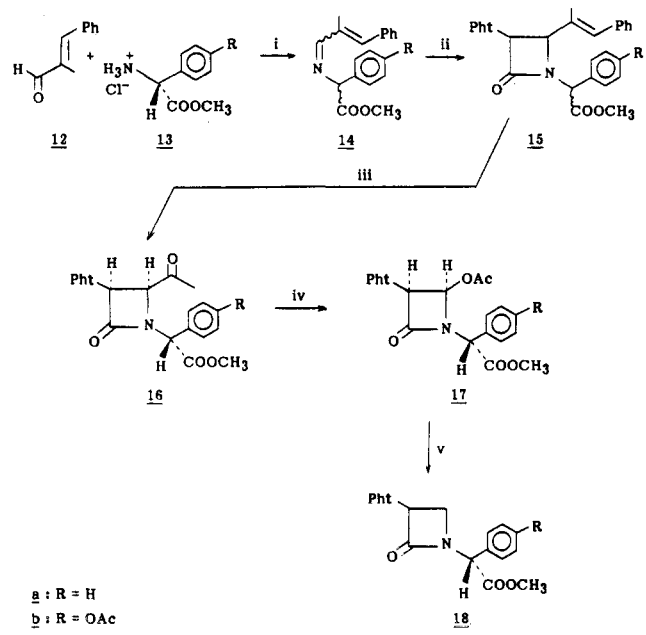
yield. Ozonolysis of **9c** with dimethyl sulfide workup[17] gave the expected methyl ketone **10c** in 80% yield. Compound **10c** could also be obtained in high yield from **9c** via permanganate oxidation of the double bond at room temperature in aqueous acetone–dioxane.[18] Although both methods were successful, the first one proved to be more convenient and gave better yields.

Similarly, treatment of Schiff base **8b** with phthalimidoacetic acid under the same conditions as those used for the preparation of **9d** followed by ozonolysis at low temperature yielded the expected *cis*-β-lactam **10d**. The magnetic nonequivalence of the two protons of the side chain adjacent to the nitrogen was as expected from the observations of Barrow and Spotswood on *N*-benzyl β-lactams,[19] and we will discuss this later. Plumet and coworkers[20] have reported the preparation of 4-benzoyl-substituted azetidin-2-ones from Schiff bases derived from phenylglyoxal; also a group of Farmitalia[21] have used this approach to synthesize a penem key intermediate. Attempts to apply this approach to the direct synthesis of 4-acetyl β-lactams were unsuccessful, probably due to the instability of Schiff bases derived from pyruvaldehyde.[22] As an extension of our procedure, β-lactams **10e–g** were prepared in yields in the range 80–86%. In all of these β-lactams the 5-Hz coupling constant between the C_3-H and the C_4-H protons was indicative of the cis stereochemistry.

Next we examined the Baeyer–Villiger oxidation[23] on 4-acetyl β-lactams **10**. First the reaction was tested from **10c** and **10d** and *m*-chloroperbenzoic acid (MCPBA) in methylene chloride at room temperature, but in both cases the reaction failed to produce any 4-acetoxy β-lactams. When **10c** was treated with an excess of MCPBA in refluxing methylene chloride for 5 h, **11c** was obtained in very low yield and the starting material was recovered unchanged. Of the solvents examined, 1,2-dichloroethane and benzene were the most satisfactory ones for carrying out the Baeyer–Villiger oxidation. Thus, treatment of **10c** with MCPBA in a molar ratio 1:4 in refluxing benzene for 2.5 h yielded a mixture of **10c** and **11c** in 50% of conversion. When this mixture was then treated with the same excess of MCPBA, complete conversion was achieved after 3 h of reflux, and the expected 4-acetoxy β-lactam **11c** was obtained in 56% yield as the only isolated product. Under similar conditions β-lactams **10e** and **10g** yielded the corresponding 4-acetoxy β-lactams **11e** and **11g** in 34% yield and 43% yield, respectively. When the Baeyer–Villiger oxidation was performed on **10d**, the reaction was faster than for **10c**, affording **11d** in 86% yield after 3 h in refluxing benzene. Similarly, **10f** upon treatment with MCPBA, molar ratio 1:4, respectively, afforded **11f** in 88% yield after 0.5 h of reaction. The relatively low yields of 4-acetoxy-*N*-*p*-methoxyphenyl β-lactams **11** could be attributed to the forceful reaction conditions needed to achieve a complete Baeyer–Villiger oxidation of the corresponding 4-acetyl-*N*-*p*-methoxyphenyl β-lactams **10**. Furthermore, the reaction took place with retention of configuration at C_3–C_4 as determined by the 5-Hz coupling constant between the C_3-H and C_4-H protons in all these 4-acetoxy β-lactams.

Scheme II[a]



[a] Reagents and conditions: (i) NEt_3, CH_2Cl_2, reflux; (ii) $PhtCH_2COOH$, NEt_3, $PhOP(O)Cl_2$, CH_2Cl_2, room temperature, 20–24 h; (iii) O_3, −70 °C, then Me_2S; (iv) MCPBA, Bz, reflux; (v) $HMe_2SiOSiMe_2H$, $F_3CSO_3SiMe_3$, $ClCH_2CH_2Cl$, reflux.

The established methodology was next extended to the preparation of 3-ANA. The initial target was the preparation of a monocyclic β-lactam of type **15**, followed by an ozonolysis–Baeyer–Villiger sequence as depicted in Scheme II. Thus, treatment of Schiff base **14a** derived from α-methylcinnamaldehyde (**12**) and D-phenylglycine methyl ester hydrochloride (**13a**) with 1 equiv of phthalimidoacetic acid in the presence of triethylamine and phenyl dichlorophosphate gave *N*-((methoxycarbonyl)phenylmethyl)-3-phthalimido-4-(α-methylstyryl)-2-azetidinone (**15a**) as an oil. Low-temperature (−70 °C) ozonolysis of **15a** gave methyl ketone **16a** in 60% yield as a 2:1 mixture of diastereomers, epimeric about the carboxyl group. The NMR spectrum of the mixture of the two isomers indicated that the phthalimido and styryl groups were cis to one another as shown by the coupling constants for the azetidinone ring (J = 5 Hz). No trace of the trans isomer could be detected by NMR spectroscopy.

