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Polyhydroxy Amino Acid Derivatives via β-Lactams Using Enantiospecific Approaches and Microwave Techniques[1]

Ajay K. Bose, Bimal K. Banik,[†,*] Chandra Mathur, Dilip R. Wagle and Maghar S. Manhas

George Barasch Bioorganic Research Laboratory, Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ 07030, USA

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Abstract—Enantiospecific synthesis has been developed for α-hydroxy β-lactams of predictable absolute configuration starting with readily available carbohydrates. Stereospecific approaches and microwave assisted chemical reactions have been utilized for the preparation of these 3-hydroxy-2-azetidinones and their conversion to natural or non-natural enantiomeric forms of intermediates for gentosamine, 6-epi-lincosamine, γ-hydroxythreonine, and polyoxamic acid.

Introduction

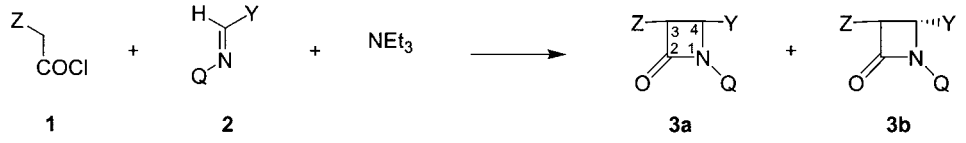
The last few decades have witnessed a remarkable growth in the field of β-lactam chemistry. The discovery of a succession of β-lactams in nature with antimicrobial activity has led to the synthesis of a variety of monocyclic and fused bicyclic β-lactams for the development of many life-saving antibiotics.[2] A recent report[3] discloses the potential of some β-lactams to serve as therapeutic agents for lowering plasma cholesterol. Undoubtedly, the search will continue for clinically useful β-lactams that are not antibiotics.

For natural products chemists, β-lactams hold a special attraction: these four membered, chiral heterocycles have been shown to be versatile synthons for a wide variety of natural products.[4] Synthetic approaches have been developed for preparing homochiral β-lactams with diverse substituents with the desired stereochemistry.[5] Therefore, many natural products are available in optically active form with the natural or non-natural absolute configuration via synthetic β-lactams.

In the course of our continuing studies[6] on lactams, we have been interested in the stereocontrolled synthesis of 3-substituted-2-azetidinones (**3a** or **3b**) by the condensation of an acid chloride (**1** or equivalent) with a Schiff base **2** in presence of triethylamine (Scheme 1). This annulation reaction can lead to four stereoisomers (*cis* and *trans* DL-pairs).

The degree of diastereoselectivity achieved in the β-lactam forming reaction determines the proportion of unwanted isomers obtained which would become chemical waste. It is essential to have an easy access to optically pure products of the desired absolute configuration; the mirror image of these products may also become chemical waste unless they can be recycled. The increasing need for reducing pollution at the source for achieving more eco-friendly chemical synthesis is thus providing a strong incentive for practicing 'atom economy'.[7] It is becoming very important, therefore, to plan for higher stereocontrol of reactions, greater yield of target compounds, and the possibility of one-pot reactions that combine two or more synthetic steps. In recent years, we have found microwave-assisted[8] reactions to be often more eco-friendly than conventional synthesis.

We wish to describe here an enantiospecific approach to polyhydroxy α-amino acid derivatives using both conventional and microwave-assisted reactions.[9] Optically active



Scheme 1.

Keywords: annulation; azetidinones; enantiospecific; amino sugars; amino acids; microwave irradiation.

* Corresponding author. Tel.: +713-792-7749; fax: +713-792-5940; e-mail: banik@mdanderson.org

† Present address: The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.

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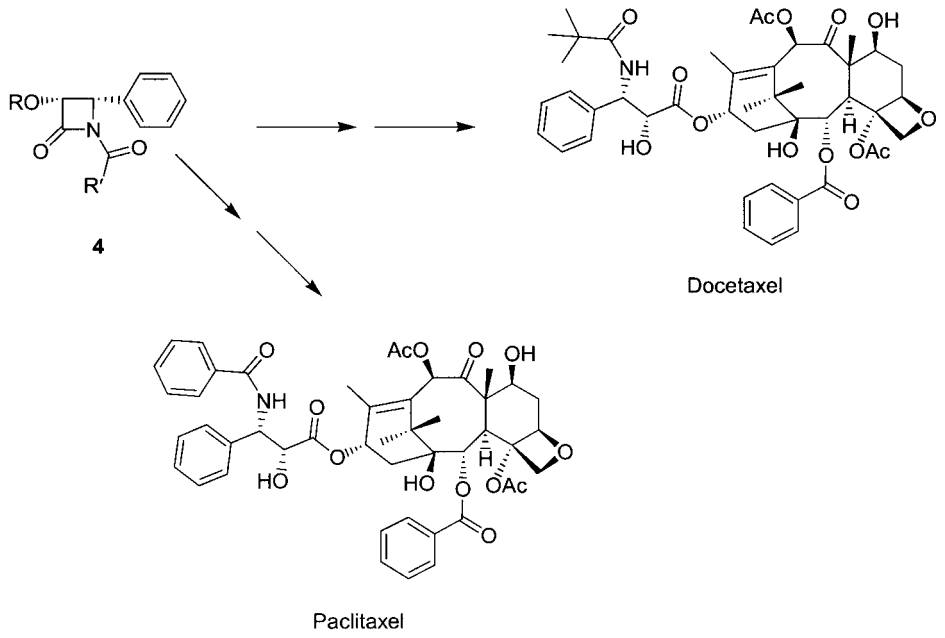


Scheme 2.

α-hydroxy-2-azetidinones were the synthons for our target compounds. Recently, 3-hydroxy-2-azetidinones of type **4** have attracted attention because the semisynthesis of the anti-tumor drug paclitaxel (Taxol™) and its analog docetaxel (Taxotere™) utilizes optically active forms of **4**[10] (Scheme 2).

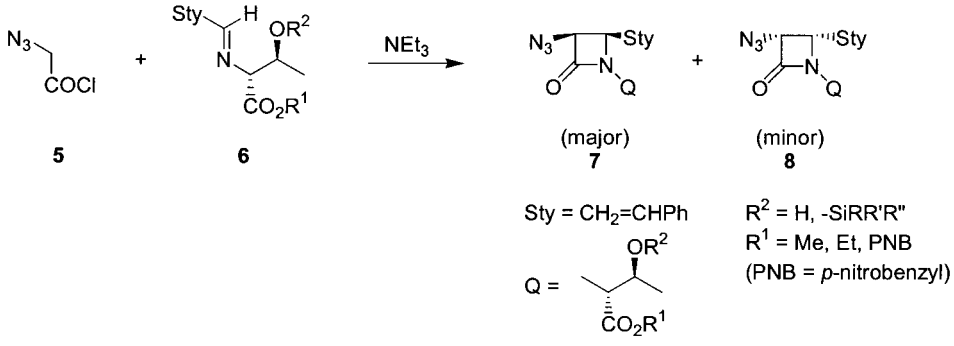
Stereocontrolled α-substituted β-lactam formation

In previous publications[11] we have reported varying levels of high diastereoselectivity during β-lactam formation by the reaction of azidoacetyl chloride (**5**) with Schiff bases **6** derived from threonine esters and an achiral aldehyde (such as cinnamaldehyde). High diastereoselectivity (**7:8**=95:5) was achieved when the hydroxy group of threonine was converted to a very bulky group, for example by the formation of triphenylsilyl ether as in **6** (R=PNB, R=$SiPh_3$, Scheme 3).

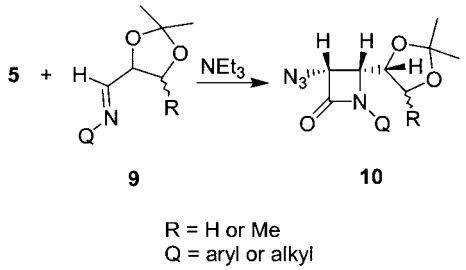
Separation of the major diastereomer (or a derivative) from this reaction as an optically pure compound was found to be easy by column chromatography and/or crystallization. Since both D- and L-threonine are equally available, access to either **7** (or analog) or its antipode **8** can be obtained conveniently.

From the point of view of atom economy[7] a more desirable approach to homochiral β-lactam synthons is the completely enantiospecific synthesis of α-amino β-lactam derivatives (for example, **10**) achieved by two laboratories[12–14] working independently. The key step was the reaction of azidoacetyl chloride (**5**) (or equivalent) and triethylamine with a Schiff base **9** derived from an optically active aldehyde and an achiral amine (Scheme 4).

Scientists at Hoffmann-La Roche Laboratories[12] had used L-glyceraldehyde acetonide prepared from L-ascorbic acid and determined the absolute configuration of the β-lactam formed by single crystal X-ray diffraction. Our initial work[14] was conducted with **9** (R=Me) derived in several steps from D-threonine and the absolute configuration of **10** (R=Me) was deduced from X-ray diffraction data. Subsequent studies involved D-glyceraldehyde acetonide and also aldehydes derived from various sugars leading to a variety



Scheme 3.

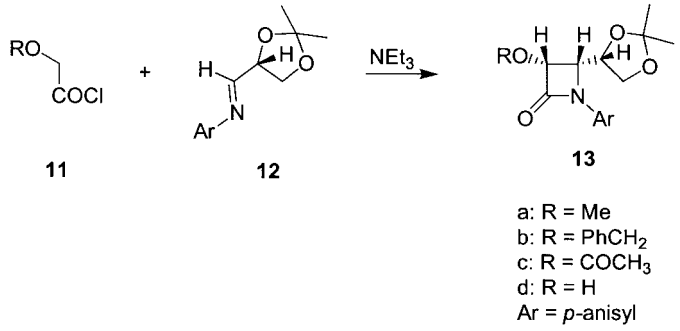


Scheme 4.

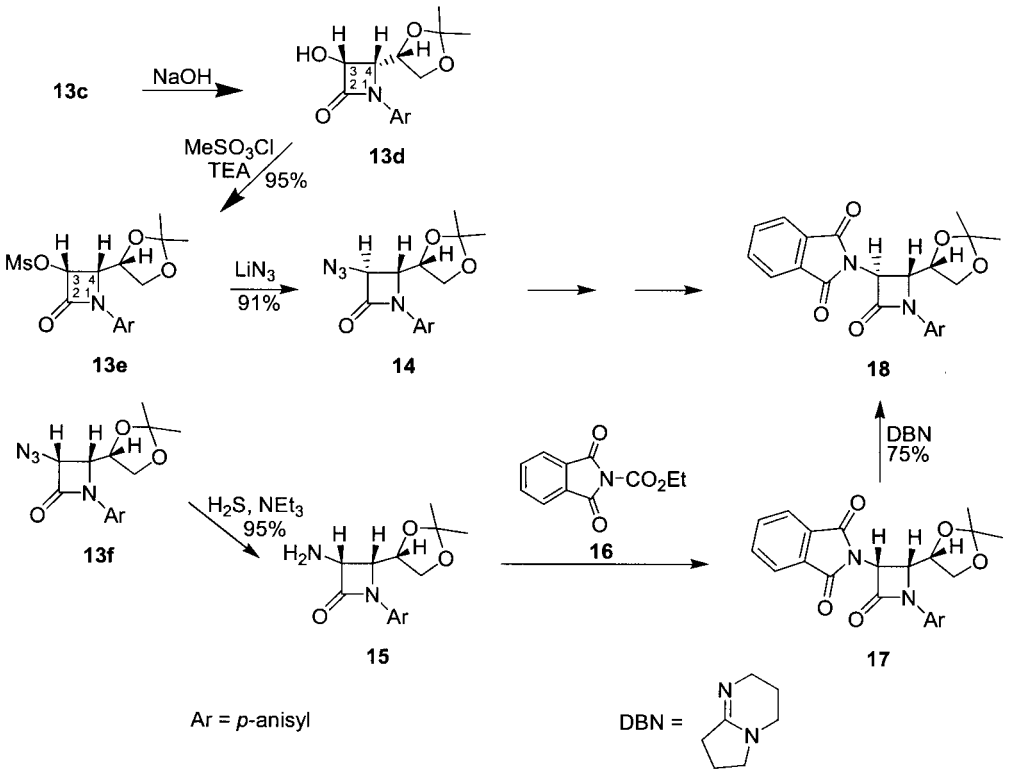
of Schiff bases. It appeared that the absolute configuration of the β-lactam obtained depended only on the chiral center next to the aldehyde group (Scheme 5).

