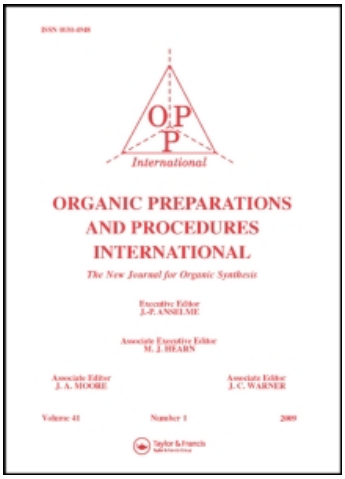

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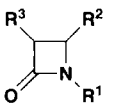
INTRODUCTION

The azetidin-2-one nucleus **1** has been recognized as the central motif of the so-called β-lactam antibiotics (*Fig. 1*). The importance and structural diversity of biologically active β-lactam antibiotics, the most widely employed family of antimicrobial agents accounting to date for 50% of the world's total antibiotic market, led to the development of efficient approaches for the construction of appropriately substituted azetidin-2-ones with attendent control of functional groups and stereochemistry.[1] The various families of β-lactam antibiotics differ in their spectrum of antibacterial activity and in their susceptibility to β-lactamase enzymes. β-Lactamases, which constitute the most common and growing form of antibacterial resistance,[2] catalyze the hydrolysis of β-lactams to give ring-opened β-amino acids which are no longer effective as inhibitors against their targets, namely, bacterial membrane-bound transpeptidases enzymes. Besides, the ever-growing new applications of azetidin-2-ones in fields ranging from enzyme inhibition[3-5] to the use of these products as starting materials to develop new synthetic methodologies, justify a renewed interest in these compounds.



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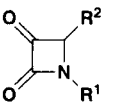


2

Figure 1

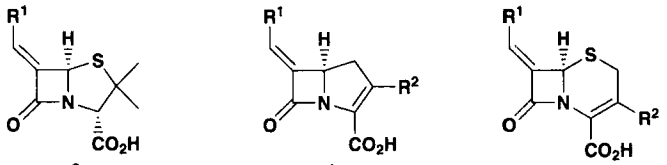
Azetidine-2,3-diones or α-keto-β-lactams **2** are potentially very useful intermediates by virtue of the high concentration of functional groups in a small ring (*Fig. 1*). However, although there have been many investigations in the β-lactam field and the chemistry of various types of substituted azetidin-2-ones, there are only a limited number of reports on the use of azetidine-2,3-diones as building blocks. As far as we know, natural products bearing the azetidine-2,3-dione skeleton, or structurally related bioactive unnatural compounds, have not been reported to date. However, a signif-

icant degree of interest has been recently focused on the synthesis and reactivity of azetidine-2,3-diones, due to their potential use as viable intermediates in the synthesis of biologically active compounds.

The present article is a survey of the salient synthetic achievements exploiting azetidine-2,3-diones, with particular emphasis on diastereoselective processes. After a brief introduction highlighting the potential usefulness of azetidine-2,3-diones for the preparation of substances of biological interest, the synthesis and synthetic application of these compounds is presented. Discussions in the text are organized in two main points, according to the nature of the β-lactam nucleus (fused or non-fused). Bicyclic systems are analyzed first because of their earlier use; the vast majority of the progress on the chemistry of azetidine-2,3-diones in the 1970s was carried out using 6-oxopenicillanates and 7-oxocephalosporanates. However, some of the most significant advances in the synthesis and synthetic application of these compounds have been recently achieved with monocyclic azetidine-2,3-diones. Because of the later development of the chemistry of monocyclic azetidine-2,3-diones they are covered last. This review covers the literature up to March 2001.

I. BICYCLIC AZETIDINE-2,3-DIONES

Azetidine-2,3-diones have been used in many areas of β-lactam chemistry, and have found utility as reactive synthetic intermediates. Although monocyclic examples have been reported in the last decade, the greatest number of investigations has traditionally involved oxoderivatives of the common bicyclic β-lactam antibiotics such as 6-oxopenicillins and 7-oxocephalosporins. Bicyclic azetidine-2,3-diones are important starting materials for the introduction of alkylidene side chains at C3 position of the β-lactam ring in compounds of type **3–5**, which are reported to be efficient β-lactamase inhibitors (*Fig. 2*).[6]



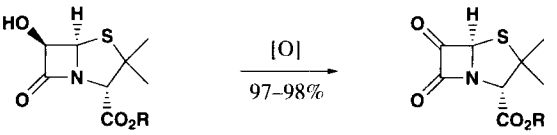
3 4 5

Figure 2

1. Preparation of Bicyclic Azetidine-2,3-diones

6-Oxopenicillanates and 7-oxocephalosporanates have been traditionally prepared *via* oxidation (Pfitzner-Moffatt and Swern oxidations) of the 6-hydroxypenicillanates and 7-hydroxycephalosporanates. However, the 6- and 7-oxo derivatives produced are relatively unstable and are not usually isolated, and thus used directly for further reactions.[7] For example, while the oxidation of the 6-hydroxypenicillanates **6** is straightforward, the 6-oxo derivatives **7a–d** formed are unstable at pH ≥

