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Vinyl-β-lactams as Efficient Synthons. Eco-friendly Approaches via Microwave Assisted Reactions[1]

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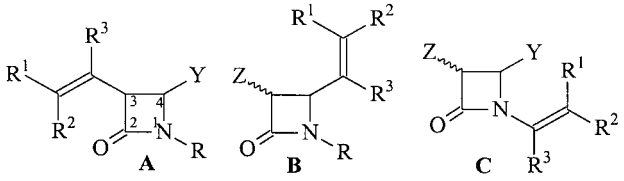
Abstract—Vinyl-β-lactams are efficient synthons for a variety of compounds of biomedical interest—such as isocephalosporins, carbapenem and thienamycin intermediates, and pyrrolidine alkaloids. Convenient methods are described for obtaining both enantiomers of some of these synthons. Microwave-induced Organic Reaction Enhancement (MORE) chemistry techniques allow highly accelerated synthesis of variously substituted vinyl-β-lactams using limited amounts of solvents and with efficient stereocontrol—thus achieving high 'atom economy'. The effect (if any) of microwaves on bond angles and bond lengths and the geometry of transition states are not well understood yet. Nonetheless, reactions under microwave irradiation in open systems are rapid, safe, and cost-effective for synthetic approaches that are much more friendly to the environment than conventional processes. © 2000 Elsevier Science Ltd. All rights reserved.

Synthetic chemists and medicinal chemists have been interested in β-lactams for more than half a century.[2] The agility with which these four-membered heterocycles can undergo ring scission and rearrangements has provided easy access to many other heterocycles and acyclic compounds. In the course of our ongoing studies on β-lactam synthons or natural products, various preparative methods for diversely substituted 2-azetidinones have been developed.



Recently, increasing attention has been paid in our laboratory to synthetic approaches that are more environmentally benign than conventional organic reactions. We wish to report here on some of our work directed to the preparation of β-lactams (A, B, C) with a vinyl substituent at various positions on the ring. The transformation of these heterocycles to compounds of interest via the manipulation of the vinyl group is also described. In several instances Microwave-induced Organic Reaction Enhancement (MORE) chemistry techniques[3] have been employed to reduce pollution at the source and to increase atom economy.[4]

3-Vinyl-2-azetidinones

Synthesis of α-vinyl-β-lactams (A)

In 1971, we[5] devised a direct synthesis of α-vinyl-β-lactams (A) by the reaction of an α,β-unsaturated acid chloride (for example, crotonyl chloride **1**) with Schiff bases **2** in the presence of triethylamine in refluxing dichloromethane or benzene. Exclusive formation of *trans*-β-lactams **3** in low yield was observed from *trans* crotonyl chloride (**1**) and the diaryl Schiff bases **2** (entry a, b, f, and g; Scheme 1).

Zamboni and Just[6] used this reaction in 1979, for preparing a number of *trans* α-vinyl-β-lactams as potential synthons for β-lactam antibiotics (Scheme 2). Thus, the reaction of β,β-dimethylacryloyl chloride **4** and the Schiff base **2** to give the *trans* β-lactam **5** (Scheme 2) was reported.

In 1991, Georg et al.[7] used crotonic acid and Mukaiyama's reagent[8] (Scheme 3) in place of crotonyl chloride for the synthesis of *trans* **3g** (R^1=Ph, R^2=PMP). In a more recent report, Torii et al.[9] have described a novel method for the synthesis of α-vinyl-β-lactams **3** which involves palladium catalyzed carbonylation of allyl diethylphosphate **7** in the presence of imines in an atmosphere of carbon monoxide under pressure. The stereochemistry of the product depends on the nature of the substituents R^1 and R^2 (Scheme 4).

Keywords: annulation; azetidinones; microwave irradiation; nitrogen heterocycles; stereocontrol; sulfur heterocycles.

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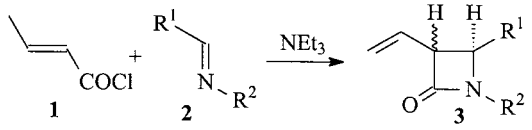
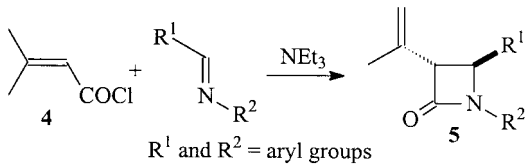


entry	R^1	R^2	Stereo-chemistry	% Yield
a	phenyl	phenyl	*trans*	65
b		*p*-anisyl	*trans*	52
c	-CO-Ph	*p*-anisyl	*cis:trans::70:30*	80
d	-CO-Ph	$-CH(CH_3)Ph$	*cis*	55
e		$-CH(CO_2PNB)CH(CH_3)OH$	*cis*	15
f	*p*-anisyl	*p*-anisyl	*trans*	55
g	phenyl	*p*-anisyl	*trans*	50
h	*trans*-cinnamyl	$-CH(CO_2PNB)CH(CH_3)OH$	*cis:trans::90:10*	60

Scheme 1.



Scheme 2.

Steric course of cyclization

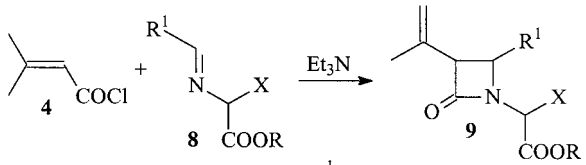
Zamboni and Just[6] showed that crotonyl chloride (**1**) and dimethylacryloyl chloride (**4**) behave in the same way during the formation of α-vinyl-β-lactams **3** and **5**, respectively. The Schiff bases **2** (R^1=Ph or furfuryl or styryl) derived from aniline or *p*-anisidine lead only to *trans* β-lactams. But, the Schiff base from cinnamaldehyde and aniline gives a mixture of *cis* and *trans* β-lactams. At room temperature the *cis* isomer predominates but higher temperature favors the *trans* product.[6] Schiff bases **8** prepared from aliphatic amines give mostly the *cis* α-vinyl-β-lactam **9** (Scheme 5).[6]

Microwave Assisted Synthesis

In the course of developing MORE[10] chemistry techniques, we[11] discovered that α-vinyl-β-lactams could be prepared in high yield in a few minutes instead of a few hours by subjecting the reaction mixture to microwave irradiation.

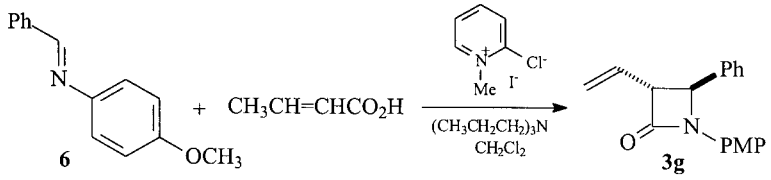
Key aspects of MORE chemistry are:

(a) the use of open systems (thus no danger of explosions

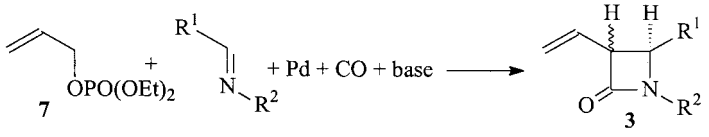


a: X = H, R = $-CH_2CH_3$, R^1 = -CH=CHPh
b: X = $-CH_2OTBDMS$, R = CH_3, R^1 = -CH=CHPh
c: X = $-CH_2OTBDMS$,R = CH_3, R^1 = furfuryl

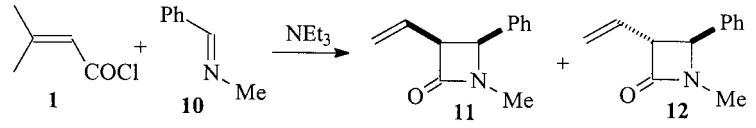
Scheme 5.



Scheme 3.



Scheme 4.



Scheme 6.

Table 1.

Length[a] of irradiation	Procedure[b]	*trans*:*cis* (12:11)[c]	Temp.[d] of reaction mixtures (°C)	Amount of water as heat sink[e] (mL)
1 min	M	40:60	78	200
2 min	M	60:40	92	200
3 min	M	70:30	95	200
4 min	M	70:30	105	200
5 min	M	80:20	108	200
10 min	M	80:20	118	200
30 s	M	25:75	55	800
1 min	M	30:70	62	800
10 min	C	80:20	115[f]	–
30 min	C	65:35	RT-115[g]	–
6 h	C	40:60	40[h]	–

[a] Reaction was complete after 5 min of irradiation.
[b] M and C indicate microwave and conventional methods, respectively.
[c] Ratio of *trans* to *cis* was based on NMR studies.
[d] The approximate temperature of the reaction mixture was determined by using a thermometer immediately after the microwave irradiation was stopped.
[e] A beaker of water was used as a heat sink to control the amount of energy entering the reaction mixture in the microwave oven.
[f] A preheated oil bath was used.
[g] The reactants were mixed at room temperature and the temperature was raised.
[h] Refluxing dichloromethane was used as the solvent.

due to rapid rise of pressure as in some sealed system reactions);
(b) careful control of the microwaves energy input into the reaction mixture such that the temperature is well below the boiling point of the mixture—therefore, no reflux condenser is needed;
(c) no solvents needed if one of the reactants is a polar liquid-molecules with dipole absorb microwave energy directly while the glass reaction vessel is nearly transparent to microwaves;
(d) minimal amounts of polar solvents used since it has been found that a slurry at room temperature is generally adequate for effective reaction at higher temperatures under microwave irradiation-less solvent means higher atom economy;
(e) simple beakers, conical flasks or glass trays are used as reaction vessels; since the reactants are energized directly, no stirrers are needed in most cases;
(f) most organic reactions on a molar scale require only a few minutes of irradiation instead of hours of reaction time as in conventional set ups;
(g) very rapid rise of temperature favors some reaction pathways over others and thus leads to selectivity and hence cleaner products.