The strategy for α-hydroxy-β-lactams

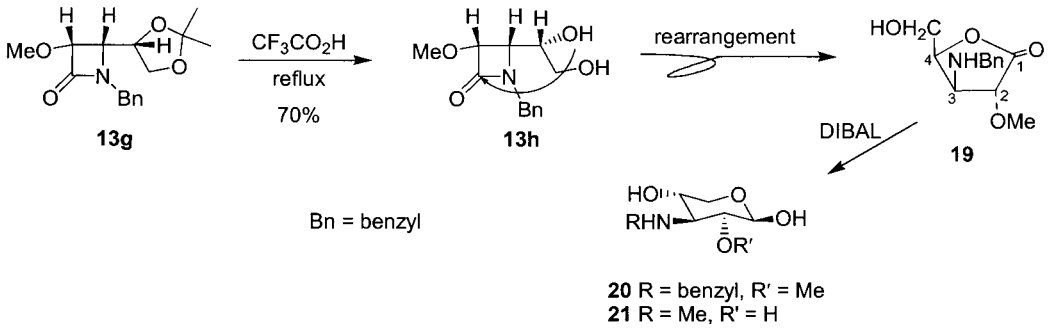
We[15] have found that the reaction of methoxy-, or acetoxy-acetyl chloride **11** (R=Me or $COCH_3$) with **12** produces a single, optically pure *cis*-β-lactam **13a** or **13c** (Scheme 5). The absolute configuration of the α-hydroxy β-lactams **13d** was established by chemical correlation with α-azido β-lactam **10** (Q=p-anisyl, R=H) of known absolute configuration. The same chirality was induced at C_3 and C_4 of the α-azido β-lactam **10** (Q=p-anisyl, R=H) as for the α-hydroxy β-lactam **13d**. Thus, the *cis* α-acetoxy β-lactam **13c** was hydrolyzed[15] under mild conditions to the *cis* α-hydroxy β-lactam **13d** (Scheme 6) and then mesylated to give the *cis* α-mesyloxy β-lactam **13e**. The mesyloxy group was replaced by an azido group to obtain a *trans* α-azido β-lactam **14** via SN2 displacement at C_3. Reduction of the azido group and subsequent reaction with Nefkens reagent (**16**) produced a *trans* α-phthalimido β-lactam (see below) which was identical with the compound **18** in all respects (Scheme 6). This optically pure *trans* β-lactam **18** had been prepared earlier from **10** of known stereochemistry. When the *cis* α-azido β-lactam **10** was converted



Scheme 5.



Scheme 6.



Scheme 7.

to a *cis* α-phthalimido β-lactam **17** via **15** and then epimerized at C_3 (Scheme 6), the *trans* β-lactam **18** of established absolute configuration was obtained.

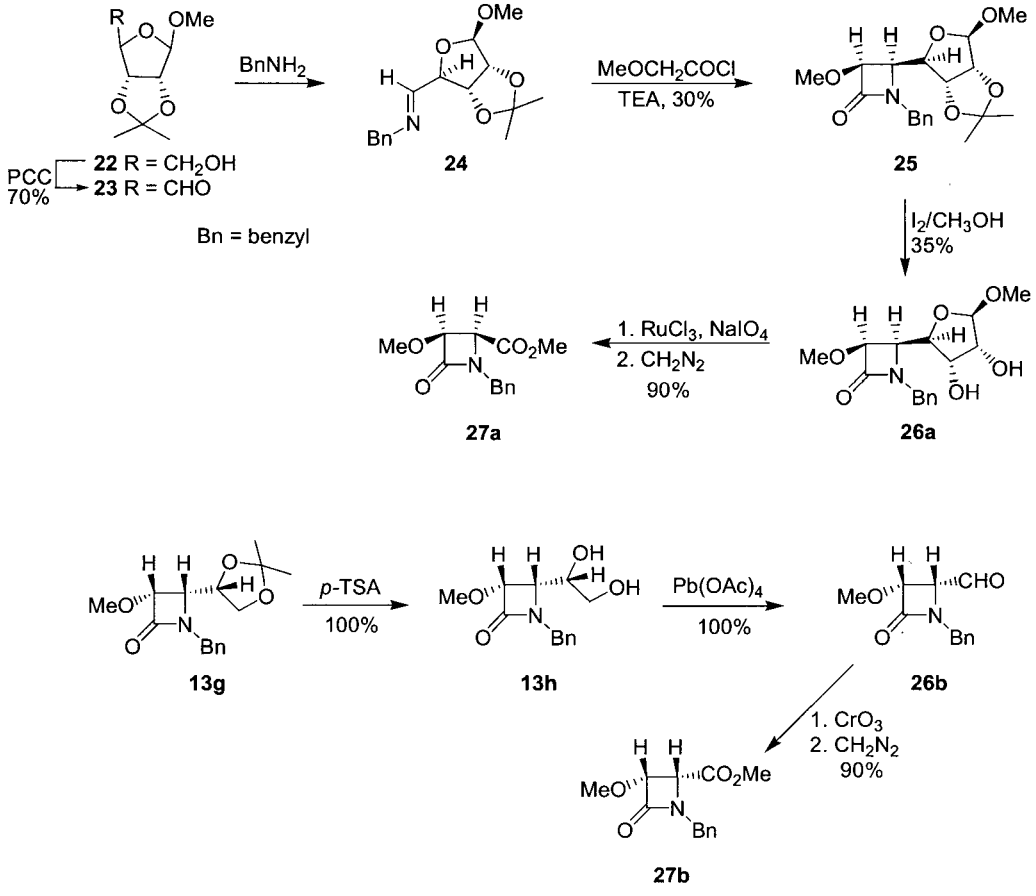
Preparation of an amino sugar lactone

Appropriately substituted β-lactams are known to undergo rearrangement[4] to generate a variety of heterocycles. When the α-methoxy β-lactam **13g** was heated under reflux with 90% trifluoroacetic acid, molecular rearrangement with β-lactam cleavage occurred. The product was a single γ-lactone **19** in 68% yield (Scheme 7). Since this γ-lactone **19** was dextrorotatory, the absolute configuration at C_4 of the sugar could be deduced by using Hudson's lactone rule. The stereochemical assignment of C_4 determined by this method was in agreement with the absolute configuration of **13**.

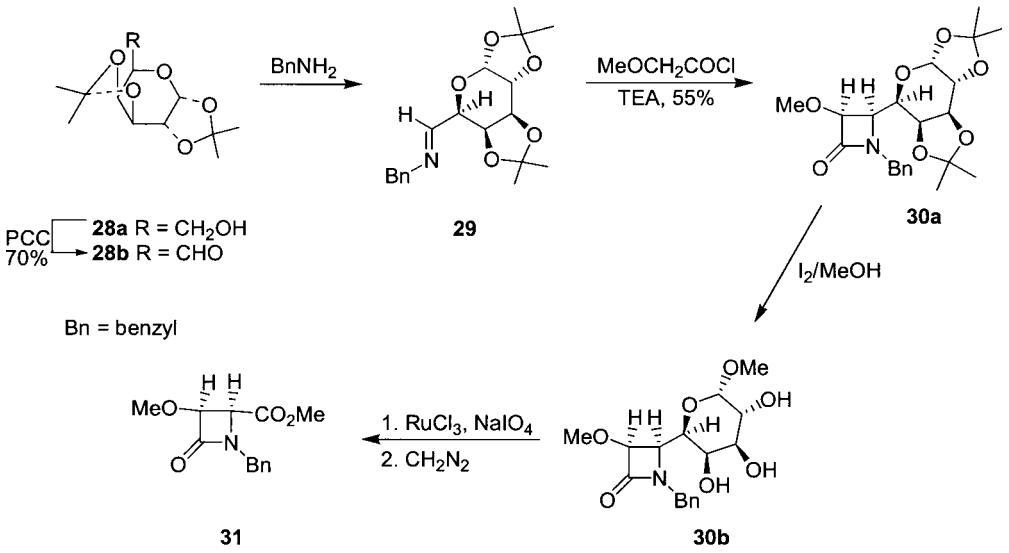
Reduction of the γ-lactone **19** by a known method (reaction with diisobutylaluminum hydride) led to the pyranose derivative, the stereostructure of which is represented by **20**. This amino sugar is a derivative of the natural enantiomer of gentosamine (**21**) which is a 3-amino sugar present in the antibiotic complex gentamicin-A

α-Hydroxy β-lactams with multiple chiral centers

To obtain information on the chirality induced by aldehydes with several asymmetric centers, β-lactams were prepared from imines derived from appropriately protected sugars.



Scheme 8.



Scheme 9.

Also arylalkyl amines (such as benzylamine) were used in place of aryl amines for the synthesis of Schiff bases.

Commercially available methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**22**) was oxidized with pyridinium chlorochromate to obtain the aldehyde **23**. The Schiff base **24** prepared from **23** and benzylamine was treated with methoxyacetyl chloride and triethylamine; a single *cis* β-lactam **25** was obtained in about 30% yield (Scheme 8).

Following a published method[16] the acetonide group in **25** was hydrolyzed with 1% solution of iodine in methanol to obtain **26a**. This β-lactam was oxidized with ruthenium tetraxide ($RuCl_3$+$NaIO_4$) to convert the sugar moiety to a carboxy group which was converted to the methyl ester by treatment with diazomethane. The *cis* β-lactam **27a** so obtained was the mirror image of the same β-lactam **27b** prepared from **26b** via **13h** and **13g** of known absolute configuration (Scheme 8).

A similar set of reactions (Scheme 9) was conducted with **28a**—the diacetonide of D-galalactose and the corresponding aldehyde **28b**. The Schiff base **29** from **28b** and benzylamine were converted to the *cis* β-lactam **30a** which was obtained as a single product in the cycloaddition reaction. The 1-benzyl-3-methoxy-4-carbomethoxy-2-azetidinone (**31**) that was prepared from the β-lactam **30a** through **30b** was identical in all respects (including specific rotation) with **27a** for which the absolute configuration had been determined earlier (Scheme 8). Again, the chirality induced in the β-lactam **30a**, was dependent on the absolute configuration of the aldehyde-bearing carbon alone and was predictable.

Preparation of a 6-epi-lincosamine derivative

The α-methoxy β-lactam **30a**, synthesized from a D-galactose derivative **28**, provided access to an epimer of lincosamine[17]—an eight-carbon amino sugar found in nature. Lincomycin (**32**) is a potent antibiotic which consists of a carbohydrate (lincosamine-a 6-amino-octopyranoside, **33** linked through an amide bond to a proline derivative) (Fig. 1).

Reduction of **30** with lithium aluminium hydride led to an eight-carbon amino sugar derivative **34**. Treatment of **30a** with sodium methoxide in methanol provided the ester **35** which was found to be a more convenient intermediate than **34** for the preparation of an amino sugar that was related to **33** (Scheme 10). Benzylation of **35** led to a crystalline product **36** which was reduced with lithium aluminum hydride to a primary alcohol **37** in good yield. Unexpectedly a chloro compound **38** was formed instead of a mesylate when **37** was treated with mesyl chloride and pyridine at 0°C. After some experimentation it was possible to obtain crystalline **39** by the reduction of **38** with an excess of a clear solution of lithium aluminum hydride in ether. Single crystal X-ray diffraction study of **39** confirmed the absolute configuration and the structure of this 6-epi-lincosamine derivative.[18]

Strategy for homochiral hydroxy amino acids

Easy access to densely substituted β-lactams of predictable absolute configuration led to a convenient strategy for the preparation of various substituted amino acids and their derivatives. Thus, with the multiple hydroxy groups (for example, in **30a**) in a suitable protected form, the β-lactam

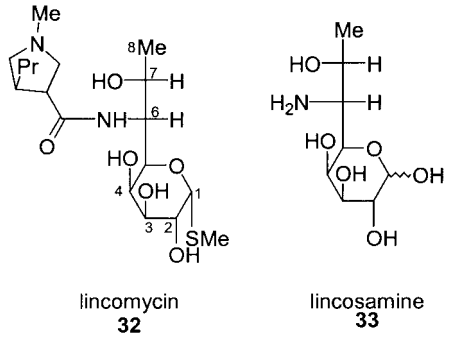
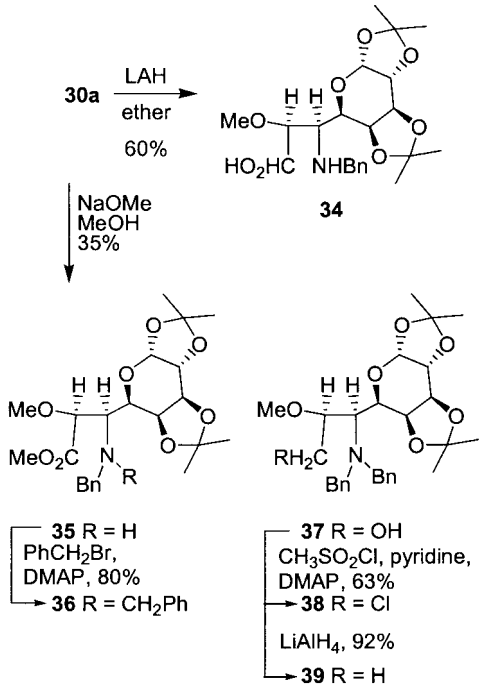


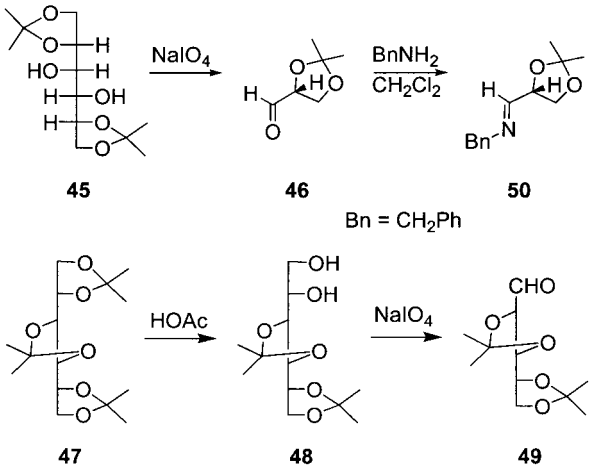
Figure 1.



