SYNTHESIS OF CARBAPENEM ANTIBIOTICS

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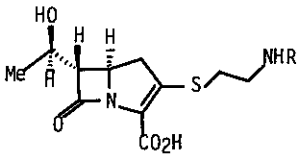
Abstract——— A family of β-lactam antibiotics, having the 1-carbapen-2-em ring system, represented by thienamycin, possesses potent and broad antibiotic activities. In this review, total syntheses and approaches of the antibiotics are summarized according to the manner for the formation of the bicyclic ring system.

Recently, intense interest has been focused on novel 1-carbapenem antibiotics[1-24], listed in Scheme 1, which were isolated from several strains of Streptomyces and possess high antibacterial potency and a wide antibacterial spectrum. Early works about isolation, structure determination, total synthesis, microbiological activity and so on were reviewed by Cooper[25]. However a number of total syntheses and approaches have been published since then and the elaboration of the method for the construction of this unique ring system is still a special challenge. Therefore we would like to summarize the synthetic studies appeared so far on journals according to the formation manner of the carbapenem and the carbapenam.[26,27]

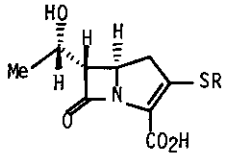
1. Ring Contraction of Ring A

The first synthesis of the carbapenam ring system was carried out by photolytic Wolff rearrangement of the diazopyrrolidine-dione (20) in 1973[28]. The high lability of this bicyclic system was pointed out at that time. The key intermediate (20) was prepared as follows. The amine (17) was coupled to tert.-butyl hydrogen malonate with dicyclohexylcarbodiimide and the product (18) was cyclized with sodium hydride in benzene. Removal of tert.-butoxycarbonyl group by heating in toluene, followed by diazo-exchange of the resulting pyrrolidine (19) gave the desired diazo-compound (20). When the photolysis was conducted at -70°C in the presence of one equivalent of β-methylphenethyl carbazate, the carbapenam (21) was obtained as a very unstable material.



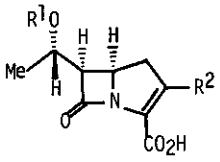
(1) R=H
thienamycin[1,2]

(2) R=Ac
acetylthienamycin[3]



(3) R=CH_2CH_2NHAc
epithienamycin C,[4,5] MM22381[6-8]

(4) R=CH=CHNHAc
epithienamycin D,[4,5] MM22383[6-8]



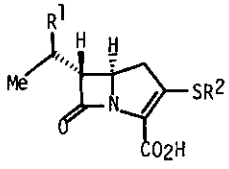
(5) R^1=H, R^2=SCH_2CH_2NHAc
epithienamycin A,[4,5] MM22380[6-8]

(6) R^1=H, R^2=SCH=CHNHAc
epithienamycin B,[4,5] MM22382[6-8]

(7) R^1=SO_3H, R^2=SCH=CHNHAc
epithienamycin E,[4,5] MM139028-11

(8) R^1=SO_3H, R^2=SCH_2CH_2NHAc
epithienamycin F,[4,5] MM17880[8-10,12]

(9) R^1=SO_3H, R^2=$\overset{O}{\uparrow}$SCH=CHNHAc
MM4550[8-11], MC696-SY2-A[13]

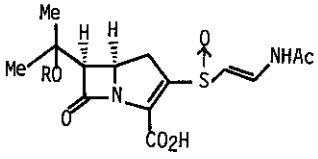


(10) R^1=H, R^2=CH_2CH_2NHAc
PS-5[14-18]

(11) R^1=H, R^2=$CH_2CH_2NH_2$
NS-5[3]

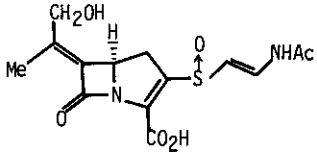
(12) R^1=Me, R^2=CH=CHNHAc
PS-6[19]

(13) R^1=H, R^2=CH=CHNHAc
PS-7[19]



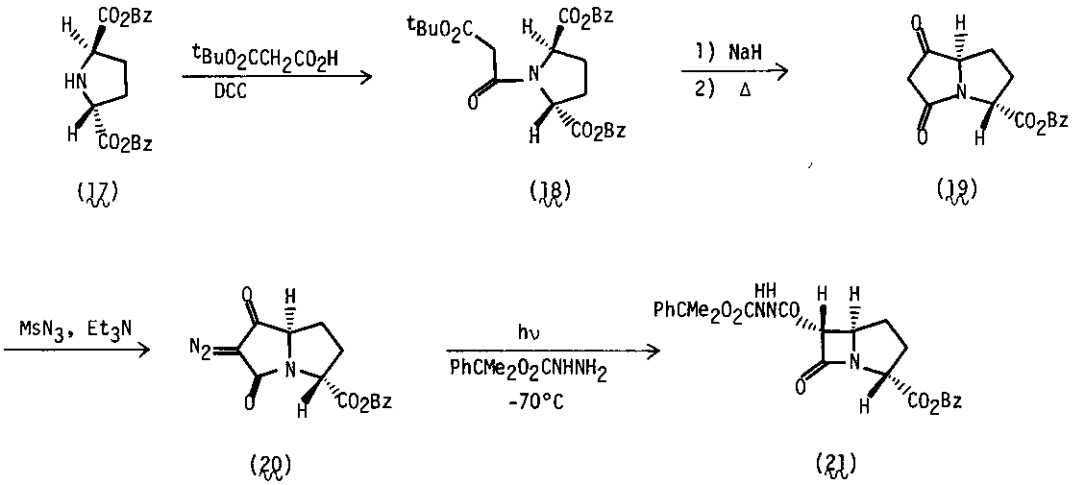
(14) R=H
carpetimycin A,[20,21] C-19393H_2[22,23]

(15) R=SO_3H
carpetimycin B,[20,21] C-19393S_2[22,23]



(16)
asparenomycin A[24]

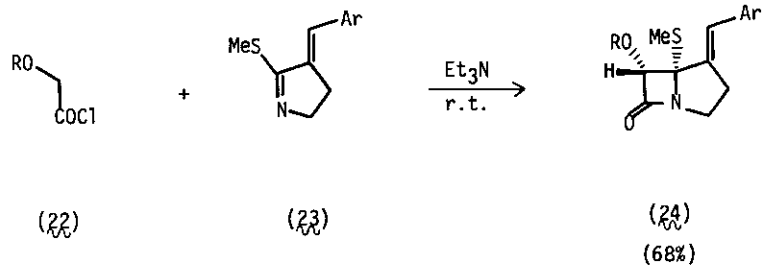
Scheme 1



Scheme 2

2. Concurrent N_4-C_7 and C_5-C_6 Bonds Formation

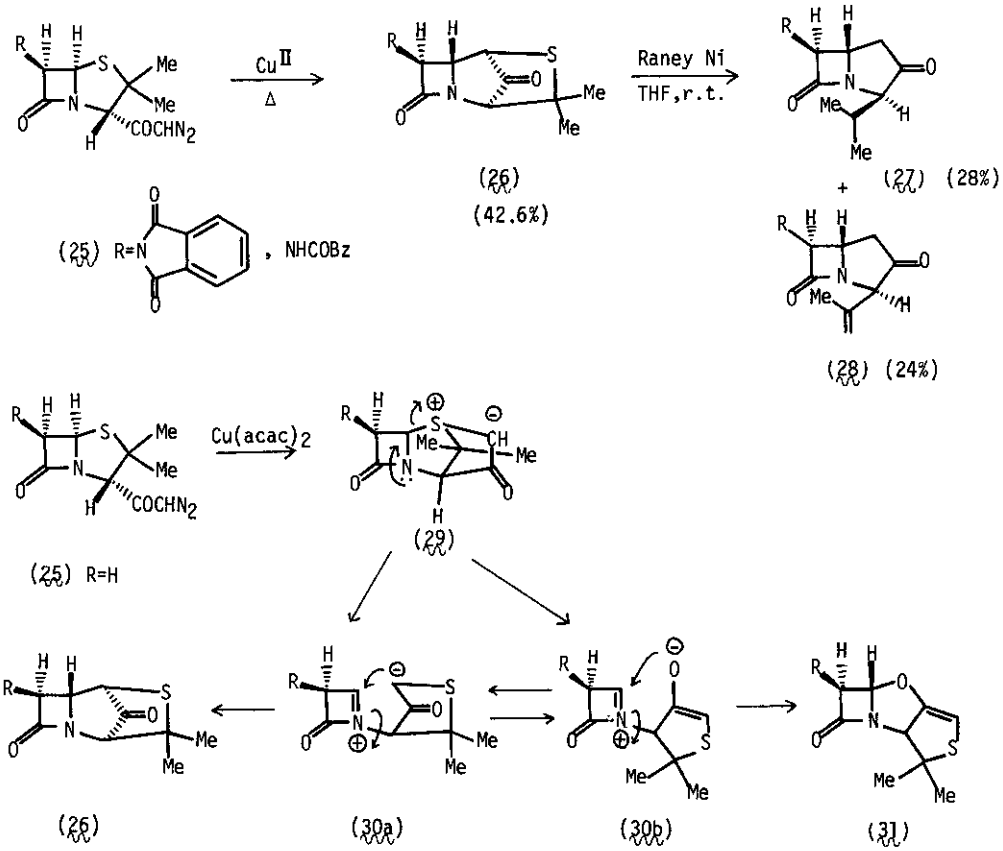
Cycloaddition of imines and ketenes is one of versatile methods for the synthesis of β-lactams[29]. Bose and coworkers prepared the 5-methylthiocarbapenams (24) by condensation of cyclic imines (23) and acid chlorides (22) in the presence of triethylamine[30]. The structure of the product (24) was determined by X-ray analysis. Further approach to the natural antibiotics has not been reported.