Similarly, the Schiff base derived from D-*p*-hydroxyphenylglycine and α-methylcinnamaldehyde (**12**) was treated first with acetyl chloride and triethylamine to give Schiff base **14b**. Treatment of **14b** with triethylamine, phthalimidoacetic acid, and phenyl dichlorophosphate gave *cis*-*N*-((methoxycarbonyl)(4-methoxyphenyl)methyl)-3-phthalimido-4-(α-methylstyryl)-2-azetidinone (**15b**). Ozonolysis of the double bond in **15b** afforded **16b** in 45% overall yield from **14b**. Compound **16b** also was obtained as a 2:1 mixture of diastereomers about the α-carbomethoxy group. However, all compounds were optically inactive. Hakimelahi and Just[24] have found similar results in the preparation of β-lactams involving Schiff bases derived from D-phenylglycine methyl ester and cinnamaldehyde. They suggested that racemization takes place

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(24) Hakimelahi, G. H.; Just, G. *Can. J. Chem.* **1979**, *57*, 1932.

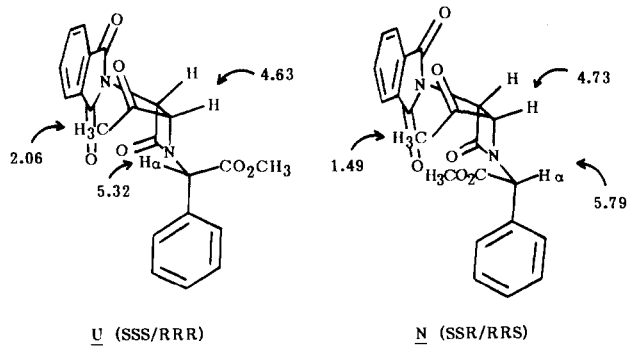
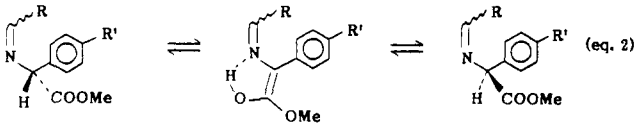


Figure 1. Significant ^1H NMR chemical shifts of U and N isomers of **16a**. The U and N notation refers to the relative stereochemistry of the unnatural and natural nocardicin,[24] respectively.

during the cycloaddition process, but we have found that Schiff bases of type **14** racemize during their formation as evidenced by the complete lack of optical rotation. According to Grigg's[25] observations (eq 2), racemization of



19

these Schiff bases could be attributed to an intermediate of type **19**. Since the chirality of the phenylglycine moiety is destroyed in the course of imine formation, it is not necessary to employ optically active phenylglycine as the starting material. Formation of β-lactam **16a** from phthalimidoacetic acid and the corresponding Schiff base, derived from DL-phenylglycine methyl ester hydrochloride and α-methylcinnamaldehyde, proceeds readily in good yield under the influence of phenyl dichlorophosphate and triethylamine.

At this stage we attempted to establish the relative stereochemistry of the carbomethoxy group in **16a** with respect to the β-lactam hydrogens. The NMR spectrum of compound **16a** showed signals at 1.49 and 2.06 ppm for the methyl protons of the ketone group and at 5.32 and 5.79 ppm for the benzylic protons adjacent to the nitrogen atom. Since our β-lactams are racemic mixtures, we have assigned the *SSR/RRS* configuration for the C_3-H, C_4-H, and N_1-C(CO_2Me)H protons, respectively, corresponding to the compound **16a**-N and the *SSS/RRR* configuration to compound **16a**-U. The structural assignment to N and U isomers rests on their H_α chemical shift parameters, according to Barrow and Spotswood's observations.[19] Thus, assuming that compound **16a** (Figure 1) is in its preferred conformation, the H_α proton cis to the acetyl substituent is shifted to higher field and the H_α protons trans to the substituent are shifted to lower field. The proton directly attached to the ring carbon carrying the substituent also shows a shift to lower field. Similarly, compound **16b** showed signals at 5.73 and 5.57 ppm for the H_α protons in **16b**-N and **16b**-U, respectively. These assumptions are also in agreement with the observations of Hakimelahi and Just on related compounds.[24]

The diastereomers whose relative stereochemistry was now established could be separated by column chromatography. Recrystallization from ethanol gave pure **16a**-N. Treatment of **16a**-N with *m*-chloroperbenzoic acid in a 1:6 molar ratio, respectively, in relfuxing benzene for 17 h gave the corresponding *cis*-4-acetoxy β-lactam **17a**-N in 80% yield. No trace of the trans isomer could be detected from the crude reaction mixture.

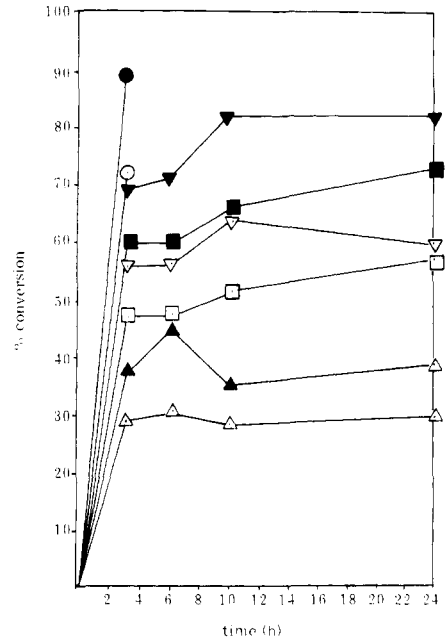
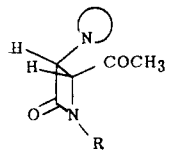
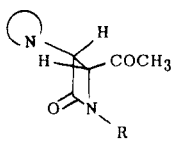


Figure 2. Baeyer–Villiger oxidation of an equimolar mixture of **16a**-N and **16a**-U under different substrate–MCPBA molar ratios: (a) 1:2, (△) N, (▲) U; (b) 1:4, (□) N, (■) U; (c) 1:6, (▽) N, (▼) U; (d) 1:10, (○) N, (●) U.