Scheme 10.

can be hyrolyzed to obtain a β-amino acid derivative (such as in **35**); or, the β-lactam amide can be reduced with lithium aluminum hydride to provide a β-amino alcohol derivative (for example **34**) which can lead to a variety of new compounds. Such homochiral β-amino diols **40** are of special interest as they can lead to α-amino acids **42** and **44** of either enantiomeric form starting with a single intermediate (Scheme 11).

Some of these strategies are illustrated here by the preparation of optically active forms of a dihydroxy amino acid and a trihydroxy amino acid. At the inception of this research, it was decided to utilize a readily available economically priced, optically pure sugar derivative that would be compatible with easy protection and deprotecion of specific hydroxy groups. An aldehyde from such a sugar derivative would permit the synthesis of α-hydroxy β-lactams of predictable absolute configuration. These



Scheme 12.

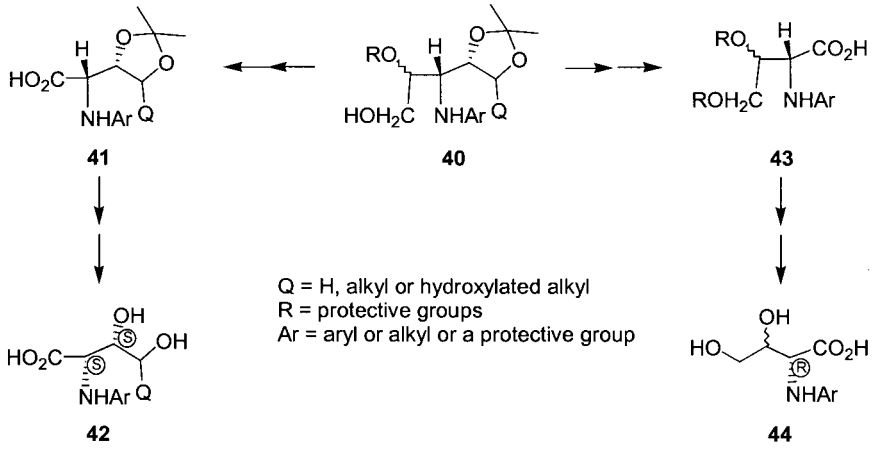
3-hydroxy-2-azetidinones could then lead to different types of target compounds. Commercially available D-mannitol was selected as one of the starting materials. D-mannitol was utilized in two different ways:

(a) In the form of the symmetrical diacetonide **45** which was cleaved with sodium periodate to provide D-glyceraldehyde acetonide (**46**).[19]
(b) In the form of the triacetonide **47** which was selectively hydrolyzed to the diacetonide **48** and then cleaved with periodic acid to the known aldehyde **49** (D-arabinose diacetonide)[20] (Scheme 12).

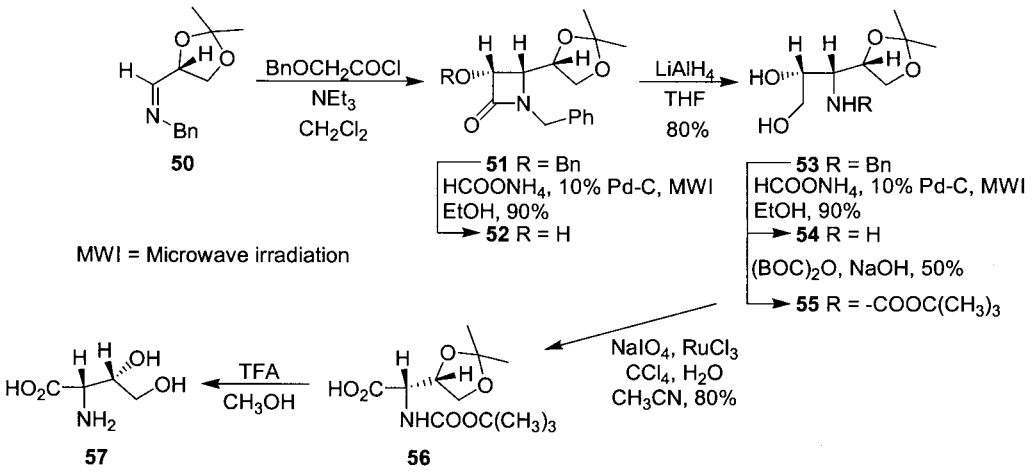
It was demonstrated that the same D-mannitol could be used for generating derivatives of antipodal forms of α-hydroxy β-lactams by starting with either **46** or **49** for the preparation of Schiff bases.

Enantiospecific synthesis of (−)-2*S*, 3*S*-2-amino-3,4-dihydroxybutyric acid

This unusual amino acid, also known as L-γ-hydroxythreonine, has received considerable attention because of the claim by Klenk and Diebold[21], that it is one of the oxidative cleavage products of sphingosine. Since then several syntheses of this compound have been reported.[22]



Scheme 11.



Scheme 13.

The starting material for our synthesis (Scheme 13) was D-glyceraldehyde acetonide (**46**) which was allowed to react with benzyl amine to form the Schiff base **50**. Treatment of **50** with benzyloxyacetyl chloride and triethyl amine produced a single *cis*-β-lactam **51** for which the absolute configuration could be predicted.[23]

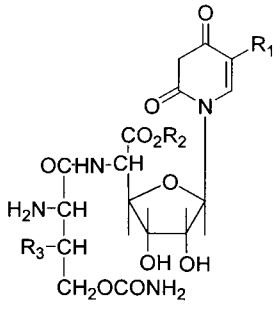
Microwave assisted catalytic transfer hydrogenation[24] of **51** was conducted at about 130°C with ammonium formate[25]as the source of hydrogen and 10% Pd/C as the catalyst. Selective hydrogenolysis to **52** was observed: the benzyloxy group was converted to a hydroxy group but the *N*-benzyl group was unaffected. Lithium aluminum hydride reduction of **52** cleaved the β-lactam ring and led to the vicinal diol **53**. After some experimentation it was discovered that protection of the amino group was necessary before conducting the planned oxidation step.

Microwave-assisted catalytic transfer hydrogenation of **53** removed the *N*-benzyl group to give the primary amino compound **54** which was converted to *t*-butoxycarbonyl derivative **55** using standard reaction conditions.

It was decided to prepare an L-amino acid. Therefore, the diol (acetonide) was left undisturbed and a carboxy group was generated by ruthenium tetraxide oxidation of the unprotected diol **55**. The amino acid derivative **56** obtained in this manner was treated with trifluoroacetic acid to remove the protective groups when the levorotatory (natural) form of γ-hydroxy threomine, the desired amino acid **57**, was obtained.

Synthesis of (−)-polyoxamic acid

Polyoxins[26] constitute a group of unusual nucleosides which acts against the pathogenic fungus that causes the sheath blight disease of the rice plant. They incorporate carbamoylated dipeptides attached to the sugar moiety. Controlled alkaline hydrolysis of polyoxins (**58**) results in several products, one of which has been idenified as (+)-(2*S*, 3*S*,



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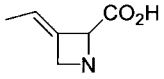
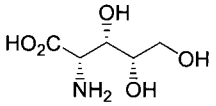
Polyoxins	R_1	R_2	R_3
B	CH_2OH	OH	OH
D	CO_2H	OH	OH
F	CO_2H		OH
G	CH_2OH	OH	H
J	CH_3	OH	OH
L	H	OH	OH



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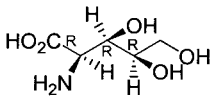

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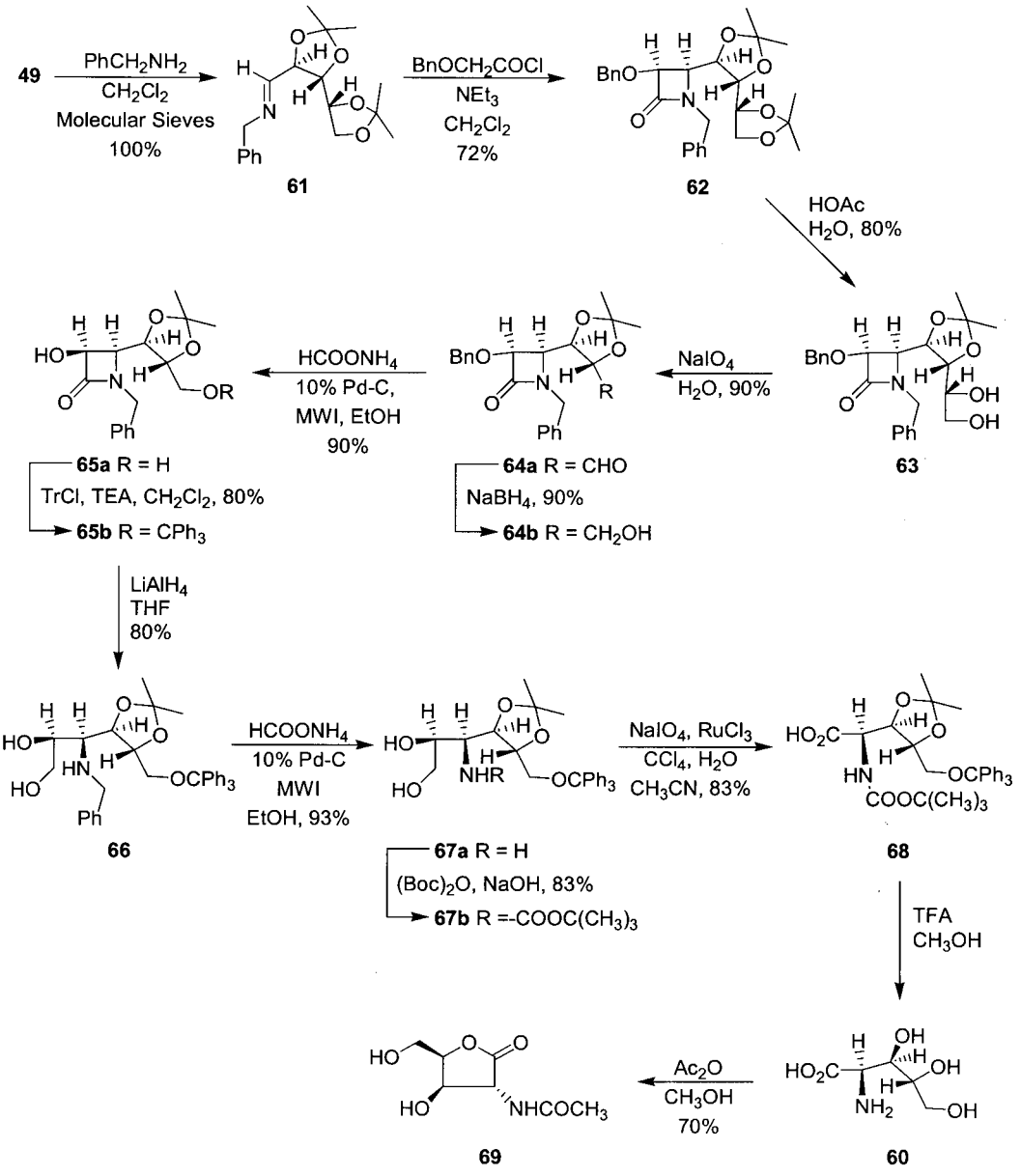
Figure 2.



