β-Lactams: Versatile Building Blocks for the Stereoselective Synthesis of Non-β-Lactam Products

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Contents

1. Introduction

Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation within both the scientific and public sectors. β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole.[1] Additional impetus for research efforts on β-lactam chemistry has been provided by the introduction of the β-lactam synthon method, a term coined by Ojima almost 20 years ago, according to which 2-azetidinones can be employed as useful intermediates in organic synthesis.[2]

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Nitrogen-containing organic molecules are without any doubt among the most important compounds in organic chemistry. Proof of this can be found in the fundamental biological activity of compounds such as amino acids or alkaloids.[3] For the synthesis of these kinds of molecules, β-lactams are considered ideal building blocks, and thus, in recent years many 2-azetidinone-based methods for the racemic and asymmetric synthesis of nitrogen-containing compounds of biological relevance have appeared. β-Lactams are precursors to β-amino alcohols and β-amino acids, which are useful building blocks for peptides containing non-proteinogenic amino acids. They have been used to introduce the C-13 side chain of the anticancer compound paclitaxel (taxol) and related analogues.[4a] The 2-azetidinone nucleus has served as precursor to the δ-lactone moiety in the total synthesis of the macrolide antitumor antibiotic lankacidin C.[4b]

Therefore, use of β-lactams as chiral building blocks in organic synthesis is now well established and routine. Others and we have successfully demonstrated the usefulness of the β-lactam nucleus in stereocontrolled synthesis on using the impressive variety of transformations which can be derived from this system. Opening of the β-lactam nucleus can occur through cleavage of any of the single bonds of the four-membered ring (Figure 1). This ring cleavage is enhanced

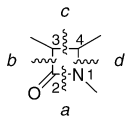

Figure 1.

by ring strain of the β-lactam system. In particular, the most useful cleavage is that of the N1−C2 bond (*a* in Figure 1). This amide bond cleavage takes place usually by nucleophilic reagents including water. Since β-lactams may be considered as cyclized forms of β-amino acids in which the amino and carboxyl groups are simultaneously protected, the more obvious application is the synthesis of β-amino acids. Besides, use of 2-azetidinones as starting materials to prepare bis-γ-lactams, pyrrolizidines, indolizidines, pyrrolidines, piperidines, cyclic enaminones, pyridones, oxazinones, complex natural products, and other types of compounds of biological and medicinal interest has been accomplished through N1−C2 bond breakage coupled to rearrangement reactions. The rigidity of the four-membered ring makes this methodology often highly stereoselective. On the other hand, ESI-MS and NMR studies have shown that the antibacterial properties of the β-lactam antibiotics arise from an acylation

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Pedro Almendros was born in Albacete (Spain) in 1966. He received his B.S. degree (1989) and Ph.D. degree (1994) from the Universidad de Murcia under the supervision of Professor Pedro Molina and Dr. Pilar M. Fresneda. After 3 years of postdoctoral work for Professor Eric J. Thomas at the University of Manchester, England, with a Spanish MEC Postdoctoral Fellowship (1995–1997) and a European Marie Curie Postdoctoral Grant (1997–1998), he joined the research group of Professor Benito Alcaide (UCM, Madrid) in 1998 as Associate Researcher (Contrato de Reincorporación de Doctores y Tecnólogos). Subsequent appointments have included Assistant Professor at the UCM (2000–2002) and Científico Titular (Tenure Research) at the Instituto de Química Orgánica General, CSIC, Madrid. In 2007 he was promoted to Investigador Científico (Research Scientist) at the IQOG, CSIC, Madrid. His research interests include β-lactam chemistry, allene chemistry, asymmetric synthesis, metal-promoted heterocyclizations, and C–C coupling reactions.

process in which the N1−C2 bond of the four-membered 2-azetidinone ring is opened. Besides, it is well known that bacterial resistance to β-lactam antibiotics stems from expression of a β-lactamase that catalyzes the hydrolytic cleavage of the substrate amide bond.

2-Azetidinones are becoming increasingly important in synthesis due inter alia to a high chirality content that can be transferred into a variety of products, leading to construction of functionalized chiral acyclic and heterocyclic building

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blocks. In this sense, the stereoselective synthesis of different sized heterocycles of biological significance has been accomplished. Ring sizes from three through to complex macrocycles have been synthesized using β-lactams. However, from the pioneering review from Bose in 1988[5] there is a lack of comprehensive and general review articles covering the importance of 2-azetidinones as synthetic intermediates. The purpose of this review is to survey the vast chemistry of 2-azetidinones for the preparation of non-β-lactam products (non-proteinogenic α-amino acids, different kinds of heterocycles, alkaloids, macrolides, taxoids, etc.), concentrating on the advances that have been made in the past decade, in particular in the last 5 years.

This review covers the chemical literature up to 2006. Although most examples have been selected from recent reports, seminal and important contributions to this area have also been conveniently credited.

2. Synthesis of Different-Sized Heterocycles

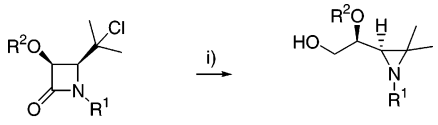
2.1. Three-Membered Heterocycles

2.1.1. Monocyclic Three-Membered Rings

4-(1-Haloalkyl)azetidin-2-ones **1** consist of an interesting class of azaheterocyclic compounds because the presence of ring strain and a halogen in these compounds makes them attractive for further reactions. In addition, these β-lactams are now readily available by performing a Staudinger reaction between α-chlorinated imines and different ketenes (prepared in situ from the corresponding acid chlorides and triethylamine). A new synthesis of stereodefined aziridines, starting from β-lactams **1**, has been described.[6] Treatment of the latter compounds with $LiAlH_4$ gave 1,2-fission of the β-lactam followed by an intramolecular nucleophilic substitution of the halogen, giving rise to formation of 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** (Scheme 1).

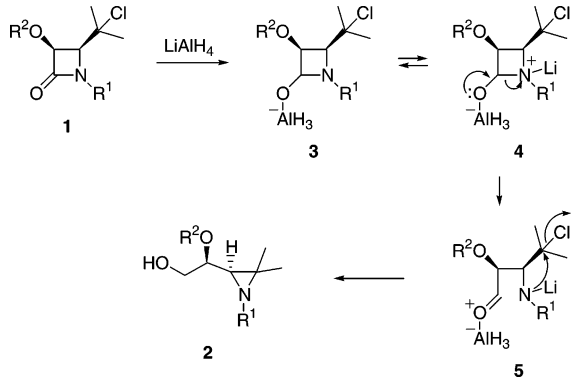
As can be seen in Scheme 2, ring transformation of 4-(1-chloroalkyl)azetidin-2-ones **1** toward aziridines **2** proceeds with retention of stereochemistry. The 1,2-fission of the

Scheme 1[a]

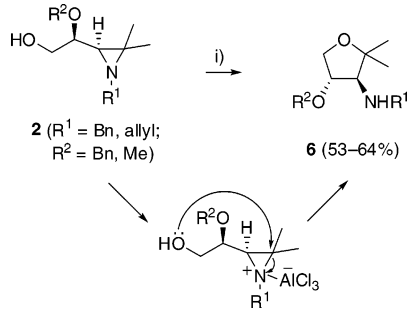


[a] Key: (i) $LiAlH_4$, Et_2O, 0 °C, 2 h.

Scheme 2



Scheme 3[a]



[a] Key: (i) $AlCl_3$, Et_2O, reflux, 48 h.

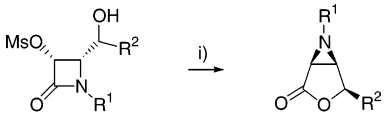
β-lactams **1** explains the obtained syn stereochemistry observed in aziridines **2**. The proposed mechanism proceeds via initial reduction of the amide functionality into hemiaminal **3**. Coordination of lithium to nitrogen triggers ring opening of azetidinium salt **4**, leading to formation of the intermediate aminoaldehyde complex **5**. Reduction of the formyl group and nucleophilic substitution of the chlorine by nitrogen leads to formation of 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** (Scheme 2).

Inasmuch as aziridines are strained heterocycles, they have been shown to serve as excellent building blocks in organic synthesis.[7] Also, aziridines **2** proved to be very useful intermediates toward the synthesis of highly substituted oxolanes. Therefore, 2-(1-alkoxy-2-hydroxyethyl)aziridines **2** were treated with $AlCl_3$ in ether under reflux for 48 h, affording *trans*-tetrahydrofurans **6** in good isolated yields (Scheme 3).[6] The reaction mechanism is explained by an initial complexation of $AlCl_3$ with nitrogen. In this way, activation of the aziridine ring facilitates ring opening after intramolecular nucleophilic attack of the hydroxyl function, leading toward oxolanes **6**.

2.1.2. Bicyclic Three-Membered Rings

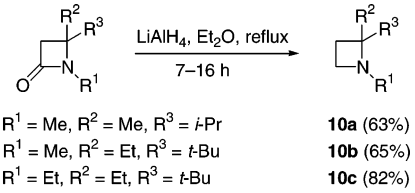
2,3-Aziridino-γ-lactones are very important intermediates in the synthesis of biologically useful 3,4-dihydroxy glutamic acids. Recently, an efficient conversion of hydroxy-β-lactams **7** into enantiopure 2,3-aziridino-γ-lactones **8** has been documented (Scheme 4).[8] Acid-catalyzed tandem intramolecular azetidinone ring opening followed by aziridine ring formation via elimination of a mesylate group is the key step in this synthesis.

Scheme 4[a]



[a] Key: (i) HCl−MeOH (20%), reflux, 18−24 h.

Scheme 5



2.2. Four-Membered Heterocycles

2.2.1. Monocyclic Four-Membered Rings

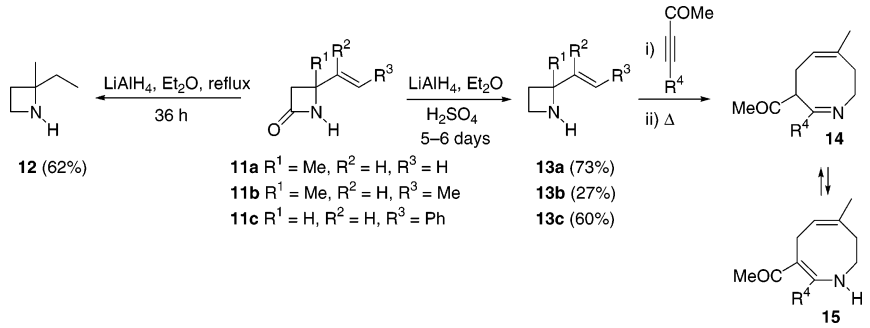
Azetidines constitute an important class of azaheterocycles, exhibiting a wide range of biological activities such as antihypertensive, anti-inflammatory, antiarrhythmic, antidepressant, and monoamine oxidase inhibitory activities.[9] However, the azetidine skeleton has been one of the most difficult amines to synthesize because of the ring strain. Several methods for the synthesis of azetidines are known. A powerful method is reduction of 2-azetidinones by nucleophilic hydrides to afford the corresponding azetidines. However, this transformation cannot be generalized because many reactions of β-lactams with reducing agents, e.g., diborane, do not lead to azetidines but instead give rise to γ-amino alcohols.[10] This reduction has been performed with a wide variety of reducing agents, including diisobutyl aluminum hydride, monochloroalane and dichloroalane, and lithium aluminum hydride. Among them, reduction with chloroalanes has proven to be a reliable method.

Lithium aluminum hydride (2 mol equiv) in diethyl ether under reflux for 7−16 h converted 1,4,4-trisubstituted β-lactams **9a**−**c** into azetidines **10a**−**c** in 63−82% yield (Scheme 5).[11]

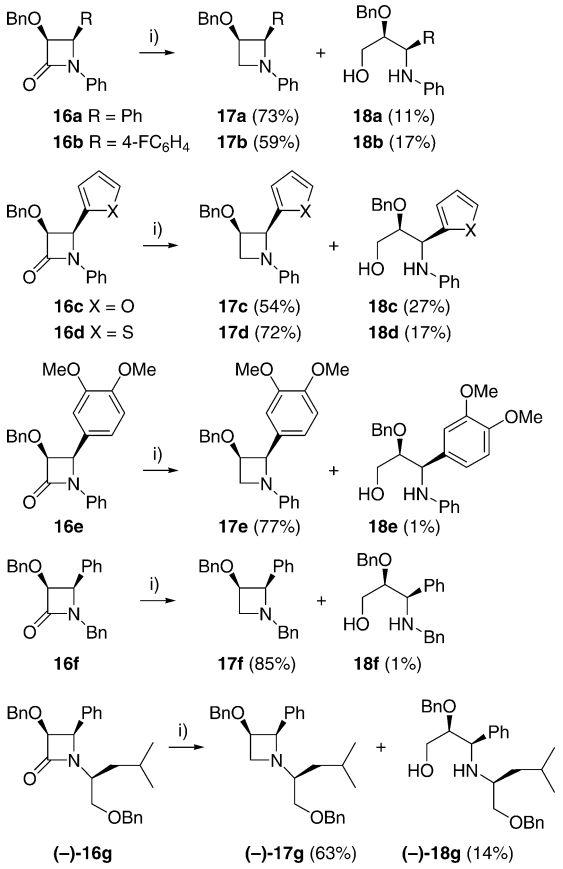
Lithium aluminum hydride reduction of 2-azetidinone **11a** led to concomitant reduction of the vinyl side chain to give 2-ethyl-2-methylazetidine **12**. However, for azetidinones **11a**−**c** use of aluminum(III) hydride (generated in situ from lithium aluminum hydride and sulfuric acid) generated the 2-vinylazetidines **13a**−**c**. Azaheterocycles **13** after Michael addition to activated acetylenes underwent Cope rearrangement when heated at 100 °C and gave rise to tautomeric mixtures of 3,4,7,8- and 1,4,7,8-tetrahydroazocines **14** and **15** (Scheme 6).[12]

Application of metal hydrides has been examined in the search for general and efficient methods for the one-step conversion of β-lactams to the corresponding azetidine.[13] Attempted reduction by BH_3·THF (22 h in refluxing dioxane) and $NaBH_4$–$AlCl_3$ (3.5 h in refluxing ether) resulted in a complete recovery of the starting 2-azetidinone. Reduction

Scheme 6

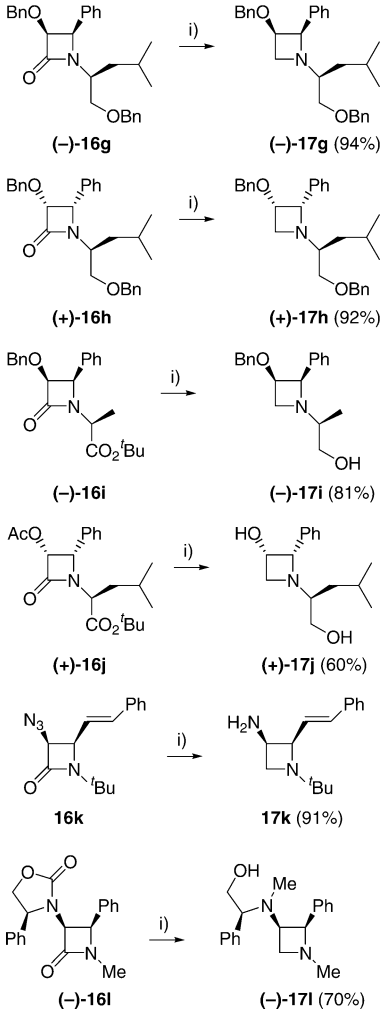


Scheme 7[a]



[a] Key: (i) DIBAL-H, THF, 65 °C, 2 h.

Scheme 8[a]



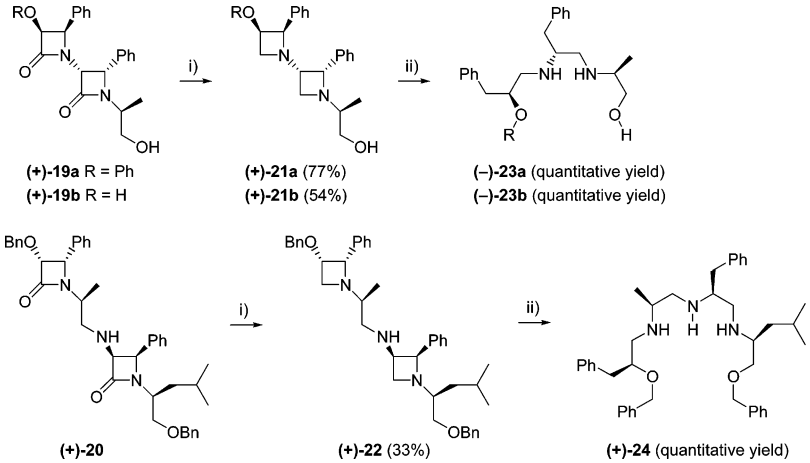
[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 1.5−4 h.

with $LiAlH_4$, $LiBEt_3H$, or LiB-*sec*-Bu_3H in THF at room temperature gave exclusively the corresponding γ-amino alcohol through 1,2-bond fission. It was found that reduction of a variety of 2-azetidinones **16a**−**g** with DIBAL-H in THF afforded the corresponding azetidines **17a**−**g** in 54−85% yields as shown in Scheme 7, although a small amount (1−27%) of γ-amino alcohols **18a**−**g**, which were separated on a silica gel column, were also produced.[14] Use of alane (AlH_3) for reduction of azetidinones **16** resulted in formation of a mixture of compounds **17** and **18**, with four-membered heterocycle **17** being the minor component (e.g., azetidine **17a** accounted for 29% yield, while γ-amino alcohol **18a** was obtained in a 59% yield).

The reactivities of monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$) were examined toward β-lactams. It was found that AlH_2Cl and $AlHCl_2$ prepared in situ from $LiAlH_4$ and $AlCl_3$ in ether converted 2-azetidinones **16** into azetidines **17** in quite high yields (50−97%) without being accompanied by γ-amino alcohols **18** (Scheme 8).[14] Acetoxy groups, *tert*-butyl esters, Evans's chiral auxiliary, and azide functionality were not tolerant to the reaction conditions. For these β-lactams bearing sensitive groups to reductive conditions, reduction of lactam carbonyl and ester, oxazolidinone, or azide moieties proceeded simultaneously. The corresponding aminoazetidines and azetidine alcohols were obtained for these particular substrates. Interestingly, chiral nonracemic β-lactams can be transformed to the corresponding azetidines without loss of enantiomeric purity.

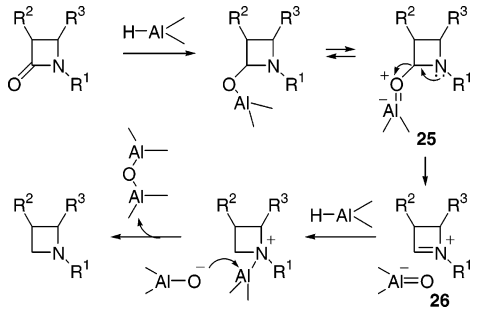
Bis-β-lactams **19** in which two-β-lactams rings are directly connected as well as bis-β-lactam **20** in which two-β-lactams rings are connected by an alkyl moiety were submitted to reduction with chlorohydroalane in refluxing ether to give the corresponding bisazetidines **21** and **22** in good yields.[15]

Scheme 9[a]



[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 6 h; (ii) H_2, Pd−C (10%), MeOH, RT, 12 h.

Scheme 10

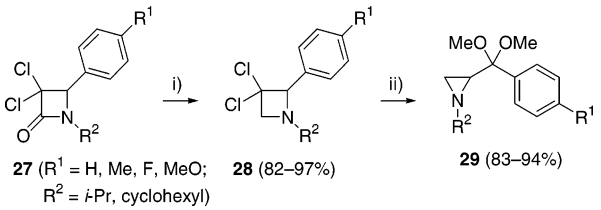


These bisazetidines can readily be converted to the corresponding open-chain chiral polyamino alcohols and polyamino ethers **23** and **24** by hydrogenolysis on Pd−C (Scheme 9). Also, the bisazetidines **21** and **22** are unique chiral polyamines bearing rigid azetidine rings as stereocontrolling factor and can be considered as potential resolution agents or chiral catalysts for asymmetric synthesis.

The selective reduction of 2-azetidinones to azetidines by hydroalanes can be rationalized as shown in Scheme 10. The contribution of the "oxonium Alanate" structure **25** must be taken into account as a crucial factor. It is quite reasonable to assume the easy cleavage of the carbon−oxygen bond because of a strong "oxophilicity" of aluminum to give the iminium salt **26**, which is readily reduced to azetidine by the action of another molecule of hydroalane. This rationale is strongly supported by the fact that the "oxonium metalate" structure cannot be realized in the reduction with lithium aluminum hydride or lithium borohydride.

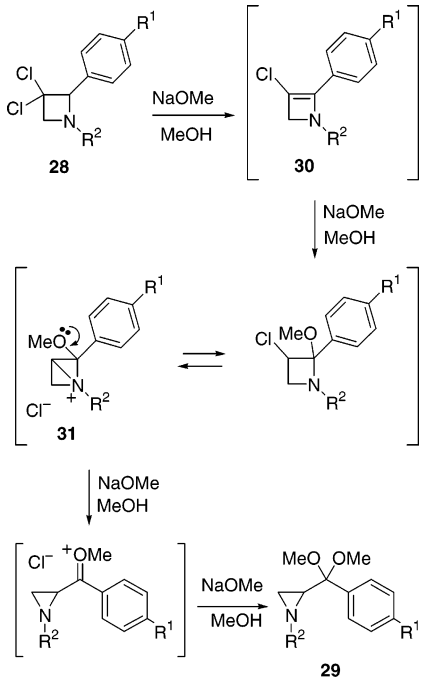
Although not always unambiguous, reduction with chloroalanes is probably the method of choice for the one-pot preparation of azetidines from β-lactams. Use of monochloroalane has been proven to be an efficient method for reduction of 4-aryl-3-chloro-, 4-aryl-3,3-dichloro-, as well as 4-aryl-3,3-difluoro-β-lactams toward their corresponding azetidines.[16] Azetidin-2-ones **27** were generated from a ketene−imine [2+2] cycloaddition of dichloroketene, derived from dichloroacetyl chloride and triethylamine, and the corresponding aldimine. 2-Azetidinones **27** were cleanly converted to 3,3-dichloroazetidines **28** by reaction with monochloroalane in ether at reflux temperature.[16a] 3,3-Dichloroazetidines **28** were converted to 2-[dimethoxy-(phenyl)methyl]-aziridines **29** in the presence of potassium carbonate and sodium methoxide (Scheme 11). Conversion

Scheme 11[a]



[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 4 h; (ii) 4 equiv of NaOMe, 2 N MeOH, Δ, 90 h.

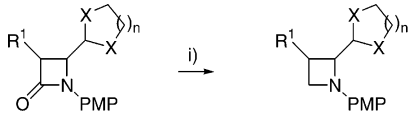
Scheme 12



of 3,3-dichloroazetidines **28** into aziridines **29** proceeds via elimination of hydrogen chloride, generating the strained heterocyclic enamine **30**. Addition of methanol and expulsion of a chloride anion by the nitrogen lone pair generates the bicyclic aziridinium intermediate **31**, which opens to give the aziridine derivatives **29** (Scheme 12).[16]

4-Acetal or thioacetal β-lactams **32** and **33** were prepared by reaction of the corresponding 4-formyl-β-lactam with the appropriate diol or dithiol under acid catalysis to yield dioxolanes or dithiolanes, while reaction with trimethyl

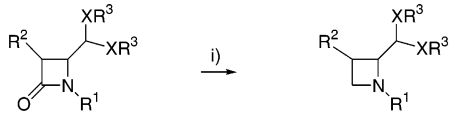
Scheme 13[a]



***cis*-32a** R^1 = Ph, X = O, n = 1 ***cis*-34a** (85%)
***cis*-32b** R^1 = Me, X = O, n = 1 ***cis*-34b** (97%)
***cis*-32c** R^1 = Me, X = O, n = 2 ***cis*-34c** (90%)
***cis*-32d** R^1 = Me, X = S, n = 1 ***cis*-34d** (95%)
***trans*-32d** R^1 = Me, X = S, n = 1 ***trans*-34d** (96%)

[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 0.5 h.

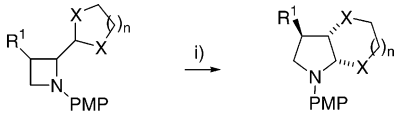
Scheme 14[a]



***cis*-33a** R^1 = PMP, R^2 = Ph, R^3 = Ph ***cis*-35a** X = S (98%)
***cis*-33b** R^1 = PMP, R^2 = Me, R^3 = Ph ***cis*-35b** X = S (100%)
***cis*-33c** R^1 = Bn, R^2 = PhO, R^3 = Me ***cis*-35c** X = O (93%)
***trans*-33a** R^1 = PMP, R^2 = Ph, R^3 = Ph ***trans*-35a** X = S (97%)
***trans*-33b** R^1 = PMP, R^2 = Me, R^3 = Ph ***trans*-35b** X = S (74%)

[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 0.5 h.

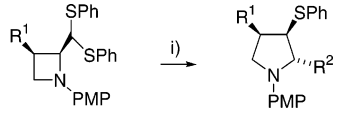
Scheme 15[a]



***cis*-34a** R^1 = Ph, X = O, n = 1 **36a** (35%)
***cis*-34b** R^1 = Me, X = O, n = 1 **36b** (35%)
***cis*-34c** R^1 = Me, X = O, n = 2 **36c** (64%)
***cis*-34d** R^1 = Me, X = S, n = 1 **36d** (82%)
***trans*-34d** R^1 = Me, X = S, n = 1 **36d** (71%)

[a] Key: (i) $AlEt_2Cl$, CH_2Cl_2, RT, 5 min to 12 days.

Scheme 16[a]



***cis*-35a** R^1 = Ph, R^2 = Et **37a** (67%)
***cis*-35b** R^1 = Me, R^2 = Et **37b** (72%)
***cis*-35b** R^1 = Me, R^2 = Me **37c** (38%)

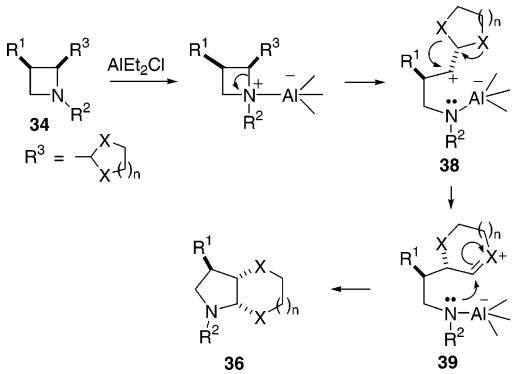
[a] Key: (i) $AlR^2{}_2Cl$, CH_2Cl_2, reflux, 10 min.

orthoformate or benzenethiol gave 4-acetal or thioacetal β-lactams, respectively. The monochloroalane reduction of cyclic and acyclic *cis*- and *trans*-4-acetal or thioacetal β-lactams **32** and **33** smoothly afforded the corresponding acetal azetidines **34** and **35** in excellent yields (Schemes 13 and 14).[17]

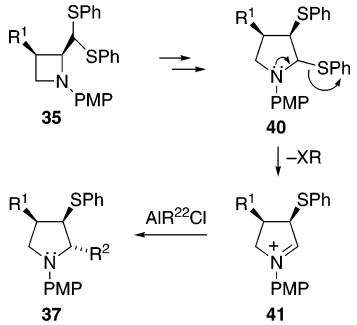
Acetal or thioacetal azetidines **34** and **35** under $AlEt_2Cl$ treatment afforded in a stereocontrolled manner pyrrolidines **36** and **37** as the only products (Schemes 15 and 16). Furthermore, thioacetal azetidines bearing a substituent at C3 on the azetidine ring, which can promote aromatization (phenoxy or exocyclic double bond), gave pyrroles under $AlEt_2Cl$-promoted reaction. These syntheses rely on the C2−N1 bond (former C4−N1 bond in the β-lactam ring) fission of the azetidine ring promoted by diethylaluminum chloride.

Formation of fused pyrrolidines **36** can be rationalized through initial coordination of the lone electron pair of nitrogen to $AlEt_2Cl$ to give a coordinate species. This coordination should promote the C2−N1 bond breakage of

Scheme 17



Scheme 18



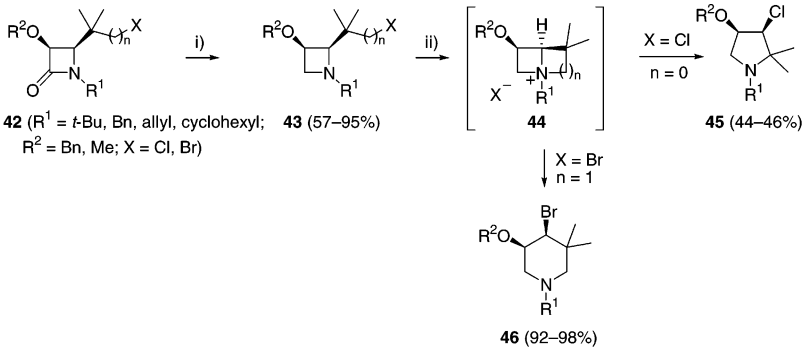
the azetidine nucleus to form a zwitterion. The acetal moiety promotes conversion of this intermediate to a new carbocation, which is, in turn, trapped intramolecularly by the nitrogen atom, to yield the double rearranged product **36**. The stereochemical result can be tentatively interpreted through species **38**, which suffers rearrangement to **39**, and the nucleophilic moiety being delivered from the less hindered face (Scheme 17). The strong preference for rearrangement of the five-membered ring in compounds **34** may be due to the increased stability of the newly formed carbocation.

Formation of monocyclic pyrrolidines **37** can be illustrated following Scheme 18. For monocyclic compounds **35** the XR group at C2 in the intermediate pyrrolidine **40** is eliminated to give an iminium salt **41**, the alkyl moiety being delivered from the organometallic reagent on the less hindered face at the iminium cation.

Reduction of 4-(haloalkyl)azetidin-2-ones **42** with chloroalane (AlH_2Cl) afforded 2-(haloalkyl)azetidines **43** in high yields. The latter compounds proved to be very useful starting materials for rearrangements toward stereospecifically defined five- and six-membered azaheterocycles, such as 3,4-*cis*-disubstituted pyrrolidines and piperidines (Scheme 19).[18] During these reactions bicyclic azetidinium intermediates were formed which were ring opened by nucleophiles. Attack of halide anion at the bridgehead carbon of this azetidinium salt **44** afforded *cis*-3-halo-4-alkoxy-pyrrolidines **45** or *cis*-3-alkoxy-4-halopiperidines **46**. Hereby, reactions proceeding via 1-azoniabicyclo[2.2.0]hexanes were reported for the first time.

Reduction of 2-azetidinones by metal hydrides to afford azetidines is not compatible with the presence of ester groups. It has been reported that reduction with diphenylsilane and catalytic amounts of tris(triphenylphosphine)rhodium(I) carbonyl hydrides resulted in an efficient, chemoselective method for the transformation of amino acid-derived β-lactams **47** into the corresponding azetidines **48**, which after

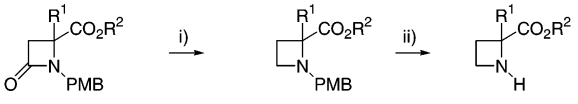
Scheme 19[a]



42 (R^1 = *t*-Bu, Bn, allyl, cyclohexyl; R^2 = Bn, Me; X = Cl, Br) **43** (57–95%) **44** **45** (44–46%) **46** (92–98%)

[a] Key: (i) AlH_2Cl, Et_2O, RT, 4 h. (ii) MeCN, reflux, 3−18 h.

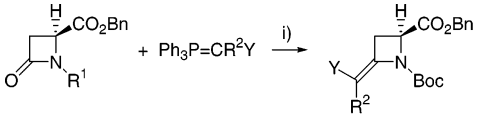
Scheme 20[a]



47a $R^1 = CH_2In$, R^2 = Me	**48a** (51%)	**49a** (70%)
47b $R^1 = (CH_2)_2CO_2t$-Bu, R^2 = *t*-Bu	**48b** (62%)	**49b** (55%)
(+)-(*S*)-47c R^1 = Bn, R^2 = Me	**(+)-(*S*)-48c** (94%)	**(−)-(*S*)-49c** (93%)
(−)-(*R*)-47c R^1 = Bn, R^2 = Me	**(−)-(*R*)-48c** (94%)	**(+)-(*R*)-49c** (93%)

[a] Key: In = indolyl; (i) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$, THF, RT; (ii) H_2, $Pd(OH)_2$.

Scheme 21[a]



(−)-50a R^1 = TBS	**(−)-51a** Y = CO_2Et, R^2 = H (80%)
(−)-50b R^1 = Boc	**(−)-51b** Y = CO_2t-Bu, R^2 = H (98%)
	(−)-51c Y = CN, R^2 = H (53%)
	(−)-51d Y = CO_2Et, R^2 = Me (50%)

[a] Key: (i) toluene, reflux, 4−48 h.

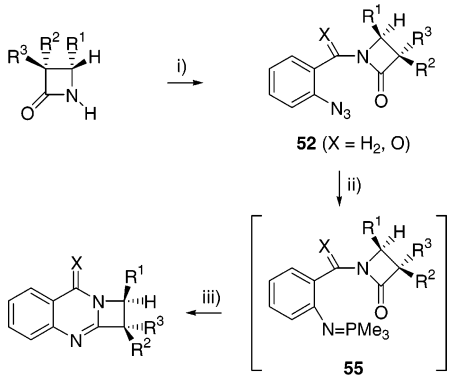
removal of the *p*-methoxybenzyl group by catalytic hydrogenation afforded a new family of conformationally restricted amino acids **49** (Scheme 20).[19] This reducing method is chemoselective with respect to carboxylic esters (Me, *t*-Bu) and urethane moieties (Boc).

β-Lactams **50** have been subjected to a range of Wittig reagents.[20] The *N*-*tert*-Butyldimethylsilyl 2-azetidinone **50a** was recovered unchanged from the reaction with the stabilized ylide (carbethoxymethylene)triphenylphosphorane. The Boc-activated compound **50b** was, however, smoothly converted to various substituted 2-exo-methylene azetidines **51** in fair yields when treated with stabilized ylides (Scheme 21). Compounds **51** were obtained as *E*-isomers without significant racemization. A more substituted ylide or substrate tends to lower the yields somewhat. Unstabilized ylides or Horner−Emmons reagents led only to decomposition of starting material.

2.2.2. Polycyclic Four-Membered Rings

In addition to the above-mentioned syntheses of azetidines from β-lactams, there is a different four-membered heterocyclic system that has been achieved from 2-azetidinones. Reaction of λ^5-phosphazenes (iminophosphoranes, phosphine imines) with carbonyl compounds affording the corresponding imination products is known as the aza-Wittig reaction. The intramolecular version of this reaction has drawn considerable attention because of its high potential in

Scheme 22[a]



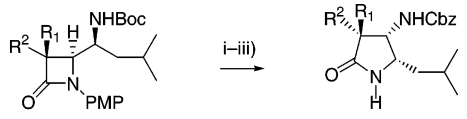
52 (X = H_2, O) **55**

53a X = H_2, R^1 = Ph, R^2 = H, R^3 = H (60%)
53b X = H_2, R^1 = 4-$NO_2C_6H_4$, R^2 = Ph, R^3 = Ph (84%)
53c X = H_2, R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = Me (40%)
54a X = O, R^1 = H, R^2 = H, R^3 = H (90%)
54b X = O, R^1 = Ph, R^2 = H, R^3 = H (88%)
54c X = O, R^1 = AcO, R^2 = H, R^3 = H (50%)

[a] Key: (i) 2-$N_3C_6H_4CH_2I$, K_2CO_3, MeCN, reflux, 20 h or 2-$N_3C_6H_4COCl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) PMe_3, toluene, RT, 10 min; (iii) toluene, reflux, 12−24 h.

heterocyclic synthesis. However, until recently there were no reported examples of successful aza-Wittig reactions involving the carbonyl group of a β-lactam ring. It has been described that the imination of the β-lactam carbonyl group by the aza-Wittig reaction is synthetically amenable when carried out intramolecularly using the reactive *P*,*P*,*P*-trimethyl-λ^5-phosphazenes as the imination reagents.[21] Conversion of compounds **52** to the corresponding azeto[2,1-b]quinazolines **53** (X = H_2) or quinazolin-8-ones **54** (X = O) was accomplished when a 1 M toluene solution of PMe_3 was used. Conversion of the azido group in **52** to the nonisolated *N*-aryl-*P*,*P*,*P*-trimethyl-λ^5-phosphazenes **55** (nitrogen evolution was observed) followed by refluxing of the resulting toluene solution under nitrogen for 12−24 h yielded the fused four-membered heterocycles **53** and **54** (Scheme 22). Due to the extreme hydrolytic susceptibility of the trimethylphosphazene group, strict anhydrous conditions were required for the success of these reactions, obtaining the corresponding benzo-fused bicyclic amidines **53** and **54** in variable yields (40−90%). In some cases the chromatographic purification of the reaction products caused oxidation of azeto[2,1-b]quinazolines **53** (X = H_2) to quinazolin-8-ones **54** (X = O), which occasionally makes isolation of pure tricycles **53** difficult. Attempts to carry out reactions similar to the ones summarized in Scheme 22 but intermolecularly by employment of several *N*-substituted (alkyl, acyl) β-lactam

Scheme 23[a]



(–)-56a R^1 = H, R^2 = Et — **(–)-57a** (55%)
(–)-56b R^1 = H, R^2 = $CH_2CH{=}CH_2$ — **(–)-57b** (48%)
(–)-56c R^1 = Me, R^2 = H — **(–)-57c** (60%)
(–)-56c R^1 = Et, R^2 = H — **(–)-57d** (40%)

[a] Key: (i) $(NH_4)_2Ce(NO_3)_6$, MeCN−H_2O, 0−5 °C; (ii) $ClSiMe_3$, MeOH, reflux; (iii) CbzCl, Et_3N,CH_2Cl_2, RT.

and the phosphazenes $PCH_2N{=}PMe_3$ and $PCON{=}PMe_3$ (generated in situ from the azides and PMe_3) failed. Other intramolecular attempts starting from aryl azides leading to five-membered aza rings or alkyl azides resulted in failure.

2.3. Five-Membered Heterocycles

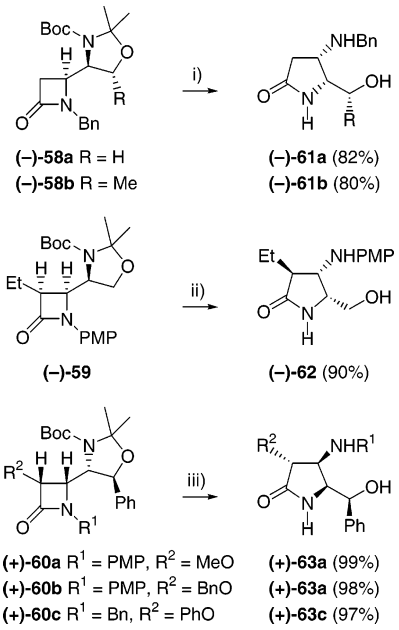
2.3.1. Monocyclic Five-Membered Rings

Highly substituted lactam rings possess different biological activity, and much recent attention has focused on excitatory amino acid chemistry, particularly as a result of the drive to better understand central nervous system (CNS) function in mammalian systems.[22] It has recently also been shown that densely functionalized pyrrolidinones, such as lactacystin[23] and pramamicin,[24] exhibit potent and selective activity in proteasome inactivation and may find application in the development of selective therapeutic agents for important parasitic infections.[25] In addition, the pyrrolidinone (γ-lactam) functionality is a prevalent theme in various natural product syntheses and serves as a crucial intermediate for numerous natural products. β-Lactams have been used as well as precursors of highly substituted monocyclic pyrrolidin-2-ones. The asymmetric synthesis of β-lactams of type **56** has been afforded via the Staudinger reaction of *N*-Boc L-serinal acetonide derived imines. Oxidative *N*-dearylation of 2-azetidinones **56** followed by further rearrangement of the resulting *N*-unsubstituted 4-(α-aminoalkyl) β-lactam under slightly acidic conditions led to formation of the corresponding 4-(α-aminoalkyl) γ-lactams. The crude compounds were transformed into their Cbz derivatives **57** and isolated by column chromatography in good overall yields (Scheme 23).[26]

The potential scope of the above methodology is further exemplified in the stereocontrolled synthesis of 3,5-dialkyl- and 3,4,5-trialkyl-4-aminopyrrolidinones from Garner's aldehyde-derived azetidinones. 4-(α-Aminoalkyl) β-lactams **58**−**60** treated with alcoholic hydrochloric acid smoothly produced 2-pyrrolidinones **61**−**63** (Scheme 24).[26,27]

A synthesis of optically pure densely functionalized γ-lactams starting from 2-azetidinone-tethered iminophosphoranes has been developed.[28] Full chirality transfer has been accomplished from the enantiomerically pure 2-azetidinones. Starting substrates, enantiopure 4-oxoazetidine-2-carbaldehydes **64**, were obtained as single cis enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde through the Staudinger reaction with the appropriate alkoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage. Addition of lithium acetylides to 4-oxoazetidine-2-carbaldehydes **64** at −78 °C smoothly yielded propargylic alcohols with excellent diastereoselectivities. Propargylic alcohols were converted to mesylates, which by reaction with sodium azide afforded the corresponding azides **65**. Treatment of β-lactams bearing an azido side chain with triphenylphosphine (TPP) gave λ^5-phosphazenes (iminophosphoranes, phosphine imines) **66**, which were not isolated. The sodium methoxide-promoted reaction of the phosphazene β-lactams smoothly provided γ-lactams **67** (Scheme 25).

Scheme 24[a]



(–)-58a R = H — **(–)-61a** (82%)
(–)-58b R = Me — **(–)-61b** (80%)
(–)-59 — **(–)-62** (90%)
(+)-60a R^1 = PMP, R^2 = MeO — **(+)-63a** (99%)
(+)-60b R^1 = PMP, R^2 = BnO — **(+)-63a** (98%)
(+)-60c R^1 = Bn, R^2 = PhO — **(+)-63c** (97%)

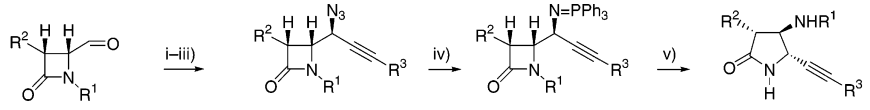
[a] Key: (i) 6 N HCl, ethanol, reflux, 48 h; (ii) 12 N HCl, ethanol, reflux, 48 h; (iii) 3 N HCl, methanol, 60 °C, 2−24 h.

From a mechanistic point of view, these results could be explained through a bond-breakage process on the four-membered lactam with concomitant ring expansion followed by hydrolysis. Initially, the selective N1−C2 bond cleavage of the β-lactam nucleus in 2-azetidinone-tethered iminophosphoranes **66** gave the nonisolable β-amino-γ-phosphine imino esters **68**, which after rearrangement under the reaction conditions followed by hydrolysis of the phosphonium salts **69** yielded the γ-lactams **67** (Scheme 26). The pyrrolidinone formation must be driven by relief of the strain associated with the four-membered ring on forming a more stable five-membered ring. Azacycles **67** showed a single set of signals in their ^{1}H NMR spectra, thus proving that this transformation proceeded without detectable epimerization.

N-Benzyl-4-phenyl-2-azetidinones **70** have been used to prepare γ-lactams **71** by lateral chain incorporation in a ring-expansion process (Scheme 27).[29] The anti products were obtained exclusively. The bulkiness of the two phenyl substituents may control the stereochemistry to get the γ-lactam with high diastereoselectivity. When the effect of substitution at the C4 position in the starting material was explored, no reaction was observed with β-lactams **70b** and **70c**.