The next question that we examined was the relative oxidation rates of the diastereomers. Thus, an equimolar mixture of the two isomers **16a**-N and **16a**-U was treated with different amounts of MCPBA in refluxing benzene, and the reaction was monitored by NMR spectroscopy, mainly by observing the change of the relative intensities of the acetyl and acetoxy groups in both isomers. The acetoxy group in **17a**-N appeared at higher field (δ 1.35) than that of the **17a**-U isomer (δ 1.81). Results of this study are presented in Figure 2. As shown, the conversion rate increased when the molar ratio of *m*-chloroperbenzoic acid was increased. Also the conversion became stabilized after 6 h of reaction, and no further changes were observed. From these results the optimum yields in the Baeyer–Villiger oxidation were obtained with a 1:10 molar ratio of substrate/oxidant in refluxing benzene for 6 h. On the other hand, the reaction proceeds much faster with the U isomer than with the N isomer. An examination of Dreiding models indicates that such diastereoselectivity could be expalined by means of steric factors. As shown in Figure 1 it seems to be clear that the less hindered keto group in the U isomer undergoes Baeyer–Villiger oxidation much faster than the corresponding keto group in the N isomer. This fact was next illustrated in the oxidation of **16b** to **17b**. Thus, treatment of **16b**-U with a tenfold excess of MCPBA in refluxing benzene for 5 h yielded the expected β-lactam **17b**-U in 88% yield, whereas the corresponding N isomer, under the same conditions, afforded the β-lactam **17b**-N together with the starting material **16b**-N in a ratio 1:1, respectively, as determined by NMR spectroscopy. When this mixture was then treated with more MCPBA under the same conditions as above, a complete conversion was achieved, affording **17b**-N in 62% yield. Generalization of these results suggests that steric factors govern the conversion rate of Baeyer–Villiger oxidation on 4-acetyl β-lactams. Therefore, the stereochemistry of the β-lactam ring must play an important role in the rate of Baeyer–Villiger oxidation. In fact (see Table I), when the *trans*-β-lactam **10c**, obtained by isomerization

(25) Grigg, R. *Bull. Soc. Chim. Belg.* **1984**, *93*, 593.

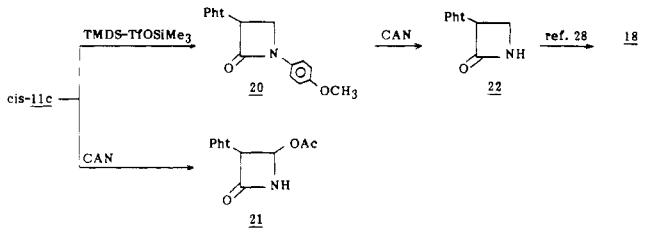
Table I. Baeyer–Villiger Oxidation of 4-Acetyl β-Lactams

compd[a]	time, h	conv,[b] %	yield,[c] %
cis-**10c**	2.5 h	50	
trans-**10c**	2.5 h	100	70
cis-**10d**	0.25	25	
	1 h	60	
trans-**10d**	0.25	100	80

[a] Molar ratio **10c**/MCPBA, 1:4; molar ratio **10d**/MCPBA, 1:2. [b] Determined by NMR spectroscopy. [c] Isolated yields.

Scheme III



of *cis*-**10c** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[26] was treated with MCPBA under the same conditions as those used in the Baeyer–Villiger oxidation of *cis*-**10c**, the expected *trans*-4-acetoxy β-lactam **11c** was obtained in 70% yield much faster than the corresponding cis isomer. Similarly, *trans*-**10d** upon treatment with MCPBA in refluxing benzene for 15 min yielded *trans*-**11d** in 80% yield, while the corresponding cis isomer afforded *cis*-**11d** in only 25% of conversion.

As previously reported,[14] one aspect of the versatility of 4-acetoxyazetidin-2-ones is their facile reaction with a variety of nucleophiles. Subsequent multistep elaboration has provided entries to a number of bicyclic β-lactams of biological interest.[14b,c] Our recent finding[15] that various 4-acetoxyazetidin-2-ones can be transformed into their corresponding 4-unsubstituted β-lactams under the influence of 1,1,3,3-tetramethyldisiloxane (TMDS) and trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) as catalyst encouraged us to explore similar reaction on compound **17**. Thus, treatment of a mixture of both diastereomers of **17a** with a sixfold excess of TMDS and trimethylsilyl triflate in a catalytic amount in refluxing benzene for 5 days afforded after workup the corresponding 4-unsubstituted β-lactam **18a** in 40% yield as a mixture of diastereomers, which were separated by column chromatography. Similarly, the β-lactam **17b**-N upon treatment with TMDS under the same reaction conditions afforded **18b**-N in 20% yield. The conversion of **18b**-N into 3-aminonocardicinic acid by sequential deprotection of the ester and amido groups has been previously reported.[27]

The relatively low yield of **18b** prompted us to devise an alternate approach to this key intermediate, Scheme III, based upon the work of Miller and Mattingly[28] on N-alkylations in β-lactams. Therefore, as depicted in Scheme III, the β-lactam **11c** was selected as starting material. Thus, treatment of **11c** with TMDS reagent and trimethylsilyl triflate as catalyst followed by oxidative removal of the *N*-aryl substituent in **20** with ammonium cerium nitrate (CAN)[29] afforded the expected N-H azetidin-2-one **22** in 95% overall yield. Finally, an attempt to prepare **22** from 4-acetoxy β-lactam **21** was made. Reduction of **21** by means of the TMDS–triflate system unfortunately gave a complex mixture of products, none of which were identifiable. Since compounds of type **22** have been converted into 3-aminonocardicinic acid and hence the nocardicins, this new route should be a valuable synthesis of these systems.

Conclusion

In summary an efficient formal synthesis of monobactams and nocardicins has been developed from the acid chloride–imine method or equivalent. The methodology is experimentally simple and allows a highly stereoselective synthesis of β-lactams that may be readily extended to further applications. Such extensions are being studied.[30]

Experimental Section

Melting points were determined on either Büchi SMP-20 or Mettler FP61 instruments and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-360 spectrometer and are reported in parts per million downfield from internal tetramethylsilane. Infrared (IR) spectra were obtained on a Shimadzu IR-435 spectrometer. Ozonation reactions were carried out by using a Fisher 502 ozone generator. Microanalytical data were obtained in these laboratories. All β-lactams prepared are racemic mixtures. All the starting materials used in this work were commercially available in 98% or higher purity and were used without further purification. Hexane and EtOAc were purified by distillation. CH_2Cl_2 and benzene were respectively distilled from P_4O_{10} and Na.

***N*-(α-Methylcinnamylidene)-*p*-anisidine (8a).**[31] A mixture of α-methylcinnamaldehyde (27.9 mL, 200 mmol), *p*-anisidine (24.6 g, 200 mmol), and magnesium sulfate in CH_2Cl_2 (200 mL) was refluxed for 2 h. The resulting mixture was filtered and the solvent was evaporated under reduced pressure to give the crude imine **8a**, which was crystallized from ethanol (36.14 g, 72%): mp 72–74 °C; IR (KBr) ν 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H, N=CH), 7.35–6.55 (m, 10 H, arom, C=CH), 3.68 (s, 3 H, OCH_3), 2.19 (s, 3 H, CH_3). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.23; H, 6.83; N, 5.57. Found: C, 81.27; H, 6.85; N, 5.60.

