SYNTHESIS OF ENANTIOPURE $\beta$-AMINO ACIDS AND THEIR DERIVATIVES VIA $\beta$-LACTAMS

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INTRODUCTION

$\beta$-Amino acids are key components of many biologically active compounds and important building blocks for $\beta$-peptides. As a result, numerous methods have been developed for the synthesis of optically pure $\beta$-amino acids. However, many of the methods suffer from drawbacks such as complex experimental procedures, and limitations in product configuration. Most of all, there have been potential issues for scale-up problems associated with the manipulation of hazardous materials, and alternative approaches are needed.

The synthesis of $\beta$-lactams has been a research objective for many years after the discovery of the $\beta$-lactam antibiotics. However, the use of the $\beta$-lactams as synthetic intermediates has drawn little attention until recently. This review focuses on the development of methods utilizing $\beta$-lactams in the synthesis of $\beta$-amino acids and on some recent applications. Since enantiomerically pure $\beta$-lactams are easily accessible through already well-established synthetic methodology, this approach is recognized as a promising method for large scale preparation of $\beta$-amino acids.

BACKGROUND

Known Methods for $\beta$-Amino Acid Synthesis

Many biologically important natural products contain the $\beta$-amino acid moiety. Representative examples include, the antifungal compound cispentacin, the antitumor agent taxol, the unsaturated $\beta$-amino acid ADDA, $\beta$-peptidic natural products such as carnosine and pantothenic acid, and the aminopeptidase inhibitor bestatin (Fig 1). Given the importance of these compounds, the development of the synthesis of $\beta$-amino acids and their derivatives in optically pure form has become an important objectives, and numerous synthetic methods have emerged in recent years.
The most widely used method for the preparation of $\beta$-peptides is the Arndt-Eistert homologation of $\alpha$-amino acids. (Eq 1) Another important approach involves the Mannich-type condensation of imines and ester enolates or their equivalents. The diastereoselective version of this reaction has been extensively studied, in which a chiral controller is attached either to the imine nitrogen, to the enolate, or both.\textsuperscript{2(b)} Other approaches include the Curtius rearrangement of a protected $\alpha$-amino acids, conjugate addition of nitrogen nucleophiles to $\alpha$, $\beta$-unsaturated esters or imides, and amino hydroxylation of olefins and subsequent protection and oxidation.\textsuperscript{2}

Racemic $\beta$-amino acids may be resolved by either using classic crystallization of diastereomeric salts or by enzymatic kinetic resolution. These methods can be applied to various types of $\beta$-amino acids. The ideal reaction would give the product in enantiomerically pure form, and the reagents should be readily available and safe to employ on large scale. In addition, it should be adaptable of diverse, densely functionalized $\beta$-amino acids, having cyclic or open chain structures.\textsuperscript{8}

$\beta$-Lactams as Synthetic Intermediates

The first $\beta$-lactam was synthesized by Staudinger in 1907, but this functional unit did not acquire importance until the 1940’s, about 20 years after the discovery of penicillin. Since the $\beta$-lactam ring was responsible for the antibiotic activity, a great deal of research has been devoted to the study of $\beta$-lactam reactions. It was found that the carbonyl group in a $\beta$-lactam is susceptible to nucleophilic attack and upon exposure to certain proteins and enzymes, the $\beta$-lactam ring opens to display its characteristic pharmacological properties. It was then anticipated that if such a ring opening could be carried out in a controlled manner by chemical methods, some interesting products would also be attainable.

This promoted widespread application of $\beta$-lactams in the synthesis of $\beta$-amino acids, and other natural products including alkaloids, amino sugars and peptides.\textsuperscript{2, 9} For example, Ojima and coworkers utilized various kinds of nucleophiles in the $N_1-C_2$ bond cleavage of $\beta$-lactams, and applied this in the semisynthesis of natural compounds (Eq 2). Access to various enantiopure $\beta$-lactams laid the crucial foundation for this methodology.\textsuperscript{6, 10}

\[\text{(2)}\]

ENANTIOPURE $\beta$-LACTAM SYNTHESES

Cyclization of $\beta$-Amino Acid Derivatives

Different $\beta$-lactams can be synthesized by cyclization of $\beta$-amino acids. The amino group is often $N$-acylated prior to the reaction in order to prevent deamination by $\beta$-elimination. When $N$-
acylated β-amino acids are used, the reaction is known to occur via aminolactol intermediate, which facilitates the conversion into the desired β-lactam (Eq 3). β-Amino acid chlorides undergo a facile cyclization to corresponding β-lactams in reasonable yield upon treatment with excess N,N-dimethylaniline. Cyclization of β-amino acid esters can be accomplished by amine deprotonation with Grignard reagents.¹