The proposed expansion mechanism proceeds via a benzylic anion intermediate **72**, which suffers rearrangement to give the imine ion **73** (which is stabilized by resonance) to release the ring strain of the small four-membered ring. Probably, the observed absence of reaction for substrates **70b** and **70c** is due to the lack of any resonance as in **73** (induced by the phenyl group). Finally, a Michael-type reaction occurs for the ring closure to give the more stable *anti*-γ-lactams **71** (Scheme 28).

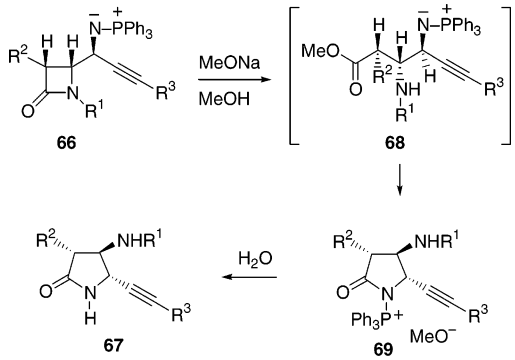
Scheme 25[a]



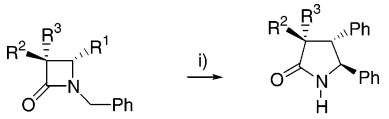
(+)-64a R^1 = PMP, R^2 = OPh	**(+)-65a**, R^3 = Ph (63%)	**(+)-66a**	**(+)-67a**, R^3 = Ph (61%)
(+)-64a R^1 = PMP, R^2 = OPh	**(+)-65b**, R^3 = TMS (71%)	**(+)-66b**	**(+)-67b**, R^3 = H (60%)
(+)-64b R^1 = allyl, R^2 = OPh	**(+)-65c**, R^3 = Ph (45%)	**(+)-66c**	**(+)-67c**, R^3 = Ph (61%)
(+)-64b R^1 = allyl, R^2 = OPh	**(+)-65d**, R^3 = TMS (38%)	**(+)-66d**	**(−)-67d**, R^3 = H (51%)
(+)-64c R^1 = PMP, R^2 = OBn	**(+)-65e**, R^3 = Ph (51%)	**(+)-66e**	**(+)-67e**, R^3 = Ph (60%)
(+)-64d R^1 = PMP, R^2 = OMe	**(+)-65f**, R^3 = Ph (37%)	**(+)-66f**	**(+)-67f**, R^3 = Ph (62%)
(+)-64d R^1 = PMP, R^2 = OMe	**(+)-65g**, R^3 = TMS (40%)	**(+)-66g**	**(+)-67g**, R^3 = H (49%)

[a] Key: (i) phenyl- or trimethylsilyl acetylene, *n*BuLi, THF, −78 °C, 4 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (iii) N_3Na, DMF, RT, 18 h; (iv) PPh_3, CH_2Cl_2, 0 °C, 3 h; (v) MeONa, methanol, RT, 2 h, then H_2O.

Scheme 26



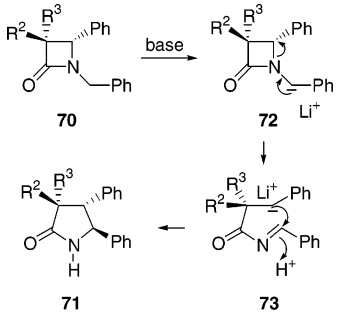
Scheme 27[a]



70a R^1 = Ph, R^2 = R^3 = H	**71a** (87%)[a]
70b R^1 = Me, R^2 = R^3 = H	**71b** (0%)
70c R^1 = H, R^2 = R^3 = H	**71c** (0%)
70d R^1 = Ph, R^2 = R^3 = Ph	**71d** (65%)
70e R^1 = Ph, R^2 = R^3 = Me	**71e** (67%)
70f R^1 = Ph, R^2 = Ph, R^3 = H	**71f** (72%)
70g R^1 = Ph, R^2 = Me, R^3 = H	**71g** (71%)

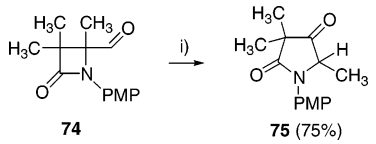
[a] Key: (i) LDA, THF, RT, 5 h; *n*BuLi, THF, −78 °C, 30 min.

Scheme 28



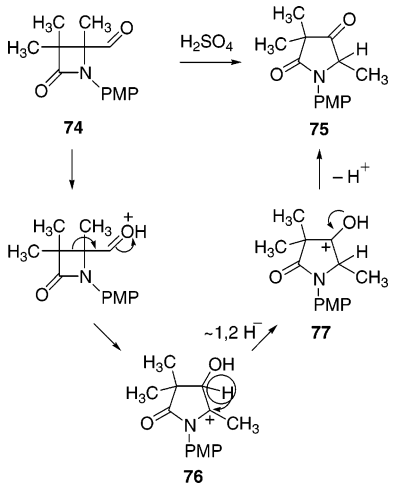
Treatment of 4-oxoazetidine-2-carbaldehyde **74** with concentrated sulfuric acid gives in 75% yield a product whose spectroscopic and analytical data are in good accordance with the structure of γ-lactam **75** (Scheme 29).[30] A C3−C4 bond breakage, through the initial shift of the C3−C4 bond to the protonated aldehyde group to give the five-membered ring carbocationic intermediate **76**, has been proposed to occur. A 1,2-hydride shift to form intermediate **77** followed by loss of a proton would give **76** (Scheme 30).

Scheme 29[a]

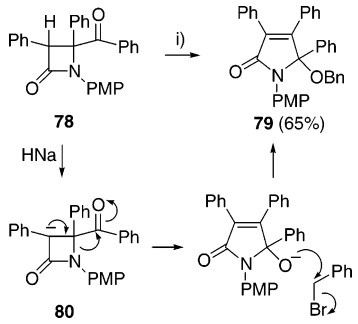


[a] Key: (i) H_2SO_4, $CHCl_3$, RT, 8 h.

Scheme 30



Scheme 31[a]

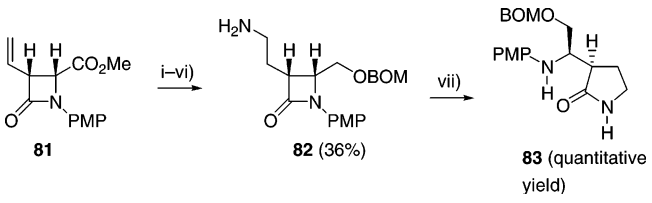


[a] Key: (i) HNa, DMF, 0 °C, then BnCl, RT.

It has been found that 4-benzoyl-2-azetidinone **78** can be transformed by treatment with sodium hydride/benzyl halide into γ-lactam **79**. This transformation could be explained via a C4−N1 bond breakage in the intermediate carbanion **80** followed by *O*-benzylation under the reaction conditions (Scheme 31).[31]

3-Vinyl-β-lactam **81** has been transformed into γ-lactam **83** using as key step the transamidation of amino β-lactam **82**. The 4-methoxycarbonyl-2-azetidinone **81** was reduced with calcium borohydride in good yield, protected as the BOM ether, and hydroborated with 9-BBN to give the

Scheme 32[a]



[a] Key: (i) $Ca(BH_4)_2$, THF−EtOH, RT; (ii) BOMCl, EtN*i*-Pr_2, RT; (iii) 9-BBN, THF, RT, then $KHCO_3$, H_2O_2; (iv) MsCl, Et_3N, CH_2Cl_2, −30 °C; (v) N_3Na, DMF, 55 °C; (vi) PPh_3, THF−H_2O, RT; (vii) EtOH, 60 °C.

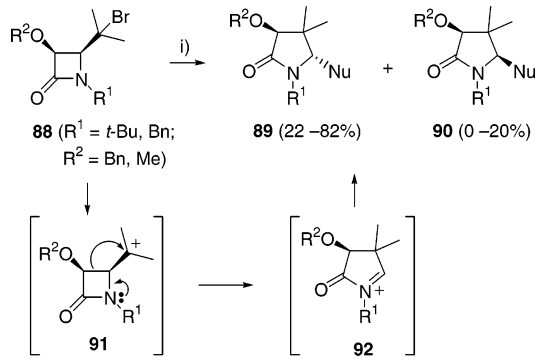
corresponding alcohol, which was finally converted into the rearrangement precursor, 2-azetidinone-tethered amine **82** (Scheme 32).[32]

3-Allyl-β-lactam **84** has been converted to the amino β-lactam **85**, which was rearranged to γ-lactam **86**,[33] a key intermediate in the preparation of the antibiotic premafloxacin **87**. Ozonolytic cleavage of the double bond followed by reduction of the resulting unstable aldehyde with $NaBH_4$ gave the corresponding alcohol, which was activated as the mesylate and displaced with benzylamine to yield 2-azetidinone **85**. Complete conversion of amino β-lactam **85** to pyrrolidinone **86** was accomplished in toluene at 85 °C in 90% yield (Scheme 33). No epimerization occurred under these conditions. When this reaction was carried out under basic conditions with LDA at −50 °C in THF epimerization occurred at the α-carbon. The transamidation could, however, be carried out under acidic conditions (AcOH, MeOH, 60 °C, 4 h) without epimerization.

The diastereoselective synthesis of highly functionalized γ-lactams starting from 4-(1-bromoalkyl)-2-azetidinones via *N*-acyliminium intermediates has been described.[34] The carbenium ions, formed by dissociation of bromide from 4-(1-bromoalkyl)-2-azetidinones **88** in polar medium, are converted via a ring expansion toward *N*-acyliminium ions, which are susceptible to attack of oxygen, nitrogen, and carbon nucleophiles. In this way, a variety of 5-hydroxy-, 5-alkoxy-, 5-cyano-, 5-allylamino-, and 5-azido-4,4-dimethyl-2-pyrrolidinones **89** and **90** were synthesized (Scheme 34). It was found that dehydrobromination of 4-(1-bromoalkyl)-2-azetidinones constituted an important side reaction when the title reactions were carried out in DMSO. When THF was used as a solvent, generally no dehydrobromination was observed, implying that higher yields of γ-lactams were obtained in THF compared to reactions performed in DMSO. The results shown in Scheme 34 suggest a reaction mechanism in which dissociation of the bromide gives rise to formation of a tertiary carbenium ion **91**, which is stabilized by an intramolecular rearrangement via opening of the C3−C4 bond toward formation of a more stable *N*-acyliminium ion **92**. This additional stability can be explained by the relief of ring strain and the fact that the positive charge is located in a polycentric molecular orbital in the case of the *N*-acyliminium ion **92**. Since the ring is flat, addition of a nucleophile to the *N*-acyliminium ion **92** is only directed by the alkoxy substituent. Therefore, attack of the nucleophile on intermediate **92** is favored at the opposite side of the alkoxy group to obtain the more stable trans stereoisomer **89**. This compound appears as the major compound in addition to the other minor stereoisomer *cis*-γ-lactam **90** (Scheme 34). It has to be noted that next to this kinetic approach, formation of *cis*- and *trans*-γ-lactams is also thermodynamically determined. Indeed, substituents of the 4-(1-bromoalkyl)-2-azetidinones play an important role concerning the obtained diastereoselectivity. Thus, the greater steric hindrance of the benzyloxy group compared to that of the methoxy group directed the attack of the nucleophile even more into a trans stereochemistry.

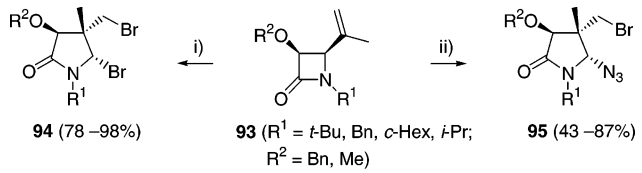
Starting from 3,4-*cis*-4-isopropenylazetidin-2-ones a new synthesis of pyrrolidin-2-ones was achieved (Scheme 35).[35]

Scheme 34[a]



[a] Key: (i) NuH, THF or DMSO, RT or 70 °C, 18 h. Nu = OH, MeO, N_3; CH_2 = $CHCH_2N$, CN.

Scheme 35[a]

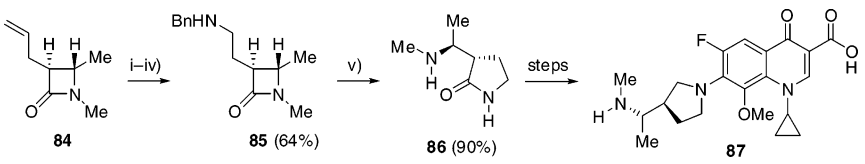


[a] Key: (i) Br_2, CH_2Cl_2, 0 °C, 30 s; (ii) NBS, $TMSN_3$, CH_2Cl_2–$MeNO_2$ (3:1), RT, 18 h.

When 4-isopropenylazetidin-2-ones **93** were treated with bromine in dichloromethane, diastereoselective electrophile-induced ring expansions toward 5-bromopyrrolidin-2-ones **94** were performed. When 4-isopropenyl-β-lactams were added to a mixture of NBS and $TMSN_3$, 5-azidopyrrolidin-2-ones **95** were obtained in moderate to high yields. These findings in the chemistry of 2-azetidinones emphasize the synthetic potential of diastereoselective ring expansions of β-lactams toward γ-lactams.

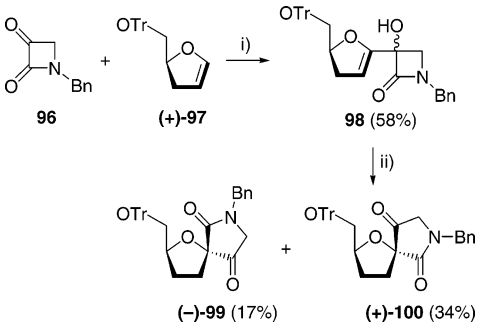
Azetidine-2,3-dione **96** and trityl dihydrofuran **97** have been used as starting materials for production of spirocyclic γ-lactams.[36] Oxacycle **97** was metalated at C5 by exposure to *tert*-butyllithium at low temperature. Condensing this reactive lithium intermediate with azetidine-2,3-dione **96** afforded the 3-hydroxy-3-substituted β-lactam **98**. In test

Scheme 33[a]



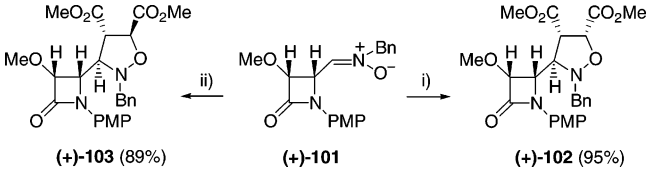
[a] Key: (i) O_3, H_2O, 0 °C; (ii) $NaBH_4$, then CH_2Cl_2 extraction; (iii) MsCl, Et_3N, THF; (iv) $BnNH_2$, 55 °C; (v) toluene, reflux, 3 h.

Scheme 36[a]



[a] Key: (i) *t*-BuLi, −78 °C, THF, then BF_3·OEt_2; (ii) PPTS, benzene, 20 °C, 24 h.

Scheme 37[a]

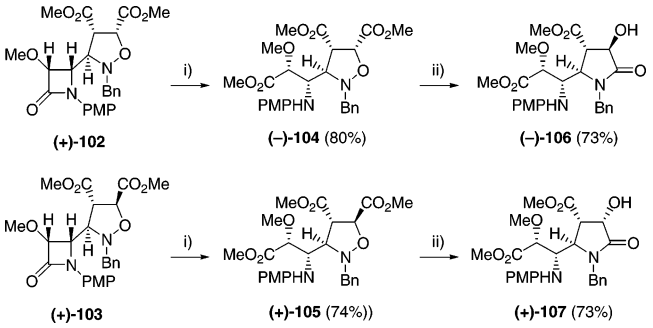


[a] Key: (i) dimethyl maleate, toluene, 110 °C; (ii) dimethyl fumarate, toluene, 110 °C.

experiments, it was discovered that β-lactam **96** exhibits a reasonably high tendency for simple enolization in the presence of cycloalkenyllithium reagents. The best conditions found for curtailing this unwanted side reaction involved precomplexation of **96** with an equivalent of boron trifluoride etherate. This modification afforded hydroxy β-lactam **98** in 58% yield as an inseparable mixture (1:1) of diastereomers. When solutions of **98** in benzene-containing pyridinium *p*-toluenesulfonate were stirred at 20 °C for 24 h, the two chromatographically separable lactams **99** and **100** were formed (Scheme 36). Ring expansion proceeds exclusively with migration of the carbonyl carbon.

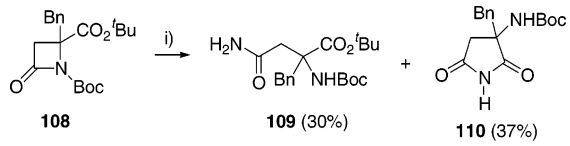
2-Azetidinone-tethered nitrone **101** was smoothly prepared by condensation of the corresponding 4-oxoazetidine-2-carbaldehyde with *N*-benzylhydroxylamine in benzene at room temperature in the presence of triethylamine. Nitrone **101** was obtained in almost quantitative yield and used for the next step without further purification. On treatment of 2-azetidinone-tethered nitrone **101** with acyclic diactivated dipolarophiles such as dimethyl fumarate or dimethyl maleate under argon atmosphere in toluene at 110 °C a smooth 1,3-dipolar cycloaddition reaction took place to give isoxazolidines **102** and **103** in a total diastereoselective manner (Scheme 37). *N,O*-Heterocycle-substituted β-lactams **102** and **103** were identified as precursors of highly functionalized β-alkoxycarbonyl γ-lactams (aza analogues of the natural product paraconic acid). First, molybdenum hexacarbonyl was tested as a reagent for the reductive ring opening of isoxazolidine derivatives **102** and **103**. However, no reaction was observed. Selective 2-azetidinone ring opening on adducts **102** and **103** to give isoxazolidinyl-β-aminoesters **104** and **105** was achieved when the reaction was conducted in methanol at reflux temperature under 37% aqueous hydrochloric acid catalysis. Reductive ring opening/lactamization in compounds **104** and **105** by use of molybdenum hexacarbonyl afforded as the only isomers highly substituted γ-lactams **106** and **107** (Scheme 38).[37] Formation of γ-lactams **106** and **107** involves a N−O bond cleavage at the five-membered ring followed by a selective rearrangement under the reaction conditions.

Scheme 38[a]



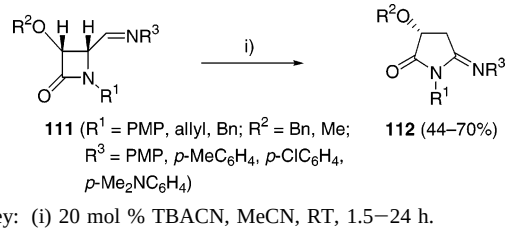
[a] Key: (i) HCl (conc), methanol, 65 °C, 8 h; (ii) $Mo(CO)_6$, MeCN, reflux, 4 h.

Scheme 39[a]



[a] Key: (i) dilute NH_3/MeOH, RT, 10 min.

Scheme 40[a]



[a] Key: (i) 20 mol % TBACN, MeCN, RT, 1.5−24 h.

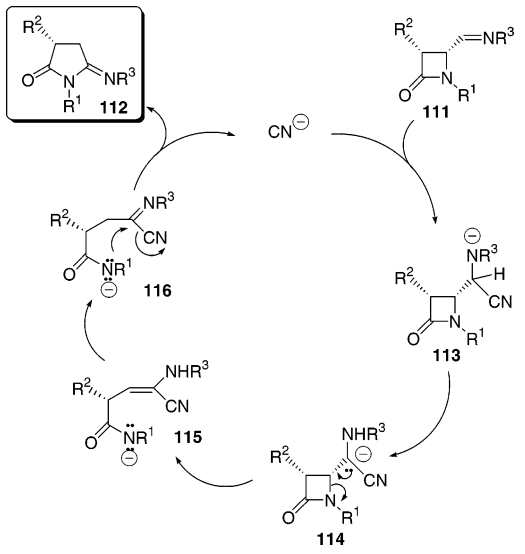
3-Heterosubstituted succinimides and derivatives are an important class of heterocyclic compounds with numerous pharmacological applications in different fields. The ring opening of 2-azetidinone **108** by dilute NH_3/MeOH solution gave a mixture of the α-alkyl asparagine derivative **109** and the succinimide **110** (Scheme 39).[38] Generation of aspartimide **110** could be explained by cyclization of the acyclic derivative **109** in the basic reaction medium.

It has been reported that tetrabutylammonium cyanide catalyzes ring expansion of 4-(arylimino)methyl-azetidin-2-ones **111** to 5-arylimino-pyrrolidin-2-ones **112** through a novel N1−C4 bond cleavage of the β-lactam nucleus (Scheme 40).[39] The presence of a bulky R^2 group decreased the rate of ring expansion. A dramatic effect on the reactivity was observed with imines derived from aliphatic amines because no conversion was observed on catalytic conditions.

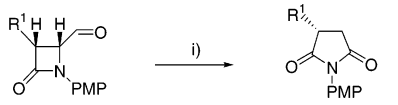
The catalytic cycle shown in Scheme 41has been proposed to account for the new ring expansion. Under the reaction conditions, nucleophilic addition of cyanide to the imino group will form species **113** which will evolve into the corresponding α-cyano carbanion **114**. Intermediate **114** is then converted into the imino nitrile amide **116** via the corresponding enamino nitrile **115** formed by N1−C4 β-lactam bond breakage. This process should be favored for aromatic R^3 groups. Finally, anionic cyclization on the imino group with concurrent cyanide elimination should afford the iminopyrrolidin-2-one **112**.

A new one-pot procedure for obtaining enantiopure pyrrolidin-2,5-diones from β-lactam aldehydes was also developed.[39] Thus, the reaction mixture obtained by sequential treatment of compound (+)-**64d** with *p*-anisidine and a catalytic (20 mol %) amount of tetrabutylammonium cyanide

Scheme 41



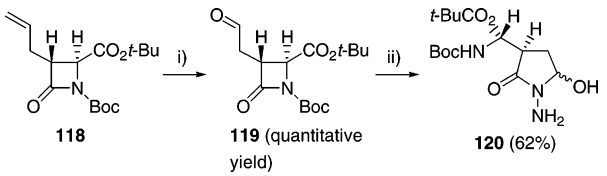
Scheme 42[a]



(+)-**64d** R^1 = OMe — (+)-**117a** (55%)
(+)-**64c** R^1 = OBn — (+)-**117b** (50%)

[a] Key: (i) (a) $PMPNH_2$, MeCN, molecular sieves (4 Å), Δ, 4 h; (b) 20 mol % TBACN, MeCN, RT, 2 h; (c) 20% aq HCl, RT, 4.5 h.

Scheme 43[a]



118 — **119** (quantitative yield) — **120** (62%)

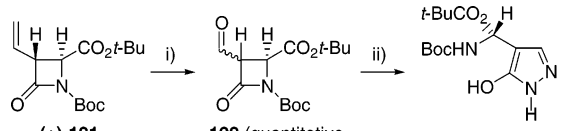
[a] Key: (i) O_3, CH_2Cl_2, −78 °C, 20 min, then Me_2S; (ii) NH_2NH_2, methanol, RT, 24 h.

(TBACN) in acetonitrile was hydrolyzed in situ with aqueous HCl. The overall yield of compound (+)-**117a** for the one-pot method was 55%. This yield represents a one-pot, three-step process involving imine formation, catalytic ring expansion, and selective imine hydrolysis. Analogous results were observed in the preparation of succinimide (+)-**117b** from aldehyde (+)-**64c** (Scheme 42).

When the aldehyde **119**, prepared from alkene-β-lactam **118** by ozonolysis using dimethyl sulfide as reducing agent, was reacted directly with hydrazine hydrate in methanol at room temperature the epimeric hydroxypyrrolidinones **120** were produced in 62% yield, which are structurally similar to the natural product dealanylalahopcin (Scheme 43).[40]

The vinyl-β-lactam urethane **121** suffers ozonolysis to give aldehyde **122** in a cis:trans ratio of 1:9, irrespective of the cis:trans ratio of the olefinic starting material. The aldehyde **122** was used directly in the next step without further purification due to its instability. When aldehyde **122** was treated with hydrazine in methanol at room temperature, as in Scheme 44, the imidazolylglycine **123** was obtained as a white solid in 75% yield.[40] The imidazole formation can be explained by initial hydrazone generation followed by rearrangement to the five-membered ring. Reaction of the aldehyde **122** with hydroxylamine, however, gave no recognizable products.

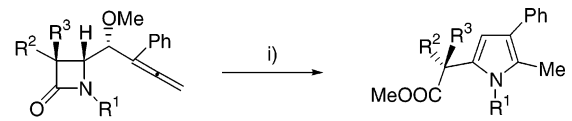
Scheme 44[a]



(+)-**121** — **122** (quantitative yield) — (+)-**123** (75%)

[a] Key: (i) O_3, CH_2Cl_2, −78 °C, 20 min, then Me_2S; (ii) NH_2NH_2, methanol, RT, 11 h.

Scheme 45[a]



(+)-**124a** R^1 = PMP, R^2 = MeO, R^3 = H — (−)-**125a** (77%)
(+)-**124b** R^1 = PMP, R^2 = PhO, R^3 = H — (−)-**125b** (50%)
(−)-**124c** R^1 = allyl, R^2 = MeO, R^3 = H — (−)-**125c** (50%)
(±)-**124d** R^1 = PMP, R^2 = Me, R^3 = H — (±)-**125d** (54%)
(+)-**124e** R^1 = PMP, R^2 = MeO, R^3 = allyl — (−)-**125e** (53%)

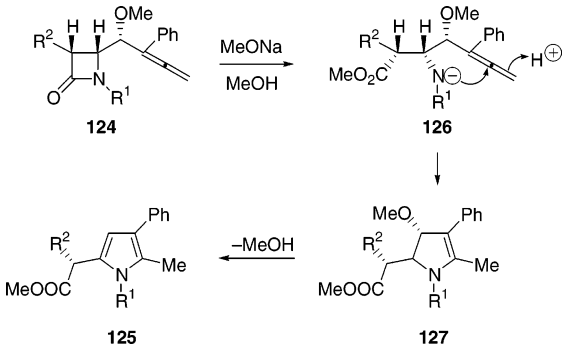
[a] Key: (i) MeONa, MeOH, RT, 8−96 h.

Of the various synthetic and naturally occurring heterocyclic structures, the pyrrole nucleus is among the most prevalent because of its remarkable pharmacological activities. During the search for a suitable protocol for the preparation of enantiopure β-allenamines an unexpected and interesting formation of highly functionalized enantiopure pyrrole derivatives was discovered. Precursors for the pyrrole formation, allenes **124** and **128**, were made starting from the appropriate 4-oxoazetidine-2-carbaldehyde or azetidine-2,3-dione via indium-mediated Barbier-type carbonyl−allenylation reaction with (3-bromoprop-1-ynyl)benzene in aqueous media. Reactions of a variety of β-lactam allenic ethers **124** with sodium methoxide in methanol at room temperature gave 1,2,3,5-tetrasubstituted pyrroles **125** in reasonable isolated yields without the need for a transition-metal catalyst.[41] No other regioisomers were observed in all cases. Typical results are shown in Scheme 45. Although complete conversion was observed by TLC and ^1H NMR analysis of the crude reaction mixtures, some decomposition was observed on sensitive pyrroles **125a**−**e** during purification by flash chromatography, which may be responsible for the moderate isolated yields.

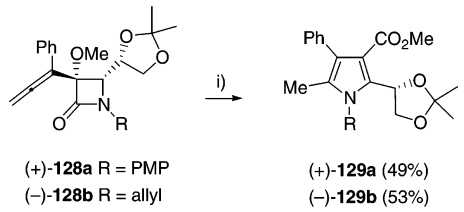
From a mechanistic point of view, the domino sequence could be explained through a bond-breakage process on the four-membered lactam followed by allene cyclization with concomitant aromatization. The selective N1−C2 bond cleavage of the β-lactam nucleus in 2-azetidinone-tethered allenes **124** gave the nonisolable allenic-β-amino ester sodium salts **126**, which after a totally regioselective cyclization onto the central allene carbon under the reaction conditions followed by aromatization of the pyrrolines **127** yielded the pyrroles **125** (Scheme 46). Pyrrole formation is driven by releasing the strain associated with the four-membered ring on forming a more stable five-membered ring.

The influence of the position of the allene moiety at the β-lactam ring for the one-pot synthesis of the pyrrole nucleus was investigated by stirring quaternary allenic ethers **128** for 48 h in a mixture of MeONa in MeOH at room temperature. After workup, the starting materials were recovered. Only after heating at reflux temperature did the β-lactam α-allenic ethers **128** react to form the corresponding

Scheme 46

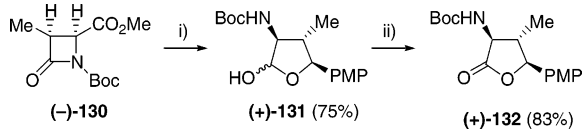


Scheme 47[a]



[a] Key: (i) MeONa, MeOH, reflux, 6−12 h.

Scheme 48[a]



[a] Key: (i) (a) 4-MeOC$_5$H$_4$MgBr, THF, −40 °C, 1 h; (b) L-Selectride, THF, −78 °C, 1 h; (ii) nicotinic acid, CrO_3, pyridine, toluene, RT, 4 h.

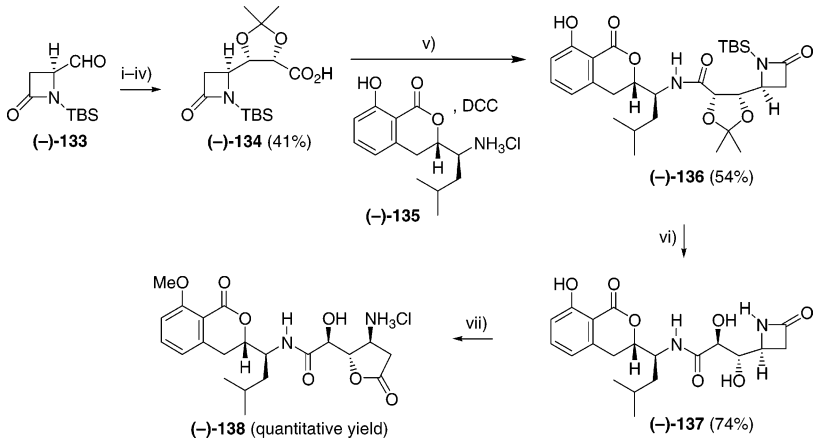
heterocycles.[41] New pentasubstituted pyrroles **129** were obtained in fair yields by means of the above metal-free procedure without the concomitant formation of any regioisomer (Scheme 47).

The cyclized form of the *N*-terminal amino acid residue found in the antibiotic family of nikkomycins has been prepared in enantiopure form starting from the 2-azetidinone **130**. Ring opening of β-lactam **130** with a Grignard reagent led to the corresponding β-amino ketone, which after L-Selectride reduction provided aminolactol **131**. Aminolactone **132** was smoothly obtained by oxidation of the lactol **131** with a chromium(VI) reagent (Scheme 48).[42]

Synthesis of the natural compound amicoumacin C **138** has been described.[43] Condensation of benzyl bis(trifluoroethyl) phosphonoacetate with 4-oxoazetidine-2-carbaldehyde **133** was achieved using potassium carbonate in the presence of 18-crown-6 and gave the corresponding (*Z*)-benzyl ester together with its (*E*)-isomer, ratio ca. 85:15. Hydroxylation of the (*Z*)-ester using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide gave the vicinal diols (ratio 80:20), and protection using 2,2-dimethoxypropane followed by hydrogenolysis gave an excellent yield of the β-lactam acid **134**. The amino-δ-lactone hydrochloride salt **135** was coupled with acid **134** using dicyclohexylcarbodiimide and 4-dimethylaminopyridine to give the amide **136**. To get a consistent yield (54%) for this reaction it was necessary to use redistilled dicyclohexylcarbodiimide and recrystallized 4-dimethylaminopyridine. Other coupling procedures, e.g., using mixed anhydrides, were less successful. Deprotection under acidic conditions followed by a sodium bicarbonate workup gave a product identified as the dihydroalkylazetidinone **137**. Treatment of the β-lactam **137** with sodium hydroxide followed by acidic methanol then gave the natural amicoumacin C **138** bearing both a δ-lactone as well as an amino-γ-lactone hydrochloride salt moieties (Scheme 49).[43] Presumably in this conversion of the azetidinone **137** into the bis-lactone **138** both the δ-lactone and the β-lactam are being cleaved by sodium hydroxide with bis-lactonization occurring on treatment with acid. No attempt was made to open the azetidinone selectively.

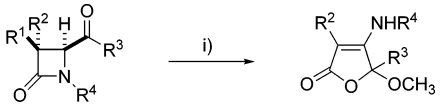
Enaminones derived from tetronic acid are valuable synthetic intermediates for construction of biologically active nitrogen heterocycles through aza-annulation reactions with acrylate derivatives. It has been stated that reaction of β-lactams **139** with Na_2CO_3 in methanol gave cyclic enaminones **140** (Scheme 50).[44] To explore the scope of this new reaction a set of different substituted 2-azetidinones **139**, having both an acyl group at position 4 and at least one leaving group on position 3 of the β-lactam ring as a structural requirement, were prepared. Thus, reaction of compounds **139** with Na_2CO_3 in methanol at room temperature after a few hours of reaction smoothly gave the corresponding substituted cyclic enaminones **140**. Pure compounds **140** were isolated in good to excellent yields (70−85%) by flash chromatography, but some decomposition was observed for the sensitive *N*-propargyl enaminone during

Scheme 49[a]



[a] Key: (i) $(F_3CCH_2O)_2P(O)CH_2CO_2Bn$, K_2CO_3, 18-crown-6, toluene, 0 °C, 1 h; (ii) OsO_4, NMO, acetone−H_2O, RT, 3 days; (iii) $Me_2C(OMe)_2$, PTSA, $CHCl_3$, RT, 18 h; (iv) H_2, Pd−C, EtOH, RT, 18 h; (v) DCC, DMAP, CH_2Cl_2, RT, 18 h; (vi) 1:1 aq HCl (3 M)−THF, RT, 6 h; (vii) NaOH, pH 12, EtOH−H_2O, 18 h, then HCl (3 M), MeOH, 0 °C, 2 h.

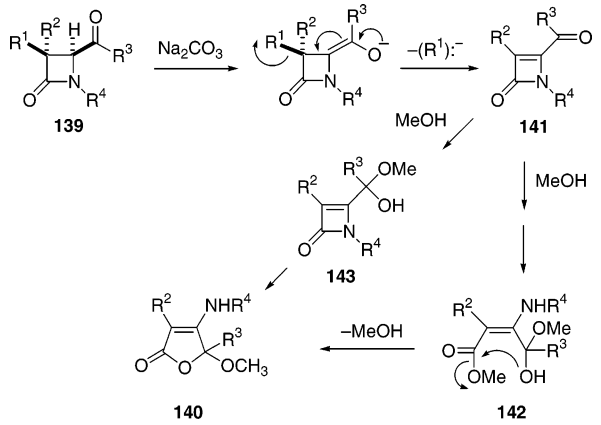
Scheme 50[a]



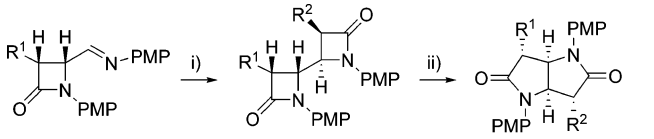
139a R^1 = Br, R^2 = Et, R^3 = H, R^4 = PMP **140a** (85%)
139b R^1 = Cl, R^2 = Me, R^3 = H, R^4 = PMP **140b** (76%)
139c R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = PMP **140c** (80%)
139d R^1 = PhO, R^2 = H, R^3 = Me, R^4 = PMP **140d** (80%)
139e R^1 = PhO, R^2 = H, R^3 = Ph, R^4 = PMP **140e** (70%)
139f R^1 = PhO, R^2 = H, R^3 = H, R^4 = PMP **140f** (80%)
139g R^1 = BnO, R^2 = H, R^3 = H, R^4 = PMP **140g** (80%)

[a] Key: (i) Na_2CO_3, MeOH, RT, 1.5−48 h.

Scheme 51



Scheme 52[a]



(+)-144a R^1 = BnO **(+)-145a** R^2 = AcO (80%) **(–)-146a** R^2 = OH (85%)
(+)-144b R^1 = BnO **(+)-145b** R^2 = Pht (80%) **(+)-146b** R^2 = Pht (65%)
144c R^1 = *i*-Pr **145c** R^2 = BnO (85%) **146c** R^2 = BnO (85%)

[a] Key: (i) R^2CH_2COCl, Et_3N, toluene, RT, 16 h; (ii) MeONa, MeOH, RT, 4−12 h.

purification. The above results strongly suggest that an acyl group able to stabilize a negative charge at the C4 position and a good leaving group on C3 are necessary for the process to occur.

Formation of compounds **140** may be rationalized through a tandem E1cB-elimination−rearrangement process of the enolate generated initially followed by ring opening of the resulting highly strained 2-azetinones **141**, as shown in Scheme 51. Further intramolecular transesterification of the resulting hemiacetal enaminoester **142** gives final enamine lactone **140**. An alternative reaction pathway involves addition of methanol to intermediate **141** and further lactonization of the resulting hemiacetal **143** to give enaminone **140**.

2.3.2. Polycyclic Five-Membered Rings

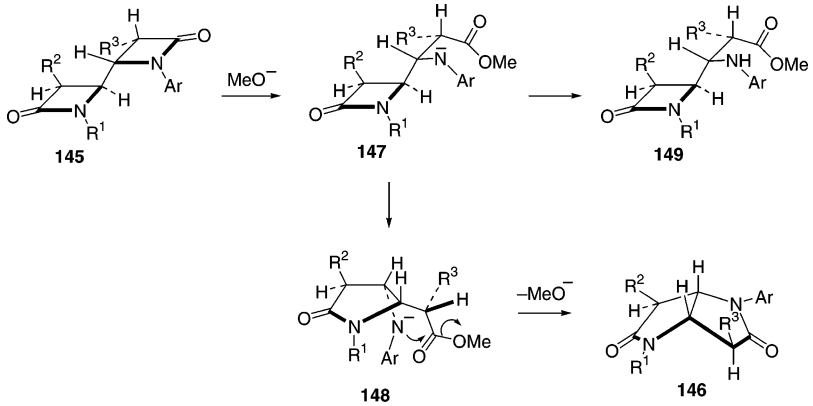
Bis-γ-lactams have interesting biological activities. These compounds may be regarded as analogs of aminosugars, namely, aminoglycaric acids with an idaric acid structure. Routes to prepare fused bis-γ-lactams in both racemic and optically pure forms have been developed starting from imino-β-lactams **144**, which were prepared through condensation of the appropriate 4-oxoazetidine-2-carbaldehyde with *p*-anisidine. Ketene cycloaddition allowed the synthesis of differently substituted *cis,cis*-C4,C4′-bis-β-lactams **145**, which were obtained in all cases as a single diastereoisomer. Bis-β-lactams **145** smoothly rearranged to fused *trans,trans*-bis-γ-lactams **146** upon basic treatment (NaOMe/MeOH) in a totally stereoselective process (Scheme 52).[45]

A reaction pathway has been proposed for formation of bis-γ-lactams **146**. Amide bond breakage of bis-β-lactams **145** by MeO^- would form the monocyclic 2-azetidinone anion **147**. Intermediate **147** would then either cyclize to the final products **146** by intramolecular ring opening to monocyclic γ-lactams **148** followed by ring closure or end up as monolactams **149**. This is the case when alkyl groups are attached to one of the lactam nitrogens in the starting material (Scheme 53). Aromatic groups decreasing the amide resonance in the β-lactam ring are needed for intermediate **147** to be produced. Only C4,C4′-bis-β-lactams having a *cis,cis*-stereochemistry or *trans,cis*-stereochemistry show a bias for this rearrangement. Placing two bulky groups on the concave face of the bis-γ-lactam molecule (the stereochemistry resulting from rearrangement of a *trans,trans*-C4,C4′-bis-β-lactam) seems unfeasible.

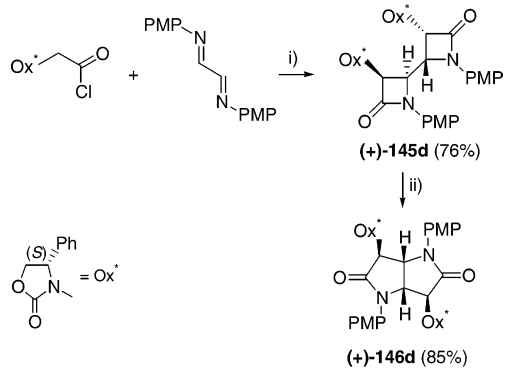
Alternatively to the above stepwise sequence from imino-β-lactams, preparation of fused bis-γ-lactams was achieved starting from glyoxal diimines through 1,4-diaza 1,3-diene−acid chloride condensation followed by base-induced reaction (Scheme 54).[46] The rearrangement described above formally is the elongation of glyoxal in four carbons bearing four contiguous stereocenters which in turn are formed in a totally stereoselective fashion.

Pyrrolizidine alkaloids are natural products widespread in nature, occurring in various plant species and insects. Their

Scheme 53

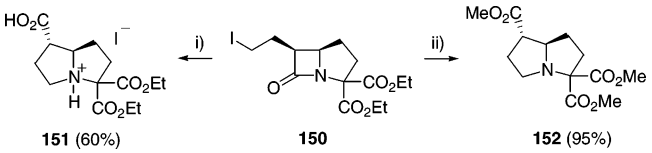


Scheme 54[a]



[a] Key: (i) Et_3N, CH_2Cl_2, −78 °C to RT, 12 h; (ii) MeONa, MeOH, RT, 12 h.

Scheme 55[a]



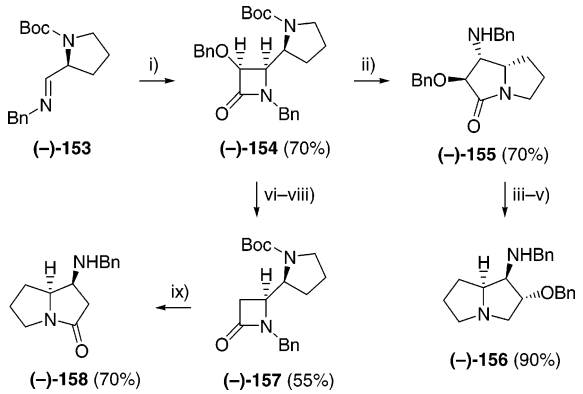
[a] Key: (i) CH_3CO_2H, CF_3CO_2H, RT, 45 min; (ii) MeONa, MeOH, RT, 6 days.

structural and stereochemical complexity, coupled with their diverse and potent biological activities, make pyrrolizidine alkaloids as well as structurally related unnatural compounds very attractive synthetic targets. It has been described that the racemic 6-(2-iodoethyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2,2-dicarboxylic acid diethyl ester **150** on reaction with acids or bases undergoes rearrangement with ring expansion.[47] Thus, on treatment with trifluoroacetic acid, bicyclic β-lactam **150** was rapidly converted into the pyrrolizidinium salt **151**. On reaction with bases such as sodium methoxide or sodium cyanide in methanol, compound **150** undergoes transesterification, giving the pyrrolizidine **152** (Scheme 55). The intramolecular reaction of **150** with bases can be explained in terms of the increased reactivity of the nitrogen by the annelated five-membered ring and the consequently enforced perturbation of the amide mesomerism. The spatial proximity of the two reactive groups leads to additional entropic promotion of the reaction. No racemization occurs either in the acidic or in the basic conversion.

