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Advances in the chemistry of β -lactam and its medicinal applications

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1. Introduction

β -Lactam or azetidin-2-one is an important structural motif of the penicillin, cephalosporin, carbapenem and carbecephem classes of antibiotics.¹ Naturally occurring as well as synthetic monobactams, such as nocardicins and tabtoxin, are also known for their unique antibacterial activities.^{2–4} Besides their importance as the key structural component of β -lactam antibiotics, β -lactams have been attracting considerable interest in organic synthesis as versatile synthetic intermediates and chiral synthons.^{5–13} In addition, the β -lactam scaffold has found new pharmaceutical applications other than its use as antibiotics, such as LHRH antagonists,¹⁴ cholesterol-absorption inhibitors,¹⁵ and anticancer agents.^{16–19} The ring strain of the β -lactam skeleton facilitates ring-opening reactions,^{8,20,21,22} and this unique property has been exploited for the synthesis of a variety of medicinally active compounds.

For the last couple of decades, a large number of β -lactam-based synthetic methods, collectively termed as “ β -lactam-synthon method”, has been developed. This method has provided highly efficient routes to a variety of non-protein amino acids, oligopeptides, peptidomimetics and nitrogen-heterocycles, as well as biologically active natural and unnatural products of medicinal interest, such as indolizidine alkaloids, paclitaxel, docetaxel, taxoids, cytophycins, lankacidins, etc.^{5,7–13}

In this report, we present an overview of the evolution of the methods for the synthesis of enantiopure β -lactams, and the applications of the “ β -lactam synthon method” for the synthesis of biologically active compounds of medicinal interest. Examples of the use of the rigid β -lactam scaffold for drug design and discovery are also described.

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2. Asymmetric synthesis of β -lactams

The Staudinger ketene-imine [2+2] cycloaddition and the chiral ester enolate-imine cyclocondensation are the two methods which are most commonly used for the synthesis of β -lactams with excellent enantiopurity. Thus, these two synthetic methods are discussed in this section.

2.1 Staudinger ketene-imine [2+2] cycloaddition

In 1907, long before the antibacterial activity of penicillin was discovered, Staudinger reported the first synthesis of a β -lactam, 1,3,3,4-tetraphenylazetidin-2-one, through the [2+2] cycloaddition of diphenylketene with a Schiff base derived from aniline and benzaldehyde.²³ Subsequently, the scope of this reaction has been extended to alkyl-, amino-, halo-, alkoxy- and siloxy-ketenes, as well as imino esters. Because of its broad scope in substrate structures and simplicity in experimental procedure, this reaction is regarded as one of the most reliable routes to β -lactams.¹ However, in spite of common practice in laboratory synthesis for decades, the mechanistic details of this reaction have been disputed and subjected to theoretical investigations since its inception.^{24,25} The most widely accepted mechanism is a two-step reaction process, which involves the nucleophilic attack of the imine nitrogen on the electrophilic central carbon of a ketene, generated *in situ* from an acid chloride and a base, to form a zwitterionic intermediate, followed by conrotatory ring closure to give the 4-membered ring system (Figure 1).^{24,25}

In the reaction of a monosubstituted ketene with an aldimine, two chiral centers are introduced to the cycloadduct. Thus, the reaction would give either a single stereoisomer (i.e. *cis*- or *trans*-) of β -lactam or a mixture of *cis*- and *trans*- β -lactams, depending on the reactants and reaction conditions.^{25,24} As Figure 1 shows, *cis*- β -lactam should be formed from the zwitterionic intermediate bearing the (*E*)-imine moiety, but if isomerization to the zwitterionic intermediate bearing the (*Z*)-imine moiety takes place, the reaction should give *trans*- β -lactam.^{26–29} This mechanism also indicates that the reaction with a (*Z*)-imine would give the corresponding *trans*- β -lactam selectively. Theoretical studies on the origin of the stereoselectivity suggest that the relative transition-state energy in the rate-determining step is dictated by electronic torque selectivity.^{30,31}

The stereoselectivity of the reaction is influenced by reaction variables such as temperature, solvent, base, additives, chiral pendant groups, order of addition of reagents, microwave irradiation, etc.^{32–34} For example, it has been shown that non-polar solvents favor the formation of *cis*- β -lactam whereas polar solvents facilitate *trans*- β -lactam formation. The result was explained by the stabilization of the zwitterionic intermediate in a polar solvent, promoting isomerization to the energetically more stable intermediate bearing the (*Z*)-imine moiety before conrotatory ring closure.³² Asymmetric ketene-imine [2+2] cycloaddition can be performed using combinations of (i) a chiral imine with an achiral ketene, (ii) a chiral ketene with an achiral amine or (iii) a chiral ketene with a chiral imine.

2.1.1 Asymmetric [2 + 2] cycloaddition of achiral ketenes and chiral imines—

Chiral imines can be prepared either from chiral amines or from aldehydes. However, the diastereoselectivity of the reaction is lower, in most cases, using a chiral imine from a chiral amine, as compared to that from a chiral aldehyde.³⁵ Nevertheless, chiral amine sources are widely used for the asymmetric synthesis of β -lactams.^{9,36} For example, the reaction of phthalimidoacetyl chloride with chiral imine **1**, derived from (*R*)-1-phenylethylamine, in the presence of triethylamine gave β -lactams **2** and **3** in 74% combined yield with high stereoselectivity (**2**:**3** = 9:1) (Scheme 1).³⁶

Commercially available enantiopure esters of α -amino acids are common sources of chiral amines. For example, 3-azido- β -lactam **5a** (R = triphenylsilyl = TPS) was obtained in 64% yield and 19:1 dr (**5a:6a**) using imine **4a** derived from (*R*)-*O*-TPS-threonine benzyl ester and cinnamaldehyde (Scheme 2).³⁷ The stereoselectivity of this reaction was found to depend critically on the bulkiness of the hydroxyl protecting group. Thus, the reaction of **4b** (R = *t*-butyldimethylsilyl = TBS) gave **5b** with 9:1 dr (**5b:6b**) and that of **4c** (R = H) afforded a 1:1 mixture of **5c** and **6c**.³⁷

Alternatively, one of the most effective routes for a large-scale synthesis of β -lactams with high enantiopurity is to use chiral imines derived from chiral aldehydes such as α -oxaldehydes and sugar-derived aldehydes (Scheme 3).^{35,38–40} For example, the [2+2] cycloaddition of various ketenes with chiral imines **9** of D-glyceraldehyde acetonide (**8**), derived from D-mannitol via **7**, afforded *cis*- β -lactams **10** exclusively in 45–70% yield.^{41,42} The acetonide moiety of β -lactams **10** was deprotected to the corresponding β -lactam diols, which were oxidized by ruthenium tetroxide, followed by diazomethane esterification, to afford the 4-carbomethoxy- β -lactams.⁴¹ The β -lactam diols was also converted into the corresponding 4-formyl- β -lactam **11**, which are versatile synthetic intermediates for further manipulations.^{13,42–44}

When a chiral aldimine derived from a chiral aldehyde as well as a chiral amine was used, clear double asymmetric induction was observed, i.e., a matching pair gave the corresponding β -lactam as a single stereoisomer, while a mismatching pair afforded the β -lactam with only modest stereoselectivity. As Scheme 4 illustrates, the reaction of chiral aldimine **13**, derived from (*R*)-threonine and chiral aldehyde **8** via **12**, with a ketene, generated *in situ* from diphenyloxazolylacetyl chloride and triethylamine, gave a 1:2.9 mixture of β -lactams **14** and **15** (i.e. mismatching pair reaction), while the reaction using chiral aldimine **16**, derived from (*S*)-threonine and **8**, afforded β -lactam **17** exclusively in 69% yield for two steps (i.e. matching pair reaction).⁴⁵

2.1.2 [2 + 2] Cycloaddition of chiral ketenes and achiral imines—The ketene–imine [2 + 2] cycloaddition using chiral ketenes has been very successful for the asymmetric synthesis of 3-amino- β -lactams. Enantiopure oxazolidinones derived from (*S*)- and (*R*)-phenylglycine are excellent chiral auxiliaries for this reaction and have been extensively utilized.^{8,9,46} For example, (*S*)-4-phenyloxazolidinon-3-ylacetyl chloride (**18**) with *N*-benzylaldimines **20** gave β -lactams **21** with 95:5–97:3 dr in 80–90% yield (Scheme 5).⁴⁶ This methodology has been successfully applied to the solid-phase synthesis of a library of β -lactams.^{47,48} Even a fused nitrogen aromatic compound, phenanthridine (**22**) was found to react with ketene **19** to afford fused tetracyclic *trans*- β -lactam **23** exclusively in 53% yield, wherein **22** apparently reacted as a (*Z*)-imine (Scheme 5).⁴⁹

It has been shown that the [2+2] cycloaddition of polyaromatic imines and ketenes, generated from acetoxy, phenoxy, and phthalimidoacetyl chloride and an amine base, exclusively gives *trans*- β -lactams, which makes a sharp contrast to the normal reaction pattern, yielding *cis*- β -lactams from the same ketene sources and diarylaldimines.^{16,17} In a similar manner, the reaction of a chiral ketene, generated from alkoxyacetic acid **24** bearing an α -glycoside group, with chresenylaldimine **25** gave a 45:55 mixture of **26** and **27** in 70% combined yield (Scheme 6). These two β -lactams were readily separated by column chromatography and the hydrolysis of the sugar chiral auxiliary afforded the corresponding enantiopure *trans*-3-hydroxy-4-phenyl- β -lactams.¹⁸

2.1.3 Synthesis of enantiopure β -lactams via enzymatic kinetic resolution—

Enzymatic kinetic optical resolution of racemic β -lactams provides a practical route to enantiopure β -lactams. This method has been successfully applied to the synthesis of 3-

hydroxy- β -lactams required for the semisynthesis of paclitaxel, docetaxel and taxoids.^{43,50–55} Hydrolytic enzymes such as PS-Amano lipase and the esterase in pig liver acetone powder (PLAP) have been shown to give excellent results for the optical resolution of racemic *cis*-3-acetoxy- β -lactams. For example, the kinetic resolution of racemic *cis*-3-acetoxy-4-phenyl- β -lactam **29**, obtained from **28**, with PS Amano lipase afforded (3*R*,4*S*)-3-acetoxy- β -lactam **30** with >99.9% ee and (3*S*,4*R*)-3-hydroxy- β -lactam **31** with >99.0% ee in good yields (Scheme 7).⁵⁴

This protocol has also been successfully employed for the kinetic optical resolution of *cis*-3-acetoxy-4-isobutenyl- β -lactam.^{43,50,55} Although kinetic optical resolution does not have good “atom economy”, it should be noted that the method is still quite economical and easily scalable. In addition, both enantiomers serve as useful chiral building blocks in organic synthesis, especially for the synthesis of non-protein amino acids, peptides and peptidomimetics.

