($CCl_4$) δ 5.33 (1, br s), 5.13 (1, br s), 4.92 (1, br s), 1.97 (3, br s); $^{13}C$ NMR δ 137.0 (s), 118.8 (t), 115.4 (s), 46.9 (d), 18.1 (q). **4-Chloro-3-methyl-2-butenenitrile (13c)** (25% yield): IR (neat) 2225 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 5.30 (1, s), 3.90 (2, s), 2.04 (3, s). ***trans*-4-Chloro-2-pentenenitrile (13d)** (50% yield): IR (film) 2215 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 6.37 (1, dd, $J$ = 16, 6.2 Hz), 5.57 (1, d, $J$ = 16 Hz), 4.53 (1, quint, $J$ = 6.2 Hz), 1.60 (3, d, $J$ = 6.2 Hz); $^{13}C$ NMR δ 153.4 (d), 116.3 (s), 100.9 (d), 54.4 (d), 23.8 (q). **4-Chloro-2,3-dimethyl-2-butenenitrile (13e)** (45% yield): IR (film) 2215 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ *Z* isomer 4.16 (2, s), 1.93 (6, br s); *E* isomer 3.96 (2, s), 1.93 (6, br s).

**General Procedure for 4-Azido-2-butenenitriles (14).** The same procedure as for azidopentenynes **2** was used and the crude product was purified by chromatography on silica gel (ether–pentane). **4-Azido-2-butenenitrile (14a)** (82% yield) (mixture of *E*/*Z* isomers, 7:3): IR (film) 2220, 2100 $cm^{-1}$; *E* isomer $^1H$ NMR δ 6.63 (1, dt, $J$ = 16.2, 4.65 Hz), 5.60 (1, dt, $J$ = 16.2, 2 Hz), 4.00 (2, dd, $J$ = 4.6, Hz, 2 Hz); $^{13}C$ NMR δ 147.3 (d), 116.5 (s), 102.0 (d), 51.3 (t); *Z* isomer $^1H$ NMR δ 6.46 (1, dt, $J$ = 11, 5.5 Hz), 5.54 (1, dt, $J$ = 11, 1.4 Hz), 4.10 (2, d, $J$ = 6.4 Hz, d, $J$ = 2.8 Hz); $^{13}C$ NMR δ 146.6 (d), 114.1 (s), 103.1 (d), 50.2 (t). **(*Z*)-4-Azido-2-methyl-2-butenenitrile (14b)** (85% yield): IR (film) 2210, 2090 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 6.09 (1, t, $J$ = 7.2 Hz), 3.99 (2, d, $J$ = 7.2 Hz), 2.04 (3, br s). **4-Azido-3-methyl-2-butenenitrile (14c)** (80% yield) (72:28 mixture of *E*/*Z* isomers): IR 2225, 2120 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ *E* isomer 5.38 (1, br s), 3.93 (2, br s), 2.05 (3, br s); *Z* isomer 5.30 (1, br s), 4.06 (2, br s), 2.05 (3, br s). ***trans*-4-Azido-2-pentenenitrile (14d)** (80% yield): IR (film) 2225, 2150 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 6.47 (1, d, $J$ = 16, 5.5 Hz), 5.47 (1, d, $J$ = 16 Hz), 4.10 (1, quint, $J$ = 6 Hz), 1.33 (3, d, $J$ = 6 Hz). **4-Azido-2,3-dimethyl-2-butenenitrile (14e)** (82% yield) (29:71 mixture of *E*/*Z* isomers): IR (film) 2210, 2100 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ *E* isomer 3.85 (2, s), 1.89 (6, br s); *Z* isomer 3.98 (2, s), 1.89 (6 br s).

**General Procedure for Tetrazoles (15).** A solution of azidobutenenitrile (**14**) (5 mmol) in chloroform (30 mL) was treated at room temperature with chlorosulfonic acid (1.16 g, 10 mmol). After 0.5 h of stirring, the mixture was washed with a saturated solution of $NaHCO_3$ and dried ($MgSO_4$). After concentration in vacuo, the crude product was recrystallized from chloroform–pentane (1:4).

**7-Methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15b).** General procedure with **14b** gives **15b** (0.61 g) (57% yield): mp 113 °C; IR ($CDCl_3$) 1520, 1460, 1245 $cm^{-1}$; $^1H$ NMR δ 6.65 (1, t, $J$ = 7.2 Hz), 4.78 (2, d, $J$ = 7.2 Hz), 2.30 (3, s); $^{13}C$ NMR δ 164.0 (s), 135.0 (d), 127.9 (s), 50.3 (t), 12.4 (q); mass spectrum, $m/e$ 123 (12), 122 (100), 94 (24), 93 (15), 79 (35), 66 (60), 65 (64), 39 (83); HRMS calcd for $C_5H_6N_4$ 122.0592, found 122.0584.

**6-Methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15c).** General procedure with **14c** gives **15c** (0.61 g) (25% yield): mp 104 °C; IR ($CDCl_3$) 1530, 1460 $cm^{-1}$; $^1H$ NMR δ 6.50 (1, br s, $W_{1/2}$ = 4 Hz), 4.73 (2, br s), 2.28 (3, s); $^{13}C$ NMR δ 164.2 (s), 154.7 (s), 112.5 (d), 53.5 (t), 16.0 (q). Anal. Calcd for $C_5H_6N_4$: C, 49.18; H, 4.92; N, 45.90. Found: C, 49.06; H, 4.73; N, 46.04.

**6,7-Dimethyl-5*H*-pyrrolo[1,2-*d*]tetrazole (15e).** General procedure with **14e** gives **15e** (0.68 g) (73% yield): mp 95 °C; IR ($CDCl_3$) 1530, 1460 $cm^{-1}$; $^1H$ NMR δ 4.74 (2, s), 2.19 (6, br s); $^{13}C$ NMR δ 164.6 (s), 132.9 (s), 120.8 (s), 53.1 (t), 13.0 (q), 9.7 (q); mass spectrum, $m/e$ 137 (12), 136 (95), 108 (26), 80 (31), 79 (100), 77 (32), 67 (30), 53 (30), 40 (66); HRMS calcd for $C_6H_8N_4$ 136.0749, found 136.0753.