Scheme 14.

4*S*)-2-amino-3,4,5-trihydroxypentanoic acid (polyoxamic acid, **59**) (Fig. 2). This polyhydroxyamino acid and its mirror image **60** have been the target of synthesis in several laboratories.[27] We describe here enantiospecific reactions leading to **60**—the mirror image of the natural form of polyoxamic acid (**59**) (Scheme 14).

Since the target was a D-amino acid, the aldehyde **49** prepared from the triacetonide **47** of D-mannitol was the starting material. The Schiff base **61** obtained by the condensation of **49** with benzylamine was allowed to react with benzyloxyacetyl chloride and triethylamine; a single optically active β-lactam **62** was the product.[28] Based on the absolute configuration of the chiral center next to the aldehyde group in **49**, it was possible to predict the absolute configuration[29] of this *cis* β-lactam to be as shown in **62**.

After initial studies it was found that the selective removal of one of the acetonide protective groups in **62** could be achieved by mild hydrolysis with aqueous acetic acid.[30] The diol **63** that was obtained was treated successively with sodium periodate and sodium borohydride to remove one of the carbons and obtain **64b**. At this stage catalytic transfer hydrogenation of **64b** was carried out to convert the benzyloxy group to a hydroxy group, as in **65a**. Reaction with trityl chloride and triethylamine gave selective protection to the primary hydroxyl group in **65a** and led to **65b**.

Lithium aluminum hydride reduction of this α-hydroxy β-lactam **65b** produced the vicinal diol **66** with a free benzylamino group. In preparation for an oxidation reaction, the *N*-benzyl group was removed by microwave-assisted catalytic transfer hydrogenation with ammonium formate and Pd/C catalyst. The primary amine **67a** so obtained was converted to a *t*-Boc derivative **67b** which was then oxidized with ruthenium trichloride–sodium periodate.

Cleavage of the diol produced an α-amino acid **68** with protected hydroxyl groups.

All the protection groups in **68** were removed simultaneously by treatment with trifluoroacetic acid in methanol. The optically active polyoxamic acid (**60**) that was formed was converted to the stable lactone **69** by reaction with acetic anhydride. The optical rotation[27c] of **60** clearly demonstrated that the non-natural enantiomer of polyoxamic acid (**59**) had been synthesized. The prediction of the absolute configuration of the β-lactam **62** was thereby shown to be correct.

Microwave-assisted eco-friendly synthetic steps

During the course of our studies on the synthesis of β-lactams and other heterocycles we have found it convenient to conduct several types of synthetic steps under microwave irradiation. We[8] have developed 'Microwave-induced Organic Reaction Enhancement (MORE)' chemistry techniques for using nontraditional methods for rapid, safe and environment friendly reactions. These reactions are performed in unmodified domestic microwave ovens in a matter of minutes using very limited amounts of high boiling solvents (such as DMF and ethylene glycol) or no solvents if one of the reactants is a suitable liquid.

Domestic microwave ovens use radiation of 2450 MHz frequency which is directed into the oven. The level of the energy is controlled by an on–off cycle that can be adjusted for various levels of energy. Microwaves are non-ionizing radiation that are absorbed by ions in solution and compounds with dipoles. Glass and many polymeric materials are nearly transparent to microwaves. Advantage is taken of this property of microwaves to sharply reduce the amount of organic solvents used as the reaction medium or microwave energy transfer agent. Upon irradiating a reaction mixture in an open glass vessel (a large beaker or Erlenmyer flask with a loose cover), microwave energy is transferred to the reactants directly without the necessity for heating the glass vessel and setting up convection currents. The energy input is controlled so that the solvent and/or the reaction mixture is not allowed to approach the boiling point too closely. Thereby the amount of vaporization is kept low and no reflux condenser is needed. Stirrers are not required if the reaction mixture is placed as a comparatively thin layer in the glass vessel used so that microwaves can penetrate the entire reaction mixture. The usual reaction time is a few minutes even on a few hundred grams scale.

It is not clear yet whether microwaves alter the transition state parameters of reactions. But, many laboratories (including our own) have reported that microwave-assisted reactions are much faster, comparatively free of by-products and sometimes susceptible to steric control. Thus, we[31] have shown that the reaction of acetoxyacetyl chloride and *N*-methylmorpholine with a Schiff base such as **2** (Y=Q=aromatic) gives mostly *cis* β-lactams **3a** at low levels of microwave irradiation but at higher energy levels producing higher temperatures—more that 90% of the β-lactam formed may be the *trans* isomer **3b**. Interestingly, with Schiff bases of type **12**, **24**, **29**, **50**, and **61** the *cis* β-lactams are formed at all levels of microwave irradiation. On a few grams scale, optically active *cis* β-lactams **51** and **62** are obtained in high yield after about 3 min of irradiation in a 800 W microwave oven.

Recent work in our laboratory has shown that the Schiff base formation step can be conducted as a solventless or 'dry' reaction under microwave irradiation. Following the method of Varma et al.[32] we have used Montmorillonite clay as a catalyst in this reaction. The next step, which is the β-lactam forming reaction, can be carried out as a one-pot reaction in combination with the first step. It is not necessary to remove the clay in the reaction mixture for the successful completion of the second step.

A major advantage of MORE chemistry techniques is the reduced amount of solvents used. A slurry at room temperature allows enough reactants to go into solution at the comparatively high temperatures reached in a microwave oven in 1 or 2 min. Reduction in the use of solvents as reaction media and lowered amounts of by-products formed, reduce pollution at the source and ensure high levels of 'atom economy'.

Another advantage of MORE chemistry techniques is the lowered energy consumption compared to conventional reactions conducted under reflux requiring input of latent heat of vaporization. Since, the reaction mixture under irradiation is not allowed to come to the boiling point, there is little vaporization and therefore little expenditure of latent heat of vaporization of liquids. Also, microwave assisted reactions—even on several hundred grams scale—require only 10–15 min of irradiation in a domestic microwave oven of 800–1000 W rating.

Recently commercial microwave ovens are being designed for kilogram scale preparative reactions. The availability of such equipment would certainly lead to the use of MORE chemistry techniques for process development research. There is little doubt that in coming decades microwave enhanced chemical synthesis will play an important role for the manufacture of speciality pharmaceuticals such as peptides, steroids, alkaloids and their analogs.

Concluding Remarks

Our studies on Schiff bases derived from chiral aldehydes and achiral amines showed that β-lactam formation was stereospecific. In all cases a single β-lactam was formed through an enantiospecific reaction. The absolute configuration of the β-lactam could be predicted based solely on the absolute configuration of the chiral center next to the imino group. This approach to versatile β-lactam synthons coupled with microwave assisted chemistry can lead to high levels of atom economy.

Experimental

Melting points were determined with a mel-temp. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer model 1310 instrument. ^{1}H and ^{13}C NMR spectra

were recorded on a Bruker Al-200 spectrometer using TMS as an internal standard and $CDCl_3$ as the solvent unless specified and all the chemical shifts were recorded in δ-scale. Chemical ionization mass spectra were recorded on a Biospect instrument either CH_4 or ammonia as the reagent gas. Thin-layer chromatography was performed with Whatmann plates, and the spots were detected in a UV viewing chamber. Optical rotations were measured on Rudolph Polarimeter. All organic solvents were dried by standard procedure. All the extracts after work-up were dried by anhydrous sodium sulfate. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, New York.

Methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside (23). To a solution of commercially available methyl 1, 2:3, 4-di-*O*-isopropylidene-β-D-galactopyranose (**22**) (2.6 g, 10 mmol) in dry dichloromethane (200 mL) was added powdered molecular sieves (4 g, 4 Å) and pyridinium chlorochromate (4.3 g, 19 mmol). The mixture was stirred overnight at room temperature. The dichloromethane layer was passed through florisil and eluted with dichloromethane. Evaporation of the solution gave the aldehyde **23** (1.8 g, 70%; bp 102°C/0.5 mmHg) which was used directly in the next step; mp 59°C; IR (neat): 1670 cm^{-1}; CIMS (NH_3) *m/e* 203 $(M+H)^+$.

1,2:3,4-Di-*O*-isoprylidene-α-D-galactohexodialdo-1,5-pyranose (28b). By following the above procedure, **28a** was oxidized, yield 70%; bp 102°C/0.5 mmHg; IR (neat) 1670 cm^{-1}; ^1H NMR: 9.57 (s, 1H), 5.62 (d, J=4.8 Hz, 1H), 4.6–4.17 (m, 4H), 1.5 (s, 3H), 1.44 (s, 3H), 1.32 (s, 6H).

General method for the synthesis of the Schiff base. A solution of the amine (50 mmol) in dichloromethane (100 mL) was cooled at 0°C, molecular sieves (20 g, 4 Å) was added and the mixture was stirred. The aldehyde (50 mmol) in dichloromethane (50 mL) was added dropwise to it. After being stirred for 1 h at room temperature, it was filtered, dried and evaporated to give the crude Schiff base which was used directly without purification.

***N*-(Benzyl)-4-(methyl-2,3-*O*-isopropylidene-β-D-ribopento-1,4 furanoside)-methylene-imine (24). 24** was prepared by condensing **23** and benzylamine in quantitative yield; CIMS (NH_3) *m/e* 292 $(M+H)^+$.

***N*-Benzyl-4-[1, 2:3, 4-di-*O*-isopropylidine-α-D-galactohexo-1,5-pyranose]-methylene-imine (29). 29** was prepared by condensing **28b** with benzylamine in quantitative yield; CIMS (NH_3) *m/e* 365 $(M+NH_4)^+$.

General procedure for the synthesis of β-lactams. The β-lactams were prepared by one of the following three methods. The yields of the β-lactams by each of these three methods were comparable.

Acid chloride-imine method (Method A). A solution consisting of an acid chloride (0.015 mol) in dry dichloromethane (50 mL) was added dropwise to a stirred solution containing Schiff base (0.013 mol) and distilled triethylamine (0.03 mol) in dry dichloromethane (100 mL) at −20°C. The reaction mixture was stirred overnight at room temperature, washed with saturated sodium bicarbonate solution (50 mL), brine (50 mL), dried and evaporated to give the crude product which was purified by column chromatography over silica gel.

Mixed anhydride method using cyanuric chloride (Method B). To a stirred solution of the potassium salt of the acid (0.02 mol), triethyl amine (0.04 mol) and Schiff base (0.01 mol) in dry dichloromethane (100 mL) maintained at −20°C under nitrogen, was added, a solution of cyanuric chloride (0.02 mol) in dichloromethane (100 mL) over a 30 min period. The mixture was left overnight, washed with saturated sodium bicarbonate solution (3×30 mL), brine (30 mL) and dried. Evaporation of the solvent afforded the crude β-lactam which was purified by column chromatography.

Microwave-assisted synthesis (Method C). To a solution of the Schiff base (10 mmol) in 1,2-dichloroethane (20 mL) in a 500 mL Erlenmyer flask was added triethylamine (30 mmol) followed by acid chloride (12 mmol). The flask vas capped with a glass funnel and placed in a microwave oven (G. E. model, 1450 W). A 500 mL beaker containing 150 mL of water was placed in the oven next to the reaction flask to serve as a heat sink. The mixture was irradiated for 3 min. After the usual work-up, the β-lactam was isolated (60–70% yield).

***cis*-1-Benzyl-4[-(3aαH,8bαH)-tetrahydro-2,2,7,7-tetrahydro-2,2,7,7-tetramethyl-5H-bis[1,3]dioxolo [4,5-b:4′,5′-d]pyran-5-yl]-3-methoxy-azetidin-2-one (30a).** Prepared by following Methods A and B; yield 55%, mp 89–90°C:$[\alpha]_D^{26}=-74.3$ (c=0.6, MeOH); IR (Nujol): 1750 cm^{-1}; ^1H NMR: 7.30 (s, 5H), 5.61 (d, 1H), 4.80 (d, 2H), 4.62 (m, 1H), 4.51 (d, 1H), 4.35 (m, 2H), 4.30 (d, 2H), 4.13 (d, 1H), 3.81 (m, 1H), 3.62 (s, 3H), 1.55 (s, 3H), 1.37 (s, 6H), 1.30 (s, 3H); ^{13}C NMR: 167.46, 136.05, 128.76, 128.43, 127.36, 109.49, 108.89, 96.10, 83.09,70.69, 70.67, 70.29, 69.69, 59.12, 55.62, 45.11, 26.01, 25.89, 24.96, 24.73; CIMS (NH_3) *m/e* 437 $(M+NH_4)^+$; Anal. Calcd for $C_{22}H_{29}NO_7$: C, 63.00, H, 7.0, N, 3.3. Found: C, 62.78, H, 7.11, N, 3.15.

