Stereocontrolled Synthesis of *N*-Vinyl-, *N*-(1′-Propenyl)-, and *N*-Unsubstituted-β-lactams from 2-Aza-1,3-butadienes via the Staudinger Reaction

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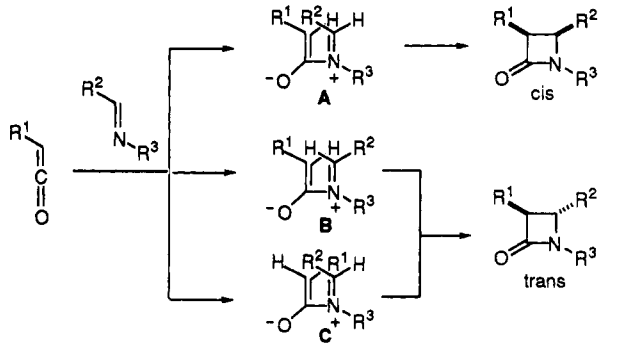
2-Aza-1,3-butadienes **2** and **5** were synthesized in good yields and on a large scale. Reaction of **2** and **5** with acid chlorides in the presence of triethylamine (Staudinger reaction) resulted in the high-yielding formation of *N*-vinyl- and *N*-(1′-propenyl)-β-lactams. Excellent cis-stereoselectivity was observed in the reaction of 2-aza-1,3-butadienes **2** and **5** with Bose–Evans ketenes and Sheehan ketenes, whereas reaction with a Moore ketene gave, as expected, a trans β-lactam. *N*-Formyl, *N*-vinyl, and *N*-(1′-propenyl) groups at the β-lactam nitrogen could be cleaved oxidatively in one step and in good yields by treatment with potassium permanganate. It was also found that the *N*-vinyl group can be removed successfully under hydrolytic conditions to yield *N*-unsubstituted-β-lactams.

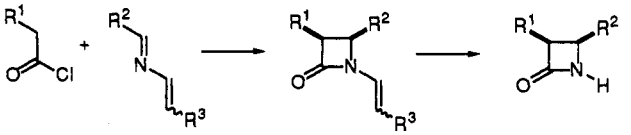
Introduction

Among various methods for β-lactam synthesis,[1-3] the Staudinger reaction,[4] involving the [2 + 2] cycloaddition reaction of imines and ketenes (Scheme I), is regarded as one of the most versatile procedures for the stereocontrolled synthesis of 3,4-bis-substituted 2-azetidinones. Typically, the ketene is generated either from acid chlorides and related derivatives in the presence of tertiary amines,[4] thermally,[5] or photochemically from metal carbenes.[6] Subsequent reaction with an imine yields the desired β-lactam in a one-flask procedure. The mechanism of the Staudinger reaction (Scheme I) and the rationale for the stereochemistry of the products are still under debate.[4,6-10] However, it is generally accepted that the imine is attacked by the ketene to generate a zwitterionic intermediate, which upon conrotatory ring closure will yield the reaction products. Attack of the imine from the least hindered side of the ketene will generate cis β-lactams via intermediate A (Scheme I). Trans β-lactams will be formed via intermediate B from (*Z*)-imines, imidates, and thioimidates. On the basis of semiempirical calculations it was recently proposed that intermediate C is formed in the reaction between chloroketene (and related Moore ketenes) and imines.[10] The mechanistic models which have been proposed are very useful to explain the stereochemical outcome of many reactions involving ketenes and imines. It is, however, important to recognize that the cis–trans ratio of β-lactam formation in the Staudinger reaction is dependent on a variety of factors such as structure of the ketene and the imine, solvent, mode of ketene generation, reaction rates, temperature, and order of addition of reagents.[3,4]

Scheme I



Scheme II



R^1 = PhO, phthalimido; R^2 = Ph, PhCH=CH, PhCH=CMe; R^3 = H, Me

Recently, we have demonstrated that *N*-vinylimines and *N*-(1′-propenyl)imines can be utilized in the Staudinger reaction to yield cis β-lactams (Scheme II) in a highly stereocontrolled fashion.[11,12] Similar studies were detailed by Palomo[13] on the conversion of *N*-phenylethenylimines to the corresponding β-lactams and by Würthwein on related reactions between diphenylketene and 1,3-diazabutadienes.[14] We would now like to report the full details

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of our investigations, including our results on the conversion of *N*-vinyl- and *N*-(1′-propenyl)-β-lactams to *N*-unsubstituted 2-azetidinones.

Nitrogen substituents which are easily removable[15] after β-lactam formation are of interest in β-lactam chemistry because *N*-unsubstituted β-lactams are useful and necessary intermediates for the synthesis of β-lactam antibiotics[16] such as the monobactam[17] carumonam,[18] penem antibiotics[19] such as PS-5,[20] α-amino acids and oligopeptides,[21] and β-amino acids such as *N*-benzoyl-3-phenylisoserine, the side chain of the antitumor agent taxol.[22]

Imines, which are often utilized in the Staudinger reaction, possess *N*-substituents which can be removed in a single chemical transformation after β-lactam formation, including *N*-benzyl and *N*-aryl groups.[15] *N*-Benzyl groups can be cleaved reductively[23,24] or oxidatively,[25-27] and *N*-aryl groups can be removed through oxidative methods.[28,29] Other nitrogen substituents, which have been described recently and can be removed in a single step, are derived from carbohydrates.[30,31] Nitrogen substituents, which have to be removed in several steps via the formation of their respective *N*-ethenyl intermediates, include β-lactams obtained from imines derived from threonine,[32,33] serine,[34,35] 2-amino-1,3-propanediols,[36] allylamine,[37] aminoacetaldehyde diethyl acetal,[37] and (phenylselenyl)ethylamine.[38]

Scheme III

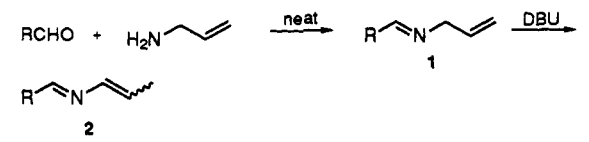

Table I. 2-Azabutadienes 2 and 5 and Intermediates 3 (Schemes III and IV)

entry	compd	R^1	R^2	yield of 3 (%)	solvent	*E*:*Z* ratio[d]	yield of 2 or 5 (%)
1	**2a**	Ph	Me		CH_2Cl_2[b]	4:1	85
2	**2b**	PhCH=CH	Me		CH_2Cl_2[b]	4:1	100[e]
3	**2c**	PhCH=CMe	Me		CH_2Cl_2[b]	2:1	97
4	**2d**	Ph_2C=CH	Me		CH_2Cl_2[b]	4:1	100[e]
5	**5a**	Ph	H	83 (**3a**)	DMF[c]		84
6	**5b**	PhCH=CH	H	79 (**3b**)	MeCN[c]		78
7	**5c**	PhCH=CMe	H	75 (**3c**)	DMF[c]		63
8	**5d**	PhC≡C	H	nd (**3d**)[a]	MeCN[c]		69

[a] Yield not determined (nd). (Isolated and used in the next step as a mixture of **3d** and *N*,*N*-dimethylethylenediamine). [b] Solvent for the conversion of **1** to **2** (**Scheme III**). [c] Solvent for the conversion of **3** to **4**. The Hoffmann elimination was carried out in DMF as the solvent (**Scheme IV**). [d] Determined by inspection of ^{1}H NMR signals. [e] Crude yields.

The results presented in this study detail the utility of 2-aza-1,3-butadiene in the Staudinger reaction (Scheme II) toward the synthesis of *N*-ethenyl-β-lactams. Only one or two steps (one-flask procedure) are required for their deprotection to obtain *N*-unsubstituted-β-lactams.