**Formation of the Anion of 15b.** Sodium hydride (30 mg) was added to a solution of **8b** (150 mg) in DMSO-$d_6$ (3 mL) in a 10-mm NMR tube. The NMR spectra were recorded after 10 min: $^1H$ NMR δ 6.62 (1, m), 6.10 (1, m), 2.1 (3, br s); $^{13}C$ NMR δ 146.5 (s), 115.0 (d), 90.5 (d), 79.1 (s), 12.1 (q).

**Acylation of 15b.** Acylation of **15b** (1.22 g) by ethyl chloroformate (1.42 g, 15 mmol) led to **5-(ethoxycarbonyl)-7-methyl-5*H*-pyrrolo[1,2-*d*]tetrazole (16)** (76%): mp 58–59 °C (chloroform–pentane); IR ($CCl_4$) 1750, 1250 $cm^{-1}$; $^1H$ NMR δ 6.69 (1, d, $J$ = 3.5 Hz), 6.20 (1, d, $J$ = 3.5 Hz), 4.38 (2, $J$ = 7.2 Hz), 2.19 (3, s), 1.38 (3, t, $J$ = 7.2 Hz); $^{13}C$ NMR δ 165.7 (s), 147.3 (s), 127.7 (s), 120.9 (d), 102.2 (d), 65.1 (t), 14.0 (q), 10.7 (q); mass spectrum, $m/e$ 195 (10), 194 (63), 168 (10), 150 (10), 143 (57), 122 (100), 93 (75), 67 (72), 41 (56); HRMS calcd for $C_8H_{10}N_4O_2$ 194.0803, found 194.0796.

**Acknowledgment.** We thank Prof. J. K. Crandall (Indiana University, Bloomington, IN) for his interest and useful suggestions.

**Registry No.** **1a**, 123810-18-4; **1b**, 123810-19-5; **1c**, 123810-20-8; **1d**, 123810-21-9; **1e**, 123810-22-0; **1f**, 38264-11-8; **2a**, 64803-97-0; **2b**, 64803-99-2; **2c**, 64803-96-9; **2d**, 64803-98-1; **2e**, 123810-23-1; **2f**, 64804-00-8; **3a**, 64804-02-0; **3b**, 64804-04-2; **3c**, 64804-01-9; **3d**, 64804-03-1; **3e**, 30435-17-7; **3f**, 64804-05-3; **4**, 123810-24-2; **5**, 123810-25-3; **6**, 123810-26-4; **7a**, 123810-27-5; **7b**, 123810-28-6; **8a**, 123810-29-7; **8b**, 123810-31-1; **9a**, 123810-30-0; **9b**, 123810-32-2; **10a**, 90935-74-3; **10b**, 51952-99-9; **11a**, 5809-59-6; **11b**, 75819-97-5; **11c**, 22410-56-6; **11d**, 6812-26-6; **11e**, 4346-65-0; **12a**, 24253-31-4; **12c**, 123810-33-3; **13b**, 92089-38-8; **13c**, 4450-34-4; **13d**, 123810-34-4; (*Z*)-**13e**, 123810-35-5; (*E*)-**13e**, 26157-52-8; (*E*)-**14a**, 123810-36-6; (*Z*)-**14a**, 123810-37-7; (*Z*)-**14b**, 123810-38-8; (*E*)-**14c**, 123810-39-9; (*Z*)-**14c**, 123810-40-2; (*E*)-**14d**, 120990-04-7; (*E*)-**14e**, 123810-41-3; (*Z*)-**14e**, 123810-42-4; **15b**, 123810-43-5; **15b** (anion), 123810-46-8; **15c**, 123810-44-6; **15e**, 123810-45-7; **16**, 123834-20-8.

# β-Lactams via α,β-Unsaturated Acid Chlorides: Intermediates for Carbapenem Antibiotics[1]

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Stereocontrolled synthesis of α-vinyl β-lactams and their transformation to convenient intermediates for PS-5, PS-6, asparenomycin, and thienamycin are described.

## Introduction

The acid chloride–imine reaction has been used extensively to synthesize various substituted β-lactams.[2] Azidoacetyl chloride–imine cycloaddition, also known as the Bose reaction,[3] has been used as a pivotal synthetic

(1) Studies on Lactams. Part 84; for part 83, see: van der Veen, J. M.; Bari, S. S.; Krishnan, L.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758.

(2) For reviews, see: (a) Manhas, M. S.; Bose, A. K. *Beta-lactams–Natural and Synthetic*; Wiley Interscience: New York, 1971. (b) *Chemistry and Biology of Beta Lactam antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2. (c) Koppel, G. A. In *Small Ring Heterocycles*; Hassner, A., Ed.; John Wiley: New York, 1983; Part 2, pp 248–301.

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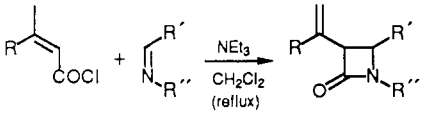
**Table I. Stereochemistry of α-Vinyl β-Lactam Formation**

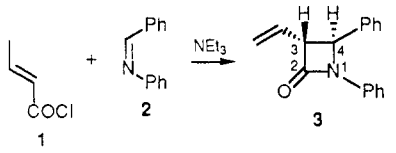


18

| entry | R | R′ | R″ | *cis*-18, % | *trans*-18, % | ref |
|---|---|---|---|---|---|---|
| 1 | H | Ph | Ph | | 40–65 | 11, 12, 13 |
| 2 | Me | furfuryl | Ph | | 70 | 12 |
| 3 | Me | furfuryl | $CH(CO_2Me)CH_2OTBDMS^a$ | 30 | | 12 |
| 4 | H | furfuryl | $CH(CO_2PNB)CH(CH_3)OH^b$ | 15 | | 13 |
| 5 | Me | PhCH=CH | $CH(CO_2Me)CH_2OTBDMS$ | 70 | | 12 |
| 6 | H | PhCH=CH | $CH(CO_2PNB)CH(CH_3)OH$ | 54 | 6 | 13 |
| 7 | H | $CO_2Me$ | $CH_2C_6H_3(OMe)_2(2,4)$ | 40 | | 12 |
| 8[c] | Me | $CO_2Me$ | $C_6H_4OMe$-*p* | 68 | | |
| 9 | H | COPh | $C_6H_4OMe$-*p* | 50 | 30 | 13 |
| 10 | H | COPh | $CH(CH_3)Ph$ | 55 | | 13 |
| 11 | H | PhCH=CH | Ph | 7 | 35 | 12 |
| 12[d] | H | PhCH=CH | Ph | 25 | 5 | 12 |