Further details about MORE chemistry techniques are provided in later sections.

For microwave assisted synthesis of α-vinyl-β-lactams, a large beaker with a loose cover was used as the reaction vessel. Triethylamine as a tertiary base was replaced with the higher boiling *N*-methylmorpholine (bp 116°C). Since benzene absorbs microwave energy very poorly, chlorobenzene, which has a substantial dipole and a reasonably high boiling point (133°C), was used as the reaction medium in place of benzene. Improved yields (70–75%) were obtained at elevated temperatures.

Schiff bases from aromatic aldehydes and substituted anilines gave only *trans* α-vinyl-β-lactams **3** (Scheme 1).[11] But, the Schiff base **10** from benzaldehyde and methylamine produced a mixture of *cis* and *trans* β-lactams **11** and **12** in a ratio depending on the temperature of the reaction mixture (Scheme 6).[11]

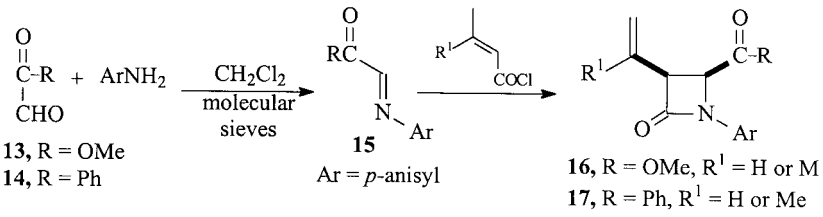
Higher temperature favored the formation of the *trans* β-lactam, which is thermodynamically more stable (Table 1). However, this was not a simple base-catalyzed isomerization; unchanged *cis* β-lactam **11** was recovered after irradiation in the presence of *N*-methylmorpholine.

Interestingly, *cis* β-lactams **16** and **17** were obtained exclusively from acid chlorides **1** or **4** and Schiff bases **15** (derived from glyoxalic esters **13** or phenyl glyoxal **14**)-irrespective of the temperature of the reaction (Scheme 7).[12]

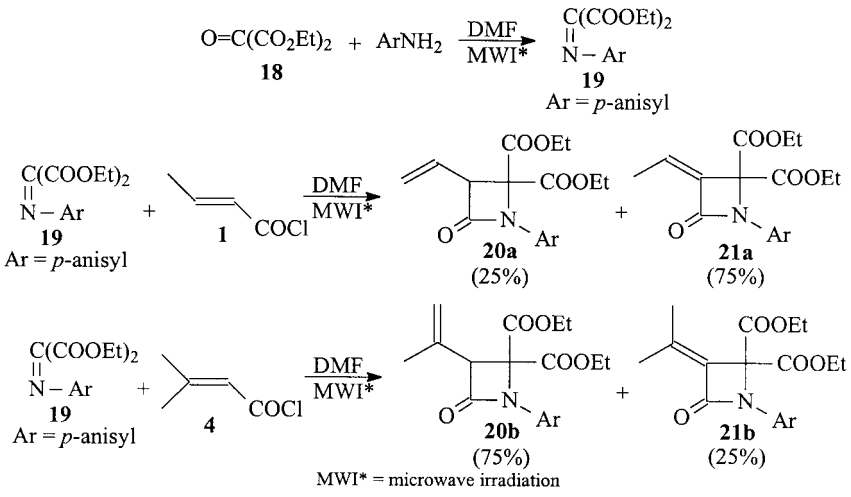
The problem of *cis*/*trans* isomerism disappears when an imine **19** derived from a ketomalonate **18** is used for the preparation of the vinyl-β-lactam **20**.[13,14] However, an isomer **21** is also produced in which the double bond in the side chain is conjugated with the β-lactam carbonyl group (Scheme 8).

α-Vinyl-β-lactams as synthons

Synthesis of α-alkyl β-lactams became of interest after the discovery of PS-5 (**28**), PS-6 (**29**), thienamycin, and asparenomycin. α-Vinyl β-lactams were employed[14] in our laboratory for the synthesis of carbapenem antibiotics

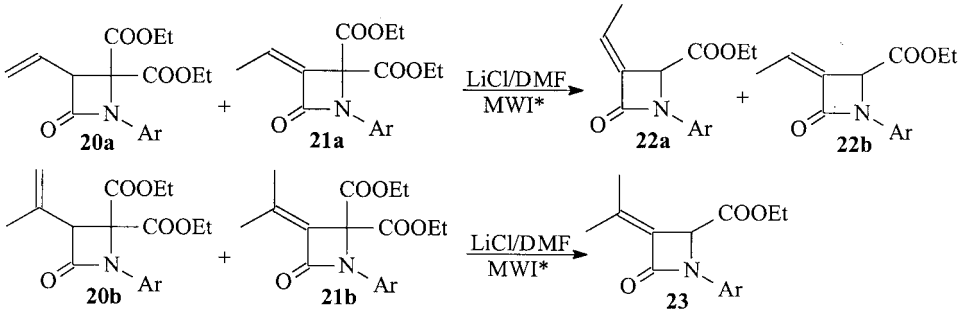


Scheme 7.

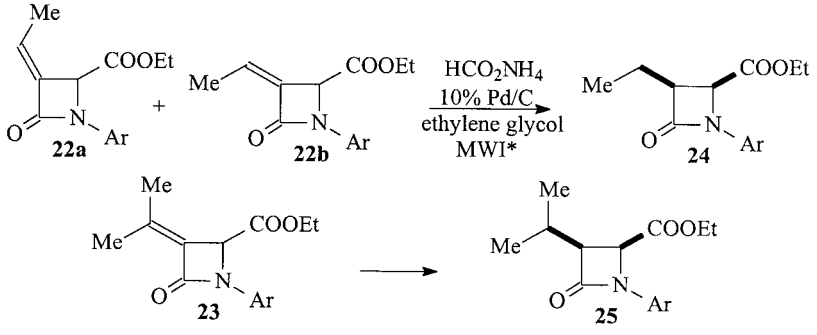


Scheme 8.

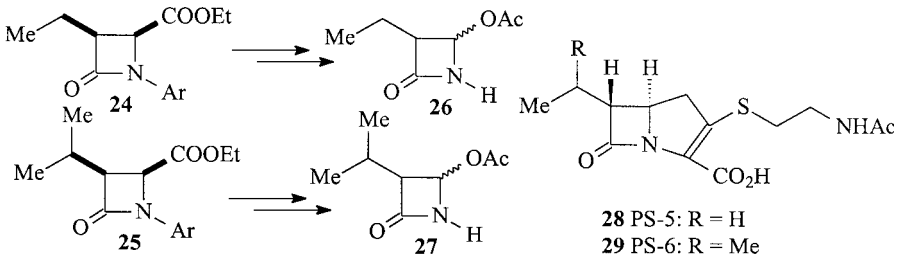
intermediates; the key steps were a combination of dealkoxycarbonylation–hydrogenation experiments under microwave irradiation. First, dealkoxycarbonylation[15] of β-lactams **20a** and **21a** was conducted under the influence of lithium chloride in DMF. The products were found to be a mixture of *E* and *Z* isomers **22a** and **22b** (1:1 ratio). Similar reactions of the mixtures of **20b** and **21b** afforded a single product **23** in good yield (Scheme 9).



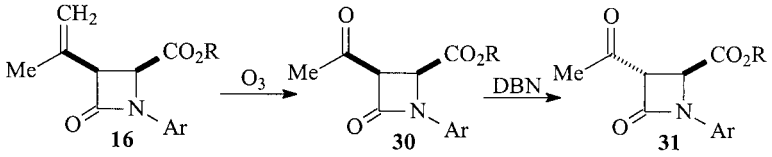
Scheme 9.



Scheme 10.



Scheme 11.



Scheme 12.

The mixture of unsaturated compounds **22** and **23** was then reduced to the saturated compounds **24** and **25**, respectively, by microwave assisted catalytic transfer hydrogenation method[16] (see below for details) developed in our laboratory.[17,18] Ethylene glycol was used as the solvent, ammonium formate as the hydrogen donor and 10% Pd/C as the catalyst. The stereochemistry of the products **24** and **25** from this study was found to be exclusively *cis* (Scheme 10).