2.1.4 Catalytic asymmetric reactions for β -lactam synthesis—A catalytic process applicable to the asymmetric [2+2] ketene-imine cycloaddition has been developed⁵⁶. Cobalticeneum tetracarbonyl cobaltate (**32**) contains both a nucleophilic Co(CO)₄ anion and a Cp₂Co cation that could act in a concerted manner. Thus, in the [2+2] cycloaddition of diphenylketene (**34**), generated from **33** and NaH, with *N*-tosylimino ester **36** via dicobalt species **35**, dicobalt complex **32** showed a good catalyst activity, giving β -lactam **37** in up to 85% yield in 5 min at room temperature (Scheme 8)⁵⁷. It should be noted that, in this process, the electronic demand of the two reactants is reversed from that in the normal ketene-imine [2+2] cycloaddition process. Thus, in this process, the imine component is made highly electrophilic by incorporating an electron-withdrawing group into the imine nitrogen and a carbalkoxy substituent to the imine carbon. The electrophilic ketene component is transformed into a nucleophilic zwitterionic enolate through the addition of a nucleophilic catalyst to the central carbon of the ketene component. Then, the nucleophilic attack of the zwitterion on the α -carbon of the imine leads to the C-C bond formation, followed by cyclization to give β -lactam **37** and regenerates the catalyst **32**. This reaction mechanism logically led to the realization of the fact that a catalyst for this reaction does not have to be a metal ion or charged and thus nucleophilic organocatalysts should be effective as well.⁵⁸ It was also hypothesized and proven that an organocatalyst, containing a nucleophilic center (e.g. tertiary amine) as well as an electrophilic center (e.g. hydrogen-bonding acceptor), would rigidify the key intermediate and the transition state to yield β -lactams with higher diastereoselectivity than that without the electrophilic center.⁵⁸

In order to accomplish the catalytic asymmetric synthesis of β -lactams based on this process, a number of optically active cinchona alkaloids were screened as potential chiral organocatalysts, and benzoylquinine (**38**) was found to give best results. Thus, the reaction of acid chlorides **39** with imine **36** in the presence of **38** as catalyst (10 mol%) and a proton sponge gave β -lactams **40** with 95–99% ee and 96:4–99:1 dr in 36–65% yield (Scheme 9).⁵⁸

In order to improve the chemical yield, metal salts were explored as effective co-catalysts to further activate imines.⁵⁹ Then, it was found that the use of triflates of Sc(III), Al(III), Zn(II) and In(III) (10 mol%) with **38** (10 mol%) gave β -lactams **40** in excellent yield and enantioselectivity (96–98% ee) as well as high diastereoselectivity (9:1–60:1 dr) (Scheme 10). Among the metal salts examined, In(OTf)₃ gave the best results followed by Zn(OTf)₂, while Al(OTf)₃ and Sc(OTf)₃ were less effective.⁵⁹

It has been shown that fused DMAP/ferrocene-based “planar-chiral” nucleophilic catalysts, such as **41**, are effective for the asymmetric synthesis of β -lactams through ketene-imine [2+2] cycloaddition. For example, the reaction of symmetrical ketenes **42** with electron-

deficient *N*-tosylaldimines **43** catalyzed by **41** (0.1 mol%) gave β -lactams **44** in 76–93% yield and 81–94% ee, while the reaction of unsymmetrical ketenes **42** (R = Ph, R¹ = *i*-Bu or Et) with **43** under the same conditions afforded β -lactams **44** in 88–98% yield with 8:1–15:1 dr and 89–98% ee (Scheme 11).⁶⁰

Recently, *N*-heterocyclic carbenes (NHCs) have been shown to serve as excellent catalysts for the asymmetric synthesis of β -lactams through ketene-imine [2+2] cycloaddition.^{61,62} For example, NHC **45a** derived from (*S*)-pyroglutamic acid catalyzed the reactions of various arylketenes **46** with *N*-Boc-aryldimines **47** to give the corresponding β -lactams **48** in moderate-to-good yields and excellent enantioselectivity⁶¹ (Scheme 12). Another NHC **45b** was used as a catalyst for the reaction of arylketenes **49** with azodicarboxylate **50**, which afforded aza- β -lactams **51** in fairly good-to-excellent yields and 33–91% ee (Scheme 12).⁶²

C-2 symmetric imidazolinium catalyst **52** and chiral triazolium catalyst **53** have been used in the reaction of diphenylketene (**34**) with *N*-tosylaldimines **54** to give the corresponding β -lactams **55** in high yields and 55–75% ee (Scheme 13).⁶³ It has also been shown that chiral imidazoliniumdithiocarboxylates, e.g. **56**, act as efficient organocatalysts for Staudinger [2+2] cycloaddition reactions of arylketenes **57** with *N*-tosylaldimine **58**, giving the corresponding β -lactams **59** as a mixture of *E* and *Z* isomers (**59-E**:**59-Z** = 25:75–11:89) in 96–99% yield with 83–96% ee for **59-Z** (major) and 48–83% ee for **59-E** (minor) (Scheme 14).⁶⁴

The β -lactam synthesis through Rh-catalyzed carbene insertion into a C-H bond is another catalytic process that is applicable to catalytic asymmetric synthesis. The construction of the β -lactam ring based on the intramolecular C-H insertion of carbene species generated from α -diazo amides, initially by photoirradiation and then by Rh₂(OAc)₄ catalysis, was used for the synthesis of carbapenems, especially thienamycin.^{65,66} Then, the Rh₂(OCOR)₄-catalyzed process was successfully employed in the intramolecular C-H insertion reaction of α -diazoacetamides to yield the corresponding β -lactams. For example, the reaction of *N*-*t*-butyl-*N*-arylmethyl- α -diazoacetamides **60** catalyzed by Rh₂(OAc)₄ gave the *trans*- β -lactams **62** exclusively via a Rh-carbenoid species **61** in 90–98% yield (Scheme 15).^{67,68}

The catalytic asymmetric synthesis of β -lactams through Rh-catalyzed intramolecular C-H insertion reactions of α -diazoacetamides has been investigated using dimeric Rh(II) complexes with chiral carboxylate ligands. For example, the reaction of α -methoxycarbonyl- α -diazoacetamides **63** catalyzed by Rh₂(*S*-PTPA)₄ (*S*-PTPA = *N*-naphthoylphenyl-(*S*)-phenylalaninate) afforded *cis*- β -lactams **64** in excellent yield and 56–74% ee (Scheme 16).⁶⁹ This reaction system was successfully applied to the asymmetric synthesis of bicyclic β -lactams, which served as key intermediates for the synthesis of enantiopure carbapenems.⁷⁰ Thus, the reaction of α -methoxycarbonyl- α -diazoacetamides **65** catalyzed by Rh₂(*N*-naphthoyl-(*S*)-AA)₄ (AA = Phe, Ala, Val, PhGly, *t*-BuGly) afforded β -lactams **66** in 85–94% yield and 83–96% ee (Scheme 16). The best result (94% yield and 96% ee) was obtained with α -diazoacetamide **65a** (R, R = -(CH₂)₅-) and Rh₂(PTA)₄ (PTA = *N*-naphthoyl-Ala). In a similar manner, β -lactam **68** (88% ee, 83% yield), a key intermediate in the synthesis of 1 β -methylthienamycin, was obtained by the reaction of diazoacetamide **67** catalyzed by Rh₂(PTA)₄, which was successfully converted into the enantiopure advanced key intermediate **69** in several steps (Scheme 16).⁷⁰

Regio- and stereospecific carbonylation of chiral aziridines catalyzed by [Rh(CO)₂Cl]₂ gives the corresponding β -lactams in high yields. For example, the reactions of **70** and **72** afforded **71** and **73** in 81 and 89% yield, respectively (Scheme 17).⁷¹ This carbonylation process was found to proceed stereospecifically at the carbon bearing a phenyl substituent with complete

retention of configuration. This process was successfully applied to the kinetic resolution of racemic 2-phenylaziridine **74** in the presence of (–)-menthol (3 equiv) and [Rh(COD)Cl]₂ (5 mol%) as catalyst at 90 °C and 20 atm CO for 24 h to give (*S*)-β-lactam **75** with 99.5% ee (25% yield) and (*R*)-**74** with 85% ee (56% yield) (Scheme 17).⁷¹ It is of interest to note that Co₂(CO)₈ was found to catalyze the regio- and stereospecific carbonylation of chiral aziridines as well, but with complete *inversion* of configuration at the more substituted carbon with alkyl or phenyl substituents.⁷² This process exhibited its exceptional stereochemical integrity in the formation of extremely strained *trans*-bicyclic β-lactams, 8-aza-7-oxo-[4.2.0]bicyclooctanes, from *cis*-cyclohexeneaziridines.⁷² However, this process has not been applied to asymmetric synthesis.

2.2 Asymmetric synthesis of β-lactams through ester enolate-imine cyclocondensation

The chiral lithium enolates generated *in situ* from *N,N*-bis(silyl)glycinates **76** reacted with *N*-PMP-aryldimines **77** to give *trans*-3-amino-β-lactams **78** exclusively in fairly good yields and excellent enantiopurity.⁷³ Among the various chiral ester auxiliaries screened, (–)-menthyl and (–)-2-phenylcyclohexyl were found to be highly effective for this reaction. For example, the reaction of **76a** (R* = (–)-menthyl) and **76b** (R* = (–)-2-phenylcyclohexyl) with *N*-PMP-benzaldimine (**77a**) in the presence of LDA in THF at –78 °C afforded (3*R*, 4*R*)-β-lactam **78a** with >99% ee in 65 and 58% yield, respectively (Scheme 18).⁷³ Under the same conditions, the reactions of **76a** with other *N*-PMP-aryldimines **77b–e** (Ar = 4-FC₆H₄, 4-CF₃C₆H₄, 4-MeOC₆H₄, 3,4-(MeO)₂C₆H₃) gave the corresponding β-lactams **78b–e** with >99% ee, albeit with small amounts of *cis*-β-lactams **78d,e** being obtained in the case of **77d** and **77e**.⁷³

It has also been shown that the chiral ester enolate-imine cyclocondensation is a highly efficient method for the asymmetric synthesis of 3-hydroxy-β-lactams with excellent enantiopurity.^{7,8} In contrast to the rigid bis(silylamino) moiety in glycinates **76**, the *O*-protected hydroxyl group is very flexible in hydroxyacetates **79**. Thus, both the chiral auxiliaries and the *O*-protecting groups were screened to find the optimal chiral ester enolate **80** for this process. Then, the combination of TIPS and (–)- or (+)-2-phenylcyclohexyl groups was found to achieve the best results. It should be noted that, in contrast to the reactions of **76**, *cis*-β-lactams **82** were formed exclusively in this process. Chiral enolate **80** was generated from (–)-2-phenylcyclohexyl TIPSO-acetate **79** with LDA in THF at –78 °C for 2 h. *N*-TMS-aryldimines **81** (R² = TMS) were added to the enolate solution and reacted at –78 °C and then gradually warmed to room temperature to give (3*R*,4*S*)-3-TIPSO-4-aryl-β-lactams **82** with 96–98% ee in 80–85% yields and 96–98% ee (Scheme 19).^{74,75} It is worthy of note that (3*R*,4*S*)-3-TIPSO-4-phenyl-β-lactam **82a** (Table 1) serves as a key intermediate for the highly efficient semisynthesis of paclitaxel and docetaxel (*vide infra*).^{74,76}

Although *N*-TMS-imines **81** (R² = TMS) are efficient to produce β-lactams **82** (R³ = H) with free NH directly, those imines are limited to arylaldimines due to the instability of *N*-TMS-alkylaldimines. Thus, *N*-PMP-imines **81** (R² = PMP) were employed to successfully expand the scope of this reaction. Table 1 summarizes representative results, including those for *N*-TMS-imines **81** (R² = TMS).^{74,75,77}

An asymmetric ester-enolate cyclocondensation process mediated by a ternary chiral ether ligand–lithium amide complex was developed. The reaction of lithium enolate **83**, generated from the corresponding 3-pentyl alkanolate (2 equiv) and LDA (2.2 equiv), with *N*-PMP-aldimine **84** in the presence of (1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane (**86**) (2.6 equiv) and additional lithium amide, e.g. LiN(Pr-*i*)Cy and LiNCy₂, (2.2 equiv) gave β-lactam **85** in 12–85% yield and 26–90% ee (Scheme 20).⁷⁸ The yield and enantioselectivity depend on

the structure of the lithium amide used. For example, the reaction of **83a** ($R^1 = \text{Me}$) with **84a** ($R^2 = \text{Ph}$) using $\text{LiN}(\text{Pr-}i)\text{Cy}$ afforded **85a** in 85% yield and 88% ee, while the same reaction using $\text{LiN}(\text{Bu-}i)\text{Cy}$ gave **85a** in 22% yield and 55% ee.

3. Synthesis of amino acids, dipeptides and their derivatives by means of β -lactam synthon method

3.1 Asymmetric synthesis of non-protein amino acids

Non-protein amino acids are amino acids which are not produced from protein amino acids by post-translational modification and these amino acids do not have a specific transfer-RNA and codon triplet, and thus the main chains of proteins do not have these amino acid residues.⁷⁹ Since various non-protein amino acids are important components of medicinally important compounds, the efficient synthesis of non-protein amino acids with high enantiopurity has significance in medicinal chemistry and organic synthesis.