Scheme 3

3. C_1-C_5 Bond Formation

Copper (II) catalyzed decomposition of penicillin-derived diazoketones (25) in aprotic solvents resulted in the formation of tricyclic ketones (26) in moderate yields. Desulfurization using Raney nickel provided a mixture of (27) and (28)[31]. This conversion found by Ernest attracted attention of several other groups.[32-34] On the reaction of penicillanic acid diazoketone (25 ; R=H) the tricyclic oxapenam (31) was gained as a minor product together with (26). The proposed mechanism is that initial formation of the S-ylide (29) by intramolecular addition of the acylcarbene to the sulfur atom and successive cleavage of the C-S bond gave the intermediates (30a and 30b) whose ring closure led the carbapenams (26) and the oxapenam (31), respectively. The above reaction was further applied to monocyclic β-lactams but satisfactory results were not obtained.[33,34]

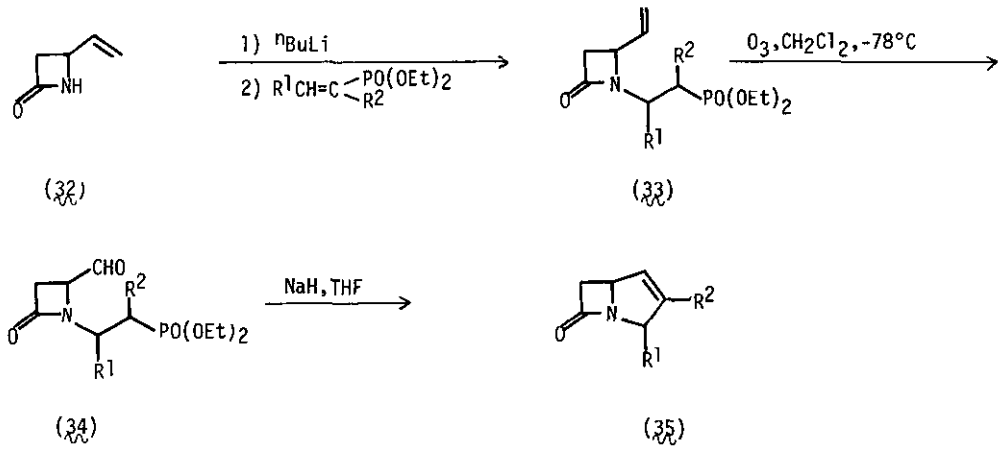


Scheme 4

4. C_1-C_2 Bond Formation

4 -1. By Wittig Reaction

By the ring closure between C_1 and C_2 positions, the carbapen-1-em ring system was constructed by two methods; the intramolecular Wittig type reaction and the aldol condensation. Canadian workers prepared the intermediate (34) for Horner-Wittig reaction, by the Michael addition of the lithium salt of 4-vinylazetidin-2-one (32) to several phosphonates followed by ozonolysis of the adduct (33). Subsequent treatment of the resulting aldehyde (34) with sodium hydride yielded the bicyclic compounds (35).[35]

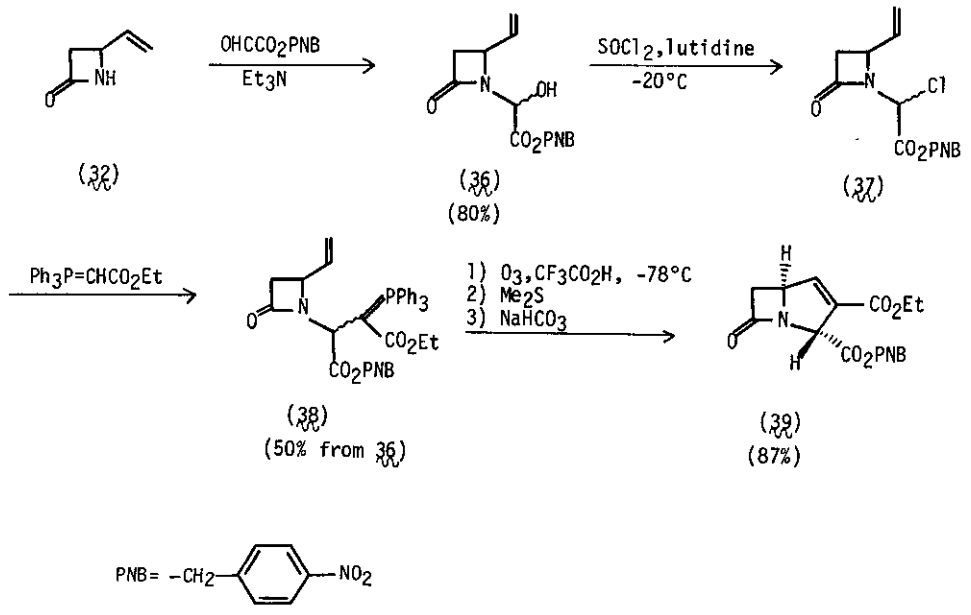


(32) (33) (34) (35)

		overall yield
(a)	R^1=H, R^2=CO_2Et	(25%)
(b)	R^1=H, R^2=$CO_2{}^tBu$	(18%)
(c)	R^1=Ph, R^2=CO_2Et	(22%)
(d)	R^1=Ph, R^2=S(O)Me	(25%)
(f)	R^1=Ph, R^2=SO_2Me	(30%)

Scheme 5

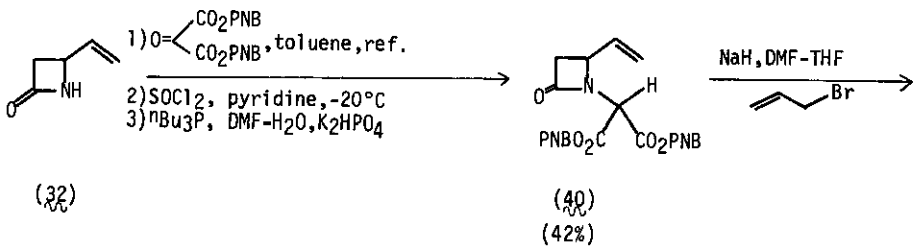
A similar strategy was independently investigated by Sharma and Stoodley[36]. Namely, condensation of 4-vinylazetidin-2-one (32) with the glyoxalate in the presence of triethylamine gave the epimeric alcohols (36), which were converted into the chloride (37). Treatment of (37) with two equivalents of ethoxycarbonyl-triphenylphosphorane[37] in ethyl acetate produced the phosphorane (38). Ozonolysis in the presence of trifluoroacetic acid, reduction of the ozonide and neutralization afforded the carbapen-1-em (39) in a high yield. However no isomerization to the carbapen-2-em by base treatment was observed.