Results and Discussion

A literature survey[39] revealed that 2-aza-1,3-butadienes of type **2** (Scheme III) derived from benzaldehyde and pivalaldehyde can be obtained from allylimines of type **1** through double-bond isomerization with potassium *tert*-butoxide in DMSO.[40,41] We, however, observed that these reaction conditions were not suitable for the synthesis of the cinnamaldehyde-derived azadienes **2b–2d** (Table I). Subsequently, we found that the desired imines **2a–2d** could be obtained via isomerization of the corresponding allylimines **1** (Scheme III) using DBU as the base.

Thus, the known aza diene **2a** and the novel *N*-(1′-propenyl)imines **2b–2d** were synthesized in a one-flask, two-step procedure and in excellent overall yields (Scheme III and Table I, entries 1–4). The aldehydes were first mixed with 2 equiv of allylamine at room temperature (1 h, neat), followed by isomerization of the resulting crude imines **1** with DBU in methylene chloride (16–20 h) to

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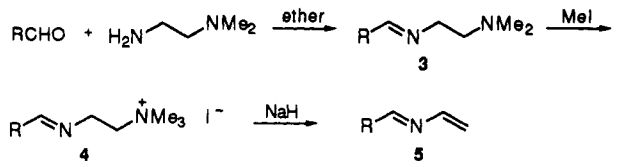
Scheme IV



yield the desired *N*-(1′-propenyl)imines **2**. The reactions were carried out at a scale of 35–50 mmol. The *N*-(1′-propenyl)imines **2** were obtained as mixtures of *E*- and *Z*-isomers. We were able to purify derivatives **2a** and **2c** by vacuum distillation. 2-Aza-1,3-butadienes **2b** and **2d**, however, polymerized upon distillation and were therefore used in the Staudinger reaction without further purification. We also prepared *N*-allylimines derived from aliphatic aldehydes but were unable to isomerize them to the corresponding *N*-(1′-propenyl)imines. The presence of an acidic α-hydrogen in these imines is probably incompatible with the strongly basic reaction conditions of this procedure.[42,43]

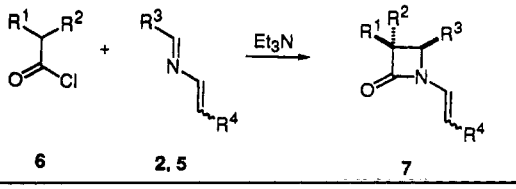
The 2-aza-1,3-butadienes **5** (Scheme IV and Table I, entries 5–8) could be synthesized in good overall yield following a procedure reported by Böhme[44] for the synthesis of **5a**. Similar reaction conditions were also suitable for the synthesis of 2-aza-1,3-butadienes **5b–5d**. Reaction of the aldehydes with *N*,*N*-ethylenediamine in anhydrous ethyl ether as the solvent and in the presence of magnesium sulfate gave imines **3a–3d**, which could either be purified by vacuum distillation or used in crude form in the next step of the reaction. In a one-flask procedure, the imines **3** were methylated with iodomethane in DMF or acetonitrile (MeCN) as the solvent to yield the intermediate ammonium iodides. The crude ammonium salts underwent Hoffmann elimination with sodium hydride in DMF to yield the desired 2-aza-1,3-butadienes **5a–5d** in good yields (Table I, entries 5–8). The reactions were carried out at a scale of 3–137 mmol, depending on the availability of the aldehyde. 2-Aza-1,3-butadienes **5a** and **5c** could be purified by distillation, whereas 2-aza-1,3-butadienes **5b** and **5d** decomposed upon distillation and were therefore used in the Staudinger reaction without further purification.

We found that the aza dienes **2** and **5** are prone to facile polymerization not only at elevated temperature but also at room temperature[45] and should therefore be stored at freezer temperature. However, long storage times of aza dienes **2** and **5**, even at low temperature, resulted in low yields of β-lactam formation. Therefore, it is advantageous to use aza dienes **2** and **5** soon after their preparation.

The newly synthesized 2-aza-1,3-butadienes **2** and **5** were subsequently utilized in the Staudinger reaction (Table II). Acid chlorides were either commercially available or prepared by standard procedures. In order to achieve high cis selectivity in the reaction, the acid chlorides were added to a mixture of imines **2** or **5** and triethylamine in methylene chloride at 0 °C.[46,47] The stereochemical outcome of the Staudinger reaction of the newly synthesized 2-aza-1,3-butadienes was investigated with three types of ketenes,[4] a Bose–Evans ketene derived from phenoxyacetyl chloride, a Sheehan ketene generated from phthalimidoacetyl chloride, and a Moore ketene prepared from butyryl chloride.

In the context of the mechanistic framework of the Staudinger reaction, we have recently suggested simple empirical rules[4] to predict the stereochemistry of the Staudinger reaction products depending on steric and electronic influences exerted by the ketene and the imine.[48] As part of these empirical rules, we have classified the ketenes into three groups (Figure 1): Bose–Evans ketenes (small size substituents R^1 such as OR, NHR, N_3), Sheehan ketenes (medium size substituents R^1 such as phthalimido and alkylidene), and Moore ketenes (large size substituents

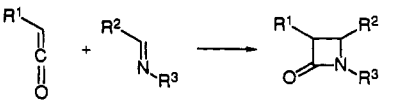
Table II. Formation of *N*-Alkenyl-β-lactams[a] via the Staudiner Reaction



6 2, 5 7

entry	compd	R^1	R^2	R^3	R^4	*E*:*Z* ratio[b]	cis:trans ratio	yield (%)
1	**7a**	PhO	H	Ph	Me	9:1	cis	66
2	**7b**	PhO	H	Ph	H		31:1	96
3	**7c**	PhO	H	PhCH=CH	Me	7.5:1	cis	88
4	**7d**	PhO	H	PhCH=CH	H		cis	86
5	**7e**	PhO	H	PhCH=CMe	Me	4:1	cis	84
6	**7f**	PhO	H	PhCH=CMe	H		cis	82[d]
7	**7g**	PhO	H	PhC≡C	H		3.2:1	59
8	**7h**	PhO	H	Ph_2C=CH	Me	4.7:1	cis	80
9	**7i**	Phth	H	Ph	Me	9:1	32:1[c]	64
10	**7j**	Phth	H	Ph	H		1.1:1	39
11	**7k**	Phth	H	PhCH=CH	Me	6:1	cis	69
12	**7l**	Phth	H	PhCH=CH	H		cis	60
13	**7m**	Phth	H	PhCH=CMe	H		cis	63
14	**7n**	H	Et	PhCH=CH	Me	6.5:1	trans	15

[a] Only the major isomer of β-lactam **7** is depicted in the chemical equation of **Table II**. [b] The *E*:*Z* ratio is given for the major isomer. [c] The *E*:*Z* ratio for trans **7i** was found to be 1:2. [d] 80% of **7f**-*cis*-*E* and 2% of **7f**-*cis*-*Z* were isolated.



Ketenes	alkyl aryl imines	diaryl imines
Bose-Evans ketenes	cis β-lactams	cis β-lactams
Sheehan ketenes	cis β-lactams	trans β-lactams
Moore ketenes	trans β-lactams	trans β-lactams

Figure 1. Empirical rules to predict the stereochemical outcome of the Staudinger reaction.[4]

(42) For the synthesis of 4-aza-3,5-heptadiene derived from propionaldehyde via the protodesilylation of *N*-[3-(triethylsilyl)propen-3-yl]-propionaldimine see: Chen, S.-F.; Ho, E.; Mariano, P. S. *Tetrahedron* **1988**, *44*, 7013. 4-Aza-3,5-heptadiene is an unstable compound and can only be formed *in situ*. See also ref 39c.

