CONVERSION OF BETA-LACTAMS TO VERSATILE SYNTHONS VIA MOLECULAR REARRANGEMENT AND LACTAM CLEAVAGE[1] 賀寿

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Abstract: Substituted β-lactams can be synthesized by a variety of methods some of which are stereocontrolled and diastereoselective. Because of their high chemical reactivity and their propensity for molecular rearrangement, these β-lactams can serve as efficient synthons for racemic or optically active forms of diverse types of natural products such as carbohydrates, alkaloids, amino acids and oligopeptides.

賀寿 Dedicated to Prof. Max Tishler on the occasion of his 80th birthday.

CONTENTS

A. INTRODUCTION

The four-membered heterocycle 2-azetidinone or β-lactam (1) was first synthesized by Staudinger in 1907[2]. During the next three decades a few alternative synthetic routes to these compounds were discovered but nothing unusual was reported about the chemical reactivity of these cyclic amides.

(1)

The discovery of penicillin in the 1930's started a new era in β-lactam chemistry. Early work on penicillin was hampered by the high reactivity of the molecule. Many chemists had initially considered the β-lactam structure unlikely for penicillin on the basis of the low reactivity reported for the synthetic β-lactams known till then.

In the course of the secret Anglo-American research on penicillin during World War II, the high chemical reactivity of the β-lactam amide bond in penicillin was recognized and several types of rearrangements of the α-amido- β-lactam ring were studied. This phase of the chemistry was fully documented in a monograph published in 1949[3].

The phenomenal success of penicillin and related antibiotics as life-saving drugs has led to extensive β-lactam research in many industrial and academic laboratories. Multi-functional β-lactams - monocyclic and bicyclic - have become available through a variety of synthetic methods. The ready cleavage of the β-lactam amide bond by reaction with various nucleophiles has been the subject of many investigations[4]. The intramolecular versions of such nucleophilic reactions between the β-lactam amide and appropriate substituents on the four-membered ring lead to useful rearrangement products.

The potential of β-lactams for generating valuable synthons via molecular rearrangement was highlighted by Manhas, Amin and Bose in 1975[5]. This review influenced Kano and coworkers[6], Wasserman et al.[7], and some others to develop a variety of synthons from β-lactams. The pace of this type of synthetic work has increased in recent years. This communication reviews the recent literature on intermediates for such natural products as carbohydrates, alkaloids, peptides, vitamins, antibiotics and diverse heterocyclic ring systems that are derived by the molecular rearrangement of synthetic β-lactams. For updating our earlier review[5], a section on intermediates from β-lactam cleavage is also included. Emphasis has been placed on the stereoselectivity of synthetic approaches with special reference to the preparation of optically pure natural products.

B. REARRRANGEMENT OF β -LACTAM RING

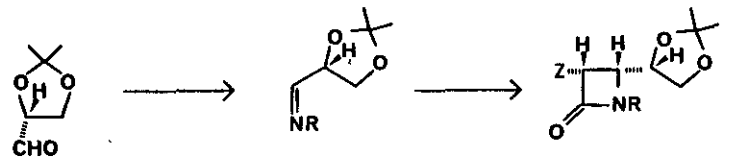
1. Synthons for Carbohydrates

A recent synthetic approach[1,8] illustrates the complete stereocontrol that is feasible for the preparation of a desired β-lactam as an advanced intermediate for a carbohydrate. With the natural product gentosamine (7) as the target compound, synthesis of optically active, multi-functional, β-lactams - such as (4) and (5) - was the initial goal.

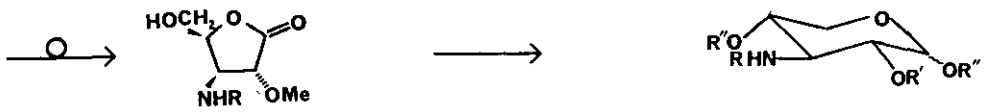
The chiral starting material used was D-glyceraldehyde acetonide (2) prepared from D-mannitol[9]. The antipode of (2) is available readily from L-ascorbic acid[10].

The Schiff base (3) from p-anisidine and (2) was allowed to react with methoxyacetyl chloride and triethylamine when a single, optically pure, cis β-lactam (4) was obtained in good yield. On refluxing with trifluoroacetic acid (4) was rearranged to a single γ-lactone (6) without modification of any asymmetric center. Reduction with diisobutylaluminum hydride converted (6) to the amino sugar (8) which was characterized as its 1,4-diacetate. The amino sugar (8) is a derivative of gentosamine (Scheme 1). Earlier work from several laboratories on the use of β-lactams for the preparation of amino sugars-but via β-lactam cleavage rather than rearrangement-is described in a later section (C-i).

Scheme 1

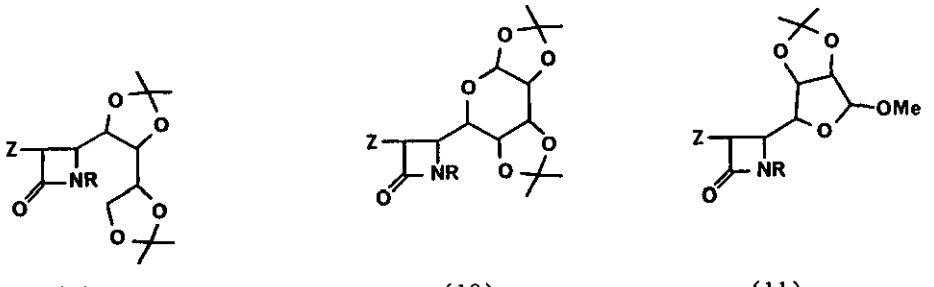


(2) (3) (4) Z=OMe, R= —⟨⟩—OMe (5) Z=OAc, R=CH_2Ph



(6) (7) R=Me, R'=R"=H (Gentosamine) (8) R= —⟨⟩—OMe, R'=OMe, R"=H

The recent availbility of the cis-3-acetoxy-2-azetidinone (5) and its trans isomer[11] allows access to gentosamine (7) and its 2-epimer (epigentosamine). Enantiospecific synthesis of β-lactams such as (9), (10) and (11) using natural sugars as the chiral starting material has greatly extended the scope of this synthetic approach to natural and unnatural amino sugars[11,12].

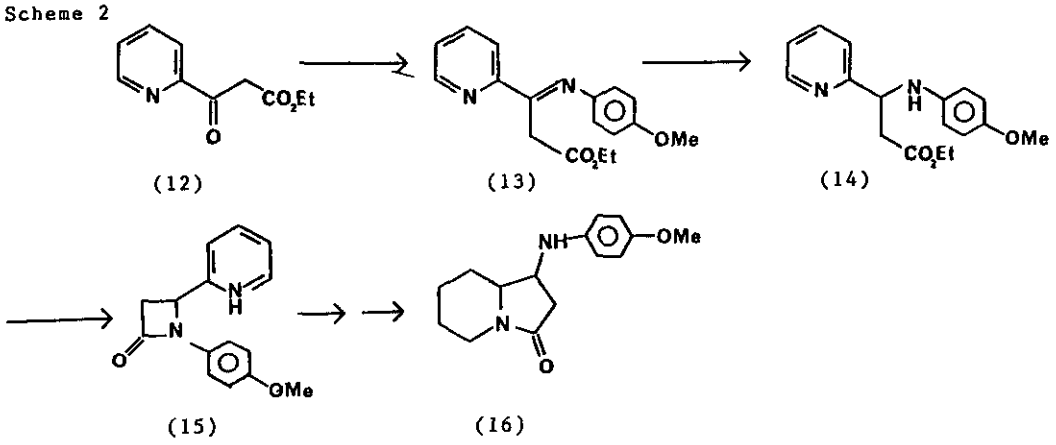


(9) (10) (11)

ii. Synthons for Alkaloids

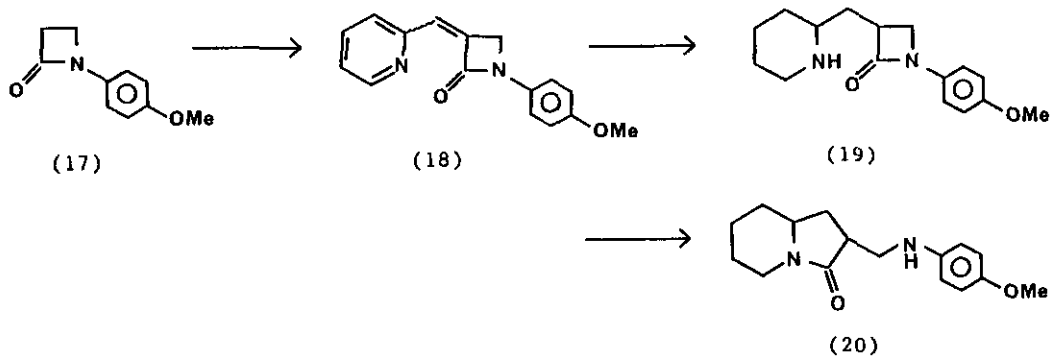
Taking advantage of the intramolecular nucleophilic cleavage of the amide bond of the β-lactams, Kano and coworkers[6a] have synthesized indolizidine alkaloid analogs. Thus, the Schiff base (13) from the β-keto ester (12) and p-anisidine was reduced to the β-amino ester (14) which was cyclized to (15) using methylmagnesium bromide. Catalytic reduction of the pyridine moiety of this substituted β-lactam, followed by base treatment afforded the indolizidine (16) (see Scheme 2).

Scheme 2



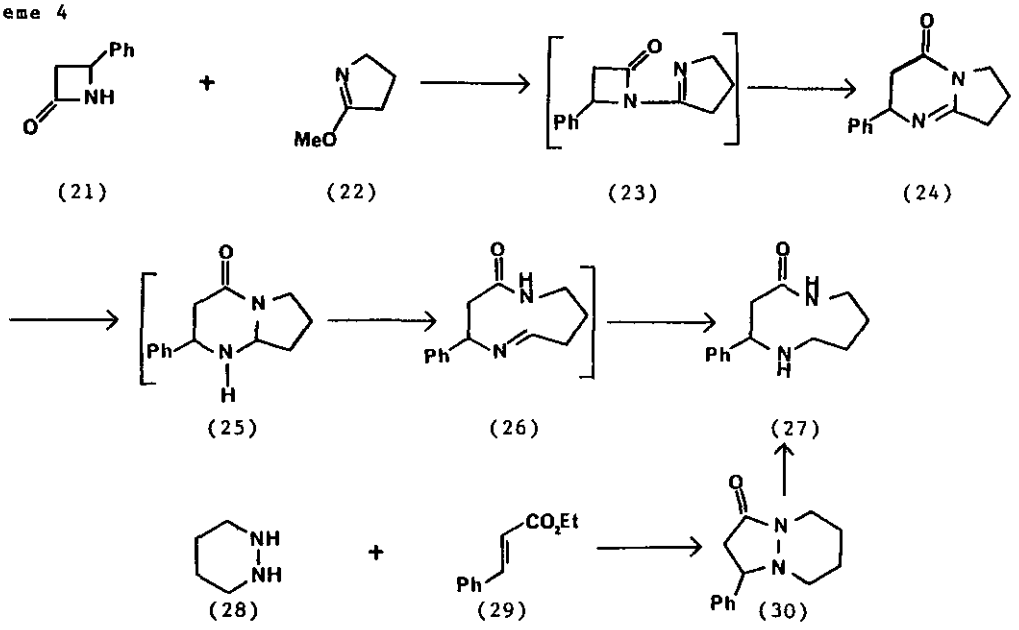
These authors[6a] have also prepared an indolizidine derivative (20) by an alternate route as shown in Scheme 3. The β-lactam (17) was condensed with 2-formylpyridine to give (18). Reduction of (18) followed by rearrangement resulted in (20).

Scheme 3



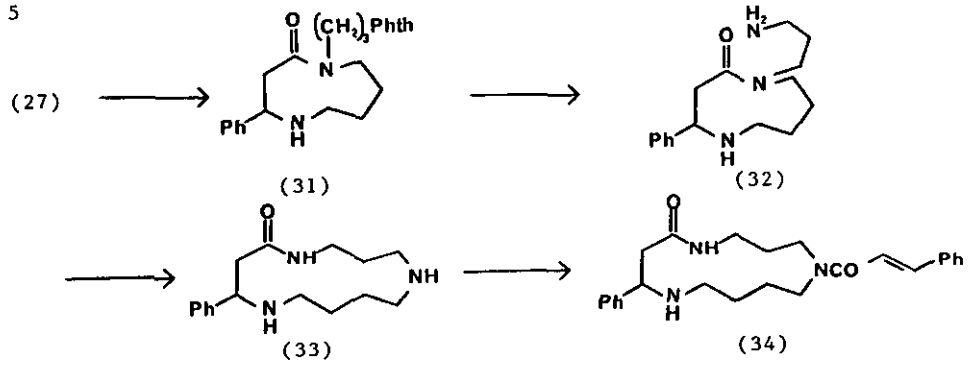
Wasserman et al.[7a] achieved the total synthesis of the macrocyclic spermidine alkaloid, celacinnine (34), through successive expansions of smaller rings to form the 13-membered ring system present in (34). The intermediate (27) was synthesized by two different routes: (a) by the interaction of 4-phenyl-2-azetidinone (21) with the imidate (22) followed by sodium cyanoborohydride reduction of the substituted 4-oxo-tetrahydropyrimidine product (24), or (b) by reacting ethyl cinnamate (29) with piperidazine (28) and reducing the bicyclic product (30) with sodium and liquid ammonia (Scheme 4).

Scheme 4



The 9-membered lactam (27) was converted to celacinnine (34) as shown in Scheme 5.

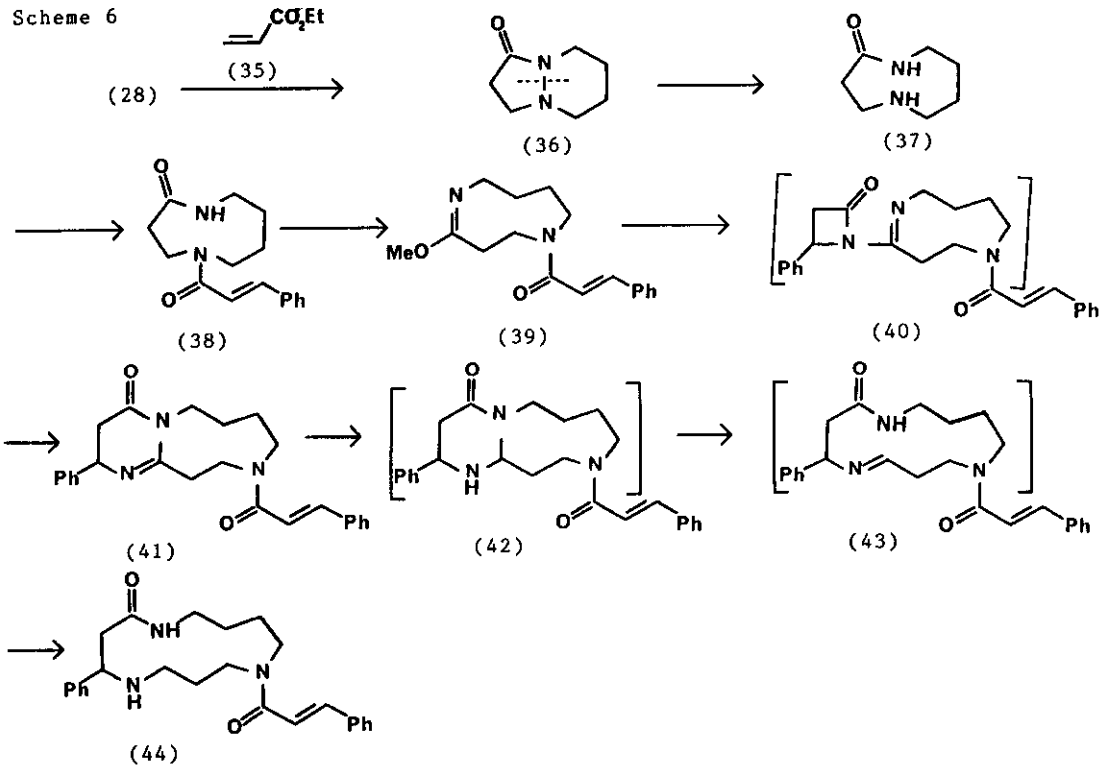
Scheme 5



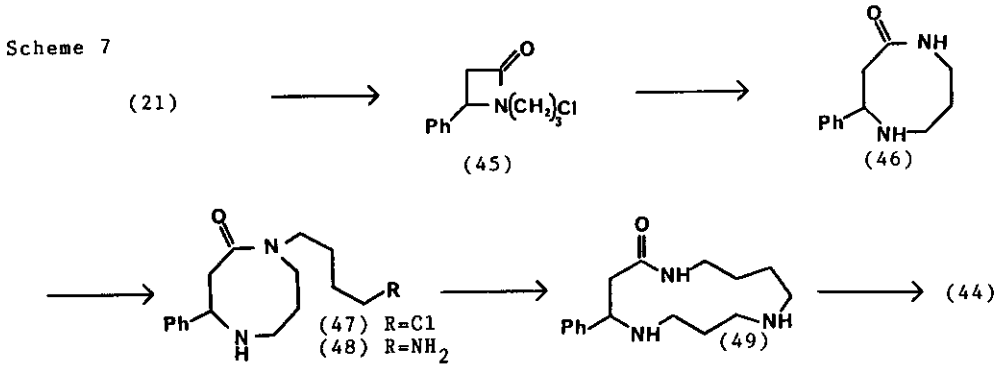
Wasserman and Matsuyama[7b] have also described a total synthesis of (±)-dihydroperiphylline (44) by the intermediate use of β-lactam (21) as shown in Scheme 6. Intermolecular N-alkylation of (21) with (39) afforded the structure (40) which through intramolecular *ring opening of the β-lactam* moiety gave (41). This compound (41) was subsequently converted to (±)- dihydroperiphylline (44). An alternative synthesis of (±)-dihydroperiphylline (44) by Crombie and coworkers[13] from 4-phenyl-2-azetidinone (21) involves two successive transamidative ring expansions. The synthetic route is illustrated in Scheme 7. The 2-azetidinone (21) was alkylated with 1-bromo-3-chloro-*propane under phase transfer conditions* to the 1-(3'-chloropropyl)-4-phenyl-2-azetidinone (45). Reaction of (45) with liquid ammonia in a sealed tube directly afforded the 8-membered azalactam (46)[14]. Alkylation of the amide nitrogen in (46) with 1-bromo-4-chlorobutane was achieved in the

presence of 1,1,1,3,3,3-hexamethyldisilazane to obtain the chloro derivative (47) which was converted to the N-(4-aminobutyl)-azalactam (48) by treatment with liquid ammonia in a sealed tube. Intramolecular transamidation to get the 13-membered azalactam (49) was accomplished under basic conditions. Selective acylation with cinnamoyl chloride in the presence of 4,4-dimethyl-aminopyridine afforded the (±)-dihydroperiphylline (44).