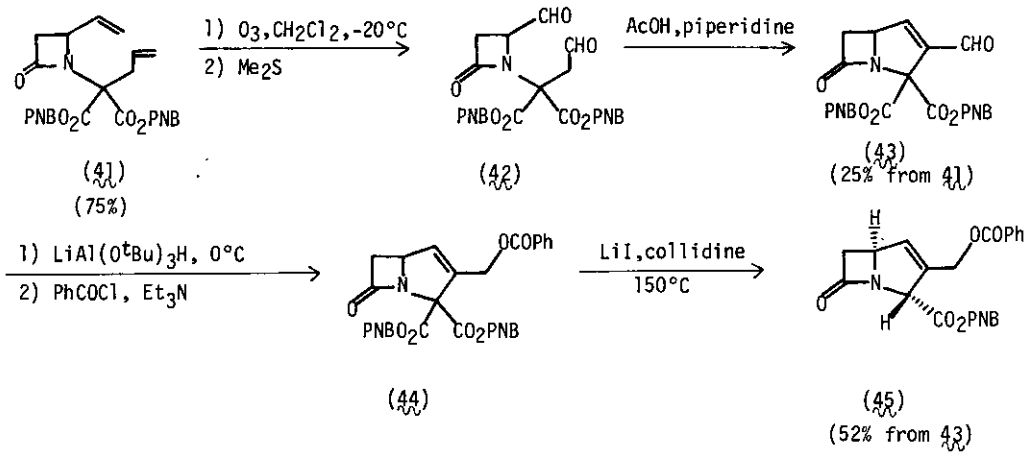


Scheme 6

4 -2. By Aldol Condensation

4-Vinylazetidin-2-one (32) was again used as the starting material for the aldol condensation[38]. According to the Merck method,[39-42] the bis-(p-nitrobenzyl) malonate derivative (40) was prepared in 3 steps from (32). After introduction of the allyl group, ozonolysis of the di-olefinic compound (41), followed by dimethyl sulfide treatment gave the labile dialdehyde (42), which was successively treated with acetic acid and piperidine.[43] Careful hydride reduction of the aldol condensation product (43) followed by benzoylation afforded (44), which was then decarboxylated to the mono-ester (45). The X-ray analysis of (45) revealed that the carboxylate group at the C_3 position and the hydrogen at the C_5 position are cis each ether. The isomerization of the double bond to the carbapen-2-em was also unsuccessful.





(41) (75%)

(42)

(43) (25% from 41)

(44)

(45) (52% from 43)

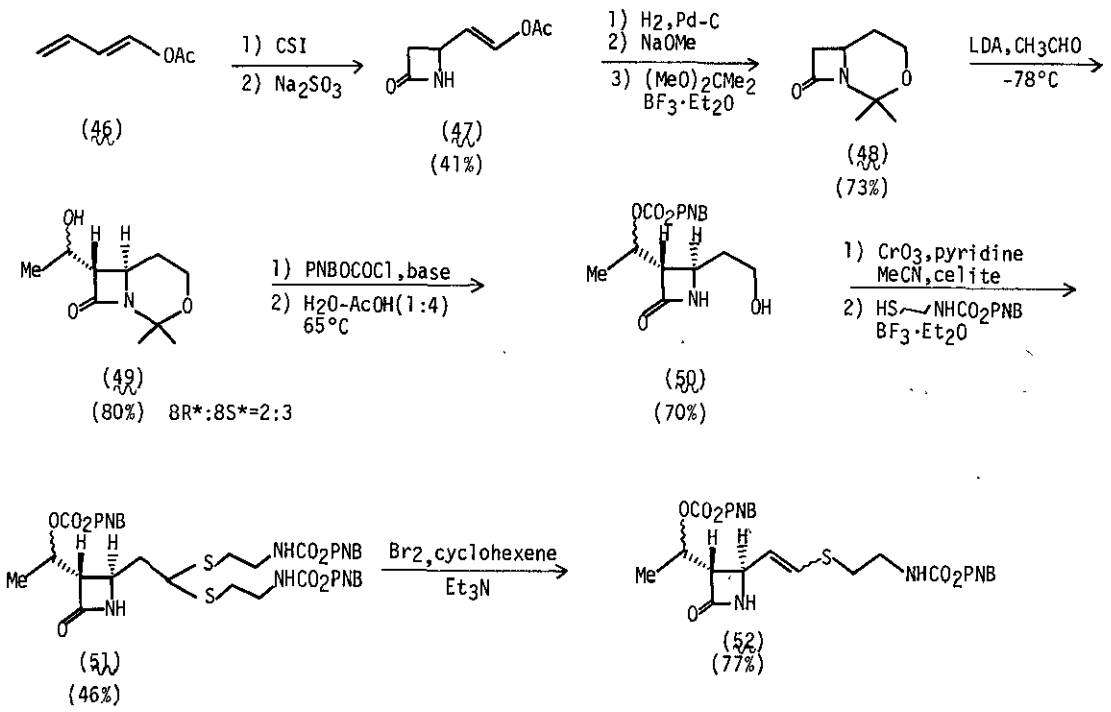
Scheme 7

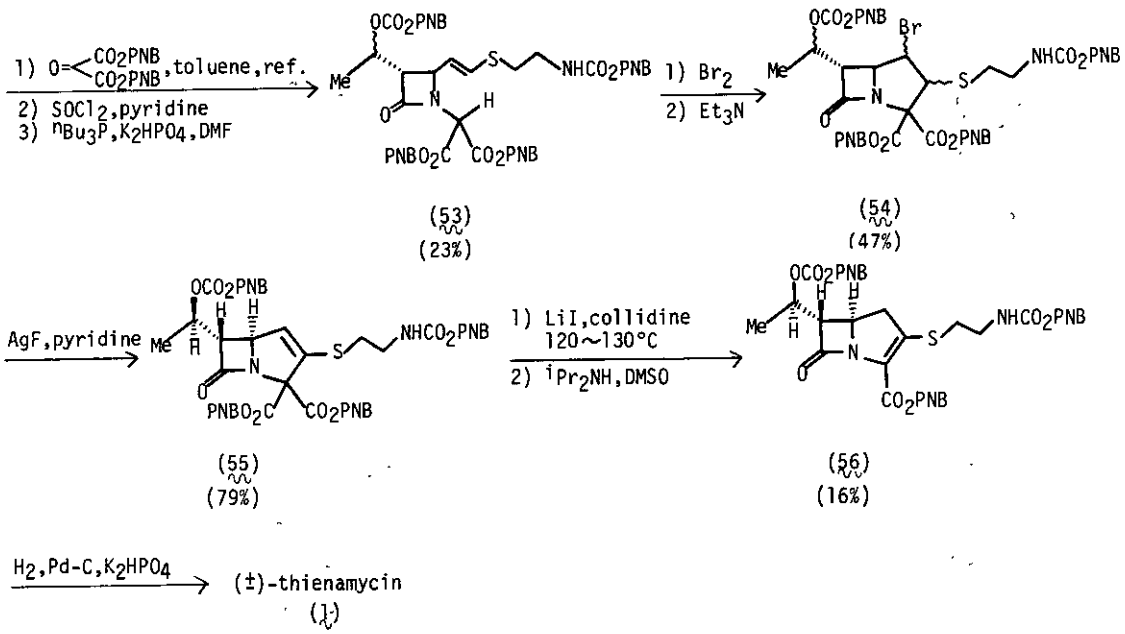
5. C_2-C_3 Bond Formation

5-1. By Substitution Reaction

The first total synthesis of thienamycin (1) was accomplished by ring closure between C_2 and C_3 positions.[39-42] The Merck synthesis is constituted of three major synthetic objectives: (1) preparation of an azetidinone suitably substituted at the C-4 position for subsequent elaboration of the second ring; (2) introduction of the hydroxyethyl side chain at the C-3 position; (3) elaboration of the resultant azetidinone to the properly functionalized carbapen-2-em. The starting β-lactam (47) was prepared by the [2 + 2] cycloaddition by chlorosulfonyl isocyanate (CSI) to 1-acetoxybutadiene (46) followed by reductive hydrolysis. Catalytic hydrogenation of (47), deacetylation and simultaneous blocking of the alcohol and lactam gave the acetonide (48). Hydroxyethylation was achieved by direct aldol reaction but four possible stereoisomers formed. The two trans-substituted azetidinones (49), obtained as major products in a ratio of 2 : 3, were not separated at this stage. The carbinol group was protected by the action with p-nitrobenzyl chloroformate and n-butyllithium or 4-(dimethylamino)-pyridine (DMAP). These laboratories found that the p-nitrobenzyl (PNB) group, removable by hydrogenolysis, was a proper protecting group for the synthesis of thienamycin derivatives.