A concise route to necines has been disclosed, a family of pyrrolizidine alkaloids bearing the 1,2-amino alcohol functionality.[48] The approach is based on the diastereoselective cycloaddition reaction of alkoxyketenes to *N*-Boc-α-amino imines. Accordingly, treatment of benzyloxyketene generated from benzyloxyacetyl chloride and triethylamine with the prolinal imine **153** gave the β-lactam **154** as a single diastereomer in 70% yield. Compound **154** upon treatment with trifluoroacetic acid followed by 12 N HCl in refluxing ethanol led to formation of the pyrrolizidinone **155** in 70% yield. Reduction of the carbonyl group provided the pyrrolizidine framework **156** in 90% yield. On the other hand, simple Barton's deoxygenation of **154** and subsequent intramolecular rearrangement of the resulting β-lactam **157** provided the aminopyrrolizidinone **158** in 70% yield (Scheme 56).

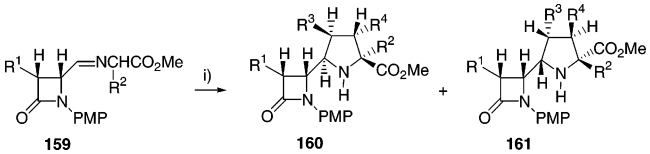
It has been shown that structurally diverse pyrrolidinyl-β-lactams, obtained from 2-azetidinone-tethered alanine (glycine)-derived azomethine ylides, are useful synthetic intermediates for the straightforward entry to highly func-

Scheme 56[a]



[a] Key: (i) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, −78 °C to RT, 20−24 h; (ii) CF_3CO_2H, CH_2Cl_2, then 12 N HCl, EtOH, reflux; (iii) BH_3–SMe_2, THF, reflux, 2 h; (iv) NaOAc−MeOH, RT, 5 min; (v) I_2, $CHCl_3$; (vi) NH_4HCO_2, Pd−C, acetone, reflux; (vii) NaH, CS_2, THF−HMPA, MeI, RT, 30 min; (viii) *n*-Bu_3SnH, AlBN, toluene, reflux, 1 h; (ix) 12 N, HCl, EtOH, reflux.

Scheme 57[a]



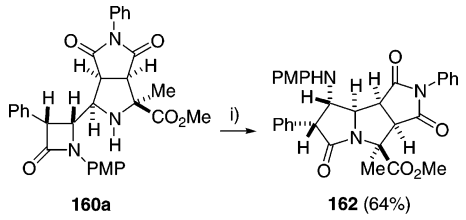
[a] Key: (i) dipolarophile, AgOAc, Et_3N, toluene, RT or 40 °C.

tionalized pyrrolizidine systems.[49] The 1,3-dipolar cycloaddition was achieved via metal-ion catalysis at room temperature. Condensation of the appropriate 4-oxoazetidine-2-carbaldehyde with various α-amino esters in the presence of 4 Å molecular sieves provided the corresponding aliphatic aldimines **159**, which were obtained in quantitative yields and used for the next step without further purification. Treatment of aldimines **159** with the appropriate dienophile (e.g., phenylmaleimide, methyl acrylate, dimethyl fumarate, and *trans*-β-nitrostyrene) in the presence of AgOAc/Et_3N in toluene at room temperature for 40 h gave with reasonable diastereoselectivity mixtures of cycloadducts **160** and **161** (dr ranging from 52:48 to 95:5 ratio) in moderate to good yields (45−80%) (Scheme 57). Furthermore, reaction with the unsymmetric monoactivated alkene, methyl acrylate, proceeded with total regioselectivity. Reaction with the less activated dipolarophile dimethyl acetylenedicarboxylate was not effective at room temperature, and as a consequence no adducts were obtained. However, when the experiment was carried out at 40 °C a good result was achieved. Fortunately, in all cases the diastereomeric cycloadducts **160** and **161** could be easily separated by gravity flow chromatography, with the isomeric products **160** being the less polar compounds.

First, sodium methoxide was tested as reagent for conversion of adducts **160** or **161** into the framework of pyrrolizidine alkaloids. In the event, maleimide-derived cycloadduct **160a** affords, after chemoselective epimerization at C4 in the former β-lactam ring (Scheme 58), the pyrrolizidine skeleton **162**. However, partial epimerization was observed for methyl acrylate- and dimethyl fumarate-derived cycloadducts.

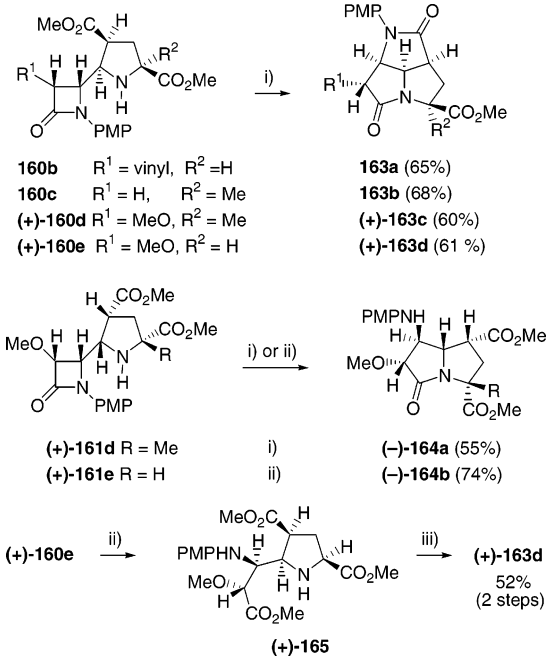
Then, attempts were made to improve the method using acidic conditions. When the reaction was conducted in a saturated solution of HCl(g) in 2-propanol at room temperature for 36 h it gave rise to racemic and optically pure pyrrolizidine systems **163** and **164** in moderate to good yields

Scheme 58[a]



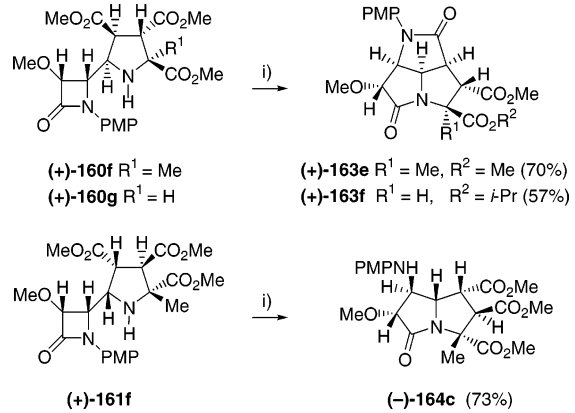
[a] Key: (i) MeONa, MeOH, RT, 2 h.

Scheme 59[a]



[a] Key: (i) HCl(g), 2-propanol, RT, 36 h; (ii) HCl(g), MeOH, RT, 36 h; (iii) PTSA, toluene, Dean−Stark apparatus, reflux, 2 h.

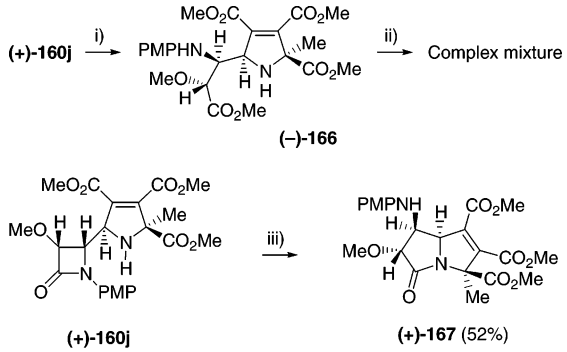
Scheme 60[a]



[a] Key: (i) HCl(g), 2-propanol, RT, 36 h.

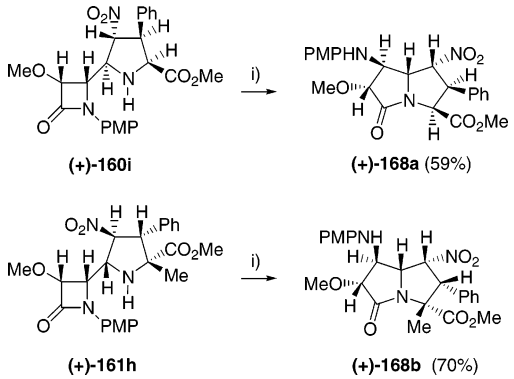
and without byproducts (Schemes 59 and 60). However, some isopropyl transesterification was observed by treatment of adducts **160g** and **161e** under the usual conditions of HCl-(g) in 2-propanol. Reaction of pyrrolidinyl-β-lactam **160g** with HCl(g) in 2-propanol afforded the transesterificated tricycle **163f** as the only product. The obtention of bicycle **164b** was more efficiently achieved via reaction of adduct **161e** in a saturated methanolic solution of HCl(g). Reaction of compounds **160e** and **160j** in a saturated solution of HCl-(g) in methanol for 36 h gave in quantitative yield compounds **165** and **166**, respectively, as crude product. Product **165**

Scheme 61[a]



[a] Key: (i) HCl(g), MeOH, RT, 36 h; (ii) PTSA, Dean−Stark apparatus, toluene, reflux, 2 h; (iii) 37% HCl(aq), MeOH, reflux, 14 h.

Scheme 62[a]

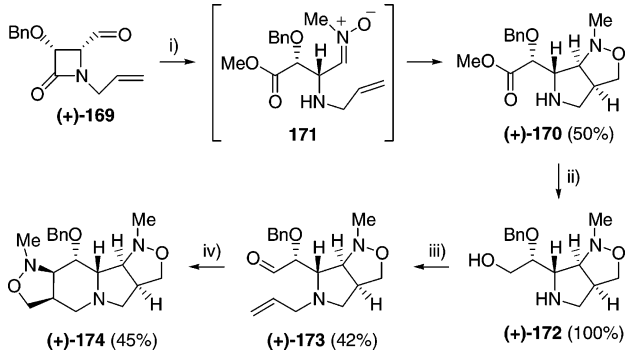


[a] Key: (i) HCl(g), 2-propanol, RT, 36 h.

has a monocyclic pyrrolidine structure which required 2 h of heating in toluene under PTSA catalysis using a Dean−Stark apparatus to give the expected pyrrolizidine system **163d**. By contrast, pyrroline **166** under PTSA catalysis gave a complex reaction mixture, bicycle **167** being a very minor component. Pyrrolidine **165** slowly evolves on standing to the tricycle **163d**. Tricycle **163d** and bicycle **167** were alternatively obtained in yields of 50% and 52%, respectively, via heating overnight the adducts **160e** and **160j** in methanol under 37% aqueous hydrochloric acid catalysis (Scheme 61). Compound **160h** derived from *trans*-β-nitrostyrene and alanine by treatment with HCl(g) failed to give the pyrrolizidine system, while reaction of pyrrolidinyl-β-lactam **160i** derived from *trans*-β-nitrostyrene and glycine, in a saturated 2-propanolic solution of HCl(g), smoothly provided in 59% yield the pyrrolizidine lactam **168a**. Cycloadduct **161h** was solved in 2-propanol and converted in good yield (70%) to pyrrolizidinone **168b** by treatment with HCl(g). Regiospecific epimerization at the hydrogen α to the bridge nitrogen atom was observed on compound **168a**, while chemospecific epimerization at the hydrogen α to the nitro moiety was observed on compound **168b** (Scheme 62). Formation of pyrrolizidine lactams **162**−**164** and **167** and **168** involves a selective C−N bond cleavage at the four-membered ring followed by a rearrangement under the reaction conditions. The overall transformation must be driven by relief of the strain associated with the four-membered ring on forming more stable polycyclic systems. The relative anti disposition of the ester and amine moieties in bicycles **164** and **167** must be responsible for the failure of the third cyclization to occur, preventing formation of a highly strained tricyclic system.

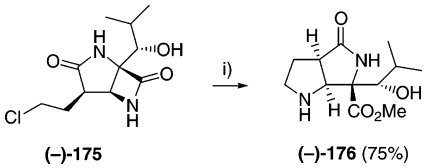
When 2-azetidinone-tethered alkenylaldehyde **169** was refluxed with *N*-methylhydroxylamine using an excess of

Scheme 63[a]



[a] Key: (i) MeNHOH, HCl, Na_2CO_3, MeOH, reflux, 30 min; (ii) $LiAlH_4$, Et_2O, RT, 2 h; (iii) (a) allyl bromide, MeCN, RT, 16 h; (b) DMP, CH_2Cl_2, RT, 90 min; (iv) MeNHOH, HCl, MeOH, reflux, 90 min.

Scheme 64[a]



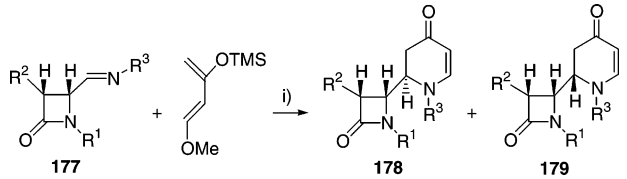
[a] Key: (i) 1 M LiOH, MeOH−H_2O (1:1), 40 °C, 3 h.

sodium carbonate in methanol fused bicyclic pyrrolidine **170** was isolated as the major component in reasonable yield (50% as pure product) instead of the expected bridged β-lactam cycloadduct. This may be due to the opening of the β-lactam ring and further cycloaddition of the resulting acyclic α-allylamino nitrone **171**.[50] It was reasoned that once the rigid angular disposition imparted by the planar lactam group in **169** has disappeared, the transition state leading to the fused pyrrolidinil ring might be sterically less demanding. Synthesis of the indolizidine system from bicyclic pyrrolidine **170** was accomplished in a four-step sequence. Reduction of compound **170** with $LiAlH_4$ in ether at room temperature resulted in a quantitative yield of amino alcohol **172**. *N*-Allylation of compound **172** with allyl bromide followed by Dess−Martin periodinane oxidation gave the alkenylaldehyde **173**, which was reacted with *N*-methylhydroxylamine/triethylamine in refluxing toluene to provide the tetracyclic indolizidine **174** in reasonable yield as pure product (Scheme 63).

A new and effective proteasome inhibitor, β-lactam **175**, has been accessed enantioselectively by multistep synthesis from readily prepared intermediates which were stereoselectively joined by a [2+2]-cycloaddition reaction to form a spiro β-lactam intermediate. This spiranic intermediate was converted to bicycle **175** in seven steps and 30% overall yield. The totally synthetic bicyclic β-lactam **175** related to salinosporamide A and omuralide has showed potent proteasome inhibition activity.[51] It seems reasonable that the pathway of proteasome inhibition by the β-lactam **175** follows that of omuralide and salinosporamide A, that is, acylation of a catalytically active threonine of a proteolytic β-subunit. It is likely also that this acylation is rendered irreversible by ring closure involving the chloroethyl group as an electrophile, as appears to be the case for salinosporamide A, since treatment of **175** with methanolic base afforded the bicyclic pyrrolidine **176** (Scheme 64).

Indolizidine alkaloids have recently attracted a lot of attention due to their widespread occurrence and utility as research tools in pharmacology. The first methodology to

Scheme 65[a]



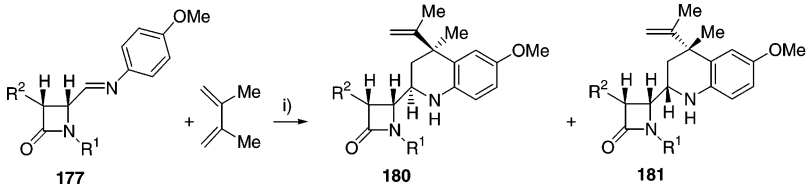
[a] Key: (i) ZnI_2, MeCN, −20 °C, 16 h.

prepare indolizidines from β-lactams has been recently developed.[52] Imines derived from 4-oxoazetidine-2-carbaldehydes have been found to be versatile Diels−Alder reagents in that they exhibit two reactivity patterns. 2-Azetidinone-tethered imines **177** underwent diastereoselective reaction with Danishefsky's diene in the presence of different Lewis acids. The effect of the amount of catalyst on the conversion rate as well as on the product ratio was studied. Under standard reaction conditions indium(III) chloride and zinc(II) iodide provided the best yield and indium(III) triflate the highest diastereoselectivity in the Lewis acid-promoted aza-Diels−Alder cycloaddition. In terms of achieving good yields with a reasonable rate of reaction, acetonitrile seemed to be the solvent of choice for this reaction. Reaction of aldimines **177** with Danishefsky's diene in acetonitrile at −20 °C in the presence of zinc(II) iodide gave cycloadducts **178** and **179** with moderate to good anti stereoselectivities (de 20−100%) in reasonable yields (48−87%) (Scheme 65). Fortunately, in all cases the diastereomeric tetrahydropyridine-4-ones **178** and **179** could be easily separated by gravity flow chromatography.

The reactivity of the above aldimines with less electron-rich dienes was studied next. Treatment of 2-azetidinone-tethered aryl imines **177** with 2,3-dimethyl-1,3-butadiene in acetonitrile at room temperature in the presence of zinc(II) iodide led to cycloadducts **180** and **181** as chromatographically separable mixtures of two diastereomers in good yield. Interestingly, the dienophilic behavior of the imine in the Diels−Alder reaction was reversed to exhibit heterodienic properties. The cycloaddition did not take place with electron-poor dienophiles such as 2-cyclohexen-1-one or methyl acrylate, confirming that an inverse electron-demand Diels−Alder reaction was involved. This azadiene behavior is well known for arylimines derived from aromatic or α,β-unsaturated aldehydes, but little is known about the use of aliphatic aldehyde-derived imines as the 4π component and even less on their optically active derivatives. No improvements in stereoselectivity were obtained with indium(III) chloride or indium(III) triflate, but the reaction was faster. Of the Lewis acids surveyed at this point, indium(III) triflate gave good yields (67−89%) and good conversion rates (Scheme 66). The *N*-substituent nature of the β-lactam nucleus appears to influence the stereoselectivity of the cycloaddition. While *N*-aryl-substituted β-lactams afforded moderate selectivities (60−75:40−25), by far the best selectivity (100:0) was observed when the *N*-functionality at the four-membered ring was an aliphatic moiety. Again, cycloadducts **180** and **181** were easily separable by column chromatography.

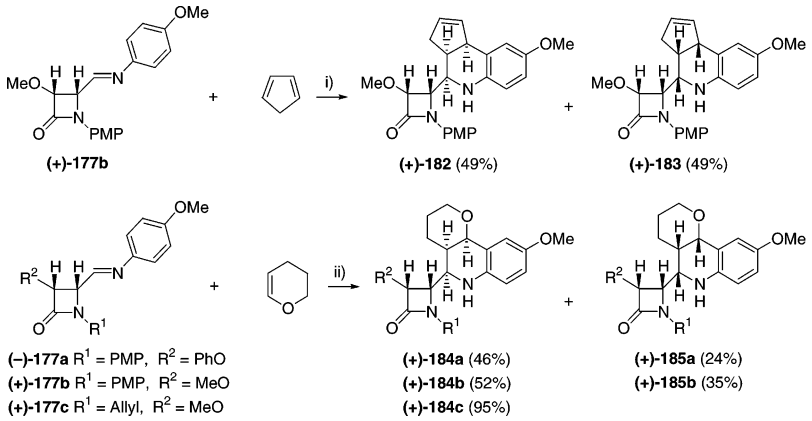
Cyclic alkenes such as cyclopentadiene and 3,4-dihydro-2*H*-pyran (DHP) were tested as well. The reactions proceeded smoothly at ambient temperature under trivalent indium salt catalysis. Thus, the indium trichloride-catalyzed (20 mol %) reaction between the 2-azetidinone-tethered aryl imines **177b** and cyclopentadiene afforded the chromato-

Scheme 66[a]



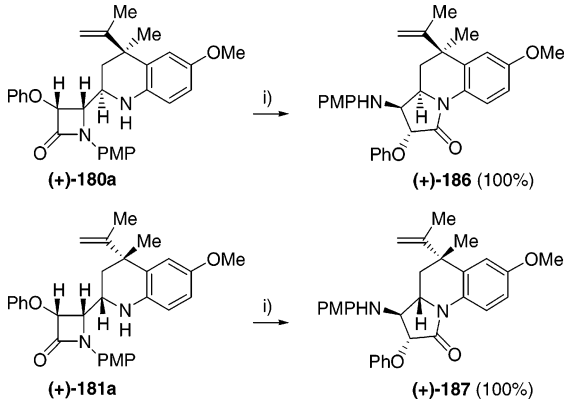
[a] Key: (i) ln(TfO)$_3$, MeCN, RT, 3 h.

Scheme 67[a]



[a] Key: (i) lnCl$_3$, MeCN, RT, 1 h; (ii) ln(TfO)$_3$, MeCN, RT, 3−5 h.

Scheme 68[a]



[a] Key: (i) MeONa, MeOH, RT, 16 h.

graphically separable derivatives **182** and **183** (1:1 mixture) in an excellent 98% yield (Scheme 67). Further reactions of *N*-benzylidene-2-azetidinones **177** with DHP in the presence of catalytic amounts of indium(III) triflate resulted in formation of isomeric pyrano[3,2-*c*]quinoline-*β*-lactams **184** and **185**. These adducts, which could be separated by column chromatography on silica gel, were obtained in good yields (70−95%) with acceptable levels of stereoselectivity (60−100:40−0). Thus, for example, adduct (+)-**184c** was obtained as a single diastereomer (Scheme 67).

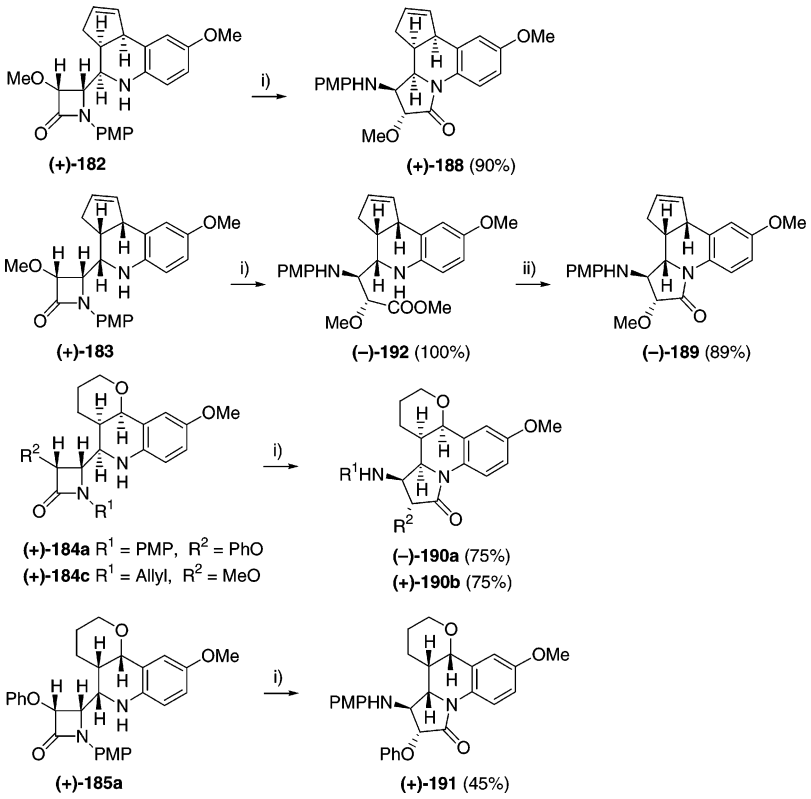
An expedient transformation of the above [4+2] cycloadducts into indolizidine systems bearing a vicinal amino alcohol or alkoxy functionality, which is a common and relevant feature of some indolizidines which act as glycosidase inhibitors, was achieved.[52] To our delight, quantitative transformation of adducts **180a** and **181a** into fused azatricycles **186** and **187** was directly effected via a sodium methoxide rearrangement reaction (Scheme 68). Similarly, tetracyclic indolizidinones **188**−**191** were obtained after aqueous workup in good yields and high purity without further purification (Scheme 69). Reaction of compound **183** with sodium methoxide in methanol overnight gave in quantitative yield as crude product compound **192**. Product **192** has a fused tricyclic tetrahydroquinoline structure, which requires 30 min of heating in toluene under PTSA catalysis using a Dean−Stark apparatus to give the expected indolizidinone system **189**. Azapolycyclic compounds **186**−**191** showed a single set of signals in their ^{1}H NMR spectra, thus proving that these transformations proceeded without detectable isomerization.

Cycloadducts **178** and **179** require further manipulation to obtain the desired alkaloid system. Thus, the dihydropyridone **178a** underwent sequential reduction of the alkene and carbonyl moieties. L-Selectride reduction of the alkene moiety at the six-membered ring was a convenient way to obtain the tetrahydropyridone **193**. Sodium borohydride reduction of the ketone moiety on compound **193** gave a 60:40 mixture of epimeric alcohols **194** and **195**, which were separated by flash chromatography. Protection of the hydroxyl group to give the corresponding *tert*-butyldimethylsilyl ethers **196** and **197**, followed by CAN-promoted oxidative cleavage of the *N*-4-methoxyphenyl substituent, provided the key intermediates oxoazetidinyl-piperidines **198** and **199** (Scheme 70). Compounds **200**−**203** were obtained in a similar way starting from the minor cycloadduct **179a** (Scheme 71). Fortunately, reduction of ketone **200** was totally stereoselective, and alcohol **201** was obtained as the sole product without any sign of the diastereomeric isomer.

Substrates **198**, **199**, and **203** were submitted to sodium methoxide treatment to afford bicyclic indolizidine lactams **204**−**206**. Enantiopure indolizidinones **204**−**206** were cleanly achieved without byproducts in quantitative yields (Scheme 72).

It was observed that the CAN-promoted oxidative cleavage of the *N*-4-methoxyphenyl substituent at *N*-protected piperidine-*β*-lactams was not a high-yielding reaction. In addition, the CAN-mediated deprotection was incompatible with the ketone group. Taking into consideration all these drawbacks, Grubbs' carbene-catalyzed *N*-deallylation was

Scheme 69[a]

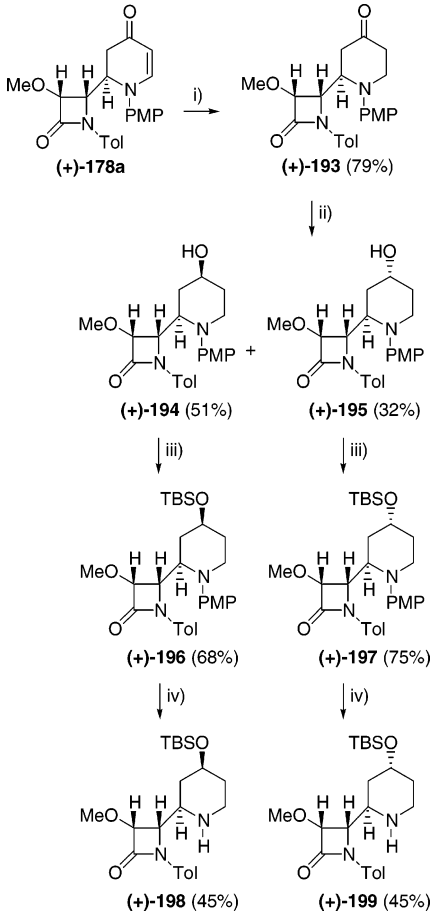


[a] Key: (i) MeONa, MeOH, RT, 16 h; (ii) PTSA, toluene, reflux, 30 min.

tested. In the event, differently functionalized *NH*-piperidine-β-lactams were achieved in good yields (Scheme 73).[53] The deprotection reactions show excellent chemoselectivity. In compounds **207c** and **208** the β,γ-unsaturated ethers remained unreacted. In addition, **207d** and **207e** show that a selective *N*-deallylation can be achieved in the presence of γ,δ-unsaturated or δ,ϵ-unsaturated amides. However, it should be noted that in Grubbs' carbene-promoted reaction of compounds **207d** and **207e** on addition of the *N*-deallylated products **210d** and **210e** the corresponding RCM products were isolated (ca. 30% yield) as minor products. Piperidine-2-azetidinones **210** and **211** were easily converted into indolizidinones **212** and **213** in excellent yields (87−100%). Thus, the ruthenium-catalyzed synthesis of *NH*-piperidines gives a novel improved access to indolizidine-type alkaloids (Scheme 73).

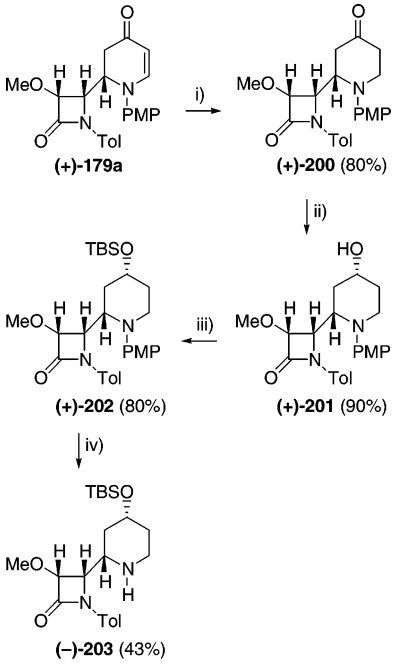
These results demonstrate that efficient asymmetric access to a plethora of stereochemically different indolizidine moieties can be achieved via β-lactam chemistry. The transformation of piperidine-2-azetidinones **180**−**185**, **198**, **199**, **203**, **210**, and **211** into indolizidine derivatives **186**−**191**, **204**−**206, 212**, and **213** involves amide bond cleavage of the β-lactam ring followed by cyclization of the resulting amino ester with concomitant ring expansion. To further illustrate the use of this chemistry in alkaloid synthesis, conversion of indolizidinones to indolizidines was easily accomplished by reduction of the amide group. Thus, the fused lactams **186**, **190b**, **205**, and **206** on treatment with a suspension of powdered lithium aluminum hydride in tetrahydrofuran or diethyl ether smoothly afforded the cyclic amines **214**−**217** (Scheme 74).

Scheme 70[a]



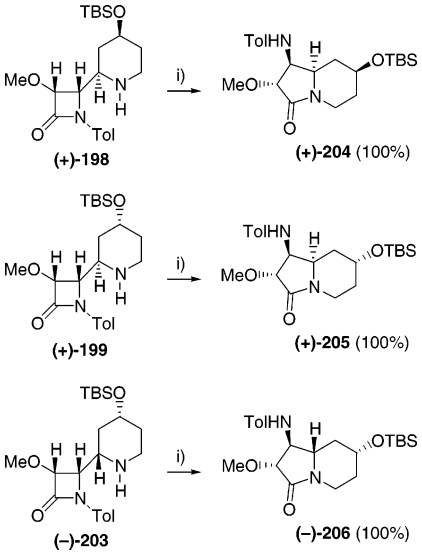
[a] Key: (i) L-Selectride, −78 °C, 5 h; (ii) $NaBH_4$, MeOH, 0 °C; (iii) TBSCl, imidazole, DMF, RT, 16 h; (iv) CAN, MeCN−H_2O, −35 °C, 30 min.

Scheme 71[a]



[a] Key: (i) L-Selectride, −78 °C, 1 h; (ii) $NaBH_4$, MeOH, 0 °C; (iii) TBSCl, imidazole, DMF, RT, 16 h; (iv) CAN, $MeCN-H_2O$, −35 °C, 30 min.

Scheme 72[a]



[a] Key: (i) MeONa, MeOH, RT, 16 h.

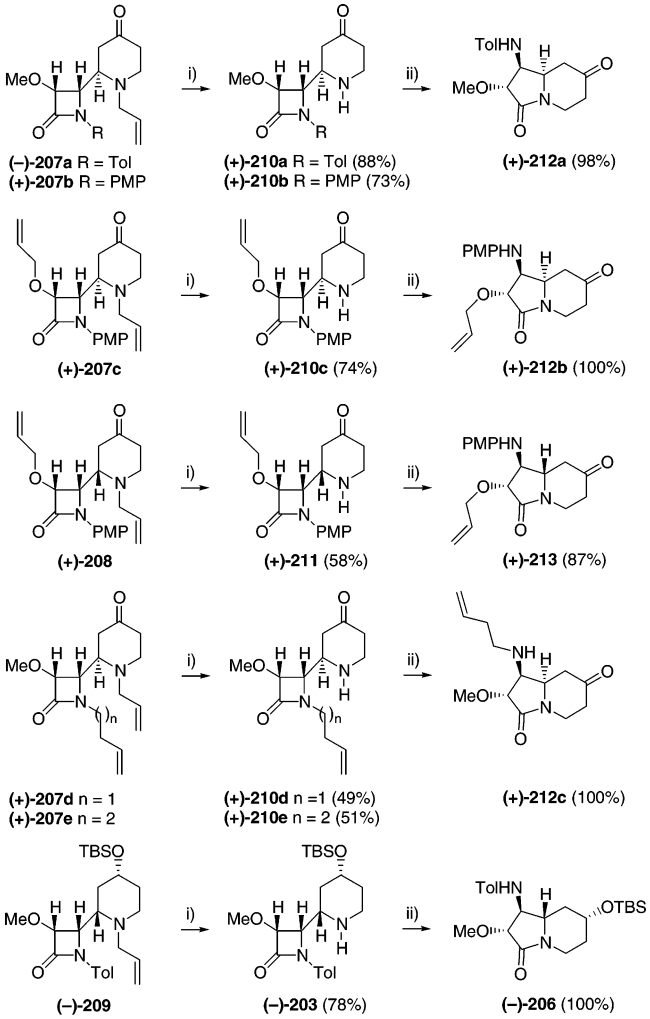
2.4. Six-Membered Heterocycles

2.4.1. Monocyclic Six-Membered Rings

Enantiopure 4-oxoazetidin-2-carbaldehydes have been used as building blocks for the synthesis of 4-aminopiperidin-2-ones.[54] The synthesis involves ring expansion of the β-lactam nucleus via methanolysis followed by a reductive cyclization of a C4 nitroethyl side chain with an ester group (Scheme 75). Reaction of nitromethane with β-lactam aldehyde **64a** in the presence of a catalytic amount of triethylamine gave a diastereomeric mixture (80:20) of nitro aldol products. Dehydration of nitro alcohol under acidic as well as basic reaction conditions did not give clean nitro olefin **218a**. Therefore, the hydroxy group was acylated by acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid at 0 °C, and the corresponding acetate was refluxed with benzene for 5 h in the presence of sodium bicarbonate to give the nitro olefin **218a** in 70% yield. The alkene **218a** was reduced to the corresponding nitro alkane by stirring with tri-*n*-butyltin hydride in dichloromethane for 24 h at room temperature. Reduction of nitro alkene **218a** or nitro alkane by catalytic hydrogenation with Pd/C or Raney Ni catalysts gave a complex mixture of products instead of either the expected 4-aminoethyl-β-lactam or 4-aminopiperidin-2-one. When the nitro alkane-β-lactam was stirred with methanolic HCl at room temperature for 24 h, the β-amino ester **219a** was obtained in 82% yield. Reduction of the nitro group was achieved by transfer hydrogenation of β-amino ester **219a** using ammonium formate and Pd/C (10%) in methanol. The lactamization occurred directly during the transfer hydrogenation of nitro ester **219a** to give the δ-lactam **220a** in 80% yield. Several other 4-amino-δ-lactams were prepared following the above route in 28−39% overall yields (Scheme 75). A direct transfer hydrogenation of nitro alkenes **218** or nitro alkanes with ammonium formate and Pd/C gave complex mixtures.

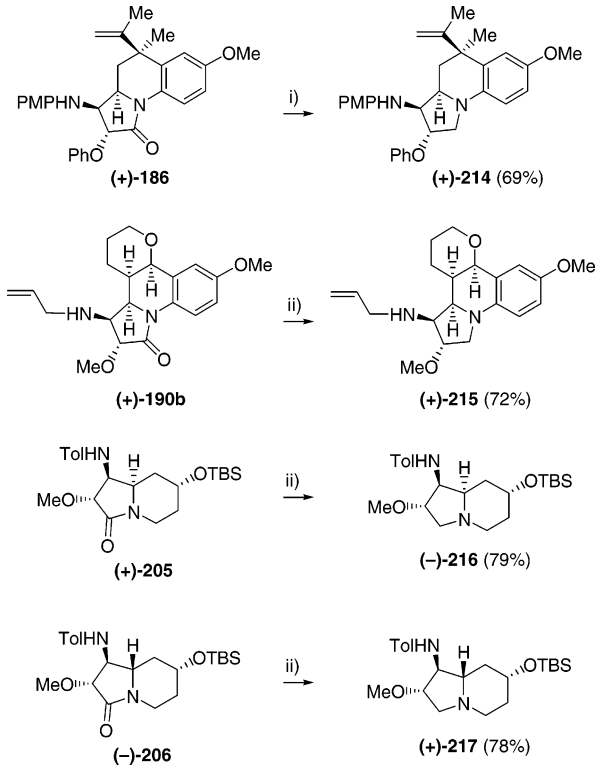
A stereocontrolled synthetic method for the preparation of dihydropyridones has been described starting from bis-dienyl-2-azetidinones **221**,[55] which have been obtained through the [2+2] cycloaddition of di-β-styryl or acryl-β-styryl methanimines with diphenylketene. When 4,4-di-β-

Scheme 73[a]



[a] Key: (i) 5 mol % $[(PCy_3)_2Cl_2Ru{=}CHPh]$, toluene, 110 °C, 0.5−5 h; (ii) MeONa, MeOH, RT, 16 h.

Scheme 74[a]

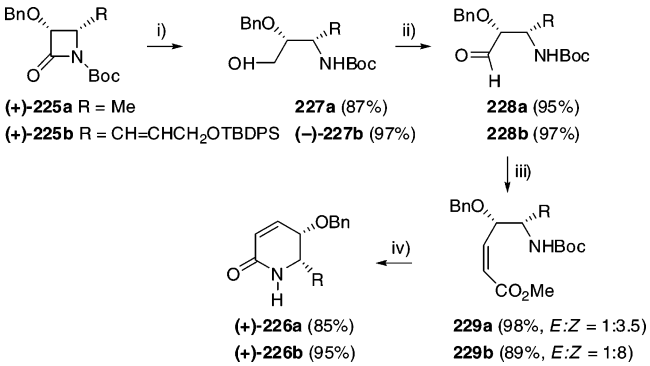


[a] Key: (i) $LiAlH_4$, THF, RT, 16 h; (ii) $LiAlH_4$, Et_2O, RT: **215**, 30 min; **216**, 45 min; **217**, 40 min.

styryl β-lactams **221** were subjected to thermal treatment (refluxing toluene for 2 h) it was found that the dihydropyridone derivatives **222** were quantitatively obtained, which were presumably formed by a [1,3] sigmatropic rearrangement with cleavage of the C3−C4 bond of the azetidinone ring in **221**. Similarly, heating adduct **221f** for 5 min caused the [1,3] rearrangement to give a mixture of two pyridones, **222f** and **223**, in 97% yield with a ratio of 82:18. The aminodiene unit of adducts **222** was used in a Diels−Alder cycloaddition to give hexahydroquinolines **224** in excellent yields with complete π-facial selectivity (Scheme 76).

It was envisaged that two-carbon addition to β-lactams could provide easy access to 5,6-dihydro-2(1*H*)-pyridones having substituents and stereochemistry preadjusted at the 2-azetidinone stage. In this context, transformation of *cis*-*N*-Boc-2-azetidinones **225** to 2-pyridones **226** was effected via a two-carbon addition reaction, as shown in Scheme 77.[56]

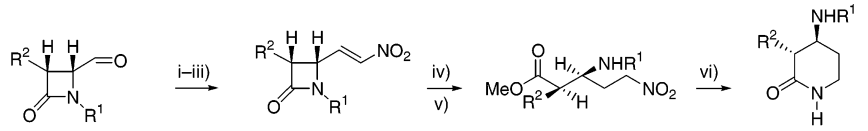
Scheme 77[a]



[a] Key: (i) $LiAlH_4$, THF, 0 °C, 10 min; (ii) IBX, DMSO, RT, 3−5 h; (iii) $Ph_3P{=}CHCO_2Me$, MeOH, RT, 12 h; (iv) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, then cat DMAP, toluene, reflux, 1 h.

Thus, β-lactams **225** were reduced to amino alcohols **227** in good yields by $LiAlH_4$ in THF. Oxidation of amino alcohols **227** by 2-iodoxybenzoic acid in DMSO for 3 h at room temperature cleanly produced 3-*N*-Boc-amino aldehydes **228**, which were used in the next step without further purification. Aldehydes **228** were dissolved in dry MeOH and after Wittig reaction with (triphenylphosphoranylidene)acetate gave a mixture of *Z*/*E*-α,β-unsaturated esters **229**, the *Z*-alkene being the major product. These two isomers were separated by flash chromatography. *Z*-*N*-Boc amino esters **229** were subjected to *N*-Boc deprotection under mild conditions (TMSOTf, 2,6-lutidine, 0 °C) and in turn cyclized with catalytic DMAP to

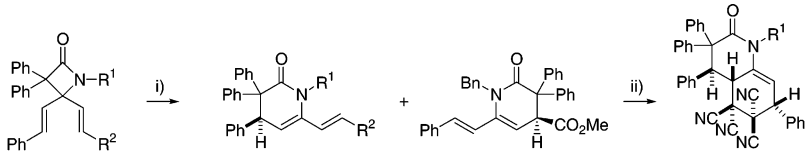
Scheme 75[a]



(+)-64a R^1 = PMP, R^2 = OPh	**(+)-218a** (70%)	**(–)-219a** (70%)	**(+)-220a** (80%)
(+)-64c R^1 = PMP, R^2 = OBn	**(+)-218b** (75%)	**(–)-219b** (66%)	**(+)-220b** (66%)
(+)-64e R^1 = Bn, R^2 = OPh	**(+)-218c** (72%)	**(–)-219c** (59%)	**(+)-220c** (62%)
(+)-64f R^1 = PMP, R^2 = H	**(+)-218d** (75%)	**(–)-219d** (68%)	**(–)-220d** (63%)

[a] Key: (i) $MeNO_2$, Et_3N, RT, 4 h; (ii) Ac_2O, H_2SO_4 (conc), 0 °C, 1 h; (iii) $NaHCO_3$, benzene, reflux, 5 h; (iv) Bu_3SnH, CH_2Cl_2–MeOH (10:1), RT, 3−24 h; (v) 20% HCl/MeOH, RT, 12−24 h; (vi) Pd/C, $HCOONH_4$, 2−16 h.

Scheme 76[a]

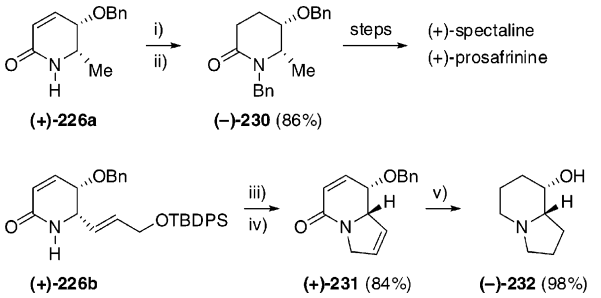


221a R^1 = Ph	**222a** R^2 = Ph (99%)	**224a** (99%)
221b R^1 = 4-$MeOC_6H_4$	**222b** R^2 = Ph (99%)	**224b** (99%)
221c R^1 = Bn	**222c** R^2 = Ph (99%)	**224c** (99%)
221d R^1 = *i*-Pr	**222d** R^2 = Ph (99%)	**224d** (99%)
221e R^1 = Me_2N	**222e** R^2 = Ph (99%)	
221f R^1 = Bn	**222f** R^2 = CO_2Me (97%, 82:18 ratio)	

223

[a] Key: (i) toluene, reflux, 5 min to 2 h; (ii) TCNE, CH_2Cl_2, RT, 5−10 min.