7 and sensitive to purification by column chromatography, and these 6-oxopenicillanates are unstable toward prolonged storage at –20° in certain cases (*Scheme 1*).[8]

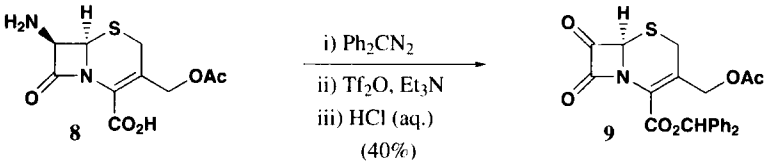


6 7

a) R = H b) R = allyl c) R = Benzhydryl d) R = Benzyl

Scheme 1

In 1994 Buynak reported a new procedure for the preparation of a 7-oxo derivative.[9] 7-Aminocephalosporanic acid (**8**) was esterified with diphenyldiazomethane and after treatment with excess triethylamine and trifluoromethanesulfonic anhydride followed by acidic hydrolysis, led to the 7-oxocephalosporanate **9** (*Scheme 2*).

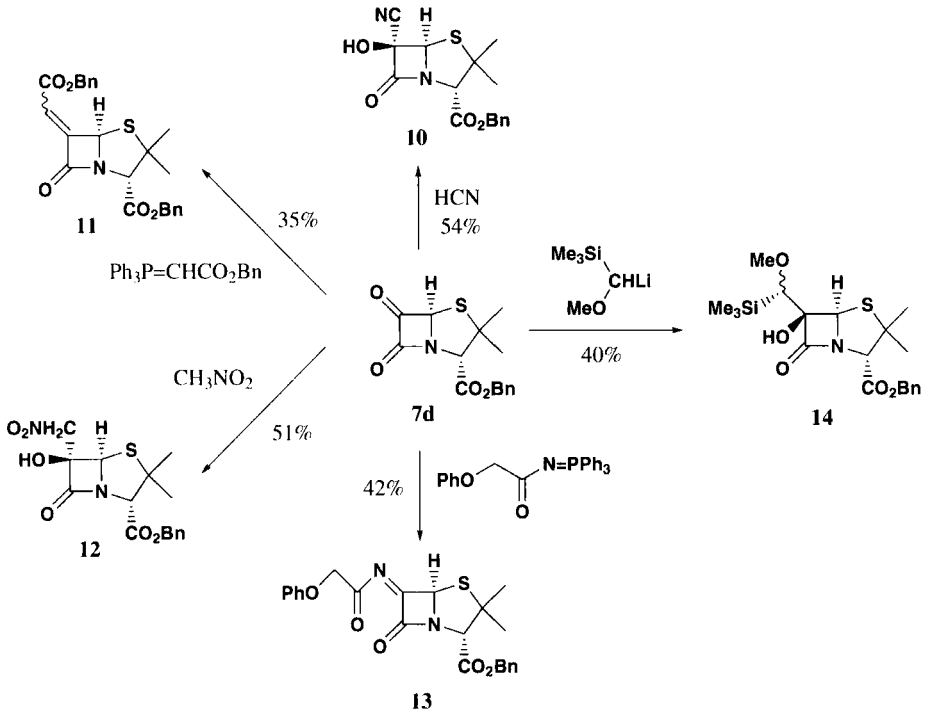


8 9

Scheme 2

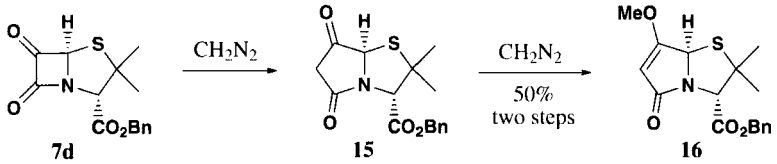
2. Reactivity of Bicyclic Azetidine-2,3-diones

In 1972, Sheehan described the preparation of 6-oxopenicillanic acid derivatives from penicillin G and showed that the keto group adjacent to the β-lactam carbonyl was chemically very active.[7b] For example, 6-oxo derivative **7d** forms a crystalline cyanohydrin **10**,[10] which readily undergoes Wittig olefination,[7e] smoothly forms imines through an aza-Wittig reaction,[10] and is conveniently receptive to the Peterson olefination[7f] and Henry reactions (*Scheme 3*).[7d]



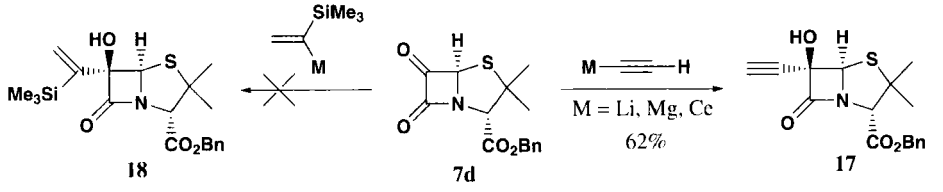
Scheme 3

Baldwin discovered some time ago an interesting ring expansion of benzyl 6-oxopenicillanate **7d**, to give an oxo-γ-lactam **16** by treatment with an excess of diazomethane (*Scheme 4*).[11]