Scheme 6



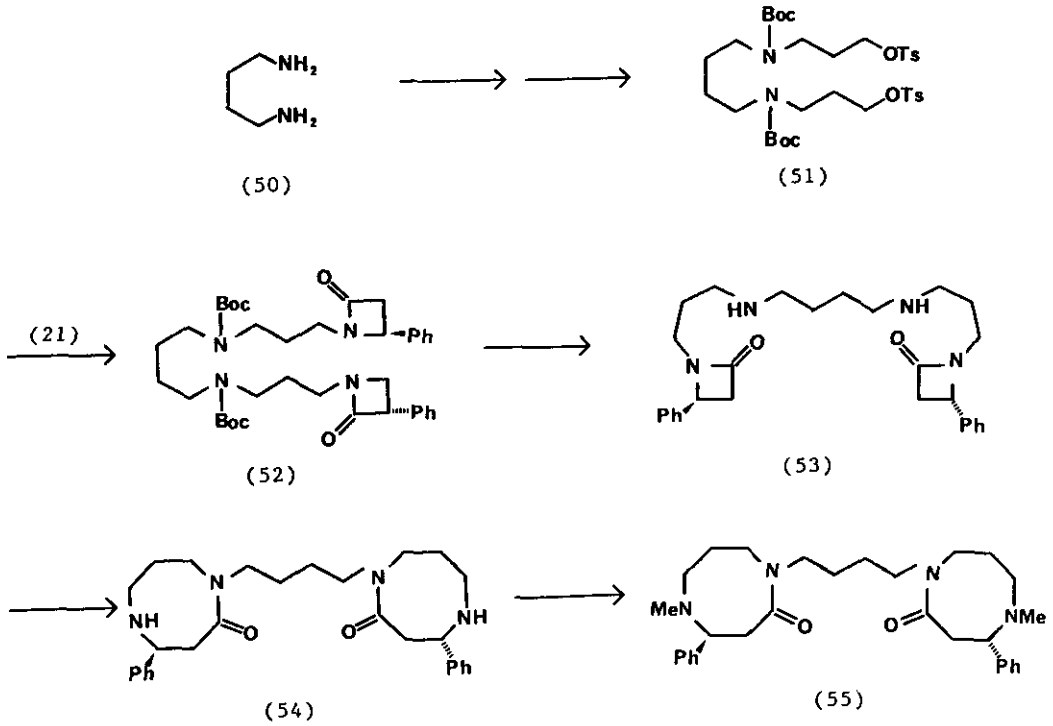
Scheme 7



The synthesis of homaline (55), by a trans-lactamization process involving the optically active β-lactam, 4-phenyl-2-azetidinone (21), was described by Wasserman and coworkers[7c,7d] (Scheme 8). Starting with putrescine (50), the ditosylate (51) was prepared through a series of reactions. Displacement of the tosyl groups with the sodium salt of β-lactam (21) yielded the adduct (52). Deprotection of the amine functionalities followed by neutralization with alkali liberated the key

intermediate (53). Refluxing (53) in quinoline for 10 h afforded the ring-expanded product (54) which was subsequently converted to homaline (55) by methylation with formaldehyde and formic acid.

Scheme 8



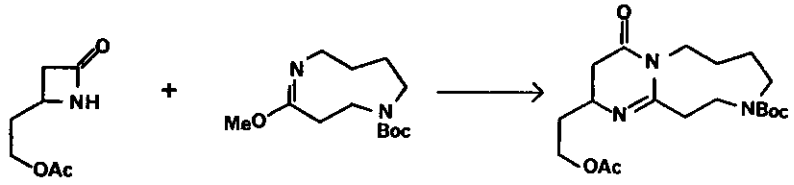
Crombie and coworkers[14] have also reported the synthesis of optically active (S)-homaline (55). The starting material for this reaction sequence is also the (S)-4-phenyl-2-azetidinone (21) reported earlier by Pietsch[15]. *Alkylation of (21) and ring expansion as described in Scheme 7* gave the optically active 8-membered (S)-azalactam (46). Double alkylation of (46) with 1,4-dibromobutane followed by reductive methylation with formaldehyde and sodium cyanoborohydride[16] gave optically active homaline (55) without racemization.

Starting with (±)-(46) these authors[14] have prepared 1:1 mixture of (±)-homaline (55) and its (R,S)-diastereomer, epi-homaline.

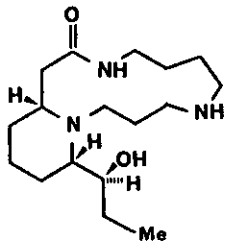
Wasserman et al.[7e] reacted the methyl imino ether (57) with the β-lactam (56) at 145°C in mesitylene. The coupled product (58) was then used as an intermediate for the synthesis of (±)-dihydropalustrine (59)[7e] and anhydrocannabisativine (60)[7f] (Scheme 9).

Crombie, Jones and Haigh[17] have also synthesized spermine alkaloids, hopromalinol (61), hopromine (62) and *hoprominol (63)*. *These alkaloids were* prepared by sequential coupling of 4-substituted 5-methyl-1,5-diazacyclooctan-2-ones (64). Intermediates of the type (64) were obtained by transamidation from variously 4-substituted 2-azetidinones (65).

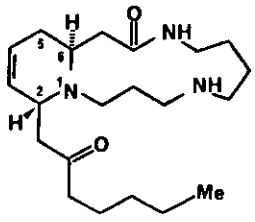
Scheme 9



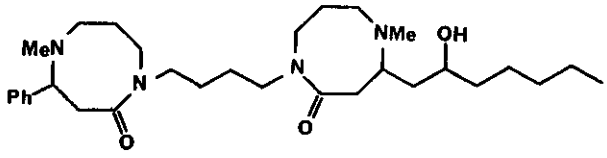
(56) (57) (58)



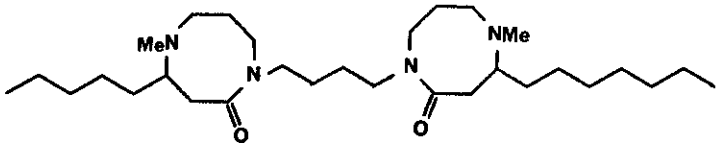
(59)



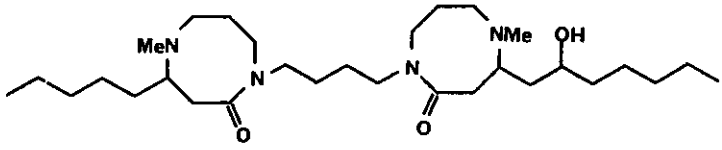
(60)



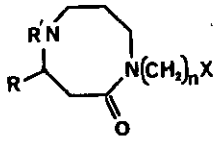
(61)



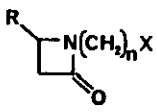
(62)



(63)



(64)

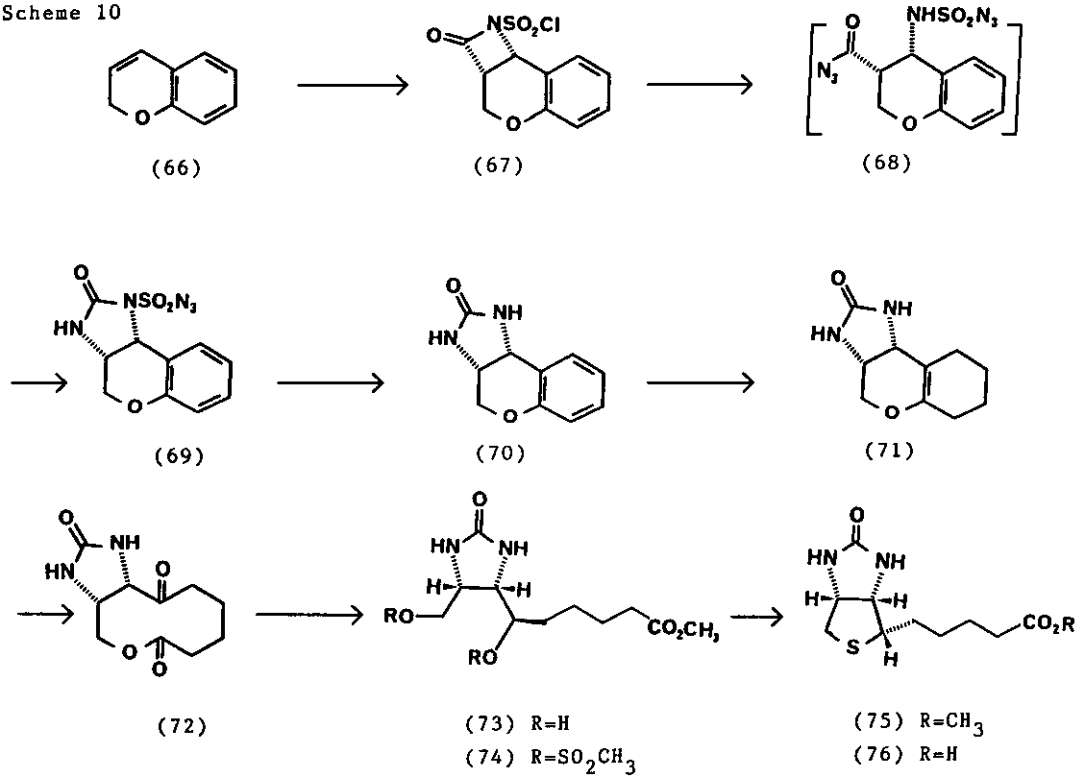


(65)

iii. Synthon for Biotin

Fliri and Hohenlohe-Oehringen[18] synthesized racemic biotin (76) starting with chromene (66) which was converted to the β-lactam (67) (Scheme 10). The reaction of (67) with sodium azide formed the imidazolidone derivative (69). The formation of (69) can be explained by in situ formation of the azido ketone (68) which through Curtius rearrangement forms the isocyanate. Subsequent intramolecular cyclization results in (69). The sulfonylazide group in (69) was removed by treatment with sodium sulfite to give (70). Benkeser reduction[19] (lithium-dimethylamine) resulted in the formation of enol ether (71). Oxidation with m-chloroperbenzoic acid, followed by treatment with sodium periodate afforded the keto lactone (72). Reduction with sodium borohydride in methanol gave the methyl ester (73) which on mesylation, followed by treatment with sodium sulfide led to the bicyclic product (75). Saponification of (75) gave (±)-biotin (76).

Scheme 10



(66) (67) (68)

(69) (70) (71)

(72)

(73) R=H
(74) R=SO_2CH_3

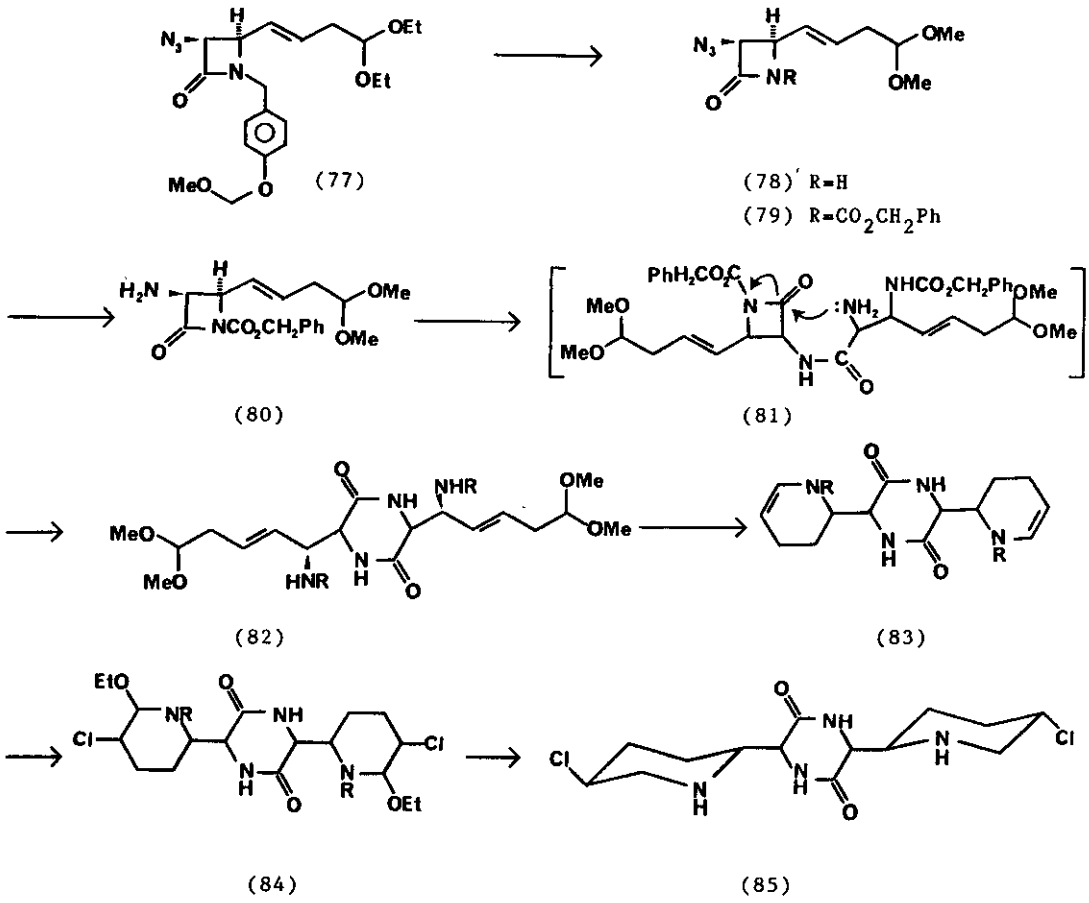
(75) R=CH_3
(76) R=H

iv. Synthon for Antibiotics

The antibiotic 593 A (85) isolated from Streptomyces griseoluteus shows antitumor activity against several neoplastic cell lines. This compound was synthesized in its racemic form by Fukuyama and coworkers[20] starting with 3-azido-2-azetidinone (77) prepared by the Bose reaction[21]. The sequence of reactions used is shown in Scheme 11. The key reaction involves the utilization of the α-amino function of the β-lactam (80) to serve as a nucleophile which cleaves the β-lactam amide bond in a bimolecular reaction.

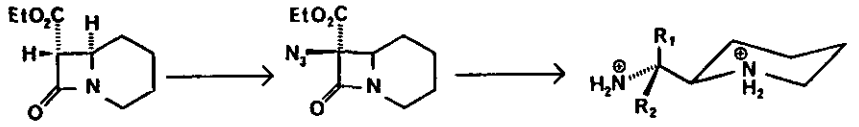
Although no mechanism has been provided for this ring enlargement reaction, one can postulate the formation of (82) from (80) as a two step process. Initially the amino group of one molecule cleaves the β-lactam amide bond of the second molecule through a nucleophilic attack resulting in the adduct (81). Subsequent scission of the β-lactam bond of (81) leads to the diketopiperizine (82) through a rearrangement reaction. This synthesis illustrates the usefulness of β-lactams as important synthons for constructing a variety of heterocycles which are otherwise not easily accessible.

Scheme 11



Golding and Smith[22] have synthesized (±)-1-aminopiperidine-2-acetic acid (88), an amino acid related to the antitumor agent 593 A (85). The bicyclic β-lactam (86) was prepared by using the method developed by Lowe and coworkers[23] and was converted to the amino acids (88) and (89) as 2:1 *diastereoisomeric mixture, see* Scheme 12. The predominant diastereoisomer was found to be (88). The structures of both (88) and (89) were established on the basis of their ^{1}H NMR spectra.