Scheme 78[a]

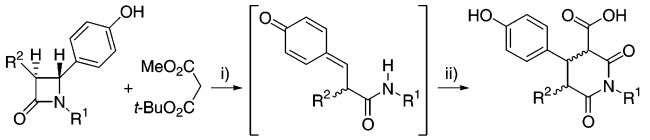


(+)-226a (−)-230 (86%)

(+)-226b (+)-231 (84%) (−)-232 (98%)

[a] Key: (i) BnBr, HNa, THF, RT, 2 h; (ii) H_2, Pd/C, AcOEt, RT, 1 h; (iii) allyl bromide, HNa, cat. *n*-Bu_4NI, THF, 0 °C, 2 h; (iv) $(Cy_3P)_2Cl_2Ru$=CHPh, benzene, reflux, 1 h; (v) H_2, $Pd(OH)_2$, EtOH, RT, 3 days.

Scheme 79[a]



233a R^1 = CH_2CO_2Me, R^2 = Me
233b R^1 = Ph, R^2 = Bn
233c R^1 = Ph, R^2 = $CH_2C_6H_{11}$

235

(+)-234a (54%; 2:1)
(+)-234b (73%; 100:0)
(+)-234c (77%; 100:0)

[a] Key: (i) *t*-BuOK, RT, 1 h; (ii) TFA, RT, 2 h.

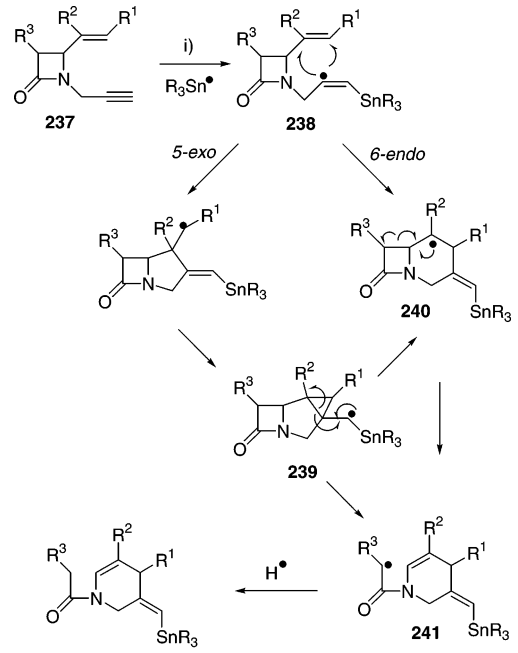
give the desired 5,6-*cis*-disubstituted-5,6-dihydro-2(1*H*)-pyridones **226** in reasonable yields.

Reduction of the double bond and *N*-benzylation at nitrogen of dihydropyridone **226a** provided **230**,[57] a key intermediate for the chiral synthesis of *Cassia* alkaloids. Since **230** was previously converted to (+)-spectaline and (+)-prosafrinine,[58] the above work represents formal syntheses of both alkaloids. *N*-Allylation of 6-olefinic-2-piperidone **226b** produced the desired diolefinic-2-piperidone, which after treatment with Grubbs' ruthenium catalyst generated the highly functionalized bicyclic lactam **231** in 95% yield despite the steric bulkiness of the TBDPSO group. Indolizidinone **231** was converted to perhydro-8-indolizidinol **232** through hydrogenation and amide reduction in good overall yield (Scheme 78).[59]

The first two-carbon ring expansion of a β-lactam through cleavage of the C4−N1 bond was recently described.[60] Treatment of 4-(4′-hydroxyphenyl)-azetidine-2-ones **233** with *tert*-butyl methyl malonate in the presence of potassium *tert*-butoxide gives the corresponding glutarimides **234** in good yields (Scheme 79). Upon potassium *tert*-butoxide addition the phenolate anion is formed followed by rearrangement to an intermediate quinone methide **235** with concomitant cleavage of the C4−N1 bond. The reactive quinone methide is then quenched by the *tert*-butyl methyl malonate anion in a Michael-type 1,6-conjugate addition at the benzylic carbon. Under these highly basic conditions the amide nitrogen attacks the carbonyl carbon of the methyl ester group to split off methanol and form the substituted glutarimide. The intramolecular condensation is selective for the methyl ester carbonyl carbon over that of the *tert*-butyl ester group. The *tert*-butyl group was subsequently removed with trifluoroacetic acid. The stereochemistry of the ring expansion is dependent on the substituent at C3 of the starting 2-azetidinone. In the case of methyl substitution both trans,trans and cis,trans stereoisomers of the glutarimide ring were present in the crude product of **234a**. The ratio of stereoisomers was 2:1. In contrast, the reactions leading to **234b** and **234c** were stereospecific as only the trans,trans stereoisomer was present.

A preparation of tetrahydropyridines **236** was found in route to carbapenams.[61] However, the synthetic interest is

Scheme 80[a]

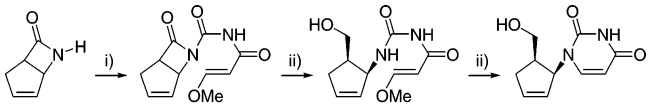


237 **238** **239** **240** **241**

236a R^1 = Ph, R^2 = Me, R^3 = OBn (10%)
236b R^1 = Me, R^2 = H, R^3 = OPh (14%)

[a] Key: (i) R_3SnH, AIBN, benzene, reflux.

Scheme 81[a]



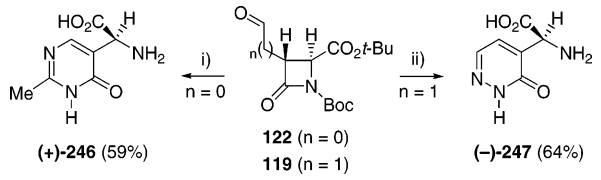
242 **243** (60%) **244** (74%) **245** (68%)

[a] Key: (i) MeOCH=CHCONCO, benzene, 60 °C, 3 h; (ii) $NaBH_4$, MeOH, RT, 20 min; (iii) H_2SO_4(aq) (2 M), reflux.

diminished owing to the low yields. These results may be understood in terms of the reaction pathway presented in Scheme 80 starting from enyne-β-lactams **237**. The first step should be addition of the in-situ-generated stannyl radical to the triple bond of compounds **237** to form the key intermediate vinyl radical **238**. For activated double bonds a 5-*exo*-*trig* ring closure occurs yielding the expected carbapenam products. Substitution at the acceptor carbon atom, or nonactivated double bonds, essentially results in inhibition of the cyclization process, even for activated double bonds. In these cases, reduction products are obtained as the main components of the reaction mixtures. Furthermore, formation of tetrahydropyridines **236** may be explained by a homolytic C3−C4 bond cleavage in the 2-azetidinone nucleus of intermediates **239** or **240** to form radical intermediates **241**, which are precursors of compounds **236**. This interesting process is closely related to the cyclobutylcarbinyl radical cleavage, a useful methodology for the synthesis of medium-sized rings. In the β-lactam case, the driving force for the cleavage may be the stability of the captodative radical **241** (Scheme 80, R^3 = PhO) together with the strain in the 2-azetidinone ring.

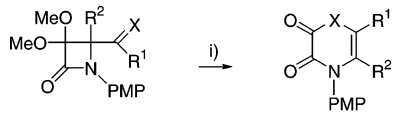
Synthesis of a 1,2-disubstituted carbonucleoside analogue containing a pyrimidine ring has been accomplished starting from the bicyclic β-lactam **242**, which was obtained in 46% yield by a [2+2] cycloaddition between cyclopentadiene and chlorosulfonyl isocyanate. The uracil derivative was prepared following the synthetic route outlined in Scheme 81, which involves reductive C−N bond cleavage of the four-membered ring as the key step.[62] Initial reaction of 2-azetidinone **242**

Scheme 82[a]



[a] Key: (i) (a) MeC(=NH)NH_2·HCl, K_2CO_3, MeOH, RT, 24 h; (b) 6 N HCl, RT, 45 min; (ii) (a) NH_2NH_2, benzene, reflux, 24 h; (b) F_3CCO_2H, CH_2Cl_2, RT, 24 h.

Scheme 83[a]



248a $R^1 = R^2 = H$, X = O	**250a** (75%)
248b $R^1 = R^2 = Me$, X = O	**250b** (88%)
248c $R^1 = Ph$, $R^2 = H$, X = O	**250c** (95%)
249a $R^1 = R^2 = H$, X = NPMP	**251a** (95%)
249b $R^1 = R^2 = Me$, X = NPMP	**251b** (99%)

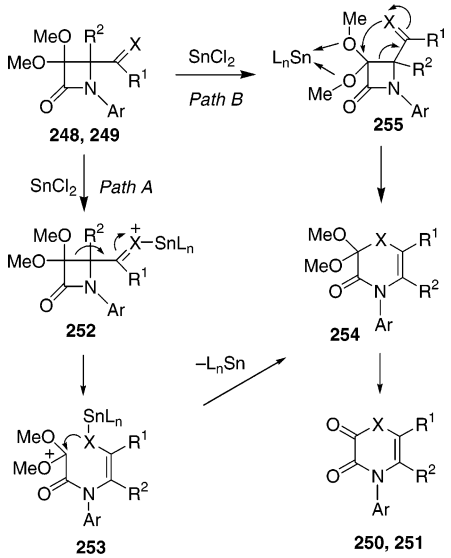
[a] Key: (i) $SnCl_2$·$2H_2O$, CH_2Cl_2, RT, 15 min to 20 h.

with 3-methoxyacryloyl isocyanate in anhydrous benzene afforded the corresponding carbamoyl derivative **243**. Reduction of compound **243** with an excess of $NaBH_4$ in methanol gave the corresponding acyclic ureide **244** with cis stereochemistry, and subsequent acidic ring closure afforded the desired uracil derivative **245**.

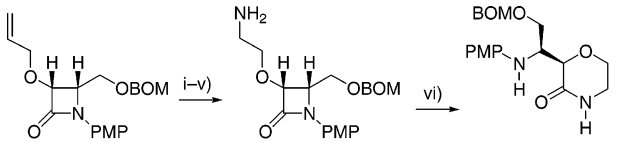
When the aldehyde **122** was reacted at room temperature with acetamidine hydrochloride in methanol containing potassium carbonate the corresponding pyrimidinone was obtained in 61% yield. Hydrolysis in 6 N aq. HCl gave the hydrochloride of the amino acid **246** in 97% yield (Scheme 82).[40] The homologous aldehyde **119** after treatment with 4 equiv of hydrazine hydrate in refluxing benzene gave as the sole product in 64% yield the Boc-protected pyridazinone, which after hydrolysis with trifluoroacetic acid in dichloromethane afforded the trifluoroacetate of the amino acid **247** in nearly quantitative yield (Scheme 82).[40]

The tandem C3−C4 bond breakage−carbocationic rearrangement of 4-acyl- or 4-imino-3,3-dimethoxy-2-azetidinones **248** and **249** promoted by tin(II) chloride has been documented as an entry to dihydro-1,4-oxazines or pyrazine-2,3-diones derivatives **250** and **251** (Scheme 83).[30] 4-Acyl-β-lactams **248** were reacted with different protic and Lewis acids. The best results were obtained by working with an equimolecular amount of $SnCl_2$·$2H_2O$ in dichloromethane at room temperature. Disappearance of the starting material occurred after a few hours. Standard workup gave the reaction product **250**, which was then purified by either crystallization or column chromatography. A control experiment demonstrated that rearrangement to the six-membered ring occurs prior to hydrolysis of the ketal group. When 4-imino-3,3-dimethoxy-2-azetidinones **249** were reacted with $SnCl_2$·$2H_2O$, a clean almost quantitative conversion to reaction products **251** was obtained. These results confirm that imine groups attached to the C4 position of the β-lactam ring are also suitable to give the C3−C4 fragmentation−rearrangement process. Clearly, in these cases the rearrangement competes favorably with hydrolysis of the imino group, which is not the case when aqueous hydrochloric acid is used. The above rearrangements also take place in the presence of protic acids (H_2SO_4 or HCl). However, yields were erratic

Scheme 84



Scheme 85[a]



[a] Key: (i) O_3, CH_2Cl_2, then Me_2S, −78 °C; (ii) BH_3, THF, 0 °C, 30 min; (iii) MsCl, Et_3N, CH_2Cl_2, −30 °C, 1 h; (iv) N_3Na, DMF, 50 °C, 4 h; (v) PPh_3, THF−H_2O, RT; (vi) EtOH, 60 °C, 120 h.

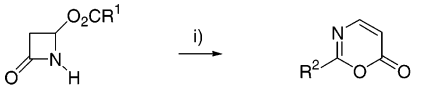
and mixtures of the different reaction products were usually obtained.

It seems clear that both imino and carbonyl groups in compounds **248** and **249** are prone to promote rearrangement to compounds **250** and **251**. Reaction pathways in Scheme 84 may account for the observed reaction products. Both mechanistic rationalizations rest in coordination of tin to the starting material as the promoter of the rearrangement. Path A involves coordination of tin to the group at C4 to yield intermediate **252**, which would evolve by C3−C4 bond breakage due to the enhanced reactivity of the double bond and the ability of the ketal to stabilize the emerging carbocation at C3 to give **253**. Annelation of intermediate **253** renders compounds **254**, which are further hydrolyzed, giving the final products **250** and **251** upon treatment with tin(II) chloride. Alternatively, compounds **248** and **249** upon dicoordination at the ketal functionality to yield **255** may evolve through a concerted or stepwise six-electron rearrangement to compounds **254**.

3-Allyloxy-β-lactam **256** has been transformed into morpholinone **258** using as a key step the intramolecular opening of the 2-azetidinone nucleus by the amino group of β-lactam **257**.[32] Transformation of alkene **256** into amine **257** was realized as outlined in Scheme 85 through ozonolysis, reduction with BH_3 to give the corresponding alcohol, and finally converting into 2-azetidinone-tethered amine **257** via an azide precursor.

A new route to 1,3-oxazin-6-ones involving a N1−C2 bond β-lactam breakage and an electrocyclic ring opening has been described.[63] *N*-Unsubstituted-4-acyloxy-β-lactams **259** were converted into 2-substituted-1,3-oxazin-6-ones **260** in the presence of acid chlorides by the action of bases. A

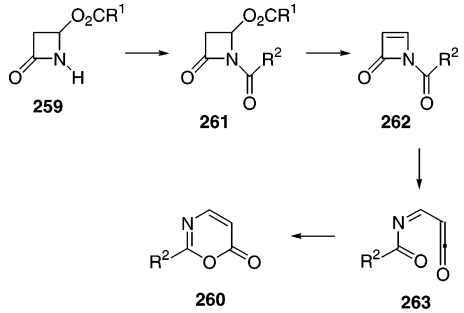
Scheme 86[a]



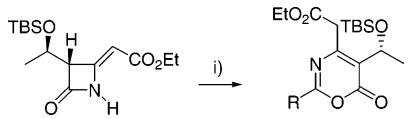
259a R^1 = Me, R^2 = Ph	**260a** (69%)
259b R^1 = Me, R^2 = 4-ClC_6H_4	**260b** (58%)
259c R^1 = Ph, R^2 = 2-furyl	**260c** (44%)
259d R^1 = Ph, R^2 = (E)-C_6H_5-CH=CH	**260d** (50%)
259e R^1 = Ph, R^2 = *t*-Bu	**260e** (76%)
259f R^1 = Ph, R^2 = Et	**260f** (40%)
259g R^1 = Ph, R^2 = 4-BrC_6H_4	**260g** (53%)

[a] Key: (i) R^2COCl (2 equiv), DBU (5 equiv), CH_2Cl_2, 25 °C, 2−5 h.

Scheme 87



Scheme 88[a]



Z-**264a** R = Me	**265a** (77%)
Z-**264b** R = OBn	**265b** (54%)
Z-**264c** R = NHBn	**265c** (60%)
Z-**264d** R = Ph	**265d** (47%)

[a] Key: (i) Acylating reagent (1 equiv), K_2CO_3 (2 equiv), acetone, 16 h.

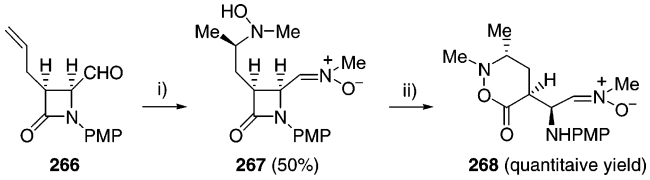
careful exploration of the reaction conditions (organic base, solvent, temperature) for conversion of **259** to **260** revealed DBU (5 equiv) to be the base of choice and CH_2Cl_2 and 25 °C as the optimal conditions for obtaining the best yields of **260** (Scheme 86).

A reasonable mechanistic explanation is the following: first, formation of the corresponding *N*-acyl-4-acyloxy-β-lactams **261** takes place and next the organic base promotes β-elimination of 1 equiv of carboxylic acid R^1CO_2H across the C3−C4 bond of the β-lactam ring, giving rise to the highly strained *N*-acylazetinone **262**, which was not stable enough to survive in the reaction conditions and rapidly experienced a retro-[*4-exo-dig*] cyclization to the *N*-acylimidoylketene **263** instead of a thermal conrotatory electrocyclic ring opening. The fourth step, which in turn is the transformation into the final 1,3-oxazin-6-one **260**, corresponds to another pseudopericyclic reaction instead of a six-electron disrotatory electrocyclization (Scheme 87).[64]

In a tentative acylation reaction of the β-lactam nitrogen of 4-alkylidene-β-lactams **264** a completely different behavior of *E* and *Z* isomers was found.[65] *N*-Acetylation of the *E* isomer with acetic anhydride and solid K_2CO_3 in acetone was rapid, whereas the *Z* isomer reacted sluggishly, rearranging to the corresponding 1,3-oxazin-6-one **265** (Scheme 88). Compound *Z*-**264**, in fact, requires at least 2 equiv of K_2CO_3 for satisfactory yields of 1,3-oxazin-6-ones **265**.

Racemic azetidinone **266** was obtained as a single cis diastereoisomer following a one-pot method from *N*,*N*-di-

Scheme 89[a]



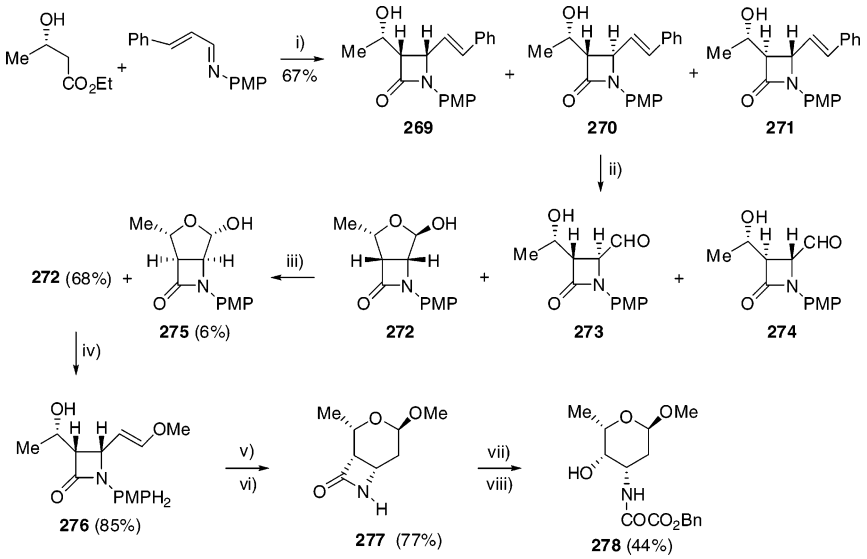
[a] Key: (i) MeNHOH·HCl (3 equiv), C_6H_6, Et_3N, RT, 3 days; (ii) $CHCl_3$, RT, 7 days.

(*p*-methoxyphenyl)glyoxal diimine. The diimine undergoes a [2+2] cycloaddition with allyl ketene to give β-lactam carbaldehyde **266** after acidic hydrolysis. Reaction of *cis*-3-allyl-4-formyl-2-azetidinone **266** with a 3-fold excess of *N*-methylhydroxylamine for 3 days gave the hydroxylamino nitrone **267** in a 50% yield. This nitrone is unstable in chloroform, and after 1 week, the oxazinone nitrone **268** was obtained in quantitative yield (^{1}H NMR monitoring) (Scheme 89).[66]

Partially deoxygenated carbon branched amino sugars are important components of several classes of medicinally useful compounds with demonstrated antibiotic and anticancer activity. However, preparation of aminosugars from β-lactams is a little explored process. The pioneering work of Hart et al. on accomplishing the enantioselective synthesis of tetrahydropyrans, analogs of the aminosaccharide daunosamine, is a nice example as outlined in Scheme 90.[67] The ester−imine condensation provided a mixture of *cis*- and *trans*-β-lactams **269**−**271** in 67% yield. Although the cis isomer could be separated from the trans compounds, it was more convenient to continue with the mixture. Sequential treatment of the mixture of 2-azetidinones **269**−**271** with ozone and dimethyl sulfide gave hemiacetal **272** and a mixture of *trans*-4-oxoazetidine-2-carbaldehydes **273** and **274**. Isomerization of **273** and **274** to **272** and **275**, respectively, was achieved using DBU in dichloromethane. DBU serves to epimerize the chiral center α to the aldehyde in addition to forming the hemiacetal. In this manner, the aforementioned mixture of β-lactams **269**−**271** was converted into **272** and **275** in 68% and 6% yields, respectively. Treatment of **272** with lithium diisopropylamide followed by (methoxymethylidene)triphenylphosphorane gave the *trans*-vinyl ether **276** (85%). Cyclization of **276** using acidic Dowex-50 in methanol and oxidative removal of the *p*-methoxyphenyl group gave the bicyclic 2-azetidinone **277** (77%). Further acylation and treatment with buffered peracid completed the synthesis of the daunosamine derivative **278** (Scheme 90).

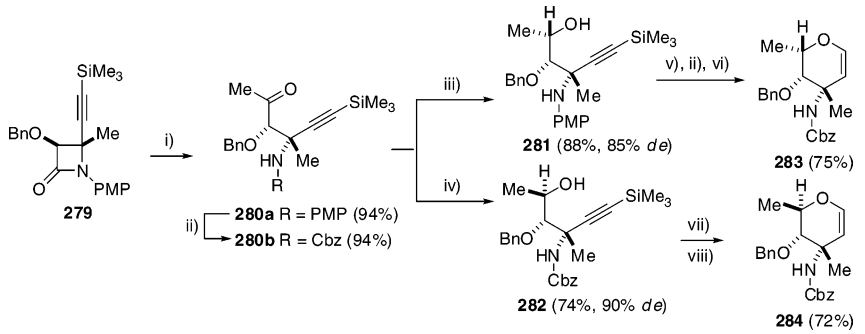
More recently, a β-lactam-based stereoselective synthesis of the C3 branched amino glycals of vancosamine and saccharosamine has appeared in the literature.[68] Condensation of *p*-anisidine and 4-trimethylsilyl-3-butyn-2-one gave in 80% yield the corresponding imine, which by combination with the ketene derived from benzyloxyacetyl chloride afforded β-lactam **279** as a single diastereomer. Synthesis of the dihydropyran derivatives began with the reaction between β-lactam **279** and methyllithium to give ketone **280a** as a single product in 94% yield. The PMP-protected β-lactam **279** was highly resistant to over alkylation by methyllithium, so that even an excess (2 equiv) of methyllithium could be used without generating any tertiary alcohol byproduct. With ketones **280** in hand, the authors explored a variety of reducing agents to selectively prepare both alkynol diastereomers **281** and **282**. Felkin−Anh selectivity could be observed for ketone reductions with both PMP- and

Scheme 90[a]



[a] Key: (i) LDA, THF, −78 °C to RT, 22 h; (ii) O_3, CH_2Cl_2, then Me_2S, −78 °C, 70 min; (iii) DBU, CH_2Cl_2, reflux, 70 min; (iv) LDA, $Ph_3P{=}CHOMe$, THF, −78 °C to RT, 10 h; (v) Dowex-50, MeOH, RT, 5 h; (vi) CAN, MeCN−H_2O, −40 to 0 °C, 30 min; (vii) BnO_2CCOCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (viii) MCPBA, Na_2HPO_4, $(ArS)_2$, CCl_4, reflux, 2 h.

Scheme 91[a]



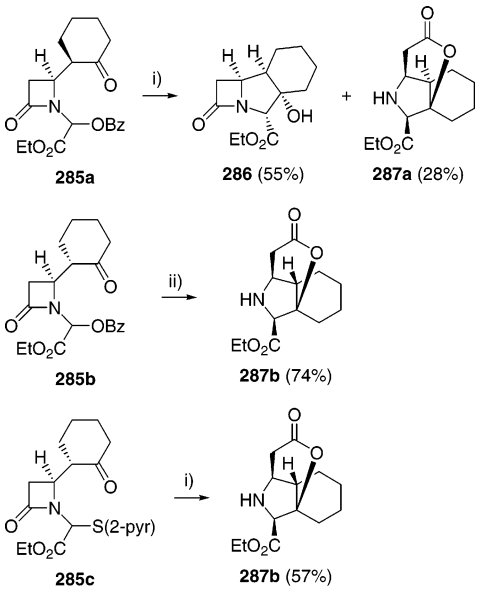
[a] Key: (i) MeLi, THF, −78 °C, 20 min; (ii) (a) CAN, MeCN−H_2O, RT, 2 h; (b) CbzCl, CAN, $NaHCO_3$, acetone−H_2O, RT; (iii) $NaBH_4$, $CeCl_3$, CH_2Cl_2, MeOH, −78 °C, 2 h; (iv) $NaBH_4$, $ZnCl_2$, CH_2Cl_2, −78 °C, 20 min; (v) K_2CO_3, MeOH, RT, 16 h; (vi) 5% $W(CO)_6$·THF, Et_3N, *hν*, 55 °C, 3 h; (vii) TBAF, THF, 0 °C, 30 min; (viii) 5% $W(CO)_6$, THF, DABCO, *hν*, 33 °C, 2.5 h.

Cbz-protected aminoketones **280a** and **280b**, favoring formation of the corresponding diastereomer **281** and **282**, but the complementary reduction with chelation control from the adjacent benzyloxy group was achieved only with the Cbz-protected ketone **280b**. Chelate-controlled reduction of **280a** gave reduced selectivity, presumably due to competing chelation with the basic anisidine substituent. The standard Luche reduction conditions ($NaBH_4/CeCl_3$) gave the best Felkin−Anh selectivity, providing **281** from the PMP-protected amino ketone **280a**, whereas $Zn(BH_4)_2$ reduction of the Cbz-protected ketone **280b** gave the best selectivity for chelation-controlled reduction to provide the alcohol diastereomer **282**. Both reactions were highly solvent dependent. The Luche reduction did not proceed with any appreciable rate even at room temperature in the absence of methanol and also exhibited poor selectivity if too much methanol was included. Likewise, the zinc borohydride reduction proceeded extremely well in the nonchelating solvent CH_2Cl_2 but with a much slower rate and lower diastereoselectivity in ethereal solvents. The tungsten-catalyzed cycloisomerization of PMP-protected amino-alkynol substrate **281** was unsatisfactory. Exchange of the PMP in **281** for the much less basic Cbz-carbamate was efficient for undergoing cycloisomerization with only 5% $W(CO)_6$ in less than 3 h to give protected vancosamine glycal **283** in 97% yield. Having established the feasibility of the Cbz-protected amine for the cycloisomerization methodology, this transformation was applied to the saccharosamine glycal. The desired glycal **284** was obtained in 74% yield using the same conditions employed for the vancosamine glycal. By replacing triethylamine with DABCO the yield of glycal **284** was increased to 98% (Scheme 91).

2.4.2. Polycyclic Six-Membered Rings

Proline plays an important role in protein folding and signal transduction, being a constituent of biologically active and pharmaceutically interesting peptides. On the synthetic side, proline has been found to be a useful and inexpensive catalyst for the direct catalytic asymmetric aldol reaction. A route to bridged δ-lactone proline derivatives employing cyclizations of derivatized β-lactams has been reported.[69] Reaction of TMS-protected 4-acetoxyazetidinone with 1.5 equiv of the trimethylsilyl enol ether of the appropriate cyclic ketone in the presence of zinc chloride afforded good yields of the corresponding C4-alkylated azetidinones after removal of the silyl protecting group with acetic acid in methanol. Next, introduction of the glycine unit at the N1 position was effectively achieved with ethyl glyoxylate, and the secondary alcohols obtained were subsequently benzoylated with benzoyl chloride, affording β-lactams of type **285**. Addition of

Scheme 92[a]



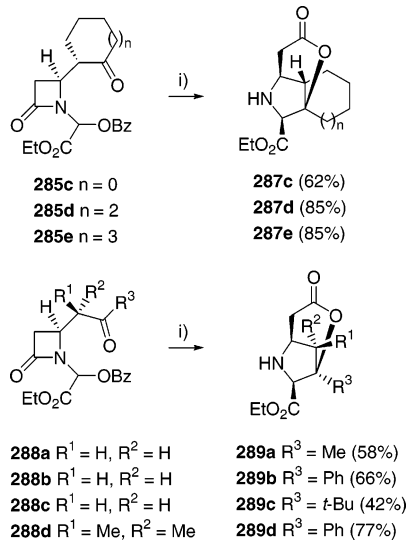
[a] Key: (i) SmI_2, THF, RT, 17 min; (ii) SmI_2, *t*-BuOH (1 equiv), THF, RT, 3 min.

β-lactam **285a** to approximately 2.5 equiv of SmI_2 in THF led to its immediate consumption and formation of two components by TLC analysis. The less polar component, the tricyclic β-lactam **286**, was obtained as a sole isomer in 55% yield. The more polar component, being an isomer to **286** according to electrospray MS but lacking the β-lactam ring, was identified as the bridged δ-lactone proline derivative **287a** and obtained in 28% yield. Diastereomer **285b** when treated with SmI_2 led only to the δ-lactone derivative **287b** as a single diastereomer in 56% yield. Lowering the temperature only led to reduced cyclization yields. Repetition of the above reductive cyclization was attempted with the corresponding 2-azetidinone thiopyridine derivative **285c**. However, subjection of compound **285c** to cyclization conditions identical to those for **285b** did not lead to a notable change in the yield of the proline compound **287b**. It was observed that addition of 1 equiv of *tert*-butyl alcohol to the benzoate **285b** prior to subjection to SmI_2 significantly increased the cyclization yield, now providing **287b** in 74% yield (Scheme 92).

Formation of the bridged δ-lactone proline derivatives proved to be general with other ring-containing β-lactam substrates (Scheme 93). All cyclization reactions were performed at room temperature and basically complete after addition of the benzoates to the ethereal solution of SmI_2. Yields of the functionalized δ-lactones ranged from 62% for the cyclopentanone derivative to 85% for the corresponding seven- and eight-membered cyclic ketones. With the acyclic ketones **288**, the bicyclic bridged δ-lactone proline compounds **289** could be isolated in 42−77% yield. The influence of the proton source was more prominent in these latter cases, as, for example, with **288c**, where no cyclization product could be isolated in the absence of *t*-BuOH.

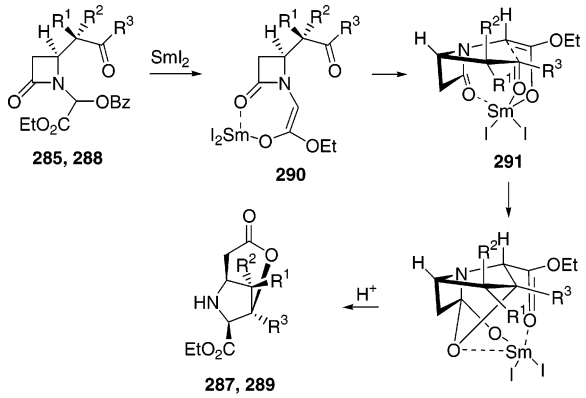
The diastereoselectivities observed in these C−C bond-forming reactions deviate from previous reactions involving cyclizations with the corresponding lithium enolates obtained by deprotonation. Scheme 94 provides a tentative rational explanation for these observations. Reductive samariation of the benzoyloxy-containing glycine results in formation of a samarium(III) enolate, **290**. The high oxophilicity of the samarium(III) ion, including its known propensity to complex

Scheme 93[a]



[a] Key: (i) SmI_2, *t*-BuOH (1 equiv), THF, RT, 3 min.

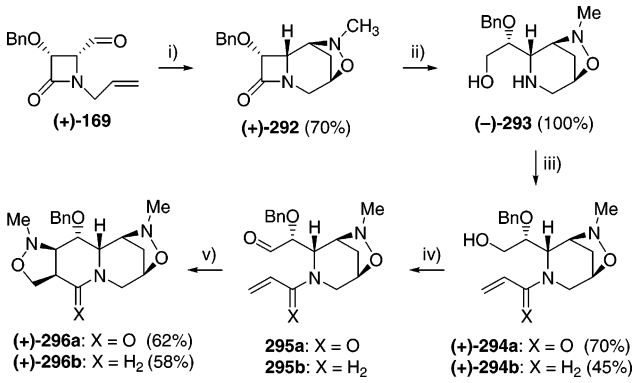
Scheme 94



strongly with amides, suggests formation of a cyclic enolate structure with the β-lactam amide functionality. Next, it may be involved in a boat conformation **291**, whereby the metal counterion is continuously coordinated to the amide group throughout the cyclization and acyl migration step. It was speculated that with the larger lanthanide metal ion compared to lithium favorable coordination to both the β-lactam and ketone carbonyl groups becomes possible, overriding the steric interactions that may arise from this conformation. This additional coordination also provides the driving force for the subsequent *trans*-acylation step.

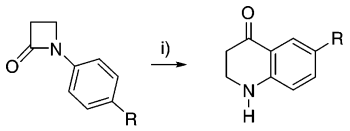
Starting from β-lactam-tethered alkenylaldehyde **169**, the tricyclic bridged 2-azetidinone cycloadduct **292** was prepared through regio- and stereocontrolled intramolecular nitrone−alkene cycloaddition. It should be noted that an interesting aspect of the reversal of the regioselectivity of this cycloaddition was used in the synthesis of bicyclic pyrrolidine **170**, as mentioned earlier (see Scheme 63). Transformation of tricyclic β-lactam **292** to quinolizidine systems was effected as shown in Scheme 95.[50] Thus, compound **292** was quantitatively reduced to piperidinyl alcohol **293** by $LiAlH_4$ in ether at room temperature for 20 min. The successive reaction with acryloyl chloride afforded the corresponding amido ester, which was converted into the amido alcohol **294a** by selective transesterification with sodium methoxide in methanol. Swern oxidation of alcohol **294a** cleanly produced pure aldehyde **295a**, which was used for the next step without further purification. Treatment of alkenylaldehyde **295a**

Scheme 95[a]



[a] Key: (i) MeNHOH·HCl, Et_3N, toluene, reflux, 30 min; (ii) $LiAlH_4$, Et_2O, RT, 1 h; (iii) For **294a**: (a) acryloyl chloride, Et_3N, CH_2Cl_2, RT, 3 h; (b) MeONa, MeOH, RT, 4 h. For **294b**: allyl bromide, MeCN, RT, 16 h. (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 2 h, then Et_3N. (v) MeNHOH·HCl, Et_3N, toluene, reflux, 90 min.

Scheme 96[a]



297a R = Cl	**298a** (97%)
297b R = F	**298b** (98%)
297c R = H	**298c** (96%)
297d R = OMe	**298d** (97%)
297e R = NO_2	**298e** (0%)

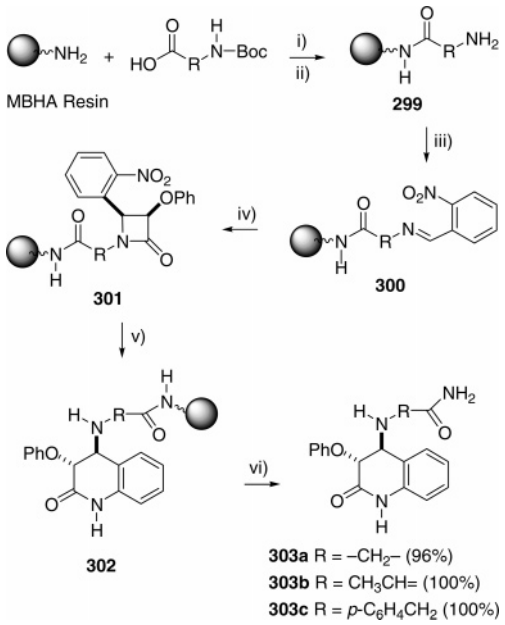
[a] Key: (i) TfOH (1.0−2.0 equiv), 1,2-dichloroethane, 0 °C to RT, 15 min.

with *N*-methylhydroxylamine proceeded smoothly in refluxing toluene to provide the fused cycloadduct with a quinolizidine lactam structure, **296a**, in good yield as the pure product (62% from alcohol **294a**). This INAC reaction showed, not unexpectedly, high regioselectivity, and the isomeric bridged adduct could not be detected in the crude reaction mixture. In addition, quinolizidine **296b** was also prepared from amino alcohol **293** following a similar strategy but using the *N*-allyl derivative **294b** as the intermediate. Compound **294b** was prepared from **293** only in moderate yield (45% as pure product) after considerable experimentation. The presence of an additional tertiary amino group must be responsible for the moderate yield of compound **294b** obtained in this reaction.

Preparation of quinolones from *N*-aryl 2-azetidinones has been described via a Fries-type rearrangement (intramolecular Friedel−Crafts reaction).[70] β-Lactams **297** were reacted with trifluoromethanesulfonic acid in 1,2-dichloroethane at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 15 min. With the exception of the highly deactivated *p*-nitrophenyl group, 2,3-dihydro-4(1*H*)-quinolones **298** were obtained in excellent yields (Scheme 96).

Recent advances in solid-phase organic synthesis have demonstrated this technology as a powerful tool for the rapid generation of a large number of organic compounds. Synthesis of 4-amino-3,4-dihydro-2(1*H*)-quinolones has been accomplished through rearrangement of β-lactam intermediates on the solid phase.[71] The reaction sequence is illustrated in Scheme 97. Three amino acids, *t*-Boc-Gly-OH, L-*t*-Boc-Ala-OH, and *t*-Boc-aminomethylbenzoic acid, were separately attached onto the polystyrene resin using normal peptide coupling conditions (DIC/HOBT/DIEA). Polystyrene

Scheme 97[a]

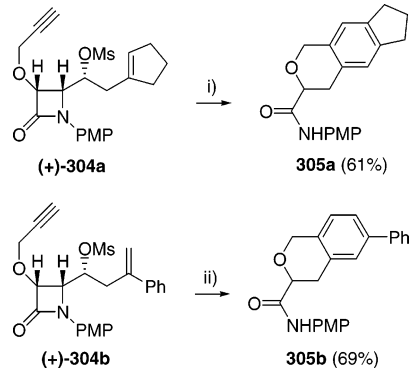


[a] Key: (i) DIC or HOBT or DIEA, CH_2Cl_2 or DMF, RT; (ii) 55% TFA, CH_2Cl_2, RT, 30 min; (iii) *o*-nitrobenzaldehyde, Na_2SO_4, CH_2Cl_2, RT; (iv) $PhOCH_2COCl$, Et_3N, CH_2Cl_2, from −78 °C to RT; (v) $SnCl_2$ (2.0 M), DMF, RT, HF/anisole (95/5).

resin was chosen because of its chemical stability to the conditions used in the synthesis. The complete coupling with each amino acid was confirmed by a negative result from the ninhydrin test. The *t*-Boc-protecting group was removed by treatment with 55% TFA in dichloromethane for 30 min at room temperature to give **299**. Resin-bound amines **299** were condensed with *o*-nitrobenzaldehyde to furnish imines **300**. After washing with dichloromethane and drying under high vacuum over phosphorus pentoxide, [2+2] cycloaddition of imines **300** with the in-situ-generated ketene of the phenoxyacetic acid gave β-lactams **301**. To monitor the reaction sequence to this point, β-lactam intermediates **301** from each amino acid were cleaved from the resin using HF/anisole (95/5) and analyzed using ^1H NMR. In all cases, *cis*-β-lactams were obtained as single products in almost quantitative yield. The nitro groups of the β-lactam intermediates were reduced to amines using tin(II) chloride. Under this reaction condition the β-lactam ring underwent rearrangement to give the *trans*-3,4-dihydro-2(1*H*)-quinolones **302** through intramolecular nucleophilic attack of the β-lactam amide moiety by the newly generated amino groups. Dihydroquinolones **303** were obtained in excellent yield after cleavage using HF/anisole. Having validated the synthetic route, the applicability to a larger selection of amino acids, *o*-nitrobenzaldehydes, and acid chlorides was examined. Using this process a library of dihydroquinolones was produced.

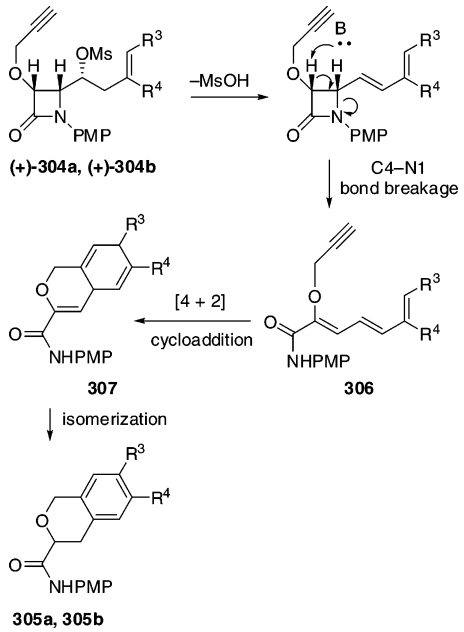
Lewis-acid-promoted carbonyl−ene reaction of enantiopure 4-oxoazetidine-2-carbaldehydes with various activated alkenes followed by reaction with methanesulfonyl chloride gives 4-[(1′-mesyloxy)homoallyl]-β-lactams **304** in reasonable yields. It has been described that treatment of enantiomerically pure enyne-β-lactam mesylates **304a** and **304b** with a slight excess of DBU (1.5 equiv) in benzene at reflux gave rise to unexpected products, the racemic isochromans **305a** and **305b** (Scheme 98).[72] Formation of compounds **305** could be rationalized in terms of a domino C4−N1 β-lactam bond-breakage/intramolecular Diels−Alder

Scheme 98[a]

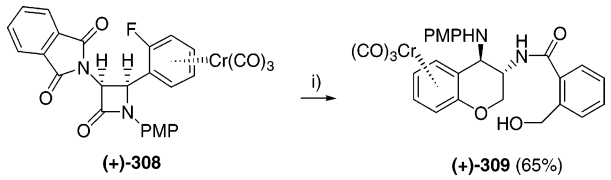


[a] Key: (i) DBU, benzene, 80 °C, 70 h.