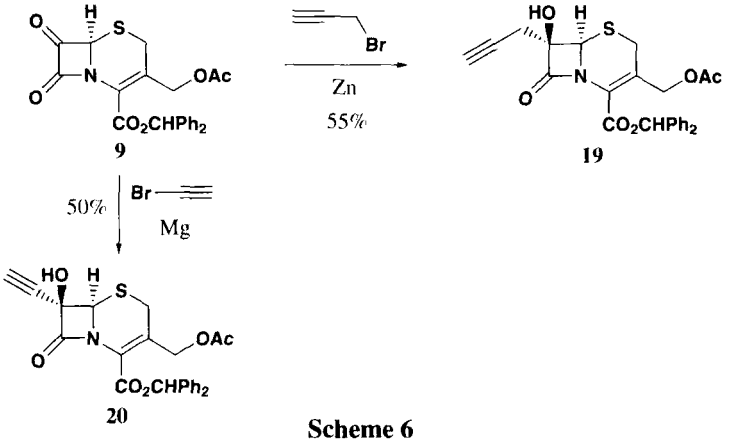
Scheme 4

In a more recent report, Buynak described the metal acetylide addition to the ketone **7d**. The corresponding propargyl alcohol **17** was obtained in a 62% yield *via* lithium acetylide coupling. However, the addition reaction of (α-metallovinyl)silanes to 6-oxo derivative **7d** to produce the expected vinyl alcohol **18** failed (*Scheme 5*).[8]



Scheme 5

Analogously, the ketonic carbonyl in 7-oxocephalosporanic acid derivatives has been recognized to possess heightened electrophilicity, and similar reactions to the 6-oxopenicillanate series have been used.[7d,12] For example, Buynak described his synthesis of 7-vinylidenecephems, the stereoselective reaction between the 7-oxocephalosporanate **9** and ethynylmagnesium bromide,[9] and Cho recently reported the propargylzincation of ketone **9** in anhydrous tetrahydrofuran (*Scheme 6*).[13]



Scheme 6

II. MONOCYCLIC AZETIDINE-2,3-DIONES

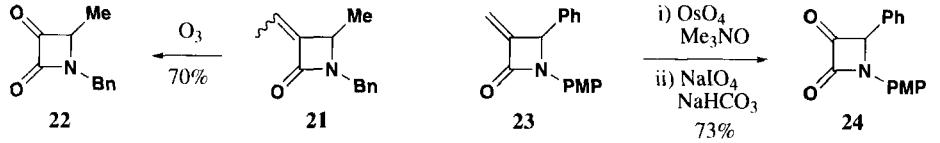
While the chemistry of 6-oxopenicillanates and 7-oxocephalosporanates has been the focus of intense effort, little was known about the synthesis and application of monocyclic azetidine-2,3-diones and even less on their optically active derivatives, until Palomo elegantly merges into this field, utilizing an azetidine-2,3-dione approach to α-amino acids.[14] On the other hand, recently, a number of investigations has been centered on the preparation and reactivity of monocyclic azetidine-2,3-diones, due to their use as building blocks in the synthesis of biologically important β-lactam products. In this context, the antibiotics nocardicin A,[15] and sulphazecin,[16] and enzyme inhibitors such as tabtoxin,[17] are representative examples.

1. Preparation of Monocyclic Azetidine-2,3-diones

In contrast to the behavior of bicyclic azetidine-2,3-diones, which are relatively unstable and not usually isolated, monocyclic azetidine-2,3-diones are usually amenable to purification by chromatography. Several methods for the preparation of monocyclic azetidine-2,3-diones in racemic and enantiopure forms have been reported by different workers.

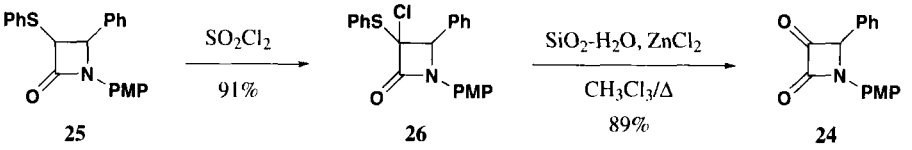
a) Synthesis in Racemic Form

Monocyclic azetidine-2,3-diones can be prepared by oxidation of α-unsaturated β-lactams. Tufariello[18] has reported a synthesis of monocyclic azetidine-2,3-diones **22** by ozonolysis of α-ethylidene β-lactams **21**,[19] while Alcaide has described the dihydroxylation of α-methyleneazetidin-2-ones **23** followed by oxidative cleavage (*Scheme 7*).[20]



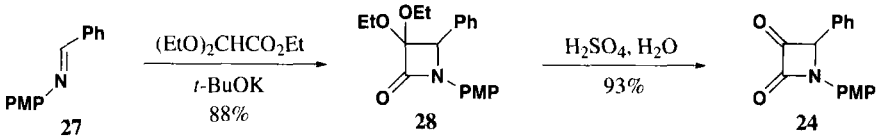
Scheme 7

Bose described the synthesis of this family of azetidin-2-one derivatives **24** *via* a Pummerer type reaction of α-phenylthio-β-lactams **25** by treatment with sulfuryl chloride, followed by hydrolysis under acidic conditions (*Scheme 8*).[21]