**The Ketene-Imine [2+2] Cycloaddition**

Among the many methodologies reported for synthesis of enantiopure β-lactams, the ketene-imine [2+2] cycloaddition, also known as asymmetric Staudinger reaction, is recognized as one of the most reliable methods available.¹¹ β-Lactams with a widely varying substitution pattern at the C-3 and C-4 positions of the ring have been constructed stereoselectively. The major product of the cycloaddition is usually the cis β-lactams, although a few exceptions showing trans selectivity are known. One asymmetric version of this reaction relies on chiral auxiliaries, and in general high diastereoselectivity has been rather difficult to achieve. (R)-1-Naphthylethylamine was used as the chiral auxiliary for synthesis of 3-phenoxy-β-lactams 1a and 1b, which are separable by column chromatography (Scheme 1).¹², ¹³

Despite the synthetic interest in the Staudinger reaction, the actual mechanism is still unclear. In the case where the chiral auxiliaries are placed at the imine, according to the accepted model, the reaction is assumed to proceed through a zwitterionic iminium-enolatae intermediate which undergoes an electrocyclic conrotatory ring closure to give the β-lactam ring.¹⁴

A catalytic system including a chiral nucleophile was developed by Lectka and coworkers in which a nucleophilic ketene was generated in the presence of 10% benzoylquinine, leading to increased reactivity of the original substrate.¹⁵ (Scheme 2) Unlike the classic Staudinger reaction, a nucleophilic ketene generated in the presence of 10% benzoylquinine leads to increased selectivity and reactivity of the original substrate, and the imine was transformed into a non-nucleophilic form, as an electron-deficient imino ester. The addition of 10% In(III) triflate improved the reaction rate as well as chemical yields, presumably

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**Scheme 1. Ketene-imine [2+2] cycloaddition**

**Scheme 2.**
through chelation to the imine.\textsuperscript{16, 17}

**The Enolate–Imine Condensation**

Another efficient route to \( \beta \)-lactams, which can be applied in the asymmetric synthesis of 3-amino- and 3-hydroxy-\( \beta \)-lactams involves the enolate-imine condensation method.\textsuperscript{18, 19} Both ester and imine components have been used in enantiomerically pure form. For example, (Eq 4) chiral lithium enolates generated \textit{in situ} from \( N,N \)-bis(silyl)glycinates undergo cyclocondensation with \( p \)-methoxyphenylimines to afford \textit{trans}-3-amino-\( \beta \)-lactams 2 bearing the PMP protecting group with up to 99% ee.\textsuperscript{20}

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\begin{align*}
\text{R}^* &= \text{trans-2-phenylcyclohexyl} \\
\text{R}_1 &= \text{Ph, } p-F-C_6H_4, p-CF_3-C_6H_4, 4-MeO-C_6H_4, 3,4-(MeO)_2C_6H_3 \\
\end{align*}
\]

\[
\begin{align*}
1. \text{LDA} \\
2. R^1-\text{CH}=\text{N-PMP} \\
3. \text{H}_2\text{O} \\
\end{align*}
\]

**RING OPENING REACTIONS AT THE N\textsubscript{1}-C\textsubscript{2} BOND OF \( \beta \)-LACTAMS**

**\( \beta \)-Lactams as Formal Acylating Agents**

The majority of the ring opening reactions of \( \beta \)-lactams performed in the earlier literature involve hydrolysis and alcoholysis of \( \beta \)-lactams under either acidic or basic reaction conditions, which limit the scope to \( \beta \)-lactams bearing no acid- or base-sensitive substituents.\textsuperscript{21, 22} However, \( \beta \)-lactamase-catalyzed hydrolysis provides an efficient process for a broader spectrum of \( \beta \)-lactams, including those with base- or acid-sensitive groups.\textsuperscript{23} In particular, the class C \( \beta \)-lactamases catalyze the alcoholysis reaction to afford \( \beta \)-amino esters as products. Generally, \( N \)-acyl \( \beta \)-lactams are used as substrates because the \( N \)-acyl group activates the \( \beta \)-lactam carbonyl towards nucleophilic attack while protecting the amino group in the resulting \( \beta \)-amino acid.