Scheme 99



Scheme 100[a]



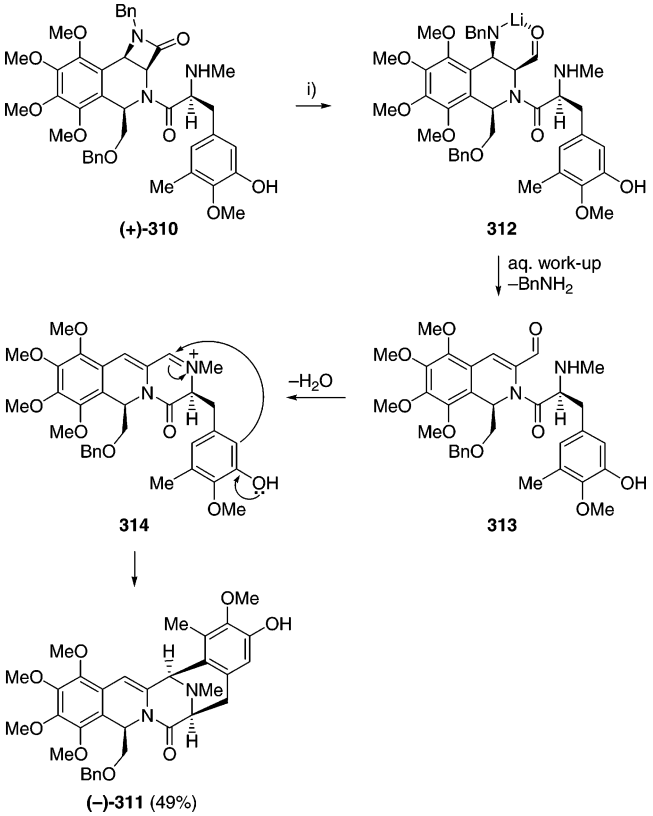
[a] Key: (i) $NaBH_4$, *i*-PrOH−H_2O, RT, 20 h.

reaction. The driving force of the reaction may be formation of the highly conjugate trienes **306** under the reaction conditions (excess of base). Isochromans **305** presumably arise from isomerization of the initially formed [4+2] cycloadducts **307** (Scheme 99). However, it is not clear whether the first step of the domino reaction is cleavage of the β-lactam ring or the Diels−Alder cycloaddition.

Sodium borohydride treatment of the tricarbonyl(η^6-arene)-chromium(0) complexed β-lactam **308** promoted a stereoselective ring-opening−ring-closing reaction sequence leading to the enantiomerically pure dihydrobenzopyran derivative **309** in good yield (Scheme 100).[73]

During synthetic studies on renieramycin H, ecteinascidin (ET-743), and related natural products it was found that exposure of the tricyclic-β-lactam **310** to $LiBEt_3H$ in THF at 0 °C furnished the pentacyclic tetrahydroisoquinoline **311**

Scheme 101[a]

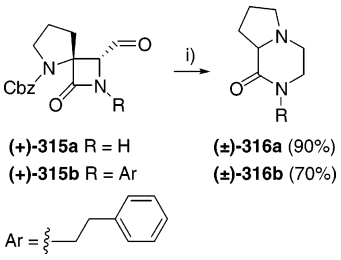


[a] Key: (i) $LiBEt_3H$, THF, 0 °C, 10 min.

directly in one step in 49% yield.[74] Polycyclic β-lactam **310** was obtained in excellent yield from the benzyl imine of 5-(benzyloxy)-2,4-dimethoxy-3-methylbenzaldehyde using an asymmetric Staudinger reaction followed by Pictet−Spengler cyclization. Conversion of **310** into **311** is envisioned to proceed by initial partial reduction of the β-lactam to the amine-coordinated lithium complex **312** that obviates over-reduction of the incipient aldehyde. It should be noted that reduction of β-lactams directly to aldehydes is a synthetically challenging reaction for which no solution yet exists. Elimination of benzylamines occurs spontaneously under the reaction conditions to afford the α,β-unsaturated aldehyde **313**, which subsequently suffers cyclization of the secondary amine on the aldehyde to generate the key iminium ion species **314**. Regioselective intramolecular Pictet−Spengler cyclization finally affords the pentacyclic compound **311** without contamination of the alternative regioisomer (Scheme 101).

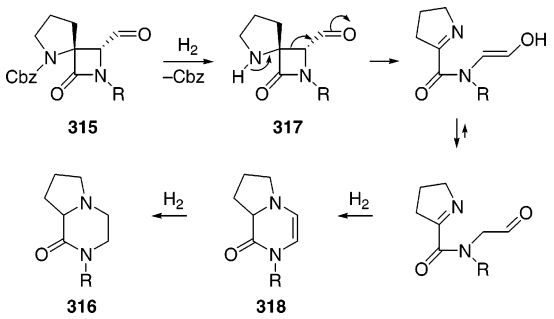
Synthesis of 1,4-diazabicyclo[4,4,0]decanes and 1,4-diazabicyclo[4,3,0]nonanes from spiro-β-lactam aldehydes has been described. The starting 4-formyl spiro β-lactams **315** were prepared by [2+2] cycloaddition of the unsymmetrical cyclic ketene derived from *N*-benzyloxycarbonyl L-proline acid chloride with a diimine followed by the standard protocol for transformation of the dioxolane ring into the corresponding aldehyde. The spiranic 2-azetidinones **315** were subjected to hydrogenolysis by treatment with hydrogen in the presence of palladium catalyst, and after the expected removal of the Cbz protecting group, the product rearranged under the reactions conditions to afford the bicyclic systems **316** (Scheme 102).[75] Unfortunately, starting from enantiopure precursors it was found that optical rotation of bicycles **316** was zero. This fact means that a racemization event took place during the rearrangement. A

Scheme 102[a]

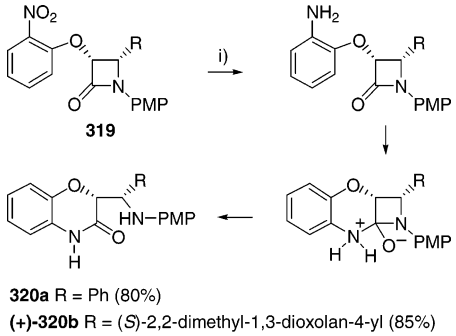


[a] Key: (i) H_2, AcOEt−MeOH, Pd−C, RT, 16 h.

Scheme 103



Scheme 104[a]

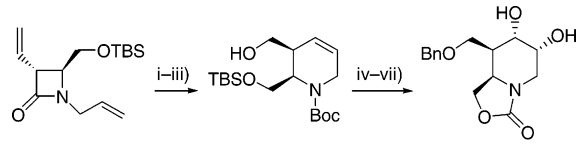


[a] Key: (i) In, EtOH−H_2O, NH_4Cl, reflux, 10 h.

plausible explanation for this transformation is outlined in Scheme 103. After the initial removal of the Cbz group of **315**, a retro-Mannich process that involves ring opening of the β-lactam ring in intermediate **317** took place. Hydrogenation of the iminic functional group and further nucleophilic addition of the secondary amine to the aldehyde group affords the bicyclic enamine **318**. Finally, hydrogenation of this enamine would lead to the bicycle **316**.

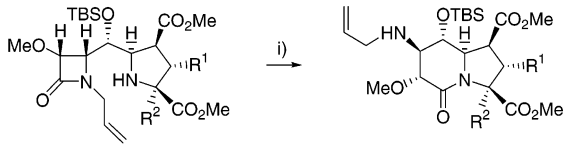
An indium-induced reduction−rearrangement reaction of nitro-substituted β-lactams has been used for facile synthesis of oxazines in aqueous ethanol.[76] Treatment of the nitro-β-lactams **319** with indium−ammonium chloride in aqueous ethanol under reflux produced oxazines **320** with an excellent yield (Scheme 104). The reaction does not proceed in the absence of water. A mixture of alcohol and water is necessary for the success of the rearrangement reaction. Other metals, such as zinc and tin, did not promote the ring-cleavage reaction effectively, the oxazines being obtained in poor yields. Reduction of the aromatic nitro group to the amino group and its nucleophilic attack to the β-lactam carbonyl presumably are the steps involved in the rearrangement toward oxazines (Scheme 104). Because of the oxophilic nature of indium, coordination to the β-lactam carbonyl is possible and may increase the vulnerability of a nucleophilic attack by the amino group.

Scheme 105[a]



[a] Key: (i) $LiAlH_4$, THF, RT; (ii) $(Boc)_2O$, CH_2Cl_2, RT; (iii) Grubbs' catalyst, CH_2Cl_2, RT; (iv) BnBr, n-Bu_4NHSO_4, H_2O, NaOH, RT; (v) n-Bu_4NF, THF, RT; (vi) DAST, CH_2Cl_2, RT; (vii) OsO_4, NMO, acetone, H_2O, RT.

Scheme 106[a]



[a] Key: (i) MeONa, MeOH, RT, 16 h.

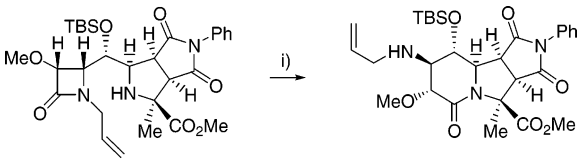
A β-lactam template has been used to induce the stereochemistry in a route to imino sugar and analogues of siastatin B.[77] Reduction of the β-lactam **321** with lithium aluminum hydride afforded the corresponding amino alcohol, which after protection as its *tert*-butyl carbamate and alkene metathesis with first-generation Grubbs' catalyst afforded the key intermediate tetrahydropyridine **322**. Treatment of compound **322** with benzyl bromide under phase-transfer conditions followed by reaction with tetrabutylammonium fluoride gave the appropriate alcohol, which was sequentially reacted with (diethylamino)sulfur trifluoride and osmium tetroxide to afford the diol **323** (Scheme 105). Osmylation has thus occurred from the least hindered side of alkene.

It has been described that the 1,3-dipolar cycloaddition reaction involving α-alkoxy β-lactam acetaldehyde-derived azomethine ylides gave, with excellent diastereoselectivity, highly functionalized 2-azetidinone-tethered prolines, which were directly used for the first preparation of azabicyclo-[4.3.0]nonane (indolizidinone) amino esters from β-lactams.[78] Transformation of pyrrolidine-*N*-allyl-β-lactams **324a**−**c** into indolizidinone amino acid derivatives **325a**−**c** was directly effected at room temperature via a sodium methoxide rearrangement reaction (Scheme 106). However, pyrrolidine-*N*-benzyl-β-lactams bearing a benzyl group at the N1 nitrogen were unreactive. It became evident that the group attached to the lactam nitrogen plays a crucial role in this reaction. The attempted transformation of adducts **324** into indolizidines with a saturated solution of HCl(g) in 2-propanol resulted in complex reaction mixtures. Transformation of proline-β-lactams **324** into indolizidine derivatives **325** involves selective amide bond cleavage of the four-membered ring followed by cyclization of the resulting β-amino ester with concomitant ring expansion. Fused indolizidinone **325d** was obtained in moderate yield from maleimide-derived cycloadduct **324d** after MeONa/MeOH treatment (Scheme 107). It deserves to be mentioned that the maleimide moiety is not altered under the basic rearrangement conditions.

2.5. Medium-Sized Heterocycles

Medium-sized ring azacycles occur in a range of natural and unnatural products possessing wide and diverse medici-

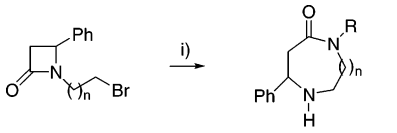
Scheme 107[a]



(+)-324d **(+)-325d** (43%)

[a] Key: (i) MeONa, MeOH, RT, 16 h.

Scheme 108[a]



326a n = 1	**327a** R = H (70%)
326b n = 2	**327b** R = H (90%)
326c n = 3	**327c** R = H (67%)
326d n = 1	**327d** R = Et (88%)
326e n = 2	**327e** R = Et (46%)
326f n = 2	**327f** R = allyl (55%)

[a] Key: (i) RNH_2, 20−85 °C, 6−14 days.

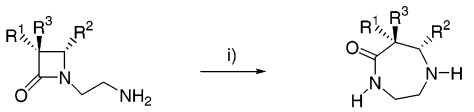
nal and biological properties. However, medium-sized rings are difficult to prepare due to enthalpic and entropic reasons, and direct cyclization methods are ineffective unless certain conformational restraints are present in the acyclic precursor. A potential solution to formation of medium-sized azacycles is to employ the cyclic 2-azetidinone skeleton as a template on which to build the medium-sized ring using the chirality and functionalization of the β-lactam nucleus as a stereocontrolling element. Another possibility is to use the strain energy of the β-lactam nucleus as the driving force for ring expansion to medium rings.

Synthesis of medium-ring heterocycles from *N*-(halogenoalkyl)-β-lactams **326** has been reported.[79] 2-Azetidinone derivatives **326**, when treated with liquid ammonia in a sealed tube, directly gave the corresponding seven-, eight-, and nine-membered ring-expanded azalactams **327** in good yields (Scheme 108). These reactions presumably involve intramolecular transamidation of *N*-aminoalkyl substitution products, and indeed, in some cases these intermediates could be isolated. Alkyl primary amines can replace ammonia in this transformation. Treatment of 2-azetidinones **326** with ethylamine and allylamine in a sealed tube gave the corresponding *N*-alkyl azalactams. Substitution products as well as products arising from intermolecular transamidation were isolated in small proportions. The seven-membered azalactam **327a** was used by the same authors in a synthesis of the spermine alkaloid homaline.[80]

It has been demonstrated that the transamidation reaction of monocyclic β-lactams having an amino group tethered at N1 is a powerful entry to seven-membered azalactams.[32,81] On standing, amino-β-lactams **328** tended to afford less polar products, identified as the monocyclic seven-membered heterocycles **329** (Scheme 109). After the intramolecular transamidation process was completed as described below, in the IR spectrum the β-lactam carbonyl signal that appeared at about 1740 cm^{-1} was replaced in 1,4-diazepin-5-ones **329** by a signal at 1660 cm^{-1}.

The ring enlargement described above on monocyclic β-lactams was extended to the bicyclic 2-azetidinone **330**.[32,81] On warming the free amine **330** in THF at reflux in the presence of the hydrogen donor 1,4-cyclohexadiene the

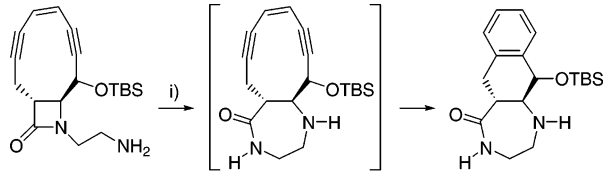
Scheme 109[a]



328a R^1 = H, R^2 = OBOM	**329a**[b]
328b R^1 = MeO, R^2 = *(E)*-CH=CHPh	**329b**[b]
328c R^1 = MeO, R^2 = OBOM	**329c**[b]
328d R^1 = PhO, R^2 = OBOM	**329d**[b]
328e R^1 = Me, R^2 = 4-ClC_6H_4, R^3 = Ph	**329e** (34%)[c]
328f R^1 = Me, R^2 = 3,5-$(MeO)_2C_6H_3$, R^3 = Ph	**329f** (40%)[c]

[a] Key: (i) EtOH, 60 °C, 8−136 h. [b]Quantitative conversion by ^1H NMR. [c]Toluene, reflux, 72 h.

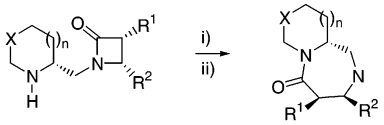
Scheme 110[a]



330 **331** **332** (45%)

[a] Key: (i) THF, 1,4-cyclohexadiene, reflux, 4 days.

Scheme 111[a]



333a n = 0, X = CH_2	**334a** R^1 = OBn, R^2 = 4-ClC_6H_4 (54%)
333b n = 0, X = S	**334b** R^1 = OMe, R^2 = 4-(1,2-OCH_2CH_2O)C_6H_4 (56%)
333c n = 1, X = CH_2	**334c** R^1 = OMe, R^2 = 4-(1,2-OCH_2CH_2O)C_6H_4 (70%)
333c n = 1, X = CH_2	**334d** R^1 = OBn, R^2 = 4-ClC_6H_4 (68%)

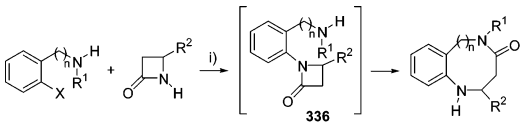
[a] Key: (i) 4 N HCl, dioxane, RT, 6 h; (ii) DMF, 200 °C, microwave, 40 min.

amine slowly disappears and gives rise to two new spots (TLC). Very small quantities of the less polar product can be isolated by fast preparative TLC. This very minor compound which possesses the enediyne group is the bicyclic azalactam **331**. The main product is the cycloaromatized tricycle **332**, which was obtained in moderate yield (45%) after completion of the reaction (Scheme 110). The half-life of **330** under these conditions was estimated to be about 24 h.

Synthesis of a collection of bicyclic fused azepinones via an intramolecular β-lactam ring-opening strategy has been recently reported.[82] After deprotection of the Boc moiety, the β-lactams **333**, obtained starting from enantiomerically enriched amines such as (*R*)- or (*S*)-2-aminomethyl pyrrolidine (piperidine) via Staudinger cycloaddition, followed by heating the resulting heterocyclic amine in a sealed tube using single-mode microwave irradiation afforded facile conversion to[1,4]diazepin-5-ones **334** in reasonable yields (Scheme 111). No epimerization was observed in any of the synthesized azalactams at these elevated temperatures.

Synthesis of medium-sized azalactams fused to a benzene ring via a tandem copper-catalyzed C−N bond formation−β-lactam ring-expansion process has been recently accomplished.[83] Using 2-bromobenzylamine and 2-azetidinone as the coupling partners the desired eight-membered heterocycle **335b** was isolated in 96% yield and none of the *N*-arylated β-lactam **336b** was observed, indicating a facile domino process involving the copper-catalyzed aryl amidation reaction and subsequent ring expansion. Although not

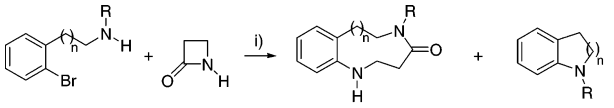
Scheme 112[a]



335a n = 0, X = I, R^1 = H, R^2 = H (92%)[b]
335b n = 1, X = Br, R^1 = H, R^2 = H (96%)
335c n = 1, X = Br, R^1 = H, R^2 = Ph (88%)
335d n = 1, X = Br, R^1 = $(CH_2)_5$, R^2 = H (90%)

[a] Key: (i) 5 mol % CuI, 10 mol % *N*,*N*′-dimethylethylenediamine, K_2CO_3, toluene, reflux, 22−24 h. [b]Coupling reaction was performed at 100 °C, 5 h. Transamidation conditions: 50 mol % Ti(*i*-OPr)$_4$, dioxane, 110 °C, 24 h.

Scheme 113[a]



335e n = 1, R = H (68%)[b]
335f n = 1, R = Bn (78%)
335g n = 2, R = H (68%)[c]
337a n = 1, R = H (18%)[b]
337b n = 1, R = Bn (17%)
337c n = 2, R = H (13%)

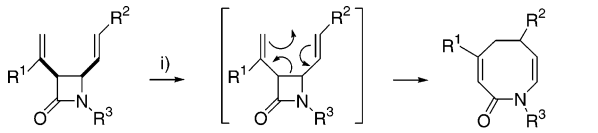
[a] Key: (i) 5 mol % CuI, 10 mol % *N*,*N*′-dimethylethylenediamine, K_2CO_3, toluene, reflux, 22−24 h. [b]Coupling reaction was performed without the ligand. [c]Transamidation conditions: 2 equiv of AcOH, THF, 60 °C, 4 h.

investigated in every case, addition of a diamine ligand, *N*,*N*′-dimethylethylenediamine, was found to be beneficial for the main cases in Scheme 112, particularly when *N*-substituted bromobenzylamines were used as coupling partners. The reaction tolerates substituents on the β-lactam ring and an aliphatic OH group. A relatively slow ring-expansion step was encountered in the preparation of seven-membered azalactam **335a** starting with 2-iodoaniline, observing less than 5% of the desired ring-expanded product at the end of the copper-catalyzed coupling reaction. Fortunately, the desired seven-membered heterocycle **335a** could be obtained if the crude mixture of the coupling reaction products was treated with 50 mol % of Ti(*i*-OPr)$_4$ in toluene at 110 °C (Scheme 112). The C−N coupling−ring-expansion reaction could also be extended to preparation of 9- and 10-membered rings. However, direct cyclization of the aryl bromide substrate providing either an indoline or a tetrahydroquinoline competed with the desired process (Scheme 113). The ratio of the desired medium ring product to the undesired five- or six-membered ring side-product **337** exhibited an interesting dependence on the diamine ligand. Thus, the *N*,*N*′-dimethylethylenediamine ligand increased the yield of the undesired five-membered heterocycle while decreasing the amount of undesired six-membered heterocycle. Formation of the five-membered ring side product was also diminished for an *N*-benzylated aryl bromide substrate.

A clean protocol for the synthesis of eight-membered lactams (tetrahydroazocinones) via a concerted C3−C4 bond breakage of the β-lactam nucleus has been published.[84] The authors reasoned that the presence of alkenyl groups attached to adjacent ring positions (C3 and C4) of the β-lactam ring might provide an opportunity to use a thermal [3,3] sigmatropic rearrangement for the synthesis of eight-membered lactams through C3−C4 bond breakage. Starting from 2-azetidinone-tethered 1,5-dienes **338** a stereoselective synthesis of tetrahydroazocinones **339** was developed. This is the first example of a Cope rearrangement in which the C3−C4 bond of the β-lactam nucleus is the central bond of the 1,5-hexadiene system (Scheme 114). Of particular interest were the reactions of enantiomerically pure substrates **338e**-α and **338e**-β, which cleanly rearranged to the corresponding optically pure products **339e**-α and **339e**-β. The high stereospecificity of these Cope rearrangements may be interpreted via a boat-like transition state as shown in Scheme 115. Synthesis of a nonpeptide β-turn mimetic of enkephalin has been reported involving a β-lactam approach.[85] The starting 2-azetidinone **340** was easily obtained via standard peptide coupling reactions. The medium-sized heterocycle formation involved opening of the four-membered ring and subsequent cyclization (Scheme 116). The triazacycle **341** was obtained in an excellent 94% yield.

Anatoxin-*a* has been isolated from a freshwater blue-green algae, and its structure was found to be a derivatized 9-azabicyclo[4.2.1]nonane. Synthesis of racemic anatoxin-*a*

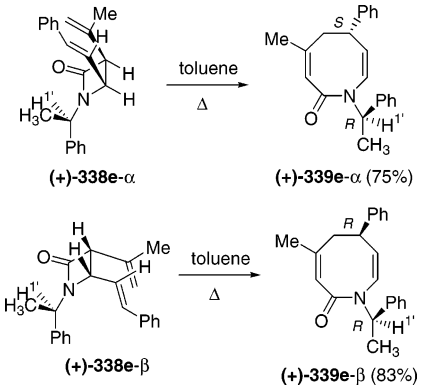
Scheme 114[a]



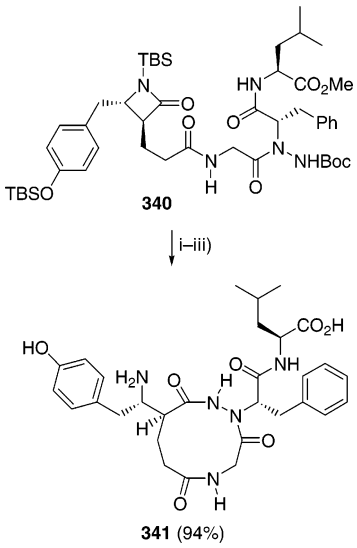
338a R^1 = H, R^2 = CO_2Me, R^3 = PMP — **339a** (86%)
338b R^1 = H, R^2 = COMe, R^3 = PMP — **339b** (85%)
338c R^1 = Me, R^2 = CO_2Me, R^3 = PMP — **339c** (90%)
338d R^1 = H, R^2 = Ph, R^3 = Bn — **339d** (79%)
(+)-338e-α R^1 = Me, R^2 = Ph, R^3 = (*R*)-CH(Me)Ph — **(+)-339e**-α (75%)
(+)-338e-β R^1 = Me, R^2 = Ph, R^3 = (*R*)-CH(Me)Ph — **(+)-339e**-β (83%)

[a] Key: (i) toluene, reflux, 3−5 h.

Scheme 115

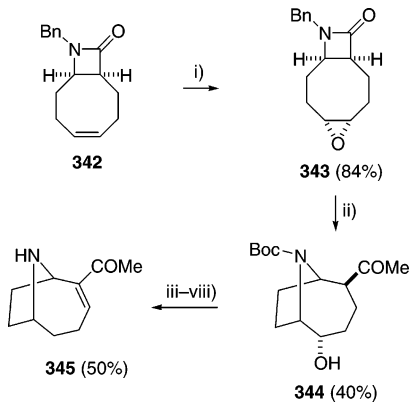


Scheme 116[a]



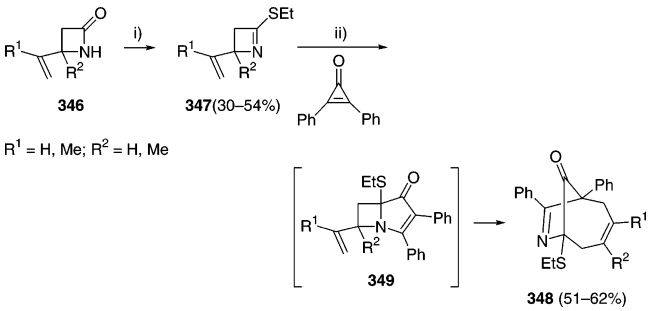
[a] Key: (i) F_3CCO_2H, CH_2Cl_2, −10 °C, 3 h; (ii) Et_3N, CH_2Cl_2, 0 °C, 1 h; (iii) TBAF, THF, RT, 2 h.

Scheme 117[a]



[a] Key: (i) MCPBA, CH_2Cl_2, RT, 24 h; (ii) MeLi, THF, −25 °C, 1 h; (iii) H_2, Pd−C, MeOH, Boc_2O; (iv) Ph_3P, I_2, imidazole, CH_2Cl_2, RT, 1 h; (v) Bu_3SnH, AIBN, toluene, reflux, 30 min; (vi) NaH, THF, cat. MeOH, RT, 7 h, then TBSCl, Et_3N, THF, −15 °C, then RT, 16 h; (vii) $Pd(OAc)_2$, MeCN, RT, 48 h; (viii) TFA, CH_2Cl_2, RT, 1 h.

Scheme 118[a]



[a] Key: (i) (a) Lawesson's reagent; (b) $Et_3O^+BF4^-$, CH_2Cl_2; (ii) MeCN, RT, 7 days.

relies on a tandem methyllithium-induced 2-azetidinone ring opening−intramolecular cyclization.[86] Treatment of the benzyl-protected β-lactam **342** with metachloroperoxybenzoic acid provided the epoxide **343**, which bears the correct relative anti relationship between the epoxide and the β-lactam moiety. The lack of amide resonance in the β-lactam ring allows nucleophilic attack to take place on the carbonyl group. Thus, the β-lactam in **343** was opened with methyllithium through a tandem ring opening−ring closing to yield the methyl ketone **344**, which was transformed through several steps into the nicotinic acetylcholine receptor agonist anatoxin-*a* **345** (Scheme 117).

A novel procedure has been developed for preparation of 2,3-disubstituted 4,1-benzothiazepines via the ring transformation of the tricyclic monochloro-β-lactam derivative 2-chloro-2a-phenyl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]-benzothiazin-1-one with sodium ethoxide in ethanol.[87] Conversion of 4-vinyl-substituted β-lactams **346** into 4-vinyl-substituted 1-azetines **347** and their subsequent reaction with diphenylcyclopropenone (DPP) results in formation of highly functionalized 7-azabicyclo[4.2.1]nonenes **348** (Scheme 118).[88] Thiation of 4-vinyl-substituted β-lactams **346** with Lawesson's reagent was facile, giving the corresponding 4-vinyl-2-thioxo analogues in 75−90% yield, which were then converted into the corresponding 1-azetines **347** in 40−60% yield using a solution of triethyloxonium tetrafluoroborate (Meerwein's reagent) in dichloromethane. The 7-azabicyclo-[4.2.1]nonene heterocyclic system is an isomer of the homotropane (9-azabicyclo[4.2.1]nonene) nucleus, which is the core structure of a class of alkaloid natural products that includes anatoxin-*a*. It is believed that the expected reaction of the 1-azetines **347** with DPP occurs to initially give the azabicyclo[3.2.0]heptenes **349**. The final process in the reaction is an aza-Cope (amino-Claisen) 3,3-sigmatropic rearrangement. Aza-Cope rearrangement in such a bicyclic ring system is facilitated by strain relief and the fact that the azabicyclo[3.2.0]heptene ring system has an inherent 'half-open book' conformation at the ring junction, which allows the vinyl substituent and second alkene to overlap. Such a proposal necessitates that the vinylic and SEt groups in species **349** adopt a trans relationship with the larger SEt group on the less hindered convex face of the molecule.

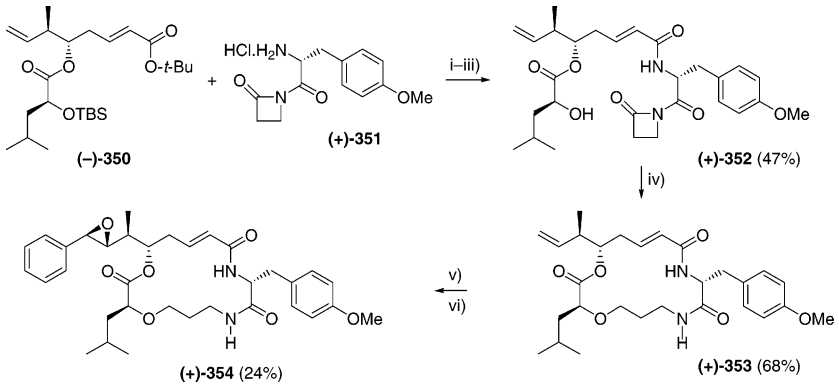
2.6. Macrocyclic Heterocycles

Cryptophycins are potent, tumor-selective tubulin-binding antimitotic agents with excellent activity against multidrug-resistant cancer cells. An efficient and concise approach to the synthesis of the macrolide core of cryptophycins has been developed, illustrating the usefulness of the β-lactam framework for construction of macrocycles.[89] The reaction sequence features a novel macrolactonization utilizing a reactive acyl-β-lactam intermediate that incorporates the β-amino acid moiety within the 16-membered macrolide core. Synthesis of cryptophycin-24 started with compound **350**, which after ester cleavage was coupled with amino-acylazetidinone **351** using HBTU/DIEA. A further acidic silyl ether cleavage provided the acyl-β-lactam intermediate **352**. Attempts to cyclize this intermediate with NaH and NaHMDS (paclitaxel conditions) were incompatible with this substrate, presumably as a result of its sensitivity to basic conditions. The key macrolactonization was achieved with the use of CH_2Cl_2-soluble Bu_4NCN to furnish the 16-membered macrolide **353** in 68% yield (Scheme 119). Introduction of the C3′-phenyl group under Heck conditions produced the desepoxy analogue in only 31% yield. The final epoxidation utilizing DMD provided a diastereomeric mixture of cryptophycin-24 (**354**, β:α = 2:1) in 76% yield, which was separated by reverse-phase HPLC.

As an extension of the above methodology, synthesis of the macrolide core of cryptophycin-52, the C6 *gem*-dimethyl-substituted derivative, which is under clinical development, was achieved.[89] Since the late-stage Heck coupling provided a poor yield, the phenyl group was placed at the octadienoate ester in an early step. Coupling of hydroxy compound **355** and β-lactam **356** with HBTU and DIEA furnished the macrolide precursor **357**, which possessed all of the elements necessary for formation of the macrocycle (Scheme 120). Initially, the simultaneous ring opening of the acyl-β-lactam followed by cyclization was tried with an excess of tetrabutylammonium cyanide. Interestingly, it was found that the key macrolactonization could be achieved using a catalytic amount of tetrabutylammonium cyanide or potassium cyanide to produce the 16-membered macrolide **358** in 65% yield. The final epoxidation of **358** utilizing DMD provided a diastereomeric mixture of dechlorocryptophycin-52 (**359**) in a 2:1 (β:α) ratio and 75% yield. The mixture was separated by reverse-phase HPLC. The preliminary biological testing of the dechlorocryptophycin-52 analogue showed good activity in both the tubulin assembly assay and the cytotoxicity assay. The α-isomer was found to be less active in both assays.

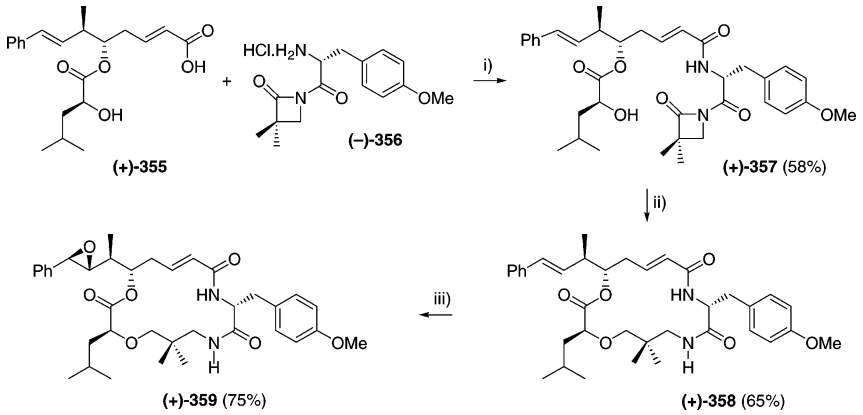
Dioxocyclams are intermediate between macrocyclic peptides and macrocyclic polyamines, having two amide and two secondary amine linkages as part of the ring periphery.

Scheme 119[a]



[a] Key: (i) TFA, CH_2Cl_2, RT, 6 h; (ii) HBTU, DIEA, MeCN, RT, 1 h; (iii) $BF_3{\cdot}Et_2O$, $CHCl_3$, RT, 1 h; (iv) Bu_4NCN, CH_2Cl_2, RT, 16 h; (v) PhI, $Pd(OAc)_2$, Et_3N, MeCN, 80 °C, 20 h; (vi) DMD, CH_2Cl_2–acetone, −30 °C, 24 h.

Scheme 120[a]



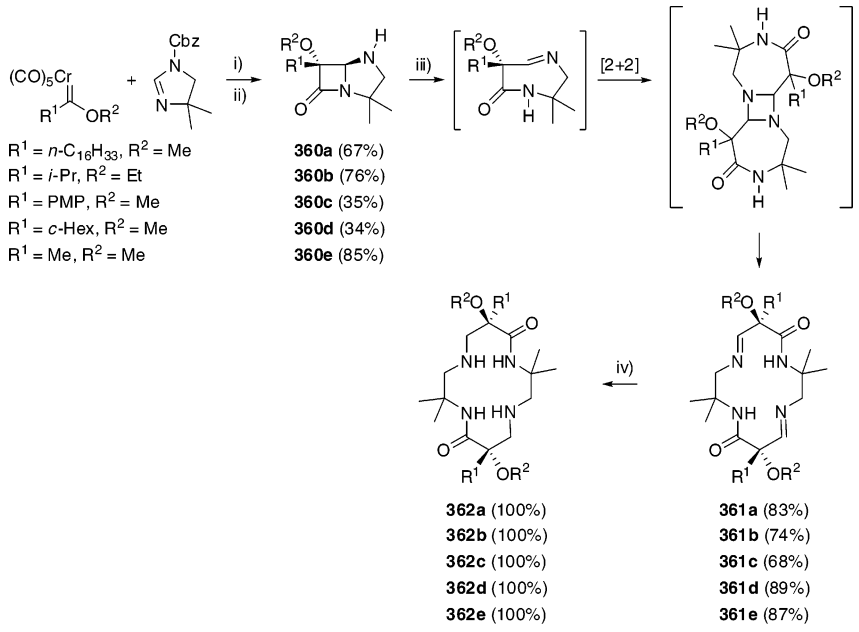
[a] Key: (i) HBTU, DIEA, MeCN, RT, 4 h;. (ii) Bu_4NCN, CH_2Cl_2, RT, 30 min; (iii) DMD, acetone, RT, 2 h.

The amines are nucleophilic and reactive toward a range of electrophiles. Use of bis-electrophiles can result in either linking or capping these macrocycles. Starting from appropriate bicyclic 2-azetidinones has resulted in efficient syntheses of variously substituted dioxocyclams and bridged bis-dioxocyclams.[90] Photolysis of chromium alkoxycarbene complexes with imidazolines produced azapenams, which after removal of the *N*-Cbz protecting group produced free azapenams **360**. Hydrogenolytic removal of the *N*-Cbz protecting group in the presence of triethylamine to prevent acid-catalyzed processes proceeded in virtually quantitative yield for the azapenams having alkyl side chains, but deprotection of aryl azapenams resulted in substantial amounts of 2-azetidinone ring-cleaved products in addition to the desired *NH*-azapenam. Treatment of azapenams **360** with 0.25 equiv of camphorsulfonic acid in methylene chloride resulted in their clean conversion to tetraaza macrocycles **361** in good yields. Since racemic azapenams were used and macrocycles **361** now contain two chiral centers, these materials were obtained as a 1:1 mixture of centro- and C_2-symmetric diastereoisomers (Scheme 121). These equilibrate under acid catalysis, and the centrosymmetric diastereoisomer preferentially crystallizes, allowing conversion of the 1:1 mixture completely to the centrosymmetric diastereoisomer **361** after three recrystallizations. Reduction with sodium cyanoborohydride led to dioxocyclams **362**.[91]

Bridged dioxocyclam **363** and bridged bis-dioxocyclam **364** have been prepared following the same methodology (Figure 2).[92] Related 5,12-dioxocyclam having quinoxaline substituents at the 6 and 13 positions have been synthesized through the same method and studied as potential DNA bis-intercalating and cleaving agents.[93]

Synthesis of cytotoxic macrocyclic taxoids according to a synthetic β-lactam route has been described, which involves a ring-opening coupling protocol followed by Ru-catalyzed ring-closing metathesis.[94] Syntheses of taxoids began with the preparation of β-lactams **365**. Reaction of 4-oxoazetidine-2-carbaldehyde **366** with vinylmagnesium bromide followed by in situ protection of the resulting alcohol with acetic anhydride gave an ester, which was subjected to hydrogenolysis to achieve an allyl-β-lactam. Reaction of **366** with the same Grignard reagent followed by protection of the resulting alcohol as the TBS ether afforded the corresponding β-lactam. To reduce the steric bulk for efficient ring-opening coupling with C2-modified baccatin both the TIPS and TBS groups were replaced with TES. Reaction of aldehyde **366** with methylenetriphenylphosphorane afforded the corresponding vinyl-β-lactam. After *N*-dearylation and protection of the resulting free NH with $(Boc)_2O$, the β-amino acid taxol side-chain precursors **365a**−**c** were obtained (Scheme 122). The ring-opening coupling of alkenyl-β-lactams **365** with C2-alkenoylbaccatins **367** was promoted by lithium hexamethyldisilazane to give the corresponding taxoid-ω,ω′-dienes **368** bearing two olefinic tethers at the C2 and C3′ positions. The RCM of dienes **368** catalyzed by first-generation Grubbs' catalyst gave the 16-, 17-, and 18-membered macrocyclic taxoids **369** in moderate to high yields (67−94%) (Scheme 123). It is noteworthy that the RCM was found to be applicable to the macrocyclization of highly

Scheme 121[a]



[a] Key: (i) *hν*, CH_2Cl_2, 60 psi CO, 35 °C; (ii) H_2, 10% Pd−C, Et_3N, MeOH; (iii) CSA, CH_2Cl_2, then CH_2Cl_2/hexanes, CSA (cat.); (iv) $NaCNBH_3$, CH_2Cl_2/MeOH, RT.

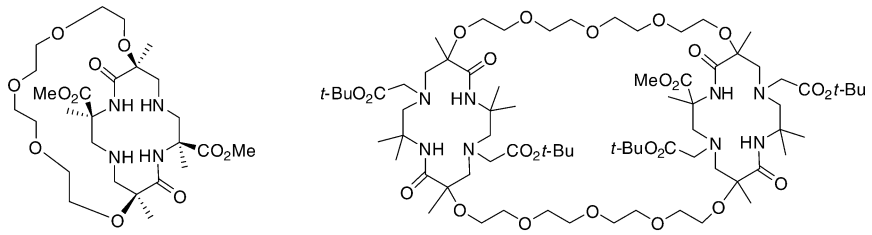
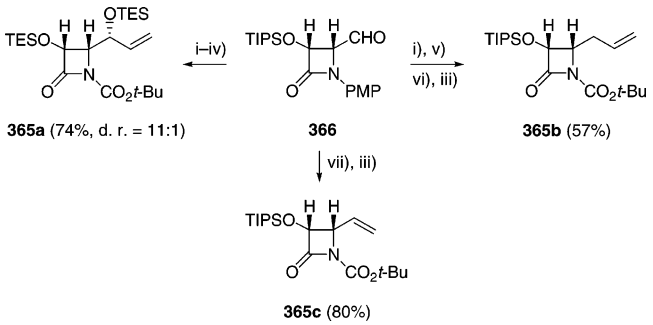


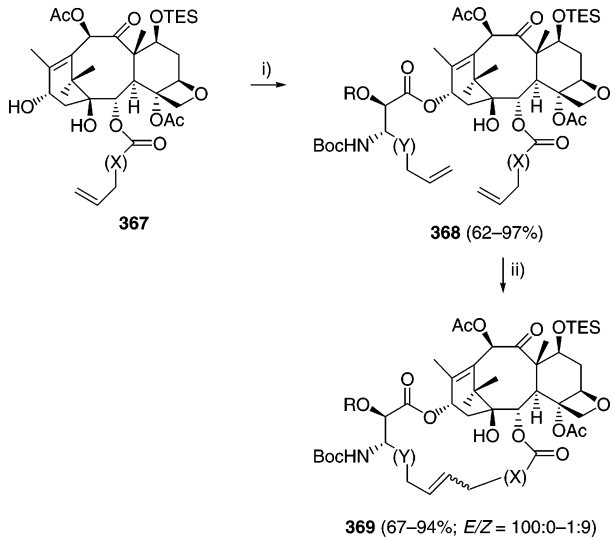
Figure 2.

Scheme 122[a]



[a] Key: (i) CH_2═CHMgBr, THF, −78 °C; (ii) TBSCl, Et_3N, reflux, 2 days; (iii) CAN, MeCN−H_2O, −10 °C, then $(Boc)_2O$, Et_3N, DMAP, RT; (iv) HF-py, RT, then TESCl, Et_3N, DMAP, RT; (v) Ac_2O, Et_3N, RT; (vi) $Pd_2(dba)_3$, HCO_2NH_4, PBu_3, dioxane, reflux; (vii) Ph_3P═CH_2, THF, −78 to 0 °C.