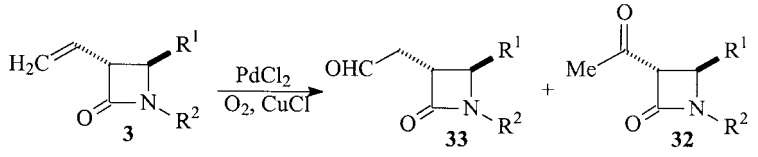
In previous publications,[12] the conversion of **24** and **25** to **26** and **27**, respectively, have been described. Kametani et al.[19] had prepared the same stereoisomeric mixtures by a different route and converted them to PS-5 (**28**) and PS-6 (**29**). The synthesis of **26** and **27** from **20a** and **20b**, respectively, can be considered therefore, as a formal synthesis of these antibiotics (Scheme 11).

Ozonolysis of **16** produced a *cis* β-lactam **30** with an α-acetyl side chain, which could be reduced to a thienamycin type compound. Epimerization of the C-3 center of **30** was achieved upon treatment with DBN (1,5-diazabicyclo[4.3.0]non-5-ene); the *trans* β-lactam **31** was the major product (Scheme 12). Conversion of a terminal double bond to an acetyl group by palladium catalyzed oxidation in the presence of cuprous chloride and oxygen is a well-established synthetic methodology.[20]

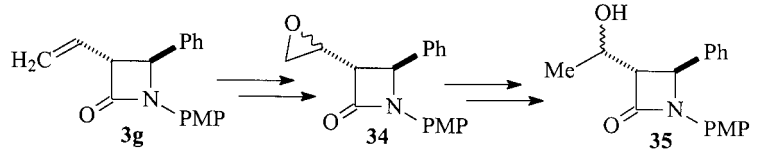
Therefore plans were made to transform the α-vinyl group of β-lactam **3** to an acetyl group (for example, **32**) through palladium-catalyzed oxidation. However, a β-lactam **33** with an aldehyde-containing side chain was the major product.[21] The yield of the expected α-acetyl-β-lactam **32** was very low. This unusual regioselectivity (anti-Markovnikov rule) of the product **33** could be explained by assuming coordination of palladium with the β-lactam carbonyl group as well as the double bond of the vinyl group (Scheme 13).

A more efficient route to the α-hydroxyethyl-β-lactam **35** was developed via the mixture of epoxides **34** obtained on *m*-chloroperbenzoic acid oxidation of **3g**. The epoxide rings were opened by reaction with potassium bromide and acetic acid and the resulting mixture of 2-bromohydrins was debrominated with tributyltin hydride. The products were two stereoisomeres of **35**, which could be separated by chromatography (Scheme 14).[22]

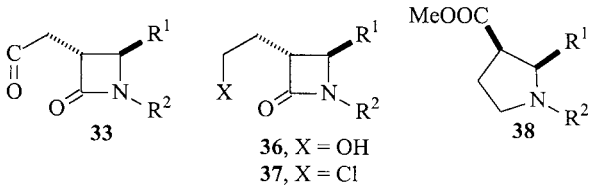
The aldehyde **33** of *trans* stereochemistry was used via its reduction product **36** for the synthesis of pyrrolidine derivatives.[21] The chloride **37**, prepared from the alcohol **36**, was heated with sodium cyanide and methanol to induce a stereospecific rearrangement.[23] The product obtained in good yield was the pyrrolidine **38** with the predictable *cis*



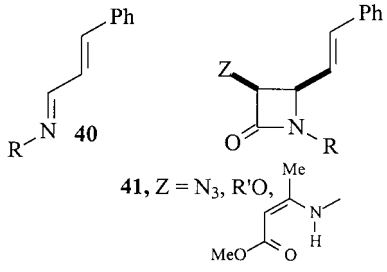
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

relationship between the carboxy group and R^1 (Scheme 15).

4-Vinyl-2-azetidinones

Synthesis of β-vinyl-β-lactams (B)

In the course of studies with β-lactam antibiotics a variety of racemic or homochiral β-vinyl-β-lactams have been prepared in our laboratory by alternative methods. Selected examples of members of this family are provided here along with some experimental data not published before. Recently, some of the conventional methods have been redesigned by employing MORE chemistry techniques.

An easy access to β-vinyl-β-lactams is provided by cycloaddition involving Schiff bases derived from α,β-unsaturated aldehydes (such as cinnamaldehyde). Low temperature reactions with various acid chlorides and triethylamine convert such imino compounds to *cis* β-lactams in most cases (Scheme 16).

Thus, the Dane salt **39** from glycine and methyl acetoacetate was allowed to react with the Schiff base **40** (from cinnamaldehyde and 3,4-dimethoxybenzylamine) in the presence of a chloroformate ester and triethylamine at low temperature when the *cis* β-lactam **41** was obtained in good yield.[24]

Deprotection of the amino group, acylation of the amine to **42** followed by oxidative removal of the dimethoxybenzyl group provided the α-amido-β-vinyl-β-lactam **43**. Permanganate oxidation converted the β-vinyl group to a carboxy group and led to **44** which is a known intermediate for various bicyclic β-lactams (Scheme 17).[24]

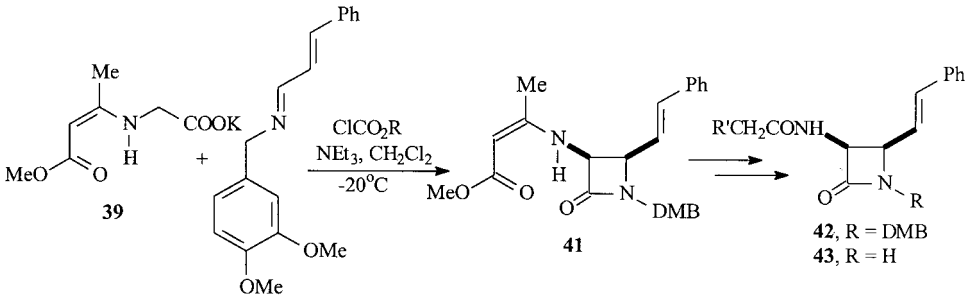
Optically active α-amido-β-vinyl-β-lactams of the type **43** were prepared by cycloaddition involving Schiff bases **46** (derived from cinnamaldehyde and D-threonine esters **45**) and azidoacetyl chloride or **39** followed by standard chemical steps (Scheme 18).[25]

The two *cis* α-amido-β-lactams **47a** and **47b** that were obtained as a mixture could be easily separated by column chromatography. They are formed in nearly equimolar quantities. However, when the triphenylsilyl ether of **45** was the starting material instead of **45**, the silyl ethers of **47a** and **47b** were in the proportion of 95:5.[26]

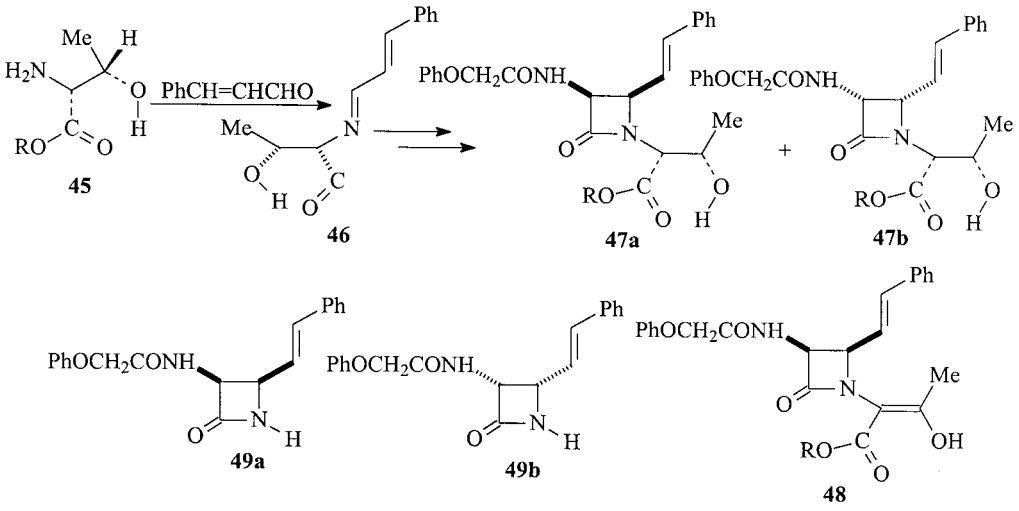
Careful oxidation of **47a** with a limited amount of Jones reagent produced optically active **48** with an enolic side chain on the β-lactam nitrogen. If an excess of Jones reagent was used for the oxidation, the product was the *N*-unsubstituted β-lactam **49a** in the optically pure form.[25] The absolute configuration of **49** was determined by X-ray crystallography and chemical correlation.[26] In the same manner, **47b** could be converted to **49b**, the mirror image of **49a**. Thus, access to both antipodes of **49**, or just **49a** became available depending on whether the starting material was **45** or its triphenylsilyl ether. Oxidation of the styryl group in **49a** or **49b** led to optically pure forms **44** or its antipode.[26]

An alternative approach to optically active β-lactams was also developed in our laboratory. The key reaction was the annulation of the Schiff base (**50**) from D-glyceraldehyde acetonide (or related carbohydrate derivatives) and an arylamine such as *p*-anisidine. Access was thus obtained to optically pure *cis* α-hydroxy or α-amino β-lactams of predictable absolute configuration (Scheme 19).[27,28] It was shown that the oxygen bearing chiral center adjacent to the imino group in the Schiff base was the deciding factor for the induction of optical activity.