***N*-(α-Methylcinnamylidene)glycine Methyl Ester (8b).** A mixture of α-methylcinnamaldehyde (1.8 mL, 13 mmol), methyl aminoacetate hydrochloride (1.25 g, 10 mmol), Et_3N (1.4 mL, 10 mmol), and $MgSO_4$ in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 24 h. The resulting mixture was filtered and washed with H_2O (2 × 20 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, which was employed without purification: ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1 H, HC=N), 7.77–7.10 (s, 5 H, arom), 6.85 (s, 1 H, HC=C), 4.32 (s, 2 H, CH_2), 3.75 (s, 3 H, OCH_3), 2.17 (s, 3 H, CH_3).

Preparation of *cis*-4-(α-Methylstyryl)-2-azetidinones (9). General Procedure. To a cooled (0–5 °C) solution of the imine **8** (10 mmol), the substituted acetic acid (10 mmol), and Et_3N (4.2 mL, 30 mmol) in dry CH_2Cl_2 (25 mL) was added phenyl dichlorophosphate (1.5 mL, 10 mmol), and the resulting suspension was stirred at room temperature for 20–24 h. Then the reaction mixture was washed with H_2O (15 mL) and 0.1 N HCl (15 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue, which was crystallized from ethanol.

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(30) While this work was in progress a paper appeared concerning the preparation of 4-styrylmonobactams from the acid chloride–imine approach. See: Dugat, D.; Just, G.; Sahoo, S. *Can. J. Chem.* **1987**, *65*, 88.
(31) Manhas, M. S.; Megde, V. R.; Wagle, D. R.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2045.

***cis*-1-(4-Methoxyphenyl)-4-(α-methylstyryl)-3-phthalimido-2-azetidinone (9c)** was prepared from phthalimidoacetic acid (2.05 g, 10 mmol) and *N*-(α-methylcinnamylidene)-*p*-anisidine (**8a**) (2.51 g, 10 mmol): yield 3.50 g (80%); mp 105–107 °C; IR (KBr) ν 1760, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67–6.58 (m, 14 H, arom) 6.37 (br s, 1 H, C=CH), 5.40 (d, 1 H, J = 5 Hz, CH), 4.67 (d, 1 H, J = 5 Hz, CH), 3.67 (s, 3 H, OCH_3), 1.67 (s, 3 H, CH_3). Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.95; H, 5.07; N, 6.39. Found: C, 74.10; H, 5.16; N, 6.40.

***cis*-1-((Methoxycarbonyl)methyl)-4-(α-methylstyryl)-phthalimido-2-azetidinone (9d)** was prepared from phthalimidoacetic acid (2.05 g, 10 mmol) and *N*-(α-methylcinnamylidene)glycine methyl ester (**8b**) (2.17 g, 10 mmol): yield 2.66 g (66%); mp 191–194 °C; IR (KBr) ν 1776, 1748, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 4 H, arom), 7.23 (m, 5 H, arom), 6.65 (m, 1 H, CH=), 5.67 (d, 1 H, J = 5 Hz, CH), 4.78 (d, 1 H, J = 5 Hz, CH), 4.72 (d, 1 H, J = 18 Hz, CH), 4.77 (d, 1 H, J = 18 Hz, CH), 3.83 (s, 3 H, OCH_3), 1.68 (s, 3 H, CH_3). Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.32; H, 4.98; N, 6.93. Found: C, 68.20; H, 5.10; N, 6.74.

***cis*-1-(4-Methoxyphenyl)-4-(α-methylstyryl)-3-phenoxy-2-azetidinone (9e)** was prepared from phenoxyacetic acid (1.52 g, 10 mmol) and *N*-(α-methylcinnamylidene)-*p*-anisidine (**8a**) (2.51 g, 10 mmol): yield 3.08 g (80%); mp 157–158 °C; IR (KBr) ν 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–6.54 (m, 14 H, arom), 6.44 (br s, 1 H, C=CH), 5.32 (d, 1 H, J = 5 Hz, CH), 4.70 (d, 1 H, J = 5 Hz, CH), 3.64 (s, 3 H, OCH_3), 1.82 (s, 3 H, CH_3). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.89; H, 6.03; N, 3.63. Found: C, 77.90; H, 6.05; N, 3.63.

***cis*-3-Methoxy-1-(4-methoxyphenyl)-4-(α-methylstyryl)-2-azetidinone (9g)** was prepared from methoxyacetic acid (0.77 mL, 10 mmol) and *N*-(α-methylcinnamylidene)-*p*-anisidine (**8a**) (2.51 g, 10 mmol): yield 1.61 g (50%); mp 117–118 °C; IR (KBr) ν 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–6.37 (10 H, arom, C=CH), 4.59 (br s, 2 H, CH), 3.67 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 1.87 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.56; N, 4.33. Found: C, 74.29; H, 6.65; N, 4.34.

Preparation of *cis*-4-Acetyl-2-azetidinones (10). General Procedure. The corresponding *cis*-4-(α-methylstyryl)-2-azetidinone (20 mmol) was dissolved in dry CH_2Cl_2 (100 mL), and the solution was cooled to −70 °C. A stream of ozone was passed through the reaction mixture until a pale blue coloration was observed and then the suspension was purged with nitrogen. A solution of Me_2S (5 mL, large excess) in CH_2Cl_2 (20 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the solution was stirred to room temperature. The reaction mixture was washed with H_2O (200 mL) and with saturated brine (2 × 200 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a syrup, which was triturated with boiling hexane and purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2–hexane (1:1) as eluant), giving the corresponding β-lactam **10**, which was crystallized from ethanol.

***cis*-4-Acetyl-1-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (10c)** was prepared from *cis*-1-(4-methoxyphenyl)-4-(α-methylstyryl)-3-phthalimido-2-azetidinone (**9c**) (8.8 g, 20 mmol): yield 4.90 g (80%); mp 175–176 °C; IR (KBr) ν 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (br s, 4 H, arom), 7.26 (d, 2 H, J = 9 Hz, arom), 6.77 (d, 2 H, J = 9 Hz, arom), 5.60 (d, 1 H, J = 6 Hz, CH), 4.68 (d, 1 H, J = 6 Hz, CH), 3.72 (s, 3 H, OCH_3), 2.15 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.43; N, 7.69. Found: C, 66.0; H, 4.37; N, 7.71.