***cis*-1-(Benzyl)-3-methoxy-4-(methyl-2,3-*O*-isopropylidene-β-D-ribopento-1,4-furanoside)-azetidin-2-one (25).** β-Lactam **25** was prepared by following Methods A and B; yield, 0.8 g (30%), mp 97–98°C; $[\alpha]_D^{26}=-37.2$ (c=0.576, MeOH), IR (Nujol): 1755 cm^{-1}; ^1H NMR: 7.25 (m, 5H), 4.95 (d, 1H), 4.85 (d, 1H), 4.65 (d, 1H), 4.61 (d, 1H), 4.50 (d, 1H), 4.45 (m, 1H), 4.35 (d, 1H), 3.81 (m, 1H), 3.65 (s, 3H), 3.0 (s, 3H), 1.52 (s, 3H), 1.31 (s, 3H); ^{13}C NMR: 168.0, 136.5,128.6, 128.5, 127.4, 127.2, 112.5, 110.3, 88.6, 84.6,83.3, 81.9, 59.4, 59.2, 55.3, 44.4, 26.5, 25.1; CIMS (NH_3) *m/e* 381 $(M+NH_4)^+$; Anal. Calcd for C, 62.8; H, 6.88; N, 3.85;. Found: C, 62.79; N, 3.53; H, 7.11.

***cis*-1-Benzyl-4-[(3aαH,8bαH)-tetrahydro-2,2,7,7-tetrahydro-2,2,7,7-tetramethyl-5H-bis(1,3)dioxolo (4,5-b:4′,5′-d)pyran-5-yl)]-3-methoxy-2-azetidinone (30a).** β-Lactam **30a** was prepared by following methods A and B; yield (55%), mp 89–90°C: $[\alpha]_D^{26}=-74.3$ (c=0.6, MeOH); IR (Nujol): 1750 cm^{-1}; ^1H NMR: 7.31 (s, 5H), 5.62 (d, 1H), 4.80 (d, 2H), 4.61 (m, 1H), 4.55 (d, 1H), 4.35 (m, 2H), 4.30

(d, 2H), 4.11 (d, 1H), 3.82 (m, 1H), 3.65 (s, 3H), 1.55 (s, 3H), 1.37 (s, 6H), 1.32 (s, 3H); ^{13}C NMR: 167.46, 136.05, 128.76, 128.43, 127.36, 109.49, 108.89, 96.10, 83.09, 70.69, 70.67, 70.29, 69.69, 59.12, 55.62, 45.11, 26.01, 25.89, 24.96, 24.73; CIMS (NH_4) *m/e* 437 $(M+NH_4)^+$. Anal. Calcd for $C_{22}H_{29}NO_7$: C, 63.00; H, 7.0; N, 3.3. Found: C, 62.78; H, 7.11; N, 3.15.

***cis*-1-Benzyl-3*S*-benzyloxy-4*R*-[1′*R*,2′*S*,3′*R*,4′-di-*O*-isopropylidene]butyl-azetidin-2-one (62)** β-Lactam **62** was prepared by following Methods A, B, and C, as described above; yield: 70–75%; mp 114°C, IR (Nujol): 3050, 2950, 2900, 1740, 1600, 1480, 1450, 1440 cm^{-1}; ^{1}H NMR: 7.38–7.21 (m, 10H), 4.98 (d, *J*=11.4 Hz, 1H), 4.90 (d, *J*=14.8 Hz, 1H), 4.7 (d, *J*=11.4 Hz, 1H), 4.62 (d, *J*=5.16 Hz, 1H), 4.15 (d, *J*=14.8 Hz, 1H), 4.10 (m, 1H), 4.05 (d, *J*=7.04 Hz), 3.8 (m, 1H), 3.79 (m, 3H), 3.71 (dd, J_1=5.09 Hz, J_2=6.76 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H), 1.21 (s, 6H); ^{13}C NMR: 167.48, 136.95, 135.68, 128.76, 128.72, 128.69, 128.54, 127.69, 110.08, 109.36, 81.02, 79.33, 78.39, 75.74, 73.13, 65.69, 57.84, 45.12, 27.50, 26.21, 25.31; CIMS *m/e* 468 $(M+H)^+$; Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 2.99. Found: C, 69.01; H, 6.73; N, 3.08.

(3*R*,4*S*)-*cis*-1-(*p*-Anisyl)-3-mesyloxy-4-(S)-2′,2′-dimethyl-1′,3′-dioxalan-4-yl)-azetidin-2-one (13e). A mixture of hydroxy β-lactam (**13d**) (2.93 g, 10 mmol), triethylamine (4.04 g, 40 mmol) and 4-dimethylaminopyridine (310 mg, 2.5 mmol) in dry dichloromethane (100 mL) was cooled to 0°C and methane sulfonyl chloride (2.28 g, 20 mmol) in dichloromethane (10 mL) was added dropwise with stirring under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight. It was washed with dilute hydrochloric acid (2×50 mL), brine (1×50 mL), dried, and evaporated to give the crude mesylate **13e** which was purified by flash chromatography (silica gel, 230–400 mesh, hexane–ethyl acetate 7:3); yield: 3.5 g (95%); mp 133°C; $[\alpha]_D^{26}$=−97.4 (*c*=0.3, MeOH); IR (Nujol) 1740 cm^{-1}; ^{1}H NMR: 7.6–6.9 (dd, 4H), 5.65 (d, *J*=5 Hz, 1H), 4.37 (m, 3H), 3.85 (m, 1H), 3.7 (s, 3H), 3.3 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H); ^{13}C NMR: 160.27, 157.13, 119.91, 114.11, 110.39, 77.93, 76.30, 66.61, 61.54, 55.47, 39.40, 26.58, 24.77; CIMS (NH_3 reagent gas) *m/e* 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*S*,4*R*)-*trans*-1-(*p*-Anisyl)-3-azido-4-[(*S*)2′,2′-dimethyl-1′,3′-dioxalan-4′-yl)]-azetidin-2-one (14). Lithium azide (2.45 g, 50 mmol) was added to a solution of the mesylate (**13e**) (3.5 g, 9.4 mmol) in dry *N*,*N*-dimethylformamide (20 mL) and the resultant mixture was heated at 80°C. When TLC indicated the absence of the starting material, it was poured onto ice water and extracted several times with dichloromethane. The organic layer was washed with water (5×100 mL), dried, and evaporated to give the title compound as an oil which was purified by flash chromatography (silica gel, 230–400 mesh, hexane–ethyl acetate, 1:1); yield: 2.59 g (91%); mp 96–98°C; $[\alpha]_D^{26}$=−119.8 (*c*=0.5, MeOH); IR (Nujol) 2120, 1750 cm^{-1}; ^{1}H NMR: 7.45–6.8 (dd, 4H), 4.5 (m, 2H), 4.05 (m, 2H), 3.85 (m, 1H), 3.81 (s, 3H), 1.52 (s, 3H), 1.42 (s, 3H); ^{13}C NMR: 160.69, 156.93, 129.85, 119.72, 114.33, 110.72, 74.62, 65.11, 65.02, 61.51, 55.40, 26.53, 24.60; CIMS (NH_3 reagent gas) *m/e* 336 $(M+NH_4)^+$; Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.66; N, 17.61. Found: C, 56.80; H, 5.96; N, 17.47.

***cis*-1-(*p*-Anisyl)-3-amino-4-[(*S*)2,2-dimethyl-1,3-dioxalan-4-yl]azetidin-2-one (15).** Hydrogen sulfide gas was bubbled through a solution containing **13f** (0.5 g, 1.6 mmol) in dry dichloromethane (50 mL) at 0°C for 20 min. The reaction mixture was quenched with triethylamine (0.6 mL, 4.3 mmol) in dichloromethane (5 mL). It was stirred for 1 h at 0°C, evaporated, the solid residue triturated with benzene (10 mL) and filtered. The filtrate upon evaporation at reduced pressure gave a residue of crude amine which was crystallized from ethyl acetate–hexanes to afford pure amine **15** in 95% yield (0.44 g); mp 169°C; $[\alpha]_D^{26}$=−81.90 (*c*=0.48, MeOH); IR (Nujol) 3420, 1730 cm^{-1}; ^{1}H NMR: 7.58–6.88 (dd, 4H), 4.4–4.15 (m, 4H), 3.91 (m, 1H), 3.82 (s, 3H), 1.80 (s,2H), 1.44 (s, 3H), 1.47 (s, 3H); ^{13}C NMR: 168.60, 156.85, 131.62, 120.16, 114.46, 110.00, 77.00, 67.28, 61.77, 60.99, 55.79, 26.62, 25.50; CIMS (NH_3 reagent) *m/e*: 310 $(M+NH_4)^+$; Anal. Calcd for $C_{15}H_{20}N_2O_4$ C, 61.64; H, 6.85; N, 9.59. Found: C, 61.38; H, 7.00; N, 9.20.

***cis*-l-(*p*-Anisyl)-3-phthalimido-4-[(*S*)2,2-dimethyl-1,3-dioxalan-4-yl]azetidin-2-one (17).** A solution of (**15**) (0.4 g, 1.4 mmol) was taken in tetrahydrofuran (25 mL) and treated with a saturated sodium carbonate solution (5 mL) followed by Nefken's reagent (**16**) (0.5 g, 2.2 mmol). The reaction mixture was stirred at room temperature for a period of 45 min, extracted with ethyl acetate and dried. The organic layer upon evaporation yielded the crude β-lactam which was purified by column chromatography using 1:1 ethyl acetate–petroleum ether to give the bright yellow crystalline β-lactam **17** in 70% yield (0.41 g); mp 174°C; $[\alpha]_D^{26}$=−33.2 (*c*=0.52, MeOH); IR (Nujol) 1750, 1710 cm^{-1}; ^{1}H NMR: 8.0–7.7 (aromatic protons, 6H), 6.91 (d, aromatic, 2H), 5.50 (d, *J*=6 Hz, 1H), 4.61–4.32 (m, 2H), 3.75 (m, 1H), 3.55 (t, 1H), 1.52 (s, 3H), 1.29 (s, 3H); ^{13}C NMR: 166.63, 161.17, 156.96, 134.88, 131.20, 130.58, 123.69, 120.29, 114.33, 110.09, 75.89, 65.91, 60.66, 55.45, 55.36, 26.56, 24.93; CIMS (CH_4 reagent gas) *m/e* 423 $(M+H)^+$; Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.4; H, 5.21; N, 6.63. Found: C, 65.3; H, 5.28; N, 6.54.

***trans*-1-(*p*-Anisyl)-3-phthalimido-4-[4(*S*)2,2-dimethyl-1,3-dioxalan-4-yl]azetidin-2-one (18).** A mixture of **17** (50 mg, 0.12 mmol) in dry benzene (9 mL) and 1,5-diazadibicyclo [4.3.0] non-5-ene (DBN) (14.7 mg, 0.12 mmol) was heated under reflux in a nitrogen atmosphere. The solvent was evaporated in vacuo and the crude product was chromatographed over florisil. Elution with 2:8 ethyl acetate–hexane afforded **18** as a white crystalline solid in 75% isolated yield (35 mg); mp 127°C; $[\alpha]_D^{26}$=+11.6 (*c*=0.5, MeOH); IR (Nujol) 1745, 1720 cm^{-1}; ^{1}H NMR (C_6D_6): 7.85–6.8 (dd, AB pattern, 4H), 7.45–7.2 (m, 4H), 5.2 (d, *J*=3 Hz, 1H), 4.56 (dd, 1H), 4.2 (q, 1H), 3.95 (m, 1H), 3.7 (m, 1H), 3.45 (s, 3H), 1.45 (s, 3H), 1.25 (s, 3H); ^{13}C NMR: 166.70, 161.36, 157.00, 134.56, 132.55, 131.71, 123.80, 120.32, 114.37, 110.94, 75.90, 65.48, 60.73, 55.51, 55.38, 26.52, 24.98;

EIMS *m/e* 423 $(M)^+$; Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.4; H, 5.21; N, 6.63. Found: C, 65.66; H, 5.54; N, 6.56.