(43) For a newer method to synthesize silyl-substituted 2-aza-1,3-dienes from an aliphatic aldehyde see: Degl'Innocenti, A.; Mordini, A.; Pinzani, D.; Reginato, G.; Ricci, A. *Synlett* **1991**, 712.

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(48) For a detailed discussion of these empirical rules see ref 4. On the basis of recent semiempirical calculations of transition states in the Staudinger reaction (reference 10), the formation of trans products with Moore ketenes may not depend on steric influences as suggested earlier[4] but may involve electrostatic interactions.[10]

R^3 such as alkyl, halide, sulfide). Typically, Bose–Evans ketenes yield cis products with alkylarylimines and diarylimines, and Sheehan ketenes have a strong preference for cis product formation with alkylarylimines, but yield trans products with diaryl imines. Moore ketenes will give trans products with both alkylaryl- and diarylimines. (The group of alkylarylimines includes *N*-alkyl-*C*-aryl- as well as *N*-aryl-*C*-alkylimines.)

As detailed in Table II, Bose–Evans ketenes (entries 1–8, Table II) and Sheehan ketenes (entries 9–13, Table II) gave β-lactams with very high selectivity for cis product formation. Two exceptions to these general trends were observed for the reaction between phenoxyacetyl chloride and imine **5d** derived from propargyl aldehyde, yielding a 3.2:1 ratio of cis and trans β-lactam **7g** (entry 7, Table II)[34] and for the formation of β-lactam **7j** in a 1.1:1 ratio of cis/trans products (entry 10, Table II). As expected, reaction of the sterically demanding Moore ketene derived from butanoyl chloride with 2-aza-1,3-butadiene **5b** yielded trans β-lactam **7n** (entry 14, Table II).

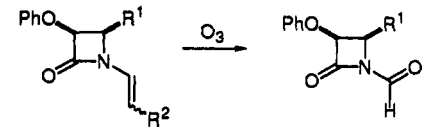
The stereochemical results, obtained in the Staudinger reaction of 2-aza-1,3-butadienes **2** and **5** with Bose–Evans ketenes and Sheehan ketenes yielding cis products and trans products with Moore ketenes parallels the stereochemistry typically obtained with alkylarylimines (see Figure 1). Thus, *N*-vinylimines and *N*-(1′-propenyl)imines displayed stereochemical results in the Staudinger reaction, which are similar to the ones observed in the reaction of these ketenes with alkylarylimines.

In our preliminary paper concerning the reactions of *N*-vinylimines **5** with various acids chlorides, we had reported that the reaction between phenoxyacetyl chloride and **5c** resulted in the formation of 80% **7f**-*cis* and 2% of the corresponding trans product. However, a careful analysis of the minor reaction product by NMR (nuclear Overhauser enhancement experiment) revealed that the minor product was β-lactam **7f**-*cis*-*Z*, possessing cis stereochemistry at the β-lactam ring and *Z*-geometry at the C-4 substituent. The major isomer is as expected **7f**-*cis*-*E* (Table II, entry 6). NMR analysis of the α-methylcinnamaldehyde, which had been utilized as the starting material for the formation of imine **5c**, and the ^{1}H NMR spectrum of **5c** both revealed the presence of the respective *E* (major) and *Z* (minor) isomers.

The low chemical yield (15%) observed for the formation of 3-ethyl-2-azetidinone **7n** was expected and can be traced to the inherent instability of alkyl ketenes.[49,50] With the exception of the low yield[51] obtained for the formation of β-lactam **7n**, derived from an alkylketene, the yields achieved in the Staudinger reaction with 2-aza-1,3-butadienes **2** and **5** were typically good (Table II).

We next investigated the cleavage of the *N*-vinyl and *N*-(1′-propenyl) groups toward the formation of *N*-unsubstituted-β-lactams. The β-lactam derivatives **7a**, **7e**, and **7f** (entries 1–3, Table III) were subjected to oxidative cleavage with ozone to produce their respective *N*-formyl derivatives. In derivatives **7e** and **7f**, the C-4 styryl group was cleaved simultaneous to yield 4-acetyl derivative **8b**. Hydrolytic cleavage of the *N*-formyl group with hydrochloric acid could not be employed successfully without β-lactam cleavage, and reaction with ammonium hydroxide

Table III. Oxidative Cleavage of Alkylidene Groups in β-Lactams 7a, 7e, and 7f with Ozone



entry	compd	R^1	R^2	compd	R^1	yield (%)
1	**7a**	Ph	Me	**8a**	Ph	62
2	**7e**	PhCH=CMe	Me	**8b**	COMe	75
3	**7f**	PhCH=CMe	H	**8b**	COMe	59

in tetrahydrofuran gave low yields (<40%) of the *N*-unsubstituted β-lactams. We therefore reasoned that oxidation of the *N*-formyl group to an *N*-carboxy group with potassium permanganate,[52] followed by spontaneous decarboxylation of the intermediate carbamic acid derivative, might potentially be a milder method for the removal of the *N*-formyl group.[53] As detailed in Table IV (entries 1 and 2), we were successful in this approach, and the desired *N*-unprotected β-lactams **9a** and **9b** were isolated in 87% and 85% yield, respectively.

We were also able to extend this approach toward a two-step, one-flask procedure for the cleavage of the *N*-vinyl and *N*-(1′-propenyl) groups. Thus, oxidative cleavage of *N*-vinyl- and *N*-(1′-propenyl)-β-lactams (Table IV, entries 3–7) with potassium permanganate yielded the *N*-unprotected β-lactams in yields ranging from 50% to 90%.[54,55] Short reaction times (about 10 min) are crucial for the success of this reaction. Longer reaction times invariably resulted in a significant decrease of chemical yields for these transformations.

Because of the enamide character of the *N*-vinyl and *N*-(1′-propenyl)-β-lactams, we felt it was worthwhile to also investigate the possibility of a hydrolytic cleavage of said groups. After an investigation of a variety of reaction conditions, it was found that the best results were obtained by refluxing *N*-vinyl-β-lactams **7b** and **7d** (Table V, method A) in tetrahydrofuran (THF) in the presence of 1% aqueous hydrochloric acid (9:1 ratio) in a pressure tube for 12 h at 55 °C. As reaction products, we obtained a mixture of *N*-unprotected-β-lactams **9** and their respective *N*-(hydroxyethyl) derivatives **10** (mixture of diastereoisomers).[56]

We found two different ways for the deprotection of the *N*-(hydroxyethyl) group. The first procedure involves the treatment of the crude mixture of **9** and **10**, obtained via the acid hydrolysis (method A), with sodium carbonate in THF/water (1:1), yielding the desired *N*-unprotected

(49) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1600.

(50) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444.

(51) For a review of strategies to obtain high yields of β-lactams in the reaction of alkyl ketenes with imines see: ref 4, p 306.

(52) For an example of oxidative removal of *N*-formyl groups with hydrogen peroxide from amino acids and oligopeptides, see: Losse, G.; Zönnchen, W. *Liebigs Ann. Chem.* **1960**, *636*, 140.

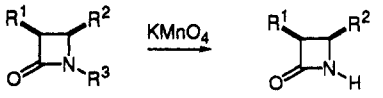
(53) Other methods for the deformylation of 2-azetidinones include their treatment with sodium methoxide in methanol or a catalytic amount of triethylamine in methanol: Aizpurua, J. M.; Cossio, F. P.; Lecea, B.; Palomo, C. *Tetrahedron Lett.* **1986**, *27*, 4359.