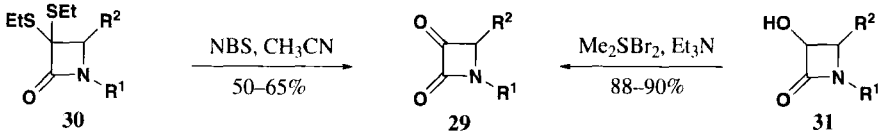
Scheme 8

An interesting access to racemic monocyclic azetidine-2,3-diones **24** has been reported by Panunzio, *via* ester enolate-imine condensation followed by mild acid hydrolysis of the acetal moiety in compound **28** (*Scheme 9*).[22]



Scheme 9

Monocyclic azetidine-2,3-diones **29** were prepared by Palomo either by oxidative hydrolysis of 3,3-*bis*(ethylthio) β-lactams **30**,[23] or by oxidation of 3-hydroxy β-lactams **31** by means of a dimethylbromosulfonium bromide-triethylamine system (*Scheme 10*).[14]

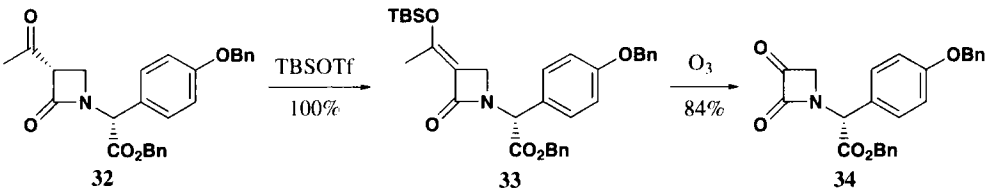


R^1 = aromatic
R^2 = unsaturated or aromatic

Scheme 10

b) Synthesis in Enantiopure Form

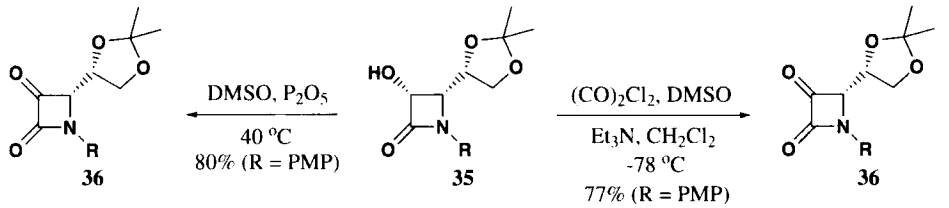
The oxidation of β-lactams bearing appropriate groups at C3 position, has been shown to be a straightforward preparation of non-racemic monocyclic azetidine-2,3-diones. Ley developed a synthesis of optically active azetidine-2,3-diones **34** *via* ozonolysis of an enol ether **33** (*Scheme 11*).[24]



32 33 34

Scheme 11

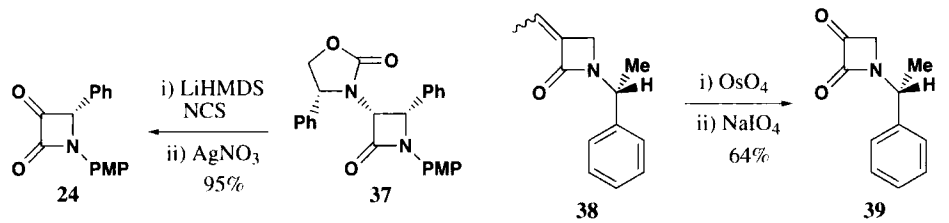
In this context, different authors have independently tested reaction conditions for the oxidation of enantiopure 3-hydroxy-β-lactams **35**. Palomo obtained the best results using dimethylsulfoxide in combination with phosphorus pentoxide,[25] while Alcaide found dimethylsulfoxide-oxalyl chloride to be the most effective oxidizing system (*Scheme 12*).[26]



36 35 36

Scheme 12

An asymmetric synthesis of azetidine-2,3-diones **24** has been reported by Palomo, in which the chiral auxiliary was oxidatively cleaved to the α-keto moiety.[27] In this context, Paquette successfully performed the preparation of enantiomerically pure azetidine-2,3-diones **39** by oxidative cleavage of α-ethylidene-azetidin-2-ones **38** bearing a chiral auxiliary at nitrogen (*Scheme 13*).[28]



24 37 38 39

Scheme 13

2. Applications of Monocyclic Azetidine-2,3-diones in Asymmetric Synthesis

a) Synthesis of 3-Amino-β-Lactams

Nocardicin **40** was isolated as the major product from the fermentation broth of *Nocardia uniform*,[15] providing the first example of a new type of monocyclic 3-amino-β-lactams (*Fig. 3*). It has been found to display antibiotic activity against a broad spectrum of Gram-negative bacteria. As 3-aminonocardicinic acid **41** is an important starting material for the synthesis of biologically active nocardicin derivatives, this compound has been synthesized by different procedures.