After hydrolysis of the acetonide, the resulting alcohol (50) was oxidized to the aldehyde, which was immediately converted to the thioacetal (51). Successive treatment of (51) with bromine in the presence of cyclohexene and then triethylamine in dimethylformamide produced a mixture of E and Z thioenol ethers (52) in a ratio of 5 : 2. Condensation[44] of the above mixture (52) with bis-(p-nitrobenzyl) ketomalonate in refluxing toluene, followed by chlorination with thionyl chloride and pyridine, and then the reduction with tributyl phosphine in dimethylformamide[45] furnished the malonic acid derivative (53). Cyclization of (53) to the carbapenam (54) was accomplished by successive treatments with bromide, followed by triethylamine in dimethylformamide. After dehydrobromination using silver fluoride and pyridine, the (8R*)- and (8S*)-epimers were separated by chromatography at this stage (55). Decarboxylation of (55) with lithium iodide in collidine, followed by isomerization of the double bond with diisopropylamine gave the carbapen-2-em (56) together with the starting material. Hydrogenolysis of (56) followed by purification using a XAD-2 column furnished (±)-thienamycin (1).

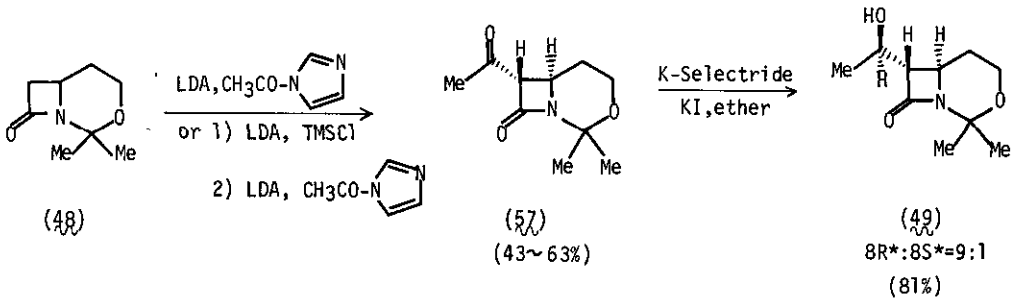




Scheme 8

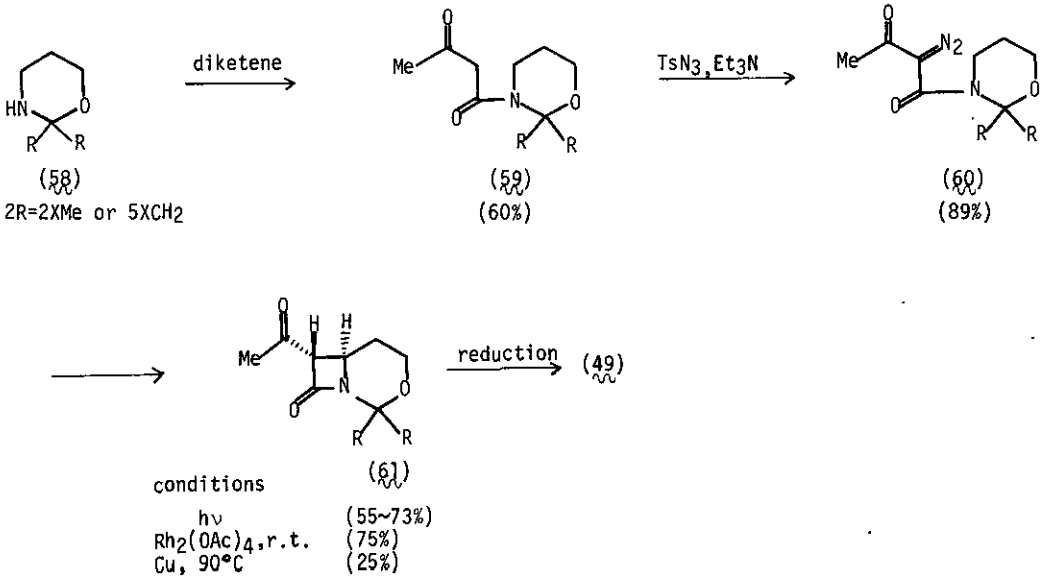
Non-stereoselectivity on the production of the hydroxyethyl compound (49) is one of defects in the above total synthesis. This problem was lately overcome by a stereoselective reduction of the corresponding ketone (57), prepared by oxidation of the alcohol (49) or the direct acylation of (48). Reduction of (57) with potassium tri-sec.-butylborohydride (K-Selectride) in the presence of potassium iodide in ether produced exclusively the (8R*)-carbinol (49); the ratio of 8R* : 8s* was about 9 : 1. It was postulated that the hydride attack on the least hindered face of a complex formed between the potassium metal and the carbonyl group caused the stereoselective formation of (49).[46]

For the purpose of assignment of the relative configuration at C_5, C_6 and C_8 positions, nmr spectroscopy was carefully investigated.[40,46] The trans- and cis-isomers are easily differentiated by the coupling constant due to the protons on the β-lactam ring; the trans-isomers have about J = 1.5 Hz, while the cis-ones show about J = 5 Hz. The hydrogen at the C_6 position (or the C_3 position of β-lactams) of the trans-(8R*)-isomers generally resonates at a slight higher field than that of the trans-(8S*)-ones with few exceptions.



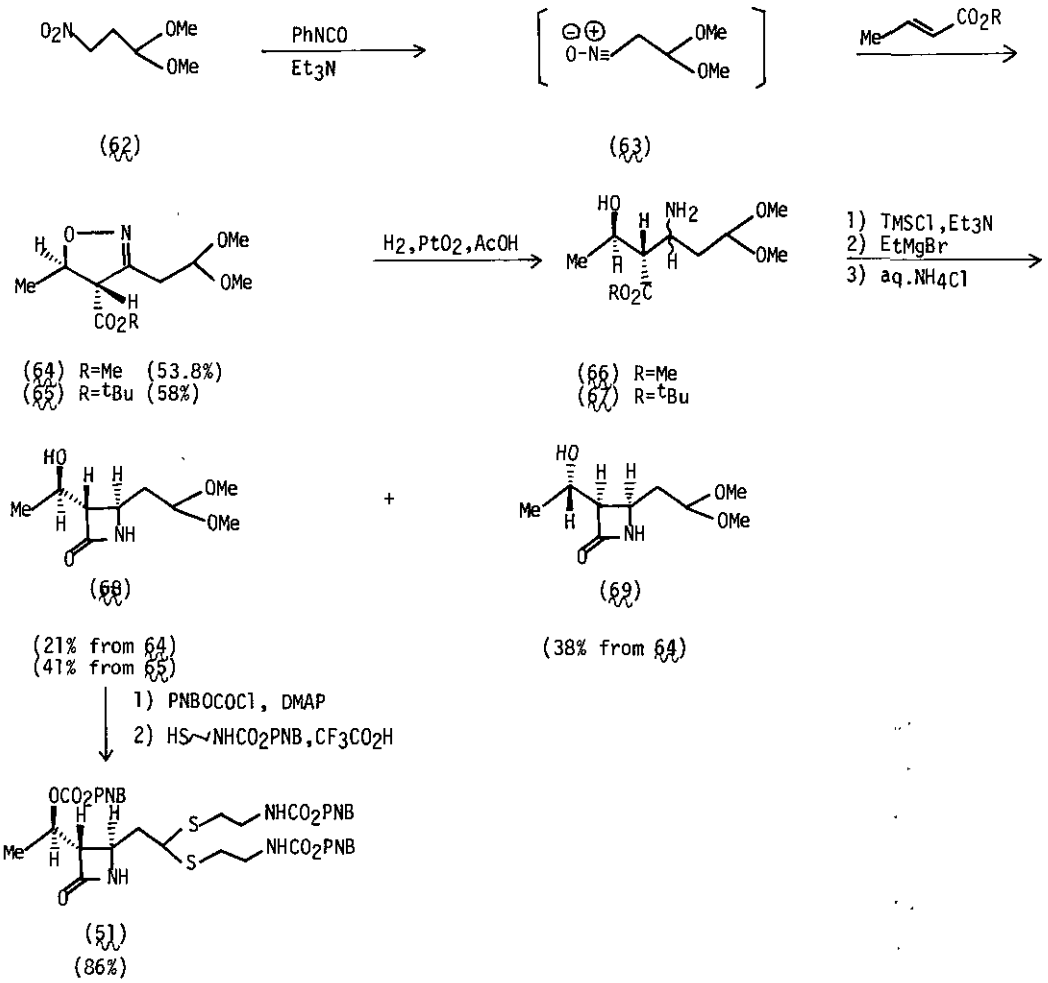
Scheme 9

Monocyclic intermediates in the above total synthesis were prepared by the following three different routes, which constituted formal total syntheses of racemic thienamycin. Beecham group started from the tetrahydro-1,3-oxazines (58), readily available from 3-aminopropan-1-ol and acetone or cyclohexanone.[47] Reaction of (58) with diketene, followed by diazo exchange of the resultant acetoacetamides (59) gave the diazo compounds (60). Cyclization was carried out by photolysis or metal catalysed decomposition as shown in Scheme 10.[47] Reduction of acetyl group with K-Selectride selectively produced the (8R*)-alcohol (49).[48]