**Ring Opening Reactions by Alcohols and Alkoxides**

The ring opening of \( N \)-acyl \( \beta \)-lactams by oxygen nucleophiles is a general method to access \( \beta \)-amino acids of various types. When free alcohols are used as nucleophiles, the reactions proceed rather slowly whereas alkoxylate salts produce the expected esters more efficiently, provided that the ring bears no base-sensitive substituents. In many cases the use of NaN\textsubscript{3} or KCN as a catalyst with the alcohol nucleophiles provided very efficient ring openings while the basic alkoxide reagents such as NaOMe or NaOEt resulted in the cleavage of the acetoxy groups present.\textsuperscript{24}
Angelaud carried out a direct opening of \( N \)-benzyloxy-protected \( \beta \)-lactams bearing a difluorobenzyl group into the corresponding \( \beta \)-amino acid. \(^{25} \) (Scheme 3) The synthesis of this new drug candidate would have been more difficult if other common methods such as Michael addition of chiral amine to the \( \alpha,\beta \)-unsaturated ester had been used due to the strong electron-withdrawing effect of the difluorophenyl ring. This methodology was further extended in a synthesis of macrocyclic precursors to the antitumor antibiotics lankacidins. \(^{26} \) Also, a \( \beta \)-lactam was coupled intramolecularly with a secondary hydroxyl group in the side chain of 3 to furnish macrocycle 4, a precursor to the immunosuppressive agent (-)-panteamine A. \(^{27} \)

**Ring Opening Reactions by Amines and \( \alpha \)-Amino Acids**

Ring opening reactions by nitrogen nucleophiles produce \( \beta \)-amino amides and \( \beta \)-amino acid-derived peptides. These molecules are found in naturally occurring macrocyclic compounds including a \( \beta \)-hydroxy aspartic acid-derived tripeptide, which is a structural unit in the macrocyclic peptide lactone antibiotic lysobactin. \(^{27} \) One remarkable application is the preparation of the aminopeptidase inhibitors bestatin 7 and phebestin 8. \(^{28} \) Coupling of the \( N \)-Boc \( \beta \)-lactam 5 with (S)-LeuOBn or (S)-ValOBn in the presence of NaN\(_3\) afforded dipeptide 6. Dipeptide 6 was further transformed into bestatin 7 and phebestin 8 by standard deprotections. (Scheme 4)

This novel peptide coupling can be carried out by solid phase synthesis. When the “Wang resin” is used, dipeptides of \( \beta \)-amino acids can now be obtained in good yield. \(^{5} \)
APPLICATIONS IN SYNTHESIS

Asymmetric Synthesis of ADDA

(2S,3S,8S,9S,4E,6E)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid or ADDA is an unusual $\beta$-amino acid component present in the cyanobacterial natural products nodularin and microcystin. They are hepatotoxins and tumor promoters, and many studies have shown that the presence of ADDA is essential to their hepatotoxicity. The stereoselective synthesis of this complex $\beta$-amino acid by Rinehart at the University of Illinois involved asymmetric Evans aldol reactions to install all of the chiral centers in ADDA. The last step employed a one-pot Mitsunobu reaction and SmI$_2$ reduction of the resulting isoxazolidinone.$^{29, 30}$ (Scheme 5) A variety of analogues of ADDA and ADDA-glutamic acid dipeptide were needed in order to probe the structure-activity relationship of ADDA. This goal was achieved by reaction of $N$-Boc $\beta$-lactam 9 with glycine methyl esters to form ADDA-glutamic acid dipeptide analogues 10 (Eq 5).$^{31}$

Taxol Side Chain Incorporation

The $\beta$-lactam ring opening method was applied to the synthesis of Taxol® (paclitaxel), an antitumor agent for the treatment of ovarian and breast cancers.$^{32}$ Holton and his group accomplished the first total synthesis starting from commercially available natural compound patchoulene oxide.$^{33}$ The reaction sequence is relatively short compared to that of the other groups with an estimated 37 steps not counting the addition of the amide side chain. Taxol became more available to patients by its semisynthesis using the $\beta$-lactam acylation method. The introduction of the side chain in this synthesis (Eq 6) was identical to that in the Nicolaou route and was based on Ojima chemistry.$^{34}$ $\beta$-Lactam 11 was coupled with sodium salt of 12, and after mild deprotection of the triethylsilyl (TES) OH protecting group, an facile and efficient semisynthesis of paclitaxel 13 was achieved.$^{35}$
CONCLUSION

The \( \beta \)-lactam ring-opening method has been illustrated by the preparation of a wide variety of functionalized \( \beta \)-amino acids. The method has found applications in various areas of organic chemistry as well as in pharmaceuticals, including preparation of biologically active and conformationally interesting analogues of ADDA, and as a powerful tool in the commercial production of the anticancer agent paclitaxel and its analogues. However, improved methods for enantioselective synthesis of \( \beta \)-lactams are needed. The development of efficient processes suitable for practical, large-scale synthesis is necessary. Therefore the research on new and improved methods for synthesis of \( \beta \)-amino acids using \( \beta \)-lactams will continue to grow and to develop further in the future.

REFERENCES

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