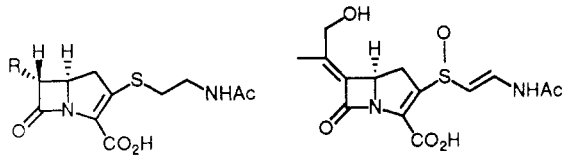
[a] TBDMS = *tert*-butyldimethylsilyl. [b] PNB = *p*-nitrobenzyl. [c] Data from this paper. [d] Reaction conducted at room temperature.

**Scheme I**



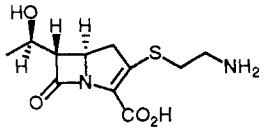
1 2 3

step for the formation of α-azido β-lactams which eventually were transformed to penicillins,[4,5] cephalosporins,[6-8] nocardicin,[9] and a number of their analogues.[10] However, very few reports describe the synthesis of 3-alkyl, 3-alkylidene, or 3-acyl β-lactams based on the acid chloride–imine cycloaddition reaction.[10] Synthesis of α-alkyl or α-acetyl β-lactams became an important target after the discovery of carbapenem antibiotics, namely, PS-5, PS-6, thienamycin, and asparenomycin, which possess an alkyl, hydroxyalkyl, or acetyl side chain at C-6 position.



PS-5: R = Et
PS-6: R = $^i$Pr

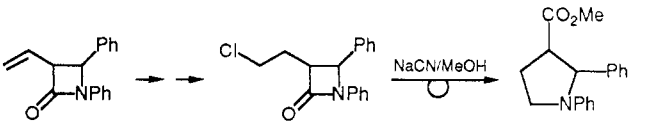
asparenomycin A



thienamycin

In 1971 we[11] developed a synthesis of α-vinyl β-lactams by the reaction of crotonyl chloride with imines in presence of triethylamine at elevated temperatures (see Scheme I). Later Zamboni and Just[12] utilized this reaction for preparing several α-vinyl β-lactams as potential synthons for β-lactam antibiotics.

We have developed renewed interest in this family of β-lactams after discovering the feasibility of stereocontrol of their formation and further transformations. In a recent communication we have described the preparation of some 3-vinyl-2-azetidinones, one of which was converted to a pyrrolidine derivative.[13]



The high concentration of a variety of functional groups on the β-lactam ring that can be eliminated (e.g., in the conversion of *N*-aryl β-lactams to N-unsubstituted β-lactams) or easily modified (e.g., in the conversion of 4-carboxy-2-azetidinone to 4-acetoxy-2-azetidinones) make these compounds versatile intermediates for diverse types of heterocycles as well as acyclic compounds. In this report we describe the stereocontrolled synthesis of several 3-vinyl-2-azetidinones and their conversion to known intermediates for PS-5, PS-6, asparenomycin, and thienamycin.

## Stereochemistry

Bose, Spiegelman, and Manhas[11] had reported the exclusive formation of the trans β-lactam (**3**) from *trans*-crotonyl chloride (**1**) and benzylideneaniline (**2**) in presence of triethylamine (Scheme I). Zamboni and Just[12] reacted both crotonyl chloride and dimethylacryloyl chloride with various Schiff bases and noted that the resulting α-vinyl β-lactams derived from aliphatic amines all had cis stereochemistry. When the Schiff base was derived from aniline and cinnamaldehyde, a mixture of cis and trans β-lactams was obtained; the relative proportion of the iso-

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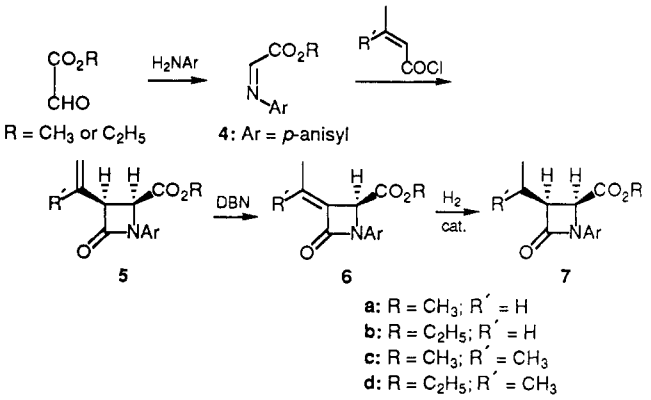
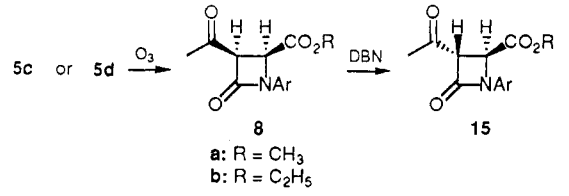
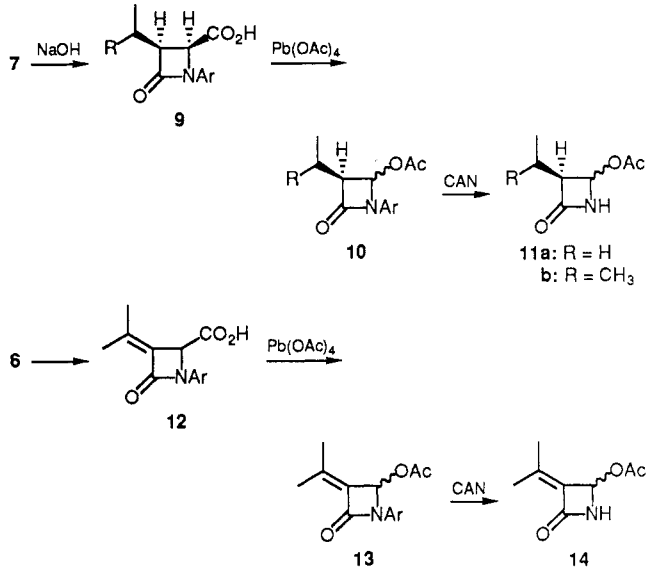
**Scheme II**




**Scheme III**




**Scheme IV**




mers appeared to depend on the temperature of the reaction.