Synthesis of β-lactams 26a and 30b. To the β-lactam **25** (2 g, 5.5 mmol) or **30a**, (4 g, 9.5 mmol) in a round bottom flask was added a 1% solution of iodine in methanol (20 mL) and (40 mL) respectively. The mixture was refluxed for 4 h and at the end of that period methanol was evaporated and the solid was taken in ethyl acetate (1 L), washed with sodium thiosulphate solution (5%, 3×30 mL), brine (50 mL) and dried. Evaporation of the solvent afforded the crude β-lactam **26a** or **30b**, respectively. The β-lactams **26a** or **30b** were recrystallized from methanol–ethyl acetate–hexane to yield 0.63 g, (35%) of pure **26a**, mp 118°C; IR (Nujol): 3350–3500, 1730 cm^{-1}; ^1H NMR: 7.31 (m, 5H), 5.42 (d, 2H), 4.73 (d, 1H), 4.25 (m, 1H), 4.2 (m, 1H), 4.05 (d, 1H), 3.85 (d, 1H), 3.75 (s, 3H), 3.65 (m, 1H), 3.1 (s, 3H), 3.0 (brs, 1H); ^{13}C NMR: 166.5, 135.6, 128.5, 127.9, 127.5, 108.8, 84.1, 83.4, 74.6, 72.6, 60.5, 59.0, 54.9, 44.6; CIMS (NH_3) *m/e* 341 $(M+NH_4)^+$ and 1.26 g (37.5%) of pure **30b**, mp 167°C; IR ($CHC1_3$): 3400, 3340,1725 cm^{-1}; ^1H NMR ($CDC1_3$+1 drop MeOH):7.30 (m, 5H), 4.81 (d, 2H), 4.52 (d, 2H), 4.31 (d, 1H), 4.09 (m, 4H), 3.72 (brs, 2H), 3.64 (s, 3H), 3.35 (s, 3H); CIMS (NH_3) *m/e* 371 $(M+NH_4)^+$; Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.8; H, 6.6; N, 4.0. Found: C, 57.93; H, 6.25; N, 3.84.

***cis*-1-(Benzyl)-3-methoxy-4-carbomethoxyazetidin-2-one (27a and 31).** To a solution of β-lactam **26a**, (0.45 g, 1.4 mmol) or **30b** (0.5 g, 1.4 mmol) in carbon tetrachloride, acetonitrile and water (8 mL:8 mL:12 mL) was added sodium metaperiodate (1.2 g, 5.6 mmol) and ruthenium trichloride (5.7 mg, 0.028 mmol) and the mixture was refluxed for 30 h. Dichloromethane (20 mL) was added and the inorganic phase separated and extracted with dichloromethane (3×10 mL). The combined dichloromethane extracts were dried and evaporated to yield a crude β-lactam acid, (0.11 g, 37%) which was used as such in the next step. It was found that the β-lactam acid derived from either **26a** or **30b** showed exactly identical IR, NMR and mass spectral data; IR (neat): 3400, 1750, 1730 cm^{-1}; ^1H NMR: 8.1 (brs, 1H), 7.32 (m, 5H), 4.91 (d, 1H), 4.70 (d, 1H), 4.15 (d, 1H) 4.10 (d, 1H), 3.52 (s, 3H); CIMS (NH_3) *m/e* 267 $(M+NH_4)^+$.

A solution of the crude β-lactam acid (0.5 g, 2 mmol), obtained from **30b** was esterified with diazomethane to afford **31** as a light yellow oil; (0.44 g, 85%); $[\alpha]_D^{26}=-43.2°$ (*c*=0.24, MeOH); IR (neat): 1760 cm^{-1}; ^1H NMR: 7.32 (m, 5H), 4.91 (d, *J*=14.65 Hz, 1H), 4.74 (d, *J*=5 Hz, 1H), 4.15 (m, 2H), 3.83 (s, 3H), 3.5 (s, 3H); ^{13}C NMR: 168.46, 165.63, 134.3, 128.81, 128.43, 127.96, 85.09, 59.27, 58.11, 52.22, 44.94; CIMS (NH_3) *m/e* 267 $(M+NH_4)^+$.

Similarly the oil **27a** obtained from **26a** was purified and it was found to be identical with **31**.

***cis*-1-(Benzyl)-3-methoxy-4-[(*S*)2′,2′-dimethyl-1′,3′-dioxalan-4′-yl]azetidin-2-one (13h).** The *cis*-methoxy-β-lactam **13g** (2.91 g, 10 mmol) and *p*-toluene sulfonic acid monohydrate (0.19 g, 1 mmol) were taken up in a (1:1) mixture of tetrahydrofuran and water (30 mL) and refluxed for 48 h. The reaction mixture was diluted with methylene chloride (200 mL) and washed with saturated sodium bicarbonate solution (3×50 mL) and water (2×50 mL), dried and evaporation of the solvent gave a white solid **13h** in quantitative yield. IR (Nujol): 3400, 1735 cm^{-1}; ^1H NMR: 7.25 (m, 5H), 4.84 (d, 1H), 4.45 (d, 1H), 4.25 (d, 1H), 4.0 (m, 1H), 3.65 (m, 3H), 3.6 (s, 3H), 3.30 (bs, 1H).

2-Methoxy-3(4′-benzylamine)-5-hydroxy-pentano-γ-lactone (19). The β-lactam **13h** (0.5 g, 1.7 mmol) was refluxed in 90% trifluoro acetic acid (10 mL), cooled to 0°C and neutralized with solid $NaHCO_3$. The resulting mixture was extracted with ethyl acetate (3×15 mL), dried, filtered and evaporated to afford crude lactone **19**, which was purified by column chromatography using 3:7 ethyl acetate–hexane as solvent; yield (0.3 g, 70%), mp 79–80°C; $[\alpha]_D^{26}=+67.4$ (*c*=0.51, $CHCl_3$); IR (Nujol) 3300, 1760 cm^{-1}; ^1H NMR: 7.4 (brs, 1H), 7.35 (s, 5H), 4.5 (d, *J*=7.81 Hz, 1H), 4.26 (m, 1H), 3.91 (m, 4H), 3.75 (m, 1H), 3.65 (s, 3H), 2.6 (brs, 1H); CIMS (NH_3) *m/e* 252 $(M+H)^{+\cdot}$ Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.57. Found: C, 61.75; H, 6.51; N, 5.83.

***cis*-1-(Benzyl)-3-methoxy-4-aldehydo-azetidin-2-one (26b).** To a stirred solution of the *cis*-methoxy β-lactam **13h** (2.5 g, 10 mmol) in dry benzene (50 mL) was added lead tetraacetate (3.7 g, 8.4 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 45 min and then filtered. The filtrate was purified through florisil column eluting with dichloromethane. Evaporation of the solvent yielded an oil **26b** in quantitative yield (2 g), IR (neat): 1750, 1730 cm^{-1}; ^1H NMR: 9.42 (d, *J*=2.93 Hz, 1H), 7.35 (m, 5H), 4.75 (d, *J*=4.88 Hz, 1H), 4.61 (d, *J*=14.65 Hz, 1H), 4.52 (d, *J*=14.6 Hz, 1H), 4.05 (m, 1H), 3.5 (s, 3H); ^{13}C NMR: 198.48, 165.61, 134.27, 129.02, 128.62, 128.31, 85.81, 63.22, 59.15, 45.71; CIMS (NH_3) *m/e*: 237 $(M+NH_4)^+$.

***cis*-1-(Benzyl)-3-methoxy-4-carbomethoxy-azetidin-2-one (27b).** To a solution of β-lactam **26b** (0.11 g, 0.5 mmol) in acetone (20 mL) was added Jones reagent (CrO_3, 1.35 g, 13.6 mmol), conc. H_2SO_4, (0.12 mL), water, (0.5 mL) and the mixture stirred at room temperature for 2 h. Ethyl acetate (25 mL) was added to it, washed with water (3×15 mL) and dried. Evaporation of the solvent yielded a β-lactam (0.11 g, 91%); IR (neat): 3420, 1750, 1730 cm^{-1}; ^1H NMR: 7.3 (m, 5H), 6.3 (brs, 1H), 4.90 (d, 1H), 4.7 (d, 1H), 4.15 (d, 1H), 4.1 (d, 1H), 3.5 (s, 3H); CIMS (NH_3) *m/e* 267 $(M+NH_4)^+$.

A solution of the above β-lactam (0.5 g, 2 mmol) was dissolved in methanol (5 mL), cooled to 0°C, and to this was added crude diazomethane in anhydrous ether (200 mL) [generated from *N*-nitroso methyl urea (1 g, 9.7 mmol) and 50% aqueous potassium hydroxide (15 mL)]. After usual work-up the resulting oil was purified on silica gel column and eluted with 3:7 ethyl acetate–hexane to yield **27b**, (0.47 g, 90%); $[\alpha]_D^{26}=+38.9°$ (*c*=0.26, MeOH); IR (neat) 1760 cm^{-1}; ^1H NMR: 7.31 (m, 5H), 4.92 (d, *J*=14.69 Hz, 1H), 4.75 (d, *J*=4.9 Hz, 1H) 4.15 (m, 2H), 3.8 (s, 3H), 3.55 (s, 3H), ^{13}C NMR: 168.4, 165.5,

134.2, 128.75, 128.33, 127.9, 85.04, 59.2, 58.09, 52.15, 44.79; CIMS (NH_3) *m/e* 267 $(M+NH_4)^+$.

Synthesis of 35. A mixture of the β-lactam **30a**, (2 g, 4.8 mmol), and sodium methoxide (0.27 g, 5 mmol) in absolute methanol (25 mL) was refluxed under nitrogen atmosphere. At the end of 4 h a further amount of sodium methoxide (0.1 g, 1.8 mmol) was added and the mixture refluxed for additional 8 h. At the end of this period methanol was evaporated and the product was dissolved in ethyl acetate (75 mL) and washed with cold water (3×30 mL) until the water washings were neutral and then it was dried. The crude mixture obtained was passed through silica gel column and eluted with ethyl acetate–hexanes (2:8) to afford **35** as a white crystalline solid, 0.39 g (35%), mp 123°C; IR (Nujol): 3320, 1740 cm^{-1}; ^1H NMR: 7.21 (m, 5H), 5.64 (d, 1H), 4.65 (q, 1H), 4.35 (d, 1H), 4.15 (d, 1H), 4.07 (m, 2H), 4.02 (d, 1H), 3.75 (d, 1H), 3.73, (s, 3H), 3.45 (s, 3H), 3.35 (q, 1H), 1.65 (bs, 1H), 1.5 (s, 3H), 1.45 (s, 3H), 1.3 (s, 6H); ^{13}C NMR: 171.36, 141.54, 128.44, 127.94, 126.4, 109.48, 108.67, 96.72, 81.84, 71.53, 71.30, 70.59, 66.65, 58.85, 58.50, 51.97, 51.47, 26.09, 25.86, 25.05, 24.71; CIMS (NH_3) *m/e* 452 $(M+H)^+$; Anal. Calcd for $C_{23}H_{33}NO_8$: C, 61.2; H, 7.4; N, 3.1. Found: C, 61.06; H, 7.34; N, 2.93.

Synthesis of 36. A stirred solution of **35**, (0.42 g, 0.9 mmol) in acetonitrile (25 mL) containing dimethyl amino pyridine, (0.88 g, 7.2 mmol) was refluxed under nitrogen with the dropwise addition of benzyl bromide (0.6 g, 3.6 mmol). At the disappearance of the starting material, acetonitrile was evaporated. The solid residue was taken in ethyl acetate (30 mL), washed with water (5×20 mL) and dried. Column chromatography on silica gel with ethyl acetate–hexane (1:4) yielded pure **36** (80%, 0.41 g) as a crystalline solid; mp 167°C; IR ($CHCl_3$): 1740 cm^{-1}; ^1H NMR: 7.21 (m, 10H), 5.73 (d, 1H), 4.71 (q, 1H), 4.55 (d, 1H), 4.4 (m, 1H), 4.10 (d, 1H), 4.0 (m, 1H), 3.85 (d, 4H), 3.55 (dd, 1H), 3.4 (s, 3H), 3.3 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR: 170.5, 140.8, 130.0, 127.7, 126.3, 109.6, 108.9, 96.6, 83.3,72.1, 71.5, 70.4, 67.9, 59.0, 57.1, 56.3, 51.3, 26.3,25.8, 25.1, 24.9; CIMS (NH_3) *m/e* 543 $(M+H)^+$.