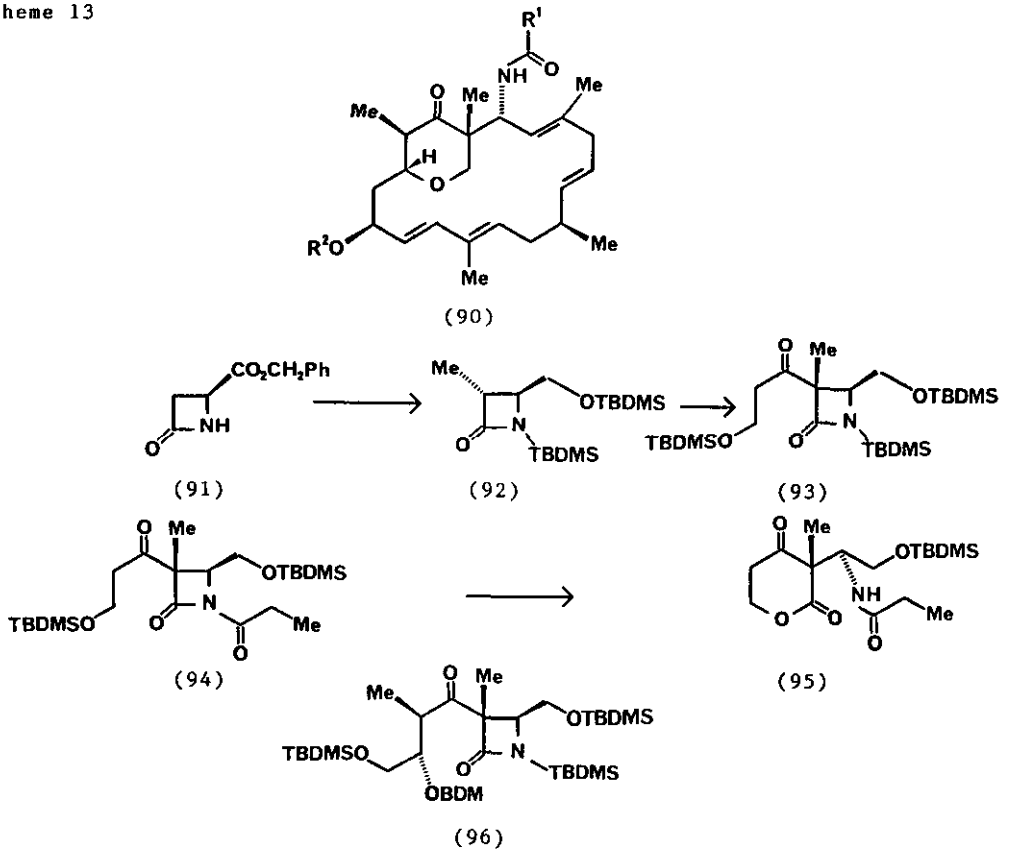
Scheme 12



(86) (87) (88) R_1=CO_2H, R_2=H; (89) R_1=H, R_2=CO_2H

Recently Thomas and Williams[24] have reported a stereoselective approach to the δ-lactone component of lankacidin (90) type of macrolide antibiotics[25] via the intermediacy of a β-lactam (91) (Scheme 13). The β-lactam (91)[26] was converted to (93) by (i) reduction of the ester function at C-4 with

Scheme 13



(90) (91) (92) (93) (94) (95) (96)

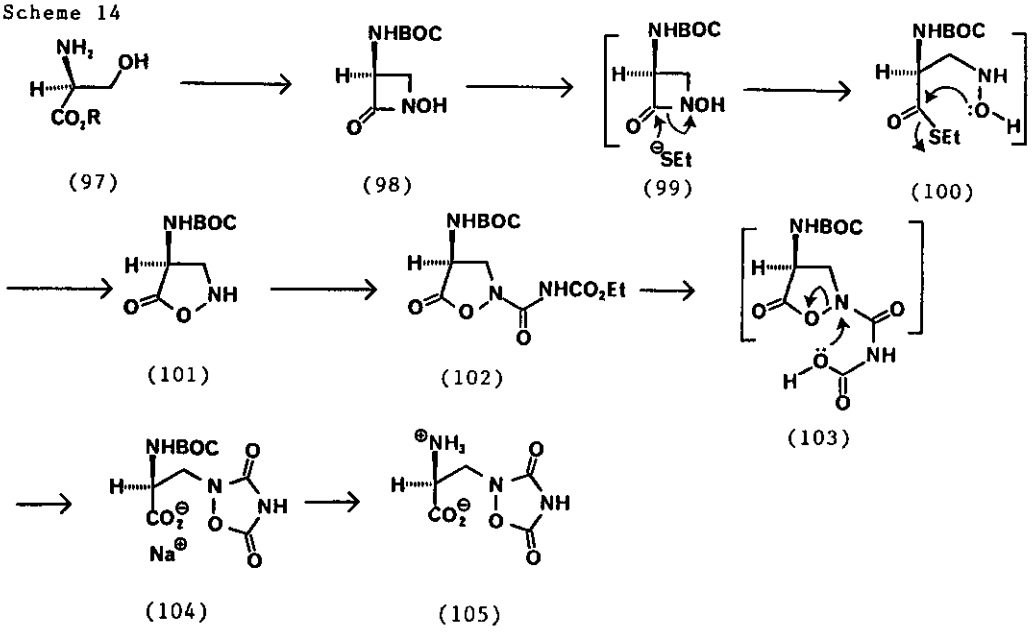
sodium borohydride, (ii) conversion to the di-t-butyldimethylsilyl derivative, (iii) introduction of the methyl group at C-3, (iv) treatment of the product with t-butyldimethylsilyl-protected β-hydroxypropionaldehyde in the presence of lithium diethylamide, and (v) oxidation. Selective N-deprotection of (93) followed by N-acylation with propionyl chloride afforded (94). Treatment of (94) with p-toluenesulfonic acid selectively removed the more easily accessible t-butyldimethylsilyl protective group; the β-lactam ring was cleaved by the nucleophilic attack of the newly generated hydroxy group to give the keto lactone (95) which constitutes a fragment of lankacidins (90). These authors have also synthesized the more elaborately substituted β-lactam (96) using the same methodology as described above. The β-lactam (96) can lead to further elaboration of the antibiotic skeleton.

v. Synthon for α-Amino Acids

Recently, Baldwin et al.[27] synthesized L-quisqualic acid (105) via the β-lactam (98) (Scheme 14). This α-amino acid (105) which is a potent agonist of the neurotransmitter L-glutamate is not readily accessible from natural sources.

L-Serine (97) was converted to (3S)-2-azetidinone (98) which was isomerized to the isooxazolidin-5-one (101) by treatment with a catalytic amount of lithium ethanethiolate. Treatment of (101) with ethoxycarbonyl isocyanate produced the urea (102). Ring opening of (102) with sodium hydroxide resulted in the formation of the salt (104) via a rearrangement reaction. Upon treatment of (104) with trifluoroacetic acid followed by ion-exchange chromatography L-quisqualic acid (105) was obtained in 89% yield from (101).

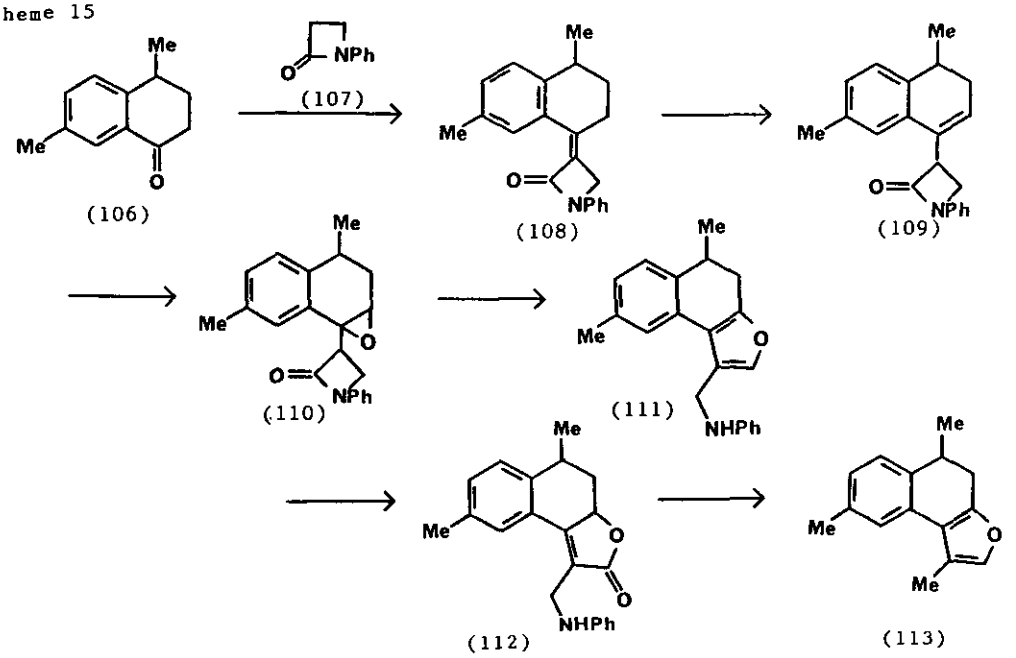
Scheme 14



vi. Synthon for (±)-Laevigatin - a Sesquiterpene

Kano and coworkers[6b] described a synthesis of (±)-laevigatin (113) via β-lactam (107) (Scheme 15). The starting material for this synthesis was 4,7-dimethyl-1-tetralone (106) which was condensed with 1-phenyl-2-azetidinone (107) to afford the 3-alkylidene-2-azetidinone (108). Rearrangement of the exocyclic double bond with lithium diisopropylamide followed by epoxidation with m-chloroperbenzoic acid resulted in the epoxide (110) which was further treated with methanesulfonic acid to give the butenolide (111). Reduction of the butenolide (111) with diisobutylaluminum hydride afforded 2-anilinomethylfuran (112). Hydrogenolysis of (112) over 10% Pd/C gave (±)-laevigatin (113).

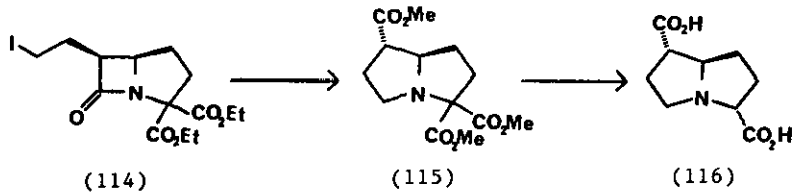
Scheme 15



vii. Synthons for Heterocycles

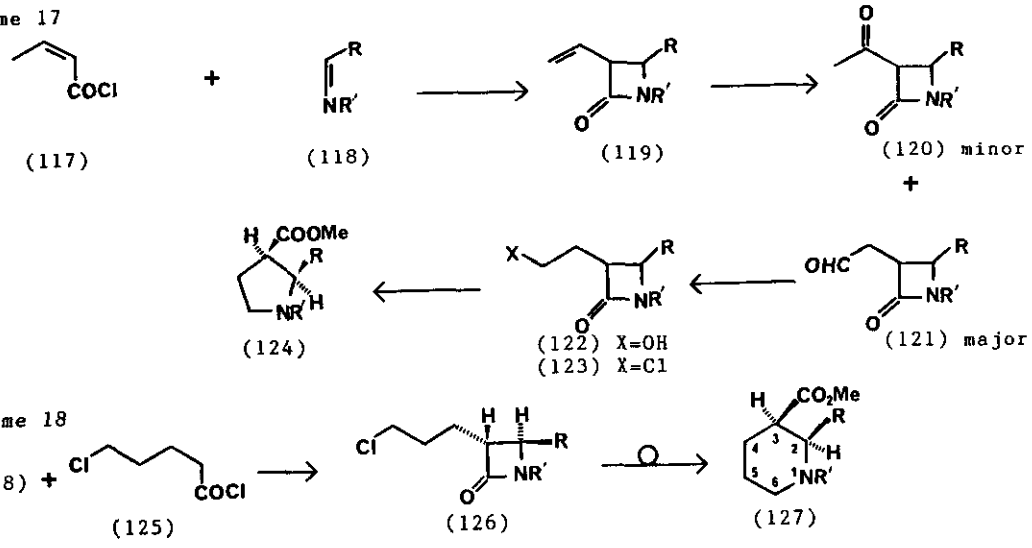
Diethyl 6-(2-iodoethyl)-7-oxo-1-azabicyclo 3.2.0 heptane-2,2-di-carboxylate (114) on reaction with bases such as sodium methoxide or sodium cyanide in methanol, undergoes trans-esterification and rearrangement, giving the pyrrolizidine (115)[28]. The sterically homogeneous 1,5-pyrrolizidine-dicarboxylic acid (116) (see Scheme 16) is obtained by the hydrolysis of (115) and decarboxylation.

Scheme 16



Recently Bose and coworkers[29] reported the synthesis of substituted pyrrolidines (124) via a rearrangement and ring expansion reaction of trans-β-lactams of the type (123). The β-lactam (123) was prepared from the corresponding α-vinyl-β-lactam (119) as shown in Scheme 17.
As an extension of this work, they have also synthesized the substituted piperidines (127)[30], morpholines (133) and (138)[31] and quinolizidines (141)[30] and the oxygen analog (143)[31].
The starting trans β-lactam (126) for the synthesis of piperidines (127) was prepared by the acid chloride-imine reaction in which the Schiff base (118) was treated with 5-chlorovaleryl chloride (125) in the presence of triethylamine in refluxing benzene. The rearrangement of (126) in refluxing methanol containing sodium cyanide afforded the six membered heterocycle (127). The disposition of the hydrogens at C-2 and C-3 in (127) was found to be cis. This change of stereochemistry from the starting β-lactam (126) is the result of the rearrangement reaction (see Scheme 18).

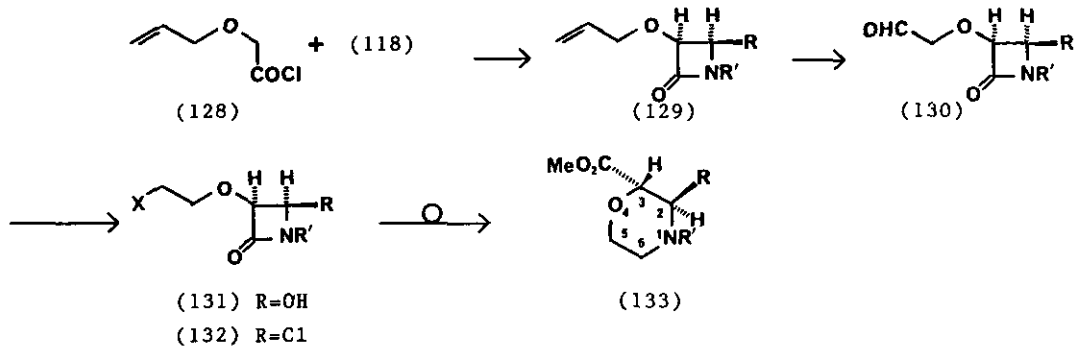
Scheme 17



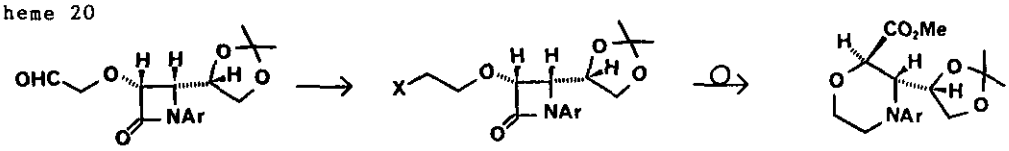
Scheme 18

The reaction of Schiff base (118) with allyloxyacetyl chloride (128) in the presence of triethylamine gave the cis α-allyloxy-β-lactams (129). Cleavage of the double bond by ozonolysis followed by reduction to the primary alcohol (131) and its conversion to the chloro derivative gave (132). Rearrangement of (132) afforded the morpholine (133) with trans stereochemistry at C-2 and C-3 (Scheme 19).
A slightly modified method was used to prepare an optically active morpholine compound (138) as shown in Scheme 20.
Using the same methodology outlined above a quinolizidine analog (141) and its oxygen isostere (143) were prepared by starting with the dihydroisoquinoline (139) as shown in Scheme 21.

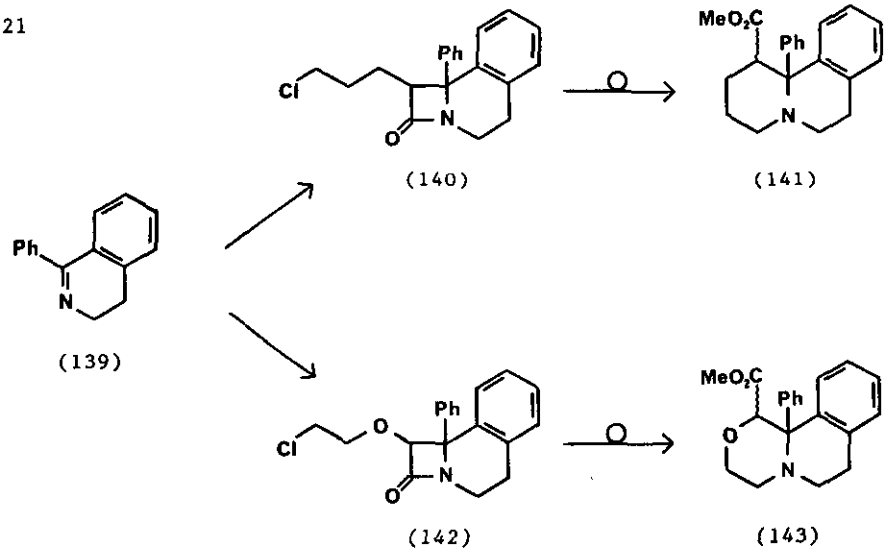
Scheme 19



Scheme 20

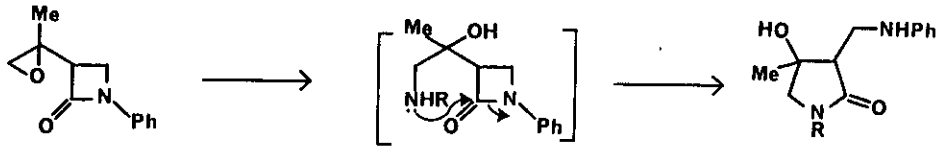


Scheme 21



Kano and coworkers[6c] have reported the conversion of 2-azetidinone (144) to pyrrolidone (146) as shown in Scheme 22. In this reaction the epoxide cleavage with an amine appears to be the first step followed by the β-lactam ring opening leading to the formation of a pyrrolidone (146).