In a recent publication[13] we have reported on the steric composition of α-vinyl β-lactams from a variety of Schiff bases. No clear-cut generalization about the steric course of α-vinyl β-lactam formation could be made.

Zamboni and Just[12] have reported that Schiff bases derived from aniline give either all trans or a mixture of trans and cis α-vinyl β-lactams. In contrast, we have now observed that reaction with the Schiff base from methyl glyoxalate and *p*-anisidine leads exclusively to cis α-vinyl β-lactams (Scheme II).

A few authors including Zamboni and Just[12] have tried to rationalize the steric course of β-lactam formation by postulating certain pathways. These postulates are, however, inadequate for predicting the stereochemistry of α-vinyl β-lactam formation (see Table I for a summary). In this connection, it is interesting to note that the Schiff base from furfuraldehyde and aniline produces only a trans β-lactam on reaction with crotonyl chloride and only a cis β-lactam on reaction with azidoacetyl chloride. This complete reversal of the steric course of annelation is not obvious on the basis of the rationalizations about β-lactam formation.[12]

## Chemical Transformations

**a. Isomerization.** Since most of the cerbapenem antibiotics are trans β-lactams, we attempted to epimerize the C-4 position of the cis β-lactam (**5**) to obtain the trans isomer. When the β-lactam (**5a**) was refluxed in benzene in presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene), a new compound in quantitative yield was isolated. The infrared spectrum of this compound exhibited absorption at 1630 (C=C), 1735 (ester C=O), and 1765 (β-lactam C=O) $cm^{-1}$. The proton NMR spectrum, however, exhibited two doublets for methyl protons at δ 1.90 and 2.12 and two quartets at δ 5.95 and 6.40, respectively. The integration of the doublet and quartet protons showed them to be in the ratio of 3:1. Carbon-13 spectra revealed two vinylic methyl carbons at δ 20 and 25 and a quarternary carbon at δ 141.5. These data indicate that the product of this reaction is a mixture of *E* and *Z* isomers of **6a**. The double bond in **5a** had isomerized to afford an α-vinylidene β-lactam **6a**, probably due to the thermodynamic stability of the α,β-unsaturated carbonyl system. We have explored this isomerization reaction with other similarly substituted β-lactams and found it to be of general nature. Thus, under similar experimental conditions, **5b–d** afforded **6b–d**, respectively (Scheme II).

**b. Reduction.** The unsaturated β-lactam **5a** was hydrogenated under atmospheric pressure in the presence of a catalytic amount of 10% Pt/C in ethyl acetate to afford the cis α-ethyl β-lactam **7a** in quantitative yield. The ethylidene β-lactam **6a** upon catalytic hydrogenation afforded the same cis β-lactam **7a** exclusively, indicating thereby that the double bond was approached by the catalyst surface from the less hindered face of **6a**. In a similar way hydrogenation of unsaturated β-lactams **5b–d** and **6b–d** gave cis β-lactams **7b–d**.

**c. 3-Acetyl-2-azetidinone.** Literature methods for the synthesis of 3-acetyl-2-azetidinone use the aldol condensation of acetaldehyde with a 3-unsubstituted β-lactam followed by oxidation[14] or the reaction of an imine with diketene[15] or the reaction of an appropriately substituted enolate with an imine.[16] All of these methods, however, have their limitations, and yields are generally not satisfactory. We have used the above described β-lactams **5c,5d** as convenient intermediates for the synthesis of 3-acetyl-4-carbomethoxy or 4-carbethoxy-2-azetidinones. Thus, the ozonolysis of β-lactams **5c** and **5d** in methylene

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chloride at −70 °C gave cis α-acetyl β-lactams **8a** and **8b** in excellent yield (Scheme III).

It was possible to isomerize **8a** to the more stable trans β-lactam **15** (Scheme III). Upon refluxing **8a** overnight in benzene solution in the presence of DBN an equilibrium mixture (80:20) of trans and cis isomers was obtained from which the trans β-lactam could be isolated by column chromatography.

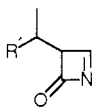
Earlier it has been noted that base-catalyzed epimerization of **5c** or **5d** to the trans isomer was not possible. Indirect access to these trans isomers, however, should be feasible by conducting Wittig type reactions on the *trans*-3-acetyl-2-azetidinone **15**.

**d. Intermediates for Antibiotics.** Hydrolysis of α-ethyl β-lactams esters **7a** and **7b** with sodium hydroxide in acetone–water led to the saponification of the ester group to give **9a** with little cleavage of the β-lactam ring. Oxidative decarboxylation of **9a** with lead tetracetate afforded **10a** in 75% yield as an 80:20 mixture of *trans*- and *cis*-1-*p*-anisyl-3-ethyl-4-acetoxy-2-azetidinone (Scheme IV).

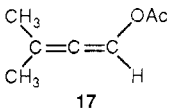
Following a literature method,[17] the *p*-anisyl group on the nitrogen was removed by oxidation with cerium(IV) ammonium nitrate (CAN), and **11a** was obtained in 78% yield (Scheme IV). In a similar fashion **6c**, **6d**, **7c**, and **7d** were converted to the corresponding isomeric mixtures of N-unsubstituted β-acetoxy β-lactams (Scheme IV).

Kametani and co-workers[18] used a different route to prepare **11a** and **11b**, which they obtained as a 50:50 mixture of cis and trans compounds. They transformed **11a** (R′ = H) to PS-5 and **11b** (R′ = $CH_3$) to PS-6 via the unsaturated intermediate **16**. The initial composition of the cis/trans mixture is therefore of no consequence. The preparation of an 80:20 mixture of trans and cis **11a** and **11b** by us could therefore be considered as a formal synthesis of PS-5 and PS-6.

The α-ethylidene β-lactam **14** was prepared by Buynak[19] et al. from an allene derivative **17** and utilized as an intermediate for asparenomycin antibiotics. Our synthesis of **14** from readily available starting materials therefore provides a convenient pathway to asparenomycin.