Synthesis of 38. To an ice cold solution containing methanesulfonyl chloride (0.2 g, 1.75 mmol) in anhydrous pyridine (1.5 mL), and a catalytic amount of DMAP (0.21 mg, 0.001 mmol) was added dropwise, the substrate **37** (0.35 g, 0.69 mmol) in dry dichloromethane (25 mL) under a nitrogen atmosphere. The reaction was allowed to warm up to room temperature. When the starting material disappeared, pyridine was evaporated, water was added (20 mL), and the product was extracted with dichloromethane (2×30 mL) and washed with brine (30 mL). The crude product was purified by chromatography (1:7 ethyl acetate–hexanes to yield pure **38** as an oil (0.196 g, 63%); IR (neat): no characteristic absorption except in the fingerprint region; ^1H NMR: 7.20 (m, 10H), 5.72 (d, 1H), 4.72 (m, 1H), 4.50 (m, 1H), 4.41 (m, 1H), 4.23 (m, 2H), 3.91 (d, 2H), 3.80 (m, 1H), 3.53 (d, 2H), 3.47 (s, 3H), 3.33 (m, 1H), 3.16 (m, 1H), 1.62 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR: 140.12, 129.58, 128.14, 126.85, 109.25, 108.50, 96.61, 83.08, 79.04, 71.9, 71.04, 70.18, 67.96, 61.33, 58.71, 57.68, 26.15, 25.74, 25.05, 24.79; CIMS (NH_3) *m/e* 533 $(M+H)^+$ with characteristic chlorine isotope peak.

Synthesis of 34. To a solution of **30a** (0.3 g, 0.69 mmol) in anhydrous ether (20 mL) was added lithium aluminum hydride (13 mg, 0.35 mmol) at room temperature under nitrogen and the mixture refluxed for 1 h. It was then cooled to 0°C and to this a saturated solution of sodium sulfate was added. The contents were allowed to warm to room temperature (2 h) and filtered. The residue was washed with ether (3×20 mL) and the combined ether layer was dried and evaporated to yield **34** (0.18 g, 60%) as a white solid; mp 99–100°C; IR ($CHC1_3$): 3600–3100 (b), 3340 cm^{-1}; ^1H NMR: 7.3(m, 5H), 5.6 (d, 1H), 4.6 (q, 1H), 4.3 (m, 1H), 4.25–4.1 (m, 3H), 4.05 (m, 2H), 3.9 (d, 1H), 3.75 (m, 1H), 3.4 (brs, 1H), 3.35 (s, 3H), 3.2 (m, 1H), 1.6 (s, 3H), 1.4 (s, 3H),1.3 (s, 6H); ^{13}C NMR: 140.12, 128.76, 128.35,126.98, 109.26, 108.79, 96.74, 77.51, 72.44, 71.19, 70.66, 67.26, 62.16, 60.35, 56.61, 52.51, 26.03, 25.84, 25.05, 24.44; CIMS (NH_3) *m/e* 424 $(M+H)^+$.

Synthesis of 37. 36 was reduced as described earlier to yield pure **37**, (94%) as a crystalline solid, mp 149–150°C; IR (neat): 3550, 3440 cm^{-1}; $[\alpha]_D^{26}=-91.87$ (*c*=0.443, MeOH); ^1H NMR: 7.30 (m, 10H), 5.75 (d, 1H), 5.51 (d, 1H), 4.65 (m, 3H), 4.42 (q, 1H), 4.15 (d, 1H), 3.9 (d, 4H), 3.45 (s, 3H), 1.65 (s, 3H), 1.5 (s, 3H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR: 139.6, 130.0, 128.1, 128.0, 127.8, 126.8, 109.1, 108.6, 96.6, 79.4, 71.8, 71.1, 70.1, 67.9, 61.5, 58.5, 56.5, 26.0, 25.6, 24.9, 24.5; CIMS (NH_3) *m/e* 515 $(M+H)^+$. Anal. Calcd for $C_{29}H_{39}NO_7$: C, 67.84; H, 7.7; N, 2.73. Found: C, 67.73, H, 7.57, N, 2.85.

Synthesis of 39. To a solution of **38** (600 mg, 1 mmol), in dry THF (10 mL) was added a clear solution of $LiAlH_4$ in THF (1 mol, 1 mL, 1 mmol). The mixture was allowed to reflux under nitrogen for 24 h. It was cooled to 0°C and the excess $LiAlH_4$ was quenched by the addition of ice-cold water, filtered, washed with THF, evaporated most of the THF, extracted with ethyl acetate (3×25 mL), washed with brine (25 mL), dried and evaporated. The crude product was purified by chromatography (ethyl acetate–hexane=1:8) and pure **39** was obtained as a white solid (0.52 g, 92%); mp 148°C; IR (Nujol): no characteristic absorption except 1480 cm^{-1}, adjacent to nujol absorption at 1440, 1360 cm^{-1}; $[\alpha]_D^{26}=-76.14$ (*c*=0.346, $CHC1_3$); ^1H NMR: 7.32 (m, 10H), 5.72 (d, 1H), 4.65 (m, 1H), 4.54 (m, 1H), 4.37 (m, 1H), 4.16 (m, 1H), 3.90 (d, 4H), 3.43 (m, 1H), 3.17 (s, 3H), 2.85 (m, 1H), 1.64 (s, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 1.3 (s, 3H), 1.05 (d, 3H); ^{13}C NMR: 141.58, 129.76,129.35, 127.74, 126.38, 109.16, 108.7, 96.79 ‘ 77.95, 72.27, 71.29, 70.31, 68.84, 58.45, 56.32, 56.09, 26.21, 25.77, 25.17, 24.97, 15.97; CIMS (NH_3) *m/e* 499 $(M+H)^+$; Anal. Calcd for $C_{29}H_{39}NO_6$: C, 70.02; H, 7.85; N, 2.82. Found: C, 69.3; H, 7.93; N, 2.79. The structure and stereochemistry were confirmed by single crystal X-ray diffraction study.

1-Benzyl-3*S*-benzyloxy-4*R*-[1′*R*,2′*S*-*O*-isopropylidene-3′*R*, 4′-dihydroxy]butyl azetidine-2-one (63). To a solution of β-lactam **62** (8 g, 17.16 mmol) in methanol (32 mL) was added water (40 mL) followed by glacial acetic acid (48 mL). The reaction mixture was stirred at room temperate for 60 h. The acid was neutralized by careful

addition of sodium carbonate solution (10%) and the mixture was extracted with ethyl acetate (4×50 mL), washed with brine, dried and evaporated. The pure product **63** was isolated after crystallization from ethyl acatate–hexanes: 5.84 g (80%); mp 100°C; IR (Nujol): 3400, 3500, 2950, 1738, 1620 cm^{-1}, ^1H NMR: 7.36–7.23 (m, 10H), 5.06 (d, J=11. 24 Hz, 1H), 4.9 (d, J=14.16 Hz, 1H), 4.75 (d, J=11. 24 Hz, 1H), 4.63 (d, J=4.92 Hz, 1H), 4.3 (dd, J_1=5.67 Hz, J_2=9.05 Hz, 1H), 4.2 (d, J=4.16 Hz, 1H), 3.6 (m, 5H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR: 163.38 135.52, 135.33, 128.85, 128.82, 128.79, 128.69, 109.85, 80.50, 79.63, 73.11, 72.04, 63.67, 58.05, 45.37, 27.29; CIMS *m/e*: 428 $(M+H)^+$; Anal. Calcd for $C_{24}H_{29}NO_6$: C, 67.43, H, 6.83, N, 3.27. Found: C, 67.62; H, 6.49; N, 3.33.

1-Benzyl-3*S*-benzyloxy-4*R*-[1′R,2′*S*-*O*-isopropylidene-3-oxo]propyl-azetidin-2-one (64a). To a mixture of β-lactam diol **63** (5 g, 11.7 mmol) in methanol (15 mL) and water (25 mL) was added a solution of sodium periodate (2.67 g, 12.5 mmol) in water (60 mL) at 0–5°C within 15 min with stirring. The stirring was continued at 0–5°C for additional 1 h. The aldehyde **64a** was isolated after extraction with ethyl acetate (4×40 mL) and drying, as a gummy solid 4.3l g (90%); IR (Nujol): 1735, 1720, 1610 cm^{-1}; ^1H NMR: 9.49 (d, J=2.23 Hz, 1H), 7.39–7.21 (m, 1H), 4.98 (d, J=11.51 Hz, 1H), 4.83 (d, J=14.4 Hz, 1H), 4.69 (d, J=11.68 Hz, 1H), 4.63 (d, J=5.14 Hz, 1H), 4.25 (d, J=14.4 Hz, IH), 4.56 (dd, J_1=6.21 Hz, J_2=8.80 Hz, 1H), 4.01 (dd, J_1=2.7 Hz, J_2=6.14 Hz, 1H), 3.67 (dd, J_1=5.13 Hz, J_2=8.81 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR: 196.67, 166.63, 135.93, 135.23, 128.31, 128.19, 127.95, 127.42, 111.77, 82.16, 79.74, 77.12, 72.57, 58.31, 44.67, 26.64, 26.21; CIMS *m/e*: 410 $(M+H)^+$; Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69,86; H, 6.37; N, 3.54. Found: C, 70.12; H, 6.61; N, 3.42.

1-Benzyl-3*S*-benzyloxy-4*R*-[1′*R*,2′*S*-*O*-isopropylidene-3′-hydroxy]propyl-azetidin-2-one (64b). Sodium borohydride (383 mg, 10.12 mmol) was added to a stirred solution of the aldehyde **64a** (4 g, 10.12 mmol) in methanol (100 mL) at 0–5°C and then the mixture was stirred at the same temperature for 1 h. Water (25 mL) was added and most of the methanol was evaporated under reduced pressure. The residue was extracted with ethyl acetate (4×40 mL), washed with brine (2×20 mL) and evaporated. The crude product on crystallization from ethyl acetate–hexanes gave the pure alcohol (**64b**, 3.49 g, 90%), mp 81°C; IR (Nujol): 3400, 3020, 2950, 2900, 1735, 1595, 1490 cm^{-1}; ^1H NMR: 7.71–7.20 (m, 10H), 4.98 (d, J=11.4 Hz, 1H), 4.60 (d, J=5.09 Hz, 1H), 4.7 (d, J= 11.4 Hz, 1H), 4.22 (dd, J_1=6.45 Hz, J_2=9.1 Hz, 1H), 4.20 (d, J=14.55 Hz, 1H), 3.84 (m, 1H), 1.40 (s, 3H), 1.23 (s, 3H); ^{13}C NMR: 166.78, 135.99, 135.57, 128.48, 128.42, 128,39, 128.2, 127.47, 109.61, 80.21, 79.99, 78.47, 72.75, 62.61, 58.6, 44.99, 27.19; CIMS *m/e*: 398 $(M+H)^+$; Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.84; N, 3.52. Found: C, 69.62; H, 6.66, N, 3.62.

1-Benzyl-3*S*-hydroxy-4*R*-[1′*R*,2′*R*-*O*-isopropylidene-3′-hydroxy]propylazetidin-2-one (65a). To a solution of the β-lactam alcohol **64b** (3.5 g, 8.81 mmol) in absolute ethanol (120 mL) was added ammonium formate (3.5 g) and 10% Pd-C (3.5 g) and the mixture was heated under reflux for 30 min. Catalyst was filtered off and ethanol was evaporated under reduced pressure. The residue was taken in ethyl acetate (150 mL) and washed with brine (2×25 mL), dried and evaporated. The semisolid residue on crystallization from ethyl acetate–hexanes gave the pure β-lactam diol **65a** (2.43 g, 90%), mp 109°C; IR (Nujol): 3300, 3050, 2950, 2900, 1730, 1580, 1400 cm^{-1}; ^1H NMR: 7.68–7.14 (m, 5H), 4.84 (d, J=4.63 Hz, IH), 4.78 (d, J=14.61 Hz, 1H), 4.21 (d, J=14.6 Hz, 1H), 4.2 (dd, J_1=9 Hz, J_2=2.25 Hz, 1H), 3.8 (m, 3H), 3.6 (dd, J_1=4.6 Hz, J_2=9 Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H); ^{13}C NMR: 168.96, 135.26, 128.62, 128.53, 128.50, 127.47, 109.35, 79.82, 78.84, 74.98, 62.42, 60.0, 45.21, 26.95; CIMS *m/e*: 308 $(M+H)^+$ Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.88; N, 4.55. Found: C, 62.35; H, 6.67; N, 4.63.

Microwave-assisted catalytic transfer hydrogenation

The standard method in our laboratory now for reduction or hydrogenolysis[25] is to use high temperature (100–150°C) catalytic transfer hydrogenation with ammonium formate as the hydrogen source, Pd/C as the catalyst, and ethylene glycol (bp 198°C) as the reaction medium. Microwave irradiation in a beaker or a conical flask for 2–3 min is adequate to raise the temperature of the reaction mixture to 120–130°C and the reduction or hydrogenolysis step is complete in near quantitative yield in another 2 or 3 min.