***trans*-4-Acetyl-1-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (10c).** To a solution of *cis*-4-acetyl-1-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (**10c**) (3.4 g, 10 mmol) in CH_2Cl_2 (100 mL) was added DBU (0.15 mL, 1 mmol). The mixture was stirred at room temperature for 24 h. Then the solution was washed with H_2O (30 mL) and 1 N HCl (2 × 30 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and subsequent crystallization gave the corresponding pure *trans*-β-lactam (**10c**): yield 1.43 g (42%); mp 180.5 °C (MeOH); IR (KBr) ν 1769, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93–7.47 (m, 4 H, arom), 7.18 (d, 2 H, J = 9 Hz, arom), 6.75 (d, 2 H, J = 9 Hz, arom), 5.25 (d, 1 H, J = 3 Hz, CH), 4.75 (d, 1 H, J = 3 Hz, CH), 3.70 (s, 3 H, OCH_3), 2.18 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.43; N, 7.69. Found: C, 63.20; H, 4.28; N, 7.32.

***cis*-4-Acetyl-1-((methoxycarbonyl)methyl)-3-phthalimido-2-azetidinone (10d).** *cis*-1-((Methoxycarbonyl)-methyl)-4-(α-methylstyryl)-3-phthalimido-2-azetidinone (**9d**) (4.04 g, 10 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and the solution was cooled to −70 °C. A stream of ozone was passed through the reaction mixture until a pale blue coloration was observed and then the solution was purged with nitrogen. A solution of Me_2S (4 mL, large excess) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the solution was stirred until room temperature. The reaction mixture was washed with H_2O (25 mL) and NaCl (saturated solution) (2 × 25 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a residue, which was triturated with boiling hexane and purified by crystallization from *n*-BuOH: yield 2.64 g (80%); mp 210–213 °C; IR (KBr) ν 1777, 1773, 1754, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (m, 4 H, arom), 5.80 (d, 1 H, J = 6 Hz, CH), 4.85 (d, 1 H, J = 6 Hz), 4.78 (d, 1 H, J = 18 Hz, CH), 4.08 (d, 1 H, J = 18 Hz, CH), 3.81 (s, 3 H, OCH_3), 2.16 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.25; H, 4.33; N, 8.55.

***trans*-4-Acetyl-1-((methoxycarbonyl)methyl)-3-phthalimido-2-azetidinone (10d).** To a solution of *cis*-4-acetyl-1-((methoxycarbonyl)methyl)-3-phthalimido-2-azetidinone (**10d**) (3.30 g, 10 mmol) in CH_2Cl_2 (100 mL) was added DBU (0.15 mL, 1 mmol). The mixture was stirred at room temperature for 24 h. The solution was washed with H_2O (30 mL) and 1 N HCl (2 × 30 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and subsequent crystallization gave the corresponding pure *trans*-β-lactam (**10d**): yield 2.24 g (68%); mp 174.5 °C (EtOH); IR (KBr) ν 1786, 1772, 1744, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.40 (m, 4 H, arom), 5.08 (d, 1 H, J = 3 Hz, CH), 4.82 (d, 1 H, J = 3 Hz, CH), 4.35 (d, 1 H, J = 18 Hz, CH), 3.92 (d, 1 H, J = 18 Hz, CH), 3.65 (s, 3 H, OCH_3), 2.15 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.10; H, 4.25; N, 8.50.

***cis*-4-Acetyl-1-(4-methoxyphenyl)-3-phenoxy-2-azetidinone (10e)** was prepared from *cis*-1-(4-methoxyphenyl)-4-(α-methylstyryl)-3-phenoxy-2-azetidinone (**9e**) (7.7 g, 20 mmol): yield 5.51 g (82%); mp 137–138 °C; IR (Nujol) ν 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–6.63 (m, 9 H, arom), 5.37 (d, 1 H, J = 5 Hz, CH), 4.65 (d, 1 H, J = 5 Hz, CH), 3.68 (s, 3 H, OCH_3), 2.17 (s, 3 H, CH_3). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.43; H, 5.51; N, 4.50. Found: C, 69.51; H, 5.54; N, 4.51.

***cis*-4-Acetyl-1-((methoxycarbonyl)methyl)-3-phenoxy-2-azetidinone (10f).** To a cooled (0–5 °C) solution of the imine **8b** (10 mmol) in dry CH_2Cl_2 (25 mL) were added Et_3N (4.2 mL, 30 mmol), phenoxyacetic acid (1.52 g, 10 mmol), and phenyl dichlorophosphate (1.5 mL, 10 mmol), and the resulting mixture was stirred at room temperature for 20–24 h. The reaction mixture was washed with H_2O (10 mL), 1 N HCl (2 × 10 mL), and $NaHCO_3$ (saturated solution) (10 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil residue. This oil was dissolved in dry CH_2Cl_2 (50 mL), and the solution was cooled to −70 °C. A stream of ozone was passed through the reaction mixture until a blue coloration was observed, and the solution was purged with nitrogen. A solution of Me_2S (4 mL, large excess) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the solution was stirred to room temperature. The reaction mixture was washed with H_2O (25 mL) and NaCl (saturated solution) (2 × 25 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a syrup, which was triturated with boiling hexane and purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2–hexane as eluant), giving the β-lactam **10f**, which was crystallized from CCl_4: yield 1.52 g (55%); mp 55–58 °C; IR (KBr) ν 1761, 1737, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (m, 5 H, arom), 5.55 (d, 1 H, J = 5 Hz, CH), 4.93 (d, 1 H, J = 18 Hz, CH), 4.86 (d, 1 H, J = 5 Hz, CH), 4.53 (d, 1 H, J = 18 Hz, CH), 3.72 (s, 3 H, OCH_3), 2.20 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 59.86; H, 5.31; N, 4.42.

***cis*-4-Acetyl-3-methoxy-1-(4-methoxyphenyl)-2-azetidinone (10g)** was prepared from *cis*-3-methoxy-1-(4-methoxyphenyl)-4-(α-methylstyryl)-2-azetidinone (**9g**) (6.5 g, 20 mmol): yield 3.75 g (75%); mp 124–125 °C; IR (Nujol) ν 1736–1720 (broad band)

cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (d, 2 H, J = 10 Hz, arom), 6.83 (d, 2 H, J = 10 Hz, arom), 4.79 (d, 1 H, J = 5 Hz, CH), 4.54 (d, 1 H, J = 5 Hz, CH), 3.76 (s, 3 H, OCH_3), 2.18 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.08; N, 5.62. Found: C, 62.71; H, 6.13; N, 5.64.

Preparation of 4-Acetoxy-2-azetidinones (11). Procedure A. To a solution of the corresponding 4-acetyl-2-azetidinone (**10**) (2 mmol) in benzene (15 mL) was added *m*-chloroperbenzoic acid (1.38 g, 8 mmol), and the resulting mixture was stirred under reflux for 3 h. Then CH_2Cl_2 (20 mL) was added and the mixture was washed with 1 N NaOH (5 × 30 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure gave a residue, which was dissolved in benzene (15 mL). Then *m*-chloroperbenzoic acid (1.38 g, 8 mmol) was added and the mixture was stirred under reflux for 3 h. After the same workup as above, a waxy residue was obtained, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2–hexane (1:2) as eluant), giving the correspond 4-acetoxy-2-azetidinone (**11**).