16



17

Our preparation of the trans β-lactams **15** constitutes a formal synthesis of thienamycin in the light of the conversion of **15** to thienamycin reported by Fetter et al.[20]

In summary, the stereocontrolled synthesis of α-vinyl β-lactams by our method and their various transformations described here provide convenient access to PS-5, PS-6, asparenomycin, and thienamycin. Since our starting materials, in particular, crotonyl chloride and *p*-anisidine, can be easily obtained in $^{14}C$-, $^{13}C$-, and $^{15}N$-labeled forms, labeled penems for metabolic and spectroscopic studies should be easily accessible.

## Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1310 instrument. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC-200 spectrometer using TMS as an internal standard. The following abbreviations are used to designate the multiplicity of individual signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet, q = quartet. Chemical ionization mass spectra were recorded on a Biospect. instrument using either $NH_3$ or $CH_4$ as the reagent gas. All organic solvents were dried by standard procedures. Thin-layer chromatography was performed with Whatmann plates, and the spots were detected in a UV viewing chamber. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, NY.

**Preparation of Imine 4a.** Methyl glyoxalate (3.52 g, 0.04 mol) was dissolved in 150 mL of dry methylene chloride, and a solution of *p*-anisidine (4.92 g, 0.04 mol) in 50 mL of methylene chloride was added slowly. The reaction mixture was stirred at room temperature for $^1/_2$ h, and then 4A molecular sieves (10 g) were added to it. After stirring for an additional 1 h the reaction mixture was filtered. Evaporation of solvent from the filtrate afforded 7.35 g of imine **4a** as a viscous red oil. This compound was used as such in subsequent reactions: IR (neat) 1635 (imine), 1730 (ester CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.8 (s, 3 H), 4.0 (s, 3 H), 6.95 (d, 2 H), 7.95 (d, 2 H), 8.0 (s, 1 H); MS *m/z* 201 (M + $NH_4^+$).

The imine **4b** was prepared from ethyl glyoxalate (4.08 g, 0.04 mol) and *p*-anisidine (4.92 g, 0.04 mol) according to the procedure described under **4a**: yield 8.12 g (90.2%); IR (neat) 1640 (imine), 1730 (ester CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.4 (t, 3 H), 3.8 (s, 3 H), 4.42 (q, 2 H), 6.9 (d, 2 H), 7.35 (d, 2 H), 7.9 (s, 1 H); MS *m/z* 225 (M + $NH_4^+$).

***cis*-1-*p*-Anisyl-3-vinyl-4-carbomethoxy-2-azetidinone (5a).** To a well-stirred solution of the imine **4a** (3.8 g, 0.02 mol) in 250 mL of methylene chloride was added triethylamine (4.4 g, 0.04 mol). The reaction mixture was heated to reflux, and a solution of crotonyl chloride (2.69 g, 0.025 mol) in 100 mL of methylene chloride was added over a period of 1 h. The reaction mixture was refluxed overnight, cooled, and washed with dilute HCl, saturated $NaHCO_3$ solution, water, and brine, and dried ($Na_2SO_4$). Filtration, followed by evaporation of solvent, afforded a dark viscous mass, which was purified by passing over a silica gel column using ethyl acetate–hexanes (1:4) as the solvent system. The compound was crystallized from methylene chloride–hexanes (3:1) as white needles: yield 3.13 g (60%); mp 87 °C; IR ($CHCl_3$) 1655 (C=C), 1725 (ester CO), 1750 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 3.8 (s, 3 H), 3.85 (s, 3 H), 4.3 (m, 1 H), 4.7 (d, 1 H, *J* = 5.8 Hz), 5.4 (m, 1 H), 5.56 (m, 1 H), 5.75 (m, 1 H), 6.95 (d, 2 H), 7.3 (d, 2 H); MS *m/z* 279 (M + $NH_4^+$), 296 (279 + $NH_3$)$^+$. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.74; N, 5.36. Found: C, 64.12; H, 5.57; N, 5.28.

***cis*-1-*p*-Anisyl-3-vinyl-4-carbethoxy-2-azetidinone (5b).** β-Lactam **5b** was prepared in 62% yield from imine **4b** (2.1 g, 0.01 mol), triethylamine (0.02 mol), and crotonyl chloride (1.56 g, 0.015 mol) according to the method described for β-lactam **5a**: mp 79 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1648 (C=C), 1730 (ester CO), 1760 (β-lactam CO); $^1H$ NMR ($CDCl_3$) δ 1.20 (t, 3 H), 2.90 (s, 3 H), 3.90 (s, 3 H), 4.30 (m, 3 H), 5.20 (d, 2 H, *J* = 5.1 Hz), 6.90 (d, 2 H), 7.35 (d, 2 H); MS *m/z* 293 (M + $NH_4^+$), 310 (293 + $NH_3$)$^+$. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.18; H, 6.21; N, 4.83.

***cis*-1-*p*-Anisyl-3-ethyl-4-carbomethoxy-2-azetidinone (7a).** To a solution of β-lactam **5a** (1.30 g, 0.005 mol) in 100 mL of ethyl acetate was added catalytic amount of 5% Pt–C. Hydrogenation was carried out under atmospheric pressure until the required amount of hydrogen was absorbed. The catalyst was filtered over a pad of Celite, and the solvent was removed to give 1.20 g (92%) of the title compound: mp 41 °C (ether–hexanes); IR ($CHCl_3$) 1735 (ester CO), 1760 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ

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1.1 (t, 3 H), 1.85 (q, 2 H), 3.5 (m, 1 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.6 (d, 1 H, $J$ = 6.1 Hz), 6.95 (d, 2 H), 7.30 (d, 2 H); MS $m/z$ 281 ($M + NH_4^+$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.46; N, 5.36. Found: C, 63.51; H, 6.21; N, 5.27.