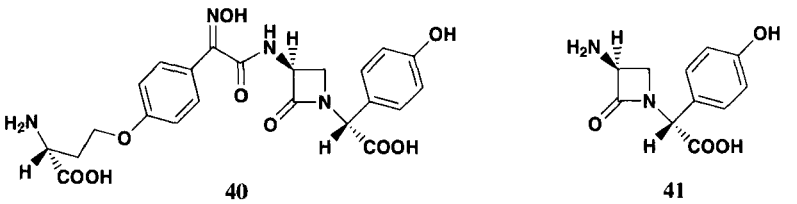
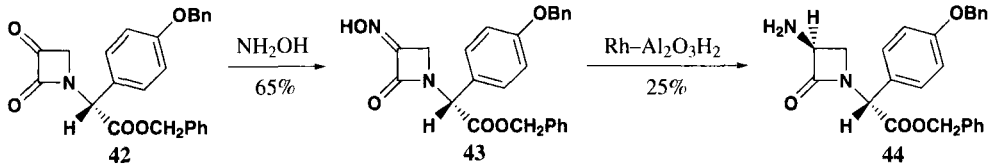


Figure 3

One of these synthetic methods for 3-aminonocardicinic acid starts from an azetidine-2,3-dione. The α-keto-β-lactam **42** was converted into the oxime **43** with hydroxylamine, which was catalytically hydrogenated over rhodium-alumina to give the 3-aminonocardicinic acid derivative **44** (*Scheme 14*).[29]



Scheme 14

A similar approach, based on oxime formation and further reduction, to 3-amino β-lactams from azetidine-2,3-diones has been reported.[30]

b) Synthesis of 3-Substituted 3-Hydroxy-β-lactams

The 3-substituted 3-hydroxy-2-azetidinone moiety, representing an efficient carboxylate mimic,[31] is present in several pharmacologically active monobactams such as sulphazecin **45** and related products,[16] and in enzyme inhibitors such as tabtoxin **46** and its analogues (*Fig. 4*).[17]

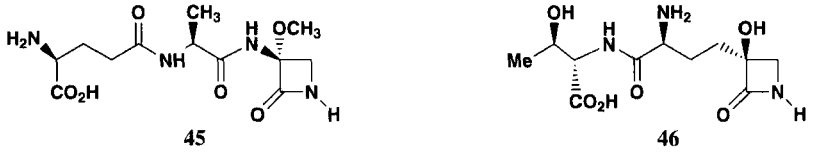


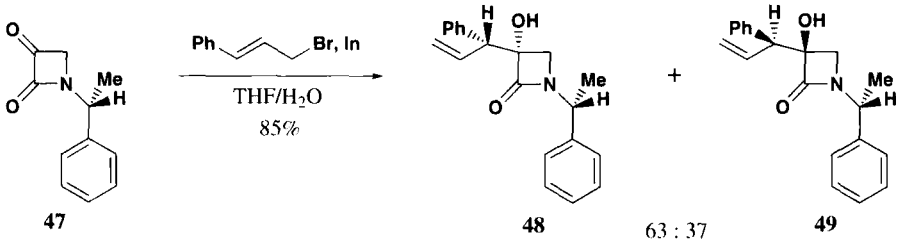
Figure 4

Moreover, these compounds with correct absolute configurations serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserines), which are key components of a large number of therapeutically important compounds. As an example, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine) and (3*R*,4*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine) are residues for peptide inhibitors of enzymes, such as renin[32] and HIV-1 protease.[33] In addition, phenylisoserine analogues are used to synthesize new taxoids.[34] However, methods for the construction of β-lactams with quaternary stereogenic centers at the C3 position are still scarce.[35] In view of their various biological activities and synthetic usefulness, natural products bearing the 3-substituted 3-hydroxy-2-azetidi-

none motif as well as structurally related unnatural compounds are stimulating new synthetic approaches.

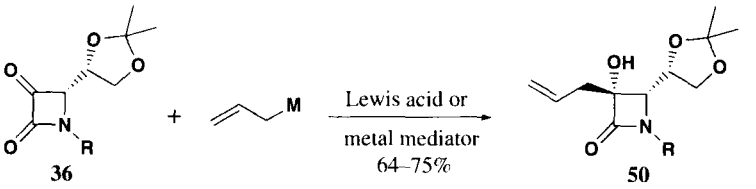
i) Carbonyl Allylation

The reactions of propenylmetal reagents with chiral carbonyl compounds are widely employed in organic synthesis, due to the versatility of homoallylic alcohols as synthetic intermediates.[36] Despite this fact, there is little information available on the use of α-keto-β-lactams as carbonyl compounds for the allylation reaction, Bose[37] and Paquette[28,38] have recently reported the allylindium addition to azetidine-2,3-diones in aqueous tetrahydrofuran. However, the asymmetric version was achieved with poor diastereoselectivity on azetidine-2,3-diones **47** bearing a chiral auxiliary at nitrogen (*Scheme 15*).[28]



Scheme 15

In connection with this work, Alcaide reported the reaction of enantiopure azetidine-2,3-diones with a variety of allylmetal reagents.[26] The diastereoselectivities of Lewis acid or metal-mediated allylation of azetidine-2,3-diones **36** were investigated under anhydrous conditions and in aqueous media. In order to control the stereochemistry of the addition, a versatile chiral substituent was placed at C-4, obtaining the homoallylic alcohols **50** as a single diastereoisomer (*Scheme 16*).