(54) Chemistry for the cleavage of *N*-vinyl groups of β-lactams was originally developed in the context of penicillin degradation: Brain, E. G.; Eglington, A. G.; Nayler, J. H. C.; Pearson, M. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1972**, 299. Harris, M. A.; McMillan, I.; Nayler, J. H. C.; Osborne, N. F.; Pearson, M. J.; Southgate, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1612.

(55) For another method of oxidative removal (ruthenium tetraoxide) of a β-lactam *N*-vinyl groups, see: Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.

(56) Hemiaminals of type **10**, derived from glyoxalic esters, are well-known intermediates toward the synthesis of cephalosporins and penems. Ernest, I.; Gosteli, J.; Greengrass, C. W.; Holick, W.; Jackman, D. E.; Pfaendler, H. R.; Woodward, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 8214.

Table IV. Oxidative Cleavage of the *N*-Alkenyl Group of β-Lactams 7 and the *N*-Formyl Group of β-Lactams 8 with Potassium Permanganate

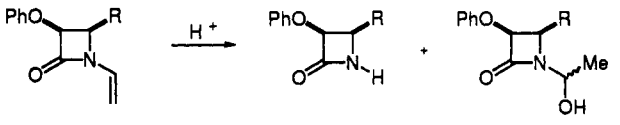


7, 8 9

entry	compd	R^1	R^2	R^3	compd	R^1	R^2	yield (%) of 9
1	**8a**	PhO	Ph	CHO	**9a**	PhO	Ph	87
2	**8b**	PhO	COMe	CHO	**9b**	PhO	COMe	85
3	**7a**	PhO	PhCH=CMe	CH=CHMe	**9b**	PhO	COMe	50
4	**7e**	PhO	Ph	$CH=CH_2$	**9a**	PhO	Ph	90
5	**7f**	PhO	PhCH=CMe	$CH=CH_2$	**9b**	PhO	COMe	78[b]
6	**7g**	PhO	PhC≡C	$CH=CH_2$	**9c**	PhO	PhC≡C	73
7	**7j**[a]	Phth	Ph	$CH=CH_2$	**9d**[a]	Phth	Ph	85

[a] A cis/trans mixture (2:1) was used in this transformation to produce **9d** (cis:trans = 2:1). [b] 15% of R^1 = PhO, R^2 = PhCH = CMe (**9e**) was also isolated.

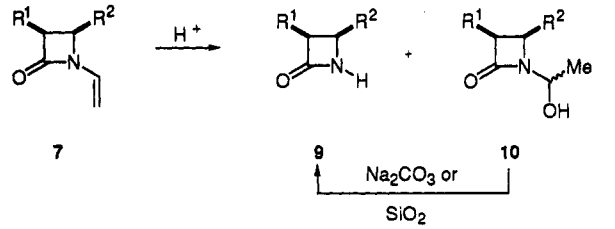
Table V. Hydrolytic Cleavage of the *N*-Vinyl Group of β-Lactams 7 with Dilute HCl (Method A)



7b, 7f 9 10

entry	R	compd	yield of 9 (%)	compd	yield of 10 (%)
1	Ph	**9a**	35	**10a**	44
2	PhCH=CMe	**9e**	41	**10b**	40

Table VI. One-Flask Procedure for the Hydrolytic Cleavage of the *N*-Vinyl Group of β-Lactams 7 with Dilute HCl Followed by Treatment with Sodium Bicarbonate (Method B) or Silica Gel (Method C)



7 9 10

entry	method	R^1	R^2	7	9	yield (%)
1	B	PhO	Ph	**7b**	**9a**	89
2	B	PhO	PhCH=CHMe	**7f**	**9e**	81
3	B	PhO	PhCH=CH	**7d**	**9f**	90
4	B	Phth	PhCH=CH	**7l**	**9g**	92
5	C	PhO	Ph	**7b**	**9a**	58
6	C	Phth	PhCH=CHMe	**7m**	**9h**	81

β-lactams **9** in excellent yields, ranging from 82 to 92% yield (Table VI, entries 1–4). The other method for deprotection was discovered fortuitously when we observed that the *N*-(hydroxyethyl) group of derivatives **10** was cleaved during chromatography on silica gel. Thus, the *N*-vinyl group of β-lactams can be removed easily (Table VI, entries 5 and 6) by first subjecting them to hydrolytic conditions and then transferring the resulting crude reaction products, containing a mixture of the *N*-unprotected β-lactam **9** and the corresponding *N*-(hydroxyethyl) derivatives **10**, to a silica gel column. Elution from the silica column (after about 12 h) gave the *N*-unprotected derivatives **9a** and **9h** in overall yields of 58% and 81%, respectively.

We also subjected *N*-(1′-propenyl)-β-lactams to the same hydrolytic reaction conditions as used for the hydrolytic cleavage of the *N*-vinyl-β-lactams but did not observe facile cleavage of the nitrogen substituent. Under a variety of hydrolytic reaction conditions we mainly recovered unreacted starting material together with small amounts <2% of *N*-unprotected-β-lactam derivatives.

In summary, we have found that *N*-(1′-propenyl)-**2** and *N*-vinylimines **5**, which can be synthesized in good yields and on a large scale from easily available starting materials, are useful reagents in the Staudinger reaction. The high cis diastereoselectivity of β-lactam formation displayed by these imines in the reaction with Bose–Evans and Sheehan ketenes and trans selectivity in the reaction with a Moore ketene parallels the results typically found with alkylarylimines (see Figure 1). Of importance is the finding that the utilization of *N*-vinyl imines in the Staudinger reaction yields β-lactams in which the *N*-vinyl group cannot only be removed oxidatively but also hydrolytically in a one-flask procedure (hydrolysis followed by column chromatography or treatment with sodium bicarbonate). This procedure should be of value for the preparation of β-lactams containing functional groups which are susceptible to reductive or oxidative reaction conditions as required for the removal of *N*-benzyl or *N*-aryl groups at the β-lactam nitrogen. Furthermore, another interesting finding is the fast, high-yielding oxidative removal of the *N*-formyl group from β-lactams **8a** and **8b** with potassium permanganate. This procedure may be of more general utility for the removal of formyl protecting groups.[52]

Experimental Procedures

General. ^1H NMR spectra were obtained as $CDCl_3$ solutions on a Varian FT-80A, a Varian XL-300, or a General Electric GE QE-300 spectrometer. Chemical shifts were recorded in parts per million (ppm) using tetramethylsilane as the internal standard. Complex coupling patterns with overlay of signals are referred to as pseudo (i.e., ps quin), describing their apparent shape. IR spectra were recorded with a Perkin-Elmer 707 or a Beckman IR-32 spectrophotometer and were reported in reciprocal wavenumbers (cm^{-1}). Melting points were measured either with a Fisher-Johns melting point apparatus or with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact (EIMS), chemical ionization (CIMS), and high-resolution mass spectra (HRMS) were recorded on a Varian CH-5 or a Ribermag R10-10 mass spectrometer by Charles Judson, Ph.D., and Robert Drake. Microanalyses were performed by Tho I. Nguyen on a Hewlett-Packard 185B CHN analyzer. Column chromatography was carried out by flash chromatography on Aldrich silica gel (70–230 mesh). Analytical thin-layer chromatography (TLC) was performed on Brinkmann precoated silica gel plastic-backed sheets, 0.25-mm thickness. Reagents and solvents were used as obtained from Aldrich unless otherwise indicated.