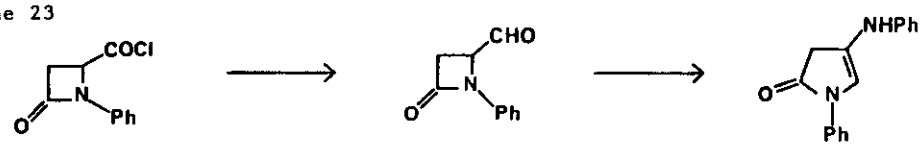
Scheme 22



(144) (145) (146)

Sorrel and Spillan[32] prepared 4-formyl-2-azetidinone (148), by reduction of (147), and rearranged it in presence of amines to the dihydropyrrole (149) (Scheme 23).

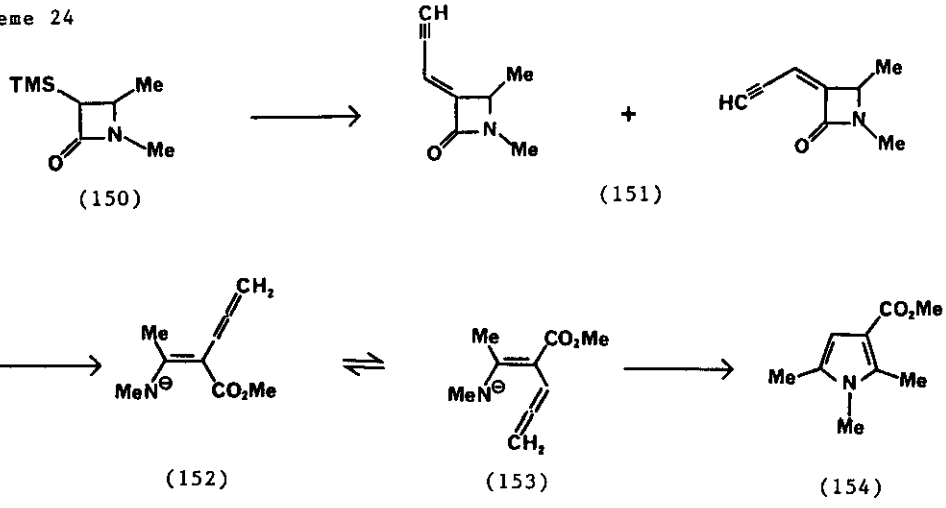
Scheme 23



(147) (148) (149)

The reaction of β-lactam enolates (150) with propargylic aldehydes resulted in the formation of E and Z isomers of 2-azetidinon-3-enynes (151). Treatment of (151) with sodium methoxide in methanol gave the pyrrole (154)[33] (Scheme 24).

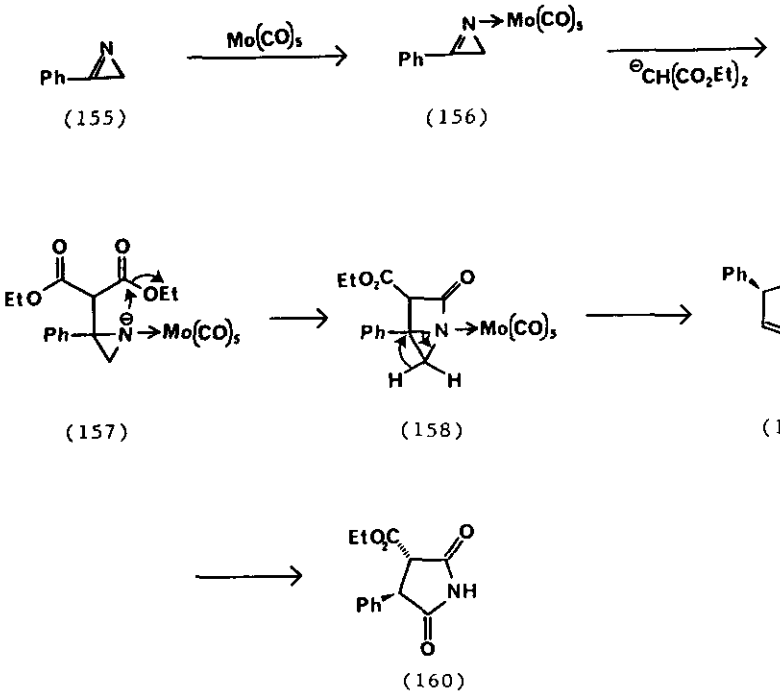
Scheme 24



(150) (151) (152) (153) (154)

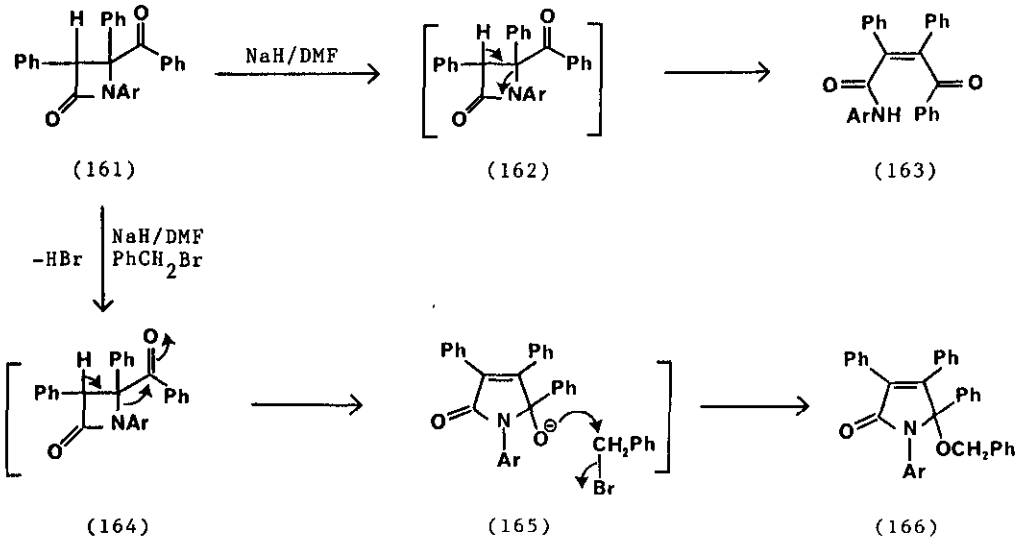
A stereospecific synthesis of imide (160) has been achieved[34] by the reaction of aziridine-molybdenum carbonyl complexes (156) with nucleophiles. A β-lactam intermediate (158) is postulated (Scheme 25) in this transformation.

Scheme 25



In a recent publication Alcaide and coworkers[35] have studied the ring expansion of 4-benzoyl-2-azetidinones. They have found that β-lactams of the type (161) when treated with sodium hydride in dimethylformamide followed by hydrolysis resulted in α,β-unsaturated amides (163). Alternatively, the reaction of (161) with alkyl halides in presence of sodium hydride in N,N-dimethylformamide yielded unsaturated γ-lactams (166). No mechanistic details have been provided. However, the generation of (164) and (165) could be postulated as shown in Scheme 26.

Scheme 26



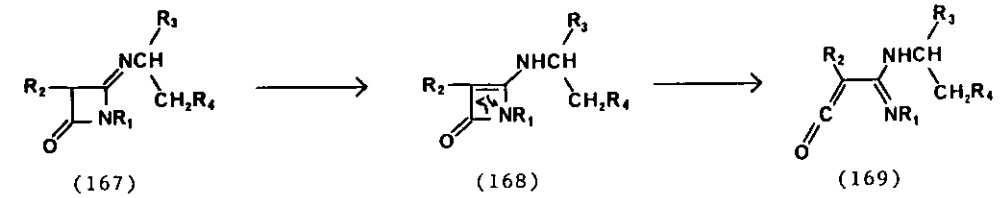
(161) (162) (163)

(164) (165) (166)

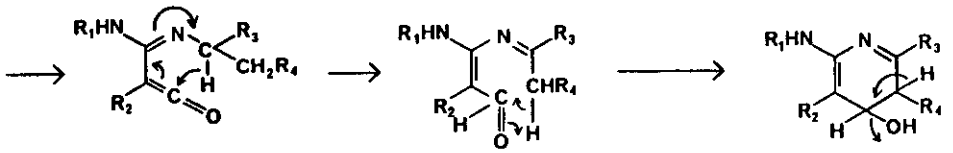
Metzger and Kurz have studied the thermal decomposition of 4-imino-2-azetidinones[36]. They found that when this category of compounds (167) are subjected to vacuum distillation at a temperature of 180-190°C, they undergo dehydration and are transformed to 2-aminopyridines (173). In this reaction the substituted malonamides (174) and acetamides (177) are also formed as by-products. The formation of (173), (174) and (177) is explained in Scheme 27.

It has been observed by the Woodward group[37] and later by Perrone and Stoodley[38] that phosphoranes of the type (178a), (178b) and (178c) under thermal conditions undergo ring closure through an internal Wittig reaction to afford penems (179a), (179b) and (179c). Under similar reaction conditions their diastereoisomers, however, followed a different course[39]. Thus, when (180a) and (180b) were heated in toluene at 80°C for 2-3 days the main products were the thiazoles (181a) and (181b), respectively. Spectroscopic analysis revealed the presence of oxazolinones (182a) and (182b) as well. The thermolysis of (180c) at 80°C for 4 days resulted in the formation of the thiazole (181a) in 70% yield. The crude product after 16 h showed a shoulder at 1810 cm^{-1} in the ir spectrum (attributable to the presence of the corresponding oxazolinone (182c) which disappeared after 44 h. (Scheme 28)

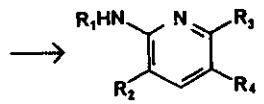
Scheme 27



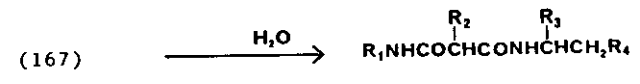
(167) (168) (169)



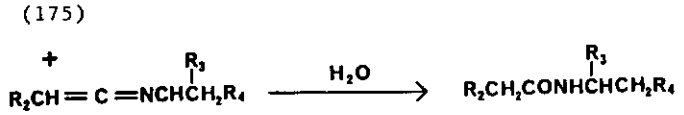
(170) (171) (172)



(173)



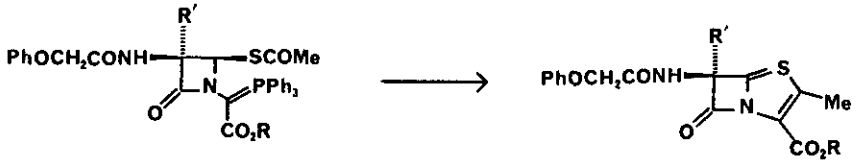
(174)



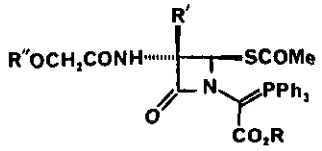
(175) (176) (177)

	R_1	R_2	R_3	R_4
(a)	*i*-Pr	*o*-ClC_6H_4	CH_3	H
(b)	*c*-C_6H_{11}	"	$-(CH_2)_4-$	

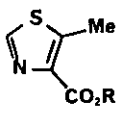
Scheme 28



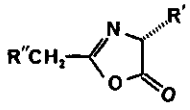
(178) (a) R=PNB, R'=H (179)
(b) R=PNB, R'=OMe
(c) R=Me, R'=OMe



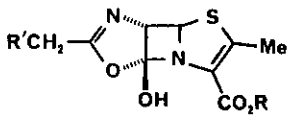
(180)
(a) R=Me, R'=H, R"=CH_2Ph
(b) R=PNB, R'=H, R"=CH_2OPh
(c) R=Me, R'=OMe, R"=CH_2Ph



(181)
(a) R=Me
(b) R=PNB



(182)
(a) R'=H, R"=Ph
(b) R'=H, R"=OPh
(c) R'=OMe, R"=OPh

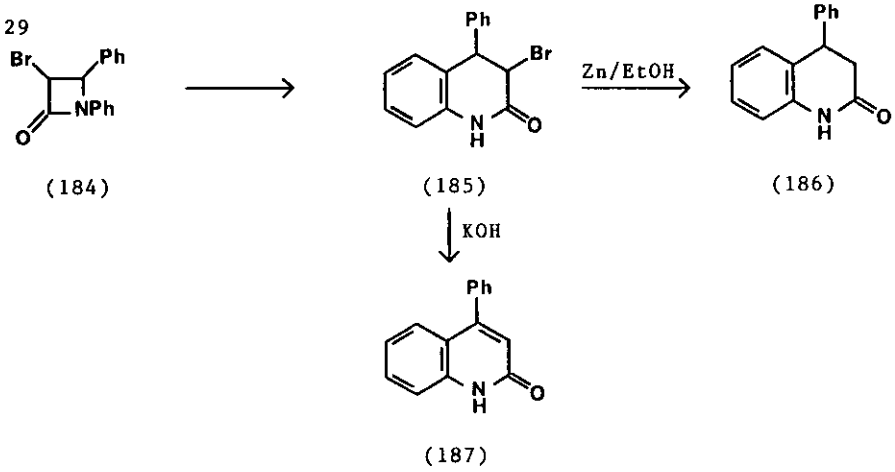


(183)

The difference in the reaction course of the diasteroisomeric β-lactams under thermolytic conditions has been explained on mechanistic grounds. The transition state (183) in the conversion of cis β-lactams to the stable penems is sterically less crowded. Atternatively, the acylamino side chain in the trans-β-lactams participates in the formation of the oxazolinones. Furthermore, steric crowding in the transition state of the type (183) derived from these β-lactams results in the scission of the tricyclic ring structure to afford the thiazoline.

Knunyants and Gambaryan[40] in 1957 discovered that substituted 2-azetidinones (184) isomerize to 3,4-dihydrocarbostyrils (185) when treated with concentrated sulfuric acid overnight (see Scheme 29). Reduction of (185) with zinc and ethanol affords the dehalogenated product (186). Dehydrohalogenation of (185) under basic conditions results in the carbostyril (187). The ring expansion in (184) involves the incorporation of the N-aryl substituent along with the N-C4 bond cleavage.

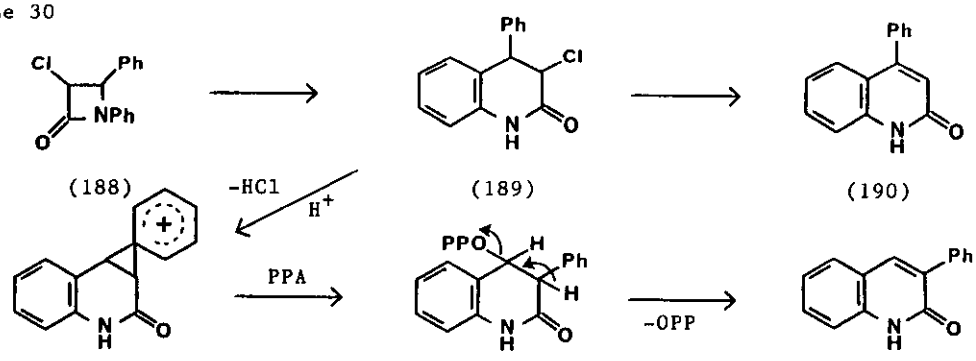
Scheme 29



(184) (185) (186) (187)

The acid catalyzed rearrangement of N-aryl-2-azetidinones has been reinvestigated by Johnson and Suschitzky[41]. These authors report that these β-lactams behave analogously, when treated with cold concentrated sulfuric acid or when heated with polyphosphoric acid at 78°C. However, at higher temperatures, the polyphosphoric acid catalyzed reaction of 3-chloro-N-aryl 2-azetidinones can result in the dehydrohalogenation of the 3-chloro-dihydrocarbostyril to afford (190); in some cases aryl migration leads to 3-phenylcarbostyril (193) in good yield (see Scheme 30). The aryl migration has been explained by the intermediate formation of the "phenonium ion" (191) which then collapses to (193) through the participation of polyphosphoric acid.

Scheme 30



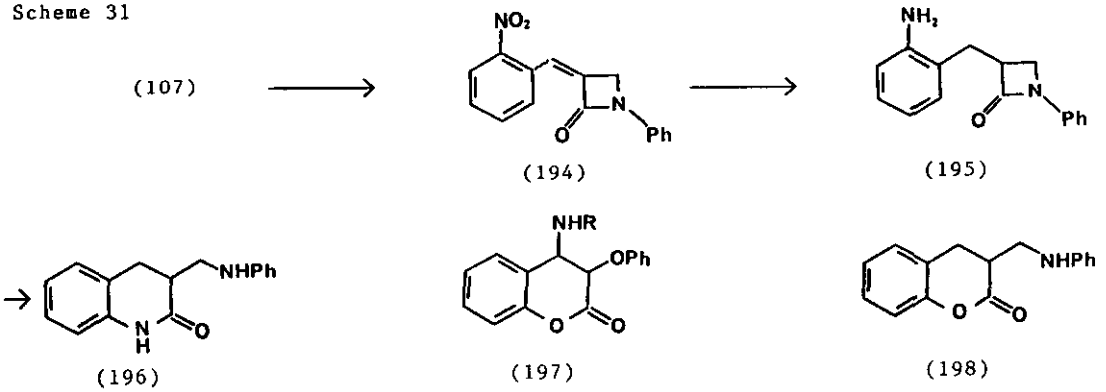
(188) (189) (190) (191) (192) (193)

The β-lactam (107) was alkylated at C-3 with o-nitrobenzaldehyde to give (194). Catalytic reduction of (194) to the amine (195) followed by cyclization under acidic conditions resulted in the formation of substituted δ-lactam (196)[6a] (Scheme 31). The same general strategy was used to cleave the β-lactam ring for generating the substituted coumarins (197)[5] and (198)[6a].