Procedure B. To a solution of the corresponding 4-acetyl-2-azetidinone (**10**) (2 mmol) in benzene (15 mL) was added *m*-chloroperbenzoic acid (1.38 g, 8 mmol), and the resulting mixture was stirred under reflux for the specified time. After the same workup as above, a solid residue was obtained, which was purified by crystallization.

***cis*-4-Acetoxy-1-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (11c)** was prepared from *cis*-**10c** (0.68 g, 2 mmol) following procedure A: yield 0.40 g (56%); mp 216 °C (EtOH); IR (KBr) ν 1785, 1780, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98–8.86 (m, 8 H, arom), 6.66 (d, 1 H, J = 5 Hz, CH), 5.59 (d, 1 H, J = 5 Hz, CH), 3.66 (s, 3 H, OCH_3), 1.79 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{16}N_2O_6$: C, 63.15; H, 4.25; N, 7.37. Found: C, 63.22; H, 4.28; N, 7.38.

***trans*-4-Acetoxy-1-(4-methoxyphenyl)-3-phthalimido-2-azetidinone (11c)** was prepared from *trans*-**10c** (0.31 g, 1 mmol) following procedure B and using a reaction time of 2.5 h: yield 0.23 g (70%); mp 186 °C (EtOH); IR (KBr) ν 1780, 1768, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83–7.45 (m, 4 H, arom), 7.23 (d, 2 H, J = 9 Hz, arom), 6.72 (d, 2 H, J = 9 Hz, arom), 6.45 (d, 1 H, J = 2 Hz, CH), 5.23 (d, 1 H, J = 2 Hz, CH), 3.68 (s, 3 H, OCH_3), 2.08 (s, 3 H, CH_3).

***cis*-4-Acetoxy-1-((methoxycarbonyl)methyl)-3-phthalimido-2-azetidinone (11d)** was prepared from *cis*-**10d** (3.30 g, 10 mmol) following procedure B and using a reaction time of 3 h: yield 2.97 g (86%); mp 145 °C (EtOH); IR (KBr) ν 1795, 1779, 1744, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (m, 4 H, arom), 6.35 (d, 1 H, J = 4 Hz, CH), 5.76 (d, 1 H, J = 4 Hz, CH), 4.24 (dd, 2 H, J = −18 Hz, CH_2), 3.82 (s, 3 H, OCH_3), 1.97 (s, 3 H, CH_3). Anal. Calcd for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.07; N, 8.09. Found: C, 55.47; H, 4.10; N, 8.04.

***trans*-4-Acetoxy-1-((methoxycarbonyl)methyl)-3-phthalimido-2-azetidinone (11d)** was prepared from *trans*-**10d** (0.33 g, 1 mmol) following procedure B and using a reaction time of 15 min. In this case the substrate/reactive molar ratio was 1:2. Yield 0.27 g (78%); mp 158 °C (EtOH); IR (KBr) ν 1802, 1776, 1753, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92–7.35 (m, 4 H, arom), 6.23 (d, 1 H, J = 2 Hz, CH), 5.30 (d, 1 H, J = 2 Hz, CH), 4.10 (s, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 2.05 (s, 3 H, CH_3).

***cis*-4-Acetoxy-1-(4-methoxyphenyl)-3-phenoxy-2-azetidinone (11e)** was prepared from *cis*-**10e** (0.62 g, 2 mmol) following procedure A: yield 0.22 g (34%); mp 93–94 °C ($CHCl_3$–hexane); IR (KBr) ν 1773, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–6.79 (m, 10 H, arom, CH), 5.35 (d, 1 H, J = 4 Hz, CH), 3.73 (s, 3 H, OCH_3), 1.95 (s, 3 H, OCH_3). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.04; H, 5.24; N, 4.28. Found: C, 66.08; H, 5.25; N, 4.29.

***cis*-4-Acetoxy-1-((methoxycarbonyl)methyl)-3-phenoxy-2-azetidinone (11f)** was prepared from *cis*-**10f** (2.77 g, 10 mmol) following procedure B and using a reaction time of 30 min: yield 2.57 g (88%); mp 83.5 °C (CCl_4); IR (KBr) ν 1784, 1745, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (m, 5 H, arom), 6.40 (d, 1 H, J = 4 Hz, CH), 5.42 (d, 1 H, = 4 Hz, CH), 4.10 (dd, 2 H, J = −18 Hz, CH_2), 3.73 (s, 3 H, OCH_3), 2.00 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.68; H, 5.21; N, 4.91.

***cis*-4-Acetoxy-3-methoxy-1-(4-methoxyphenyl)-2-azetidinone (11g)** was prepared from *cis*-4-acetyl-3-methoxy-1-(4-methoxyphenyl)-2-azetidinone (**10g**) (0.50 g, 2 mmol) following procedure A: yield 0.23 g (43%) as a colorless oil; IR (Nujol) ν 1765, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–6.52 (m, 4 H, arom), 6.35 (d, 1 H, J = 4 Hz, CH), 6.35 (d, 1 H, J = 4 Hz, CH), 3.65 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 2.05 (s, 3 H, CH_3).

***N*-(2-Methylcinnamylidene)-α-phenylglycine Methyl Ester (14a).** To a suspension of D-(−)-phenylglycine methyl ester hydrochloride (2 g, 10 mmol) in EtOAc (50 mL) were successively added Et_3N (1.4 mL, 10 mmol), α-methylcinnamaldehyde (1.39 mL, 10 mmol), and $MgSO_4$, and the resulting mixture was stirred under reflux for 3 h. Then the suspension was filtered off and washed with H_2O (30 mL). The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give the crude imine (±)-**14a**, which was crystallized from ethanol: yield 2.34 g (80%); mp 69–70 °C; IR (KBr) ν 1728, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (s, 1 H, CH=N), 7.63–7.05 (m, 10 H, arom), 6.91 (br s, 1 H, CH=), 5.13 (s, 1 H, CH), 3.74 (s, 3 H, OCH_3), 2.21 (s, 3 H, CH_3). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 73.75; H, 6.20; N, 4.53. Found: C, 73.76; H, 6.72; N, 4.50.