***cis*-1-*p*-Anisyl-3-ethyl-4-carbethoxy-2-azetidinone (7b).** Hydrogenation of β-lactam (1.1 g, 0.004 mol) **5b** was performed by following the method described for **7a**: mp 38 °C (ether–hexanes); IR ($CHCl_3$) 1730 (ester CO), 1765 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.20 (t, 3 H), 1.79 (q, 2 H), 3.6 (m, 1 H), 3.85 (s, 3 H), 4.05 (q, 2 H), 4.8 (d, 1 H, $J$ = 5.9 Hz), 6.98 (d, 2 H), 7.25 (d, 2 H); MS $m/z$ 278 ($M + H^+$), 294 ($M + CH_5^+$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.85; N, 5.05. Found: C, 64.79; H, 6.73; N, 4.91.

***cis*-1-*p*-Anisyl-3-ethyl-4-carboxy-2-azetidinone (9a).** β-Lactam **7a** or **7b** (0.01 mol) was dissolved in 20 mL of acetone, and a solution of NaOH (0.5 g, 0.011 mol) in 15 mL of water was added. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. When there was no starting material left, acetone was removed under reduced pressure. The resulting solution was diluted with water and extracted twice with ethyl acetate. The aqueous solution was neutralized with 3 N HCl and extracted with ethyl acetate. The organic layer was washed with water and brine and dried ($Na_2SO_4$). Removal of solvent gave **9a** as a white solid: mp 166 °C (ethyl acetate–hexanes); yield 83%; IR (Nujol) 1700 (acid CO), 1760 (β-lactam CO), 3350 (OH) $cm^{-1}$; $^1H$ NMR ($CDCl_3$–DMSO-$d_6$) δ 1.0 (t, 3 H), 1.70 (q, 2 H), 3.40 (m, 1 H), 3.80 (s, 3 H), 4.60 (d, 1 H, $J$ = 6.15 Hz), 6.95 (d, 2 H), 7.30 (d, 1 H), 9.30 (br, 1 H); MS $m/z$ 248 ($M - H^+$), 284 ($M + Cl^-$). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.73; H, 6.11; N, 5.59.

**1-*p*-Anisyl-3-ethyl-4-acetoxy-2-azetidinone (10a).** To a solution of acid **9a** (2.49 g, 0.01 mol) in 20 mL of DMF was added 5 mL of acetic acid at room temperature. The reaction mixture was heated to 60 °C on an oil bath. Lead tetraacetate (4.04 g, 0.015 mol, purchased from Aldrich Chemical Co. and used as such) was added to the reaction mixture. Evolution of $CO_2$ was noticed. The reaction mixture was heated for an additional 5 min, cooled to room temperature, diluted with an excess of water, and extracted with ethyl acetate. The organic layer was washed with aqueous $NaHCO_3$ and brine and dried ($Na_2SO_4$). Removal of solvent gave the title compound **10a** in 72% yield (1.89 g): mp 91 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1730 (ester CO), 1780 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.0 (t, 3 H), 1.80 (q, 2 H), 2.1 (s, 3 H), 3.1 (t, 1 H), 3.75 (s, 3 H), 6.1 (s, 1 H, $J$ = 1.3 Hz), 6.5 (s, 1 H, $J$ = 4 Hz), 6.9 (d, 2 H), 7.3 (d, 2 H); MS $m/z$ 264 ($M + H^+$), 286 ($M + CH_5^+$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.46; N, 5.32. Found: C, 63.79; H, 6.40; N, 5.27.

**3-Ethyl-4-acetoxy-2-azetidinone (11a).** β-Lactam **10a** (2.63 g, 0.01 mol) was dissolved in 50 mL of acetonitrile, cooled at −30 °C, and a solution of cerric(IV) ammonium nitrate (15 g) in 50 mL of water was added. The reaction mixture was stirred, and the progress of the reaction was monitored by TLC. When no more starting material was left, the reaction mixture was diluted with excess water and extracted with ethyl acetate (three times). The organic layer was washed with aqueous $Na_2SO_3$, aqueous $NaHCO_3$, and brine and dried over $Na_2SO_4$. Removal of solvent yielded **11a** as a pale yellow oil: yield 83% (1.3 g); IR (neat) 1740 (ester CO), 1780 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.06 (t, 6 H), 1.80 (q, 4 H), 2.15 (s, 6 H), 3.18 (t, 2 H), 5.58 (s, 1 H), 5.85 (d, 1 H), 6.90 (s, 2 H); MS $m/z$ 175 ($M + NH_4^+$), 193 ($175 + NH_3$)$^+$.

***cis*-1-*p*-Anisyl-3-(1′-methylvinyl)-4-carbomethoxy-2-azetidinone (5c).** The title β-lactam was prepared in 67% yield from imine **4a** (1.93 g, 0.01 mol), triethylamine (0.02 mol), and 3,3-dimethylacryloyl chloride (1.78 g, 0.015 mol) according to the method described for synthesis of **5a**: mp 87 °C ($CH_2Cl_2$–hexanes); IR (Nujol) 1640 (ester CO), 1770 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.85 (s, 3 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 4.25 (d, 1 H, $J$ = 6 Hz), 4.6 (d, 1 H, $J$ = 6 Hz), 5.2 (m, 2 H), 6.9 (d, 2 H), 7.3 (d, 2 H); MS $m/z$ 293 ($M + NH_4^+$). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.31, H, 6.02; N, 4.91.

***cis*-1-*p*-Anisyl-3-(1′-methylvinyl)-4-carbethoxy-2-azetidinone (5d).** This β-lactam was obtained from imine **4b** (2.07 g, 0.01 mol), 3,3-dimethylacryloyl chloride (1.78 g, 0.015 mol), and triethylamine (0.015 mol) in 68% yield (1.96 g). It was crystallized from methylene chloride–hexanes: mp 86 °C; IR ($CHCl_3$), 1735 (ester CO), 1775 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.85 (s, 3 H), 3.82 (s, 3 H), 4.25 (m, 3 H), 4.70 (d, 1 H, $J$ = 6 Hz), 5.20 (d, 2 H), 6.9 (d, 2 H), 7.35 (d, 2 H); MS $m/z$ 307 ($M + NH_4^+$). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.29; H, 6.18; N, 4.69.