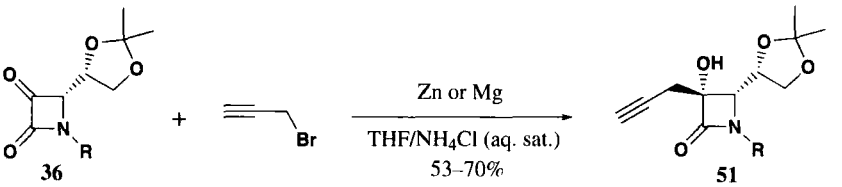


Scheme 16

ii) Carbonyl Propargylation/Allenylation

Metal-mediated carbon-carbon bond formation between a carbonyl compound and a propargyl halide has been the subject of a number of investigations over the past two decades, by virtue of its synthetic usefulness and mechanistic intrigue.[39] The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics.[40] This metallotropic rearrangement often results in poor regioselection in the end

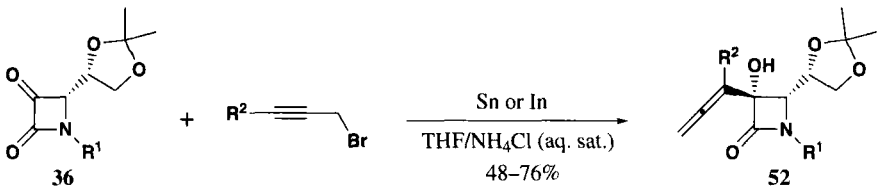
organic product, because both organometallic species can react with the carbonyl compounds. Hence, a pertinent synthetic challenge is to tune the regioselectivity toward either acetylenic or allenic products. Although much efforts have been made in these fields on various types of carbonyl compounds, the information available on the use of β-lactams as chiral building blocks for the propargylation reaction is still very scarce. Two reports have been published to date, the propargylation of 6-oxopenicillanates in anhydrous tetrahydrofuran (*Scheme 6*),[13] and addition of propargylzinc of monocyclic azetidine-2,3-diones **36** with propargyl bromide in aqueous media to give homopropargyl alcohols **51** (*Scheme 17*).[41]



R = aliphatic or aromatic

Scheme 17

The allenylation of azetidine-2,3-diones has just been reported by Alcaide *via* Barbier-type reaction.[41] Metal-mediated reactions of α-keto-β-lactams **36** with propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position, afforded the homoallenyl alcohols **52** as essentially regio- and diastereoisomerically pure products (*Scheme 18*).



R^1, R^2 = aliphatic or aromatic

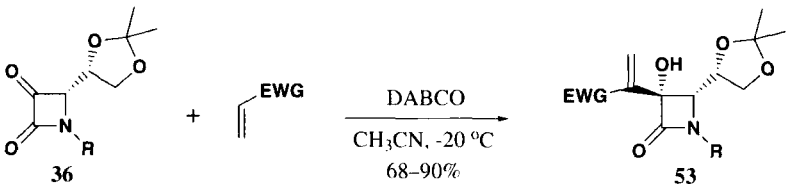
Scheme 18

iii) Baylis-Hillman Reaction

The Baylis-Hillman reaction is an emerging carbon-carbon bond forming reaction for the preparation of β-hydroxy-α-methylene ketones, nitriles, esters, etc. involving an activated alkene, a carbon electrophile and a suitable catalyst (particularly a tertiary amine).[42] This fascinating reaction has most of the basic properties that an efficient synthetic method should have, *e. g.*, it is selective, economical in atom count and requires mild conditions, providing densely funtionalized products. However, the reaction suffers from poor reaction rates as it takes several days and even weeks for completion.

Alcaide and his group have reported that Baylis-Hillman adducts **53** can be prepared, in a few hours, nearly as single diastereoisomers by the DABCO-promoted reaction of activated vinyl

systems with the appropriate azetidine-2,3-dione **36** (*Scheme 19*). These workers, found that the process can be significantly accelerated by increasing the amount of the catalyst.[26]



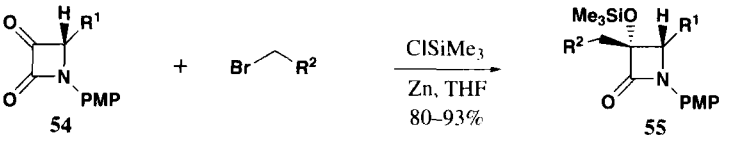
36 **53**

R^1, R^2 = aliphatic or aromatic
EWG = $COCH_3$, CO_2CH_3, CN

Scheme 19

iv) Other Reactions

Palomo has described the stereocontrolled addition of α-bromoesters or α-bromonitriles to azetidine-2,3-diones **54** promoted by zinc-trimethylchlorosilane (Reformatsky reaction), as a general route to 3-substituted 3-trimethylsilyloxyazetidin-2-ones **55** (*Scheme 20*).[43]