***N*-(2-Methylcinnamylidene)-α-*p*-hydroxyphenylglycine Methyl Ester (14b).** Following the above procedure starting from D-(−)-*p*-hydroxyphenylglycine methyl ester hydrochloride (2.4 g, 11 mmol) the crude imine (±)-**14b** was obtained as a white solid: yield 2.16 g (70%); mp 160–161 °C; IR (KBr) 3351, 1734, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (s, 1 H, HC=N), 7.42–7.00 (m, 8 H, arom OH), 6.82–6.55 (m, 3 H, arom), 4.98 (s, 1 H, CH), 3.60 (s, 3 H, OCH_3), 2.12 (s, 3 H, CH_3). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.12; N, 4.53. Found: C, 73.75; H, 6.17; N, 4.50.

***cis*-4-Acetyl-1-((methoxycarbonyl)phenylmethyl)-3-phthalimido-2-azetidinone (16a).** To a solution of phthalimidoacetic acid (2.05 g, 10 mmol), Et_3N (4.2 mL, 30 mmol), and *N*-(2-methylcinnamylidene)-α-phenylglycine methyl ester (**14a**) (2.93 g, 10 mmol) in CH_2Cl_2 (25 mL) was added phenyl dichlorophosphate (1.5 mL, 10 mmol), and the resulting mixture was stirred for 24 h at room temperature. Then the mixture was washed with 1 N HCl (15 mL), $NaHCO_3$ (saturated solution) (15 mL), and finally H_2O (15 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, which was dissolved in CH_2Cl_2 (20 mL) and cooled at −70 °C. Then a stream of ozone was passed through the reacton mixture until an excess of ozone was observed. The solution was purged of excess ozone with a stream of dry nitrogen for 15 min, and then a solution of Me_2S (4 mL) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the obtained solution was stirred until room temperature. The reaction mixture was washed with H_2O (10 mL) and NaCl (saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a residue, which was triturated with boiling hexane and filtered off to give 2.45 g (60%) of a 2:1 mixture of N and U diastereomers, respectively: ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H, CH_3 U), 1.49 (s, 3 H, CH_3N). Anal. Calcd for $C_{22}H_{18}N_2O_6$: C, 65.01; H, 4.47; N, 6.89. Found: C, 65.32; H, 4.68; N, 6.71.

***cis*-4-Acetyl-1-((methoxycarbonyl)(4-acetoxyphenyl)-methyl)-3-phthalimido-2-azetidinone (16b).** To a cooled (0–5 °C) solution of *N*-(2-methylcinnamylidene)-α-*p*-hydroxyphenylglycine methyl ester (3.09 g, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise acetyl chloride (0.7 mL, 10 mmol) in dry CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 1 h. Then Et_3N (4.2 mL, 30 mmol) and phthalimidoacetic acid (2.05 g, 10 mmol) were added. The suspension was cooled to 0–5 °C and phenyl dichlorophosphate (1.5 mL, 10 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and then washed with H_2O (15 mL), 1 N HCl (15 mL), and $NaHCO_3$ (saturated solution) (15 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, the NMR spectrum of which indicated that a mixture of two diastereomeric β-lactams had been obtained in a ratio 2:1. The oil was dissolved in dry CH_2Cl_2 (20 mL) and cooled at −70 °C. Then a stream of ozone was passed through until a blue coloration was observed. The solution was purged of excess ozone with a stream of dry nitrogen, and then a solution of Me_2S (4 mL) in CH_2Cl_2 (10 mL) was added dropwise at −70 °C. When the addition was completed, the bath was removed and the solution was stirred to room temperature. The reaction mixture was washed with H_2O (10 mL) and NaCl (saturated soution) (2 × 10

mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave an oil. NMR analysis of this oil showed a diastereomeric mixture of **16b**-N and **16b**-U in ratio 2:1, respectively, which were separated by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane (2:1) as eluant). **16b**-N: yield 1.39 g (30%); mp 171 °C; IR (KBr) ν 1786, 1784, 1772, 1750, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (s, 4 H, arom), 7.43 (d, 2 H, J = 9 Hz, arom), 7.12 (d, 2 H, J = 9 Hz, arom), 5.73 (s, 1 H, CH), 5.68 (d, 1 H, J = 5 Hz, CH), 4.78 (d, 1 H, J = 5 Hz, CH), 3.78 (s, 3 H, OCH_3), 2.25 (s, 3 H, CH_3CO), 1.57 (3, 3 H, CH_3COO). Anal. Calcd for $C_{24}H_{20}N_2O_8$: C, 62.06; H, 4.35; N, 6.03. Found: C, 62.15; H, 4.30; N, 6.12. **16b**-U: yield 0.47 g (10%); mp 197 °C; IR (KBr) ν 1785, 1772, 1745, 1737, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (s, 4 H, arom), 7.53 (d, 2 H, J = 9 Hz, arom), 7.12 (d, 2 H, J = 9 Hz, arom), 5.57 (d, 1 H, J = 6 Hz, CH), 5.57 (s, 1 H, CH), 4.77 (d, 1 H, J = 6 Hz, CH), 3.72 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3CO), 2.07 (s, 3 H, CH_3COO). Anal. Calcd for $C_{24}H_{20}N_2O_8$: C, 62.06; H, 4.35; N, 6.03. Found: C, 62.30; H, 4.40; N, 6.10.

***cis*-4-Acetoxy-1-((methoxycarbonyl)phenylmethyl)-3-phthalimido-2-azetidinone (17a).** To a solution of 4-acetyl-1-((methoxycarbonyl)phenylmethyl)-3-phthalimido-2-azetidinone (**16a**) (2.0 g, 5 mmol) in dry benzene (60 mL) was added *m*-chloroperbenzoic acid (8.6 g, 50 mmol). The resulting suspension was refluxed for 6 h and then washed with 1 N NaOH (3 × 20 mL) and H_2O (20 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was dissolved in benzene (15 mL). Then *m*-chloroperbenzoic acid (8.6 g, 50 mmol) was added, and the mixture was stirred for 8.5 h. After the same workup as above, a waxy residue was obtained, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane as eluant): yield 1.56 g (80%); ^1H NMR ($CDCl_3$) of the diastereomeric mixture, δ 1.82 (s, 3 H, CH_3 U), 1.35 (s, 3 H, CH_3 N). Anal. Calcd for $C_{22}H_{18}N_2O_7$: C, 62.55; H, 4.30; N, 6.63. Found: C, 62.9; H, 4.32; N, 6.72.