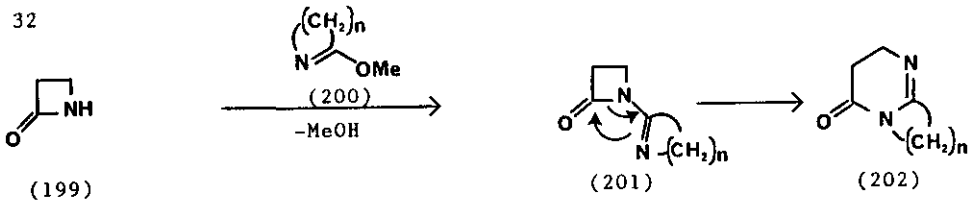
Bormann[42] has studied the reaction of N-unsubstituted β-lactams with lactam ethers and has reported the synthesis of several tetrahydro-4-pyrimidones as shown in Scheme 32. Thus, the reaction of (199) with (200) at elevated temperatures results in the formation of the tricyclic compound (202). β-lactams substituted at C-3 and/or C-4 and bicyclic β-lactams can also be used in this reaction.

Fries-type acid-catalyzed rearrangement of 1-aryl-2-azetidinone has been studied by Kano and coworkers[6d,e,f]. They found that treatment of an N-aryl-2-azetidinone (203) under reflux for 1 h with trifluoroacetic acid gave 2,3-dihydro-6-methoxy-4(1H)-quinolone (205) in 95% yield as shown in Scheme 33. Other acids such as concentrated sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid and boron trifluoride-diethylether at 100°C afforded (205) in varying yields. No rearrangement was observed when acetic acid and formic acid were used in this reaction.

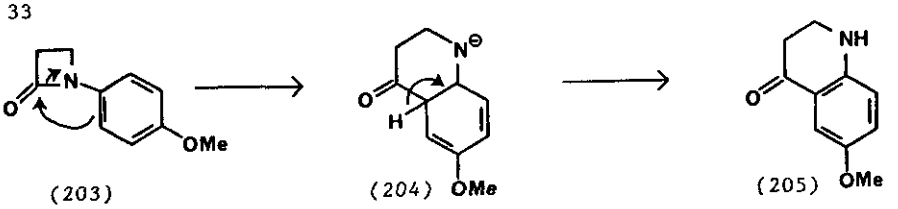
Scheme 31



Scheme 32



Scheme 33

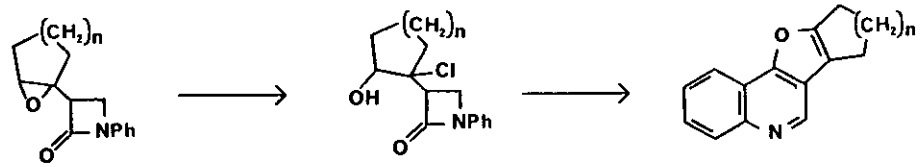


An interesting application of this rearrangement reaction was the synthesis of several polycyclic heterocyles and butenolides. Thus, when the β-lactam (207), obtained from the epoxide (206), was refluxed with methanesulfonic acid in benzene, the furano derivative (208) and the butenolide (209) were formed. (see Scheme 34)

The reaction of 4-acetoxy-2-azetidinone (210) with esters of salicylic acid (211) or o-mercaptobenzoates (215) and (216) in the presence of sodium hydroxide has been studied by Arnoldi and coworkers[43] (Scheme 35). The product (212), expected on the nucleophilic displacement of the acetoxy group of the β-lactam by the phenoxy group of (211), was formed in low yield; the major product was a 2,3-dihydro-1,3-benzoxazin-4-one (213).

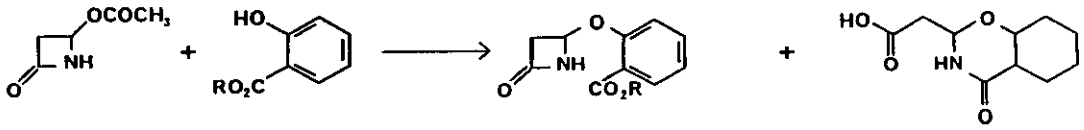
Thiosalicylic acid and its benzyl ester and (210) gave the expected β-lactam (214). On the other hand, the substituted benzyl ester (215) and (216) reacted with (210) to produce 2,3-dihydro-1,3-benzthiazin-4-one (217).

Scheme 34

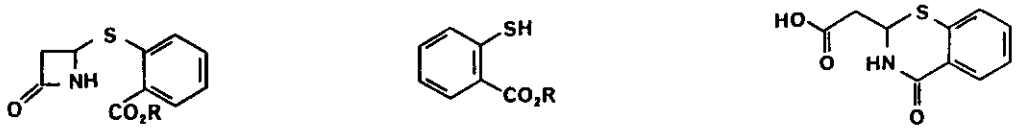


(206) (207) (208) (209)

Scheme 35



(210) (211) (212) (213)



(214) R=H, CH_2Ph

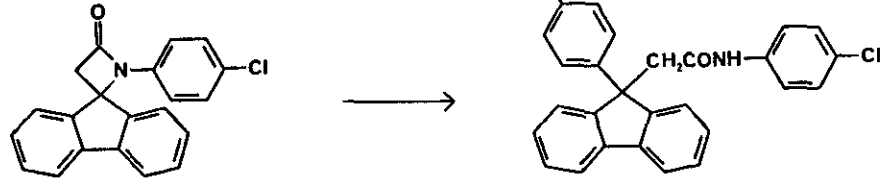
(215) R= $CH_2C_6H_4O$-^tBu(p)

(216) R= $CH_2C_6H_4$-3,4-Cl_2

(217)

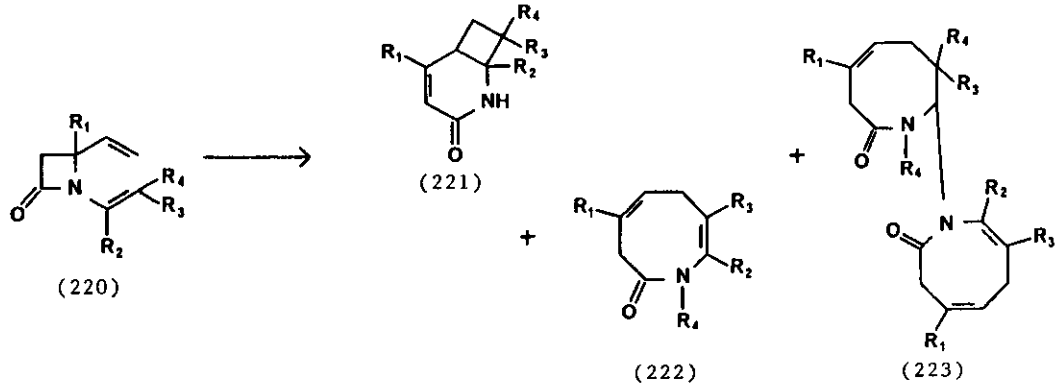
Bird and Irwin[44] have observed the formation of dihydrocarbostyrils by sulfuric acid treatment of N-aryl substituted 2-azetidinones. The reaction, however, took a different course and open chain amides were formed when a Lewis acid such as boron trifluoride was used as a catalyst. In these cases the N-C4 bond was cleaved and solvent molecules were incorporated at C-4 of the starting β-lactam. Thus, refluxing (218) with boron trifluoride in toluene gave (219) (See Scheme 36). The Cope rearrangement of 1,4-divinyl-2-azetidinones was investigated by Schnabel[45]. He found, as shown in Scheme 37, that β-lactams with this functionality (220) when heated at 160-210°C rearrange to give compounds of the type (221), (222) and (223). The proportion of the rearranged products in such reactions is highly dependent upon the nature of the substitutents on the vinyl groups. Bose, Fahey and Manhas[46] have reported that 5-methylthiopenicillin analogs can undergo ring transformations under trifluoroacetic acid treatment to yield novel rearrangement products. Thus, the penam (225), obtained by the cycloaddition of 2-methylthio-2-thiazoline (224) and methoxyacetyl chloride in presence of triethylamine, when treated with trifluoroacetic acid afforded 1,4-thiazepine (227). Presumably the reaction preceeds through the protonation of the amide nitrogen of (225) followed by the abstraction of the β-lactam ring proton and simultaneous ring opening to form the thiazepine (227). The structure of (227) was confirmed on the basis of its analytical and spectral data and its subsequent conversion to a new bicyclic β-lactam (230) as shown in Scheme 38. While exploring the usefulness of β-lactams as intermediates for medium ring heterocycles via their rearrangement reactions Bose, Hoffman and Manhas[47] discovered that the methylthio group in β-lactams of the type (231) can be replaced during oxidation with sodium periodate in aqueous isopropyl alcohol. The β-lactam ring is cleaved and a 9-membered lactam of the type (234) is formed (Scheme 39).

Scheme 36



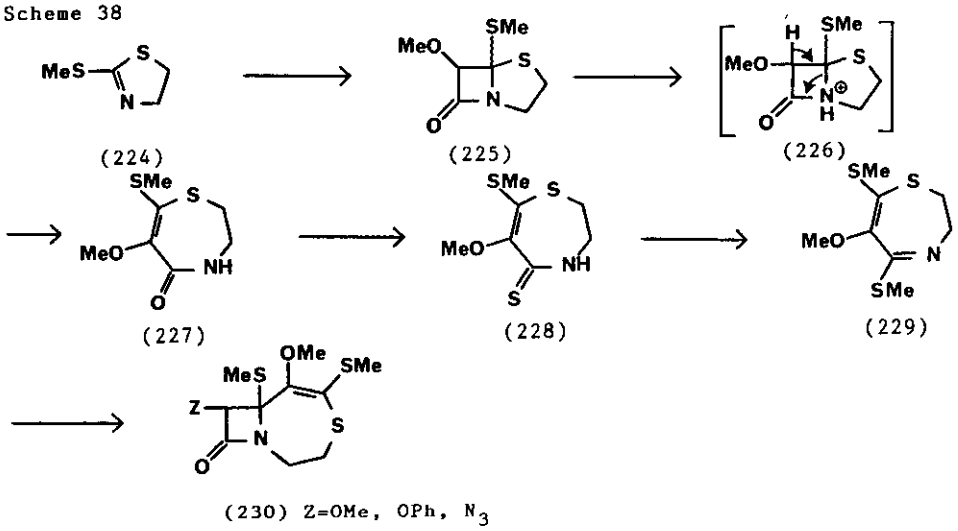
(218) (219)

Scheme 37



(220) (221) (222) (223)

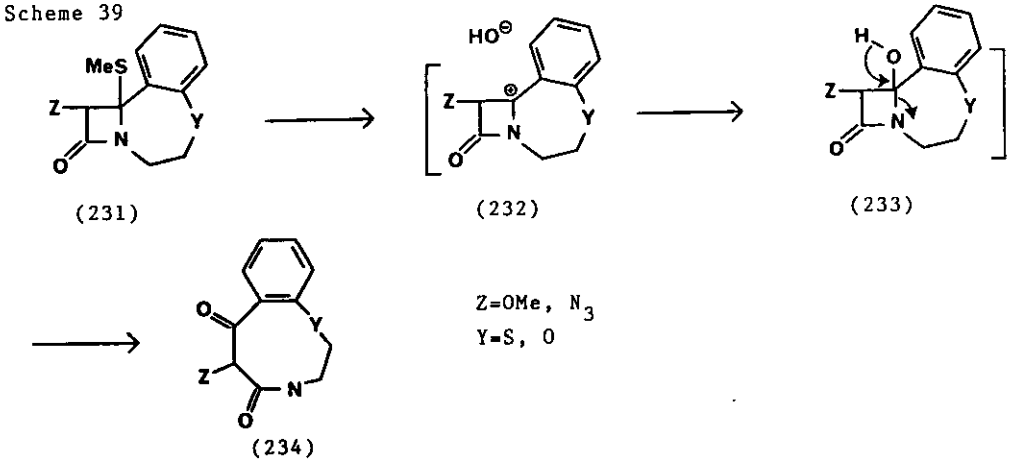
Scheme 38



(224) (225) (226) (227) (228) (229)

(230) Z=OMe, OPh, N_3

Scheme 39

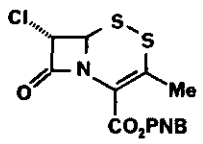


(231) (232) (233) (234)

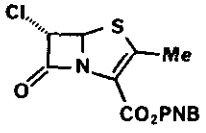
Z=OMe, N_3
Y=S, O

During their attempts to synthesize penems by ring contraction of 2-thiacephems, the Hoechst group[48] in U.K. has discovered a rearrangement reaction involving the β-lactam ring. They found that the desulfurization of 2-thiacephem (235) with triphenylphosphine in a variety of solvents afforded 2S-chloropenem (236) in 50% yield. However, when the desulfurization reaction was attempted with trimethyl phosphite only the thiazepine (237) was obtained. Presumably the thiazepine results from the attack of the intermediate enethiolate on the β-lactam carbonyl and the loss of hydrogen sulfide.

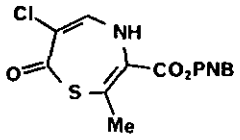
The acid catalyzed rearrangement of fused β-lactams to α-piperidylidene-acetoacetates has been described[49]. Thus, when bicyclic 2-azetidinone (238) was treated with alumina, piperidylidene acetoacetate (242) resulted. Under acidic conditions (238) gave (243) together with (242). The mechanism of formation of (242) and (243) is illustrated in Scheme 40.



(235)

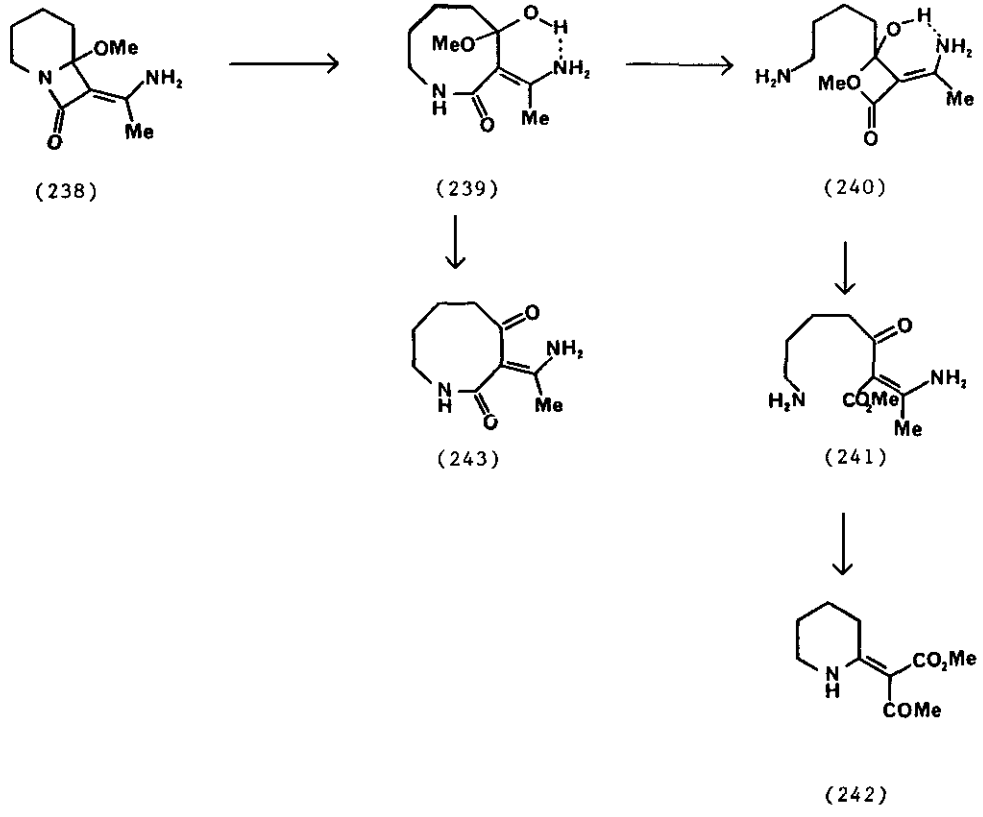


(236)



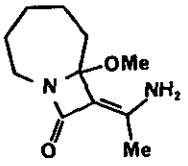
(237)

Scheme 40

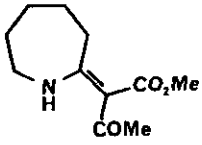


(238) (239) (240) (243) (241) (242)

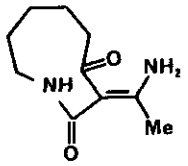
Similarly β-lactam (244) produced (245), (246) and (247).



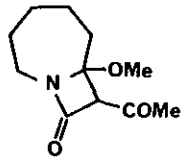
(244)



(245)



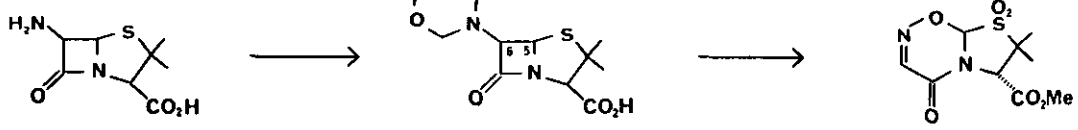
(246)



(247)

Steele and Stoodley[50] have reported a new oxidative two-atom expansion of a β-lactam ring of a 6-aminopenicillanic acid derivative (249), obtained by the treatment of 6β-aminopenicillanic acid (6-APA)(248) with formaldehyde followed by esterification with diazomethane. Upon oxidation with potassium permanganate in acetic acid (conditions normally used for preparing sulfones) (249) is transformed into an oxathiadiazabicyclononene derivative (250). This transformation provides a rare example of the 5-6 bond cleavage[4a,51] in penicillin ring systems (Scheme 41).
Simultaneons rupture of C-5-C-6 and N-C-7 bonds in penams has been documented. Thus, penicillin G methyl ester (251) when refluxed with trifluoroacetic acid undergoes such cleavage to give the thiazoline (252)[52] as shown in Scheme 42.