3.1.1 Synthesis of α,β -diamino acids, azetidines and polyamines— α,β -Diamino acids are often components of peptidic antibiotics such as lavendomycin and glutamycin.⁸⁰ It has been shown that α,β -diamino acids are readily obtained through the hydrolysis of enantiopure 3-amino- β -lactams, which were prepared by chiral ester-enolate cyclocondensation or asymmetric [2+2] ketene-imine cycloaddition reactions (*vide supra*).^{7,9} Thus, the hydrolysis of 3-amino- β -lactam (3*S*,4*R*)-**87** and its epimer, (3*R*,4*R*)-**87**, using 6 M hydrochloric acid gave the corresponding α,β -diamino acids (2*S*,3*R*)-**88** and (2*R*,3*R*)-**88**, respectively, as hydrochlorides in quantitative yields (Scheme 21). The epimerization of (3*S*,4*R*)-**87** to (3*R*,4*R*)-**87** was readily realized through imine formation, deprotonation and protonation.⁷ Moreover, (3*R*,4*S*)-**87** can be prepared just by switching the chiral auxiliary to the other enantiomer in the asymmetric ketene-imine [2 + 2] cycloaddition or from the other enantiomer obtained in the enzymatic optical resolution (*vide supra*). Thus, (3*S*,4*S*)-**87**, (2*R*,2*S*)-**88** and (2*S*,2*S*)-**88** can be prepared in the same manner. Furthermore, α,β -diamino acids **88** were reduced to the corresponding α,β -diamino alcohols **89** in high yields using LiAlH_4 (Scheme 21). Thus, this protocol provides facile access to all four diastereoisomers of α,β -diamino acids **88** and amino alcohols **89**.^{7,8}

Azetidine is a very challenging amine to synthesize, but the selective reduction of β -lactams using monochloroalane (AlH_2Cl) or dichloroalane (AlHCl_2) provides one of the most straightforward and efficient routes to enantiopure azetidines.^{75,81} The reduction of enantiopure 4-aryl- β -lactam **90** with monochloroalane (AlH_2Cl) in ether gave the corresponding 2-arylaziridine **91** in high yield without epimerization. Then, the hydrogenolysis of **91** at the N-C2 bond afforded the enantiopure diamine or amino alcohol **92** in quantitative yield (Scheme 22).⁷⁵ In the same manner, the monochloroalane reduction of tetrapeptide synthon bis- β -lactam **93** gave bisazetidine **94** in moderate yield, which was converted into polyamino ether **95** in quantitative yield via hydrogenolysis. It should be noted that the reductive cleavage of the two azetidine moieties of **94** were much faster than debenzylolation in this case (Scheme 22).^{9,82}

3.1.2 Synthesis of α -alkyl- α -amino acids and their dipeptides—Various α -alkyl- α -amino acids are known to act as potent substrate-based inhibitors of decarboxylases and aminotransferases.⁸⁰ In addition, the strategic incorporation of α -alkyl- α -amino acid residues into physiologically active peptides can introduce conformational constraints to stabilize 3D peptide structures.⁸⁰ The access to enantiopure α -alkyl- α -amino acids is not easy because conventional enzymatic resolution cannot be applied effectively. Fortunately, the β -lactam synthon method provides highly efficient routes to α -alkyl- α -amino acids with high enantiopurity through extremely stereoselective alkylation of 3-amino- β -lactams.

Two protocols have been developed for asymmetric alkylations, i.e. (i) the alkylation of the C-3 position of a β -lactam (Type 1) and (ii) the alkylation of the side chain ester enolate (Type 2) (Figure 2).^{7,9} As Figure 2 illustrates, in the Type 1 alkylation, an electrophile attacks the β -lactam enolate at the C-3 position from the back side of the C-4 aryl group, while, in the Type 2 alkylation, an electrophile attacks the C1' position of the lithium enolate, forming a chelate with the β -lactam oxygen, from the opposite side of the C-4 aryl group.

A typical example of the Type 1 alkylation is shown in Scheme 23. The stereoselective methylation of β -lactam **96** (X = H or MeO) with MeI and LiHMDS gave 3-methyl- β -lactam **97** with >99.5% de in excellent yield. Birch reduction of **97** gave the corresponding amide of α -methyl- α -amino acid **98** (>99.5% ee) in high yield.^{7,83} Acidic hydrolysis of **98a** (X = H) and **98b** (X = MeO) should afford (*S*)- α -methylphenylalanine and (*S*)-*O*,*O*-dimethyl- α -methyldopa with > 99.5% ee, respectively. It should be noted, however, that similar Type 1 alkylations of a bicyclic *trans*- β -lactam **99**, which did not have a 4-aryl group, gave 3-alkyl- β -lactams **100** with >97% de. in 51–80% yields, wherein the electrophiles attacked the C3 position of the β -lactam moiety of **99** from the front face with retention of configuration (Scheme 23).⁸⁴

The Type 2 alkylation was first examined with enantiopure β -lactam ester **101** with 1.0 equivalent of LDA and alkyl halides (BnBr and EtBr). As Scheme 24 shows, deprotonation took place exclusively at C1' of the ester moiety, leaving C3 of the β -lactam moiety intact. Thus, the alkylation proceeded at C1' exclusively to give **102** (>98% de), which was subjected to hydrogenolysis on Pd/C to give *N*-acyl- α -alkyl- α -amino acid ester **103** and subsequent acidic hydrolysis afforded α -alkyl-(*R*)-alanine **104** (>98% ee) in excellent yield (Scheme 24).^{7,9,83} The results indicated that the Type 2 alkylation process should be applicable for the asymmetric synthesis of dipeptides or depsipeptide fragments bearing an α -alkyl- α -amino acid residue at the C-terminus.

The Type 2 alkylation was successfully applied to the sequential asymmetric double alkylation of chiral β -lactam ester **105** (>99% de, >99% ee) to give phenylalanyl- α -alkylalanines, (*S,S*)-**108** (via (*R*)-**106** and (*S*)-**107**) and (*S,R*)-**108** (via (*S*)-**106** and (*R*)-**107**) in good overall yields and >99% de, and . In this process, the double alkylation took place exclusively at C1' and the absolute configuration of C1' was controlled by changing the order of addition of the two alkyl halides (Scheme 25).^{9,85}

The highly efficient triple alkylation of **105** was also achieved through sequential Type 2 double alkylation and Type 1 alkylations (Scheme 26).^{9,85} For example, sequential double alkylation of β -lactam **105** with methyl iodide and allyl bromide proceeded in the same manner as that in Scheme 25, giving **107b** (>99% de), which was followed by the third (Type 1) alkylation with methyl iodide to afford **109** (>99% de) uneventfully in 80% yield for 3 steps. Then, triply alkylated β -lactam **109** was converted into (*S*)- α -methylphenylalanyl-(*R*)- α -allylalanine, **110** in 62% yield through deprotection, Birch reduction and separation on a Dowex column (Scheme 26).

3.1.3 Asymmetric synthesis of α -hydroxy- β -amino acids and their dipeptides

— α -Hydroxy- β -amino acids (isoserines) are key structural motifs in numerous therapeutically important substances. (2*R*,3*S*)-3-Amino-2-hydroxy-5-methylhexanoic acid (norstatine) and its analogues, for example, are readily found in peptide-based inhibitors of enzymes such as renin,^{86,87} HIV-I protease⁸⁸ and angiotensin-converting enzyme (ACE),⁸⁹ as well as in a variety of natural products.⁹⁰ (2*R*,3*S*)-3-Phenylisoserines are indispensable constituents of paclitaxel and docetaxel, which are two of the most widely used anticancer drugs in chemotherapy.^{91,92} Therefore, extensive efforts have been made to develop

efficient methods for the syntheses of isoserines with excellent enantiopurity. The β -lactam synthon method has made a significant contribution to solve this synthetic challenge.

Acidic hydrolysis of 3-TIPSO- β -lactams **112** with excellent enantiopurity, obtained from 1-PMP- β -lactam **111**, provides a ready access to norstatine (**113a**, R = *isobutyl*) and isoserines **113** (Scheme 27).^{7,93} The ring opening of β -lactams at the N1-C2 bond is substantially accelerated when an electron-withdrawing group, e.g. acyl, carbalkoxy, carbamoyl, sulfonyl, etc., is introduced into the N1 position. For example, the ring-opening coupling of *N*-Boc-3-hydroxy- β -lactams **114** with various amino acid esters **115** proceeded smoothly to give the corresponding dipeptides **116**, bearing an isoserine residue at the N terminus, in high yields without epimerization or racemization under mild conditions without any coupling agent (Scheme 28). Proline methyl ester as well as the Wang resin-bound amino acids were also successfully employed for this coupling.^{7,94} The high efficiency and atom-economy in this ring-opening coupling process is one of the most salient features of the β -lactam synthon method. It is also worthy of note that enantiopure *N*-Boc-3-siloxy- β -lactams were readily converted into the corresponding hydroxyethylene isosteres and dihydroxyethylene isosteres, which are key components in various enzyme inhibitors, mimicking tetrahedral intermediates.^{95,96}

It has been shown that the incorporation of fluorine(s) into a medicinally active compound often improves its pharmacological properties, such as increased membrane permeability, enhanced hydrophobic binding and stability against metabolic oxidation among other merits.^{43,97,98} As fluorine is absent in living tissue, the incorporation of fluorine(s) into biologically relevant molecules as marker(s) provides a valuable means to monitor protein structures and dynamics as well as drug-protein interactions *in vitro* and *in vivo* by ¹⁹F NMR. Accordingly, efficient and convenient methods for the synthesis of fluorine-containing compounds of biological and medical interest are in high demand.

The β -lactam synthon method has provided convenient and efficient routes to fluorine-containing α -hydroxy- β -amino acid derivatives and congeners. Enantiopure 3-TIPSO-4-Rf- β -lactams (Rf = fluorine-containing substituent) were prepared through (i) functional-group transformations of 4-isobutenyl- β -lactams, (3*R*,4*S*)-**82i** or (3*S*,4*R*)-**82i**, and (ii) ketene-imine [2+2] cycloaddition followed by enzymatic resolution using PS Amano lipase.¹³ For instance, the ozonolysis of (3*R*,4*S*)-**82i** afforded the corresponding 4-formyl- β -lactam (3*R*,4*R*)-**11f** (R¹ = PMP; R² = TIPSO) in high yield, which was reacted with diethylaminosulfur trifluoride (DAST) and CBr₂F₂/Zn to give 4-difluoromethyl- β -lactam (3*R*,4*R*)-**117** and 4-difluorovinyl- β -lactam (3*R*,4*R*)-**118**, respectively, with >99.9% ee in high yields (Scheme 29).^{13,44,99} (3*R*,4*R*)- and (3*S*,4*S*)-1-PMP-4-trifluoromethyl- β -lactams with >99% ee were obtained through enzymatic resolution of racemic *cis*-3-acetyl-4-CF₃- β -lactam prepared through ketene-imine [2+2] cycloaddition.^{13,43} Enantiopure 1-PMP-3-TIPSO-4-Rf- β -lactams **119**, thus obtained, were deprotected by cerium ammonium nitrate (CAN) to give NH-free β -lactams **120**, which were converted into the corresponding 1-acyl-, 1-carbalkoxy-, and 1-arenesulfonyl- β -lactams **121** in good yields through reactions with acyl chlorides, chloroformates, and arenesulfonyl chlorides in the presence of an appropriate base (Scheme 30; only one enantiomer is shown for simplicity).¹³

Methanolysis of β -lactams **121** in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) at room temperature afforded the corresponding β -Rf- α -siloxy- β -amino acid methyl esters **122** in modest-to-quantitative yields (Scheme 31).¹³ Furthermore, the ring-opening coupling of β -lactams **121** with various α - and β -amino acid esters gave the corresponding dipeptides, **123** and **124**, bearing fluoroisoserine residues, in 50–100% yields (Scheme 31).¹³ [Note: Scheme 31 only shows the reactions of (3*R*,4*R*)-**121** for simplicity, but (3*S*,4*S*)-**121** reacted in a similar manner.]