Scheme 10

The hydroxyethyl group was incorporated prior to construction of the β-lactam ring in the following two syntheses. Our strategy was a stereoselective synthesis of thienamycin *via* a *trans*-isoxazoline-ester in which the stereochemical relationship between the C_6 and C_8 positions has already been set up.[49] The isoxazoline derivatives (64 and 65) were prepared by 1,3-dipolar cycloaddition of the nitrile oxide (63),[50] derived from 3-nitropropanal dimethyl acetal (62) and crotonic esters. By catalytic



(62) (63)

(64) R=Me (53.8%)
(65) R=^{t}Bu (58%)

(66) R=Me
(67) R=^{t}Bu

(68) (21% from 64) (41% from 65)

(69) (38% from 64)

(51) (86%)

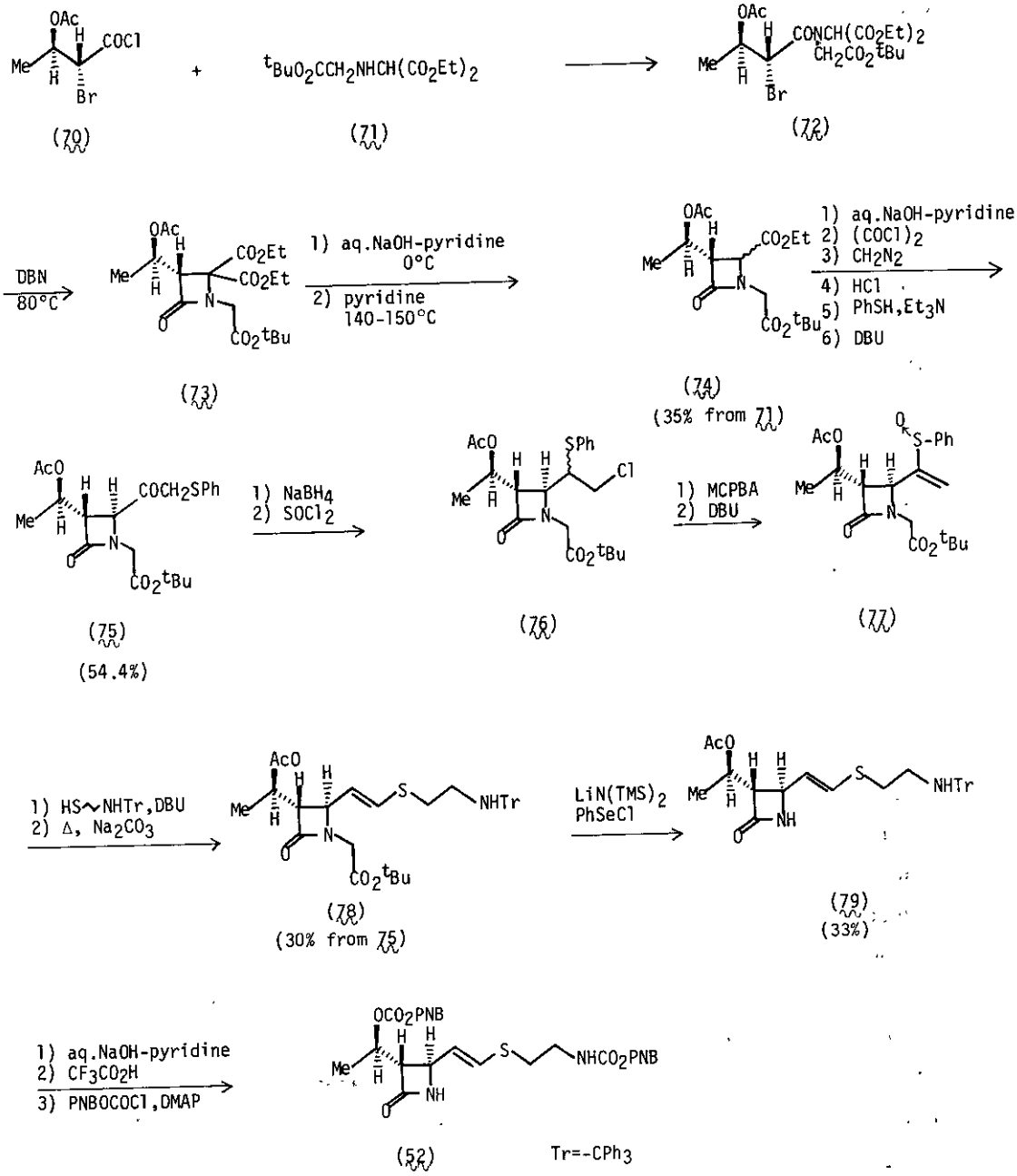
Scheme 11

hydrogenation over platinium oxide in acetic acid, the isoxazolines were quantitatively reduced to amino-esters (66 and 67). If hydride attacked from the reverse side of the ester group, the amino-ester formed would have the same relative configuration as that of thienamycin. Therefore the desired amino-ester having the correct stereo-

chemistry was more selectively produced from the more hindered ester (65). After many investigations, the conversion of the epimeric mixtures into the β-lactam (68) was accomplished by the succesive treatments; trimethylsilylation, cyclization with Grignard reagent and deblocking.[51] Selective cyclization was observed in the case of tert.-butyl ester and only the trans-azetidinone (68) was obtained. On the other hand, the cis-azetidinone (69) having the same relative configuration as those of epithienamycins A (5) and B (6) was gained as a major product from the methyl ester (64). N,O-Bissilylated amino-esters were used in the case of the cyclization of the methyl esters, whereas O-mono-protected tert.-butyl ester was precursor for the β-lactam formation. When the cyclization of the corresponding β-amino acid was carried out with dicyclohexylcarbodiimide, significant epimerization was observed.[49] After protection of the carbinol group of (68), the resultant acetal was treated with the protected cysteamine in trifluoroacetic acid[52] to furnish the thioacetal (51), the intermediate to (±)-thienamycin.

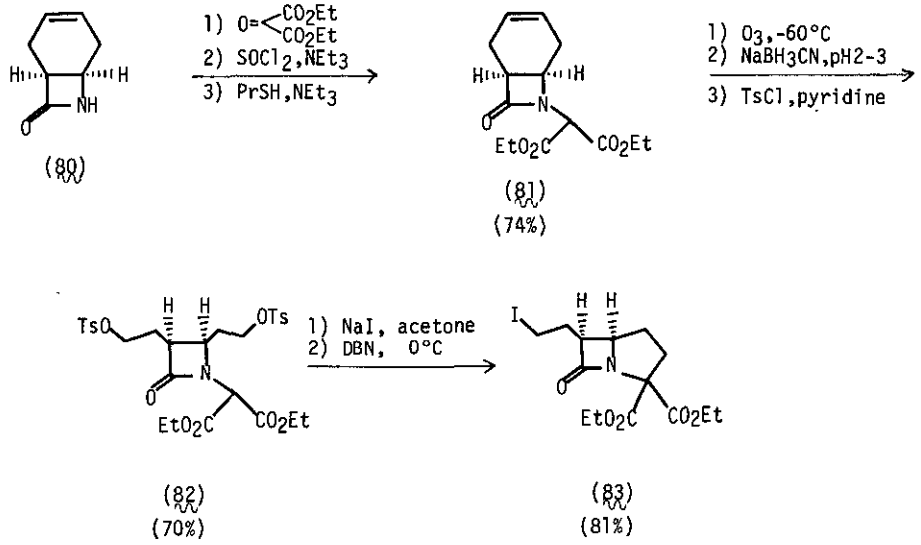
The above cis-azetidinone (69) was selectively transformed into the trans-compound (68) by the following sequences; selective N-protection with tert.-butyldimethylsilyl (TBS) group, oxidation, reduction of the resulting trans-ketone with K-Selectride, and deprotection.[53] Furthermore, the asymmetric synthesis of the azetidinones (68 and 69) was investigated through isoxazoline derivatives prepared by 1,3-dipolar cycloaddition using an optically active crotonate. It was proved that (4R)-β-lactams having an alkyl group at the C_4 position showed a negative Cotton effect around 212 - 214 nm.[54]

Sankyo group synthesized in stereoselective manner the thioenol ether (52) after long process.[55] Namely, the acid chloride (70) derived from the corresponding (±)-erythro-acid was reacted with the lithium salt of amine (71) to give the amide (72), which was cyclized with DBN to the azetidinone (73) via a SN_2 type substitution. After conversion of (73) into the phenylthiomethyl ketone, the resulting isomeric mixture was epimerized to the thermodynamically stable trans-isomer (75) with DBU. Reduction of (75) with sodium borohydride and chlorination gave the migrated sulfide (76), which was oxidized to a sulfoxide and then subjected to elimination of hydrogen chloride. Michael addition of N-tritylcysteamine to the olefinic sulfoxide (77), followed by heating in the presence of sodium carbonate gave the vinyl thioether (78). Phenylselenylation produced the unexpected secondary β-lactam (79), which was converted into (52) in three steps.