Scheme 41



(248) (249) (250)

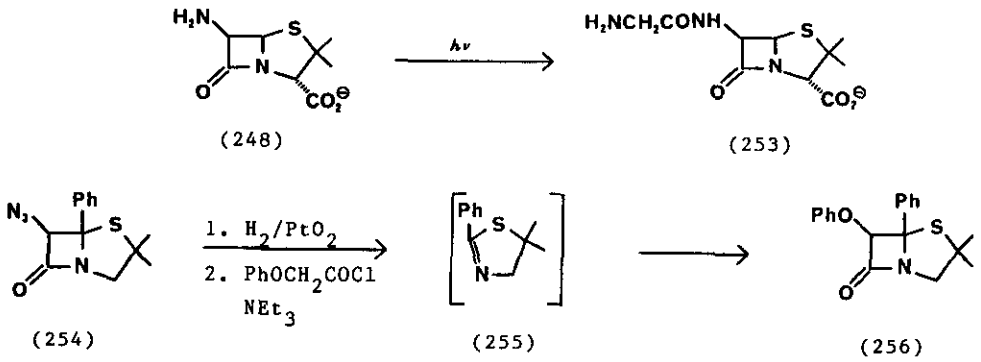
Scheme 42

(251) (252)

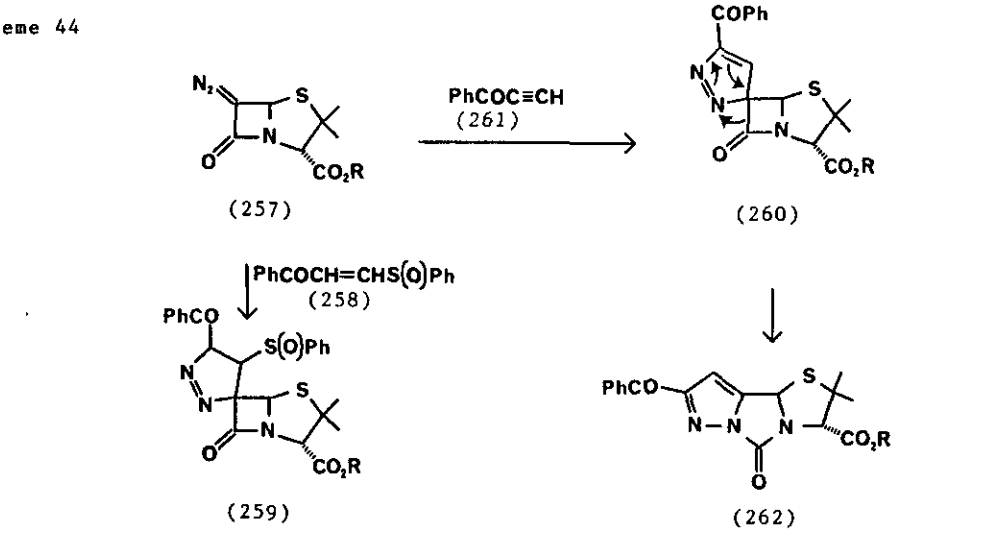
Godtfredsen and coworkers[53] studied the photolysis of potassium salt of 6-APA (248) and isolated (253) (Scheme 43). The formation of (253) can only be explained on the basis of the β-lactam ring cleavage to form in situ amino-ketene which reacted with 6-APA to give (253). Bose and coworkers[54] have also observed a similar cleavage when the 6-azidopenam (254) was reduced under catalytic conditions. In an attempt to acylate the expected 6-amino compound with phenoxyacetyl chloride they isolated a 6-phenoxypenam (256) which could result only from the thiazoline (255) formed during the reductive step (see Scheme 43).

An unusual β-lactam ring cleavage in penams has been reported by Sammes and coworkers[55]. They have observed, as shown in Scheme 44, that the reaction of trichloroethyl 6-diazopenicillanate (257) with β-phenylsulphinylpropenophenone (258) or propiolophenone (261) resulted in the formation of (262) the structure of which was derived from X-ray crystallographic analysis. This formation of (262) has been explained by the intermediate formation of a spiro β-lactam of the type (260). Further rearrangement through the scission of the 6,7-bond gives the fused pyrazole (262).

Scheme 43



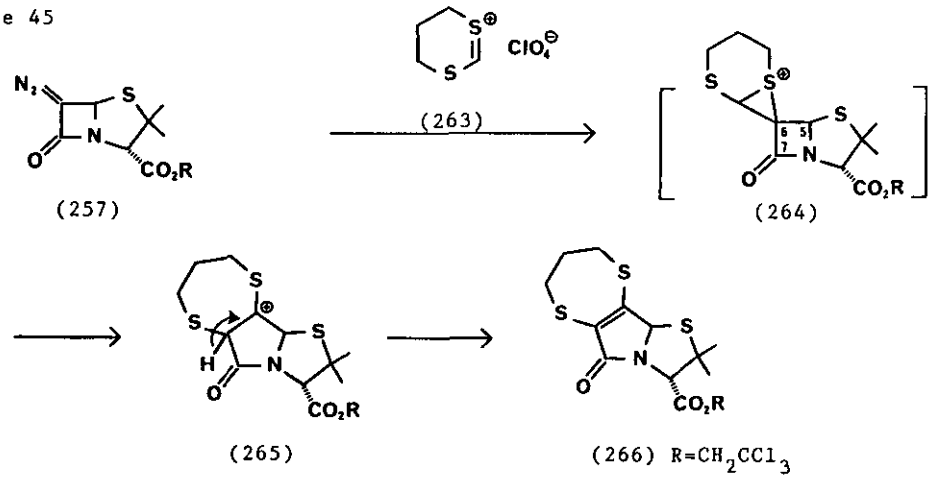
Scheme 44



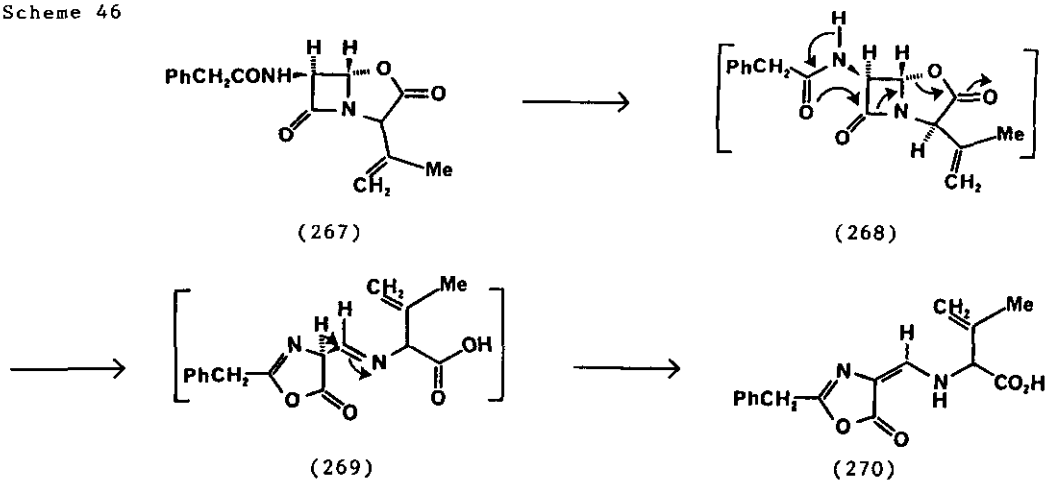
A similar β-lactam ring expansion has recently been reproted[56] (See Scheme 45). When trichloroethyl 6-diazopenicillanate (257) was treated with dithienium perchlorate (263) in acetonitrile at temperatures ranging from -50 to 80°C the rearranged product (266) was formed in about 20% yield. Compound (266) results by the initial formation of the spirosulphenium ion (264) which collapses to (265) through the cleavage of the 5,6 or 6,7 bond migration. Deprotonation of (265) leads to (266).

In a recent study Sako and coworkers[57] have shown that 1-dethia-1-oxa-5-epi-anhydropenicillin (267) under acidic conditions undergoes ring transformation to give an oxazolinone derivative (270) as a mixture of E and Z isomers (Scheme 46). This rearrangement takes place through the participation of the acylamino side chain in the parent bicyclic compound.

Scheme 45



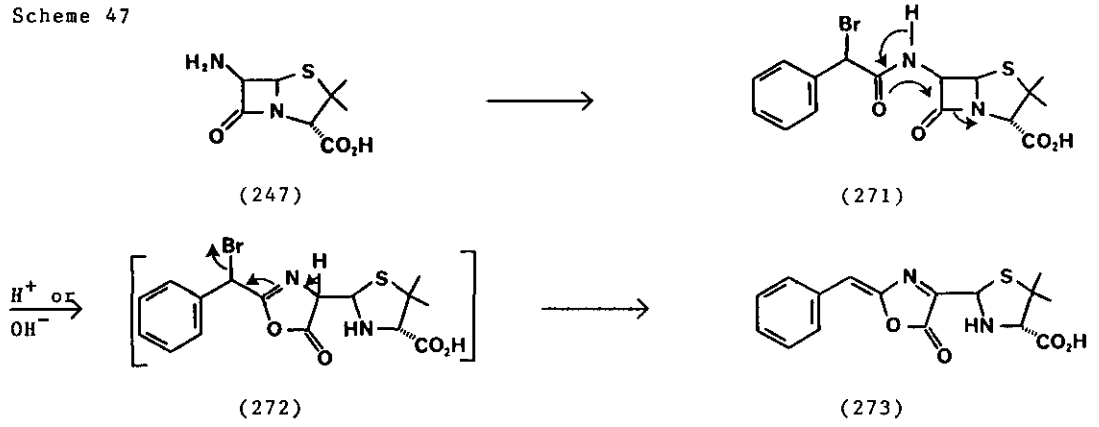
Scheme 46



Decomposition of penicillins under acidic conditions has been studied by several groups of workers[58] and a variety of products have been identified. *Awang and coworkers*[58d] *have proposed an* oxazolone-thiazolidine intermediate for explaining the formation of degradation products of penicillin. The existence of oxazolone-thiazolidine structure for penicillin was proposed by Robinson in 1942. All attempts to prepare this category of compounds were unsuccessful because of their instability.

Gottstein[59] is the first to report the formation and characterization of an intact oxazolone-thiazolidine ring system. 6-Aminopenicillanic acid (248) was acylated with α-bromophenylacetyl *chloride in aqueous sodium bicarbonate. The acid work up of the product* (271) resulted in a yellow crystalline compound to which structure (273) was assigned on the basis of analytical and spectral analysis. Compound (273) seems to originate through the dehydrohalogenation of (271). The stereochemistry of the exocyclic double bond has not been established (Scheme 47).

Scheme 47



C. CLEAVAGE OF β-LACTAM RING

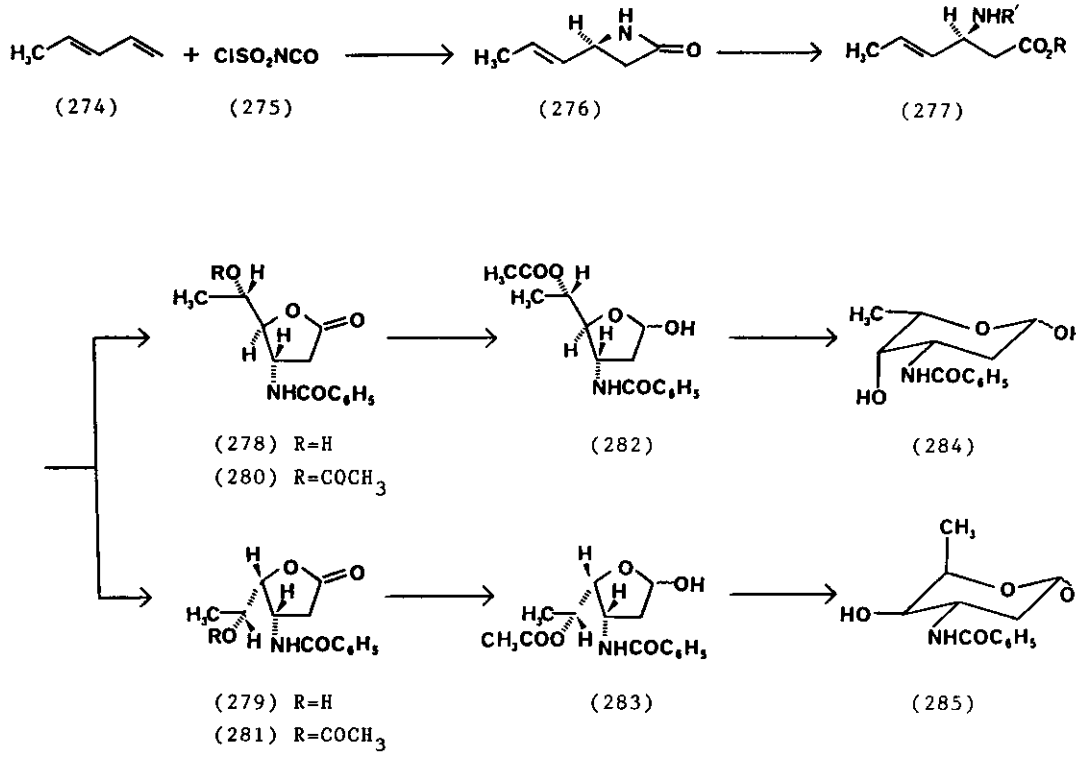
The synthetic approaches reviewed briefly in this section involve β-lactam cleavage but not molecular rearrangement. A comprehensive review on such syntheses was published earlier by us[5].

i. Synthons for Carbohydrates

Hauser and coworkers[60] developed a route for preparation of racemic N-benzoyldaunosamine (284) *based on the use of the 4-propenyl-2-azetidinone* (276) *as an intermediate* (Scheme 48). Cycloaddition of chlorosulfonyl isocyanate (275) to (E)-1,3- pentadiene (274) followed by reductive cleavage of the N-chlorosulfonyl moiety with sodium sulfite furnished the 4-propenyl-2-azetidinone (276). Methanolysis of (276) cleaved the β-lactam amide bond and gave the methyl ester amine hydrochloride (277). In order to provide both steric bulk and protection for the amine group, (277) was converted to the benzamide derivative (277, R'=COPh). cis-Hydroxylation of the olefinic bond in (277, R'=COPh) using a catalytic amount of osmium tetroxide with trimethylamine N-oxide[61]

directly furnished the lactones (278) and (279). These lactones were converted to the acetates (280) and (281), respectively. Reduction of the acetates with diisobutylaluminum hydride gave good yields of the acetoxy furanoses (282) and (283), respectively. Ammonolysis of (282) and (283) furnished DL-N-benzoyldaunosamine (284) and the xylo isomer (285).

Scheme 48



Hauser et al.[62] have also prepared optically active N-benzoyldaunosamine (284). The racemic aminoester (277) (R'=H) was resolved with (-)- dibenzoyl-L-tartaric acid and then benzoylated to obtain optically active (277) (R'=COPh). Conversion to optically active aminohexoses was achieved by following the procedure described in Scheme 48.

Bose, Manhas and coworkers have extensively studied the molecular rearrangement of β-lactams and their use in the synthesis of a variety of heterocycles[5]. One of the extensions of this work has been the use of variously substituted β-lactams to synthesize amino sugars. The strategy involved the cleavage of the amide bond of a 3,4-disubstituted 2-azetidinone (286) to a α-amino derivative (287) and its subsequent modification to the structural features of amino sugars as shown in Scheme 49.

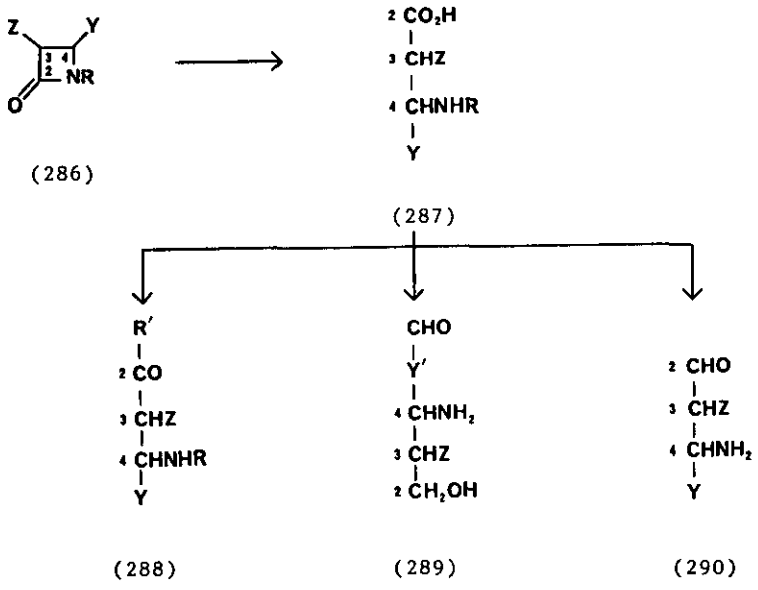
The carboxy group in the amino acid (287) can be used to extend the chain length as in (288) or to shorten it as in (290). If the substitutent at C-4 of the β-lactam (286) is derived from a sugar moiety, it is possible to increase the chain length of the resulting amino sugar by three carbon

atoms as in (289). Furthermore, the relative configuration of the amino sugar at carbons carrying the Z group and the N-atom will depend upon the stereochemistry (cis or trans) of the starting β-lactam (286).

The nature of the subsituent at C-3 of the β-lactam (286) can play a significant role in determining the structure of the amino sugars synthesized by using this methodology. Thus, it may be noted that the presence of an oxygen function at C-3 such as OMe, OPh, OAc or OBzl can result in a monoamino sugar whereas a nitrogen function such as N_3 or phthalimido at this center will result in a diamino sugar. A β-lactam unsubstituted at C-3 can yield the corresponding deoxy sugars. SR or SAr groups at C-3 can be easily removed by hydrogenation. This category of compounds can also serve as synthons for generating the deoxy products.