When the optically pure α-mesyloxy-β-lactam **54** (obtained by the mesylation of **53**) was treated with lithium iodide, a mixture of 3α- and 3β-iodo-β-lactams **55** was obtained. Obviously, 3-iodo-2-azetidinones also underwent S_N2 type



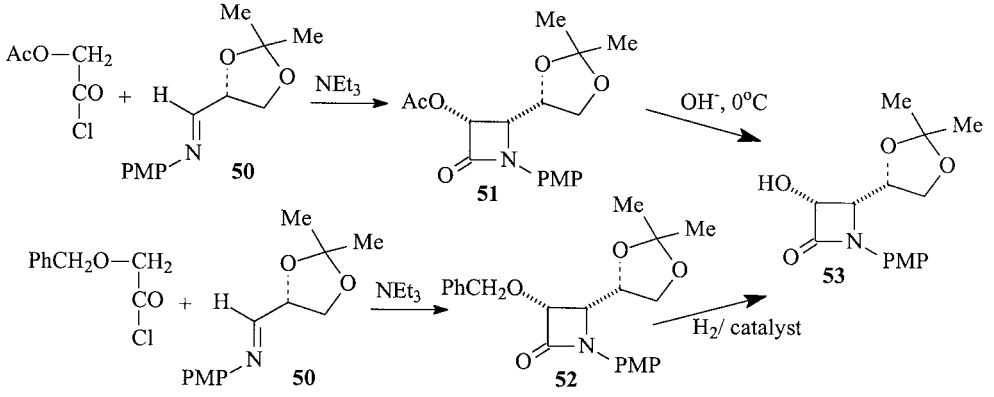
Scheme 17.



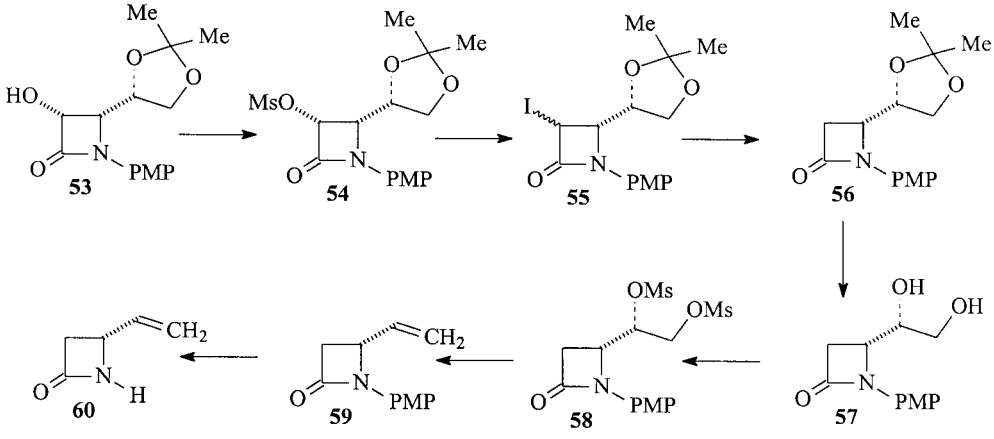
Scheme 18.

reactions with iodide ions. This mixture was dehalogenated with tributyltin hydride to give a single product—the 3-unsubstituted-2-azetidinone **56** in high yield.

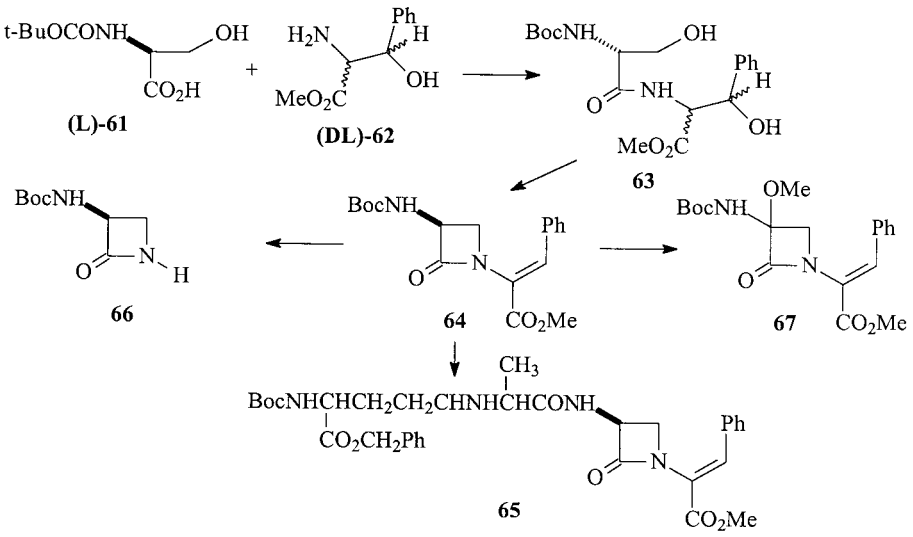
The next step involved the cleavage of the isopropylidine group under mild acid treatment. The diol **57** so obtained was converted to the dimesylate **58** which was allowed to react with lithium iodide and zinc in DMF at 80°C for several hours. The probable diiodo intermediate thus formed was converted to the β-vinyl-β-lactam **59**. Removal of the *p*-anisyl group by oxidation with cerium(IV) ammonium nitrate[29] in acetonitrile led to the desired 4-vinyl-2-azetidinone **60** (Scheme 20). The optical purity of this compound was established by ^{1}H NMR studies using a chiral shift



Scheme 19.



Scheme 20.



Scheme 21.

reagent. The β-lactam **60** showed the same properties as those reported in the literature[30] for the corresponding racemic compound.

4-Vinyl-azetidinine-2-one (**60**) is a versatile intermediate for a variety of heterocycles. It has been used by the Merck group for the synthesis of thienamycin.[31] This compound has also been used as an intermediate for the synthesis of Aspartame,[32] a sweetening agent.

1-Vinyl-2-azetidinones

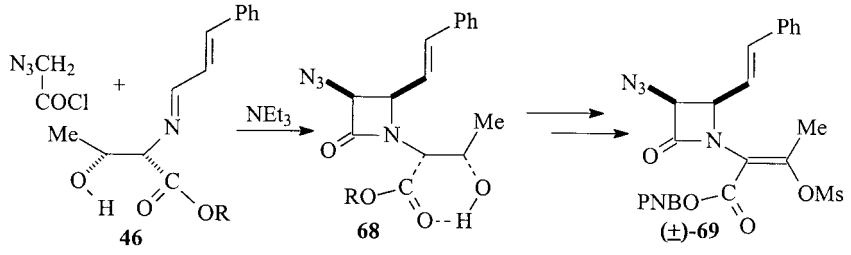
Synthesis of *N*-vinyl-β-lactams (C)

In the course of our preparation of optically active α-amino-β-lactams from L-serine derivatives by the Mitsunobu type reaction,[33,34] it was found that the dipeptide (*N*-Boc)-serinylphenylserine (**63**) was a convenient starting material for the synthesis of *N*-vinyl-β-lactams.[23] The desired dipeptide was prepared from *t*-Boc-L-serine (**61**) and the methyl ester of DL-phenylserine (**62**) under the influence of dicyclohexylcarbodiimide. The β-hydroxy groups required no protection. Reaction of **63** with triphenylphosphine and diethyl azodicarboxylate led in good yield to the β-lactam **64** with an *N*-vinyl group. After deprotection of the *t*-Boc amino group by treatment with formic or trifluoroacetic acid, and acylation with an appropriate group, **65** with a dipeptide side chain similar to that in the monobactam sulfazecin was obtained.[35]

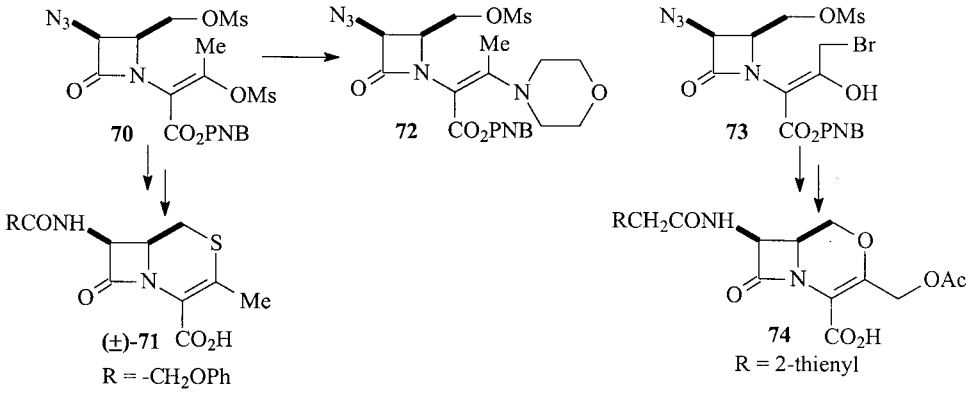
The *N*-vinyl groups could be removed easily by ozonation followed by mild base treatment. The optically active, *N*-unsubstituted β-lactam **66** prepared by this method was identical with a β-lactam prepared by Miller et al.[36] This compound had served previously as a key intermediate for optically active nocardicin and analogs (Scheme 21). The α-amido-β-lactam **64** was converted to a racemic, α-methoxy-α-amido-β-lactam (**67**), which has a cephamycin type side chain at 3-position.[35]