***cis*-1-*p*-Anisyl-3-isopropyl-4-carbomethoxy-2-azetidinone (7c).** Hydrogenation of β-lactam **5c** (1.37 g, 0.005 mol) in the presence of a catalytic amount of 5% Pt–C under atmospheric pressure gave **7c** in quantitative yield: mp 38 °C (ether–hexanes); IR (Nujol) 1735 (ester CO), 1775 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.15 (d, 3 H), 1.35 (m, 1 H), 3.79 (s, 3 H), 3.82 (s, 3 H), 3.90 (m, 1 H), 4.43 (d, 1 H, $J$ = 4.9 Hz), 6.9 (d, 2 H), 7.3 (d, 2 H); MS $m/z$ 278 ($M + H^+$), 294 ($M + CH_5^+$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.85; N, 5.05. Found: C, 64.79; H, 6.71; N, 4.83.

***cis*-1-*p*-Anisyl-3-isopropyl-4-carbethoxy-2-azetidinone (7d).** Atmospheric hydrogenation of unsaturated β-lactam **5d** (2.89 g, 0.01 mol) afforded the title compound in quantitative yield as a liquid: IR (neat) 1740 (ester CO), 1765 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.08 (d, 3 H), 1.20 (d, 3 H), 1.31 (m, 1 H), 1.72 (q, 2 H), 3.79 (s, 3 H), 4.05 (q, 2 H), 3.5 (m, 1 H), 4.6 (d, 1 H, $J$ = 5.05 Hz), 6.8 (d, 2 H), 7.15 (d, 1 H); MS $m/z$ 308 ($M + NH_4^+$).

***cis*-1-*p*-Anisyl-3-isopropyl-4-carboxy-2-azetidinone (9b).** β-Lactam **7c** (1.66 g, 0.006 mol) or **7d** (1.45 g, 0.005 mol) was hydrolyzed by NaOH in acetone–water according to the procedure described for **9a** to give **9b** in 81% yield: mp 186 °C (ethyl acetate–hexanes); IR (Nujol) 1705 (acid CO), 1775 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$–DMSO-$d_6$) δ 1.05 (m, 6 H), 1.40 (m, 1 H), 3.90 (s, 6 H), 4.35 (m, 1 H), 4.90 (d, 1 H, $J$ = 5.6 Hz), 6.90 (d, 2 H), 7.45 (d, 2 H), 9.23 (br, 1 H); MS $m/z$ 262 ($M - H^+$), 298 ($M + Cl^-$). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.46; N, 5.32. Found C, 63.70; H, 6.31; N, 5.19.

**1-*p*-Anisyl-3-isopropyl-4-acetoxy-2-azetidinone (10b).** The acid **9b** (0.01 mol) was reacted with of lead tetraacetate (4.46 g) in 20 mL of DMF and 5 mL of acetic acid at 60 °C for 5 min to yield 2.04 g (74%) of **10b** as a white crystalline solid: mp 76 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1740 (ester CO), 1775 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.05 (d, 3 H), 1.10 (d, 3 H), 2.10 (s, 3 H), 3.0 (dd, 1 H), 3.75 (s, 3 H), 6.3 (d, 1 H, $J$ = 1.5 Hz), 6.80 (d, 2 H), 7.30 (d, 2 H); MS $m/z$ 295 ($M + NH_4^+$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.85; N, 5.05. Found: C, 65.01; H, 6.83; N, 5.00.

**3-Isopropyl-4-acetoxy-2-azetidinone (11b).** Reaction of β-lactam **10b** (0.27 g, 0.001 mol) with cerric(IV) ammonium nitrate (1.6 g, 0.003 mol) in acetonitrile–water (3:1) gave the N-unsubstituted compound **11b** in 82% yield (0.15 g) as an oil; IR 1735 (ester CO), 1775 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.05 (d, 6 H), 1.15 (d, 6 H), 2.15 (s, 6 H), 3.05 (dd, 2 H), 5.67 (s, 1 H), 5.85 (d, 1 H), 7.00 (s, 2 H); MS $m/z$ 189 ($M + NH_4^+$).

**1-*p*-Anisyl-3-ethylidene-4-carbomethoxy-2-azetidinone (6a).** To a solution of β-lactam **5a** (0.26 g, 0.001 mol) in 50 mL of benzene was added 2 drops of DBN, and the reaction mixture was refluxed under $N_2$ atmosphere for 6 h. It was then washed with dilute HCl, aqueous $NaHCO_3$, and brine and dried over $Na_2SO_4$. Removal of benzene afforded the title compound as an equimolar mixture of $E$ and $Z$ isomers in quantitative yield: mp 138 °C ($E$ isomer), 147 °C ($Z$ isomer); IR ($CHCl_3$) 1630 (double bond), 1735 (ester CO), 1765 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.90 (d, 3 H), 2.12 (d, 3 H), 3.82 (s, 12 H), 5.95 (q, 1 H), 6.40 (q, 1 H), 6.9 (q, 4 H), 7.3 (d, 4 H); MS $m/z$ 279 ($M + NH_4^+$). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.74; N, 5.36. Found: C, 64.29; H, 5.74; N, 5.21.

**1-*p*-Anisyl-3-isopropylidene-4-carbomethoxy-2-azetidinone (6b).** Isomerization of the double bond of β-lactam **5c** (1.37 g, 0.005 mol) was carried out in quantitative yield according to the procedure described for **6a**: mp 112 °C (chloroform–hexanes); IR (Nujol) 1635 (C=C), 1730 (ester CO), 1750 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CHCl_3$) δ 1.85 (s, 2 H), 2.01 (s, 2 H), 3.8 (s, 3 H), 4.42 (s, 1 H), 6.90 (d, 2 H), 7.25 (d, 2 H); MS $m/z$ 276 ($M + H^+$).

**1-*p*-Anisyl-3-isopropylidene-4-carboxy-2-azetidinone (12).** To a solution of β-lactam **6c** or **6d** (1.37 g, 0.005 mol) in 30 mL of acetone was added a solution of NaOH (0.35 g, 0.008 mol) in 10 mL of water. The reaction mixture was stirred at room temperature for 4 h. After the usual workup, 1.12 g (82%) of the title compound was obtained: mp 159 °C (ethyl acetate–hexanes); IR (Nujol) 1625 (C=C), 1700 (acid CO), 1745 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$–DMSO-$d_6$) δ 1.95 (s, 3 H), 2.15 (s, 3 H), 3.80

(s, 3 H), 4.9 (s, 1 H), 6.90 (d, 2 H), 7.30 (d, 2 H), 7.60 (s, 1 H); MS $m/z$ 260 ($M - H^+$), 296 ($M + Cl^-$).