Scheme 123[a]

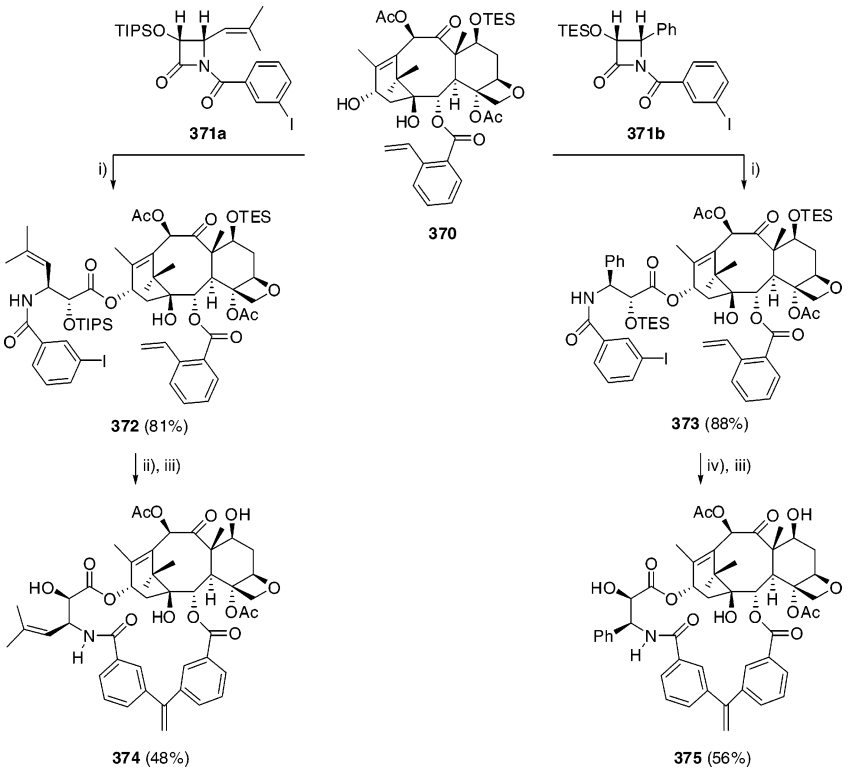


[a] Key: (i) LiHMDS, **365**, THF, −40 °C, 30 min; (ii) 20−50 mol % $Cl_2(Cy_3P)_2Ru$═CHPh, CH_2Cl_2 or toluene, 25−70 °C, 8−52 h.

complex and multifunctionalized systems. Another interesting feature observed in these RCM reactions is the stereoselective formation of the olefin moiety, with the stereochemistry of the double bond in **369** being predominantly or exclusively *E* in most cases. It is also worthy of note that the Ru-catalyzed RCM takes place exclusively at the terminal olefin moieties of taxoid-*ω*,*ω*′-dienes bearing an additional inner olefin.

However, it was found that RCM reactions using Grubbs' carbene were rather sensitive to the substitution pattern in the proximity of the terminal olefin, e.g., certain allylic substitutions substantially slowed or inhibited ring-closing metathesis to form macrocyclic taxoids. Consequently, it was decide to explore the intramolecular Heck reaction as an alternative approach.[95] Macrocyclization precursors were synthesized as before through the *β*-lactam ring-opening coupling reaction with properly modified baccatins. Modified

Scheme 124[a]

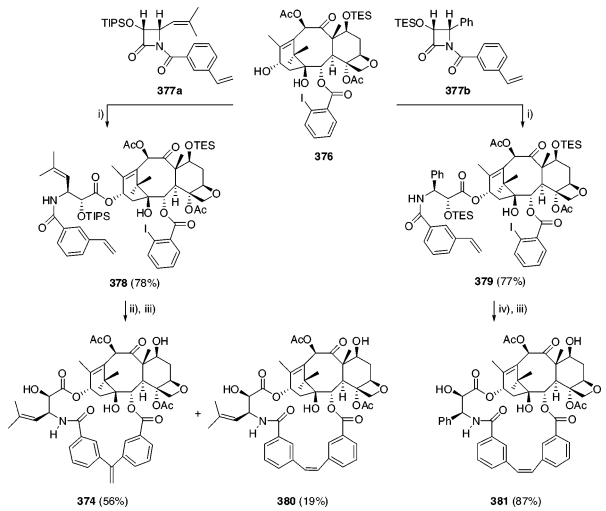


[a] Key: (i) LiHMDS (1.5 equiv), 371 (1.5−2.0 equiv), THF, −40 °C, 30 min; (ii) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, MeCN, 55 °C, 16 h; (iii) HF-py, MeCN, 16 h; (iv) $Pd_2(dba)_3$ (0.05 equiv), $AsPh_3$ (0.2 equiv), Et_3N, MeCN, 55 °C, 24 h.

baccatin **370** was coupled with 2-azetidinone **371a** in the presence of LiHMDS to afford **372** in high yield. For the synthesis of **373**, 3-TESO-β-lactam **371b** was employed since 4-phenyl-β-lactams bearing a large silyl group at C3 are difficult to couple with baccatins. Coupling of β-lactam **371b** with baccatin **370** proceeded smoothly to afford **373** in excellent yield (Scheme 124). The Heck reaction of **372** was carried out in acetonitrile with a catalytic amount of $Pd(PPh_3)_4$ and excess triethylamine at 55 °C overnight. The reaction gave only the *exo*-cyclization product in 65% isolated yield, which is substantially higher than those achieved in most of the macrocyclic intramolecular Heck reactions. Then, deprotection with HF−pyridine afforded macrocyclic taxoid **374** in 74% yield. Taxoid **373** was subjected to the same conditions but failed to give any cyclized product. However, use of triphenylarsine, a weaker σ-donor ligand, in place of triphenylphosphine solved the problem. Thus, reaction of **373** using $Pd_2(dba)_3$ as the Pd source and $AsPh_3$ as the ligand afforded the *exo*-adduct exclusively. Removal of silyl protection groups by HF−pyridine gave **375** in 56% yield for two steps (Scheme 124).

The positions of the iodide and olefin moieties were switched in order to examine a possible effect of this change on the regioselectivity of the Heck reaction. Thus, baccatin **376** was coupled with β-lactams **377a** and **377b** to give taxoid substrates **378** and **379**, respectively, in good yields (Scheme 125). Macrocyclization of **378** was carried out using the same conditions as those employed for **372**, which gave a mixture of *exo* and *endo* products (*exo:endo* = 3:1) in 68% isolated yield. Deprotection with HF−pyridine and HPLC separation afforded macrocyclic taxoids **374** (*exo* isomer, 56%) and **380** (*endo* isomer, 19%). For **380**, only the *Z* isomer was formed. When the macrocyclization of the taxoid **379** was examined, the corresponding *endo* product was afforded exclusively. Deprotection with HF−pyridine gave

Scheme 125[a]

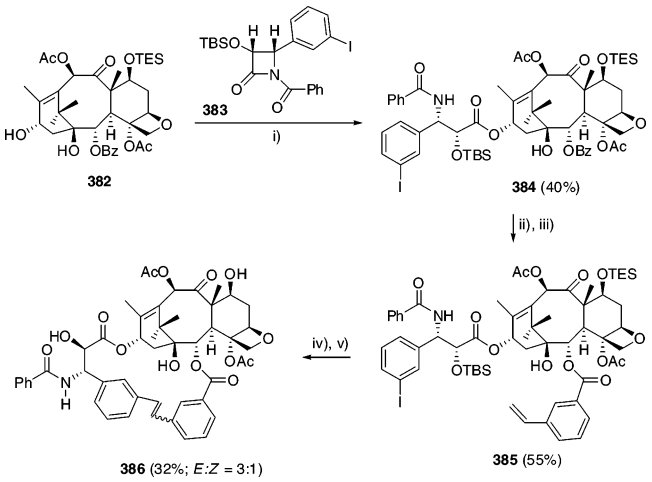


[a] Key: (i) LiHMDS (1.5 equiv), 377 (1.5−1.8 equiv), THF, −40 °C, 35 min; (ii) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, MeCN, 50 °C, 16 h; (iii) HF−py, MeCN, 16 h; (iv) $Pd(PPh_3)_4$ (0.07 equiv), Et_3N, MeCN, 50 °C, 11 h.

macrocyclic taxoid **381** in 87% yield for two steps (Scheme 125). Again, only the *Z* isomer was formed. Some of these macrocyclic taxoids, especially the *exo* isomers, were found to be significantly cytotoxic against the LCC6-WT human breast cancer cell line.

An intramolecular Heck reaction to construct C2−C3′ linked macrocyclic taxoids using a stoichiometric amount of Pd has been reported as well.[96] Coupling of the 7-*O*-TES-baccatin **382** with β-lactam **383** resulted in formation of **384** in 40% yield. The low yield is apparently due to the presence of the *meta*-iodo substituent at the 4-phenyl group. When iodine is present in the aromatic precursor in the Heck

Scheme 126[a]



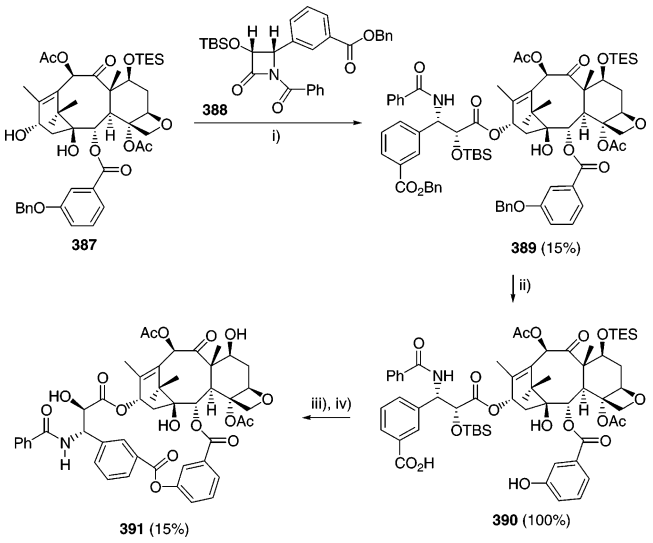
[a] Key: (i) NaH (10 equiv), **383** (10 equiv), THF, 35 °C; (ii) *t*-BuOK (1.4 equiv), H_2O (1.2 equiv), THF, −15 °C; (iii) DCC (20 equiv), DMAP (20 equiv), 3-vinylbenzoic acid (20 equiv), toluene, 55 °C; (iv) $Pd(OAc)_2$ (1 equiv), PPh_3, Ag_2CO_3, MeCN, 60 °C; (v) HF−py, pyridine.

cyclization the alkene component was introduced next. Selective hydrolysis of the benzoate moiety followed by treatment with an excess of 3-vinylbenzoic acid, DCC, and DMAP resulted in the macrocyclization precursor **385**. Utilization of acetonitrile as solvent and Ag_2CO_3 as an additive were critical for success of the Heck reaction. A stoichiometric amount of Pd promoter was used to ensure an effective concentration of catalyst over the time course of the reaction. The macrocyclic Heck product was obtained in 40% yield as a mixture of isomers, predominantly the *E* isomer. Removal of the silyl protecting groups with HF−pyridine gave the stable macrocycle **386** (Scheme 126).

A β-lactam-based synthesis of conformationally restricted paclitaxel analogues has been described using macrolactonization as the key step.[96] Modified baccatin **387** was reacted with 2-azetidinone **388**. However, formation of the side-chain coupling product **389** was uncharacteristically poor (15%). Catalytic hydrogenolysis of the benzyl protecting groups resulted in the macrolactonization precursor **390**. Macrolactonization was mediated by BOPCl under high-dilution conditions to give the macrocycle in 21% yield as a 1: 1 mixture of atropoisomers. Silyl deprotection resulted in the macrolactone taxoid **391** (Scheme 127).

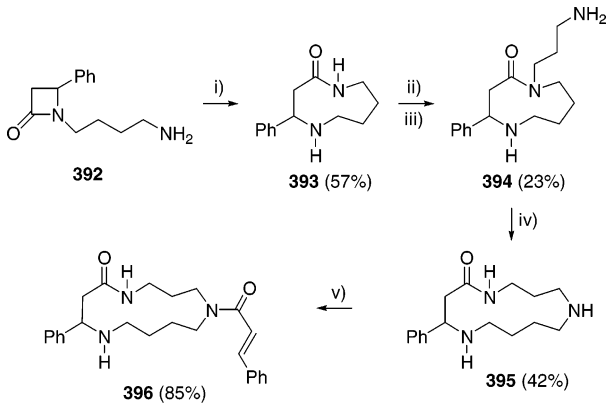
Alkaloids derived from the polyamines spermine and spermidine comprise a large family of natural products showing a wide spectrum of biological activity.[97] A strategy for forming the macrocyclic system in these alkaloids has been developed through use of β-lactams as reactive sources of β-amino acyl units.[98] It has been found that ring opening of these strained entities by intramolecular nucleophilic attack could serve as a general method for incorporation of the four-atom fragment. Syntheses of the spermidine alkaloids celacinnine and the spermine alkaloid verbascenine established the viability of the ring-expansion approach.[99] Synthesis of celacinnine started with the transamidation of amino-β-lactam **392** to give the 9-membered azalactam **393**. 2-Azetidinone **392** was inert in warm 1 N NaOH but slowly underwent conversion to the azalactam **393** in refluxing 2,4-lutidine. Despite long reaction times up to 64 h, significant amounts of starting material were invariably recovered. This result suggested an equilibrium between **392** and **393**, with **393** being only slightly more stable than **392** because the strain associated with the 9-membered azalactam **393** is comparable

Scheme 127[a]



[a] Key: (i) NaHMDS, THF, −78 °C; (ii) H_2, Pd−C, THF; (iii) BOPCl, Et_3N, CH_2Cl_2; (iv) HF−py, pyridine.

Scheme 128[a]

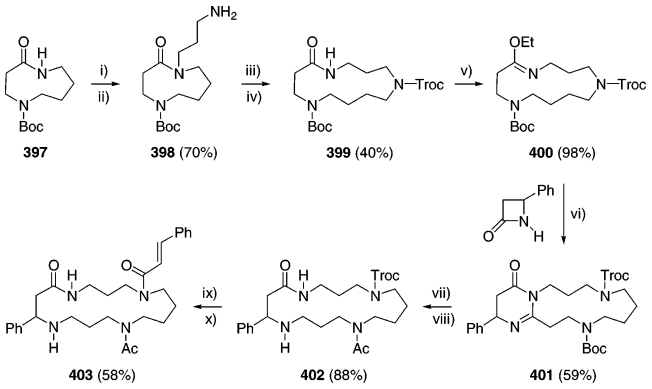


[a] Key: (i) 2,4-lutidine, reflux, 64 h; (ii) DMF, NaH, 50 °C, then *N*-(3-iodopropyl)phthalimide, RT, 2 h; (iii) $N_2H_4 \cdot H_2O$, EtOH, reflux, 1 h; (iv) 1 N NaOH, MeOH, 55 °C, 50 h; (v) *trans*-cinnamoyl chloride, DMAP, CH_2Cl_2, from −78 to −20 °C, 10 h.

in magnitude to that of the β-lactam **392**. Alkylation of the sodium salt of **393**, formed in DMF at 50 °C by NaH deprotonation, with *N*-(3-iodopropyl)phthalimide was not very efficient (23%). Treatment of the alkylated compound with hydrazine hydrate in refluxing ethanol furnished the free amine **394** in quantitative yield. Transamidation to the 13-membered azalactam **395** took place by warming the mixture in 2:1 NaOH/dioxane. Synthesis of racemic celacinnine **396** was complete by treatment of a solution of DMAP in dichloromethane with *trans*-cinnamoyl chloride at low temperature (Scheme 128).

Synthesis of the spermine alkaloid verbascenine required preparation of a suitably protected 13-membered azalactam derivative having the same core structure as **396**. The 17-membered azalactam system of verbascenine was accessed via subsequent amide *O*-alkylation, condensation with 4-phenylazetidin-2-one, and reductive ring expansion. Attachment of a 3-aminopropyl side chain to the Boc derivative **397** was carried out as in the celacinnine synthesis. Thus, alkylation of **397** using *N*-(3-bromopropyl)phthalimide in NaH/DMF followed by phthalimide cleavage afforded **398** in high yield. The amino azalactam **398** proved to be quite resistant toward transamidative ring expansion. The rearrangement reaction

Scheme 129[a]

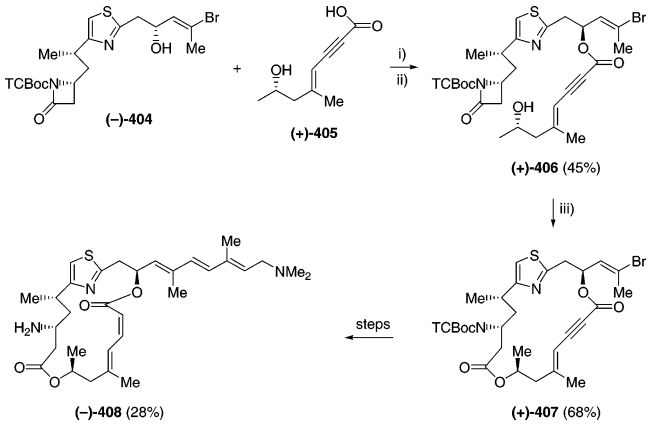


[a] Key: (i) DMF, NaH, 50 °C, then *N*-(3-bromopropyl)phthalimide, RT, 3 h; (ii) $N_2H_4 \cdot H_2O$, EtOH, reflux, 1 h; (iii) 2,4-lutidine, reflux, 19 h; (iv) $ClCO_2CH_2CCl_3$, DMAP, CH_2Cl_2, RT, 45 min; (v) Et_3OBF_4, molecular sieves, CH_2Cl_2, RT, 4.5 h; (vi) C_6H_5Cl, reflux, 15 h; (vii) HCl(g), CH_2Cl_2, 0 °C, 1 h, then MeCOCl, DMAP, RT, 1 h; (viii) $NaBH_3CN$, AcOH, RT, 15 h; (ix) Zn, AcOH, RT, 18 h; (x) *trans*-cinnamoyl chloride, DMAP, CH_2Cl_2, from −78 to −20 °C, 18 h.

took place when **398** was heated to reflux in 2,4-lutidine (19 h), the conditions used previously for expansion of the amino β-lactam **392**. The rearranged product was treated with 2,2,2-trichloroethyl chloroformate to obtain the differentially protected azalactam **399**. Lactim ether formation was carried out by treatment of **399** with triethyloxonium tetrafluoroborate in dichloromethane at room temperature. The reaction time was an important factor since after prolonged exposure to the conditions cleavage of the Boc group occurred. This may have been due to the presence of acid (HBF_4) generated by reaction of the triethyloxonium ion with traces of water in the reaction mixture. The optimized procedure for the alkylation involved carrying out the reaction in the presence of molecular sieves for a period of 4−5 h. An excellent yield of *Z*-lactim ether **400** was obtained after basic workup. Condensation of **400** with 4-phenylazetidin-2-one occurred in refluxing chlorobenzene to give **401** in 59% yield. After exchange of the Boc group for an acetyl group followed by reductive opening with $NaBH_3CN$, the 17-membered lactam **402** was obtained in 88% yield. Removal of the Troc protecting group was achieved using Zn/AcOH. The final step, selective cynnamoylation, was carried out under conditions similar to those for the analogous acylation in the celacinnine synthesis. In this way, racemic verbascenine **403** was obtained in a reasonable yield (Scheme 129).

Pateamine A is a natural product isolated from a marine sponge which displays potent immunosuppressive properties.[100] This unique natural product bears a thiazole and an *E,Z*-dienoate within a 19-membered macrocycle and a trienylamine side chain. Construction of the 19-membered dilactone macrolide has been achieved using a β-lactam-based macrocyclization as the key strategy.[101] Thus, a β-lactam has been used to install the C3-amino group (pateamine numbering) and then serve as an activated acyl group for macrocyclization. Transamidation of an aldol adduct to the corresponding *N*-benzyloxy amide followed by an intramolecular Mitsunobu cyclization reaction, reductive cleavage of the N−O bond with SmI_2, and protection of the β-lactam nitrogen as the trichloro-*tert*-butoxy carbamate gave the β-lactam **404** in good overall yield. Coupling of the β-lactam **404** with the enyne acid **405** was readily accomplished by a Mitsunobu reaction in 86% yield. The Mitsunobu coupling proceeded with inversion of configuration and minimal loss of stereochemical integrity. A

Scheme 130[a]



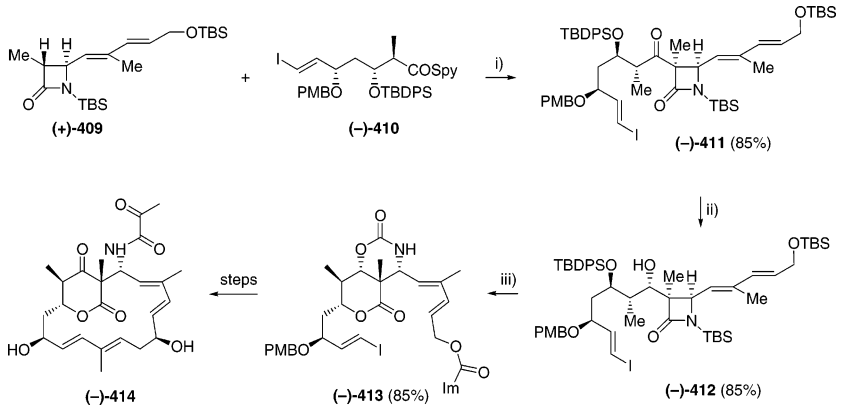
[a] Key: (i) Ph_3P, DIAD, THF, −20 °C, 1.5 h; (ii) HF−py, pyridine, THF, RT, 22 h; (iii) Et_4NCN (9 equiv), CH_2Cl_2 (0.0018 M), RT, 6 h.

subsequent desilylation of the TIPS ether provided the alcohol **406**, the substrate for the key β-lactam-based macrocyclization. Use of strong bases (NaHMDS, LiHMDS, NaH) for the intramolecular alcoholysis of the 2-azetidinone ring gave unsatisfactory yields of the expected macrocycle. The intramolecular acylation of the alcohol with the β-lactam moiety in **406** was accomplished under syringe pump addition of compound **406** to a 0.55 M solution of KCN in DMF (0.002 M, final substrate concentration). Use of Et_4NCN, a CH_2Cl_2-soluble source of cyanide ion, led to practical rates of formation of the desired macrocycle **407** in 7 h. Stirring both the hydroxy-β-lactam **406** and Et_4NCN in CH_2Cl_2 over freshly activated, powdered molecular sieves prior to reaction to remove traces of water led to slight improvement in yields. Use of CH_2Cl_2 as solvent instead of DMF in the macrocyclization greatly simplified product isolation. The total synthesis of (−)-pateamine A **408** was achieved after several additional steps from the macrocycle **407** (Scheme 130).

On the basis of the structural analysis of pateamine A, preliminary biological studies, and molecular modeling studies, a hypothesis was developed regarding the presence of distinct binding and scaffolding domains in the pateamine A structure with respect to interactions with its putative cellular receptor(s). Using a process similar to that previously employed in the total synthesis of (−)-pateamine A **408**, additional pateamine A derivatives with only minor structural variations were prepared from the β-lactam building block **404**. The simplified derivative of pateamine A devoid of the C3-amino and C5-methyl groups was found to have similar to greater potency than pateamine A in the interleukin-2 reporter gene assay. This result provides evidence for the hypothesis that this sector of the molecule (C1−C5) merely serves as a scaffold for the remaining conformationally rigid sectors (C6−C24) of the molecule including the thiazole, dienoate, and triene side chain.[102]

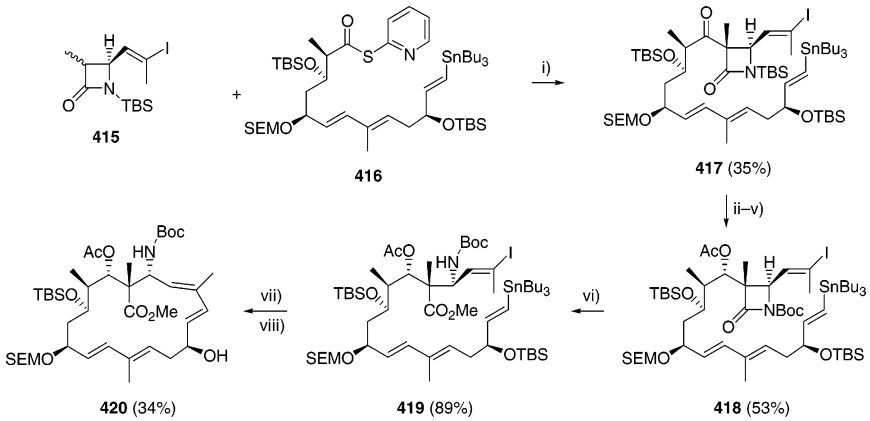
The antitumor antibiotic lankacidin C **414** is the parent member of a group of 17-membered macrocyclic tetraenes isolated from various species of *Streptomyces*. The lankacidins show strong antimicrobial activities against a variety of Gram-positive bacteria, including several strains resistant to the conventional macrolide antibiotics. An intramolecular N-to-O acyl migration of a β-lactam derivative has been used as a key step in the total synthesis of (−)-lankacidin C.[103] 2-Azetidinone **409** is the C1−C8 synthon for the lankacidin synthesis. Azetidinone **409** was prepared from L-aspartic acid

Scheme 131[a]



[a] Key: (i) LDA, THF, −78 °C, 10 min; (ii) KEt_3BH, Et_2O, −78 °C, 10 min; (iii) (a) TBAF, THF, RT, 2 h; (b) MsOH, RT, 2 h; (c) Et_3N, CDI, RT, 12 h.

Scheme 132[a]



[a] Key: (i) LDA, THF, −78 °C; (ii) KEt_3BH, Et_2O, −78 °C; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT; (iv) KF, MeOH, RT; (v) Boc_2O, DMAP, MeCN; (vi) MeOH, KCN, DMF, RT; (vii) TBAF, THF; (viii) $Pd_2(dba)_3$ (30 mol %), $AsPh_3$ (1.2 mol %), DMF, THF, RT.

in fair yield using cyclization, Swern oxidation, and Wittig olefination reactions as key steps. Treatment of a THF solution of β-lactam **409** with LDA at −78 °C resulted in formation of the lithium enolate. Subsequent addition of a solution of the 2-thiopyridyl ester **410** followed by stirring at −78 °C for 10 min afforded the β-ketolactam **411** in 85% yield as a single diastereomer. It was found that selective reduction of ketone **411** by potassium triethylborohydride in diethyl ether at −78 °C produced the single carbinol **412**. Preferred attack of the borohydride anion on the β-face of the ketone carbonyl generates the (*S*)-carbinol. All three silyl protecting groups were first removed with tetrabutylammonium fluoride. Subsequent addition of methanesulfonic acid to the reaction mixture catalyzed the β-lactam ring opening with concomitant δ-lactone formation. After 2 h at room temperature, triethylamine was added to quench the acid followed by 1,1′-carbonyldiimidazole trapping to yield 85% of the bicyclic lactone carbamate **413**. Thus, deprotection, N-to-O transacylation, and subsequent protection of the hydroxy amine were achieved in a one-pot fashion. The total synthesis of (−)-lankacidin C **414** was completed after a few more steps, involving the Stork−Takahashi protocol as the macrocyclization step (Scheme 131).

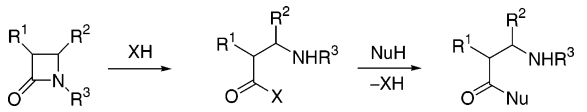
An alternative β-lactam-based strategy for synthesis of lankacidins has been described more recently.[104] Acylation of the azetidinone **415** using the thioester **416** and LDA as base was highly stereoselective and gave mainly a single stereoisomer of the product. This was identified as the required isomer **417**, although the yield was disappointing (35%). Reduction of the ketone using potassium triethylborohydride was stereoselective and gave a single alcohol. Treatment of this hydroxyvinylstannane with potassium fluoride in methanol−tetrahydrofuran removed the *N*-silyl group, leaving the *O*-silyl groups unchanged. However, conversion of the azetidinone moiety into its Boc derivative was complicated by accompanying acylation of the C18-hydroxyl group. The vinylstannane was therefore converted into its acetate before *N*-desilylation and conversion into the *N*-Boc β-lactam **418**. Ring opening of the azetidinone was now carried out using potassium cyanide in methanolic *N*,*N*-dimethylformamide to give the Boc-protected amino-ester **419**. The C13-hydroxyl group was now deprotected selectively by treatment with tetrabutylammonium fluoride in tetrahydrofuran to give the corresponding alcohol, since the presence of this silyl group was detrimental to the Stille cyclization. Intramolecular cyclization of the iodovinylstannane was better carried out using the prereduced palladium catalyst $Pd_2(dba)_3$ and gave the 17-membered macrocycle **420** (Scheme 132). Macrocyclic tetraene **420** contains all the functionality present in the large-ring system of lankacidin C.

3. Synthesis of Amino(hydroxy) Acid Derivatives

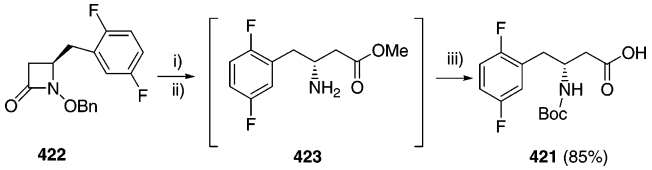
3.1. β-Amino Acids

The selective synthesis of β-amino acids has been the subject of tremendous effort, mainly due to their important

Scheme 133

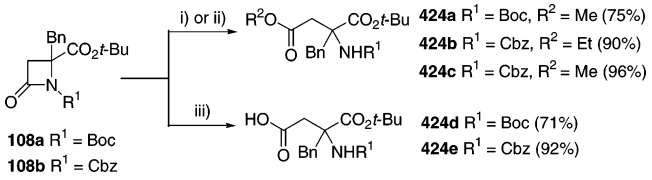


Scheme 134[a]



[a] Key: (i) MeONa, MeOH, RT, 10 min; (ii) H_2, Pd−C (10%), 1 h; (iii) $(Boc)_2O$, THF, Et_3N, RT, 10 min, then LiOH·H_2O, RT, overnight.

Scheme 135[a]



[a] Key: (i) R^2ONa, R^2OH, 24 h; (ii) MeOH, DBU, THF, 10 min; (iii) 2 N NaOH, THF, 24 h.

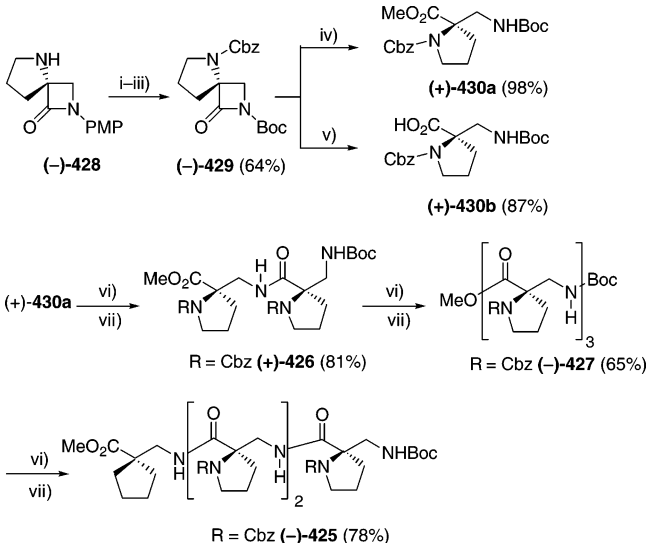
biological activity as enzyme inhibitors or α-amino acid surrogates in the construction of peptides possessing unique conformational properties (*β*-peptides).[105] Furthermore, the *β*-amino acid pattern can be found in some interesting naturally occurring compounds.[106] Use of *β*-lactams for preparation of *β*-amino acids and derivatives is well documented in the literature. Thus, several strategies have been reported and reviewed in recent years.[107,108]

Synthesis of *β*-amino acids from *β*-lactams takes place through ring opening at the N1−C2 bond of the four-membered ring by *O*- or *N*-nucleophiles (Scheme 133). Of particular interest is the reaction when the nucleophile is an amino acid because it allows the synthesis of *β*-peptide derivatives. The importance of the use of *N*-acyl *β*-lactams in order to activate the *β*-lactam carbonyl moiety toward attack of these nucleophiles as well as protect the amino function in the *β*-amino acid product has been found. This topic has been widely reviewed, so the aim of this section is to describe the most important recent aspects and update with the developments found in the literature during the last 10 years.[107,108]

Synthesis of chiral *β*-amino acid pharmacophore **421** on a kilogram scale from a *β*-lactam has been carried out (Scheme 134).[109] Treatment of azetidinone **422** with sodium methoxide in methanol and subsequent catalytic hydrogenation gave the corresponding *β*-aminoester **423**, which was saponificated directly due to its instability. In situ Boc trapping then revealed the desired optically pure (*R*)-*β*-amino acid **421** in 85% overall yield from azetidinone **422**.

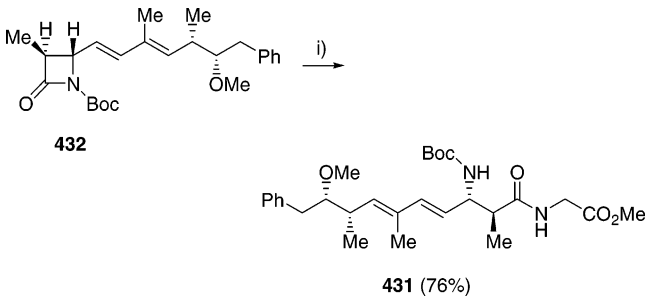
α-Alkyl asparagine derivatives have been prepared by controlled ring opening of activated *β*-lactams **108**.[38] Alcoholysis of azetidinones **108** afforded the α-benzyl asparigine derivatives **424a**−**c** in good yields (Scheme 135). Alternatively, when the reaction was performed with the corresponding alcohol in the presence of DBU, compound **424c** was obtained. On the other hand, hydrolysis of *β*-lactams **108a** and **108b** with NaOH afforded the corresponding diprotected asparagine derivatives **424d** and **424e** in good yields (71−92%) with a free carboxyl group at the side chain.

Scheme 136[a]



[a] Key: (i) $ClCO_2Bn$, $AcOEt/H_2O$, $NaHCO_3$, RT, 2 h; (ii) CAN, MeCN/H_2O, 0 °C; (iii) $(Boc)_2O$, DMAP, MeCN, 0 °C to RT, overnight; (iv) KCN (cat.), MeOH; (v) 2 N NaOH, THF; (vi) CF_3CO_2H, CH_2Cl_2, 0 °C, 2 h; (vii) (+)-**430b**, DCC, HOBt, THF, 0 °C to RT, overnight.

Scheme 137[a]



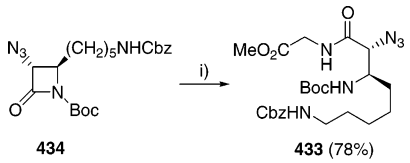
[a] Key: (i) Gly-OMe, NaN_3, DMF, RT.

The utility of spiro *β*-lactams in the preparation of *β*-peptides has been described. A representative example is the preparation of the homo-tetra-*β*-peptide **425**. Synthesis of *β*-peptides **425**−**427** was carried out using standard techniques for peptide coupling. As Scheme 136 illustrates, the synthesis starts with protection of the NH group at spiro *β*-lactam **428** with benzyl chloroformate. Oxidative removal of the *N*-protecting *p*-methoxyphenyl group with CAN followed by treatment with di-*tert*-butyldicarbonate in the presence of catalytic amounts of DMAP afforded *N*-Boc azetidinone **429**. Ring opening of this spiro *β*-lactam was carried out under mild conditions using KCN in a catalytic amount leading to *β*-aminoester **430a** or NaOH leading to *β*-amino acid **430b**. The availability of the Boc-protected *β*-aminoester **430a** and the *β*-amino acid **430b** has allowed experimentalists to proceed with the reiterative coupling to obtain the dipeptide **426**, the tripeptide **427**, and the desired tetra-*β*-peptide **425** (Scheme 136).[110]

Ring opening of the azetidinone skeleton to obtain *β*-amino acids and derivatives has also been promoted by nitrogen nucleophiles. Synthesis of the ADDA-containing analogue **431** has been prepared by coupling azetidinone **432** with glycine methyl ester and sodium azide at room temperature (Scheme 137).[111]

In the same context, the enantioselective synthesis of differentially protected *erythro*-α,*β*-diamino acids from 3-azido *β*-lactams has been reported.[112] An example is shown

Scheme 138[a]



[a] Key: (i) Gly-OMe, *i*-Pr_2NEt, NaN_3 (cat.), DMF, RT.

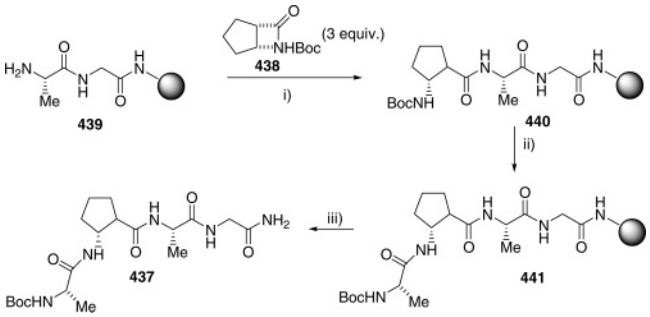
in Scheme 138. Starting from *trans*-3-azido-β-lactam **434** was prepared from a carboxylic acid precursor using a nucleophilic addition/N−O bond reduction protocol: (a) conversion to the corresponding β-keto esters using the Masamune−Brooks reaction, (b) subsequent sodium borohydride reduction to provide a β-hydroxy ester, which was converted in a single step to the corresponding hydroxamate using trimethylaluminum and *O*-benzylhydroxylamine hydrochloride, (c) subjection of this hydroxamate to activated triphenylphosphine under basic conditions to provide the cyclized dehydration product, (d) hydrogenolysis of the benzyl moiety, and (e) either a two-step sequence of tosylation followed by treatment of the isolated tosylate with $TMSN_3$ in the presence of Hunig's base or treatment with tosyl azide to generate the tosylate in situ followed by addition of excess azide. Dipeptide **433** bearing three fully differentiated amino moieties was obtained in good yield by coupling the urethane-protected β-lactam **434** with the methyl ester of glycine in the presence of a catalytic amount of sodium azide at room temperature.

Reaction of the β-lactam **108a** with ammonia in MeOH afforded compound **109** in excellent yield (89%).[38] Treatment of Boc-substituted azetidinone **108a** with AlaOMe in methanol provided a mixture of the expected diastereomeric β-aspartic dipeptides **435a** and **436a**. Alternatively, compounds **435b** and **436b** were obtained in excellent yields when DBU was used as additive for the ring opening of β-lactam **108b** (R = Cbz). Compounds **435** and **436** were obtained as diastereomeric mixtures in approximately the same ratio (Scheme 139).

Taking advantage of the same concept, synthesis of tetrapeptide **437** by a solid-phase technique has been reported utilizing Boc chemistry. Ring opening of the bicyclic β-lactam **438** with the solid-supported amino acid **439** in the presence of KCN as promoter in DMF produced peptide **440**. Coupling of peptide **440** with 3 equiv of Boc-protected alanine in the presence of DCC afforded tetrapeptide **441**. Finally, isolation of tetrapeptide **437** was achieved in the conditions shown in Scheme 140. The HPLC analysis indicated that no epimerization occurred during the synthesis.[113]

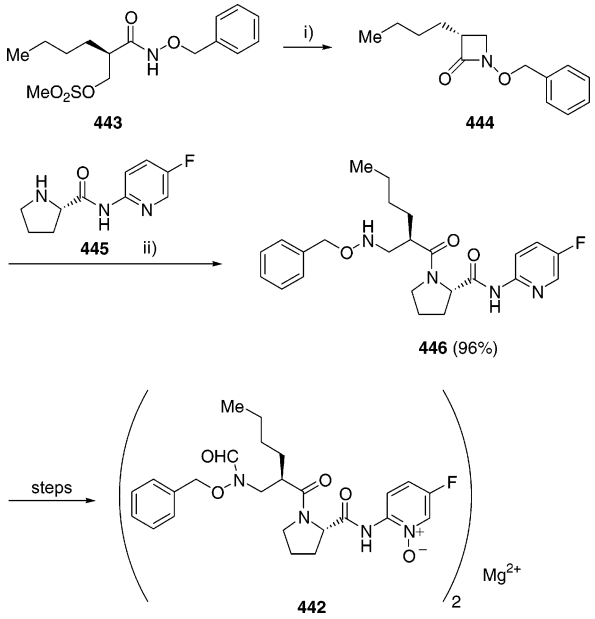
The same methodology has been applied to the formal synthesis of the peptide-deformylase inhibitor **442**.[114] As Scheme 141 illustrates, the synthesis starts with β-lactam

Scheme 140[a]



[a] Key: (i) KCN (3 equiv), DMF, 40 °C, 24 h; (ii) (a) Boc-Ala (3 equiv), DCC (3 equiv), HOBt (3 equiv), DMF, 24 °C, 2 h; (b) TFA (50% in CH_2Cl_2), RT, 30 min; (iii) liquid HF/dimethyl sulfide/*p*-cresol/*p*-thiocresol (86:6:4:2), 0 °C, 1 h.

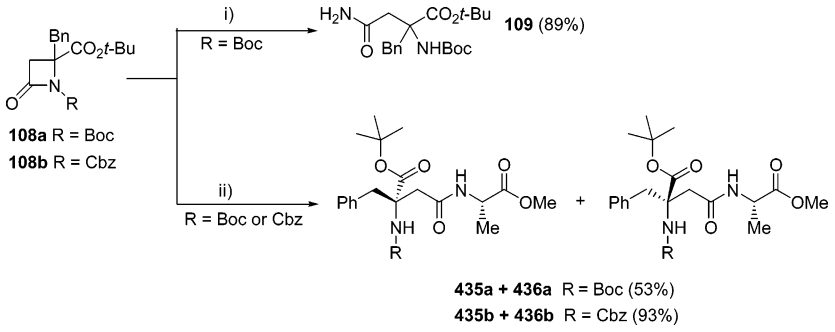
Scheme 141[a]



[a] Key: (i) K_2CO_3, Bu_4NBr, THF; (ii) THF, 2-ethylhexanoic acid.

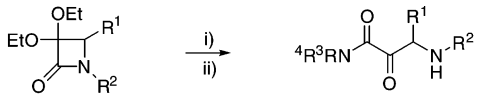
ring formation from **443** using potassium carbonate and tetrabutylammonium bromide in THF affording azetidinone **444**. Initial studies on the aminolysis of azetidinone **444** with 1.2 equiv of compound **445** were disappointing. When the reaction was carried out in neat methanol or 8% aqueous methanol product formation was negligible. However, when

Scheme 139[a]



[a] Key: (i) NH_3 (satd), MeOH, 5 min; (ii) for R = Boc, Ala-OMe, MeOH, 6 days; for R = Cbz, Ala-OMe, DBU, THF, 25 days.

Scheme 142[a]



447a R^1 = Ph, R^2 = *p*-Ts
447b R^1 = Ph, R^2 = $CO_2CH_2CH{=}CH_2$
447c R^1 = Et, R^2 = $CO_2CH_2CH{=}CH_2$
447d R^1 = Et, R^2 = *p*-Ts

448a R^3R^4N = *p*-MeOBnN (83%)
448b R^3R^4N = L-Val-OMe (48%)
448c R^3R^4N = L-phenylalaninol (64%)
448d R^3R^4N = Wang resin-bound Ph-Ala (84%)

[a] Key: (i) nucleophile; for **447a**, *p*-MeOBnNH$_2$, THF, RT; for **447b**, L-Val-OMe, KCN, DMF, 70 °C; for **447c**, L-phenylalanimol, KCN, DMA, RT; for **447d**, Wang resin-bound Ph-Ala, THF, 60 °C. (ii) TFA/acetone/H_2O (9:1:0.1).

40% aqueous methanol was used the desired compound **446** was obtained in 80% yield. The yield was successfully improved up to >96% using 2-ethylhexanoic acid as the catalyst and THF as solvent. The total synthesis of inhibitor **443** was achieved after a few additional steps from compound **446**.