Schiff bases (**46**) derived from cinnamaldehyde and D-threonine esters described in an earlier section (Scheme 18) have been used for preparing monocyclic and bicyclic *N*-vinyl-β-lactams. Cycloaddition with azidoacetyl chloride in the presence of triethylamine converted **46** to a 1:1 mixture of two optically active *cis*-α-azido-β-lactams **68** that differed in the absolute configuration at C-3 and C-4. These diastereomers could be separated with difficulty on a small scale by thin layer chromatography. The 1:1 mixture of the two *cis*-β-lactams was utilized without separation for the next synthetic step. Controlled oxidation with Jones reagent led to an enolic side chain on the β-lactam nitrogen (as in the formation of **48** in Scheme 18). Treatment with mesyl chloride and a base provided **69** in which the enol form could no longer equilibrate with the keto-ester form. In this process, the two chiral centers on the side chain of **68** were lost and the racemic form of **69** was obtained (Scheme 22).

Ozonolysis of **69** followed by reduction with a borane–tetrahydrofuran complex produced a carbinol side chain at



Scheme 22.



Scheme 23.

C-4. Mesylation of this primary alcohol led to the dimesylate **70**, which proved useful as an intermediate for bicyclic β-lactams. The crude dimesylate was treated with hydrogen sulfide–triethylamine following a published procedure to form a second ring and also to reduce the azido group to an amino group. Acylation and deesterification led to the isocephalosporin derivative **71** described earlier by Doyle et al.[37] (Scheme 23).

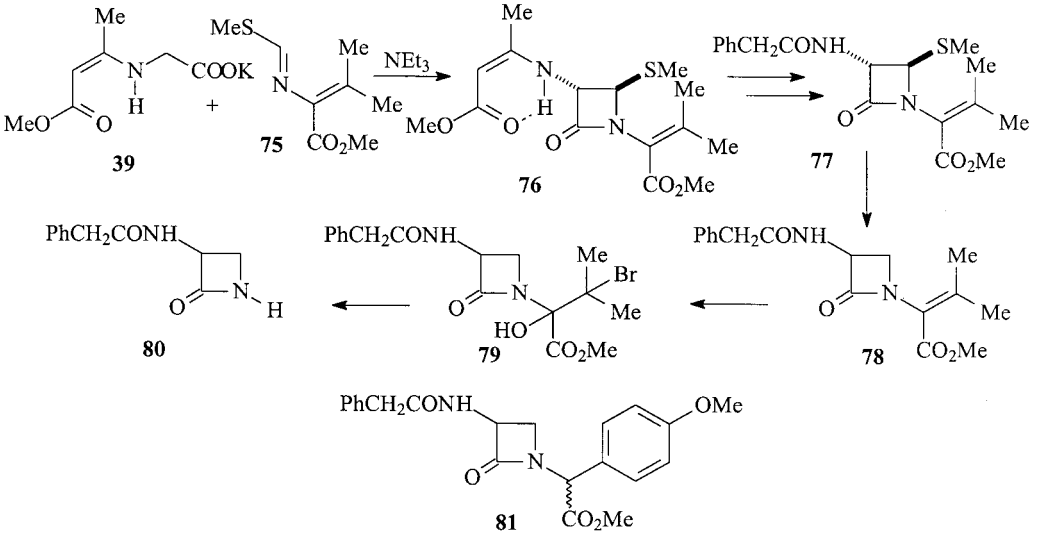
The dimesylate **70** was converted to the enamino compound **72** by reaction with an excess of morpholine. A pyridine solution of **72** was treated with bromine at low temperature to obtain a bromo compound that was hydrolyzed with *p*-toluenesulfonic acid hydrate to the enolic bromo compound **73**. Reaction with an excess of potassium acetate in DMF converted **73** to an oxa-isocephem derivative that was changed into an oxa-analog **74** of isocephalosporin by standard reactions involving the azido group (Scheme 23). Parallel reactions with **47a** (or **47b**) would have provided the homochiral forms of **74**.

A direct access to a C-4 unsubstituted *N*-vinyl-β-lactam was established by starting with **75**—a known degradation product of penicillin G. Cycloaddition with **39** (as in Scheme 17) converted **75** to the *trans* β-lactam **76**. Modification of the C-3 side chain to an amido substituent was achieved by standard reactions to form **77**. Removal of the thiomethyl group gave the desired β-lactam **78**. Transformation of the *N*-vinyl group via the bromohydrin **79** led to the *N*-unsubstituted β-lactam **80** which has been shown to be an intermediate[38] for nocardicin analogs **81** (Scheme 24).

Eco-friendly Synthetic Approaches Under Microwave Irradiation

MORE chemistry techniques

Domestic microwave ovens optimized for heating water are equipped with inexpensive microwave generators (magnetrons) that produce 600–1200 W of 2450 MHz microwave beams directed into the oven area. Microwaves are a non-ionizing radiation that transfer energy to ions in solution and other compounds with a dipole. Metals reflect microwaves and thus are not heated. Glass, ceramics and many polymeric materials are essentially transparent to microwaves. Hydrocarbons (e.g. hexane, benzene and cyclohexane) and symmetrical molecules (therefore without dipole) such as carbon tetrachloride absorb very little microwave energy. But, chloroform, *N*,*N*-dimethylformamide (DMF), ethylene



Scheme 24.

glycol, chlorobenzene, and other organic compounds with dipole moment are heated very rapidly.[39]

The usual reaction vessel is either a large Erlenmeyer flask with a funnel as a loose top or a tall beaker with a loose cover. Any small amount of vapor produced by the reaction is condensed by the unheated glass walls of these vessels. Milligram scale reactions are conducted conveniently in a test tube or vial with a septum as a cap. If necessary, two hypodermic needles are temporarily inserted through the septum to replace the gas inside the capped vial.

The temperature inside a domestic microwave oven is controlled by an on/off cycle. To fine tune the energy absorbed by the reaction mixture, a beaker of water or DMF (*N*,*N*-dimethylformamide) is placed near the reaction vessel. This extra polar liquid acts as a heat sink by absorbing a portion of the microwave energy. The quantity of liquid required in the heat sink can be determined easily by doing one or two pilot experiments.

DMF, with its high dielectric constant, (ϵ=36.7) and high boiling point (154°C), is an efficient microwave energy transfer agent and a convenient solvent because it is miscible with water. The reaction temperature can be raised to ~140°C without significant DMF vaporization. Ethylene glycol (bp 196°C) and 1,3-propanediol are convenient replacements for alcohols used in traditional reactions. In place of the usual aromatic solvents—benzene, toluene and xylene, which absorb microwave energy poorly—chlorobenzene (bp 132°C), 1,2-dichlorobenzene (bp 180°C), and 1,2,4-trichlorobenzene (bp 214°C) can be employed. Ether and THF (tetrahydrofuran) can be replaced by dioxane (bp 101°C), diglyme (bp 162°C), or triglyme (bp 216°C).

It is convenient and economical to use a minimal amount of solvent because, in many cases, a slurry at room temperature provides adequate solubility for reactants during the rapid temperature rise that occurs under microwave irradiation. In the case of crystalline products, much of the product crystallizes out when the small amount of the reaction medium cools down. Many reactions can be conducted without a solvent if one of the reactants is a liquid that absorbs microwave energy efficiently. Less solvent used means less solvent waste, and therefore, reduced pollution.

Catalytic transfer hydrogenation

In earlier years, catalytic reduction and hydrogenolysis of vinyl β-lactams was conducted by using hydrogen under about 40 psi pressure. A fair amount of hydrogen had to be wasted to flush out all the air in the hydrogenation apparatus. Also complete reduction usually required one or more hours of hydrogenation. Currently, catalytic transfer hydrogenation has become the established eco-friendly procedure in our laboratory. Ammonium formate is used as the hydrogen donor. At about 110°C the reduction process takes only about a few minutes and the yield is nearly quantitative.

It was observed that cleavage of the β-lactam ring by the hydrogenolysis of the N–C-4 bond of 4-aryl-2-azetidinones takes place readily in presence of 10% Pd/C catalyst. But, if Raney nickel catalyst be used, there is rapid reduction of double bonds without any scission of the β-lactam ring.

Rapid synthesis of β-lactams

Following a method described by Varma et al.[3a] it is customary in our laboratory now to use a small amount of Montmorillonite clay to accelerate Schiff base formation under microwave irradiation. We have found it unnecessary to remove the clay before proceeding to β-lactam formation by reaction with an acid chloride and a tertiary amine. If the aldehyde or the amine is a liquid, no solvent need be added during the Schiff base formation. However, if the reaction mixture is a very thick slurry, the addition of a small amount of ethylene dichloride is helpful. During the next step it is necessary to add ethylene dichloride or chlorobenzene as the microwave energy transfer reagent (reaction medium). This microwave assisted one-pot synthesis of β-lactams is more eco-friendly and much faster than the conventional method.