The Type 1 alkylation of 3-siloxy- β -lactams **125** proceeded with excellent diastereoselectivity to give 3-alkyl-3-siloxy- β -lactams **126** with >99% de, which were converted into NH- β -lactams via CAN deprotection, followed by acidic hydrolysis to afford the corresponding α -alkyl- α -hydroxy- β -amino acids **127** in excellent yields (Scheme 32).^{13,100} β -Lactams **126** were also converted into 1-Boc- β -lactams **128** via NH- β -lactams via CAN deprotection and subsequent reaction with Boc-anhydride.^{13,100} The facile methanolysis of 1-Boc- β -lactams **128** proceeded at room temperature to give *N*-Boc- α -alkyl- α -hydroxy- β -amino acid methyl esters **129** in excellent yields (Scheme 32).¹⁰⁰ 1-Boc-3-hydroxy- β -lactams **130** were prepared by deprotection of β -lactams **128** with HF/pyridine and subjected to ring-opening coupling with (*S*)-Leu-OMe to give the corresponding dipeptides **131** in high yields (Scheme 33).¹⁰⁰

4. Applications of β -lactam synthon method for the synthesis of medicinally active compounds

4.1 Synthesis of paclitaxel, docetaxel and new-generation taxoids

Paclitaxel (Taxol®; Figure 3), a complex diterpene isolated from the bark of *Taxus brevifolia* (Pacific yew), is a leading FDA-approved drug for the treatment of advanced ovarian cancer (1992), breast cancer (1994), AIDS-related Kaposi's sarcoma (1997), non-small-cell lung cancer (1999) and other cancers (Figure 3).^{91,101,102} Docetaxel (Figure 3), the first semisynthetic analogue ("taxoid") of paclitaxel, was also approved by the FDA in 1996 against breast cancer and has been extensively used for the treatment of various cancers such as those of lung, ovarian, prostate and others.^{91,92,102}

Paclitaxel and docetaxel are cytotoxic drugs which act as mitotic spindle poisons by accelerating tubulin polymerization in microtubules, but stabilize them and arrest cell mitosis at the G₂/M phase, leading to apoptosis.^{103–106} Although the total synthesis of paclitaxel has been accomplished as outstanding hallmark of academic research by six research groups *via* very long steps,^{107–112} the semisynthesis of paclitaxel from 10-deacetylbaccatin III, **132** (P = R¹ = H), a renewable natural product abundantly isolated from the leaves of *Taxus baccata* (European yew) and *Taxus wallichiana* (Himalayan yew), has been found to be the practical approach for the manufacturing of this drug.^{7,74,113–115}

The β -lactam synthon method has played a crucial role in the highly efficient semisynthesis of paclitaxel and docetaxel. For instance, paclitaxel was synthesized through ring-opening coupling of (3*R*,4*S*)-1-benzoyl-3-EEO-4-phenyl- β -lactam **132a** (R = Ph) with 7-TES-baccatin **133a** (R¹ = Ac, P = Et₃Si) at the C13 position, affording **134a**, followed by deprotection of the 1-ethoxyethyl (EE) and TES groups with 0.5% HCl in ethanol in high overall yield (Scheme 34).⁷ β -Lactam **132a** and this ring-opening coupling protocol were also employed to complete the total synthesis of paclitaxel.^{107–110} In a similar manner, docetaxel was obtained in high overall yield via ring-opening coupling of (3*R*,4*S*)-1-Boc-3-EEO-4-phenyl- β -lactam **132b** (R = *t*-BuO) with 7,10-diTroc-baccatin **133b** (R¹ = P = Cl₃CCH₂OCO), giving **134b**, followed by deprotection with Zn/acetic acid/methanol (Scheme 34).^{7,76} β -Lactams **132a** and **132b** were derived from (3*R*,4*S*)-3-TIPSO-4-phenyl- β -lactams **82a** or **82d** (see Table 1) prepared by chiral ester enolate-imine cyclocondensation (see Section 2.2)^{74,75} or (3*R*,4*S*)-3-acetoxy-4-phenyl- β -lactam **30** (see Scheme 7) prepared by ketene-imine [2+2] cycloaddition followed by enzymatic optical resolution.⁵⁴

This highly efficient ring-opening coupling process, "Ojima-Holton coupling", opened an avenue for the synthesis and structure-activity relationship (SAR) studies on a variety of paclitaxel congeners, "taxoids".^{76,77,115–119} The standard procedure for the coupling quickly

evolved to the use of 1-acyl- or 1-carbalkoxy-3-TIPSO- β -lactams and LiHMDS as the base.⁷

Extensive SAR studies on taxoids have led to the discovery of highly potent new-generation taxoids, which have modifications at C3', C10 and/or C2 and possess 2-to-3 orders of magnitude higher potencies than paclitaxel and docetaxel against multidrug resistant (MDR) as well as paclitaxel-resistant cancer cell lines. Selected new-generation taxoids exhibit much better efficacy than paclitaxel and docetaxel against human tumor xenografts in animal models.^{77,117–119} Selected new-generation taxoids are listed in Table 2 and their *in vitro* activities against several cancer cell lines in Table 3.

In order to investigate the bioactive conformation of paclitaxel, conformationally restricted macrocyclic paclitaxel congeners were designed and synthesized by using a combination of the β -lactam synthon method and an intramolecular Heck reaction or Ru-catalyzed ring-closing metathesis (RCM).^{119–121}

For example, a 3'-N-C2-linked novel macrocyclic taxoid **138** was synthesized using an intramolecular Heck reaction in the macrocyclization step (Scheme 35).¹²¹ Enantiopure 1-(3-iodobenzoyl)-3-TESO-4-phenyl- β -lactam **135** was prepared from (3*R*,4*S*)-3-TIPSO-4-phenyl- β -lactam **82a** (see Table 1). The ring-opening coupling of **135** with 2-(2-vinylbenzoyl)-7-TES-baccatin (**136**) under the standard conditions gave the iodo-vinyl-taxoid **137** in high yield. The intramolecular Heck reaction of **137** catalyzed by a Pd(0)-AsPh₃ complex at 55 °C, followed by deprotection afforded the 19-membered *exo*-methylene-macrocyclic taxoid **138** in 56% yield. The macrocyclic taxoid **138** exhibited a very good IC₅₀ value of 67 nM against LCC6-WT human breast cancer cell line.¹²¹

3'NBz-C14 β -linked novel macrocyclic taxoids, **SB-T-2053** and **SB-T-2054**, were synthesized using Ru-catalyzed intramolecular coupling reactions of taxoid-dienes **141**. Taxoid-dienes **141a** and **141b** were synthesized through ring-opening coupling of (3*R*,4*S*)-1-(2-allylbenzoyl)-3-TESO-4-phenyl- β -lactam **139a** and (3*R*,4*S*)-1-(2-vinyl)-4-phenyl-3-TESO- β -lactam **139b** with 7-TES-14 β -allyloxybaccatin III (**140**), respectively, in high yields under the standard conditions (Scheme 36).¹²⁰

The RCM of **141a** using the first-generation Grubbs Ru catalyst at room temperature, followed by deprotection of the silyl groups, gave the expected 15-membered macrocyclic taxoid **SB-T-2053** in high yield (Scheme 36).^{120,122} However, the attempted RCM of **141b** did not occur and an unanticipated novel coupling took place to give the 15-membered macrocyclic taxoid **SB-T-2054**, in which the double bond of the linkage was conjugated to the benzoyl moiety, in good yield after deprotection (Scheme 36).¹²⁰ This novel coupling reaction is mediated by the Ru complex, but not catalytic, and likely to involve Ru-allyl complexes as key intermediates.¹²⁰ These macrocyclic taxoids were examined for their activities in tubulin polymerization and microtubule stabilization as well as their potencies against six human cancer cell lines. It was found that both SBT-2053 and SBT-2054 possessed virtually the same activity as that of paclitaxel in the tubulin polymerization/depolymerization assay. Moreover, **SBT-2054** was found to be as potent as paclitaxel in the cytotoxicity assay, which is the closest conformationally restricted paclitaxel congener to date, mimicking the binding structure of paclitaxel in microtubules.^{120,123}

4.2 Synthesis of cryptophycins by means of *N*-acyl- β -lactam macrolactonization

Cryptophycins are macrocyclic cytotoxins produced by cyanobacteria, which exhibit potent tumor-selective antitumor activities by binding microtubules and disrupting cellular mitosis (Figure 4). These compounds are particularly active against MDR cancer cell lines. Synthetic cryptophycin-52 (Cr-52) is currently under clinical development for treatment

against solid tumors and has shown an exceptionally potent cytotoxicity against the MCF-7 breast cancer cell line ($IC_{50} = 0.037$ nM).¹²⁴ Dechlorocryptophycin-52 also exhibits good activity in the tubulin assembly assay ($IC_{50} = 3$ μ M; for Cr-1, $IC_{50} = 2.5$ μ M) and excellent cytotoxicity against the MCF-7 cell line ($IC_{50} = 0.3$ nM).¹²⁴

An efficient synthesis of the macrolide core of cryptophycins has been achieved by using the *N*-acyl- β -lactam macrolactonization protocol.^{125,126} The key steps in the total synthesis of cryptophycin-24 (arenastatin A) are illustrated in Scheme 37, which represents the synthetic strategy for this class of compounds.¹²⁶ The key β -lactam **144** was prepared in 53% yield for 3 steps through the coupling of the Northern/Western fragment **142** with *N*-(*p*-MeO-Phe)- β -lactam **143**, the Eastern fragment. The macrolactonization of **144** proceeded through cyanide-initiated β -lactam ring opening using Bu₄NCN and subsequent lactonization to give the 16-membered macrocycle **145** in 68% yield. The attempted direct ring-opening coupling using NaH and NaHMDS as base was unsuccessful, presumably due to the instability of **144** under basic conditions. The introduction of the C3'-phenyl moiety through the Heck reaction gave the desired product, but only in modest yield. Epoxidation of the resulting styryl double bond with dimethyldioxirane (DMD) gave cryptophycin-24 as a 2:1 (β : α) diastereomeric mixture, which was separated by reverse-phase HPLC. This strategy was also employed for the total synthesis of dechlorocryptophycin-52.¹²⁶

4.3 Synthesis of β -turn mimetics of enkephalin via β -lactam macrocyclization

In connection with the investigations into the binding conformation of enkephalins,¹²⁷ endogenous opioid pentapeptides, to specific opiate receptors, conformationally constrained non-peptide β -turn mimetics **146** (Figure 5) were designed and synthesized using a β -lactam macrocyclization protocol.¹²⁸

The synthesis of the novel 4 $\rightarrow$ 1 β -turn mimic **146a** (X = NH) is illustrated in Scheme 38 as a typical example.¹²⁸ β -Lactam **147**, an (*S*)-Tyr-Gly-Gly mimic synthon, was prepared from (3*S*,4*S*)-1-TBS-3-but-3-enyl-4-(4-TBSO-benzyl)- β -lactam, which was obtained through highly stereoselective alkylation of (4*S*)-1-TBS-4-(4-TBSO-benzyl)- β -lactam, via NaIO₄ oxidation and peptide coupling with a glycinate. (*S*)-Tyr-(*S*)-Leu-OMe hydrazide **148** was prepared by coupling Leu-OMe with (*S*)-BocNHNH-Tyr-OH, which was derived from (*R*)-Tyr and BocNHNH₂ via diazonium species. The coupling of **147** with **148** was carried out by converting **147** into the corresponding acid chloride, followed by reaction with **148** in the presence of AgCN to give the β -lactam key intermediate **149a** in 49% yield. Then, the Boc group was removed from **149a** with trifluoroacetic acid (TFA) and the subsequent β -lactam macrocyclization, followed by silicon group deprotection, gave Leu-enkephalin mimic **146a** in 94% yield for 3 steps.¹²⁸

4.4 Stereoselective synthesis of indolizidine alkaloids via β -lactam ring expansion

Indolizidine alkaloids are among the most abundant naturally occurring alkaloid natural products and possess various biological activities of medicinal interest. For example, indolizidine (-)-205A, an alkaloid from poison dart frogs extracts, as well as castanospermine and swainsonine, extracted from plant sources have been extensively studied for their syntheses and biological activities.^{129–131}

The β -lactam synthon method was applied to the construction of the indolizidine skeleton through ring expansion of piperidinyl- β -lactams **153**.¹³² The preparation of β -lactams **153** is illustrated in Scheme 39. An aza-Diels-Alder reaction of β -lactam **150** with Danishefsky's diene **151** gave a 3:1 mixture of cycloadducts **152a** and **152b**, which were separated by column chromatography.¹³² β -Lactam **152a** was reduced successively with L-selectride and NaBH₄ to give a 3:2 mixture of epimeric alcohols, which were protected with TBS and

separated by chromatography to afford piperidiny- β -lactams **153a** and **153b**. It is interesting to note that the same reduction-protection sequence for β -lactam **152b** gave **153c** exclusively.¹³³

The ring-expansion reaction of three piperidiny- β -lactams, **153a**, **153b** and **153c**, catalyzed by sodium methoxide proceeded smoothly at 0 °C to afford the corresponding epimeric indolizidines, **154a**, **154b** and **154c**, respectively, in quantitative yields (Scheme 40).¹³³ Although the preparation of piperidiny- β -lactams needs improvements, the ring-expansion process is highly efficient and this methodology can be applied to the construction of other izidine alkaloid skeletons.