(1*E*,3*E*)- and (1*E*,3*Z*)-2-Aza-1-phenyl-1,3-pentadiene (2a). Scheme III and Table I. To freshly distilled benzaldehyde (5.3 g, 50 mmol) was added dropwise allylamine (6 mL, 80 mmol) at

room temperature. The mixture was stirred under an atmosphere of nitrogen for 1 h. Excess allylamine was removed under reduced pressure (rotary evaporator) to afford the crude aldimine. Then, the solution of the crude aldimine in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this solution was added dropwise DBU (13 mL, 87 mmol), and the reaction mixture was stirred at room temperature for 16–20 h. The progress of the reaction was monitored by ^1H NMR. After completion of the reaction, the reaction mixture was poured into a flask containing saturated NH_4Cl (40 mL) and ethyl ether (50 mL). The aqueous layer was extracted with ether (3 × 50 mL), dried, and evaporated to give the crude product as an orange oil, which was distilled under reduced pressure (70–75 °C, 2 Torr) to give 6.16 g (85%) of the product. The ratio of *E,E*:*E,Z* was 4:1 as determined by ^1H NMR. The ^1H NMR data of reaction product **2a** were in agreement with the data reported for **2a** by Worley.[40] An attempt to further purify **2a** and to separate the *E*- and *Z*-isomers by chromatography was unsuccessful due to the decomposition of the product: IR ($CHCl_3$) 1670, 1640 cm^{-1}; ^1H NMR (300 MHz) δ 1.83 (d, *J* = 6.8 Hz, 3H), 2.04 (dd, *J* = 7.0 and 1.5 Hz, 3H), 5.69 (ps quin, $J_1 = J_2 = 7$ Hz, 1H), 6.14 (ps sept, *J* = 13 and 6.5 Hz, 1H), 6.77 (dd, *J* = 7.6 and 1.6 Hz, 1H), 6.82 (dd, *J* = 13 and 1.4 Hz, 1H), 7.25–7.70 (m, 10H), 8.10 (s, 1H), 8.15 (s, 1H).

(1*E*,3*E*,5*E*)- and (1*E*,3*E*,5*Z*)-4-Aza-1-phenyl-1,3,5-heptatriene (2b). Scheme III and Table I. Compound **2b** was prepared from cinnamaldehyde (5.0 g, 38 mmol) in the same way as **2a**. Crude **2b** (pure by NMR) was obtained (6.5 g, 100%) as an orange oil and was used in the Staudinger reaction without further purification: *E,E,E*:*E,E,Z* = 4:1 as determined by ^1H NMR (80 MHz): IR ($CHCl_3$) 1640, 1610 cm^{-1}; ^1H NMR (80 MHz) δ 1.80 (dd, *J* = 7 and 1.5 Hz, 3H), 1.95 (dd, *J* = 7 and 1.5 Hz, 3H), 5.30 (ps quin, $J_1 = J_2 = 7$ Hz, 1H), 5.70–6.25 (dq, *J* = 13 and 7 Hz, 1H), 6.55 (m, 1H), 6.70 (m, 1H), 6.7–7.5 (m, 14H), 7.80 (m, 2H).

(1*E*,3*E*,5*E*)- and (1*E*,3*E*,5*Z*)-4-Aza-2-methyl-1-phenyl-1,3,5-heptatriene (2c). Scheme III and Table I. Compound **2c** was prepared from α-methylcinnamaldehyde (8.8 g, 50 mmol) in the same way as **2a**. Vacuum distillation (86–90 °C, 3.0 Torr) afforded **2c** as a light yellow oil (9.05 g, 97%), *E,E,E*:*E,E,Z* = 2:1 as determined by ^1H NMR: IR ($CHCl_3$) 1670, 1620 cm^{-1}; ^1H NMR (80 MHz) of **2c**-*E*: δ 1.83 (dd, *J* = 7.1 and 1.7 Hz, 3H), 2.21 (d, *J* = 1.30 Hz, 3H), 6.1 (ps sept, *J* = 13 and 6.5 Hz, 1H), 6.5–7.5 (m, 7H), 7.8 (s, 1H). **2c**-*Z*: δ 2.02 (dd, *J* = 7.0 and 1.7 Hz, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 5.48 (ps quin, $J_1 = J_2 = 7$ Hz, 1H), 6.5–7.5 (m, 7H), 7.90 (s, 1H).

(1*E*,3*E*,5*E*)- and (1*E*,3*E*,5*Z*)-4-Aza-1,1-diphenyl-1,3,5-heptatriene (2d). Scheme III and Table I. Compound **2d** was prepared from β-phenylcinnamaldehyde (7.1 g, 34 mmol) in the same way as **2a**. Crude **2d** was obtained (8 g, 100%) as a viscous light yellow oil and was used in the Staudinger reaction without further purification. *E,E,E*:*E,E,Z* = 4:1 as determined by ^1H NMR: IR ($CHCl_3$) 1660, 1615 cm^{-1}; ^1H NMR (300 MHz) δ 1.70 (d, *J* = 7.3 Hz, 3H), 1.90 (d, *J* = 7.3 Hz, 3H), 5.30 (ps quin, $J_1 = J_2 = 7$ Hz, 1H), 6.00 (ps sept, *J* = 13 and 6.5 Hz, 1H), 6.2–7.5 (m, 24H), 7.75 (d, *J* = 9 Hz, 1H), 7.80 (d, *J* = 9 Hz, 1H).

***N,N*-Dimethyl-*N'*-(phenylmethylene)-1,2-ethylenediamine (3a).** Scheme IV and Table I. To a solution of freshly distilled benzaldehyde (10 mL, 99 mmol) and *N,N*-dimethylethylenediamine (10.8 mL, 99 mmol) in anhyd ethyl ether (150 mL) was added anhyd $MgSO_4$ (4 g). The mixture was stirred at room temperature for about 1 h. During the reaction, small aliquots were taken, and the reaction progress was monitored by following the disappearance of the aldehyde signal and appearance of the imine resonance using ^1H NMR. After the reaction was complete, the mixture was filtered to remove the $MgSO_4$. The residue was rinsed with ethyl ether (3 × 15 mL). Removal of the solvent gave crude **3a**, which was distilled (42 °C, 1 Torr) to afford **3a** as a light yellow oil (17.4 g, 83%): IR ($CHCl_3$) 1645, 1575, 1460 cm^{-1}; ^1H NMR (80 MHz) δ 2.30 (s, 6H), 2.62 (t, *J* = 7.5 Hz, 2H), 3.72 (t, *J* = 7.5 Hz, 2H), 7.20–7.80 (m, 5H), 8.27 (s, 1H).

1-Aza-1-[(*N,N*-dimethylamino)ethyl]-4-phenyl-1,3-butadiene (3b). Scheme IV and Table I. Following the same procedure for the preparation of **3a** using cinnamaldehyde (8 mL, 64 mmol) and *N,N*-dimethylethylenediamine (13.9 mL, 127 mmol). Vacuum distillation (95–100 °C, 1.5 Torr) afforded **3b** as a light yellow oil (10.2 g, 79%): IR ($CHCl_3$) 1635, 1460 cm^{-1}; ^1H NMR (80 MHz) δ 2.30 (s, 6H), 2.62 (t, *J* = 7.6 Hz, 2H), 3.60 (t, *J* = 7.6 Hz, 2H), 6.80–7.5 (m, 7H), 7.95–8.10 (m, 1H).

1-Aza-1-[(*N,N*-dimethylamino)ethyl]-3-methyl-4-phenyl-1,3-butadiene (3c). Scheme IV and Table I. Following the same procedure for the preparation of **3a** using α-methylcinnamaldehyde (7.0 mL, 50 mmol) and *N,N*-dimethylethylene (8.3 mL, 75 mmol). Vacuum distillation (98–100 °C, 2 Torr) afforded **3c** as a light yellow oil (8.1 g, 75%): IR ($CHCl_3$) 1660, 1620 cm^{-1}; ^1H NMR (80 MHz) δ 2.03 (d, *J* = 1.2 Hz, 3H), 2.30 (s, 6H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.67 (t, *J* = 7.5 Hz, 2H), 6.77 (s, br, 1H), 7.10–7.50 (m, 5H), 8.0 (s, 1H).