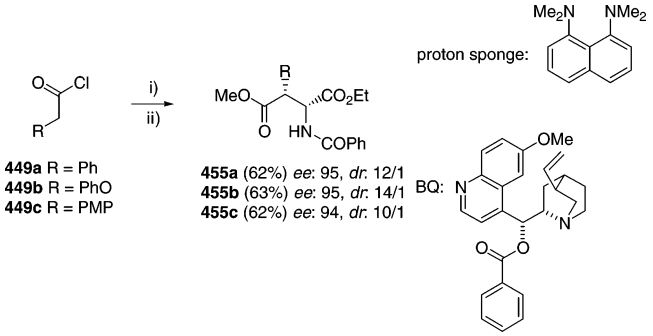
The ring-opening reaction of activated 3,3-dialkoxy-azetidin-2-ones **447a**−**d** with various amine nucleophiles followed by acidic hydrolysis of the resulting ketal intermediates to obtain the corresponding α-keto amino amides **448a**−**d** in good overall yields has been described (Scheme 142).[115]

During the course of investigations related to the asymmetric synthesis of β-amino acids from β-lactams it has been found that in the presence of methanol benzoylquinine (BQ) greatly enhanced the rate of β-lactam ring opening. Even at elevated temperatures a large difference was observed between the BQ-catalyzed and the uncatalyzed methanolysis reactions.[116] According to the mechanism shown in Scheme 143 the one-pot procedure involves up to four different steps, each of them catalyzed by the chiral nucleophilic catalyst benzoylquinine: catalytic dehydrohalogenation of acid chlorides **449** to form ketenes **450** or derived zwitterionic intermediates **451** (step A); dehydrohalogenation of α-chloroamine **452** to form the corresponding imine **453** (step B); catalyzed cycloaddition to produce intermediate azetidinones **454** (step C); and nucleophilic ring opening to form α,β-amino acids **455** in the presence of a nucleophile (step D).

Taking advantage of the above proposed mechanism, reaction of different acid chlorides **449a**−**c** with *N*-acyl-α-chloroglycine has provided β-amino acids **455a**−**c** in a one-pot procedure (Scheme 144). When sodium hydride was used as the stoichiometric base, comparable yields (57−62%) and selectivities (ee, 94−65, dr, 10/1−14/1) were obtained. Besides, addition of catalytic amounts (10 mol %) of Lewis acids [In(OTf)$_3$, or Cu(OTf)$_2$] increased the rate of β-lactam ring opening (1 h). The comparable control reaction without addition of a Lewis acid but in the presence of BQ took over 14 h. On the basis of the results obtained a plausible explanation to support the catalytic role of the metal salts is that Lewis-acid activation involves formation of a number of closely related chelation modes between the Lewis acid and the *N*-acyl-β-lactam.

Ring opening of the azetidinone skeleton has also been promoted by strong acids.[117] In this context, an efficient synthesis of 3-amino-2-hydroxydecanoic acid (AHDA) **456**, a non-proteinogenic amino acid, using enantiopure azetidinone **457** as a building block has been described.[118] Hydrogenolysis of the benzyl group followed by treatment with HCl (3 M) and subsequent purification by ion-exchange chromatography afforded pure (2*R*,3*S*)-AHDA **456** (Scheme 145). Following a similar synthetic protocol, synthesis of

Scheme 144[a]

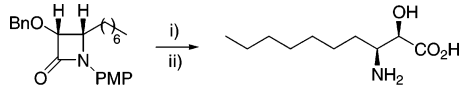


449a R = Ph
449b R = PhO
449c R = PMP

455a (62%) *ee*: 95, *dr*: 12/1
455b (63%) *ee*: 95, *dr*: 14/1
455c (62%) *ee*: 94, *dr*: 10/1

[a] Key: (i) *N*-acyl-α-chloroglycine, proton sponge, BQ, toluene, RT, overnight; (ii) MeOH, reflux.

Scheme 145[a]



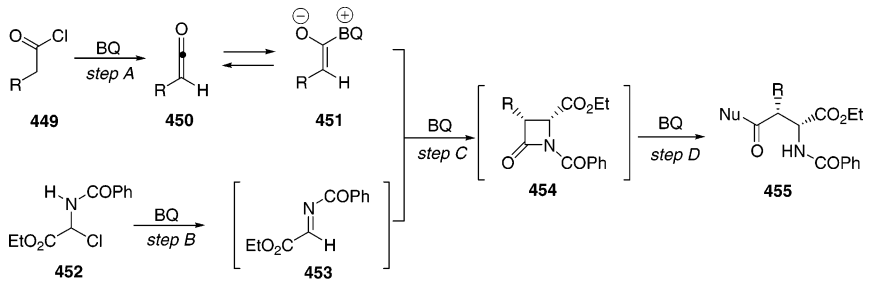
457 (2*R*, 3*S*)-AHDA **456** (66%)

[a] Key: (i) $HCOONH_4$, Pd−C (10%), MeOH, reflux, 6 h; (ii) 3 M HCl, 50 °C, ion-exchange resin, Dowex 50W × 2−400, 5% NH_4OH.

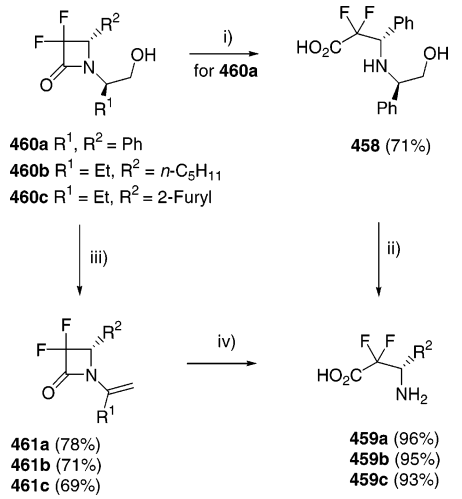
the other enantiomer (2*S*,3*R*)-AHDA from (3*S*,4*S*)-3-benzyloxy-4-formyl-azetidin-2-one has also been carried out.

The same conceptual approach has been applied to the synthesis of α,α-difluoro-β-amino acids **458** and **459** from azetidinones **460** (Scheme 146).[119] The route to the *N*-protected 3,3-difluoroazetidin-2-ones **460** was performed with high diastereoselectivity using the Reformatsky-type reaction of ethyl bromodifluoroacetate with chiral 1,3-oxazolidines. Reaction of azetidinone **460a** in acidic conditions provided the amino acid **458** without any trace of epimerization. Hydrogenolysis of the nitrogen appendage cleaved the phenylglycinol part of the molecule in a selective manner, leading to 3-amino-2,2-difluoro-3-phenyl-propanoic acid **459a** as the (*S*)-enantiomer in excellent yield. On the other hand, preparation of the β-amino acids **459a**−**c** was

Scheme 143

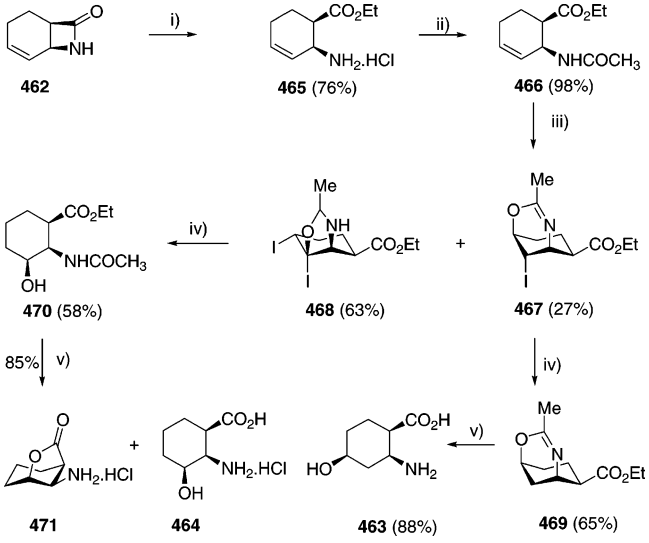


Scheme 146[a]



[a] Key: (i) 6 N HCl, reflux, 5 h; (ii) for **458**, H_2 (1 bar), Pd−C (10%), MeOH; (iii) (a) Tf_2O, py, CH_2Cl_2, −10 °C; (b) for **460a**, DBU, CH_2Cl_2, −10 °C, 1 h; for **460b** and **460c**, *t*-BuOK, THF, −10 °C, 10 min; (iv) 6 N HCl, reflux, 2 h.

Scheme 147[a]

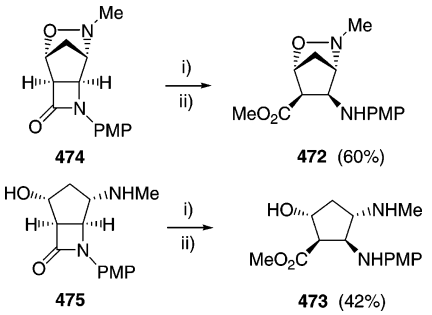


[a] Key: (i) 12% HCl, EtOH, reflux, 2 h; (ii) MeCOCl, Et_3N, $CHCl_3$, RT, 2 h; (iii) NaI, I_2, $NaHCO_3$, CH_2Cl_2, 0 °C, 20 h; (iv) Bu_3SnH, AIBN, toluene, 60 °C, 6 h, N_2; (v) 10% HCl, H_2O, reflux, 30 h.

carried out by transforming the alcohol functionality in azetidinones **460a**−**c** to triflate, which was smoothly eliminated with DBU or *t*-BuOK providing enamides **461a**−**c**. Reaction of enamides **461a**−**c** with 6 N aqueous hydrochloric acid at reflux afforded α,α-difluoro-*β*-amino acids **459a**−**c** as hydrochloric salts in nearly quantitative yield.

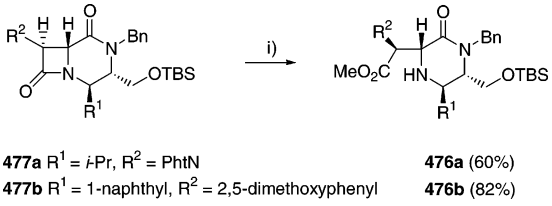
Syntheses of racemic 3- and 4-hydroxy-2-aminocyclohexanecarboxylic acids by iodocyclization via iodooxazine, iodooxazolidine, and iodolactone intermediates have been developed from bicyclic *β*-lactam **462**.[120] Scheme 147 shows the synthetic pathway to obtain the hydroxyamino acids **463** and **464**. Ring opening of *β*-lactam **462** with ethanolic hydrogen chloride resulted in the corresponding amino ester hydrochloride salt **465**. Subsequent acylation of compound **465** followed by iodocyclization of *N*-acylamino ester **466** with iodine and sodium iodide in a two-phase solvent system resulted in a 30:70 mixture of iodooxazine **467** and iodooxazolidine **468**. Fortunately, isomers **467** and **468** were successfully separated. Treatment of **467** with tributyltin hydride in the presence of a catalytic amount of AIBN gave the deiodinated compound **469** in reasonable yield (65%). Hydrolysis of oxazine **469** under acidic conditions resulted in 4-hydroxyamino acid **463**. On the other hand, when deiodination of **468** was attempted under the above radical conditions the oxazoline moiety proved to be unstable and only ring-opened product **470** could be isolated. Hydrolysis of *N*-acetylamino ester **470** furnished a mixture (2:1) of hydroxyamino acid **464** and amino lactone **471**.

Scheme 148[a]



[a] Key: (i) 4 M H_2SO_4, dioxane, Δ. (ii) MeOH, 65 °C.

Scheme 149[a]



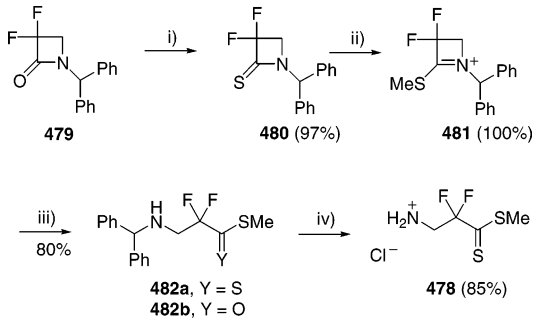
[a] Key: (i) TMSCl, MeOH, RT.

Bridged tricyclic *β*-lactam **474** has been prepared in 73% yield by use of an intramolecular nitrone−alkene cycloaddition reaction of an easily available monocyclic 2-azetidinone-tethered alkenylaldehyde. Fused bicyclic *β*-lactam **475** has been prepared in an excellent 82% yield by reduction of **474** with Zn in AcOH/H_2O/THF (2:1:1). Synthesis of functionalized cyclopentane-based *cis*-*β*-amino esters **472** and **473** has been achieved from azetidinones **474** and **475** by heating at reflux with a 1:1 mixture of 4 M sulfuric acid/dioxane and subsequent esterification with boiling methanol (Scheme 148).[121]

Synthesis of 2-oxopiperazine-3-acetic acid methyl esters **476a** and **476b** has also been reported. The highly diastereoselective synthesis of fused oxopiperazino-*β*-lactams **477** by Staudinger reaction between functionalized ketenes and 5,6-dihydropyrazin-2(1*H*)-ones has been carried out in good yield. As shown in Scheme 149, compounds **476a,b** were obtained in good yields by reaction of bicyclic *β*-lactams **477a,b** with trimethyl chlorosilane in methanol at room temperature.[122]

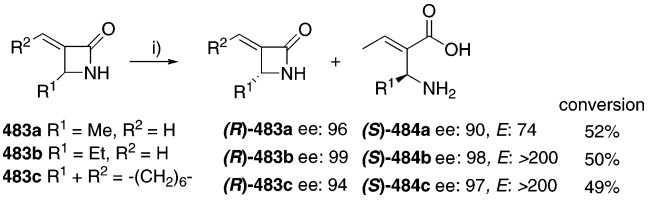
ω-Aminodithioester **478** has been prepared from 3,3-difluoro-1-benzhydrylazetidin-2-one **479**.[123] Reaction of *β*-lactam **479** with Lawesson's reagent afforded the corresponding azetidin-2-thione **480** in excellent yield (97%). Treatment of *β*-thiolactam **480** with methyl triflate furnished the salt **481**. When a stream of hydrogen sulfide was bubbled into the solution of **481**, dithioester **482a** was formed along with the side product thiolester **482b** due to some competitive hydrolysis. Compound **482a** was *N*-deprotected by dehydrogenation with DDQ followed by acidic hydrolysis of the resulting benzophenoneimine. Methyl 3-amino-2,2-difluoro-

Scheme 150[a]



[a] Key: (i) Lawesson's reagent, THF, reflux, 3 h; (ii) MeOTf, CH_2Cl_2, 20 °C, 30 min; (iii) H_2S/DMF, RT, 15 min; (iv) (a) DDQ, toluene, 4 Å molecular sieves, 60 °C, 1 h; (b) 0.1 N HCl, RT, 15 min.

Scheme 151[a]



			conversion
483a R^1 = Me, R^2 = H	***(R)*-483a** ee: 96	***(S)*-484a** ee: 90, *E*: 74	52%
483b R^1 = Et, R^2 = H	***(R)*-483b** ee: 99	***(S)*-484b** ee: 98, *E*: >200	50%
483c $R^1 + R^2 = -(CH_2)_6-$	***(R)*-483c** ee: 94	***(S)*-484c** ee: 97, *E*: >200	49%

[a] Key: (i) Lipase Chirazime L-2, from *Candida antarctica*, H_2O, 70 °C, 24−86 h.

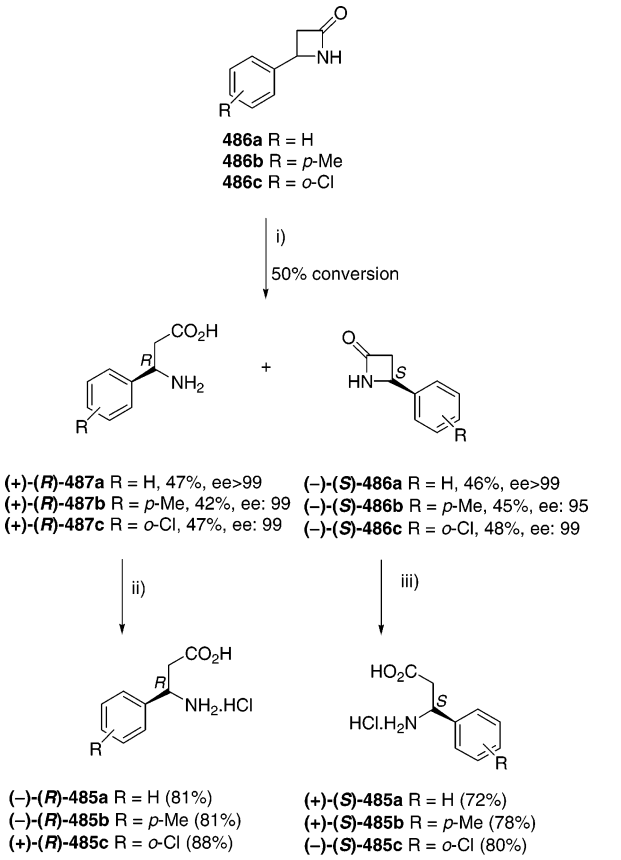
propanedithioate **478** was isolated in 85% yield as the hydrochloride salt (Scheme 150).

In recent years, there has been increasing interest in use of hydrolytic enzymes to obtain both cyclic and acyclic enantiopure β-amino acids and derivatives by ring opening of β-lactams, and several direct and indirect enzymatic methods for their preparation have been reported.[124] In particular, lipases and esterases have been successfully applied for the highly enantioselective hydrolysis and alcoholysis of azetidinones. Next, we are going to offer an overview of the enzymatic methods leading to enantiopure cyclic β-amino acids and their derivatives.

Treatment of racemic β-lactams **483a**−**c** with the lipase Chirazyme L-2 (from *Candida antarctica*) afforded the corresponding (*R*)-β-lactams **483a**−**c** and (*S*)-β-amino acids **484a**−**c** in almost 50% conversion (Scheme 151). Perfect kinetic resolution was achieved for the ethyl derivative **484b**, for which ee's of 99% for the lactam **483b** and 98% for the corresponding amino acid **484b** were obtained. However, in the case of the sterically less-demanding methyl derivative **483a** a slightly decreased enantioselectivity was obtained with 96% ee for the (*R*)-β-lactam **483a** and 90% ee for the amino acid **484a**.[125] The experiments carried out at room temperature were highly selective but very slow, whereas at relatively high temperature (70 °C) the reaction rate was enhanced considerably but the enzyme rapidly lost activity.

A very simple and inexpensive enzymatic method has been developed for the enantioselective ring opening of alicyclic-fused β-lactams[126] and unsaturated racemic β-lactams[127]and for synthesis of enantiopure β-amino acids as (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin). Synthesis of optically pure β-aryl-substituted β-amino acid hydrochlorides **485** has been developed through the CAL-B (lipase B from *Candida antarctica*) catalyzed enantioselective ring cleavage ($E > 200$) of the corresponding racemic β-lactams **486** in organic medium (Scheme 152).[128] Several experiments have been carried out in an attempt to enhance the reaction rate, and the authors concluded that use of *i*-Pr_2O as the

Scheme 152[a]



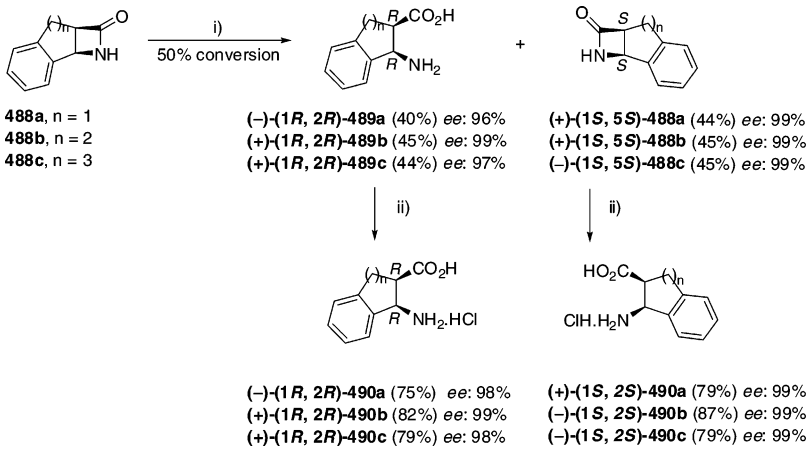
[a] Key: (i) CAL-B, H_2O/*i*-Pr_2O, 60 °C, 24 h; (ii) 22% HCl/EtOH; (iii) 18% HCl, reflux, 2 h.

solvent and H_2O (1 equiv) as the nucleophile were the optimum conditions to perform the reaction. In addition, it was observed that increasing the amount of enzyme increased the reactivity for the hydrolysis of β-lactams. Fortunately, the (*R*)-β-amino acids **487** (ee ≥ 98%, yields ≥ 42%) and unreacted (*S*)-β-lactams **486** (ee ≥ 95%, yields ≥ 45%) were separated. Treatment of amino acids **487** with 22% EtOH/HCl resulted in enantiopure hydrochlorides (*R*)-**485**. Ring opening of β-lactams (*S*)-**486** with 18% HCl afforded the corresponding enantiomers, the β-amino acid hydrochlorides (*S*)-**485**.

Interest in cyclic β-amino acids has increased over the past few years. In fact, some cyclic β-amino acids are bioactive compounds, for example, cispentacin, show antibacterial activity.[129] Synthesis of benzocispentacin and its 6- and 11-membered homologues through the lipolase (lipase B from *Candida antarctica*) ring opening of 3,4-benzo-6-azabicyclo-[3.2.0]heptan-7-one **488a**, 4,5-benzo-7-azabicyclo[4.2.0]-octan-8-one **488b**, and 5,6-benzo-8-azabicyclo[5.2.0]nonan-9-one **488c** with H_2O in *i*-Pr_2O at 60 °C has been reported.[130] The (1*R*,2*R*)-β-amino acids **489a**−**c** were obtained with 96−99% ee and 40−45% yields and converted into their hydrochlorides (1*R*,2*R*)-**490a**−**c** (Scheme 153). Ring opening of β-lactams (1*S*,5*S*)-**488a**−**c** with HCl resulted in the enantiomeric β-amino acid hydrochlorides (1*S*,2*S*)-**490a**−**c** (ee 99%).

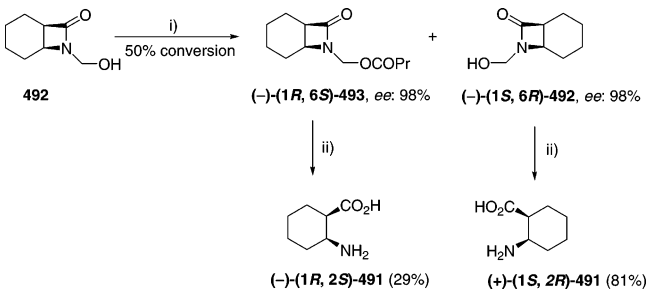
The indirect enzymatic method consists on treatment of *N*-hydroxymethylated β-lactams with lipases affording optically active precursors for synthesis of enantiopure β-amino acids and derivatives. In comparison with the direct enzymatic methods, the indirect ones take place with the same

Scheme 153[a]



[a] Key: (i) H_2O, *i*-Pr_2O, Lipolase, 60 °C, 6 h; (ii) 18% HCl, reflux, 3 h.

Scheme 154[a]



[a] Key: (i) lipase PS, vinyl butyrate in acetone, RT, 5 h; (ii) 18% HCl, reflux, 70 °C, 2 h, then ion-exchange chromatography.

high enantioselectivity (E > 200) but involve addition and removal of the *N*-hydromethyl group, and the overall yield is comparatively lower.

Alicyclic enantiopure β-amino acids have been prepared through the lipase-catalyzed enantioselective ring cleavage of fused bicyclic β-lactams.[131] Twelve-membered cyclic *cis*- and *trans*-β-lactams and the corresponding cyclic *cis*- and *trans*-β-amino acid enantiomers have been prepared through the enzymatic enantioselective ring cleavage of racemic *cis*-13-azabicyclo[10.2.0]tetradecan-14-one and *trans*-13-azabicyclo[10.2.0]tetradecan-14-one.[131a] High enantioselectivities (E > 200) were observed for the ring opening of both the *cis*- and *trans*-β-lactams when the Lipolase-catalyzed reactions were performed with 0.5 equiv of H_2O in *i*-Pr_2O at 70 C. The resolved β-lactams (yield ≥ 47%) and β-amino acids (yield ≥ 32%) could be easily separated. Enantiopure β-amino acids **491** have been obtained by resolution of the racemic *N*-hydroxymethylated β-lactam **492** with lipase-catalyzed acylation of the primary hydroxyl group.[131b] High enantioselectivity (E > 200) was obtained when the enzymatic reactions were performed with lipase PS as catalyst and vinyl butyrate as acyl donor. Hydrolysis of optically active β-lactams **492** and **493** with hydrochloric acid afforded both enantiomers of β-amino acid **491** in 29% and 81% yield, respectively (Scheme 154).

3.2. α-Hydroxy-β-amino Acids

α-Hydroxy-β-amino acids, isoserines, are found in many bioactive compounds. Paclitaxel (antitumor agent) and kinostatins (HIV-1 protease inhibitors) are some of the most representative examples of biologically active agents containing the α-hydroxy-β-amino acid unit (Figure 3). There are several reviews in the literature concerning the preparation of this type of compounds. In this context, different protocols for the semi-synthesis of taxol and related analogues have been widely developed.[107]

Dipeptide isosteres are essential building blocks for the synthesis of enzyme inhibitors such as rennin and HIV-1 protease.[132] These peptide isosteres are effective transition-state mimics of the substrates for the peptidases, which bind to the enzymes tightly and inhibit their actions. Different synthetic approaches for their preparation have been described.[107] Synthesis of optically pure α-alkylisoserines **494** and **495** has been developed from enantiopure 3-alkyl-β-lactams **496** (Scheme 155).[133] Removal of the PMP moiety with CAN in azetidinones **496a**−**e** afforded β-lactams **497a**−**e** (16−70%) together with the corresponding desilylated products. Acidic treatment of β-lactams **497a** and **497b** with 6 N hydrochloric acid gave α-alkylisoserine hydrochlorides **494a** and **494b**, respectively. On the other hand, protection of compounds **497a**−**e** as their carbamates smoothly afforded 2-azetidinones **498a**−**e**. Methanolysis of compounds **498a**, **498b**, and **498e** gave desilylated α-alkylisoserine methyl esters **495a**, **495b**, and **495e**, respectively. For 3-TES-protected β-lactams **498c** and **498d**, treatment with HF/pyridine followed by methanolysis is required to produce **495c** and **495d**.

Introduction of a fluorine, difluoromethyl, or trifluoromethyl group to a biological active molecule usually increases its pharmacological properties.[134] Thus, fluorine-containing α-hydroxy-β-amino acids are of special interest in medicinal chemistry. In this context, it has been demonstrated that trifluoromethyl- and difluoromethyl-β-lactams are versatile building blocks for synthesis of fluorinated amino acids, dipeptides, and fluoro-taxoids.[135] Enantiopure α-hydroxy-β-amino acid methyl esters bearing a CF_2H group or

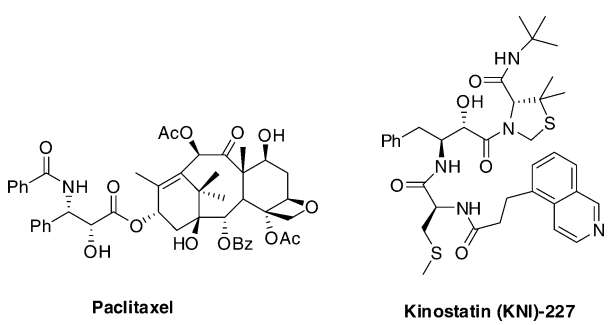
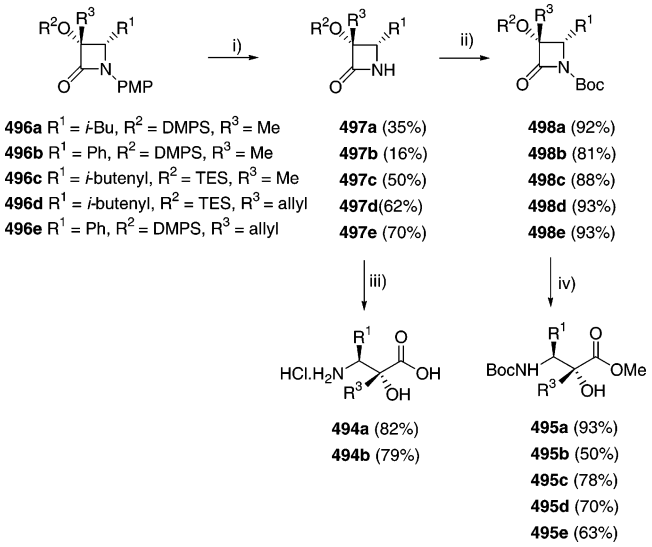


Figure 3.

Scheme 155[a]

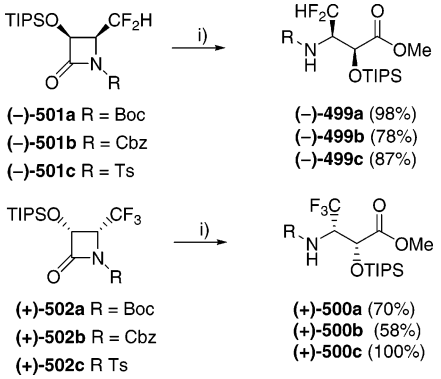


496a R^1 = *i*-Bu, R^2 = DMPS, R^3 = Me — **497a** (35%) — **498a** (92%)
496b R^1 = Ph, R^2 = DMPS, R^3 = Me — **497b** (16%) — **498b** (81%)
496c R^1 = *i*-butenyl, R^2 = TES, R^3 = Me — **497c** (50%) — **498c** (88%)
496d R^1 = *i*-butenyl, R^2 = TES, R^3 = allyl — **497d**(62%) — **498d** (93%)
496e R^1 = Ph, R^2 = DMPS, R^3 = allyl — **497e** (70%) — **498e** (93%)

494a (82%) — **495a** (93%)
494b (79%) — **495b** (50%)
495c (78%)
495d (70%)
495e (63%)

[a] Key: (i) CAN, MeCN/H_2O; (ii) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; (iii) 6 N HCl; (iv) for **498c** and **498d**, (a) HF/pyridine, (b) MeOH; for **498a**, **498b**, and **496a**, MeOH, Et_3N, DMAP.

Scheme 156[a]



(–)-501a R = Boc — **(–)-499a** (98%)
(–)-501b R = Cbz — **(–)-499b** (78%)
(–)-501c R = Ts — **(–)-499c** (87%)

(+)-502a R = Boc — **(+)-500a** (70%)
(+)-502b R = Cbz — **(+)-500b** (58%)
(+)-502c R Ts — **(+)-500c** (100%)

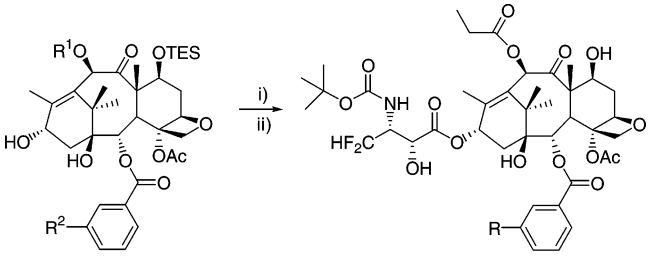
[a] Key: (i) MeOH, DMAP, Et_3N, 25 °C, 12 h.

CF_3 group at the C3 position, **499** and **500**, respectively, have been prepared through methanolysis of β-lactams **501** and **502** in the presence of triethylamine and a catalytic amount of DMAP at room temperature in good to quantitative yields (Scheme 156).

Synthesis of CF_2H- and CF_3-containing dipeptides has been achieved through ring opening of *N*-acyl-β-lactams with various amino acid methyl esters. In particular, treatment of (3*S*,4*S*)- and (3*R*,4*R*)-*N*-acyl-β-lactams **501a** and **502b** with glycine methyl ester and (*S*)-phenyl glycine methyl ester in the presence of *N*-methylmorpholine at room temperature gave the corresponding dipeptides, **503**, in reasonable yield. Alternatively, the coupling reaction of β-lactams **501a** and **502b** with β-alanine ethyl ester produced dipeptides **504** in moderate yields (Scheme 157).

To highlight the scope of this methodology, CF_2- and CF_3-containing taxoid anticancer agents have been prepared through ring opening of *N*-acyl-β-lactams with baccatins (Scheme 158). Thus, reactions of 4-CF_2H-β-lactam **501a** and

Scheme 158[a]



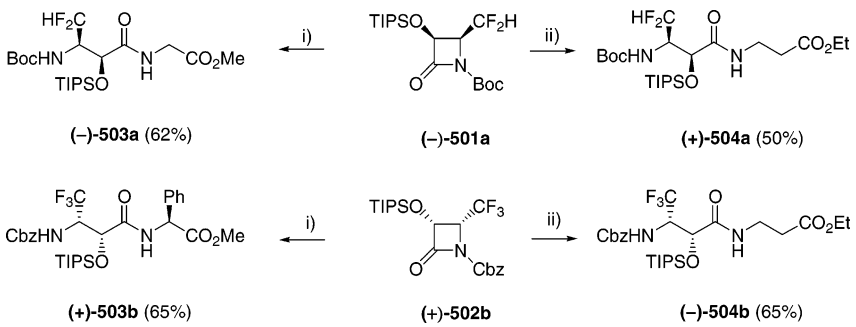
505a R^1 = EtCO, R^2 = Cl — **506a** (69%)
505b R^1 = EtCO, R^2 = N_3 — **506b** (81%)

[a] Key: (i) LiHMDS, THF, −40 °C, 2 h; for **505a**, *enant*-**501a** (1.8 equiv); for **505b**, *enant*-**502b** (1.8 equiv); (ii) HF-py, py/MeCN (1:1), 25 °C, 26 h.

4-CF_3-β-lactam **502a** with baccatins **505a** and **505b**, respectively, were carried out in the presence of LiHMDS as the base in THF at −40 °C. Subsequent removal of the silyl protecting groups by HF/pyridine readily afforded the corresponding fluoro-taxoids **506a** and **506b** in good overall yields. The cytotoxicity of both fluoro-taxoids has been evaluated in vitro against two human breast cancer cell lines and the corresponding drug-resistant cell lines. Results have shown that compounds **506** possess more than 2 orders of magnitude higher cytotoxicity than paclitaxel against the drug-resistant cell lines, MCF7-R and LCC6-MDR, and several times higher potency than paclitaxel against the drug-sensitive cell lines, MC7-S and LCC6-WT.

The same conceptual approach has been applied for the synthesis of docetaxel and butitaxel analogues **507a**−**f** through kinetic resolution of racemic β-lactams **508a**−**f** with 7-*O*-triethylsilylbaccatin **505c** (Scheme 159). It has been reported that the *tert*-butyldimethylsilyl protecting group at the C3 position of the azetidinone ring provides optimum kinetic resolution in comparison with less sterically demanding groups such as triethylsilyl and triisopropylsilyl groups. In addition, the C4 *tert*-butyl-β-lactams (**508d**−**f**) gave better diastereoselectivity than the corresponding C4 phenyl β-lactams (**508a**−**c**).[136]

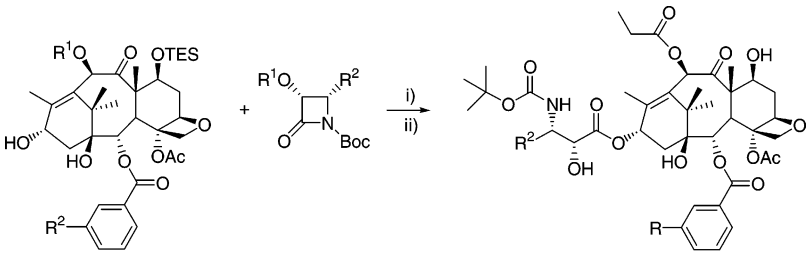
Scheme 157[a]



(–)-503a (62%) — **(–)-501a** — **(+)-504a** (50%)
(+)-503b (65%) — **(+)-502b** — **(–)-504b** (65%)

[a] Key: (i) NMM, CH_2Cl_2, 25 °C; for **501a**, Gly-OMe·HCl, 18 h; for **502b**, (*S*)-Phe-Gly-OMe·HCl, 96 h; (ii) NMM, CH_2Cl_2, 25 °C, β-Ala-OEt·HCl; for **501a**, 18 h; for **502b**, 48 h.

Scheme 159[a]



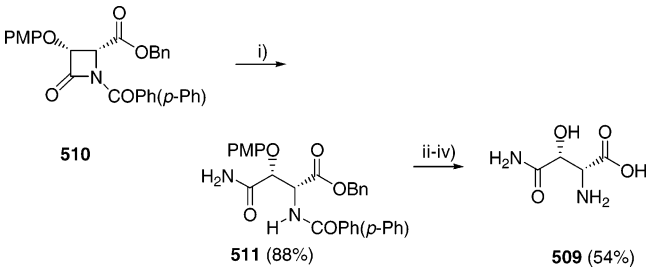
505c R^1 = Ac, R^2 = H

508a R^1 = TIPS, R^2 = Ph
508b R^1 = TBS, R^2 = Ph
508c R^1 = TES, R^2 = Ph
508d R^1 = TIPS, R^2 = *t*-Bu
508e R^1 = TBS, R^2 = *t*-Bu
508f R^1 = TES, R^2 = *t*-Bu

507a (80%) dr: 32:1
507b (81%) dr: 41:1
507c (84%) dr: 10:1
507d (76%) dr: 57:1
507e (84%) dr: 82:1
507f (78%) dr: 40:1

[a] Key: (i) (a) LiHMDS, THF, −40 °C; (b) HF-py.

Scheme 160[a]



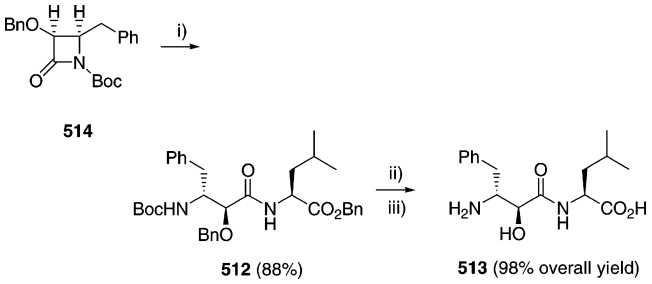
510

511 (88%)

509 (54%)

[a] Key: (i) NH_3, −78 °C, 5 h; (ii) Pd−C/H_2, EtOH/DMF, 2 h; (iii) Na/Hg, MeOH, 2 h; (iv) CAN, MeCN, H_2O, 1 h.

Scheme 161[a]



514

512 (88%)

513 (98% overall yield)

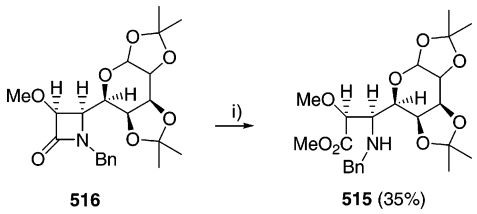
[a] Key: (i) (*S*)-LeuOBn, NaN_3 (1 equiv), DMF, RT, 16−20 h; (ii) TFA, CH_2Cl_2, 0 °C; (iii) H_2, Pd/C, EtOH, RT.

Synthesis of the unnatural amino acid L-threo-*β*-hydroxyasparagine **509**, a subunit of the antibiotic lysobactin, has been reported by aminolysis of *β*-lactam **510** as the key step of the synthetic route.[116b] As shown in Scheme 160, *β*-lactam **510** was converted to L-threo-*β*-hydroxyasparagine derivative **511** by reaction with ammonia at low temperature. Hydrogenation of compound **511** cleanly removed the benzyl ester. Finally, deprotection of the biphenyl protecting group followed by CAN oxidation produced the expected amino acid **509**.

Synthesis of dipeptide **512**, a precursor of bestatin **513**, has been prepared by N1−C2 bond cleavage of *N*-Boc-*β*-lactam **514** with (*S*)-leucine benzyl ester and NaN_3 (Scheme 161). Acidic treatment of compound **512** followed by hydrogenolysis gave (−)-bestatin **513** in 98% overall yield.[137]

Ring opening of the *β*-lactam moiety to afford α-hydroxy acid derivatives has also been promoted by reaction with reductive agents or alkoxides. As an example, synthesis of enantiopure α-alkoxy-*β*-amino acids **515** has been achieved

Scheme 162[a]

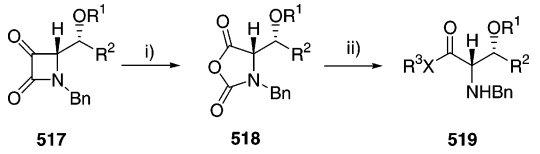


516

515 (35%)

[a] Key: (i) MeONa, MeOH, reflux, 12 h.

Scheme 163[a]



517

518

519

[a] Key: (i) MCPBA, CH_2Cl_2, −40 °C; (ii) MeOH, RT or R^3NH_2.

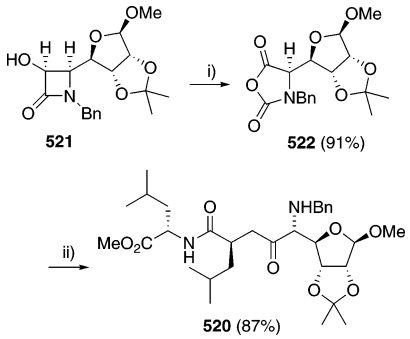
by reaction of the densely substituted *β*-lactam **516** with sodium methoxide in methanol (Scheme 162).[138]

3.3. α-Amino Acids

α-Amino acids and α-amino amides play a central role in chemistry, biology, and medicinal chemistry due to their biological properties.[139] They are present in Nature as building blocks of peptides and proteins and also extensively in other natural products.[140] In addition, use of both natural and unnatural α-amino acids and their derivatives as chiral reagents, auxiliaries, catalysts, and ligands for asymmetric synthesis is widespread.[141] It has been reported that palladium-catalyzed hydrogenolysis of optically pure 4-aryl-*β*-lactams proceeded exclusively with 1,4-bond cleavage of the four-membered ring to produce enantiomerically pure α-amino amides, α-alkyl-α-amino acids, and peptides.[107c,142] An elegant strategy based on the Baeyer−Villiger oxidation of azetidin-2,3-diones **517** to obtain *N*-carboxy anhydrides (NCA) **518** followed by coupling reaction with amines or alcohols affording the corresponding α-amino acid derivatives **519** has been described (Scheme 163).[108d,e]

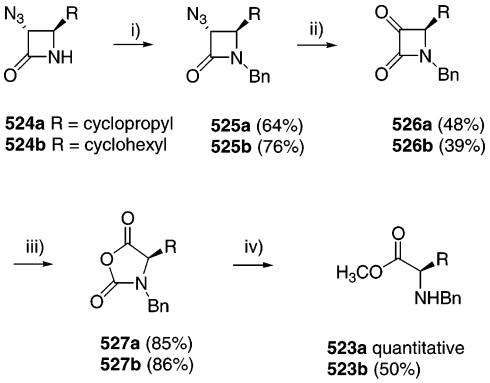
A more direct method for preparation of NCAs from 3-hydroxy-*β*-lactams has been reported using TEMPO as the oxidant agent. An example is shown in Scheme 164. α-Aminofuranuronic acid derivative **520** has been prepared from *β*-lactam **521** by cyclo-expansion with TEMPO to afford the NCA **522** in 91% yield followed by coupling

Scheme 164[a]



[a] Key: (i) NaOCl, KBr, TEMPO, H_2O, −5 to 0 °C, 0.5−2 min; (ii) (*S*,*S*)-Leu-LeuOBn, CH_2Cl_2, RT, 24 h.