5. Synthesis of 3- to 8-membered nitrogen-heterocycles from β -lactams

As any of the four bonds in the β -lactam ring can be selectively cleaved by varying either the reaction conditions and/or the substrate, the β -lactam ring system can be used for the construction of *N*-containing heterocycles of different ring sizes. Various examples of intramolecular ring expansions leading to functionalized enaminones, γ -lactams and lactones as well as peptide- and non-peptide based macrocycles through intra- or intermolecular nucleophilic attack have been reported in literature.^{11,134–136}

5.1 Formation of aziridines through ring contraction of β -lactams

The reductive cleavage of the N1-C2 bond of 4-(2-chloroisopropyl)- β -lactam **155** with LiAlH₄ gave β -hydroxyethylaziridine **156** in modest-to-fairly good yield through a tandem reduction-cyclization process (Scheme 41).¹³⁷

Treatment of 2-aryl-3,3-dichloroazetidines **158**, derived from β -lactams **157** by monochloroalane reduction, with sodium methoxide in methanol gave aziridine ketals **159** in 60–90% yield for two steps (Scheme 42). This reaction is likely to involve 2-azetines **160** and highly strained azabicyclo[1.1.0]cyclobutanes **161**, as key intermediates. The ring contraction of **161** through C-N bond cleavage generates aziridine oxonium salts **162**, which react with methoxide ion to give **159** (Scheme 42).¹³⁸

5.2 Formation of pyrrolidines through one-carbon ring expansion of β -lactams

The reaction of (2*R*,3*R*)-3-alkoxy-4-formyl- β -lactams **11** (see Scheme 3) with *t*-BuMe₂SiCN (TBSCN) catalyzed by molecular iodine gave 5-cyanopyrrolidin-2-ones **163** in moderate-to-high yield with high *syn* selectivity (86–100%) (Scheme 43).^{139,140} The *syn*/*anti* selectivity depends mostly on the *N*-substituents and PMP gave the best results, i.e. 100% *syn* selectivity. This skeletal rearrangement involves the C3-C4 bond cleavage, acyliminium ion formation and cyanide addition. This mechanism was supported by a DFT calculation using 4-formyl- β -lactam **11** (R¹ = Me, R² = Ph) and TMSCN. Other nucleophiles such as allyltrimethylsilanes and propargylsilane can be used in this unique reaction.¹³⁹

The ring-expansion reaction of enantiopure 4-(arylimino)- β -lactams **164**, which were readily derived from 4-formyl- β -lactams **11** with arylamines, in the presence of a catalytic amount of tetrabutylammonium cyanide (Bu₄NCN) proceeded smoothly in acetonitrile at room temperature to give the corresponding 5-aryliminopyrrolidin-2-ones **165** without racemization in 44–70% yields via N1-C4 bond breakage (Scheme 43).¹⁴¹ The acidic hydrolysis of **165a** (R¹ = Me; R² = PMP; R³ = PMP) gave succinimide **166** in 64% yield. It is worth mentioning that the same reaction sequence in one pot from 4-formyl- β -lactam **11** afforded succinimide **166** in 50–55% yields, which were better than the overall yields in the original three-step process (Scheme 41).¹⁴¹

5.3 Formation of 6-membered nitrogen-heterocycles via two-carbon ring expansion of β -lactams

Reduction of 4-(2-TBSO-ethyl)- β -lactams **167** with monochloroalane, followed by TBS deprotection and mesylation, gave 2-(2-TBSO-ethyl)azetidines **168** in 3 steps. The subsequent reaction of **168** with sodium acetate in acetonitrile, followed by basic hydrolysis, gave *cis*-3-alkoxy/phenoxy-4-hydroxypiperidines **170** in moderate overall yields through two-carbon ring expansion (Scheme 44).¹⁴² This ring expansion process involves the ammonium ion of 1-azabicyclo[2.2.0]hexane **169** as the key intermediate, which can explain the 3,4-*cis* stereochemistry of **170** as the result of *exo*-attack of acetate ion to cleave the 1–4 bond.¹⁴² Closely related reactions using 3-alkoxyl-4-(2-bromo-1,1-dimethylethyl)- β -lactams afforded 3,3-dimethyl-4-X-5-alkoxypiperidines (X = Br, OAc, OH, CN, N₃) in high-to-excellent yields.^{143,144} The reaction of **168** (R¹ = *i*-Pr) with LiBr in acetonitrile gave *cis*-3-alkoxy-4-bromopiperidine **171**, which was converted into piperidin-3-one **172** via the enol-ether in fairly good yield for 2 steps (Scheme 44).¹⁴²

Two-carbon ring expansion of β -lactams **173** through the N1-C4 bond cleavage via **175** to form **176**, followed by 1,6-conjugate addition of a malonate to **176**, lactamization via **177**, and deprotection of the resulting **178**, gave glutarimides **174** (Scheme 45). *Trans*-4-hydroxyphenyl- β -lactams **173** were reacted with *t*-butyl methyl malonate in the presence of potassium *t*-butoxide to give 1,3,4,5-substituted glutarimides **174** in 54–77% yields, as illustrated in Scheme 45.¹⁴⁵ The relative stereochemistry of the 3, 4 and 5 positions depends on the nature of R¹ and R². Thus, the reactions of *trans*- β -lactams **173a** (R¹ = benzyl; R² = Ph) and **173b** (R¹ = cyclohexylmethyl; R² = Ph) exclusively gave *trans-trans* glutarimides **174a** and **174b**, respectively, while that of **173c** (R¹ = Me; R² = CH₂CO₂Me) afforded **174c** as a 2:1 mixture of *trans-trans* and *cis-trans* isomers.¹⁴⁵

The reaction of 4-acyloxy- β -lactams **179** with an acid chloride and DBU afforded 1,3-oxazin-6-ones **180** in modest-to-good yields (Scheme 46).¹⁴⁶ The mechanism of this unique process is likely to involve the formation of highly strained *N*-acylazetone **181**, which rapidly undergoes electrocyclic ring opening to generate *N*-acylimidoalkene **182**. Then, the cyclization of **182** gave 1,3-oxazin-6-one **180**.¹⁴⁷ A theoretical study on this reaction based on *ab initio* and DFT analysis has confirmed that two pseudopericyclic reactions are involved. The first key reaction is a retro-[4-*exo-dig*] cyclization to generate **183** instead of a thermal conrotatory electrocyclic ring opening, followed by another exothermic pseudopericyclic reaction to form **180** in place of a six-electron disrotatory electrocyclization.¹⁴⁶

The C3-C4 bond cleavage of 4-formyl- β -lactam **183a** (X = O) and 4-arylimino- β -lactam **183b** (X = ArN) was mediated by stannous chloride and the subsequent 6-membered ring formation gave 1,4-dihydrooxane **184a** (X = O) and pyrazine-2,3-dione **184b** (X = ArN), respectively, in good-to-excellent yield (Scheme 47).²²

5.4 Formation of 8-membered rings through [3,3] sigmatropic rearrangement of β -lactams

The [3,3] sigmatropic (Cope) rearrangement of 3,4-dialkenyl- β -lactams **185** proceeded at 120 °C in a sealed tube using toluene as solvent to give the 8-membered lactams, tetrahydroazocinones **186**, in 60–100% yield (Scheme 48).¹⁴⁸ This rearrangement involves the cleavage of the C3-C4 bond of the β -lactam.

This sigmatropic rearrangement was found to be completely stereospecific. Thus, the reactions of enantiopure (3*S*,4*R*)- β -lactam **185a** and (3*R*,4*S*)- β -lactam **185a**, bearing a (*R*)-1-phenylethyl group at N1, gave (6*S*)-**186a** and (6*R*)-**186a** in 75 and 83% yield, respectively, as a single product in each case. The observed excellent stereospecificity was

attributed to the boat-like conformations of these diastereomeric β -lactams, as illustrated in Scheme 49.¹⁴⁸

6. Use of β -lactam skeleton as a uniquely rigid scaffold for drug discovery

6.1 β -Lactam cholesterol absorption inhibitors

Atherosclerotic coronary heart disease (CHD) is the major cause of death in the United States, and it has been shown that CHD is associated with elevated serum cholesterol levels, to which cholesterol from dietary or intestinal sources is the major contributor.¹⁵ Accordingly, the serum cholesterol level should be effectively controlled by blocking the intestinal sources of cholesterol. Then, the cholesterol absorption in the intestine can be blocked by inhibiting acyl-CoA:cholesterol *O*-acyltransferase (ACAT).¹⁵ Thus, ACAT inhibitors have been extensively studied, including β -lactams, which led to the discovery of ezetimibe, a *trans*- β -lactam, as a potent and highly efficacious cholesterol absorption inhibitor.¹⁵ Ezetimibe was approved by the FDA for the treatment of hypercholesterolemia in 2002 and combination therapies with statins have been extensively studied as well.

In a patented asymmetric synthesis of ezetimibe (Scheme 50), a key intermediate, (*S*)-hydroxypentanoyl-(*S*)-oxazolidinone **189** (99:1 dr), was prepared by the Corey-Bakshi-Shibata (CBS) asymmetric reduction of **188** in excellent yield. Oxazolidinone **188** was obtained through coupling of δ -keto acid **187** and (*S*)-phenyloxazolidinone in excellent yield. The asymmetric enolate-imine cyclocondensation of **189** with imine **190** (via *in situ* silylation and TMS-enolate formation) afforded β -amino amide **191** with high stereoselectivity. The *N*-silylation followed by TBAF-catalyzed cyclization of **191** gave ezetimibe in high yield.^{15,149}

Another synthesis of ezetimibe includes a one-step highly diastereoselective formation of *trans*- β -lactam **194** through enolate-imine cyclocondensation of (*S*)-hydroxy- γ -lactone **192** with 4-BnO-C₆H₄CH=NC₆H₄-F-4 (**193**) (Scheme 51). The sodium periodate oxidation of the diol moiety of **194** to the corresponding 3-formyl- β -lactam, which was subjected to Mukaiyama aldol condensation with (TMSO)(4-F-C₆H₄)C=CH₂ (**195**), followed by desilylation, to give the β -lactam **196**. Hydrogenation of the double bond, followed by asymmetric CBS reduction of the ketone moiety and removal of the benzyl protection by hydrogenolysis, afforded ezetimibe with >99% ee in good overall yield.¹⁵⁰

6.2. β -Lactam-based combretastatin mimics

Combretastatins are naturally occurring diarylstilbenes, isolated from the stem of *Combretum caffrum* (South African bushwillow tree).^{151,152} These compounds exhibit strong cytotoxicity and are known to share the same tubulin-binding site as colchicine.¹⁵³ Among these, the highly potent combretastatin A-4 was selected for drug development and its phosphate derivative, combretastatin A-4-phosphate, a water-soluble prodrug, is currently in clinical trials for the treatment of thyroid cancer (Figure 6).^{152,154} As the *cis*-olefin moiety of combretastatin A-4 is prone to isomerization, which causes a loss of activity, the rigid β -lactam ring system was used to develop a series of β -lactam-based structurally stable combretastatin mimics, some of which exhibited promising activities (Figure 6).¹⁹

Combretastatin A-4 mimic **197a** was synthesized via the Reformatsky reaction of phenylbromoacetate **198** and imine **199**, followed by desilylation (Scheme 52).¹⁹ Mimics **197b** and **197c** were synthesized through the Staudinger ketene-imine cycloaddition reaction of ketenes generated from **200a** and **200b** with imine **199**, forming β -lactams **201a** and **201b**, respectively, followed by desilylation and reductive removal of the benzyl or Cbz group (Scheme 52).¹⁹ The reported chemical yields for these mimics are modest, at best, for

some reason. The IC₅₀ values of these mimics were determined to be 9.6, 0.8, and 4.5 nM, respectively, indicating that they are as potent as, or more potent than, combretastatin A-4 against the MCF-7 human breast cancer cell line.¹⁹ Although these mimics have been found to be potent and promising, a substantial improvement in the syntheses is necessary for their further development as drug candidates.