OAc
H
COCl
Me
H
Br
(70)
+
$^tBuO_2CCH_2NHCH(CO_2Et)_2$
(71)
CONCH(CO2Et)2
CH2CO2tBu
(72)
DBN
80°C
CO2Et
CO2Et
CO2tBu
(73)
1) aq.NaOH-pyridine
0°C
2) pyridine
140-150°C
1) aq.NaOH-pyridine
2) (COCl)2
3) CH2N2
4) HCl
5) PhSH,Et3N
6) DBU
(74)
(35% from 71)
AcO
COCH2SPh
(75)
(54.4%)
1) NaBH4
2) SOCl2
SPh
Cl
(76)
1) MCPBA
2) DBU
O
S-Ph
(77)
1) HS~NHTr,DBU
2) Δ, Na2CO3
S
NHTr
(78)
(30% from 75)
LiN(TMS)2
PhSeCl
NH
(79)
(33%)
1) aq.NaOH-pyridine
2) CF3CO2H
3) PNBOCOCl,DMAP
OCO2PNB
NHCO2PNB
(52)
Tr=-CPh3

Scheme 12

Recently, Hoechst group also studied the synthesis of the bicyclic system by intramolecular substitution.[56] The β-lactam (80)[57] was transformed into the malonic derivative (81), which was further converted into the bis-tosylate (82). After iodination, the resulting bis-iodide was cyclized with DBN to the cis-compound (83).



(80)

(81)
(74%)

(82)
(70%)

(83)
(81%)

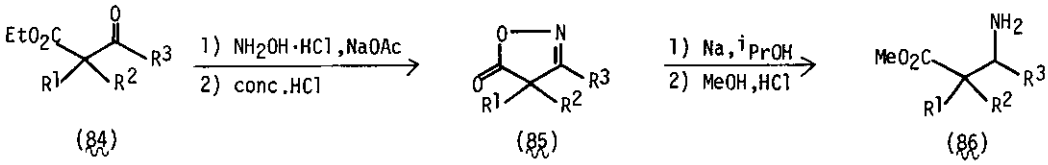
Scheme 13

5-2. By Aldol Condensation

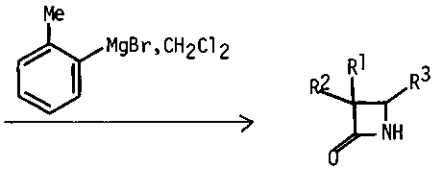
Shibuya and Kubota prepared 2-azetidinones having an olefinic side chain at the C_4 position via isoxazolones. Namely reaction of β-keto esters (84) with hydroxylamine, followed by reduction of the resulting isoxazolones (85) with sodium in isopropyl alcohol and esterification gave β-amino esters (86) in good yield. The β-lactam formation was carried out by reaction with o-tolylmagnesium bromide in dichloromethane.[58]

Aldol condensation was applied for an unenolizable aldehyde (88) derived from one of the above products (87d). Condensation of (87d) with bromoacetate followed by ozonolysis and reductive treatment gave the aldehyde (88). Reaction of (88) with lithium hexamethyldisilazide followed by quenching with p-toluenesulfonic acid, chlorotrimethylsilane or methanesufonyl chloride provided the carbapenams (89a∿c) respectively. Stereochemistry, determined by the nmr nuclear overhauser effect, is explicable in terms of a chelated transition state during the aldol condensation.

Elimination of the mesylate (89c) with 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.1]-1-decene gave the stable carbapenem (90).[59]



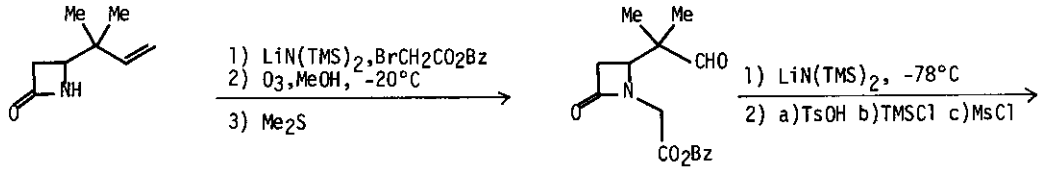
(84) (85) (86)



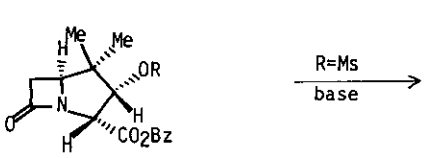
(87)

(yield from 86)

(a) $R^1=R^2=H$, $R^3=CH_2CH_2CH=CH_2$ (33%)
(b) $R^1=H$, $R^2=CH_2CH_3$, $R^3=CH_2CH_2CH=CH_2$ (86%;cis:trans=1:1)
(c) $R^1=R^2=CH_3$, $R^3=CH_2CH_2CH=CH_2$ (95%)
(d) $R^1=R^2=H$, $R^3=C(CH_3)_2CH=CH_2$ (44%)



(87d) (88)



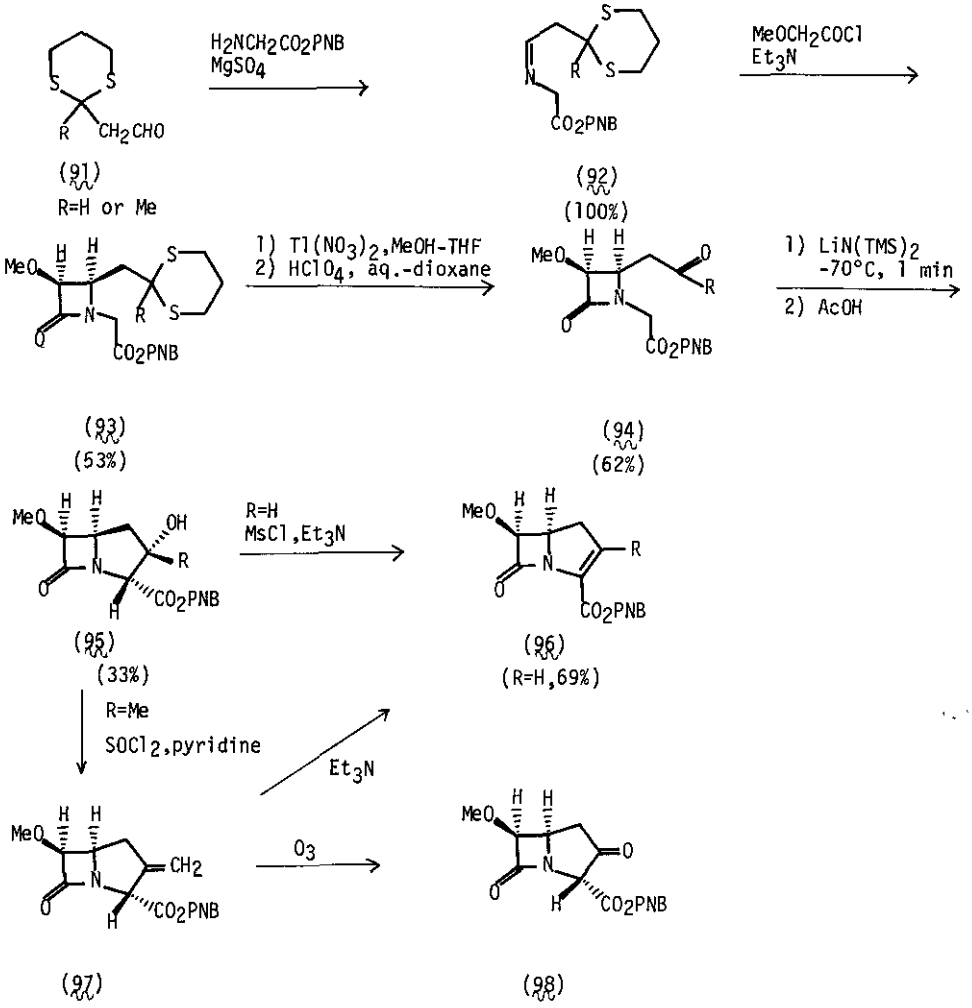
(89) (90)