***N*-[(*N',N'*-Dimethylamino)ethyl]-1-phenylpropynylimine (3d).** Scheme IV and Table I. Following the same procedure for the preparation of **3a** using phenylpropargyl aldehyde (1.4 g, 11 mmol) and *N,N*-dimethylethylenediamine (2.4 mL, 22 mmol). Vacuum distillation (77–81 °C, 2 Torr) afforded an orange oil (1.72 g) of a 2:1 mixture of **3d** and *N,N*-dimethylethylenediamine. This mixture was used in the next step without further purification: IR ($CHCl_3$) 1660, 1630 cm^{-1}; ^1H NMR (80 MHz) δ 2.27 (s, 6H), 2.65 (t, 7.5 Hz, 2H), 3.65 (t, 7.5 Hz, 2H), 7.10–8.10 (m, 5H), 7.75 (s, br, 1H).

(*E*)-2-Aza-1-phenyl-1,3-butadiene (5a). Scheme IV and Table I. Purified **3a** (12 g, 68 mmol) was treated with iodomethane (8.5 mL, 137 mmol) in DMF (250 mL) at 25 °C for about 30 min to afford a quaternary ammonium salt which precipitated out of solution. Then, the reaction mixture was diluted with DMF (75 mL) and was cooled to 0 °C. Sodium hydride (4 g, 166 mmol) was added to the reaction mixture in several portions. After 12 h at 0–10 °C, the reaction was quenched with a mixture of ice–water and ethyl ether (200 mL) and extracted with ethyl ether (3 × 150 mL). The combined organic phases were washed with water (5 × 50 mL), dried ($MgSO_4$), and then concentrated to yield the crude product. Kugelrohr distillation (40–45 °C, 1 Torr) of the crude product gave **5a** as a light yellow liquid (7.5 g, 84%): IR ($CHCl_3$) 1610, 1580 cm^{-1}. The ^1H NMR data for **5a** were identical to the ones reported by Böhme:[44] ^1H NMR (80 MHz) δ 5.05 (d, *J* = 7 Hz, 1H), 5.55 (d, *J* = 15 Hz, 1H), 7.00 (dd, *J* = 15 and 7 Hz, 1H), 7.25–7.90 (m, 5H), 8.25 (s, 1H).

(3*E*,4*E*)-3-Aza-6-phenyl-1,3,5-hexatriene (5b). Scheme IV and Table I. Compound **5b** was prepared from **3b** (9.1 g, 45 mmol) in the same way as **5a** except using CH_3CN as solvent in the methylation step. The quaternary ammonium salt was filtered and washed with ethyl ether and then dissolved in DMF (200 mL). Sodium hydride (2.72 g, 113 mmol) was added to the reaction mixture in several portions. After 12 h at 0–10 °C, the reaction was worked up as described for **5a**. Crude **5b** was obtained as an orange oil (5.5 g, 78%) and was used without further purification in the Staudinger reaction: IR ($CHCl_3$) 1670, 1630, 1570 cm^{-1}; ^1H NMR (80 MHz) δ 5.07 (d, *J* = 8 Hz, 1H), 5.45 (d, *J* = 15 Hz, 1H), 6.5–8.1 (m, 9H).

(3*E*,4*E*)-3-Aza-5-methyl-6-phenyl-1,3,5-hexatriene (5c). Scheme IV and Table I. Compound **5c** was prepared from **3c** (12.4 g, 57 mmol) in the same way as was **5a**. Kugelrohr distillation (85–93 °C, 1.3 Torr) afforded **5c** as a light yellow oil (6.17 g, 63%): IR ($CHCl_3$) 1670, 1570 cm^{-1}; ^1H NMR (80 MHz) δ 2.25 (d, *J* = 1.2 Hz, 3H), 4.95 (d, *J* = 8 Hz, 1H), 5.45 (d, *J* = 15 Hz, 1H), 6.75–7.10 (m, 2H), 7.15–7.70 (m, 5H), 8.00 (s, 1H).

(*E*)-2-Aza-1-(phenylethynyl)-1,3-butadiene (5d). Scheme IV and Table I. Compound **5d** was prepared from **3d** (1 g, 2.9 mmol) in the same way as was **5b**, using CH_3CN as solvent in the methylation step. Crude **5d** was obtained (314 mg, 69%) as an orange oil: IR ($CHCl_3$) 1670, 1550 cm^{-1}; ^1H NMR (80 MHz) δ 5.13 (d, *J* = 7.5 Hz, 1H), 5.60 (d, *J* = 15 Hz, 1H), 6.92 (dd, *J* = 15 and 7.5 Hz, 1H), 7.10–7.60 (m, 5H), 7.65 (s, 1H).

Formation of β-Lactams 7 (Table II). *cis*-3-Phenoxy-4-phenyl-1-[(*E*)-1'-propenyl]-2-azetidinone and *cis*-3-Phenoxy-4-phenyl-1-[(*Z*)-1'-propenyl]-2-azetidinone (7a-*cis*-*E* and -*Z*). To a 25-mL two-necked flask containing a solution of imine **2a** (198 mg, 1.73 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (0.54 mL, 3.9 mmol) under N_2 at 0 °C. A solution of phenoxyacetyl chloride (701 mg, 4.11 mmol) in CH_2Cl_2 (5.5 mL) was introduced dropwise. The reaction was warmed to room temperature and stirred for 12 h. The reaction progress was monitored by TLC (EtOAc/hexanes (1:4)). After the reaction was complete, the reaction mixture was poured into water (10 mL), stirred for 15

min, and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, EtOAc/hexanes (1:5)) to afford *N*-(1-propenyl)-β-lactam **7a**-*cis* as a colorless solid (253 mg, 66%), mp 93–94 °C (recrystallized from EtOAc/hexanes); *E*:*Z* = 9:1 as determined by ^1H NMR (80 MHz): IR ($CHCl_3$) 1755 cm^{-1}; ^1H NMR (300 MHz) **7a**-*cis*-*E* δ 1.59 (d, *J* = 7 Hz, 3H), 4.85–5.08 (m, 1H), 5.12 (d, *J* = 4 Hz, 1H), 5.45 (d, *J* = 4 Hz, 1H), 6.55 (d, *J* = 15 Hz, 1H), 7.37–6.68 (m, 10H). **7a**-*cis*-*Z*: 1.59 (d, *J* = 7 Hz, 3H), 4.85–5.08 (m, 1H), 5.34 (d, *J* = 4 Hz, 1H), 5.53 (d, *J* = 4 Hz, 1H), 6.22 (d, *J* = 10 Hz, 1H), 7.37–6.68 (m, 10H); EIMS *m*/*e* 279 (M^+), 196 (base); HRMS $C_{18}H_{17}NO_2$ requires *m*/*e* 279.1258, found 279.1266. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.14; N, 5.01. Found: C, 77.77; H, 6.50; N, 5.00.