***cis*-4-Acetoxy-1-((methoxycarbonyl)(4-acetoxyphenyl)-methyl)-3-phthalimido-2-azetidinone (17b-N).** To a suspension of 4-acetyl-1-((methoxycarbonyl)(4-acetoxyphenyl)methyl)-3-phthalimido-2-azetidinone (**16b**-N) (2.32 g, 5 mmol) in dry benzene (60 mL) was added *m*-chloroperbenzoic acid (8.63 g, 50 mmol). The reaction mixture was refluxed for 6 h. The reaction mixture was diluted with CH_2Cl_2 (70 mL) and washed with 1 N NaOH (3 × 20 mL) and H_2O (20 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure gave an oil. This oil was dissolved in dry benzene (60 mL), and *m*-chloroperbenzoic acid (8.63 g, 50 mmol) was added and the mixture was refluxed for 6 h again. After the same workup as above, a solid residue was obtained, which was purified by crystallization from ethanol: yield 1.49 g (62%); mp 211 °C; IR (KBr) ν 1794, 1758, 1742, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.88–7.58 (m, 4 H, arom), 7.43 (d, 2 H, J = 9 Hz, arom), 7.07 (d, 2 H, J = 9 Hz, arom), 6.68 (d, 1 H, J = 4 Hz, CH), 5.73 (s, 1 H, CH), 5.58 (d, 1 H, J = 4 Hz, CH), 3.82 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3COO), 1.47 (s, 3 H, CH_3COO). Anal. Calcd for $C_{24}H_{20}N_2O_9$: C, 59.99; H, 4.20; N, 5.83. Found: C, 60.02; H, 4.15; N, 5.80.

***cis*-4-Acetoxy-1-((methoxycarbonyl)(4-acetoxyphenyl)-methyl)-3-phthalimido-2-azetidinone (17b-U).** To a suspension of 4-acetyl-1-((metoxycarbonyl)(4-methoxyphenyl)methyl)-3-phthalimido-2-azetidinone (**16b**-U) (2.32 g, 5 mmol) in dry benzene (60 mL) was added *m*-chloroperbenzoic acid (8.63 g, 50 mmol). The reaction mixture was refluxed for 5 h. Then the reaction mixture was diluted with CH_2Cl_2 (70 mL) and washed ($MgSO_4$). Evaporation of the solvents under reduced pressure gave a solid, which was purified by crystallization from ethanol: yield 2.11 g (88%); mp 184 °C; IR (KBr) 1794, 1772, 1742, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00–7.67 (m, 4 H, arom), 7.50 (d, 2 H, J = 9 Hz, arom), 7.13 (d, 2 H, J = 9 Hz, arom), 6.27 (d, 1 H, J = 4 Hz, CH), 5.53 (s, 1 H, CH), 5.50 (d, 1 H, J = 4 Hz, CH), 3.73 (s, 3 H, OCH_3), 2.23 (s, 3 H, CH_3COO), 1.83 (s, 3 H, CH_3). Anal. Calcd for $C_{24}H_{20}N_2O_9$: C, 59.99; H, 4.20; N, 5.83. Found: C, 60.05; H, 4.25; N, 5.79.

***cis*-1-((Methoxycarbonyl)phenylmethyl)-3-phthalimido-2-azetidinone (18a).** A mixture of *cis*-4-acetoxy-1-((methoxycarbonyl)phenylmethyl)-3-phthalimido-2-azetidinone (**17a**) (0.39 g, 1 mmol), 1,1,3,3-tetramethyldisiloxane (1.09 mL, 6 mmol), and trimethylsilyl trifluoromethanesulfonate (2 drops) in dry benzene (5 mL) was refluxed under nitrogen for 120 h. Then the reaction mixture was washed with H_2O (2 mL) and 0.1 N NaOH (2 × 2 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, which was triturated in boiling hexane, and the residue was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane (1:1) as eluant), yield 0.11 g (30%). **18a**-N: mp 157 °C; IR (KBr) ν 1771, 1744, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (s, 4 H, arom), 7.40 (s, 5 H, arom), 5.73 (s, 1 H, CH), 5.43 (dd, 1 H, J = 3 Hz, J' = 5 Hz, CH), 3.90 (t, 1 H, J = 5 Hz, CH), 3.77 (s, 3 H, CH_3), 3.37 (dd, 1 H, J = 3 Hz, J' = 5 Hz, CH). Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.43; N, 7.69. Found: C 65.56; H, 4.45; N, 7.76. **18a**-U: mp 151 °C; IR (KBr) 1761, 1734, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (s, 4 H, arom), 7.32 (s, 5 H, arom), 5.68 (s, 1 H, CH), 5.30 (dd, 1 H, J = 3 Hz, J' = 5 Hz, CH), 4.07 (dd, 1 H, J = 3 Hz, J' = 5 Hz, CH), 3.80 (s, 3 H, CH_3), 3.55 (t, 1 H, J = 5 Hz, CH). Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.92; H, 4.43; N, 7.69. Found: C, 65.62; H, 4.13; N, 7.46.

***cis*-1-((Methoxycarbonyl)(4-acetoxyphenyl)methyl)-3-phthalimido-2-azetidinone (18b-N).** A mixture of 4-acetoxy-1-((methoxycarbonyl)(4-acetoxyphenyl)methyl)-3-phthalimido-2-azetidinone (**17b**-N) (0.48 g, 1 mmol), 1,1,3,3-tetramethyldisiloxane (1.06 mL, 6 mmol), and trimethylsilyl trifluoromethanesulfonate (2 drops) in dry benzene (5 mL) was refluxed for 100 h. The reaction mixture was washed with H_2O (2 mL) and 0.1 N NaOH (2 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oil, which was dissolved in dry benzene (5 mL). 1,1,3,3-Tetramethyldisiloxane (1.06 mL, 6 mmol) and trimethylsilyl trifluoromethanesulfonate (2 drops) were added, and the reaction mixture was refluxed for 72 h again. After the same workup as above, an oil was obtained, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane (1:1) as eluant): yield 0.08 g (20%); mp 166 °C; IR (KBr) ν 1751, 1743, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93–7.57 (m, 4 H, arom), 7.43 (d, 2 H, J = 9 Hz, arom), 7.13 (d, 2 H, J = 9 Hz, arom), 5.73 (s, 1 H, CH), 5.43 (dd, 1 H, J = 5 Hz, J' = 3 Hz, CH), 3.88 (t, 1 H, J = 5 Hz, CH), 3.77 (s, 3 H, OCH_3), 3.40 (dd, 1 H, J = 5 Hz, J' = 3 Hz, CH), 2.23 (3, 3 H, CH_3COO). Anal. Calcd for $C_{22}H_{18}N_2O_7$: C, 62.55; H, 4.30; N, 6.63. Found: C, 62.11; H, 4.11; N, 6.47.

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