The carboxy group of the β-amino acid (287) may serve as the C-1 of an amino sugar. Alternatively, the carboxy substituent at C-4 can serve as C-1 of the amino sugar and the C-2 of the β-lactam (286) can serve as the terminal carbon.

Scheme 49

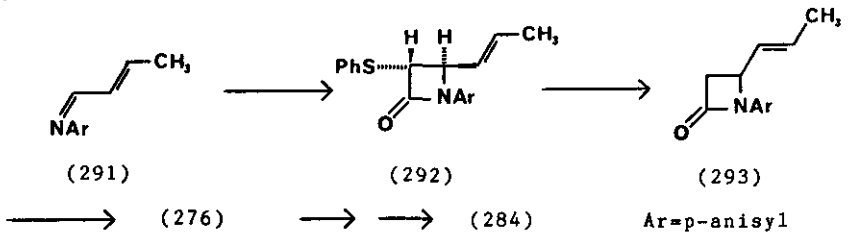


In a recent publication[63] Bose et al. have described a formal total synthesis of daunosamine (284) (Scheme 50). The Schiff base (291) was treated with the potassium salt of thiophenoxyacetic acid in the presence of cyanuric chloride[64] and triethylamine to afford 3-thiophenoxy-2-azetidinone (292). Raney nickel desulfurization of (292) gave (293) which was oxidized with cerium (IV) ammonium nitrate to generate the N-unsubstituted β-lactam (276). The compound (276) was synthesized by Hauser and coworkers[62] by an alternative route and used for the synthesis of (±) daunosamine (284) described in Scheme 48.

Manhas and coworkers[63] have also reported the synthesis of sugar lactones via β-lactams as shown in Scheme 51. Thus, the Schiff base (291) when treated with methoxyacetyl chloride in presence of triethylamine gave cis-β-lactam (294). Oxidative cleavage of the aryl group followed by cleavage of the β-lactam amide bond in refluxing methanolic potassium hydroxide yielded the β-amino acid

(296). Protection of the amino group, followed by esterfication gave (298). cis-Hydroxylation with osmium tetroxide in the presence of N-methylmorpholine-N-oxide afforded two separable lactones (301) and (302). The formation of these lactones can be visualized as proceeding via the cyclization of the intermediate glycols (299) and (300). The stereochemistry of these sugar lactones (301) and (302) was confirmed by ^{1}H nmr spectroscopy.

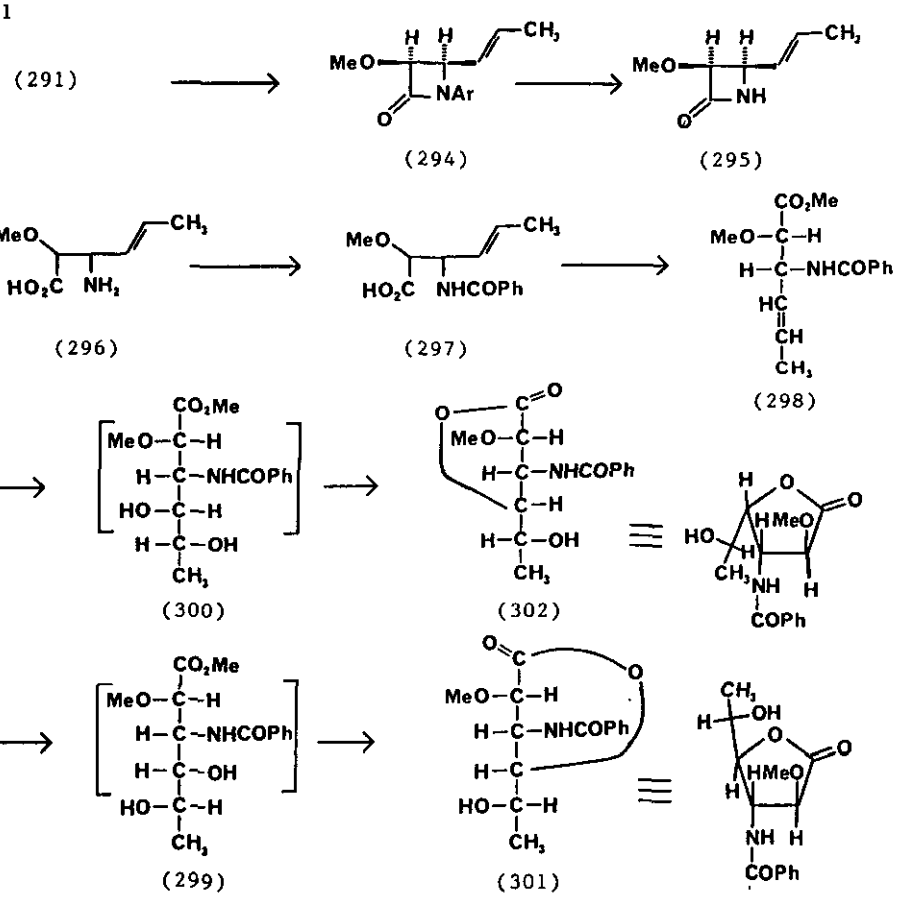
Scheme 50



(291) (292) (293)

(276) (284) Ar=p-anisyl

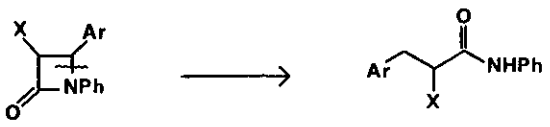
Scheme 51



ii. Synthons for α-Amino Acids and Peptides

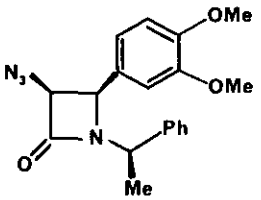
One of the main areas of interest in 2-azetidinone cleavage is the synthesis of peptides, which relies[65] on 1,4-bond cleavage rather than the more usual hydrolysis of 1,2-bond. The basic reaction is shown in Scheme 52.

Scheme 52

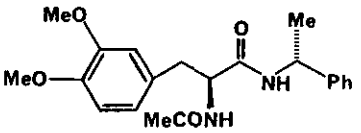


(303) X= N_3 or OCH_2Ph (304) X= NH_2 or OH

Ojima[65] reported that palladium catalysed hydrogenolysis of 2-azetidinones with an aryl substituent at C-4 proceeded exclusively with 1,4-bond cleavage producing amides of α-amino acids in 62-99% yield. An asymmetric synthesis of propionamide (306) was achieved from 2-azetidinone (305) with 40% enantiomeric excess[65]. This reaction sequence, therefore, leads to important biologically active aromatic amino acids such as dihydroxyphenylalanine (DOPA), p-fluorophenylalanine, tryptophan, and phenylacetic acid[66].



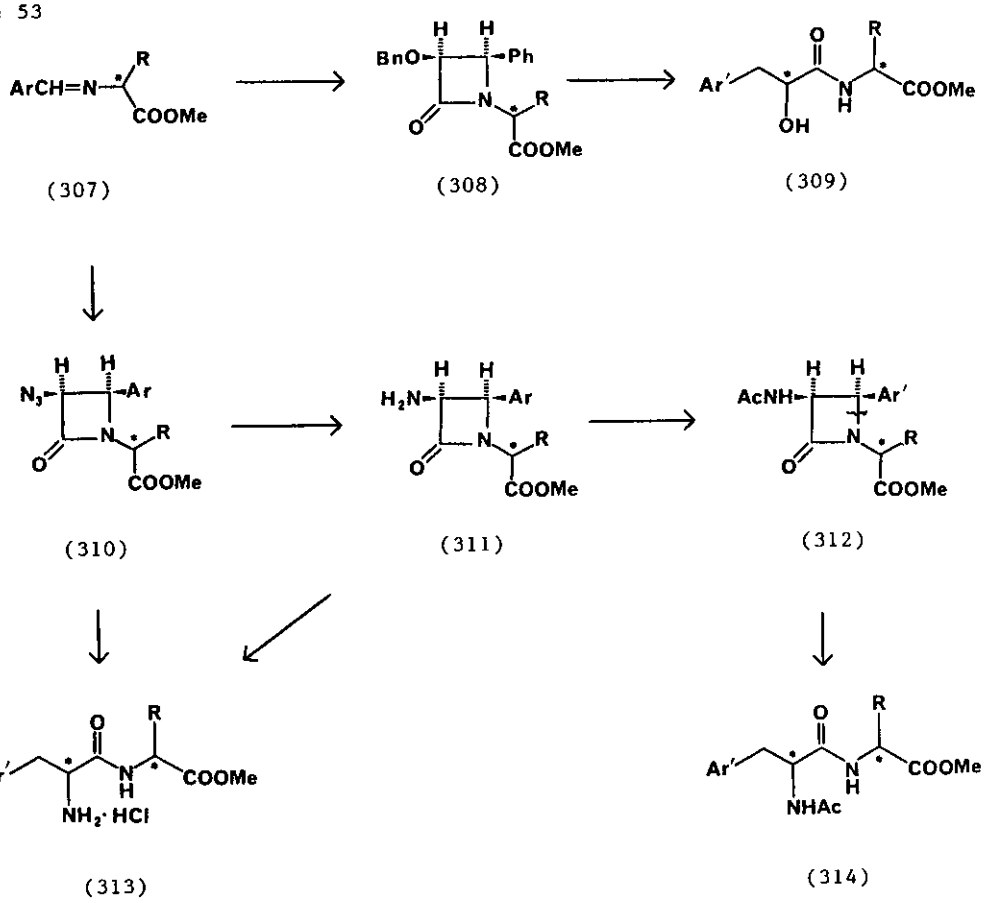
(305)



(306)

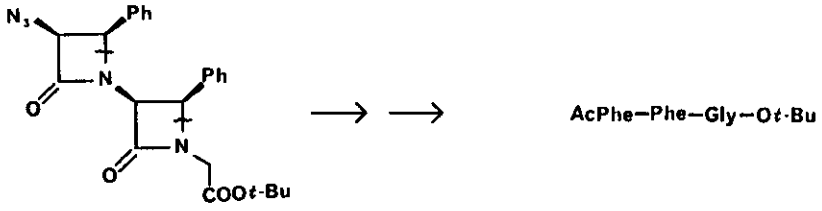
As illustrated in Scheme 53, Ojima et al.[67] reported the synthesis of dipeptides and their derivatives from β-lactams. β-lactam (308) and (310) were prepared by using a modified version of the Bose reaction[21]. Their hydrogenolysis on palladium catalyst resulted in the corresponding dipeptides, (309), (313) and (314) in excellent yields as shown in Scheme 53.

Scheme 53

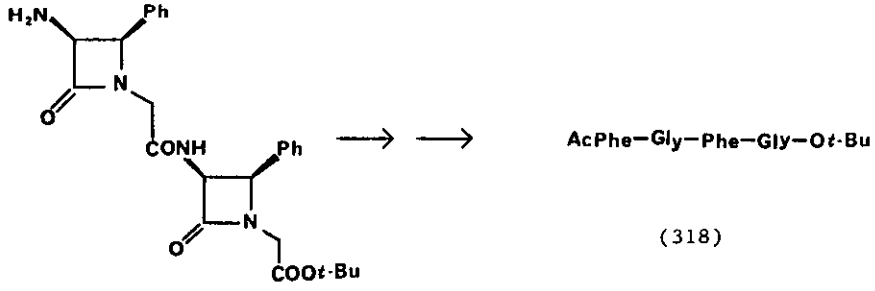

ArCH=N
R
COOMe
(307)
BnO
H
H
Ph
N
R
O
COOMe
(308)
Ar'
O
R
N
H
COOMe
OH
(309)
N3
Ar
(310)
H2N
Ar
(311)
AcNH
Ar'
(312)
NH2· HCl
(313)
NHAc
(314)

Similarly[66] the 2-azetidinones (315), (317) and (319) led to the tri- (316), tetra- (318) and higher oligopeptides (320), respectively (Scheme 54).

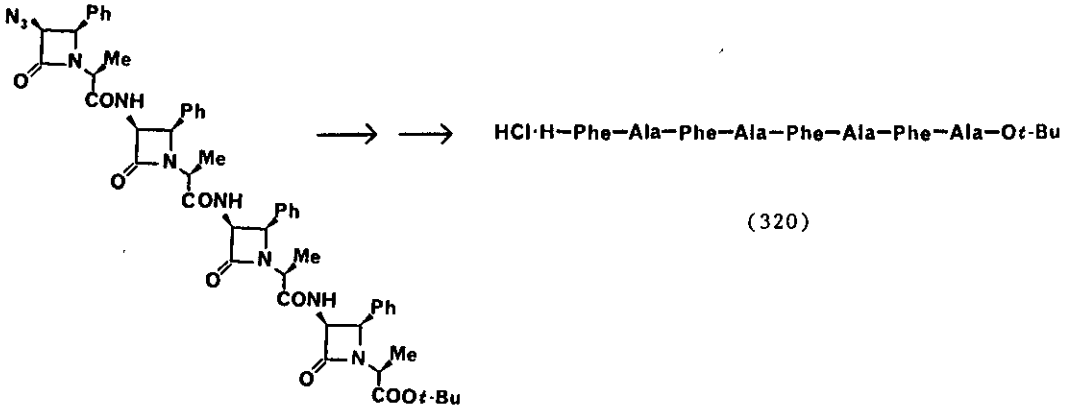
Scheme 54



(315) (316)



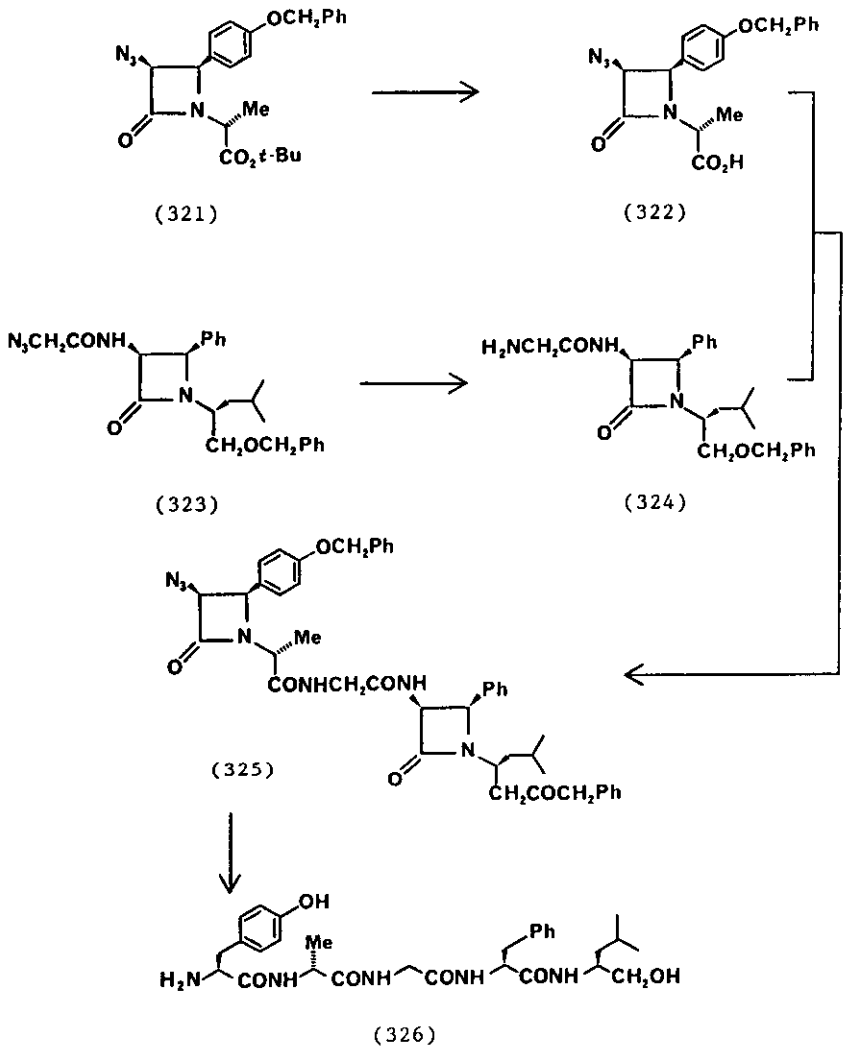
(317) (318)



(319) (320)

Ojima and coworkers[66] have also applied this method to the synthesis of an enkephalin analog (326) as shown in Scheme 55.

Scheme 55

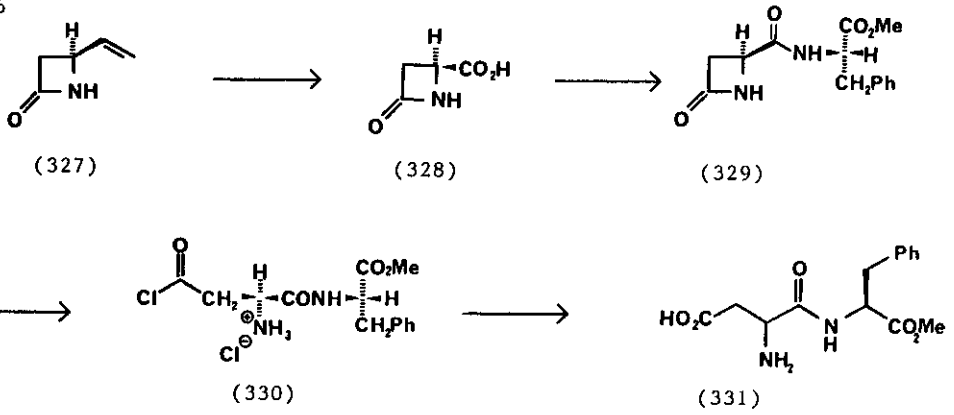


(321) (322) (323) (324) (325) (326)

β-Lactams have been used for the synthesis of aspartame (327)-a sweetening agent. Peitsch[68] utilized (4S)-4-vinyl-2-azetidinone (327) as his starting material. Oxidation of the vinyl group

in (327) followed by amidation with S-phenylalanine methyl ester gave the (S,S)-amide (329) which was subsequently converted to aspartame (331) as shown in Scheme 56.