(a) R=H (52%)
(b) R=TMS (78%)
(c) R=Ms (53%)

(82%)

Scheme 14

Lately, Glaxo group applied the aldol condensation to enolisable oxo-derivatives. The Schiff's bases (92), formed from the aldehydes (91), reacted with methoxyacetyl chloride in the presence of triethylamine to give the cis-azetidinones (93), which was converted into the carbonyl compounds (94). Short treatment of (94) with lithium hexamethyldisilazide at -70°C, followed by quenching with acetic acid provided the carbapenams (95). Dehydration of (95; R=H) via the mesylate gave the carbapenem (96 : R=H). On the other hand, treatment of (95 ; R=Me) with thionyl chloride in pyridine yielded the exo-methylene compound (97), which was isomerized to the carbapenem (96 ; R=Me). Ozonolysis of (97) furnished the 2-oxo-carbapenam (98).[60]

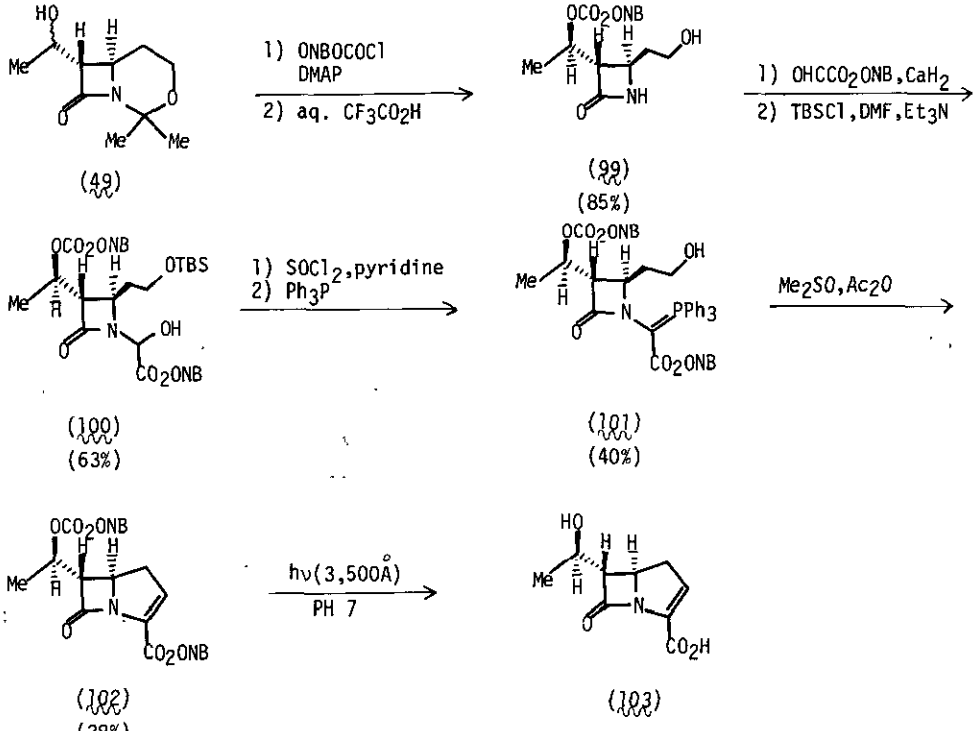


Scheme 15

5-3. By Wittig Reaction

5-3-1. Intramolecular Reaction between Aldehyde and Phosphorane

It has been made clear from results by several workers that cyclization by intramolecular Wittig reaction of the aldehyde group produced the carbapen-2-em derivatives in reasonable yield.[49,61-63] By this methodology, Merck research group synthesized (±)-descysteaminylthienamycin (103), whose dextro-isomer was derived from thienamycin by hydrogenolysis of the corresponding N-phenoxyacetyl derivative.[64] o-Nitrobenzyl group, readily removable by photolysis, was chosen as a protecting group for the synthesis. The β-lactam (49), which had been previously synthesized, was used as the starting material and the carbinol group was protected with o-nitrobenzyl carbonate. The two isomers were separated at this stage. After removal of the acetonide group, condensation of (99) with the glyoxalate, followed by blocking with tert.-butyldimethylsilyl group gave (100). Conversion into an ylide, debrocking and oxidation of the resulting alcohol (101) provided the carbapenem (102) with spontaneous cyclization. The rather low yield was due to formation of methyl thiomethyl ether of (101) during the oxidation step. Photolytic removal of the ester group gave (±)-descysteaminylthienamycin (103).[61]



(49)

(99)
(85%)

(100)
(63%)

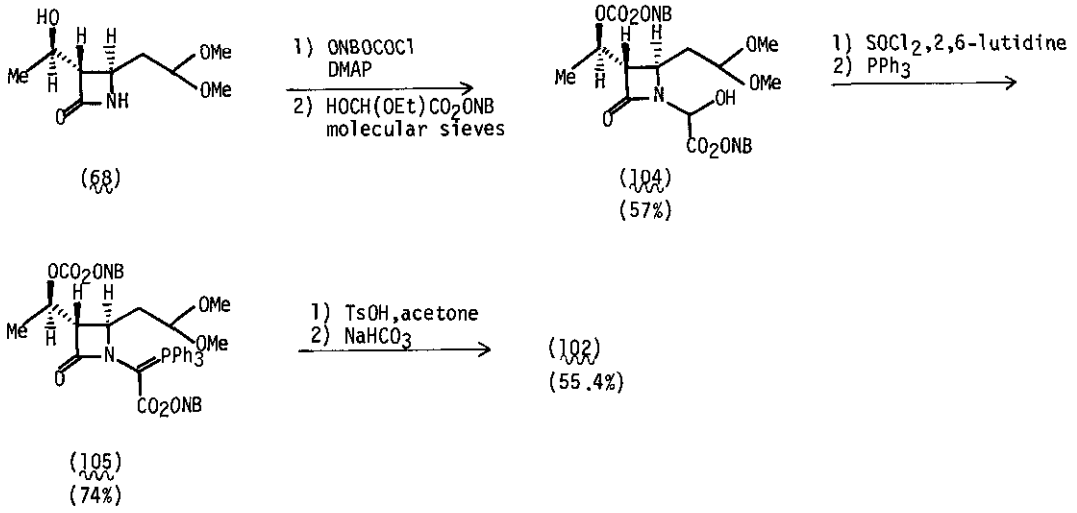
(101)
(40%)

(102)
(28%)

(103)

Scheme 16

Our monocyclic β-lactam (68)[49] having the protected aldehyde group was also converted into (±)-descysteaminylthienamycin. After protection of the carbinol group, the resulting β-lactam was condensed with hemiacetal in the presence of molecular sieves 3A[65] to give (104) as a mixture of epimers. After conversion into the phosphorane (105), deprotection of the acetal group, followed by neutralization with sodium bicarbonate spontaneously caused the intramolecular Wittig reaction to produce the protected (±)-descysteaminylthienamycin (102).[49]



(68)

(104)
(57%)

(105)
(74%)

(102)
(55.4%)