Scheme 165[a]



[a] Key: (i) CsF, BnBr, DMF; (ii) (a) H_2, Pd−C (10%), THF, 20 min; (b) *t*-BuOCl, THF, −78 °C, 20 min; (c) DBU, THF, −78 °C to RT, 1.5 h; (d) oxalic acid (satd), 10 min; (iii) TEMPO (cat.), 0.7 M NaOCl, CH_2Cl_2, 0.1 M KBr, phosphate buffer solution (4.2 M, pH = 6.9), 0 °C, 1 h; (iv) TMSCl, MeOH, RT; for **527a**, 4 days; for **527b**, 15 min.

reaction with the dipeptide (*S*,*S*)-Leu-LeuOBn. Tripeptide **520** was isolated in 87% yield.[143]

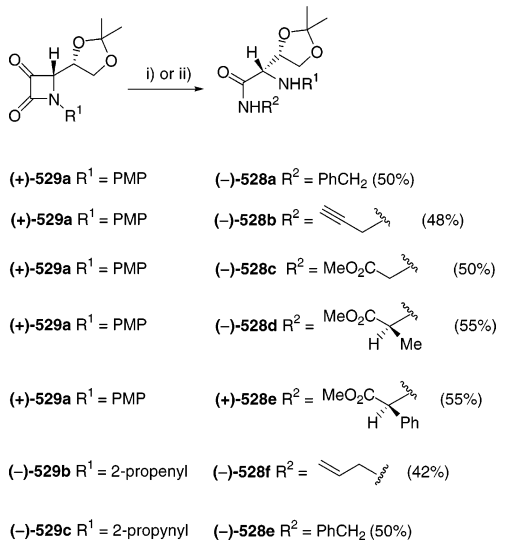
On the basis of the above methodology synthesis of α-amino acids **523** from *trans*-azido β-lactams has been described.[144] Treatment of β-lactams **524** with benzyl bromide and CsF afforded benzyl derivatives **525** in good yields. Preparation of α-keto β-lactams was achieved in a four-step "single-pot" procedure obtaining the desired compounds **526** in moderate yield. TEMPO-mediated ring expansion afforded the corresponding NCAs **527**, which after treatment with methanol and TMSCl smoothly afforded α-amino esters **523** (Scheme 165).

α-Amino amides **528** have been obtained directly by reaction of α-keto lactams **529** with primary amines. The starting azetidine-2,3-diones **529** were available in high yields by Swern oxidation of the corresponding 3-hydroxy-β-lactams. Of particular interest was the reaction of azetidine-2,3-diones **529** with α-amino esters, such as glycine methyl ester, alanine methyl ester, or phenylglycine methyl ester, showing the utility of this approach in the synthesis of optically pure dipeptides (Scheme 166).[145]

In order to explore the scope of this new reaction, different experiments were carried out with secondary amines, affording α-amino amides **530a**−**c** and dipeptide **530d** without detectable epimerization (Scheme 167).

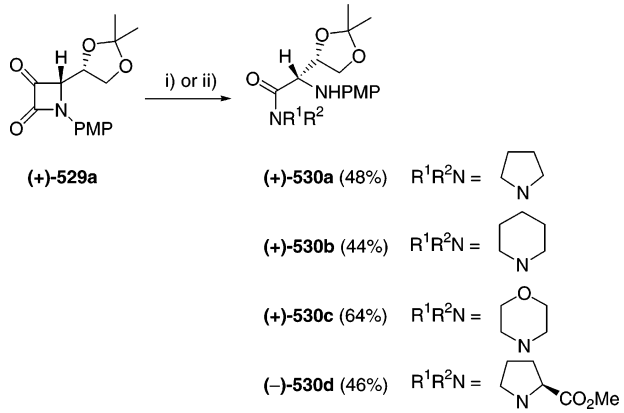
Formation of α-amino amides **528** and **530** from azetidine-2,3-diones **529** can be rationalized by a concerted process involving formation of the intermediate **531** as shown in Scheme 168. The above methodology has been also successfully applied to the reaction of oxygenated nucleophiles

Scheme 166[a]



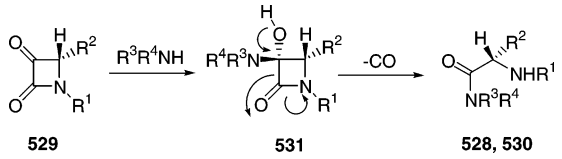
[a] Key: (i) R^2NH_2, THF, RT, 2−24 h; (ii) R^2NH_2, THF, sealed tube, 90 °C, 2−6 h.

Scheme 167[a]

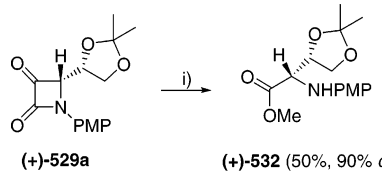


[a] Key: (i) R^1R^2NH, THF, RT, 20−72 h; (ii) R^1R^2NH, THF, sealed tube, 90 °C, 2 h.

Scheme 168



Scheme 169[a]

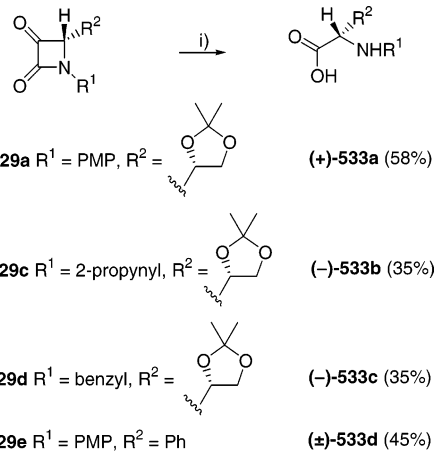


[a] Key: (i) MeONa, MeOH, reflux, 1 h.

instead amines. Reaction of azetidinone **529a** with sodium methoxide/methanol afforded α-amino ester **532** in 50% yield with partial epimerization (5%) (Scheme 169).

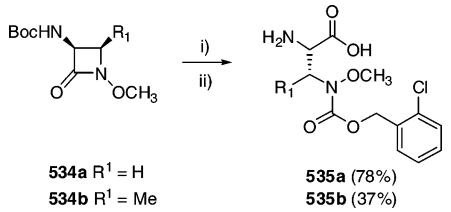
On the other hand, treatment of azetidine-2,3-diones **529a,c**−**e** with cadmium/ammonium chloride in wet methanol (5% water) afforded α-amino acids **533a**−**e** (Scheme 170). Addition of metal and the presence of ammonium chloride play a special role to promote the ring opening of

Scheme 170[a]



[a] Key: (i) Cd, NH_4Cl, MeOH (containing 5% water), RT, 2−4 days.

Scheme 171[a]



[a] Key: (i) For **534a**, LiOH, THF/H_2O, 20 h; for **534b**, LiOH, MeCN/H_2O; (ii) *N*-(2-chlorobenzyloxycarbonyloxy)succinimide, $NaHCO_3$.

the β-lactam skeleton. Formation of α-amino acids **533** from β-lactams **529** could be explained in an analogous manner as formation of α-amino amides **528** and **530**. It may be possible that chelation of the ketone and amide moieties with the metal activates the ketone group as effectively as that required for water attack. Concerted CO extrusion produces, finally, the α-amino acids **533**.

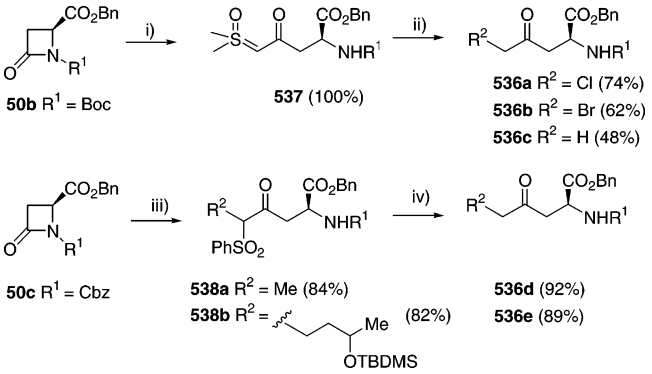
Basic ring opening of β-lactams **534a,b** with LiOH smoothly afforded the corresponding *N*-methoxyamines which after in situ nitrogen protection with *N*-(2-chlorobenzyloxycarbonyloxy) succinimide afforded β-amino acids **535a,b** respectively (Scheme 171).[146]

4. Synthesis of β-Amino Ketone Derivatives

β-Amino ketones are very attractive molecules for organic synthesis because of their wide use as biologically active compounds.[147] Ring opening of the β-lactam skeleton by carbon nucleophiles to afford the corresponding β-amino ketones and derivatives has been reported. In this context, when the β-lactam ring has the adequate substitution, more functionalized compounds were obtained, such as keto α-amino acids.

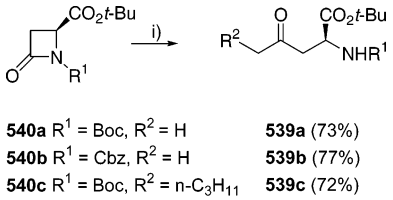
The ylide methodology has been applied for preparation of δ-halomethyl-γ-keto-α-amino acids **536a**−**c** from β-lactam **50b** (Scheme 172).[148] The authors describe the nucleophilic ring opening of the β-lactam **50b** with trimethylsulfoxonium iodide, giving the α-ketosulfoxonium species **537** in quantitative yield. Treatment of compounds **537** with different reagents which either alkylate or protonate the stabilized ylide and nucleophilically displace the sulfoxonium group led to different γ-keto-α-amino acids **536a**−**c** in moderate to good yields. Use of sulfone-stabilized carbon nucleophiles as reagents for the reaction with activated monocyclic β-lactam **50c** has also been investigated, affording the ketosulfone α-amino esters **538**. The sulfone moiety was easily removed in high yield by reduction with Al/Hg amalgam leading to α-amino acids **536d** and **536e** in excellent yields.

Scheme 172[a]



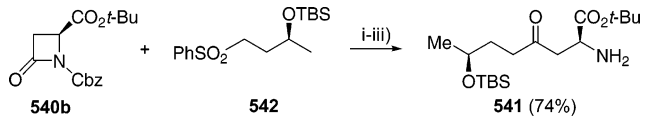
[a] Key: (i) $Me_3S^+OI^-$, NaH, DMSO, RT. (ii) For R^2 = Cl, HCl/AcOH (1 equiv), DMF; for R^2 = Br, 47% HBr/AcOH (1 equiv); for R^2 = H, 35% aq HI (1 equiv). (iii) $PhSO_2R^2$ (2 equiv), *n*-BuLi (2 equiv), THF, −78 °C, 20 min. (iv) Al/Hg, deoxygenated THF/H_2O (9:1).

Scheme 173[a]



[a] Key: (i) $PhSO_2CH_2R^2$ (2 equiv), *n*-BuLi (2 equiv), THF, 20 min; (ii) Al/Hg, deoxygenated THF/H_2O (9/1).

Scheme 174[a]



[a] Key: (i) *n*-BuLi (2 equiv), THF, −78 °C, 10 min; (ii) Al/Hg, deoxygenated THF/H_2O 9:1; (iii) H_2, 5% Pd/$CaCO_3$, AcOEt.

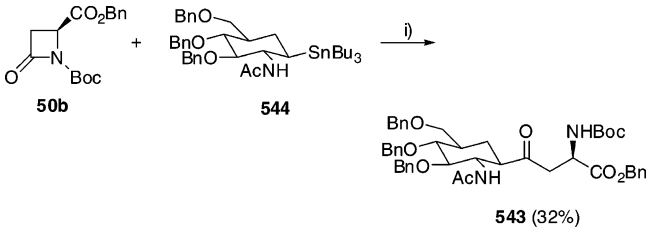
γ-Keto α-amino acids **539** have been prepared via carbon nucleophilic ring opening of monocyclic β-lactams **540** (Scheme 173). Reaction of azetidinones **540** with lithiated methylphenylsulfone and butylphenylsulfone smoothly afforded the corresponding β-ketosulfones. The sulfone moiety was reductively removed by treatment with Al/Hg amalgam, providing the expected compounds **539a**−**c** in excellent overall yields.[149]

The above methodology has been applied for synthesis of the angiotensin-converting enzyme (ACE) inhibitor WF-10129. Compound **541** has been obtained by ring opening of the azetidinone **540b** with the metalate sulfone **542** followed by reductive removal of the sulfone group and subsequent hydrogenolysis (Scheme 174).

Synthesis of *C*-glysosylated amino acid **543** has been achieved by reaction of azetidinone **50b** with the β-configured stannyl derivative **544** in the presence of MeLi and BuLi (Scheme 175). Compound **543** has been isolated in moderate yield (32%) without racemization of the stereogenic center of the peptidic moiety.[150]

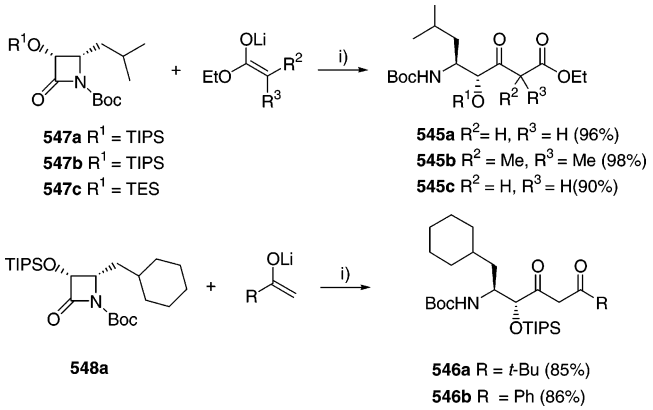
Isoserine-dipeptide isosteres **545** and **546** have been prepared through reaction of *N*-Boc azetidinones **547** and **548** with the lithium enolates of ketones and esters (Scheme 176). The corresponding hydroxy(keto) ethylene dipeptides

Scheme 175[a]



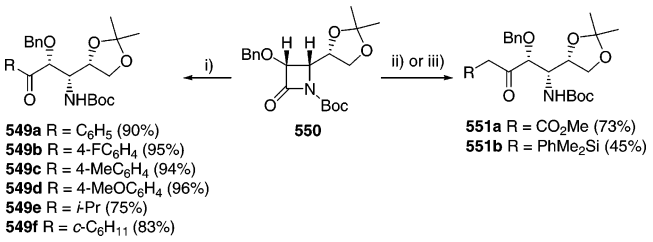
[a] Key: (i) **544,** MeLi (1 M in hexane), THF, −78 °C, 10 min, then BuLi (1.5 M in hexane), −65 °C, 10 min, then **50b**.

Scheme 176[a]



[a] Key: (i) THF, −78 °C, 15−45 min.

Scheme 177[a]



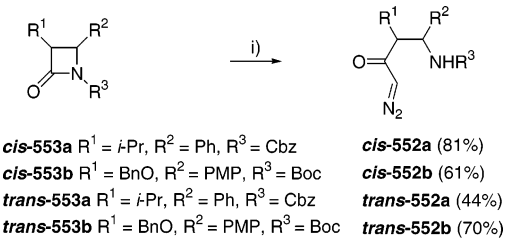
[a] Key: (i) RMgX (3.0 M in Et_2O), X = Br or Cl, THF, −78 to −40 °C, 1 h; (ii) MeOC(OLi)=CH_2 (2 equiv), THF, −78 °C; (iii) $PhMe_2SiCH_2MgCl$, THF, −20 °C.

have been obtained in high yields. It has been observed that lithium ester enolates are more reactive than lithium ketone enolate and that the reaction is complete within a few minutes at −78 °C.[151]

α,γ-Disubstituted β-amino ketones **549** have been obtained by ring opening of *N*-Boc-β-lactams **550** promoted by Grignard reagents (Scheme 177).[152] Reaction of aryl and secondary alkylmagnesium halides with *N*-Boc β-lactam **550** at low temperature (−40 °C) has provided the corresponding β-aminoketones **549a**−**f** as the only compounds in excellent yields. Alternatively, reaction of azetidinone **550** with lithium enolate of methyl acetate or $PhMe_2SiCH_2MgCl$ afforded compounds **551a** and **551b**, respectively, in good yields. In both cases compounds **549** and **551** were isolated without traces of the corresponding β-amino carbinols formed from overaddition at the resulting carbonyl groups.

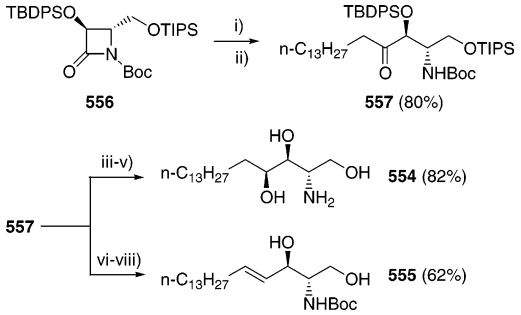
Synthesis of diazoketones **552** has been accomplished by reaction of *cis*- or *trans*-β-lactams **553** with $TMSCHN_2$ in THF at −78 °C (Scheme 178). The stereochemistry of the β-lactams was unaltered during ring cleavage, and no epimerized product was formed, probably due to the stability of the corresponding enolate of the α-diazoketone.[153]

Scheme 178[a]



[a] Key: (i) $TMSCHN_2$, THF, −78 °C.

Scheme 179[a]



[a] Key: (i) *n*-$C_{14}H_{29}SO_2C_6H_4Me$, *n*-BuLi, THF, −78 °C, 1 h; (ii) Li−naphthalenide, THF, −78 °C, 20 min; (iii) $LiEt_3BH$, THF, −78 °C, 2 h; (iv) TBAF, THF, RT, 2 h; (v) HCl (10%), MeOH, 40 °C, 9 h; (vi) $KN(TMS)_2$, THF, −78 °C, 1 h, then $PhN(Tf)_2$, THF, −23 °C, 20 min; (vii) HCO_2H, Et_3N, $Pd(OAc)_2(PPh_3)_2$ (cat.), DMF, 60 °C, 7 h; (viii) TBAF, THF, RT, 2 h.

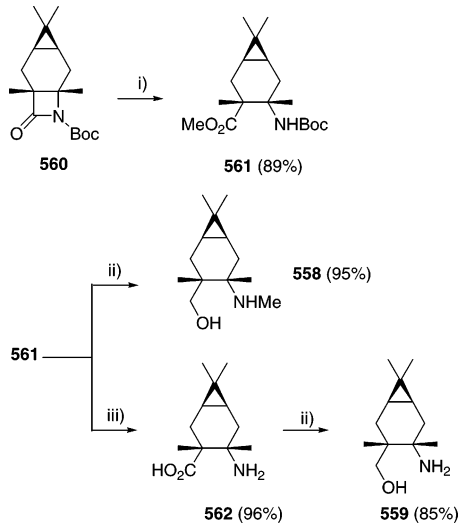
The importance of sphingosines is due to their presence in almost all sphingolipids in eukaryotic cells as well as lipophilic components of glycosphingolipids and ceramides.[154] Synthesis of L-lyxo-phytosphingosine **554** and D-erythro-sphingosine **555** from azetidinone **556** has been described.[155] Treatment of azetidinone **556** with 4-tolyl tetradecylsulfone and *n*-BuLi afforded α-sulfonyl ketone as a mixture (1:1) of two diastereoisomers at the C5 position. Subsequent reaction with lithium naphthalenide in THF cleanly removed the sulfonyl moiety, yielding compound **557** in good yield. L-Lyxo-phytosphingosine **554** was obtained after several synthetic steps involving the stereoselective reduction of the ketone moiety and deprotection of the hydroxyl groups. Analogously, the D-erythro-sphingosine **555** was prepared as shown in Scheme 179.

5. Synthesis of γ-Amino Alcohol Derivatives

Synthesis of γ-amino alcohols is of considerable interest because they are found in many natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir and lopinavir.[156] They have also been used as ligands in asymmetric synthesis and as synthetic intermediates.[157]

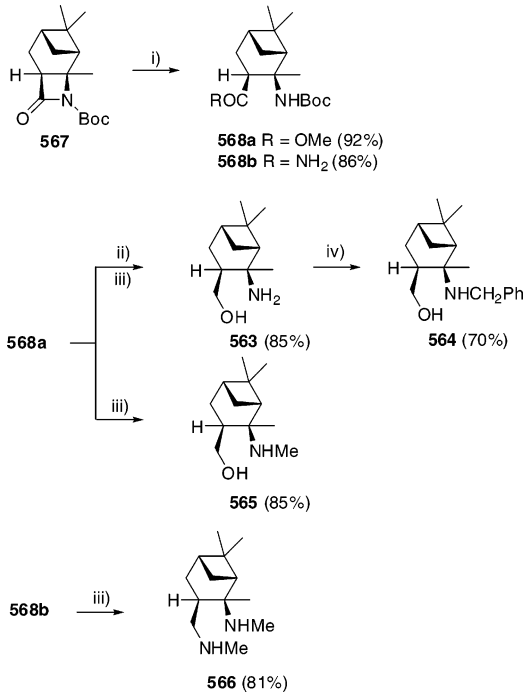
Synthesis of amino alcohols **558** and **559** has been achieved from tricyclic β-lactam **560** derived of (+)-3-carene.[158] As shown in Scheme 180, treatment of tricyclic azetidinone **560** with catalytic amounts of sodium methoxide in dry methanol promoted ring opening of the β-lactam skeleton providing β-amino ester **561** in good yield. Reduction of *N*-Boc amino ester **561** with lithium aluminum hydride gave the expected *N*-methyl amino alcohol **558** in excellent yield. The same reaction conditions were applied for preparation of γ-amino alcohol **559** from β-amino acid **562**.

Scheme 180[a]



[a] Key: (i) MeONa (cat.), MeOH, RT, 2 h; (ii) $LiAlH_4$, THF, RT, 2 h; (iii) TFA/CH_2Cl_2, RT, 2 h.

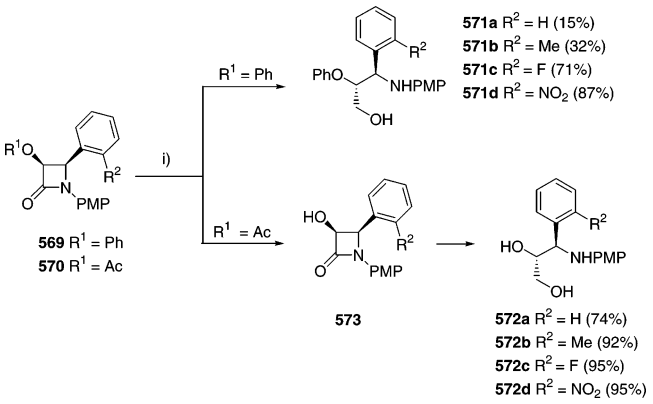
Scheme 181[a]



[a] Key: (i) for **568a**, MeONa (cat.), MeOH, RT, 0.5 h; for **568b**, NH_3, MeOH, 4 °C, 12 h. (ii) TFA, CH_2Cl_2, RT, 2 h. (iii) $LiAlH_4$, THF, RT, 2 h. (iv) PhCHO, EtOH, then $NaBH_4$, EtOH, RT, 12 h.

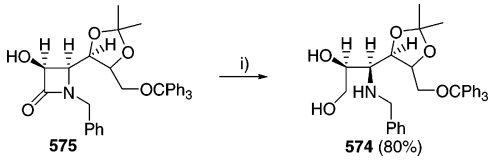
γ-Amino alcohols **563**−**565** and diamine **566** have been synthesized from β-lactam **567** derived from (−)-α-pinene (Scheme 181).[159] Ring opening of *N*-Boc-β-lactam **567** in the presence of a catalytic amount of sodium methoxide or dimethylamine in dry methanol gave ester **568a** and carboxamide **568b**, respectively, in good yields. Deprotection of *N*-Boc amino ester **568a** with trifluoroacetic acid followed by reduction with lithium aluminum hydride resulted in formation of the primary alcohol **563** (86%). Treatment of γ-amino alcohol **563** with benzaldehyde followed by reduction of the in-situ-formed Schiff base with sodium borohydride afforded the *N*-benzylamino alcohol **564** in good yield (70%). Alternatively, reduction of *N*-Boc amino ester **568a** gave *N*-methylamino alcohol **565**. Finally, treatment of compound **568b** with lithium aluminum hydride smoothly afforded diamine **566**.

Scheme 182[a]



[a] Key: (i) $NaBH_4$, *i*-Pr_2O, H_2O, RT, 20 h.

Scheme 183[a]



[a] Key: (i) $LiAlH_4$, THF, reflux, 3 h.

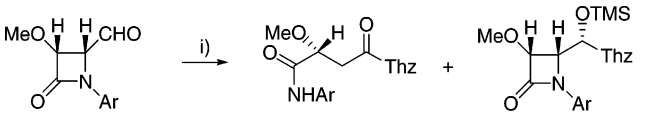
Treatment of azetidinones **569** and **570** with sodium borohydride afforded 2-phenoxy-3-aryl-3-aminopropan-1-ols **571a**−**d** or 2-hydroxy-3-aryl-3-aminopropan-1-ols **572a**−**d** according to the substitution pattern at the 3-position of 2-azetidinone ring (Scheme 182).[160] Mixtures of the starting β-lactam and open-chain product **571** were obtained from 3-phenoxy azetidinones **569**. However, the behavior of 3-acetoxy-2-azetidinones **570** was different since sodium borohydride first reduces the acetate to obtain the corresponding 3-hydroxy-2-azetidinones **573a**−**d**, which is followed by ring opening of the latter products to afford amino diols **572a**−**d** in good yields, independent of the electronic nature of the substituent R^2. Amino diols **572** were obtained along with 3-hydroxy-2-azetidinones **573**. These results have been explained in terms of the carbonyl LUMO energies of both compounds **569** and **570** calculated with the AM1 method. Decreasing the LUMO energies in the series **569** justifies the reactivity better for electron-poor substrates toward hydride, while the much lower LUMO energies of **570** account for their better reactivity and the lack of sensitivity toward R^2.

Synthesis of β,γ-aminodiol **574** has been achieved by lithium aluminum hydride reduction of α-hydroxy β-lactam **575** (Scheme 183).[138]

6. Miscellaneous

Recently, a new N1−C4 bond breakage in β-lactams lacking an aryl moiety at C4 affording α-hydroxy acid derivatives **576** (Scheme 184) has been described.[161] During the investigation on the diastereoselective reaction of *cis*-4-formyl-β-lactams **64a**−**c** with 2-(trimethylsilyl)thiazole (TMST) in dichloromethane it was found that besides the expected addition products, **577a**−**c** as a minor components, the enantiomerically pure α-hydroxy acid derivatives **576a**−**c** were isolated in moderate yields (33−58%). By placing a less electron-donating substituent in the para position of the

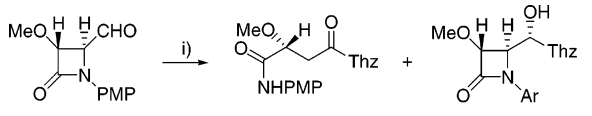
Scheme 184[a]



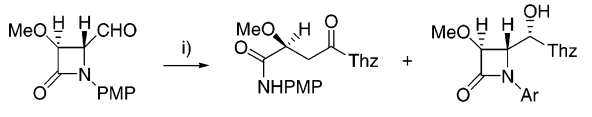
(+)-64a, Ar = 4-MeOC$_6$H$_4$ **(+)-576a** (58%) **(+)-577a** (31%)
(+)-64b, Ar = 4-MeC$_6$H$_4$ **(+)-576b** (33%) **(+)-577b** (31%)
(+)-64c, Ar = 2,4-MeOC$_6$H$_3$ **(+)-576c** (51%) **(+)-577c** (10%)

[a] Key: (i) TMST, CH_2Cl_2, 0 °C, overnight.

Scheme 185[a]



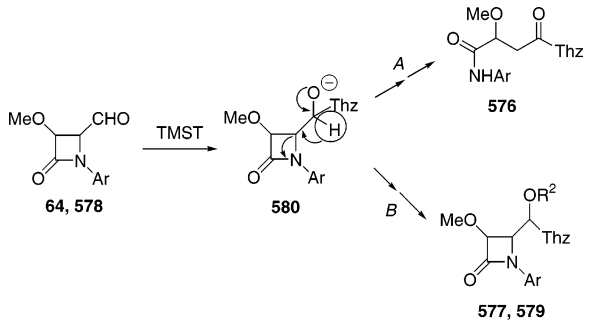
(–)-578a **(+)-576a** (52%) **(+)-579a** (15%)



(+)-578a **(–)-576a** (50%) **(+)-579b** (15%)

[a] Key: (i) TMST, CH_2Cl_2, 0 °C, overnight.

Scheme 186



64, 578 **580** **576** **577, 579**

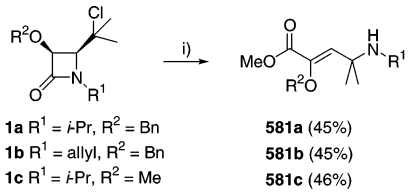
N-aryl substituent, such as in β-lactam **64b**, the selectivity of the process was observed to decrease, obtaining compounds **576b** and **577b** in almost the same ratio. However, the selectivity was improved by placing a more electron-rich aromatic ring, such as in β-lactam **64c**, affording compound **576c** in reasonable yield (51%).

When this reaction was carried out with *trans*-4-formyl-β-lactams **578**, the corresponding enantiopure α-alkoxy carboxamides were obtained (Scheme 185). The (3*R*,4*S*)-4-formyl-β-lactam (−)-**578a** gave compound (*R*)-**576a** (52%), while its enantiomer (+)-**578a** yielded compound (*S*)-**576a** (50%). Therefore, it has been demonstrated that synthesis of both enantiomers of α-hydroxy acid derivatives can be achieved by a subtle variation in the stereochemistry of the starting material.

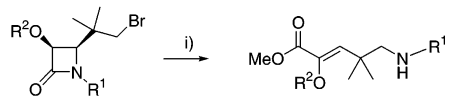
Synthesis of α-alkoxy-γ-keto acid derivatives **576** can be rationalized by formation of alkoxide **580**. This intermediate **580** may suffer a 1,2-migration of hydrogen with concomitant N1−C4 β-lactam bond cleavage to obtain the α-alkoxy-β-keto acid derivatives **576** (*A* in Scheme 186) or accept an electrophile to give addition products **577** or **579** (*B* in Scheme 186).

Reaction of 4-(1-haloalkyl)-2-azetidinones **1a**−**c** and 4-(2-bromoalkyl)-2-azetidinones **42a**−**c** with sodium methoxide in methanol yielding ring-opened products, the methyl 2-alkoxy-4-(alkylamino) pentenoates **581a**−**c**, and the methyl

Scheme 187[a]



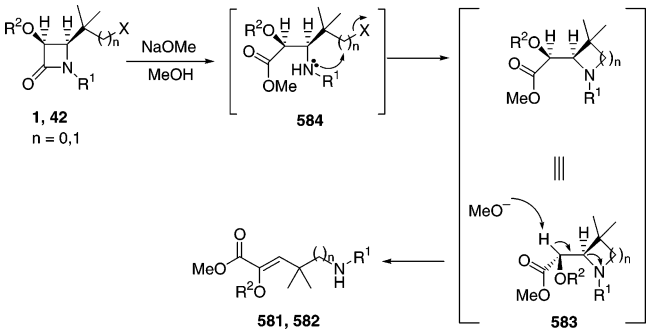
1a R^1 = *i*-Pr, R^2 = Bn **581a** (45%)
1b R^1 = allyl, R^2 = Bn **581b** (45%)
1c R^1 = *i*-Pr, R^2 = Me **581c** (46%)



42a R^1 = *i*-Pr, R^2 = Bn **582a** (65%)
42b R^1 = Et, R^2 = Bn **582b** (66%)
42c R^1 = allyl, R^2 = Bn **582c** (60%)

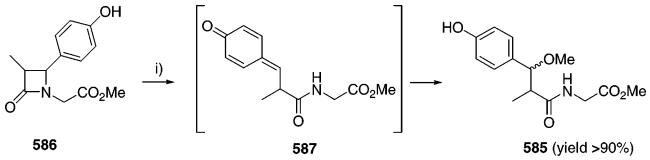
[a] Key: (i) 4 equiv. MeONa, MeOH, reflux, 4 h.

Scheme 188



1, 42 n = 0,1 **584** **581, 582** **583**

Scheme 189[a]



586 **587** **585** (yield >90%)

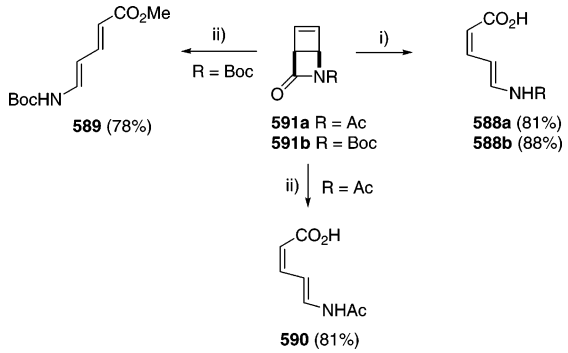
[a] Key: (i) MeONa, MeOH.

5-(alkylamino) pentenoates **582a**−**c**, respectively, in moderate yields (Scheme 187) has been documented.[162]

The proposed reaction course to explain formation of compounds **581** and **582** starts with nucleophilic attack of sodium methoxide to the amide functionality of azetidinone **1** or **42**, resulting in ring opening (Scheme 188). The secondary amine thus formed then attacks the halogenated carbon, leading to ring closure by intramolecular nucleophilic substitution to give the ring-closed products **583** aziridine ($n = 0$) and azetidine ($n = 1$) derivatives. However, in the presence of excess of sodium methoxide, deprotonation at the α-position of the ester **583** occurs and anti elimination gives the stereospecific formation of alkenoates **581** and **582**. According to the reaction mechanism the products obtained should be the *Z*-alkenoates if no isomerization occurs during the reaction. Experimentally obtained products consisted of one isomer exclusively, and the *Z* geometry was established by NOE experiments on derivatives **582**.

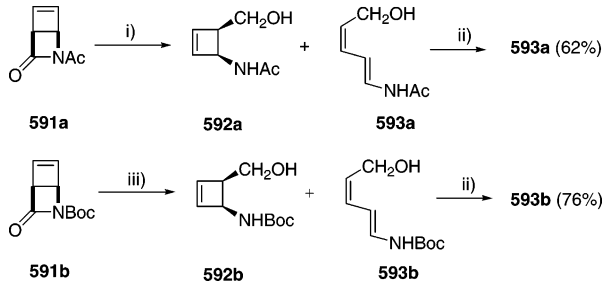
The β-alkoxy acid derivative **585** has been prepared from β-lactam **586** by treatment with sodium methoxide in methanol.[163] Formation of this compound has been explained by phenolate formation followed by rearrangement to an intermediate quinone methide **587** with concomitant cleavage of the N1−C4 β-lactam bond (Scheme 189). The very reactive quinone methide is quenched by methoxide anion in a Michael-type 1,6-conjugate addition at the benzylic carbon to give the β-alkoxy acid derivative **585**.

Scheme 190[a]



[a] Key: (i) LiOH, THF, H_2O, RT, 16 h. (ii) MeOH, LiOH, RT, 4 h.

Scheme 191[a]



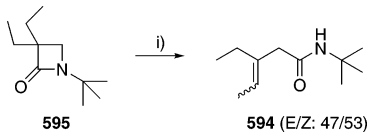
[a] Key: (i) $LiAlH_4$, THF, −78 to −20 °C, 6 h; (ii) toluene, reflux, 10 min; (iii) $NaBH_4$, MeOH, −20 °C, 1 h.

Dienic amino acid derivatives **588**−**590** were prepared from cyclobutane-fused lactams **591** by methanolysis, hydrolysis, or reduction (Scheme 190).[164] The starting lactams **591** were obtained in good yields from the commercially available 2-hydroxypyridine in one step, in aqueous solution, through a photochemical electrocyclic reaction. First, hydrolysis of β-lactams **591a,b** with LiOH provided dienes **588a,b** by a conrotatory process with outward rotation of the nitrogen substituent and preference of CO_2H for the 2-(*Z*)-position. On the other hand, methanolysis of azetidinone **591b** (R = Boc) afforded the (*E*,*E*)-isomer **589**. One possible explanation for this result is isomerization of the *cis*-cyclobutene intermediate to the trans compound, under base catalysis, prior to ring opening. However, when the reaction was carried out with β-lactam **591a** (R = Ac), this isomerization was not observed and diene **590** was obtained instead. This unexpected result is probably due to a moderate 'push−pull' character of diene **590** in which a strongly electron-withdrawing group is attached to nitrogen.

Reaction of **591a** with lithium aluminum hydride at low temperature led to a selectivity in favor of reduction of the lactam moiety with respect to the acetyl group. A mixture of *N*-[4-hydroxymethylcyclobut-2-enyl]acetamide **592a** and diene **593a** was thus obtained. The latter was isolated in 62% overall yield after isomerization of the cyclobutadiene compound by heating the mixture in refluxing toluene. In a similar manner, treatment of azetidinone **591b** with sodium borohydride led to a mixture of diene **593b** and cyclobutene **592b**, which was completely converted to diene **593b** by briefly heating the mixture (Scheme 191).

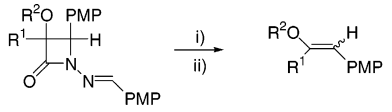
Several examples concerning the synthesis of alkenes from β-lactams have been described. In this context, β,γ-unsaturated carboxylic amide **594** has been obtained through a N1−C4 cleavage by thermolysis of 4,4-disubstituted β-lactam **595** (Scheme 192).[165]

Scheme 192[a]



[a] Key: (i) Preparative GC (130 °C).

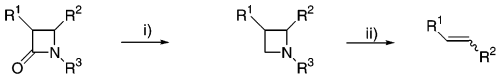
Scheme 193[a]



***cis*-597a** R^1 = H, R^2 = Bn	**596a** (64%) *E*/*Z*: 72:28
***trans*-597a** R^1 = H, R^2 = Bn	**596a** (52%) *E*/*Z*: 8:92
***cis*-597b** R^1 = H, R^2 = *t*-Bu	**596b** (40%) *E*/*Z*: 100:0
***cis*-597c** R^1 = Me, R^2 = Bn	**596c** (60%) *E*/*Z*: 92:8
***trans*-597c** R^1 = Me, R^2 = Bn	**596c** (55%) *E*/*Z*: 12:88

[a] Key: (i) O_3, CH_2Cl_2, −78 °C; (ii) $NaBH_4$, $MeOH/H_2O$.

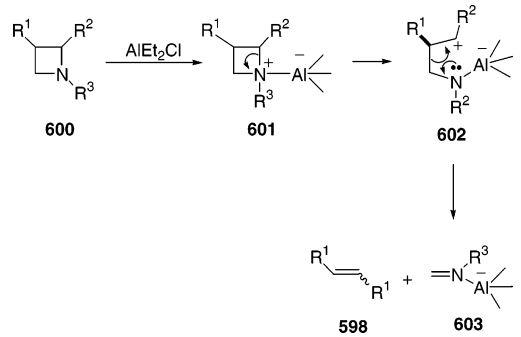
Scheme 194[a]



***cis*-599a** R^1 = PhO, R^2 = PMP, R^3 = Bn	***cis*-600a** (91%)	**598a** (57%) *E*/*Z*: 0:100
***cis*-599b** R^1 = PhO, R^2 = 2-Furyl, R^3 = Allyl	***cis*-600b** (97%)	**598b** (58%) *E*/*Z*: 0:100
***trans*-599b** R^1 = PhO, R^2 = 2-Furyl, R^3 = Allyl	***trans*-600b** (85%)	**598c** (61%) *E*/*Z*: 67:33
***cis*-599c** R^1 = PhO, R^2 = 2-Furyl, R^3 = Bn	***cis*-600c** (85%)	**598d** (53%) *E*/*Z*: 0:100
***trans*-599d** R^1 = Ph, R^2 = PMP, R^3 = Bn	***trans*-600d** (54%)	**598e** (68%) *E*/*Z*: 0:100

[a] Key: (i) AlH_2Cl, Et_2O, 34 °C, 0.5 h; (ii) $AlEt_2Cl$, CH_2Cl_2, RT.

Scheme 195



Also, an efficient and stereoselective synthesis of vinyl ethers **596** by ozonolysis of *N*-imino-β-lactams **597** followed by treatment with $NaBH_4$ has been reported (Scheme 193).[166] Vinyl ethers **596** have been obtained with moderate to excellent *E*/*Z* selectivities. This transformation has been explained through a fragmentation of the 2-azetidinone ring.

Alkenes **598** have been obtained via fragmentation of the azetidine ring promoted by $AlEt_2Cl$.[17] As shown in Scheme 194, starting from β-lactams **599a**−**d**, azetidines **600a**−**d** were obtained in good yields by treatment of **599** with in-situ-generated AlH_2Cl (from $LiAlH_4/AlCl_3$). Due to their instability, azetidines **600** were used for the following step without further purification. Reaction of azetidines **600** with $AlEt_2Cl$ in dichloromethane at room temperature afforded the corresponding alkenes **598** in moderate yields. The stereochemistry of the azetidine was transferred unaltered to the olefin in the tested cases, except for *trans*-azetidine **600b**, which gave an *E*/*Z* mixture of olefins.

A reasonable mechanism has been proposed for formation of olefins **598** (Scheme 195). Initial coordination of the lone electron pair of the azetidine nucleus to the $AlEt_2Cl$ gives intermediate **601**. This coordination should promote the C2−

N1 bond breakage to form zwitterion **602**. Due to the presence of electron-donor aryl groups (R^2 = furyl, PMP), the C3−C4 bond would break to yield the observed olefin **598** together with the iminium salt **603**.

7. Conclusions

The 2-azetidinone nucleus has been recognized as the central motif of the so-called β-lactam antibiotics, the most widely employed family of antimicrobial agents to date. Besides their significance as bioactive agents, the importance of β-lactams as synthetic intermediates has been widely recognized in organic synthesis because ring cleavage of any of the four single bonds of the β-lactam system is enhanced by ring strain. As a small ring, 2-azetidinone provides a structural scaffold of unique bond angles and well-defined configurations of the substituents. Therefore, selective bond cleavage of the strained β-lactam ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks. 2-Azetidinones have been used as precursors for the preparation of α- and β-amino acids, alkaloids, different-sized heterocycles, taxoids, and other types of compounds of biological and medicinal interest. Because of the reliability and popularity gained by the β-lactam synthon method coupled to the availability of isomerically pure 2-azetidinones, it is predicted that further developments in the β-lactam-based methodology for the synthesis of compounds of chemical and medicinal significance are likely.

8. Abbreviations

Ac	acetyl
ADDA	3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-deca-4,6-dienoic acid
AIBN	α,α′-azobisisobutyronitrile
Ala	alanine
Ar	aryl
Asp	asparagine
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BQ	benzoylquinine
BT	benzotriazole
CAL-B	lipase B from *Candida antarctica*
CAN	ceric ammonium nitrate
cat	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1′-carbonyldiimidazole
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminum hydride
DIC	*N*,*N*′-diisopropylcarbodiimide
DIEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMD	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess−Martin periodinane
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
de	diastereomeric excess
dr	diastereomeric ratio
E	enantioselectivity
ee	enantiomeric excess
ET	ecteinascidin
Gly	glycine
GC	gas chromatography
HBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazane
HOBT	*N*-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
IBX	2-iodoxybenzoic acid
INAC	intramolecular nitrone−alkene cycloaddition
IR	infrared
LDA	lithium diisopropylamide
Leu	leucine
MBHA	4-methylbenzhydrylamine
MCPBA	*m*-chloroperbenzoic acid
MS	mass spectrometry
NCA	*N*-carboxy anhydride
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Pht	phtalimidoyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
py	pyridine
RCM	ring-closing metathesis
RT	room temperature
satd	saturated
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCBoc	trichloro-*tert*-butoxy carbonyl
TCNE	tetracyanoethylene
TEMPO	2,2,6,6-tetramethylpiperidinyl-1-oxyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Thz	2-thiazolyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMST	2-(trimethylsilyl)thiazole
Tol	tolyl
TPP	triphenylphosphine
Troc	2,2,2-trichloroethyl carbonyl
Val	valine

9. Acknowledgments

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