Concluding Remarks

Ecologically friendly processes for preparing chemicals for research and manufacture are increasingly in demand. Fortunately, many of the traditional synthetic methods can be modified to achieve higher 'atom economy' (less waste chemicals) and reduced use of solvents. It is also possible in many cases to find less toxic substitutes for such widely used reagents as chromium oxides, osmium tetroxide, benzene, etc.

In the course of our studies on the chemistry of vinyl-β-lactams which was started more than a quarter century ago, attempts have been made to redesign synthetic steps to make them more friendly to the environment. In particular, MORE chemistry techniques have been employed successfully for this purpose.

Environmentally benign syntheses and reduction of pollution at the source are becoming accepted goals for both academic and industrial laboratories. There are strong indications that the newly emerging technology of microwave assisted chemistry will play a special role in the development of eco-friendly synthetic processes.

Experimental

Melting points were determined with a Mel-temp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer infrared spectrophotometer and NMR spectra were recorded on a Bruker AC-20 spectrometer using TMS as an internal standard. Chemical ionization mass spectra were recorded on a Biospect Instrument using CH_4 as the reagent gas. Thin layer chromatography was performed with Whatman plates; the spots were detected by UV. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, NY.

General procedure for β-lactams

Conventional or microwave assisted syntheses of Schiff

bases and various β-lactams are described in our previous publications.[10b] Also see the section above on 'Rapid Synthesis of β-Lactams'.

Stereoselectivity of α-vinyl-β-lactam formation under microwave irradiation: In an Erlenmeyer flask (capacity 250 mL), Schiff base **10** (2 g, 16.80 mmol) was placed in chlorobenzene solution (10 mL). *N*-methylmorpholine (5.09 g, 50.4 mmol) and crotonyl chloride (2.09 g, 20 mmol) were added to it and the mixture was shaken well. A beaker (500 mL capacity) containing water (200 mL) was placed in the microwave oven as a heat sink. The reaction mixture was irradiated at low power setting for 5 min after which TLC indicated disappearance of the starting material. Ethyl acetate (50 mL) was added and the organic phase was washed successively with dilute hydrochloric acid (10%, 2×10 mL), brine (2×10 mL), dried with sodium sulfate and evaporated. The crude product showed the presence of **11** and **12** in the ratio of 20:80. This was chromatographed over silica gel using ethyl acetate and hexane (10:90) as the eluent.

11: yield, 15%, oil; IR (CH_2Cl_2): 1740, 1630 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ: 7.64–6.94 (m, 5H), 5.29–5.16 (m, 2H), 5.08–4.94 (m, 1H), 4.73 (d, *J*=5.4 Hz, 1H), 4.28–4.10 (m, 1H), 2.81 (s, 3H); CIMS (CH_4 reagent gas): m/e 188 $(M+H)^+$; Anal. calcd for $C_{12}H_{13}NO$: C, 76.97; H, 6.99; N, 7.48. Found: C, 76.69; H, 6.81; N, 7.09.

12: yield 55%, oil; IR (CH_2Cl_2): 1740, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.46–7.28 (m, 5H), 6.09 (m, 1H), 5.39–5.22 (m, 2H), 4.35 (d, *J*=2.12 Hz, 1H), 3.59 (brs, 1H), 2.79 (s, 3H); CIMS (CH_4 reagent gas): m/e 188 $(M+H)^+$; Anal. calcd for $C_{12}H_{13}NO$: C, 76.97; H, 6.99; N, 7.48. Found: C, 76.69; H, 6.84; N, 7.51.

Catalytic transfer hydrogenation

Experimental details about the general procedure are provided in our recent publications.[18] An unmodified domestic microwave oven placed in a hood was used; 1,3-propanediol is environmentally more acceptable than ethylene glycol as a reaction medium. The catalyst used was 10% Pd/C, ammonium formate was the hydrogen donor. To prevent risk of fire, the catalyst was first placed in an Erlenmeyer flask under a layer of glycol; the compound to be reduced was added next; finally ammonium formate was added. Under microwave irradiation a temperature of 110–130°C was reached in 3–5 min; reduction and/or hydrogenolysis was usually complete in less than 10 min.

Microwave assisted synthesis of β-lactams

Microwave assisted synthesis of **3g** (Scheme 1), previously described,[21] illustrates the application of MORE (Microwave induced Organic Reaction Enhancement) chemistry techniques. The Schiff base **2** (R^1=Ph, R^2=PMP) was prepared by subjecting a mixture of benzaldehyde, *p*-anisidine and Montmorillonite clay and a minimal amount of ethylene dichloride to medium power microwave irradiation in a domestic microwave oven. Monitoring by TLC showed that on 2–5 g scale of the aldehyde and the amine, Schiff base formation was achieved in near 100% yield in about 5 min.

After allowing the reaction mixture to cool to room temperature, a small amount of ethylene dichloride, crotonyl chloride (**1**) and *N*-methylmorpholine (in place of triethylamine) were added. Microwave irradiation for a few minutes resulted in the formation of **3g** in about 50% overall yield based on benzaldehyde. This yield has not been optimized; indications are that the use of higher boiling chlorobenzene instead of ethylene dichloride will allow a higher temperature of the reaction mixture and an improved yield. The clay was removed by filtration only after completing the one-pot synthesis of **3g**.

The preparation of the previously known **53**[10b] (Scheme 19) provides another illustration of the application of MORE chemistry techniques. The cyclization reaction to obtain a *cis* β-lactam from **50** and benzoyloxyacetyl chloride gave 70% yield of **52** after about 3 min of irradiation. Microwave assisted catalytic transfer hydrogenation with ammonium formate in presence of 10% Pd/C catalyst at about 130°C led to 90% yield of the hydrogenolysis product **53** in about 2 min.

(*3R,4S*)-*cis*-1-(*p*-Anisyl)-3-mesyloxy-4-[(*S*)3′,3′-dimethyl-2′,4′-dioxalanyl]azetidin-2-one (54). To a mixture of the hydroxy β-lactam **53** (2.93 g, 10 mmol), triethylamine (4.04 g, 40 mmol) and 4-dimethyl-aminopyridine (310 mg, 2.5 mmol) in dry methylene chloride (10 mL) at 0°C was added methanesulfonyl chloride dropwise with stirring under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. It was washed with dilute hydrochloric acid (2×50 mL) and brine (1×50 mL), dried (Na_2SO_4), filtered and evaporated to give the crude mesylate (**54**) which was purified by flash column chromatography (silica gel, 230–400 mesh, hexane–ethyl acetate 7:3). Yield, 3.5 g (95%). mp 133°C; $[\alpha]_{26}^{D}$=+97.4° (*c*=0.3, MeOH); IR and NMR spectra were satisfactory. CIMS (NH_3 reagent gas) *m/z* 389 $(M+NH_4)^+$; Anal. calcd for $C_{16}H_{21}NO_7S$: C, 51.75, H, 5.66, N, 3.77, S, 8.63. Found: C, 51.06, H, 5.36, N, 3.72, S, 8.69.

(3*R*,4*S*)-*cis*-1-(*p*-Anisyl)-3-iodo-4[(*S*)2′,2′-dimethyl-1,3′-dioxalan-4′-yl]-azetidin-2-one and (3*S*,4*S*)-*trans*-1-(*p*-anisyl)-3-iodo-4-[(*S*)2′,2′-dimethyl-1′,3′-dioxalan-4′-yll-azetidin-2-one (55). Lithium iodide (3.2 g, 24 mmol) was added to a solution of 54, (3 g, 8.0 mmol, [21]) in dry *N*,*N*-dimethylformamide (50 mL) under anhydrous conditions and the resultant mixture was heated at 80°C with continuous stirring. When TLC indicated the absence of the starting material, it was poured into water (150 mL) and extracted (6×75 mL) with methylene chloride–diethyl ether (1:5). The combined organic extracts were washed with water (5×100 mL), dried (Na_2SO_4), and evaporated to give a crude mixture of the title compounds 55. Purification by flash chromatography (silica gel, 230–400 mesh, hexane–ethyl acetate, 1:1) yielded the pure mixture (2.38 g, 74%) as colorless oil. IR and NMR spectra were satisfactory. CIMS (NH_3) reagent gas) *m/z* 421 $(M+NH_4)^+$.

1-(*p*-Anisyl)-4-[(*S*)-2′,2′-dimethyl-1,3′-dioxalan-4′-yl]-azetidin-2-one (56). To a solution of the pure mixture

obtained from **55**, (1 g, 2.48 mmol) in benzene (40 mL), containing azo-bis-(isobutyronitrile) (AIBN), (catalytic amount), under nitrogen was added tributyl tin hydride (0.722 g, 0.66 mL, 2.48 mmol) dropwise at room temperature. The reaction was monitored by TLC and at the disappearance of the starting material, it was evaporated to dryness, redissolved in methylene chloride (50 mL) and washed with water (6×30 mL), brine (1×30 mL) and dried (Na_2SO_4). The organic layer was then evaporated and purified by silica column chromatography to yield pure **56** (0.54 g, 78.6%). mp 108–109°C; $[\alpha]_{26}^{D}=+72.84°$. IR and NMR spectra were satisfactory; CIMS (NH_3 reagent gas) *m/z* 295 $(M+NH_4)^+$. Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97, H, 6.91, N, 5.05. Found: C, 64.78, H, 6.97, N, 4.97.