6.3 β -Lactam-based novel vasopressin V1a antagonists

Vasopressin and oxytocin are neurohypophyseal hormones which bind to specific receptors of the G protein-coupled receptor (GPCR) superfamily.¹⁵⁵ Vasopressin V1a, V1b and oxytocin receptors activate phospholipase C, which leads to secretion of inositol 1,4,5-triphosphate and diacylglycerol that mobilize intracellular calcium and activation of protein kinase C.¹⁵⁵ Besides their functions in the cardiovascular system, vasopressin antagonists have been recommended for some CNS applications.¹⁵⁶ Although numerous vasopressin V1 receptor antagonists have been developed, none of them had been reported to penetrate the central nervous system (CNS) efficiently, until novel β -lactam-based antagonists such as **202a** (SRX246) were discovered.

Based on its structural similarities to ketoconazole, a known antagonist of the luteinizing hormone releasing hormone (LHRH) receptor, LY307174 (IC₅₀ = 45 nM for human V1a receptor) was identified as the lead structure for extensive SAR studies (Figure 7).¹⁴ After systematic SAR studies, two highly potent compounds, **202a** (SRX246) and **202b** (SRX251) (Figure 7 and Scheme 53) were discovered, which exhibited *K_i* values of 0.3 and 0.66 nM, respectively. When administered orally, these two compounds reached ca. 100-fold higher brain levels in rats than their *in vitro* receptor affinities. Thus, these two compounds are currently under drug development for human clinical evaluation.¹⁴

The synthetic routes to **202a** and **202b** are illustrated in Scheme 53.¹⁴ A key intermediate β -lactams **206** were synthesized using the asymmetric Staudinger ketene-imine cycloaddition of (*R*)-phenyloxazolidinylacetyl chloride (**18**; see Scheme 5) with functionalized imines **205** in the presence of a base, which proceeded with excellent stereoselectivity. Imine **205** was prepared from (*R*)-*N*-Cbz-Asp-OBu-*t* (**203**) via coupling with an amine [**a**: (*S*)-1-phenylethylamine; **b**: *N*-methyl-(3-trifluoromethyl)phenylmethylamine] to give amides **204**, followed by removal of benzyl protection and imine formation with cinnamaldehyde. The asymmetric Staudinger cycloaddition of **18** with **205** in the presence of triethylamine, followed by treatment with formic acid gave β -lactam **206** in 64–69% yield. The amide coupling of **206a** and **206b** with 1,4'-dipiperidine afforded **202a** (SRX246) and **202b** (SRX251), respectively, in >90% yield (Scheme 53).¹⁴

7. Conclusions

This Tetrahedron Report has summarized the recent advances in the synthesis of β -lactams with high enantiomeric purity, the chemistry of β -lactams, the β -lactam synthon method and its applications to the synthesis of non-protein amino acids, their derivatives and peptides as well as biologically active natural and unnatural compounds of medicinal interest. In addition, the discovery and development of novel β -lactams with anticancer activity, cholesterol absorption inhibitory activity and CNS activity by exploiting the rigid and unique β -lactam scaffold are described. Traditionally, the organic chemistry and medicinal chemistry of β -lactams have been directly related to β -lactam antibiotics. However, it is obvious that the potential of β -lactams has been explored extensively in an impressive breadth, which has created an entirely new field of chemical and medicinal research. Thus, it is safe to say that this field of research will continue to expand and flourish.

References

1. Georg, GI. The Organic Chemistry of β -Lactams and references cited therein. VCH; New York: 1992.
2. Aoki H, Sakai H, Kohsaka M, Konomi T, Hosoda J. J Antibiotics. 1976; 29:890–901. [PubMed: 993130]
3. Hashimoto M, Komori T, Kamiya T. J Am Chem Soc. 1976; 98:3023–3025. [PubMed: 1262632]
4. Imada A, Kitano K, Kintaka K, Muroi M, Asai M. Nature. 1981; 289:590–591. [PubMed: 7007891]
5. Ojima I, Shimizu N, Qiu X, Chen HJC, Nakahashi K. Bull Soc Chim France. 1987:649–658.
6. Hatanaka N, Abe R, Ojima I. Chem Lett. 1981; 10:1297–1298.
7. Ojima I. Acc Chem Res. 1995; 28:383–389.
8. Ojima, I. Advances in Asymmetric Synthesis. Hassner, A., editor. JAI Press, Inc; Greenwich, CT: 1995. p. 95-146.
9. Ojima I, Delalogue F. Chem Soc Rev. 1997; 26:377–386.
10. Deshmukh AR, Bhawal BM, Krishnaswamy D, Govande VV, Shinkre BA, Jayanthi A. Curr Med Chem. 2004; 11:1889–1920. [PubMed: 15279573]
11. Alcaide B, Almendros P. Curr Med Chem. 2004; 11:1921–1949. [PubMed: 15279574]
12. Palomo C, Aizpurua JM, Ganboa I, Oiardide M. Curr Med Chem. 2004; 11:1837–1872. [PubMed: 15279571]
13. Ojima, I.; Kuznetsova, L.; Ungureanu, IM.; Pepe, A.; Zanardi, I.; Chen, J. ACS Symp Ser 911: Fluorine-containing Synthons. Soloshonok, V., editor. American Chemical Society/Oxford University Press; Washington, D.C: 2005. p. 544-561.
14. Guillon CD, Koppel GA, Brownstein MJ, Chaney MO, Ferris CF, Lu SF, Fabio KM, Miller MJ, Heindel ND, Hunden DC, Cooper RDG, Kaldox SW, Skelton JJ, Dressman BA, Clay MP, Steinberg MI, Bruns RF. Bioorg Med Chem. 2007; 15:2054–2080. [PubMed: 17234419]
15. Burnett D. Curr Med Chem. 2004; 11:1873–1887. [PubMed: 15279572]
16. Banik I, Becker FF, Banik BK. J Med Chem. 2003; 46:12–15. [PubMed: 12502355]
17. Banik BK, Becker FF, Banik I. Bioorg Med Chem. 2004; 12:2523–2528. [PubMed: 15110834]
18. Banik BK, Banik I, Becker FF. Euro J Med Chem. 2010; 45:846–848.
19. O'Boyle N, Carr M, Greene L, Bergin O, Nathwani S, McCabe T, Lloyd D, Zisterer D, Meegan M. J Med Chem. 2010; 53:8569–8584. [PubMed: 21080725]
20. Del Buttero PMG, Roncoroni M. Tetrahedron Lett. 2006; 47:2209–2211.
21. Palomo C, Aizpurua JM, Ganboa I, Oiardide M. Amino Acids. 1999; 16:321–343. [PubMed: 10399019]
22. Alcaide B, Martin-Cantalejo Y, Rodriguez-Lopez J, Sierra M. J Org Chem. 1993; 58:4767–4770.
23. Staudinger H. Justus Liebigs Ann Chem. 1907; 356:51–123.
24. Venturini A, Gonzalez J. Mini Rev Med Chem. 2006; 3:185–194.
25. Cossio FP, Arrieta A, Sierra MA. Acc Chem Res. 2008; 41:925–936. [PubMed: 18662024]
26. Dumas S, Hegedus LS. J Org Chem. 1994; 59:4967–4971.
27. Georg, GI.; Ravikumar, VT. Organic Chemistry β -lactams. GIG, editor. VCH Publishing; New York, NY: 1993. p. 295-368.
28. Hegedus LS, Montgomery J, Narukawa Y, Snustad DC. J Am Chem Soc. 1991; 113:5784–5791.
29. Cossio FP, Ugalde JM, Lopez X, Lecea B, Palomo C. J Am Chem Soc. 1993; 115:995–1004.
30. Lopez R, Sordo TL, Sordo JA, Gonzalez J. J Org Chem. 1993; 58:7036–7037.
31. Cossio FP, Arrieta A, Lecea B, Ugalde JM. J Am Chem Soc. 1994; 116:2085–2093.
32. Wang Y, Liang Y, Jiao L, Du DM, Xu J. J Org Chem. 2006; 71:6983–6990. [PubMed: 16930052]
33. Li B, Wang Y, Du DM, Xu J. J Org Chem. 2007; 72:990–997. [PubMed: 17253821]
34. Linder MR, Podlech J. Org Lett. 2001; 3:1849–1851. [PubMed: 11405727]
35. Palomo C, Oiartide M, Esnal A, Landa A, Miranda J, Linden A. J Org Chem. 1998; 63:5838–5846. [PubMed: 11672185]
36. Aszodi J, Bonnet A, Teusch G. Tetrahedron. 1990; 46:1579–1586.

37. Bose A, Manhas M, van der Veen J, Bari S, Wagle D. *Tetrahedron*. 1992; 48:4831–4844.
38. Hubschwerlen C, Schmid G. *Helv Chim Acta*. 1983; 66:2206–2209.
39. Banik B, Manhas M, Kaluza Z, Barakat J, Bose A. *Tetrahedron Lett*. 1992; 33:3603–3606.
40. Chincholkar P, Puranik VG, Deshmukh ARAS. *Tetrahedron*. 2007; 63:9179–9187.
41. Wagle DR, Garai C, Chiang J, Monteleone MG, Kurys BE, Strohmeyer TW, Hegde VR, Manhas MS, Bose AK. *J Org Chem*. 1988; 53:4227–4236.
42. Li L, Thomas SA, Klein LL, Yeung CM, Maring CJ, Grampovnik DJ, Lartey PA, Plattner JJ. *J Med Chem*. 1994; 37:2655–2663. [PubMed: 7914927]
43. Kuznetsova L, Ungureanu I, Pepe A, Zanardi I, Wu X, Ojima I. *J Fluor Chem*. 2004; 125:487–500.
44. Ojima, IV.; KL; Sun, L. ACS Sym Ser 949: Current Fluoroorganic Chemistry New Synthetic Directions, Technologies, Materials and Biological Applications. Soloshonok, V.; Yamazaki, KMT.; Welch, JT.; Honek, J., editors. American Chemical Society/Oxford University Press; Washington, D.C: 2007. p. 288-304.
45. Niu C, Miller MJ. *Tetrahedron Lett*. 1995; 36:497–500.
46. Evans DA, Sjogren EB. *Tetrahedron Lett*. 1985; 26:3783–3786.
47. Ruhland B, Gordon ABE, Gallop M. *J Am Chem Soc*. 1996; 118:253–254.
48. Delpiccolo C, Mata E. *Tetrahedron: Asymm*. 2002; 13:905–910.
49. Alcaide B, Rodriguez-Vicente A. *Tetrahedron Lett*. 1999; 40:2005–2006.
50. Chen, J.; Kuznetsova, L.; Ungureanu, I.; Ojima, I. *Enantioselective Synthesis of Amino Acids*. 2. Juaristi, E.; Soloshonok, V., editors. John Wiley; New York: 2005. p. 447-476.
51. Brieva R, Crich JZ, Sih CJ. *J Org Chem*. 1993; 58:1068–1075.
52. Banik BK, Manhas MS, Bose AK. *J Org Chem*. 1994; 59:4714–4716.
53. Patel, RN. *Eur. Pat. Appl*. 634492 A1. 1995.
54. Holton, RA.; Vu, P. *PCT Int. Appl. WO* 2001/029245. 2001.
55. Kuznetsova LV, Pepe A, Ungureanu IM, Pera P, Bernacki RJ, Ojima I. *J Fluor Chem*. 2008; 129:817–828. [PubMed: 19448839]
56. France S, Weatherwax A, Taggi AE, Lectka T. *Acc Chem Res*. 2004; 37:592–600. [PubMed: 15311958]
57. Wack H, Drury W, Taggi A, Ferraris D, Lectka T. *Org Lett*. 1999; 1:1985–1988. [PubMed: 10836055]
58. Taggi A, Hafez A, Wack H, Young B, Drury W, Lectka T. *J Am Chem Soc*. 2000; 122:7831–7832.
59. France S, Wack H, Hafez A, Taggi A, Witsil D, Lectka T. *Org Lett*. 2002; 4:1603–1605. [PubMed: 11975639]
60. Hodous BL, Fu GC. *J Am Chem Soc*. 2002; 124:1578–1579. [PubMed: 11853423]
61. Zhang YR, He L, Wu X, Shao PL, Ye S. *Org Lett*. 2008; 10:277–280. [PubMed: 18085789]
62. Huang X, Chen X, Ye S. *J Org Chem*. 2009; 74:7585–7587. [PubMed: 19722509]
63. Duguet N, Campbell CD, Slawin AMZ, Smith DAD. *Org Biomol Chem*. 2008; 6:1108–1113. [PubMed: 18327339]
64. Sereda O, Blanrue A, Wilhelm R. *Chem Commun*. 2009; 45:1040–1042.
65. Ponsford, RJaSR. *JCS CHEM COMM*. 1979:846–847.
66. Brown P, Southgate R. *Tetrahedron Lett*. 1986; 27:247.
67. Doyle MP, Shanklin MS, Oon SM, Pho HQ, van der Heide FR, Veal WR. *J Org Chem*. 1988; 53:3384–3386.
68. Doyle MP, Oon SM, van der Heide FR, Brown CB. *Bioorg Med Chem Lett*. 1993; 3:2409–2414.
69. Watanabe N, Anada M, Hashimoto S, Ikegami S. *Synlett*. 1994:1031–1033.
70. Anada M, Watanabe N, Hashimoto S. *Chem Commun*. 1998:1517–1518.
71. Calet S, Urso F, Alper H. *J Am Chem Soc*. 1989; 111:931–934.
72. Piotti, MEaAH. *J Am Chem Soc*. 1996; 118:111–116.
73. Ojima I, Habus I. *Tetrahedron Lett*. 1990; 31:4289–4292.