**1-*p*-Anisyl-3-isopropylidene-4-acetoxy-2-azetidinone (13).** Reaction of β-lactam **12** (1.04 g, 0.004 mol) with lead tetraacetate (2.21 g, 0.005 mol) by following the method described for **10a** gave the title compound in 79% yield: mp 105 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1620 (C=C), 1720 (ester CO), 1750 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.15 (s, 3 H), 2.20 (s, 3 H), 3.80 (s, 3 H), 6.90 (d, 2 H), 7.05 (s, 1 H), 7.40 (d, 2 H); MS $m/z$ 293 ($M + NH_4^+$). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.37; H, 6.01; N, 4.98.

**3-Isopropylidene-4-acetoxy-2-azetidinone (14).** Reaction of **13** (1.1 g, 0.004 mol) with cerric(IV) ammonium nitrate (6.15 g, 0.011 mol) in 25 mL of acetonitrile and 25 mL of water as solvent gave the title compound in 83% yield: mp 92 °C (methylene chloride–hexanes); IR (Nujol) 1620 (double bond), 1745 (ester CO), 1780 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.8 (s, 3 H), 2.05 (s, 3 H), 2.15 (s, 3 H), 6.20 (s, 1 H), 6.97 (br s, 1 H); MS $m/z$ 187 ($M + NH_4^+$). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.38; N, 8.15.

**1-*p*-Anisyl-3-ethyl-4-carbomethoxy-2-azetidinone (7a).** To a solution of β-lactam **5a** or **6a** (0.15 g, 0.0006 mol) in 25 mL of ethyl acetate was added a catalytic amount of 5% Pt–C. The hydrogenation was carried out under atmospheric pressure. Workup of the reaction mixture yielded the β-lactam in quantitative yield. This compound is identical in all respect with the compound prepared from **5a**.

***cis*-1-*p*-Anisyl-3-acetyl-4-carbomethoxy-2-azetidinone (8a).** To a well-cooled (−75 °C) solution of β-lactam **5c** (0.82 g, 0.003 mol) in 50 mL of methylene chloride was passed ozone until the color of the reaction turned blue. Excess ozone was removed by passing $N_2$ through the reaction mixture. Finally, 1.5 mL of dimethyl sulfide was added to it. The reaction mixture was stirred at −78 °C for 15 min and at room temperature for $^1/_2$ h, washed with water and brine, and dried over $Na_2SO_4$. Removal of solvent gave a colorless gummy mass, which was passed through Florisil. Subsequent crystallization from methylene chloride–hexanes gave **8a** as a crystalline solid: mp 103 °C; yield 87%; IR (Nujol) 1650 (ketone CO), 1755 (ester and lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$–DMSO-$d_6$) δ 2.24 (s, 3 H), 3.8 (s, 3 H), 3.85 (s, 3 H), 4.55 (d, 1 H, $J$ = 5.85 Hz), 4.65 (d, 1 H, $J$ = 5.85 Hz), 6.83 (d, 2 H), 7.2 (d, 2 H); MS $m/z$ 295 ($M + NH_4^+$).

***trans*-1-*p*-Anisyl-3-acetyl-4-carbomethoxy-2-azetidinone (15).** β-Lactam **8a** (0.27 g, 0.001 mol) was dissolved in 25 mL of dry benzene. To it 2 drops of DBN was added, and the reaction mixture was refluxed overnight under nitrogen. After cooling the organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, water, and brine successively. Removal of solvent gave an oil, which was purified through column chromatography to yield 0.22 g (83%) of the title compound: mp 139 °C (methylene chloride–hexanes); IR (Nujol) 1720 (ketone, ester CO), 1760 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.1 (s, 3 H), 3.9 (s, 3 H), 3.95 (s, 3 H), 4.4 (d, 1 H, $J$ = 2.8 Hz), 4.9 (d, 1 H, $J$ = 2.8 Hz); MS $m/z$ 295 ($M + NH_4^+$).

**1-*p*-Anisyl-3-isopropylidene-4-carbethoxy-2-azetidinone (6d).** The title β-lactam was obtained in quantitative yield from **5d** (1.44 g, 0.005 mol) according to the method used to prepare **17**: mp 94 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1660 (C=C), 1725 (ester CO), 1745 (β-lactam CO) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.9 (s, 3 H), 2.20 (s, 3 H), 3.80 (s, 3 H), 4.30 (q, 2 H), 4.9 (s, 1 H), 6.92 (d, 2 H), 7.38 (d, 2 H); MS $m/z$ 290 ($M + H^+$).

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# Ruthenium-Catalyzed Dehydrogenative N-Heterocyclization: Indoles from 2-Aminophenethyl Alcohols and 2-Nitrophenethyl Alcohols

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Indole derivatives **3** were readily obtained from 2-aminophenethyl alcohols **1** in the presence of 2 mol % (based on **1**) of $RuCl_2(PPh_3)_3$ under reflux in toluene. Indole (**3a**) was afforded from 2-aminophenethyl alcohol (**1a**) quantitatively. Other indoles (**3**) were also obtained in 73–99% isolated yields from the corresponding **1**, which were easily prepared by condensation between the corresponding 2-nitrotoluenes and aldehydes followed by reduction. During the reaction, a stoichiometric amount of hydrogen was spontaneously evolved into the gas phase. With a heterogeneous and homogeneous binary catalyst system, indoles were afforded in one pot from 2-nitrophenethyl alcohols **2** under a hydrogen atmosphere.

## Introduction

The Fischer indole synthesis is most widely used to construct an indole skeleton and has been extensively reviewed.[1] It involves the rearrangement of arylhydrazones on heating and/or with acid catalysts. α-Arylamino ketones and aldehydes are readily prepared from α-halocarbonyl compounds and arylamines, and they cyclize to indoles with acid catalysts (Bischler synthesis).[2] Treatment of *o*-alkylanilides with strong bases such as sodium amide and potassium *tert*-butoxide at 200–400 °C results in the formation of indoles (Madelung synthesis).[3] As for

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