1-(*p*-Anisyl)-4-[1′,2′-dihydroxy ethyl] azetidin-2-one (57). To a stirred solution of the β-lactam **56** (9 g, 32–49 mmol) in tetrahydrofuran:water (75 mL, 3:1), was added *p*-toluene sulfonic acid (1.62 g, 8.51 mmol) and the mixture refluxed for 3 h. It was cooled to room temperature and solid sodium bicarbonate was added until the solution was neutral. It was extracted with EtOAc (4×30 mL), dried (Na_2SO_4) and the organic solvent upon evaporation yielded the crude β-lactam **57**, which was purified by flash column chromatography to yield a white solid (5.65 g, 74%). mp 118–120°C; $[\alpha]_{26}^{D}=+99.9°$ (*c*=1.796, MeOH); IR and NMR spectra were satisfactory; CIMS (NH_3 reagent gas) *m/z* 255 $(M+NH_4)^+$. Anal. calcd for $C_{12}H_{15}NO_4$, C, 60.75, H, 6.37, N, 5.90. Found: C, 61.08, H, 6.42, N, 5.78.

1-(*p*-Anisyl)-4-[(*S*)-1′,2′-dimesyloxy ethane] azetidin-2-one (58). Mesyl chloride (1.14 mL, 14.76 mmol) was added dropwise to a stirred solution of the β-lactam **57**, (1 g, 4.22 mmol), and triethylamine (2.65 mL, 19 mmol) in methylene chloride (50 mL) at 0°C under a nitrogen atmosphere. The reaction was allowed to warm to room temperature overnight. It was washed with saturated sodium bicarbonate solution (2×30 mL), water (1×30 mL), brine (1×30 mL) and dried (Na_2SO_4). Removal of the solvent yielded the crude β-lactam **58** which was purified by silica gel flash column chromatography to yield a white solid (1.51 g, 91%). mp 115–117°C; $[\alpha]_{26}^{D}=+67.88°$ (*c*=1.787, CH_2Cl_2); IR and NMR spectra were satisfactory; CIMS (NH_3 reagent *m/z* 411 $(M+NH_4)^+$. Anal. calcd for $C_{14}H_{19}NO_8S_2$, C, 42.74, H, 4.87, N, 3.56, S, 16.30. Found C, 42.81, H, 4.76, N, 3.42, S, 16.70.

1-(*p*-Anisyl)-4-(*R*)-vinyl-azetidin-2-one (59). To a solution of the β-lactam **58**, (2 g, 5.1 mmol) in dry DMF (100 mL) was added LiI (6.8 g, 51 mmol) and metallic zinc (3.32 g, 51 mmol). The mixture was heated under a nitrogen atmosphere at 80°C for 8 h at the end of which it was cooled to room temperature and poured into water (200 mL). It was then extracted (3×100 mL) with ether: CH_2Cl_2 (5:1) and the combined organic layers washed with water (3×100 mL), brine (1×100 mL) and dried (Na_2SO_4). Evaporation of the solvent yielded the pure β-lactam **59**, (1.03 g, 95%) as a light yellow oil. IR and NMR spectra were satisfactory; CIMS (NH_3 reagent gas) *m/z* 221 $(M+NH_4)^+$.

4(*R*)-Vinyl-azetidin-2-one (60). To a solution of the β-lactam **59**, (0.2 g, 0.985 mmol) in 3 mL of acetonitrile at 0°C was added a solution of ceric ammonium nitrate (1.61 g, 2.96 mmol) dropwise over a 5 min period. The reaction was stirred at 0°C for 30 min and diluted with 10 mL of water. The mixture was extracted with ethyl acetate (2×10 mL). The organic extracts were combined and washed with 10% sodium bicarbonate solution and the aqueous washes were back extracted with ethyl acetate (2×5 mL). The combined organic extracts were washed with 10% sodium bisulfite (until the aqueous phase remained colorless), 10% sodium bicarbonate solution and brine. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the crude **60** which was purified by silica gel flash column chromatography using 40% ethyl acetate in hexane as elutant to afford a colorless liquid (0.070 g, 73%). IR and NMR spectra were satisfactory; CIMS (NH_3 reagent gas) *m/z* 115 $(M+NH_4)^+$.

***cis*-1-(1′-*p*-Nitrobenzyloxycarbonyl-2′-mesyloxypropenyl)-3-azido-4-styryl-azetidin-2-one (±69).** To a stirred solution of the known compound **68**[25] (16.62 g, 36.85 mmol) in acetone (1000 mL) at room temperature was added 16.6 mL of Jones Reagent, prepared by dissolving CrO_3 (26.72 g) in concentrated sulfuric acid (23 mL) and diluting the solution to a volume of 100 mL with water. Vigorous stirring was maintained for 1 h, after which time the mixture was filtered to remove the chromous salts, the filtrate (acetone solution) evaporated, and the residue taken up in chloroform (600 mL). This solution was washed with 5% $NaHCO_3$ (2×300 mL), dried (Na_2SO_4), and evaporated to yield 15.95 g of a crude oil. Chromatography on 300 g of silica gel (100–200 mesh), with an eluent of chloroform–ethyl acetate (10:1) afforded the enol ***cis*-1-(1′-*p*-nitrobezyloxycarbonyl-2′-hydroxypropenyl)-3-azido-4-styryl-azetidin-2-one** (12.86 g, 77.7%), mp 98–101°C. IR (neat): 2950–2825, 2100, 1762, 1745, 1650, 1605 cm^{-1}, ^1H NMR ($CDCl_3$) δ: (2.13 (s, 3H), 4.55 (dd, 1H, *J*=5.5, 9.0 Hz), 4.90 (d, 1H, *J*=5.5 Hz), 5.33 (s, 2H), 6.20 (dd, 1H, *J*=9.0, 16.0 Hz), 6.70 (d, 1H, *J*=16.0 Hz), 7.43 (s, 5H), 7.55 (d, 2H, *J*=9.0 Hz), 8.25 (d, 2H, *J*=9.0 Hz), 12.30 (s, 1H).

To a solution of this enol (6.56 g, 14.6 mmol) in anhydrous methylene chloride (190 mL) was added triethylamine (1.62 g, 16.1 mmol). The solution was cooled to 0°C, and freshly distilled methanesulfonyl chloride (1.84 g, 16.1 mmol) in anhydrous methylene chloride (10 mL) was added dropwise with stirring over 20 min. After an additional hour, the solution was washed with brine (2×100 mL), dried (Na_2SO_4), and evaporated to yield 8.80 g of a crude oil which was chromatographed on 300 g of silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1) to afford the enol mesylate **69** (6.10 g, 79.2%) as an oil. IR (neat): 2110, 1760, 1723, 1520, 1360 cm^{-1}; ^1H NMR ($CHCl_3$) δ: 2.60 (s, 3H), 3.28 (s, 3H), 4.90 (m, 2H), 5.32 (s, 2H), 6.25 (m, 1H), 6.62 (d, 1H, *J*=16.0 Hz), 7.35 (s, 5H), 7.50 (d, 2H, *J*=8.0 Hz), 8.20 (d, 2H, *J*=8.0 Hz).

***cis*-1-(1′-*p*-Nitrobenzyloxycarbonyl-2′-mesyloxypropenyl)-3-azido-4-mesyloxymethyl-azetidin-2-one (70).** A stream of ozone was passed through a cooled (−78°C) solution of **69** (527 mg, 1 mmol) in anhydrous methylene chloride (60 mL) for 3 min. The blue color was dissipated by flushing the system with oxygen for 1 min. Dimethyl sulfide

(0.5 mL) was added at −78°C and the solution allowed to warm to room temperature. This solution was washed with brine (30 mL), dried (Na_2SO_4), and evaporated to yield 560 mg of a crude oil. This procedure was repeated five more times, and the combined preparations resulted in 3.30 g of a crude oil which upon chromatography on 150 g of silica gel (100–200 mesh), chloroform-ethyl acetate (10:3) as eluent, yielded an aldehyde ***cis*-1-(1-*p*-nitrobenzyloxycarbonyl-2′-mesyloxypropenyl)-3-azido-4-formyl-azetidin-2-one** (2.10 g, 77.3%) as an oil. IR (neat): 3250–3200, 2110, 1760, 1723, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.58 (s, 3H), 3.30 (s, 3H), 4.85 (m, 1H), 5.10 (d, 1H, J=6.0 Hz), 5.32 (s, 2H), 7.55 (d, 2H, J=7.5 Hz), 8.25 (d, 2H, J=7.5 Hz), 9.70 (d, 1H, J=3.0 Hz).