74. Ojima I, Habus I, Zhao M, Zucco M, Park Y, Sun C, Brigaud T. *Tetrahedron*. 1992; 48:6985–7012.
75. Ojima I, Habus I, Zhao M. *J Org Chem*. 1991; 56:1681–1683.
76. Ojima I, Sun CM, Zucco M, Park YH, Duclos O, Kuduk SD. *Tetrahedron Lett*. 1993; 34:4149–4152.
77. Ojima I, Slater JS, Kuduk SD, Takeuchi CS, Gimi RH, Sun CM, Park YH, Pera P, Veith JM, Bernacki RJ. *J Med Chem*. 1997; 40:267–278. [PubMed: 9022793]
78. Fujieda H, Kanai M, Kambara T, Iida A, Tamioka K. *J Am Chem Soc*. 1997; 119:2060–2061.
79. Dunnill P. *Nature*. 1966; 210:1265–167. [PubMed: 5967806]
80. Jung, M. *Chemistry and Biochemistry of Amino Acids*. Chapman and Hall; New York: 1985.
81. Brandi A, Cicchi S, Cordero FM. *Chem Rev*. 2008; 108:3988–4035. [PubMed: 18781723]
82. Ojima I, Zhao M, Yamato T, Nakahashi K, Abe R. *J Org Chem*. 1991; 56:5263–5277.
83. Ojima I, Chen HJ, Qiu X. *Tetrahedron*. 1988; 44:5307–5318.
84. Colson, P-JaHLS. *J Org Chem*. 1993; 58:5918–5924.
85. Ojima I, Chen HJ, Nakahashi K. *J Am Chem Soc*. 1988; 110:278–281.
86. Thaisrivongs S, Pals DT, Kroll LT, Turner SR, Han FS. *J Med Chem*. 1987; 30:976–982. [PubMed: 3295239]
87. Iizuka K, Kamijo T, Kubota T, Akahane K, Umeyama Y, Kiso Y. *J Med Chem*. 1988; 31:701–704. [PubMed: 3127587]
88. Huff JR. *J Med Chem*. 1991; 34:2305–2314. [PubMed: 1875332]
89. Okino TM, Matsuda H, Murakami M, Yamaguchi K. *Tetrahedron Lett*. 1993; 34:501–504.
90. Cardillo G, Tomasini C. *Chem Soc Rev*. 1996; 25:117–128.
91. Rowinsky EK. *Ann Rev Med*. 1997; 48:353–374. [PubMed: 9046968]
92. Kingston DGI. *J Nat Prod*. 2009; 72:507–515. [PubMed: 19125622]
93. Ojima I, Park YH, Sun CM, Zhao M, Brigaud T. *Tetrahedron Lett*. 1992; 33:5739–5742.
94. Ojima I, Sun CM, Park YH. *J Org Chem*. 1994; 59:1249–1250.
95. Ojima I, Wang T, Ng EW. *Tetrahedron Lett*. 1998; 39:923–926.
96. Palomo C, Aizpurua JM, Cuevas C. *J Chem Soc Chem Commun*. 1994; 1994:1957–1958.
97. Kukhar, VP.; Soloshonok, VA. *Fluorine Containing Amino Acids: Synthesis and Properties*. Wiley; Chichester, UK: 1994.
98. Ojima, I. *Biomedical Frontiers of Fluorine Chemistry*. American Chemical Society; Washington, DC: 1996.
99. Ojima I, Lin S, Slater JC, Wang T, Pera P, Bernacki RJ, Ferlini CGS. *Bioorg Med Chem*. 2000; 8:1576–1585.
100. Ojima I, Wang T, Delalogue F. *Tetrahedron Lett*. 1998; 39:3663–3666.
101. Suffness, M. *Taxol: Science and Applications*. CRC Press; New York: 1995.
102. Rowinsky EK, Onetto N, Canetta RM, Arbuck SG. *Semin Oncol*. 1992; 19:646–662. [PubMed: 1361079]
103. Schiff PB, Fant J, Horwitz SB. *Nature*. 1979; 277:665–667. [PubMed: 423966]
104. Schiff PB, Horwitz SB. *Proc Natl Acad Sci, U S A*. 1980; 77:1561–1565. [PubMed: 6103535]
105. Jordan M, Wilson L. *Nat Rev Cancer*. 2004; 4:253–265. [PubMed: 15057285]
106. Jordan MA. *Curr Med Chem: Anti-Cancer Agents*. 2002; 2:1–17.
107. Holton RA, Kim HB, Somoza C, Liang F, Biediger RJ, Boatman PD, Shindo M, Smith CC, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi KK, Gentile LN, Liu JH. *J Am Chem Soc*. 1994; 116:1599–1600.
108. Nicolaou KC, Yang Z, Liu JJ, Ueno H, Nantermet PG, Guy RK, Claiborne CF, Renaud J, Coulaudouros EA, Paulvannan K, Sorensen EJ. *Nature*. 1994; 367:630–634. [PubMed: 7906395]
109. Danishefsky S, Masters J, Young W, Link J, Snyder L, Magee T, Jung D, Isaacs R, Bornmann W, Alaimo C, Coburn C, Di Grandi M. *J Am Chem Soc*. 1996; 118:2843–2859.

110. Wender PA, Badham NF, Conway SP, Floreancig PE, Glass TE, Houze JB, Krauss NE, Lee D, Marquess DG, McGrane PL, Meng W, Natchus MG, Shuker AJ, Sutton JC, Taylor RE. *J Am Chem Soc.* 1997; 119:2757–2758.
111. Mukaiyama T, Shiina I, Iwadare H, Saitoh M, Nishimura T, Ohkawa N, Sakoh H, Nishimura K, Tani Y, Hasegawa M, Yamada K, Saitoh K. *Chem-Eur J.* 1999; 5:121–161.
112. Morihira K, Hara R, Kawahara S, Nishimori T, Nakamura N, Kusama H, Kuwajima I. *J Am Chem Soc.* 1998; 120:12980–12981.
113. Denis JN, Greene AE, Guénard D, Guéritte-Voegelein F, Mangatal L, Potier PA. *J Am Chem Soc.* 1988; 110:5917–5919.
114. Guénard D, Guéritte-Voegelein F, Potier P. *Acc Chem Res.* 1993; 26:160–167.
115. Holton, RA.; Biediger, RJ.; Boatman, PD. *Taxol®: Science and Applications.* Suffness, M., editor. CRC Press; New York: 1995. p. 97-121.
116. Georg, GI.; Boge, TC.; Cheruvallath, ZS.; Clowers, JS.; Harriman, GCB.; Hepperle, M.; Park, H. *Taxol®: Science and Applications.* Suffness, M., editor. CRC Press; New York: 1995. p. 317-375.
117. Ojima I, Slater JC, Michaud E, Kuduk SD, Bounaud PY, Vrignaud P, Bissery MC, Veith J, Pera P, Bernacki RJ. *J Med Chem.* 1996; 39:3889–3896. [PubMed: 8831755]
118. Ojima I, Chen J, Sun L, Borella CP, Wang T, Miller ML, Lin S, Geng X, Kuznetsova L, Qu C, Gallagher D, Zhao X, Zanardi I, Xia S, Horwitz SB, Mallen-StClair J, Guerriero JL, Bar-Sagi D, Veith JM, Pera P, Bernacki RJ. *J Med Chem.* 2008; 51:3203–3221. [PubMed: 18465846]
119. Ojima I, Das M. *J Nat Prod.* 2009; 72:554–565. [PubMed: 19239240]
120. Sun L, Geng X, Geney R, Li Y, Simmerling C, Li Z, Lauher JW, Xia S, Horwitz SB, Veith JM, Pera P, Bernacki RJ, Ojima I. *J Org Chem.* 2008; 73:9584–9593. [PubMed: 18975909]
121. Geng X, Miller M, Lin S, Ojima I. *Org Lett.* 2003; 5:3733–3736. [PubMed: 14507217]
122. Geney R, Sun L, Pera P, Bernacki RJ, Xia S, Horwitz SB, Simmerling CL, Ojima I. *Chem & Biol.* 2005; 12:339–348. [PubMed: 15797218]
123. Sun L, Simmerling C, Ojima I. *ChemMedChem.* 2009; 4:719–731. [PubMed: 19360801]
124. Eggen MJ, Georg GI. *Med Res Rev.* 2002; 22:85–101. [PubMed: 11857635]
125. Eggen M, Nair S, Georg G. *Org Lett.* 2001; 3:1813–1815. [PubMed: 11405718]
126. Vidya R, Eggen MJ, Nair SK, Georg GI, Himes RH. *J Org Chem.* 2003; 68:9687–9693. [PubMed: 14656095]
127. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. *Nature.* 1975; 258:577–579. [PubMed: 1207728]
128. Gardner B, Nakanishi H, Kahn M. *Tetrahedron.* 1993; 49:3433–3448.
129. Michael JP. *Nat Prod Rep.* 2004; 21:625–649. [PubMed: 15459758]
130. Cenci di Bello I, Fleet G, Namgoong SK, Tadano K, Winchester B. *Biochem J.* 1989; 259:855–861. [PubMed: 2499316]
131. Olden K, Breton P, Grzegorzewski K, Yasuda Y, Gause BL, Oladipa A, Oredipe A, Newton SA, White SL. *Pharmacology and Therapeutics.* 1991; 50:285–290. [PubMed: 1754603]
132. Alcaide B, Almendros P, Alonso JM, Moustafa FA, Torres MR. *SynLett.* 2001; 10:1531–1534.
133. Alcaide B, Almendros P, Alonso JM, Aly MF. *Chem Eur J.* 2003; 9:3415–3426. [PubMed: 12866084]
134. Alcaide B, Almendros P, Aragoncillo C. *Chem Eur J.* 2002; 8:3646–3652. [PubMed: 12203291]
135. Alcaide B, Aly M, Rodriguez C, Rodriguez-Vicente A. *J Org Chem.* 2000; 65:3453–3459. [PubMed: 10843630]
136. Banfi L, Guanti G, Rasparini M. *Eur J Org Chem.* 2003; 2003:1319–1336.
137. Van Brabandt W, Dejaegher Y, Van Landeghem R, De Kimpe N. *Org Lett.* 2006; 8:1101–1104. [PubMed: 16524278]
138. Dejaegher Y, Mangelinckx S, De Kimpe N. *J Org Chem.* 2002; 67:2075–2081. [PubMed: 11925211]
139. Alcaide B, Almendros P, Cabrero G, Callejo R, Ruiz M, Arno M, Domingo L. *Adv Synth Catal.* 2010; 352:1688–1700.