We[23] used the above technique to convert the α-benzyloxy β-lactam **51** to the α-hydroxy β-lactam **52** in excellent yield. We prepared 25 g of **52** in only one day starting with mannitol diacetonide (**45**). Fortunately the *N*-benzyl group of a β-lactam is unaffected under these conditions. But the *N*-benzyl group can be successfully removed from the open amines as shown by the conversion of **53** to **54,** and **66** to **67a**. However, an aryl group at C_4 leads to the scission of the C_4–N bond a shown by Ojima et al.[33] Selective reduction has been achieved without β-lactam scission by using Ra–Ni catalyst in place of Pd/C catalyst.[25]

General procedure for hydrogenation in a microwave oven. A detailed experimental procedure and safety principle for catalytic transfer hydrogenation experiment is described in our earlier publication.[25b] To 10 mL of ethylene glycol (or 1,3-propanediol) in an Erlenmeyer flask were added β-lactam (2.72 mmol), ammonium formate (10.84 mmol) and 10% Pd-C (1 g). This reaction mixture was irradiated in a microwave oven for 3 min, at low power setting and filtered. The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (3×20 mL). Evaporation of the solvent gave the product in 90% yield. β-Lactam **65a** was prepared following the microwave irradiation method in 90% yield.

1-Benzyl-3*S*-hydroxy-4*R*-[1′*R*,2′*R*-*O*-isopropylidene-3′-triphenylmethoxy]propyl azetidin-2-one (65b). Trityl chloride (2.44 g, 8.79 mmol) in dry dichloromethane (50 mL) was added dropwise to a stirred solution of the β-lactam diol **65a** (2.7 g, 8.79 mmol) in dry dichloromethane (100 mL) and triethylamine (2.66 g, 26.38 mmol) at −30°C. Stirring at this temperature was continued for 2 h and then the mixture was kept at 0°C for 24 h. The reactants

were washed with dilute hydrochloric acid (2%, 4×l0 mL), water (2×25 mL), sodium bicarbonate solution (5%, 2×25 mL), brine, dried and evaporated. The crude product on crystallization from ethyl acetate gave the pure trityl β-lactam **65b** (3.86 g, 80%); mp 210°C; IR (Nujol): 3800, 3020, 1735, 1620 cm^{-1}; ^1H NMR: 7.34–7.22 (m, 20H), 4.88 (d, J=14.74 Hz, 1H), 4.81 (dd, J_1=4.57 Hz, J_2=8.86 Hz), 4.14 (d, J=14.74 Hz, 1H), 4.04–3.98 (m, 2H), 3.69–3.65 (m, 1H), 3.34 (d, J=9.15 Hz, 1H), 3.41–3.39 (m, 1H), 3.1–3.08 (m, 1H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (DM SO): 169.14, 136.52 128.45, 127.76, 126.97, 117.92, 109.95, 78.00, 77.2, 74.81, 63.9, 60.0, 43.92, 27.5, 27.15; CIMS *m/e*: 551 $(M+H)^+$, Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.48; H, 6.42; N, 2.54. Found; C, 76.02; H, 5.95; N, 2.65.

(2*R*,3*R*-*O*-Isopropylidene-4*S*-) (*N*-benzylamino)-5*R*,6-dihydroxyhexyl-triphenylmethyl ether (66). To a solution of the trityl β-lactam **65b** (2.4 g, 4.37 mmol) in dry tetrahydrofuran (60 mL) was added $LiAlH_4$ (332 mg, 8.74 mmol) and the mixture was refluxed for 3 h. After usual work-up as described for **39**, the crude product on flash chromatography afforded the pure amino alcohol **66** (1.93 g, 80%); IR (Nujol): 3350, 3050, 2900, 1590 cm^{-1}; ^1H NMR: 7.44–7.11 (m, 20H), 4.21–3.85 (m, 4H), 3.61 (s, 2H), 3.34–3.27 (m, 2H), 2.90–2.84 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR: 143.71, 139.72, 128.65, 128.5, 128.17, 127.86, 127.25, 127.09, 108.91, 79.27, 77.65, 70.68, 64.4, 58.31, 53.68, 27.22, 26.98; CIMS *m/e*: 555$(M+H)^+$ Anal. Calcd for $C_{35}H_{39}NO_5$: C, 75.92, H, 7.10; N, 2.53. Found: C, 75.71; H, 6.99; N, 2.50.

Synthesis of the amino-alcohol 53. Amino-alcohol **53** was prepared in a similar way as described for **66**, yield 80%, IR (Nujol) 3400, 3020, 1590 cm^{-1}; ^1H NMR: 7.35 (brs, 5H), 4.26 (d, J=6.38 Hz, 1H), 4.08 (dd, J=6.44, 8.26 Hz, 1H), 3.91 (d, J=1 2.74 Hz, 2H), 3.77 (dd, J=6.77, 8.16 Hz, 1H), 3.67 (m, 2H), 2.77 (dd, J_1=3.9 Hz, J_2=6.05 Hz, 1H), 1.43 (s, 3H), 1.36 (s, 3H), ^{13}C NMR: 139.71, 128.60, 128.44, 127.27, 109.20, 76.41, 70.29, 67.09, 64.86, 60.80, 53.42, 26.57, 25.22; CIMS *m/e*: 282 $(M+H)^+$. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04, H, 8.24; N, 4.97. Found: C, 63.81; H, 8.27; N, 4.95.

Synthesis of the *t*-Boc derivative 67b. To a solution of the alcohol **66** (4 g, 7.23 mmol) in dry ethanol (150 mL) was added ammonium formate (2.28 g, 36.16 mmol) followed by Pd-C (10%, 2.28 g). This mixture was heated under reflux for 10 min. After usual work-up **67a** was obtained as an oil (3.1 g, 93%) which was used as such for the next step without purification. **67a** was also prepared by following the microwave irradiation method in 95% yield.

A soluton of di-*tert*-butyldicarbonate (1.41 g, 65 mmol) in dioxane (10 mL) was added to a solution of the amino alcohol **67a** (2 g, 6.03 mmol) in NaOH solution (l N, 9 mL) at 0–5°C. Stirring at this temperature was done for 1 h and continued for 3 h at room temperature. The reaction mixture was extracted with ethyl acetate (5×25 mL), washed with brine (2×25 mL), dried and evaporated. The crude product was purified by flash chromatography over silica gel to afford the pure **67b** (2 g, 83%); IR (Nujol): 3400, 3050, 2950, 2900, 1695, 1590, 1480 cm^{-1}; ^1H NMR: 7.48–7.18 (m, 15H), 5.24 (d, 1H), 4.08–3.85 (m, 5H), 3.58 (brs, 1H), 3.44–3.23 (m, 3H), 2.82 (brs, 1H), 1.44 (s, 3H); ^{13}C NMR: 157.00, 143.54, 128.91, 128.75, 128.56, 128.51, 127.07, 126.93, 109.74, 87.09, 80.49, 80.21, 74.22, 63.71, 62.62, 49.58, 28.22, 28.02; CIMS *m/e*: 565 $(M+H)^+$. Anal. Calcd for $C_{33}H_{41}NO_7$: C, 70.32; H, 7.33; N, 2.48. Found: C, 70.30; H, 7.21; N, 2.47.

Synthesis of the *t*-Boc derivative 55. The compound **55** was prepared by conventional and microwave-assisted method in a similar way from **54** in 50% yield as described for **66;** yield 60%, IR (Nujol): 3450, 1690, 1600 cm^{-1}; ^1H NMR: 5.14 (d, J=9.60 Hz, 1H), 4.43–4.37 (m, 1H), 4.12–4.05 (m, 1H), 3.94–3.42 (m, 5H), 3.15 (brs, 2H), 1. 46 (s, 12H),1.37 (s, 3H); ^{13}C NMR: 110.18, 80.78, 74.19, 66.91, 63.16, 5 1.00, 28.67, 26.61, 25.44; CIMS *m/e*: 292 $(M+H)^+$. Anal. Calcd for $C_{13}H_{25}O_6N$: C, 53.60; H, 8.65; N, 4.80. Found: C, 53.60; H, 8.57; N, 4.69.

Oxidation of diol 67b to the carboxylic acid 68. To a solution of diol **67b** (1.52 g, 2.66 mmol) in carbon tetrachloride (16 mL), acetonitrile (16 mL) and water (24 mL) was added sodium periodate (3.42 g, 16 mmol) and the mixture was stirred. After 5 min, $RuCl_3$ (25 mg) was added and the stirring was continued at room temperature for 6 h. The mixture was filtered and the residue was washed with ethyl acetate (50 mL), washed with brine (2×25 mL), dried and evaporated. The residue after chromatographic purification over silica gel with ethyl acetate–hexanes (1:1) as eluent gave the pure acid **68** (1.2 g, 83%); mp 172°C; IR (Nujol): 3350, 3050, 2950, 1720, 1695, 1600 cm^{-1}; ^1H NMR: 9.35 (brs, 1H), 7.56–7.23 (m, 15H), 5.36 (d, 1H), 4.6–4.52 (m, 2H), 4.15–4.02 (m, 1H), 3.47–3.29 (m, 2H); ^{13}C NMR: 176.0, 156.05, 143.6, 129.72, 127.85, 127.07, 110.0, 87.02, 80.05, 63.8, 53.2, 28.25, 26.87; CIMS *m/e*: 549 (M +H) +; Anal. Calcd for $C_{32}H_{37}NO_7$: C, 70.18, H, 6. 81; N, 2.55. Found: C, 69.99, H, 6.51, N, 2.47.

Oxidation of diol 55 to the carboxylic acid 56. Carboxylic acid **56** was prepared in a similar way as described for **67b**, yield 80%, mp 166°C; IR (Nujol) 3340, 1715, 1695 cm^{-1}; ^1H NMR: 5.23 (d, J=8.99 Hz, 1H), 4.67–464 (m, 1H), 4.46–4.41 (m, 1H), 4.17–4.09 (m, 1H) 3.86–3.79 (m, 1H), 1.47 (s, 12H), 1.36 (s, 3H); CIMS *m/e*: 276 $(M+H)^+$; Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.36; H, 7.69; N, 5.08. Found: C, 52.97; H, 8.24; N, 4.74; CIMS *m/e*: 276 $(M+H)^+$.

(−)-Polyoxamic acid (60). To the acid **68** (330 mg, 0.6 mmol) was added cold methanol and TFA mixture (1:10, 12 mL) and the mixture was kept at room temperature for 1.5 h. Dry ether (120 mL) was added to it, cooled for 2 h, filtered, the residue washed with dry ether and the white amorphous solid subjected to ion-exchange chromatography ($AG50W\text{-}X8H^+$ column, aqueous ammonia as the eluent) to afford pure **60** (90 mg), mp 165–172°C (dec); $[\alpha]_D^{25}=-5.1°$ (c=1. 0, H_20); IR (KBr): 3400, 2950, 1687, 1500 cm^{-1}; ^1H NMR (D_20):4.86 (m, 1H), 4.53 (d, J=3.1 Hz, 1H), 4.39–4.29 (m, lH), 4.16–4.01 (m, 2H).

Synthesis of L-γ-hydroxythreonine (57). 57 was prepared in a similar way as described for **60**; mp 200–210°C (dec.); $[\alpha]_D^{26}=-10°$ (c=1.0, H_20); IR (Nujol) 3380, 1690,

1500 cm^{-1}; ^1H NMR (D_20): 4.21–4.14 (m, 1H), 3.85–3.79 (m, 1H), 3.73–3.71 (m, 2H).

Synthesis of the lactone 69. To the amino acid **60** (70 mg, 0.42 mmol) was added dry methanol (8 mL) followed by distilled acetic anhydride (0.4 mL) and stirred vigorously for 24 h. After evaporation of the solvent and excess reagent under reduced pressure, the residue was chromatographed over silica gel using methanol–ethyl acetate as eluent to afford the lactone **69** (56 mg, 70%); mp 148°C; IR (KBr): 3510, 3283, 3056, 2929, 2843, 1769, 1748, 1652, 1642, 1535 cm^{-1}; IR ($CHC1_3$): 3500–3400, 2950, 1765, 1650 cm^{-1}; ^1H NMR ($CDC1_3$, + trace of DMSO): 8.34 (d, 1H), 5.53 (d, J=5.01 Hz, 1H), 4.81 (t, J=5.64 Hz, IH), 4.60–4.50 (m, 3H), 3.88–3.82 (m, 1H), 1.98 (s, 3H); ^{13}C NMR ($CDC1_3$ + trace of DMSO): 173.08, 168.0, 78.2, 71.0, 58.5, 57.0, 21.9; HRMS for $C_7H_{11}NO_5$: Calculated: 190.07155 $(M+H)^+$. Found: 190.07155 $(M+H)^+$.

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