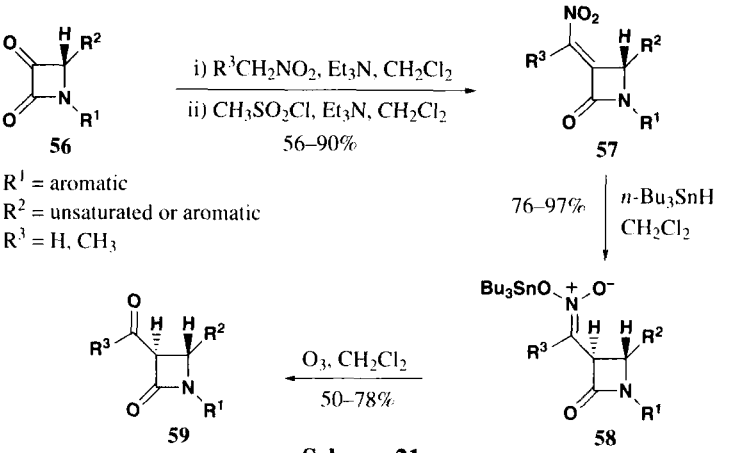


54 **55**

R^1 = unsaturated or aromatic
R^2 = CN, CO_2Et

Scheme 20

This group also reported the use of azetidine-2,3-diones **56** for the preparation of 3-acyl-β-lactams **59** *via* queing Henry reaction/dehydration processes and subsequent *n*-tributyltin hydride reduction and ozonolysis (*Scheme 21*).[44]

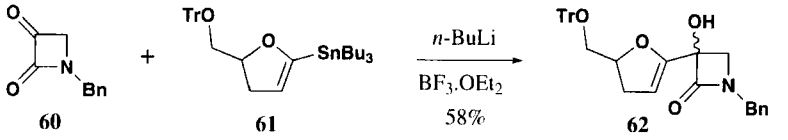


56 **57** **58** **59**

R^1 = aromatic
R^2 = unsaturated or aromatic
R^3 = H, CH_3

Scheme 21

The condensation of the azetidine-2,3-dione **60** with the cycloalkenyl-lithium reagent **61**, affording an inseparable mixture of the diastereoisomeric alcohols **62**, has been described by Paquette in his approach to dideoxyhydantocidin analogues (*Scheme 22*).[45]

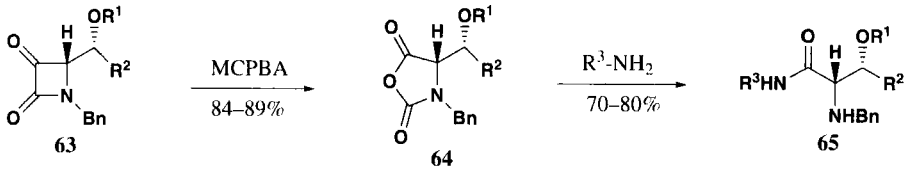


Scheme 22

c) Synthesis of Amino Acids and Peptides

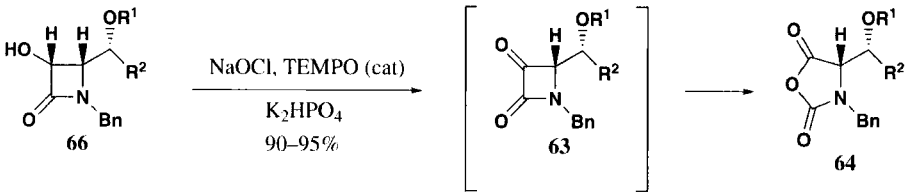
i) Synthesis of α-Amino Acids

In addition to their interest in β-lactam antibiotic synthesis, azetidine-2,3-diones are important starting materials for the preparation of amino acid derivatives. In 1988, Palomo found that azetidine-2,3-diones could be converted into α-amino acid derivatives.[14] This two-step route starts with the Baeyer-Villiger oxidation of azetidine-2,3-diones **63** to give *N*-carboxy anhydrides (NCA, **64**), which produced α-amino acid derivatives **65** through coupling with amines (*Scheme 23*).[25]



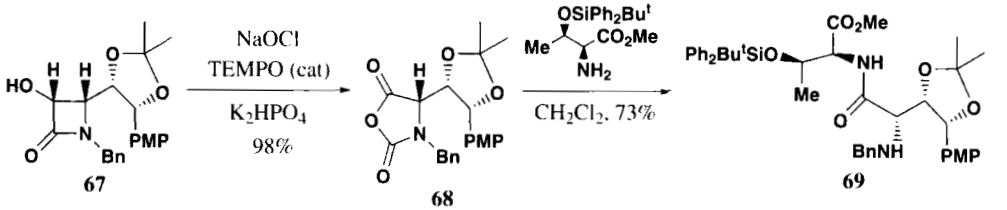
Scheme 23

These workers have also developed an alternative procedure for the obtention of NCAs starting from α-hydroxy-β-lactams. Ring expansion of α-hydroxy-β-lactams **66** by means of sodium hypochlorite and a catalytic amount of TEMPO leads to the formation of NCAs **64** in a straightforward manner.[46] The process occurs through a regioselective Baeyer-Villiger rearrangement of an azetidine-2,3-dione **63** generated *in situ* (*Scheme 24*).[47]