To a stirred solution of this aldehyde (420 mg, 0.927 mmol) in anhydrous tetrahydrofuran (4.2 mL) at room temperature was added 3.71 mL of a borane-tetrahydrofuran complex solution (1 M in tetrahydrofuran) under anhydrous conditions. The reaction mixture was stirred at room temperature for 8 h, after which time it was quenched with brine (10 mL). It was then diluted with methylene chloride (25 mL) and the organic layer separated. The residual aqueous phase was extracted once more with methylene chloride (25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to yield a crude oil which upon chromatography on 50 g of silica gel (100–200 mesh), chloroform–ethylacetate (10:3) as eluent, yielded the alcohol ***cis*-l-(1′-*p*-nitrobenzyloxycarbonyl-3-azido-4-hydroxymethyl-2(mesyloxypropenyl)-azetidin-2-one** (185 mg, 43.9%) as an oil with some unreacted aldehyde (160 mg, 38.1%).

To a solution of this alcohol (53 mg, 0.12 mmol) in anhydrous methylene chloride (1.0 mL) was added methanesulfonic anhydride (101 mg, 0.58 mmol). The solution was allowed to stir at room temperature under a nitrogen atmosphere for 24 h. The solution was then washed with brine (1 mL), dried (Na_2SO_4), and evaporated to yield 60 mg of a crude oil which, after preparative thick layer chromatography, afforded the dimesylate **70** (40 mg, 64.4%) as an oil and some unreacted alcohol (15 mg, 28.3%). IR (neat): 2110, 1770, 1725, 1630–1600, 1520 cm^{-1}; ^1H NMR ($CHCl_3$) δ: 2.58 (s, 3H), 3.03 (s, 3H), 3.30 (s, 3H), 4.46 (m, 3H), 4.94 (d, 1H, J=5.0 Hz), 5.36 (s, 2H), 7.59 (d, 2H, J=8.5 Hz), 8.28 (d, 2H, J=8.5 Hz).

***cis*-3-Methyl-7-(phenoxyacetamido) (2-isocephem)-4-carboxylic acid (71).** A crude sample of **70** (220 mg) was dissolved in anhydrous methylene chloride (4.5 mL), and the solution was cooled to 0°C. Hydrogen sulfide was passed through the reaction mixture for 15 min, after which time triethylamine (123 mg, 1.20 mmol) in anhydrous, methylene chloride (2.5 mL) was added dropwise with stirring over 5 min. The solution was allowed to warm to room temperature over the next 1.5 h. The solution was then washed with brine (5 mL), dried (Na_2SO_4), and evaporated to yield the crude 7-amino-isocephem. This was dissolved in anhydrous methylene chloride (5 mL), to which was added triethylamine (41 mg, 0.41 mmol). The solution was cooled to 0°C and phenoxyacetyl chloride (69 mg, 0.41 mmol) was added. The reaction mixture was allowed to stir with warming to room temperature over 2 h after which time it was washed with brine (5 mL), dried (Na_2SO_4), and evaporated to yield a crude oil which, after preparative thick layer chromatography, afforded the amide ***p*-nitrobenzyl-3-methyl-7-(phenoxyacetamido)-(2-isocephem)-4-carboxylate** (52 mg, 26.5%) as an amorphous solid. IR (neat): 3310, 1755, 1710, 1680, 1600–1580, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 2.72 (dd, 1H, J=4.5, 12.0 Hz), 3.00 (m, 1H), 3.92 (d, 1H, J=5.0, 10.0 Hz), 4.44 (s, 2H), 5.23 (d, 2H, J=4.0 Hz), 5.46 (dd, 1H, J=5.0, 7.0 Hz), 6.70–7.45 (m, 6H), 7.52 (d, 2H, J=8.5 Hz), 8.13 (d, 2H, J=8.5 Hz). Analysis: $C_{23}H_{21}N_3O_7S$ requires: C 57.14; H 4.38; N 8.69; found: C 57.31; H 4.49; N 8.35.

This isocephem ester (40 mg, 0.0828 mmol) was dissolved in 1,4-dioxane (1.2 mL) and methanol (0.6 mL) containing 10% palladium-on-charcoal (20 mg) and the mixture hydrogenated on a Parr shaker at room temperature and 50 psi for 3 h. The catalyst was filtered off and the solution evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate (10 mL) and washed with 10% HC1 (3×5 mL), and with brine (5 mL). The combined organic layers were treated with charcoal and evaporated under reduced pressure to a solid. The solid was dissolved in very dilute $NaHCO_3$ containing slightly more than one equivalent of base. The aqueous solution was washed with ethyl acetate, acidified to pH 2 with 10% HC1, and extracted twice with ethyl acetate. The combined organic solutions were dried (Na_2SO_4) and evaporated in vacuo to yield the acid **71** (19 mg, 65.9%) as an off-white solid. The product was recrystallized from ethyl acetate, mp 219–220°C, (lit. mp 219–220°C)[35]. IR (nujol mull): 3340, 1755, 1745, 1705, 1660, 1590 cm^{-1}; ^1H NMR (DMSO-d6) δ: 2.12 (s, 3H), 2.73 (dd, 1H, J=4.0, 12.0 Hz), 3.26 (dd, 1H, J=9.5, 12.0 Hz), 3.70 (m, 1H), 4.50 (s, 2H), 5.45 (dd, 1H, J=5.0, 8.0 Hz), 6.60–7.50 (m, 5H), 8.65 (d, 1H, J=8.0 Hz).

7β(2-Thienylacetamido)-3-acetoxymethyl-O-2-isocepham-4-carboxylic acid (74). To a stirred solution of dimesylate **70** (533 mg, 1.0 mmol) in anhydrous methylene chloride (25 mL) at room temperature was added morpholine (209 mg, 2.4 mmol). After 2 h, TLC analysis indicated virtually complete reaction of **70**. The solution was worked up as usual and on concentration yielded an enamine **72** (520 mg, 100%) as an oil, sufficiently pure for the further use. IR (Neat): 3300–2900, 2110, 1770, 1725, 1650, 1620, 1520 cm^{-1}.

The enamine **72** (520 mg, 1.0 mmol) and pyridine (158 mg, 2.0 mmol) were dissolved in anhydrous methylene chloride (15 mL) and the solution cooled to 20°C. Bromine (80 mg, 1.0 mmol) in anhydrous methylene chloride (1 mL) was then slowly added dropwise with stirring. The reaction mixture was maintained at −20°C and then analyzed by TLC after 30 min, which showed incomplete bromination. With an excess of bromine, an excellent yield of the bromide was obtained. The solution was worked up and on concentration afforded 610 mg of a crude bromide with small residual traces of pyridine. IR (Neat): 3300–2900, 2110, 1775, 1725, 1650, 1620, 1515 cm^{-1}.

The unpurified bromide (610 mg) was then dissolved in 1,4-dioxane (20 mL) to which *p*-toluenesulfonic acid monohydrate (456 mg, 2.4 mmol) was added. The reaction was

then stirred for 2 h after which time TLC indicated complete enamine hydrolysis and still an essentially one-component system. The solution was evaporated to dryness in vacuo, the residual oil dissolved in chloroform (30 mL), and this solution washed with brine (2×5 mL), dried (Na_2SO_4), and again evaporated to yield 545 mg of the crude bromo-enol **73**. IR (neat); 3500–2900, 2115, 1775, 1725, 1655, 1620, 1525 cm^{-1}.

The enol **73** (545 mg) and potassium acetate (392 mg, 4.0 mmol) were dissolved in dimethylformamide (5 mL) to which one drop of water was added. After stirring at room temperature for 1.5 h, a new major component in the reaction mixture was detected by TLC. The solution was then diluted with ethyl acetate (25 mL), and the resulting mixture washed with brine (2×15 mL), and dried (Na_2SO_4) and evaporated to afford 410 mg of the crude isocephem as an oil. Preparative thick layer chromatography of this crude product yielded a pure isocephem (230 mg, 55.0% of dimesylate 70) as an oil. IR (Neat): 3000–2850, 2110, 1780, 1745, 1720, 1610, 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H), 3.65–4.10 (m, 2H), 4.68 (dd, 1H, J=3.0, 9.0 Hz), 5.11 (d, 2H, J=3.0 Hz), 5.20 (m, 1H), 5.26 (d, 2H, J=6.0 Hz), 7.67 (d, 2H, J=9.0 Hz), 8.28 (d, 2H, J=9.0 Hz); MS: M+/e=417, [(M+)−28]/e=389.

Using a known procedure for converting azido-β-lactams to amido-β-lactams, the isocephem was converted to isocephalosporin **74**; mp: 181–2°C (dec); lit.[40] mp 182°C (dec); IR (Nujol mull): 3300–2500, 1780, 1750, 1720, 1680, 1535 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-D6): δ 2.02 (s, 3H), 3.60–4.10 (m, 2H), 3.70 (s, 2H), 4.50 (d, 1H, J=6.0 Hz), 4.96 (s, 2H), 5.55 (dd, 1H, J=4.5, 8.0 Hz), 6.90–7.30 (m, 3H), 8.75 (d, 1H, J=8.0 Hz), –COOH not detected. Analysis: $C_{16}H_{16}N_2O_7S$ requires: C 50.53; H 4.21; N 7.37; Found: C 50.69; H 4.17; N 7.31.

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