Scheme 56

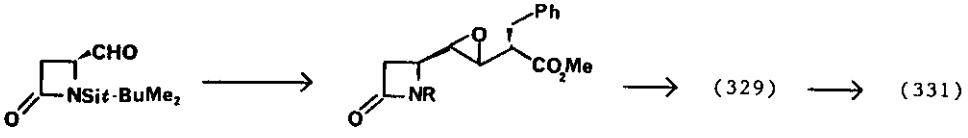


(327) (328) (329) (330) (331)

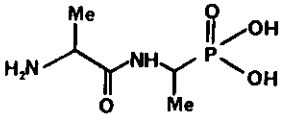
Recently Duhamel, Goument and Plaquevent[69] have reported an alternate formal synthesis of an aspartame intermediate (329). These workers converted (S)-N-t-butyldimethylsilyl-4-formyl-2-azetidinone (332) to (329) as shown in Scheme 57. The substituted β-lactam (329) has been converted to aspartame (331) by Pietsch[68].

Aminophosphonic acids, as analogs of natural amino acids, are of increasing interest as biologically active compounds. One such compound, alahosphin (334), has been found to inhibit alanine racemase[70].

Scheme 57



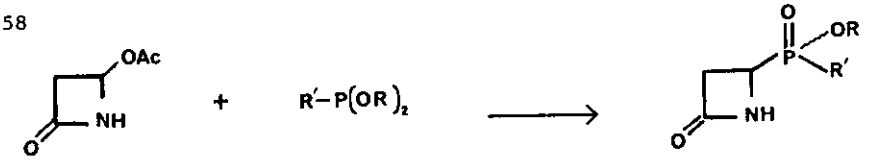
(332) (333) (329) (331)



(334)

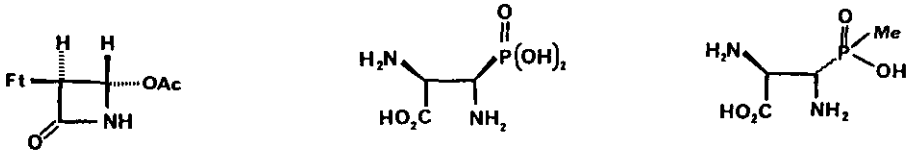
In an extension of this study[71] a variety of 4-phosphono- and 4-phosphino-2-azetidinones (336) were synthesised via an Arbusov reraction from 4-acetoxy-2-azetidinone (210)[72]. Acidic hydrolysis of (336) provided phosphino and phosphono aspartic acids (337) and (338)[73,74] (see Scheme 58). Arbusov reaction on the optically active trans-3-phthalimido-4-acetoxy-2-azetidinone (339) with phosphites and phosphonites followed by acidic hydrolysis gave the chiral 2,3-diamino-3-phosphono- and phosphino-propanoic acids (340) and (341).

Scheme 58



(210) (335) R= Me, Et, CH_2Ph; R'= Me, OR (336)

(337) (338)



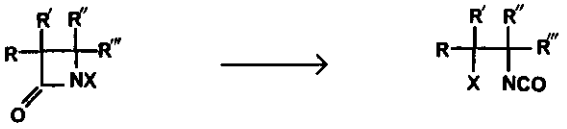
(339) (340) (341)

iii. Synthons for Heterocycles

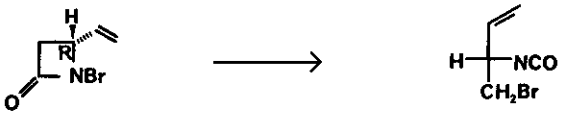
The fragmentation of N-halo-2-azetidinones (342) to haloalkylisocyanates (343), as shown in Scheme 59, has been extensively studied[75] using radical initiators, photolysis and thermolysis. Thus, enantiomerically pure N-halo-2-azetidinones R-(344) and S-(344) gave optically active haloalkyl isocyanates S-(345) and R-(345).

These isocyanates have been used to synthesize a variety of compounds, such as, aziridines and 2-oxazolidinones as shown in Scheme 60.

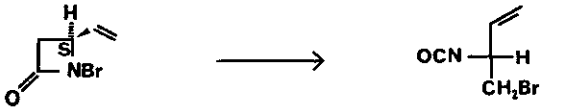
Scheme 59



(342) X= Cl or Br (343)

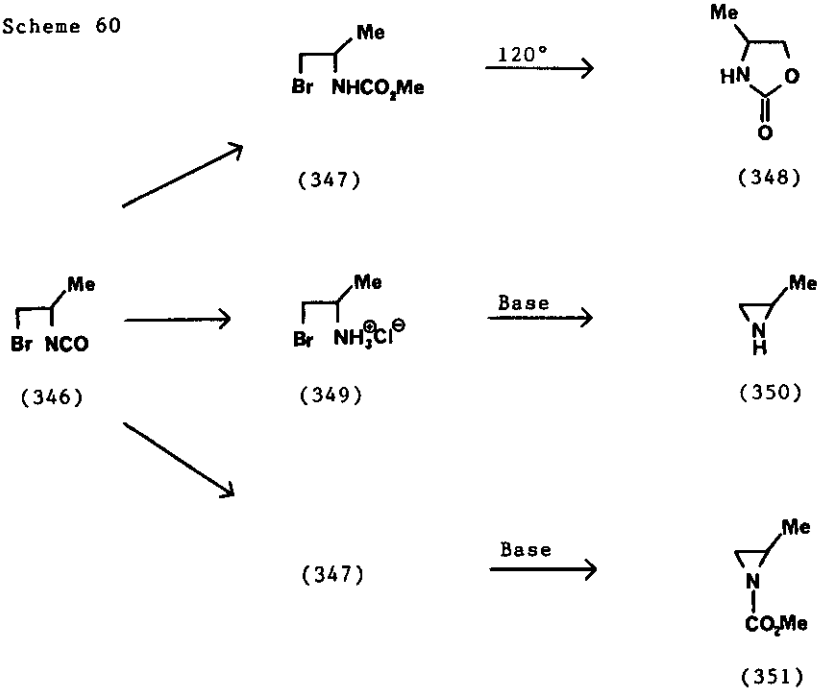


R-(344) S-(345)



S-(344) R-(345)

Scheme 60



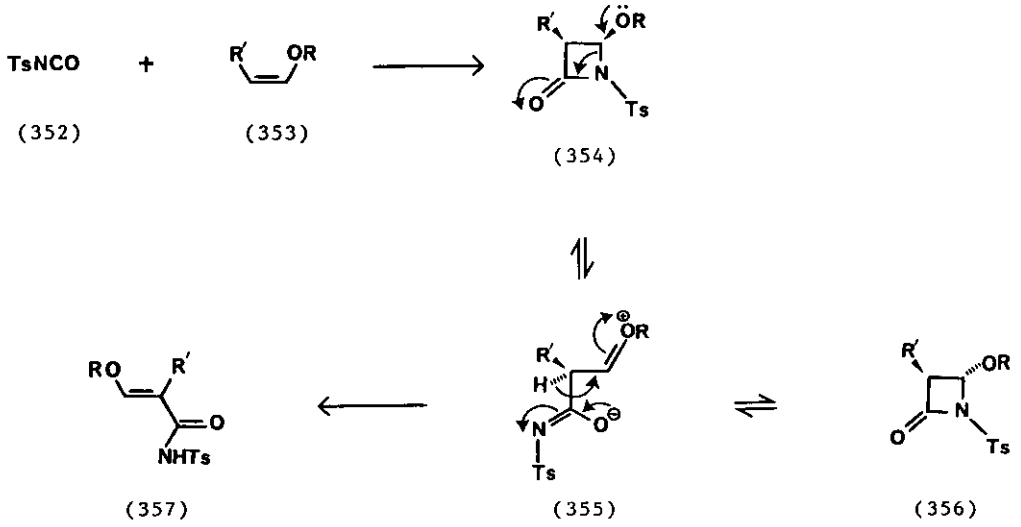
(346) (347) (348) (349) (350) (347) (351)

Effenberger and coworkers[76] have studied the reaction of arylsulfonylisocyanates (352) and enol ethers (353) and synthesized several 4-alkoxy-2-azetidinones (354) and (356). The reaction conditions are of critical importance for obtaining the β-lactams. At room temperature the 2-azetidinones can be isolated to the extent of 60-100% of the theoretical yield. Higher temperatures favor the formation of 3-alkoxyacrylamides (357).

Effenberger et al.[76c] have also studied the stereochemistry of this reaction spectroscopically. Both cis- and trans-enol ethers react with equal case. The reaction has been conceived as proceeding partially stereospecifically to give β-lactams. Thus, cis-1-ethoxy-1-hexene (353) when treated with p-toluenesulfonyl isocyanate (352) gives 70% of the corresponding cis β-lactam (354) and 30% of the trans isomer (356) whereas the trans alkene (353) under similar conditions gives 33% of the cis β-lactam (354) and 67% of the trans-isomer (356).

These 4-alkoxy-2-azetidinones (354) and (356) undergo isomerization via a zwitter ion intermediate (355)[76c]. This transformation is slow in the solid state but faster in solution; the trans isomer (356) predominates the equilibrium mixture. Furthermore, these 2-azetidinones (354) and (356), by a much slower irreversible rearrangement, are transformed to β-alkoxyacrylamides (357) (see Scheme 61).

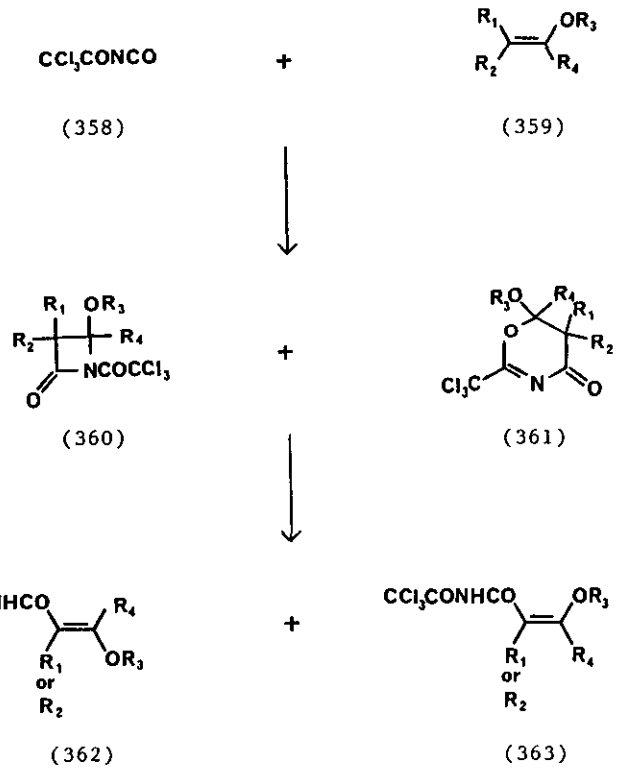
Scheme 61



Martin and co-workers[77] have investigated the reaction of trichloroacetyl isocyanate (358) with unsaturated ethers (359). In most of these reactions the 1:1 adducts, 3-alkoxy-N-(trichloroacetyl)-acrylamides (362) and (363) were linear, however, both 4- and 6-membered intermediates, 3-alkoxy-1-(trichloroacetyl)-2-azetidinones (360) and 6-alkoxy-5,6-dihydro-2-(trichloromethyl)-4H-1,3-

oxazin-4-ones (361), were observed by infrared and NMR spectroscopy. The initially formed mixture of intermediates (360) and (361) isomerized smoothly to the linear product. The intermediate β-lactam (360) was converted to the linear product via (361). The cyclic intermediates appear to be formed stereospecifically, and the observed rate enhancement with increasing solvent polarity suggests polar transition states for the formation of both cyclic intermediates and the linear products (see Scheme 62).

Scheme 62

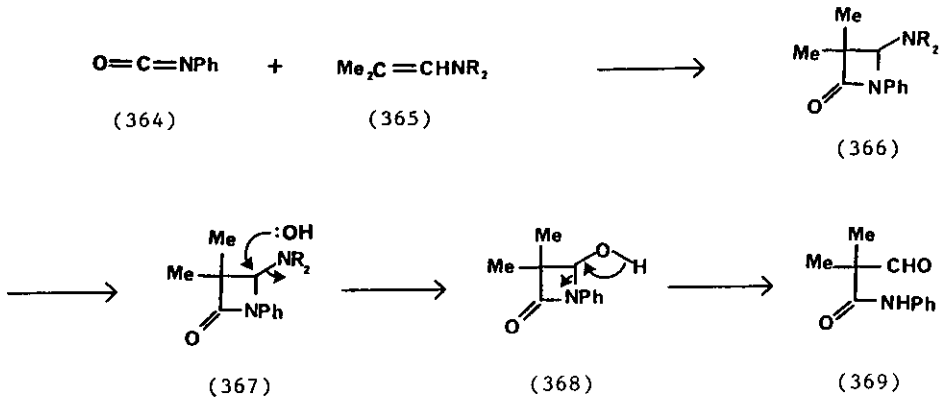


Two groups of workers[78,79] published simultaneously a synthesis of β-lactams of the type (366) in which phenyl isocyanate (364) is allowed to add to an enamine (365) without a β-hydrogen. The 4-amino-2-azetidinones (366) so obtained were very sensitive to moisture and were hydrolyzed to an amidoaldehyde (369) as shown in Scheme 63.

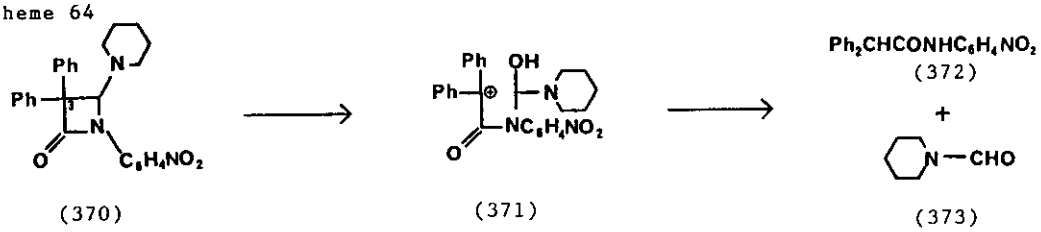
Bose and Kugajevsky[80] have shown (see Scheme 64) that 3,3-diphenyl-4-amino-2-azetidinone (370) also undergo facile decomposition in the presence of traces of moisture to give substituted amides (372). These authors have suggested that the formation of the amides (372) proceeds via the formation of a carbocation (371) at C-3 stabilized by two phenyl groups.

The rearrangement of a 4,4-dichloro-N-methyl-2-azetidinone (376), obtained from the reaction of diphenylketene (374) and N,N-dimethyl dichloromethyleneiminium chloride (375) has been studied[81] under different conditions. The results are summarized in Scheme 65. The reaction of (376) with phenyl hydrazine produced the mesoionic triazole (379) via a C-2-C-3 bond cleavage of the β-lactam. Alkaline hydrolysis resulted in the amide (378).

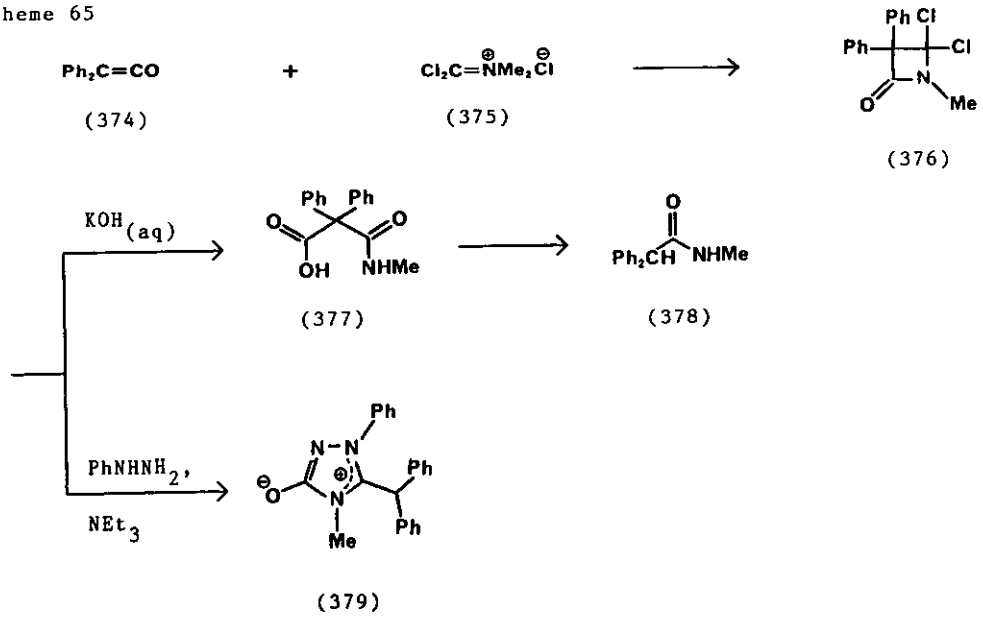
Scheme 63



Scheme 64



Scheme 65



D. CONCLUSIONS

β-Lactams, because of their high chemical reactivity and their propensity for undergoing molecular rearrangement, can serve as versatile synthons for the preparation of medium sized heterocycles with one or more heteroatoms in the ring. The rearrangement of these β-lactams in turn can provide access to polyheteroatom ring systems not readily prepared by other methods. Many of the heterocycles obtained from β-lactams are of interest to synthetic and medicinal chemists. A large variety of natural products such as sugars, alkaloids, oligopeptides, etc., are also accessible through appropriately substituted, optically active β-lactams.

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