140. Alcaide B, Almendros P, Cabrere G, Ruiz MP. Chem Comm. 2008;615–618. [PubMed: 18209807]
141. Alcaide B, Almendros P, Cabrero G, Ruiz M. Org Lett. 2005; 7:3981–3984. [PubMed: 16119947]
142. Mollet K, Catak S, Waroquier M, van Speybroeck V, D’hooghe M, De Kimpe N. J Org Chem. 2011; 76:8361–8375.
143. Van Brabant W, Van Landeghem R, De Kimpe N. Org Lett. 2006; 8:1105–1108. [PubMed: 16524279]
144. Mollet K, Broeckx L, D’hooghe M, De Kimpe N. Heterocycles. 2011; 84:431–447.
145. Cabell LA, McMurray JS. Tetrahedron Lett. 2002; 43:2491–2493.
146. Alajarin M, Sanchez-Andrada P. J Org Chem. 2001; 66:8470–8477. [PubMed: 11735527]
147. Alajarin M, Vidal A, Sanchez-Andrada P, Tovar F, Ochoa Gines. Org Lett. 2000; 2:965–968. [PubMed: 10768198]
148. Almendros P, Aragoncillo C, Cabrero G, Callejo R, Carrascosa R, Luna A, del Campo TM, Pardo MC, Quiros MT, Redondo MC, Rodriguez-Ranera C, Rodriguez-Vicente A, Ruiz MP. Arkivoc. 2010; 2010:74–92.
149. Tiruvettipuram, KT.; Fu, X.; Tann, CH.; McAllister, TL.; Chiu, JS.; Colon, C. US Pat. 6,207,822 B1. 2001.
150. Wu G, Wong YS, Chen X, Ding Z. J Org Chem. 1999; 64:3714–3718. [PubMed: 11674502]
151. Watt, JM.; Gerdina, M. The Medicinal and Poisonous Plants of Southern and Eastern Africa. E. & S. Livingstone Ltd; Edinburgh and London, U.K: 1962.
152. Cooney M, Ortiz J, Bukowski R, Remick S. Curr Oncol Rep. 2005; 7:90–95. [PubMed: 15717941]
153. Cragg, G.; Kingston, D.; Newman, D. Anticancer Agents from Natural Products. CRC Press; Boca Raton, FL: 2005.
154. Young SL, Chaplin DJ. Expert Opin Invest Drugs. 2004; 13:1171–1182.
155. Neumann, IDaLR. Advances in Vasopressin and Oxytocin: from genes to behaviour to disease. Elsevier; 2008.
156. Tribollet E, Barberis C, Jard S, Dubois-DAuphin M, Dreifuss JJ. Brain Research. 1988; 442:105–118. [PubMed: 2834008]

Biographies

Anushree Kamath was born in Mangalore, India. She obtained her B.S. Chem (Hons) from St. Stephen’s College, Delhi in 2005 and M.S. from the Indian Institute of Technology, Roorkee in 2007. In the same year, she moved to France to join Dr. Andrew E. Greene’s group at the Universite de Grenoble for her doctoral thesis, where she worked under Dr. Philippe Delair on the total synthesis of natural products. Since June, 2011, she has been working as a postdoctoral research associate with Prof. Iwao Ojima at the Institute of Chemical Biology and Drug Discovery (ICB&DD), Stony Brook University, New York. Her current research focuses on the development of drug-delivery platforms for tumor-targeted cancer chemotherapy.

Iwao Ojima received his B.S., M.S., and Ph.D. (1973) from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position of Senior Research Fellow until 1983. He joined the faculty at the Department of Chemistry, State University of New York at Stony Brook (now Stony Brook University) first as Associate Professor (1983), was promoted to Professor (1984), Leading Professor (1991), and then to Distinguished Professor (1995). He served as the Department Chairman (1997–2003). He has been serving as the founding Director for the Institute of Chemical Biology and Drug Discovery (ICB&DD) from 2004. His research program includes the discovery and development of anticancer agents, targeted drug delivery systems and new-generation antimicrobials. His awards and honors include Arthur C. Cope Scholar Award (1994), E. B. Hershberg Award for Important Discoveries of Medicinally Active Substances (2001), the Medicinal Chemistry Hall of Fame (2006) from the American Chemical Society; The Chemical Society of Japan Award (1999); Outstanding Inventor Award (2002) from the Research Foundation of the State University of New York; Elected Fellows of J. S. Guggenheim Memorial Foundation (1995), American Association for the Advancement of Science (1997), The New York Academy of Sciences (2000), and American Chemical Society (2010).

Figure 1.
Mechanism of Staudinger [2+2] ketene-imine cycloaddition

Figure 2.
Type 1 and Type 2 asymmetric alkylations

Figure 3.
Chemical structures of paclitaxel and docetaxel

cryptophycin-1: R = Me, R¹ = H, X = Cl

cryptophycin-24: R = H, R¹ = H, X = H (**arenastatin A**)

cryptophycin-52: R = R¹ = Me, X = Cl

dechlorocryptophycin-52: R = R¹ = Me, X = H

Figure 4.
Cryptophycins

$X = \text{NH}, \text{NH-CMe}_2\text{CH}_2, \text{NHCMe}_2(\text{CH}_2)_2, \text{NH-CMe}_2\text{CH=CHCH}_2$

Figure 5.
Conformationally constrained non-peptide β -turn mimics

Figure 6.
Combretastatin A-4, its derivative and β -lactam-based mimics

Figure 7.
Rational design of b-lactam based LHRH receptor antagonists

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.

Scheme 14.

Scheme 15.

Scheme 16.

Scheme 17.

Scheme 18.

Scheme 19.

Scheme 20.

Scheme 21.

Scheme 22.

Scheme 23.

Scheme 24.

Scheme 25.

Scheme 26.

R = *i*-Bu, cyclohexylmethyl, 2-phenylethenyl, phenyl, 4-fluoromethyl, 4-(trifluoromethyl)phenyl, 2-furyl, 2-(2-furyl)ethenyl, crotyl, isobutenyl etc.

Scheme 27.

Scheme 28.

Scheme 29.

R_f = CHF₂, CF₃, CH=CF₂; R = CO₂Bn, CO₂Bu-t, SO₂Tol-*p*, COC₆H₄-F-4

Scheme 30.

Scheme 31.

Scheme 32.

Scheme 33.

Scheme 34.

Scheme 35.

Scheme 36.

Scheme 37.

Scheme 38.

Scheme 39.

Scheme 40.

Scheme 41.

Scheme 42.

Scheme 43.

i) AlH_2Cl , Et_2O , rt, 0 °C, 2 h; ii) TBAF, THF, 0 °C to rt, (48-50% for 2 steps);
 iii) MsCl , Et_3N , DMAP, CH_2Cl_2 , 0 °C (85-90%); iv) NaOAc , MeCN, heat, 15 h
 (55-66%); v) K_2CO_3 , MeOH (56-70%); vi) LiBr , MeCN, heat, 15 h (47-65%);
 vii) NaH , DMSO, 150 °C, 15 h (56-60%); viii) 2 M HCl , H_2O , 40 °C, 40 h (78-85%).

Scheme 44.

Scheme 45.

Scheme 46.

Scheme 47.

Scheme 48.

Scheme 49.

Scheme 50.

i) LDA; 2) 4-BnO-C₆H₄CH=NC₆H₄-F-4 (**193**); iii) LiCl; iv) NaIO₄; v) (TMSO)(4-F-C₆H₄)C=CH₂ (**195**); vi) *p*-TsOH; vii) H₂, (Ph₃P)₃RhCl; viii) CBS reduction; ix) H₂, Pd-C, EtOH

Scheme 51.

Scheme 52.

Table 1

Asymmetric synthesis of 3-TIPSO- β -lactams **82** through chiral ester enolate-imine cyclocondensation.

Entry	R ¹	R ²	R ³	β -Lactam	Yield (%)	ee (%)
1	Ph	TMS	H	82a	85	96
2	4-MeOC ₆ H ₄	TMS	H	82b	80	96
3	3,4-(MeO) ₂ C ₆ H ₃	TMS	H	82c	80	98
4	Ph	PMP	PMP	82d	89	98
5	4-FC ₆ H ₄	PMP	PMP	82e	81	98
6	4-CF ₃ -C ₆ H ₄	PMP	PMP	82f	84	99
7	2-furyl	PMP	PMP	82g	78	92
8	(<i>E</i>)-PhCH=CH ₂	PMP	PMP	82h	85	96
9	2-furyl-CH=CH ₂	PMP	PMP	82i	72	94
10	c-C ₆ H ₁₁ CH ₂	PMP	PMP	82j	85	90
11	Me ₂ CHCH ₂	PMP	PMP	82k	85	92
12	Me ₂ C=CH	PMP	PMP	82l	60	94

Table 2

Selected examples of new-generation taxoids.

Taxoid	R ¹	R ²	R ³	X	Y
paclitaxel	Ph	Ph	Ac	H	H
docetaxel	Ph	<i>n</i> -BuO	H	H	H
SBT-1213	Me ₂ C=CH	<i>n</i> -BuO	EtCO	H	H
SBT-1214	Me ₂ C=CH	<i>n</i> -BuO	<i>c</i> -PrCO	H	H
SBT-1216	Me ₂ C=CH	<i>n</i> -BuO	Me ₂ NCO	H	H
SBT-11033	Me ₂ CHCH ₂	<i>n</i> -BuO	EtCO	MeO	H
SBT-121303	Me ₂ C=CH	<i>n</i> -BuO	EtCO	MeO	H
SBT-121313	Me ₂ C=CH	<i>n</i> -BuO	EtCO	MeO	MeO
SBT-121602	Me ₂ C=CH	<i>n</i> -BuO	Me ₂ NCO	Me	H
SBT-12823-3	CF ₃	<i>n</i> -BuO	Me ₂ NCO	Cl	H
SBT-12854	F ₂ C=CH	<i>n</i> -BuO	Me ₂ NCO	H	H
SBT-12855-1	F ₂ C=CH	<i>n</i> -BuO	MeOCO	MeO	H

Table 3
Cytotoxicity (IC₅₀, nM) of selected new -generation taxoids against human cancer cell lines.

Taxoid	MCF-7 ^a	HT-29 ^b	CFPAC-1 ^c	DLD-1 ^d	LCC6-MDR ^e	NCI/ADR ^f
paclitaxel	1.7	12	68	300	346	550
docetaxel	1.0	--	--	--	120	723
SBT-1213	0.18	0.37	4.6	3.9	--	4.0
SBT-1214	0.20	0.73	0.38	3.8	--	3.9
SBT-1216	0.13	0.052	0.66	5.4	--	7.4
SBT-11033	0.36	--	--	--	--	0.61
SBT-121303	0.36	--	0.89	--	0.90	0.79
SBT-121313	0.30	3.6	0.025	13	--	--
SBT-121602	0.08	0.003	0.31	0.46	--	--
SBT-12823-3	0.17	0.45	--	--	--	1.9
SBT-12854	0.18	0.46	0.35	0.25	--	4.3
SBT-12855-1	0.11	--	--	--	--	0.92

^a breast cancer cell line (Pgp-).

^b colon cancer cell line (Pgp-).

^c pancreatic cancer cell line.

^d colon cancer cell line (Pgp+).

^e breast cancer cell line (Pgp+).

^f ovarian cancer cell line (Pgp+).