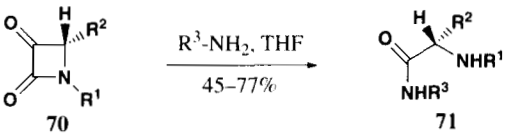
Scheme 24

The preparation of the southwest portion of echinocandin B, dipeptide fragment **69**, which displays antifungal and antiyeast activities, illustrates this approach to peptide synthesis (*Scheme 25*).[48]



Scheme 25

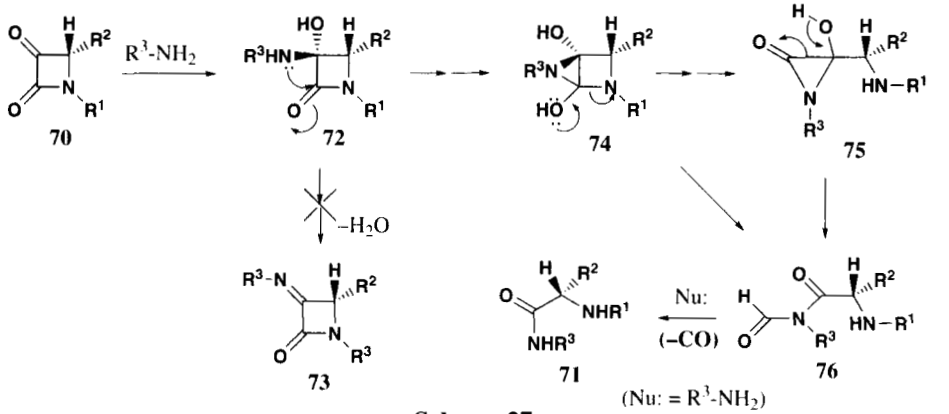
A conceptually different strategy to access to α-amino acid derivatives from azetidine-2,3-diones has been just reported by Alcaide.[49] Treatment of azetidine-2,3-diones **70** with primary amines forms in one-pot flask α-amino acid and dipeptide derivatives **71** (*Scheme 26*). α-Amino acid derivatives **71** can be smoothly prepared in both the racemic and the enantiopure forms, without loss of optical purity.



R^1 = Aliphatic or aromatic
R^2 = Ph, (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl
R^3 = Aliphatic

Scheme 26

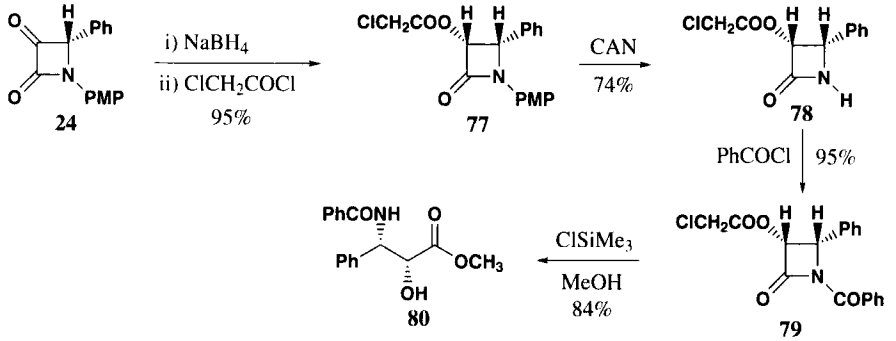
This new process can be rationalized through an initial nucleophilic addition of the amine to the ketone moiety of the azetidine-2,3-dione **70**, forming an intermediate carbinolamine **72**. This intermediate **72** may react through two different pathways to give the expected 3-imino-β-lactam **73** or the intermediate **74**, but presumably evolves to the formation of the fused aziridine-β-lactam **74**. The N1-C2 bond of intermediate **74** should be very labile, evolving to aziridinone **75**. Under the reaction conditions, compound **75** furnishes *N*-formylamide **76** which appears as the final but not isolable intermediate in the reaction (*Scheme 27*).



Scheme 27

ii) Synthesis of β-Amino Acids

Palomo[50] described the utility of azetidine-2,3-diones as useful precursors to α-hydroxy-β-amino acids such as (2*S*,3*R*)-3-phenylisoserine **80**, the side-chain of the potent antitumor agent taxol (*Scheme 28*).



Scheme 28

III. CONCLUSION

As we have seen, there are several methods available for the preparation of azetidine-2,3-diones in both the racemic and the enantiopure forms. This easy access makes α-keto β-lactams valuable intermediates in organic sythesis. Its high concentration of functional groups in a small ring provides an excellent handle for further chemical manipulations, as well as excellent building blocks in asymmetric synthesis.

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