***cis*-3-Phenoxy-4-phenyl-1-vinyl-2-azetidinone (7b-*cis*) and *trans*-3-Phenoxy-4-phenyl-1-vinyl-2-azetidinone (7b-*trans*).** Azetidinone **7b** was prepared from **5a** (1.0 g, 7.6 mmol) following the procedure described for the synthesis of **7a**. The crude product was purified by chromatography (silica gel, EtOAc/hexanes (1:4)) to afford *N*-vinyl-β-lactams **7b**-*cis* and **7b**-*trans* in a ratio of 31:1 (1.94 g, 96%), which could be separated by column chromatography. **7b**-*cis*: colorless solid, mp 84–85 °C; IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (300 MHz) δ 4.38 (d, *J* = 15 Hz, 1H), 4.46 (d, *J* = 8 Hz, 1H), 5.17 (d, *J* = 5 Hz, 1H), 5.48 (d, *J* = 5 Hz, 1H), 6.60–7.50 (m, 11H); EIMS *m*/*e* 265 (M^+), 77 (base); HRMS $C_{17}H_{15}NO_2$ requires *m*/*e* 265.1102, found 265.1096. **7b**-*trans*: colorless oil; IR ($CHCl_3$) 1750 cm^{-1}; ^1H NMR (300 MHz) δ 4.32 (d, *J* = 16 Hz, 1H), 4.45 (d, *J* = 9 Hz, 1H), 4.81 (d, *J* = 1.7 Hz, 1H), 5.05 (d, *J* = 1.7 Hz, 1H), 6.76 (dd, *J* = 16 and 9 Hz, 1H), 6.80–7.60 (m, 10); EIMS *m*/*e* 265 (M^+), 77 (base); HRMS $C_{17}H_{15}NO_2$ requires *m*/*e* 265.1102, found 265.1109.

***cis*-3-Phenoxy-4-(2′-phenylethenyl)-1-[(*E*)-1′-propenyl]-2-azetidinone and *cis*-3-Phenoxy-4-(2′-phenylethenyl)-1-[(*Z*)-1′-propenyl]-2-azetidinone (7c-*cis*-*E* and -*Z*).** Following the procedure for the preparation of **7a** (**2b**, 1.71 g, 10 mmol) and subsequent chromatography silica gel, 1:5 EtOAc/hexanes eluent) afforded **7c**-*cis* as a colorless solid (2.7 g, 88%), mp 124–126 °C; *E*:*Z* = 7.5:1 as determined by ^1H NMR (80 MHz): IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR (300 MHz) **7c**-*cis*-*E* δ 1.67 (dd, *J* = 6.8 and 1.6 Hz), 4.74 (dd, *J* = 8.5 and 4.7 Hz, 1H), 5.24–5.38 (m, 1H), 5.37 (d, *J* = 4.7 Hz, 1H), 6.24 (dd, *J* = 16 and 8.5 Hz, 1H), 6.50 (dd, *J* = 14 and 1.6 Hz, 1H), 6.76 (d, *J* = 16 Hz, 1H), 6.95–7.40 (m, 10H). **7c**-*cis*-*Z*: δ 1.79 (dd, *J* = 7.2 and 1.6 Hz, 3H), 4.90 (dd, *J* = 8.4 and 4.8 Hz, 1H), 5.0–5.1 (m, 1H), 5.44 (d, *J* = 4.8 Hz, 1H), 6.15 (dd, *J* = 9 and 1.7 Hz, 1H), 6.24 (dd, *J* = 16 and 8.4 Hz, 1H), 6.74 (d, *J* = 16 Hz, 1H), 6.95–7.40 (m, 10H); EIMS *m*/*e* 305 (M^+), 77 (base); HRMS $C_{20}H_{19}NO_2$ requires *m*/*e* 305.1415, found 305.1414.

***cis*-4-Phenyl-3-phthalimido-1-vinyl-2-azetidinone (7j-*cis*) and *trans*-4-Phenyl-3-phthalimido-1-vinyl-2-azetidinone (7j-*trans*).** Following the procedure for the preparation of **7a** using imine **5a** (124 mg, 0.94 mmol) **7j** was obtained in a 1.1:1 ratio of **7j**-*cis* and **7j**-*trans* as determined by 300-MHz NMR (107 mg, 39%). **7j**-*cis*: colorless solid, mp 181–182 °C; IR ($CHCl_3$) 1780, 1765 cm^{-1}; ^1H NMR (300 MHz) δ 4.45 (d, *J* = 16 Hz, 1H), 4.6 (d, *J* = 9 Hz, 1H), 5.27 (d, *J* = 5.7 Hz, 1H), 5.61 (d, *J* = 5.4 Hz, 1H), 6.81 (dd, *J* = 16 and 9 Hz, 1H), 7.0–7.3 (m, 5H), 7.6–7.7 (m, 4H). Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.29; H, 4.38; N, 8.60. **7j**-*trans*: colorless solid, mp 157–159 °C; IR ($CHCl_3$) 1780, 1765 cm^{-1}; ^1H NMR (300 MHz) δ 4.37 (d, *J* = 16 Hz, 1H), 4.49 (d, *J* = 8 Hz, 1H), 5.16 (d, *J* = 2.7 Hz, 1H), 5.23 (d, *J* = 2.8 Hz, 1H), 6.81 (dd, *J* = 16 and 9 Hz, 1H), 7.2–7.5 (m, 5H), 7.7–8.0 (m, 4H); EIMS *m*/*e* 318 (M^+, base); HRMS $C_{19}H_{14}N_2O_3$ requires *m*/*e* 318.1004, found 318.1009.

Oxidative Cleavage of *N*-Alkenyl Groups with Ozone (Table III). *cis*-1-Formyl-4-phenyl-3-phenoxy-2-azetidinone (8a). β-Lactam **7a** (30 mg, 0.1 mmol) dissolved in a mixture of CH_2Cl_2 (5 mL) and methanol (0.1 mL) was cooled to −78 °C, and ozone was introduced until the blue color persisted for 5 min. The excess of Ozone was removed with a stream of nitrogen, and dimethyl sulfide (0.08 mL, 1.0 mmol) was added to the reaction mixture. The mixture was stirred at −20 °C for 30 min and then at room temperature for an additional 2 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (15 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography on silica gel using EtOAc/hexanes (1:5) as eluent gave **8a** as a yellow oil (16.5 mg, 62%): IR ($CHCl_3$) 1820, 1720 cm^{-1}; ^1H NMR (80 MHz) δ 5.33 (d, *J* = 5.6 Hz, 1H), 5.51 (d, *J* = 5.6 Hz, 1H), 6.66–7.30 (m, 10H), 8.97 (s, 1H); EIMS *m*/*e* 267 (M^+), 77 (base); HRMS $C_{16}H_{13}NO_3$ requires *m*/*e* 267.0894, found 267.0893.

Oxidative Cleavage of the *N*-Formyl Group (Table IV). *cis*-3-Phenoxy-4-phenyl-2-azetidinone (9a). A solution of β-lactam **8a** (43.4 mg, 0.16 mmol) in THF/water (1.0 mL, 1:1) was stirred in the presence of $KMnO_4$ (98 mg, 0.64 mmol) at 25 °C under an inert atmosphere. After 2 h additional $KMnO_4$ (30 mg, 0.2 mmol) was added, and the reaction mixture was stirred for 2 more h. The brown precipitate was filtered off, and the THF was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), dried ($MgSO_4$), and evaporated to give **9a** as a colorless crystalline compound (33 mg, 87%): mp 175–176 °C (from $CHCl_3$/hexanes); IR ($CHCl_3$) 3400 (NH), 1780 cm^{-1}; ^1H NMR (300 MHz) δ 5.03 (d, *J* = 4.6 Hz, 1H), 5.49 (dd, *J* = 4.6 and 2.4 Hz, 1H), 6.35 (br, s, 1H), 6.70–6.74 (m, 10H); EIMS *m*/*e* 239 (M^+), 77 (base); HRMS $C_{15}H_{13}NO_2$ requires *m*/*e* 239.0946, found 239.0942. Anal. Calcd for $C_{15}H_{13}NO_2 \cdot 0.38H_2O$: C, 73.23.; H, 5.28; N, 5.69. Found: C, 73.18; H, 5.60; N, 5.50.

Oxidative Removal of *N*-Vinyl and *N*-Propenyl Groups with Potassium Permanganate (Table IV). *cis*-3-Phenoxy-4-phenyl-2-azetidinone (9a) from 7e. A solution of **7e** (0.397 g, 1.5 mmol) in acetone/water (10 mL, 8:2) was stirred vigorously at 0 °C for 10 min under a nitrogen atmosphere. During that time, $KMnO_4$ (0.83 g, 5.25 mmol) was added in three portions. The brown precipitate was filtered off and washed three times with acetone (3 × 15 mL). The acetone was evaporated *in vacuo*, and the remaining residue was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuo* to afford the *N*-unsubstituted-2-azetidinone **9a** (322 mg, 90%).

Hydrolysis of 1-Vinyl-2-azetidinones (Method A, Table V). *cis*-3-Phenoxy-4-phenyl-2-azetidinone (9a) and *cis*-3-Phenoxy-4-phenyl-1-(1′-hydroxyethyl)-2-azetidinone (10a). β-Lactam **7b** (95 mg, 0.36 mmol) was dissolved in a mixture of THF (25 mL) and 1% HCl (1 mL) in a pressure tube (15 mL) and heated at 55 °C. The reaction was monitored by TLC for disappearance of the starting material. After 3 h, the solution was saturated with NaCl and extracted with ether (1 × 10 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a mixture of the *N*-unsubstituted-2-azetidinone **9a** and 1-(1′-hydroxyethyl)-2-azetidinone **10a**. Chromatography on silica gel using EtOAc/hexanes (1:1) as eluent gave **9a** as a colorless solid (33.5 mg, 35%) and **10a** as a colorless solid (45 mg, 44%).

***cis*-3-Phenoxy-4-phenyl-1-(1′-hydroxyethyl)-2-azetidinone (10a).** Colorless solid, mp 123–125 °C. A pair of diastereomers in a ratio of 1:1.3 was obtained as determined by NMR: IR ($CHCl_3$) 3500 (br), 1760 cm^{-1}; ^1H NMR (300 MHz) δ 1.10 (d, *J* = 6.2 Hz, 3H), 1.55 (d, *J* = 6.1 Hz, 3H), 4.15 (s, br, 1H), 4.5 (s, br, 1H), 5.10 (d, *J* = 4.6 Hz, 1H), 5.22 (q, *J* = 6.2 Hz, 1H), 5.23 (d, *J* = 4.6 Hz, 1H), 5.40 (d, *J* = 4.8 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 1H), 5.65 (q, *J* = 6.1 Hz, 1H), 6.60–7.60 (m, 20H); CIMS *m*/*e* 284 (M + 1), 240 (base), 266, 196, 77. HRMS, $C_{17}H_{17}NO_3$ requires *m*/*e* 283.1208, found 283.1216. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.00; H, 6.00; N, 4.94. Found: C, 72.13; H, 5.61; N, 5.18.

Hydrolysis of 1-Vinyl-2-azetidinones (Method B, Table VI). *cis*-3-Phenoxy-4-phenyl-2-azetidinone (9a). β-Lactam **7b** (30 mg, 0.1 mmol) was dissolved in a mixture of THF and 1% HCl (25:1) (15 mL) in a pressure tube and heated at 55 °C. The reaction was monitored by TLC for disappearance of the starting material. After 3 h, the solution was saturated with NaCl and extracted with ether (1 × 10 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield a mixture of the *N*-unsubstituted-2-azetidinone **9a** and 1-(1′-hydroxyethyl)-2-azetidinone **10a**. The mixture was treated with Na_2CO_3 (150 mg, 1.78 mmol) in a solution of THF/H_2O (8 mL, 1:1) and refluxed for 1 h. Then, the reaction was cooled, saturated with NaCl, and extracted with ether (10 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and

evaporated under reduced pressure. Chromatography on silica gel using EtOAc/hexanes (1:1) as eluent afforded 21.3 mg (89%) of **9a**.

***cis*-4-(1′-Methyl-2′-phenylethenyl)-3-phenoxy-2-azetidinone (9e).** Following method B for the hydrolytic cleavage of **9a**, using **7f** (250 mg, 0.82 mmol) as the starting material. Chromatography (silica gel, 1:1 EtOAc/hexanes eluent) afforded **9e** as a colorless solid (185 mg, 81%): mp 140–142 °C; IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR (300 MHz) δ 1.95 (d, J = 1.4 Hz, 3H), 4.61 (d, J = 4.8 Hz, 1H), 5.47 (dd, J = 4.8 and 2.4 Hz, 1H), 6.30 (s, br, 1H), 6.59 (s, 1H), 6.9–7.5 (m, 10H); EIMS m/e 279 (M^+), 186 (base); HRMS $C_{18}H_{17}NO_2$ requires m/e 279.1259, found 279.1242.

Hydrolysis of 1-Vinyl-2-azetidinones (Method C, Table VI). *cis*-3-Phenoxy-4-phenyl-2-azetidinone (9a) from 7b. β-Lactam **7b** (95 mg, 0.36 mmol) was dissolved in a mixture of THF and 1% HCl (9:1) (15 mL) and stirred at room temperature for 7 days. The reaction was monitored by TLC for disappearance of the starting material. After saturated NaCl solution (4 mL) and NaCl (1 g) were added the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude reaction mixture, dissolved in CH_2Cl_2 (15 mL), was placed on a silica gel column (prepared with 25 g SiO_2, EtOAc/hexanes (1:1)) for 4 days. Elution with EtOAc/hexanes (1:1) afforded **9a** as a colorless solid (50 mg, 58%).

***cis*-4-(1′-Methyl-2′-phenylethenyl)-3-phthalimido-2-azetidinone (9h).** β-Lactam **7m** (25 mg, 0.07 mmol) was dissolved in a mixture of THF and 1% HCl (30:1) (5 mL) in a pressure tube and heated at 55 °C. The reaction was monitored by TLC for disappearance of the starting material. After 3 h, the solution was saturated with NaCl and extracted with ether (3 × 10 mL) and CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude reaction mixture was dissolved in a 1:1:2 mixture of CH_2Cl_2, EtOAc, and hexanes (5 mL) and was then transferred to a silica gel column, prepared with EtOAc/hexanes (1:1) as the mobile phase. After 1.5 days, elution with EtOAc and hexanes (1:1) afforded **9h** as a colorless solid (19 mg, 81%): mp 155–158 °C; IR ($CHCl_3$) 1780, 1770, 1740 cm^{-1}; ^1H NMR (300 MHz) δ 1.68 (s, 3H), 4.59 (d, J = 4.8 Hz, 1H), 5.54 (dd, J = 4.8 and 2.1 Hz, 1H), 6.32 (s, br, 1H), 6.72 (s, 1H), 7.05–7.30 (m, 5H), 7.65–7.90 (m, 4H); EIMS m/e 332 (M^+), 185 (base); HRMS $C_{20}H_{16}N_2O_3$ requires m/e 332.1161, found 332.1175.

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Supplementary Material Available: Spectral and analytical data (^1H NMR, IR, MS, HRMS, and elemental analyses) for compounds **7d–7i**, **7k–7n**, **8b**, **9b–9g**, and **10b** and ^1H NMR spectra for compounds **2a–2d**, **3a–3d**, **5a–5d**, **7a–7n**, **8a–8b**, **9a–9g**, and **10a–10b** (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.