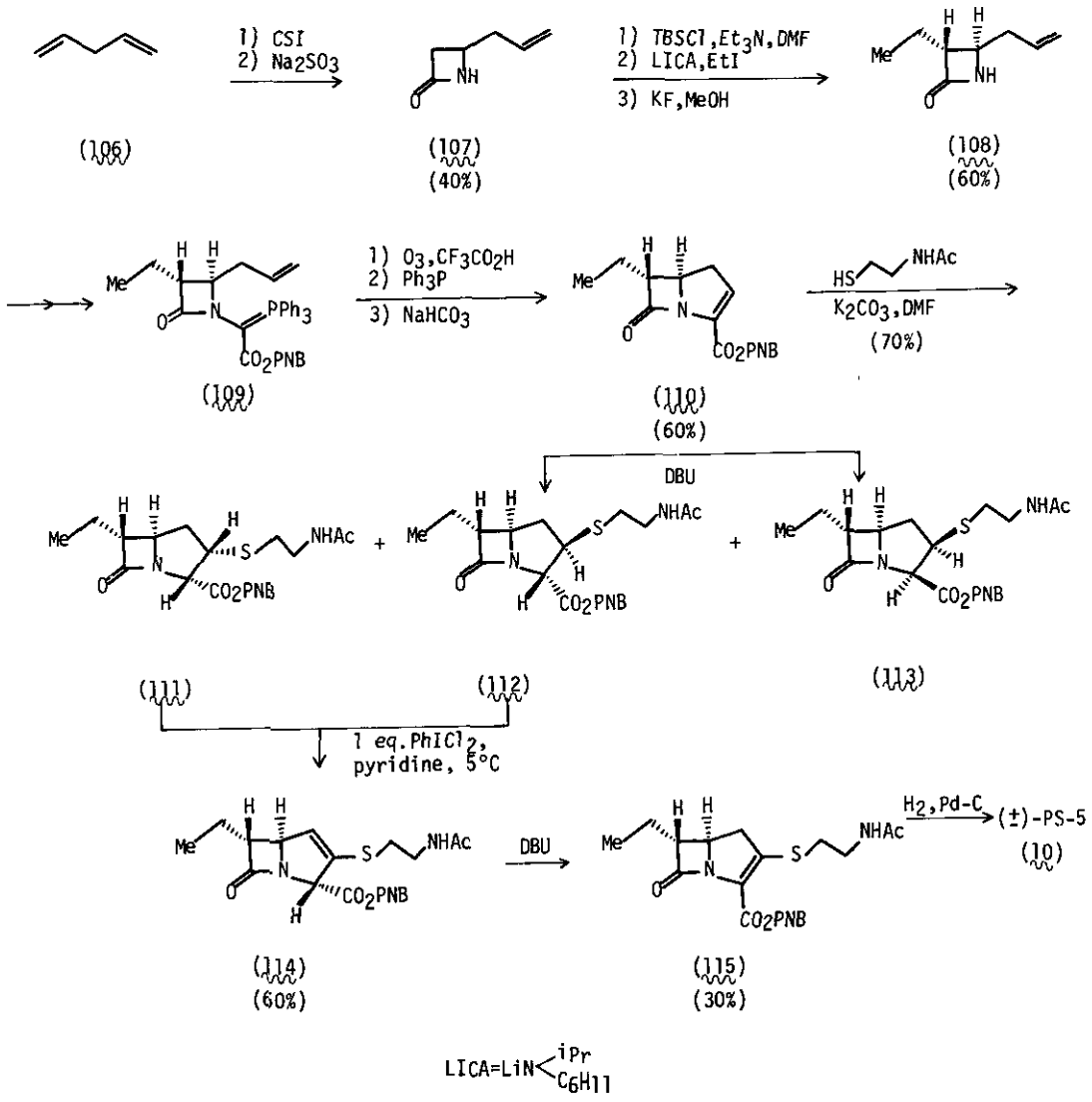
Scheme 17

Beecham group has extensively studied the synthesis of carbapen-2-em derivatives by the intramolecular Wittig reaction[63,67,68] and succeeded in the total synthesis of several natural products by this strategy.[48,69] 4-Allylazetidinone (107) was prepared by interaction of penta-1,4-diene (106) and CSI followed by reduction.[63] After conversion[44] into the ylide (109) via (108), selective oxidation of the terminal double bond in the presence of the phosphorane group was achieved by ozonolysis in the presence of trifluoroacetic acid.[44] Reduction of the ozonide with triphenylphosphine followed by treatment with aqueous sodium bicarbonate resulted in the bicyclic system (110).

Michael addition of N-acetylcysteamine to (110) gave an inseparable mixture of three

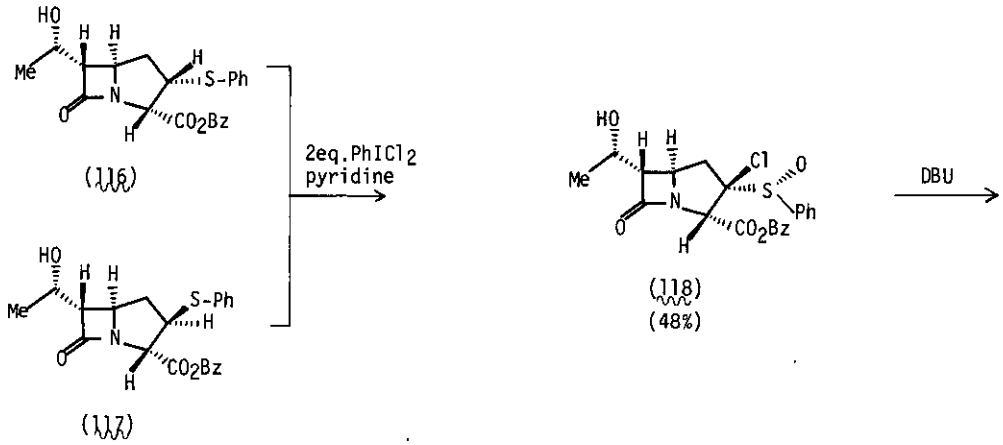
isomers, (111), (112), and (113) in the ratio of 5 : 3 : 2. The thermodynamically less favoured epimer (113) was isomerized to (112) by the action with DBU.

Oxidation of the mixture of (111) and (112) with one equivalent of iodobenzene dichloride in the presence of pyridine gave the carbapen-1-em (114), which was isomerized with DBU to give the carbapen-2-em (115) together with the starting material (114). Deprotection by hydrogenolysis furnished (±)-PS-5 (10).[69]



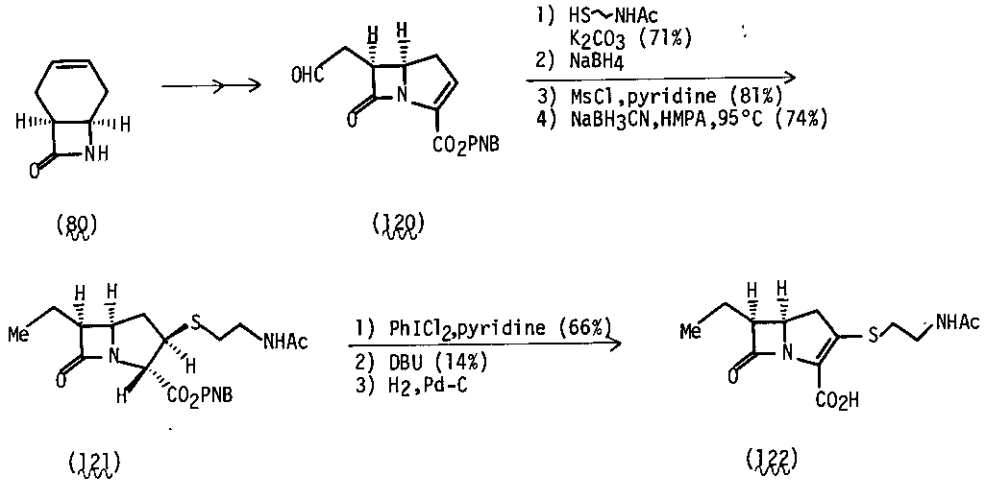
Scheme 18

The ratio of the Michael adducts was varied by the substituent at the C_6 position and a kind of thiols. Treatment of a mixture of (116) and (117) with two equivalents of iodobenzene dichloride gave a single α-chlorosulfoxide (118), whose stereochemistry was established by X-ray analysis. Dehydrochlorination with DBU produced the carbapen-2-em (119).[68]



Scheme 19

By the similar methodology, the cis-substituted epi-PS-5 was synthesized from the β-lactam (80),[57] derived from cyclohexa-1,4-diene and CSI.[69] The Michael addition to carbapenem (120), prepared via the corresponding phosphorane, produced the three stereoisomers, which were subjected, without separation, to reduction of the aldehyde group and mesylation. After separation of the stereoisomers, reduction with sodium cyanoborohydride yielded (121), which was further converted into (±)-epi-PS-5 (122) by the same treatments as above.



(80) (120) (121) (122)

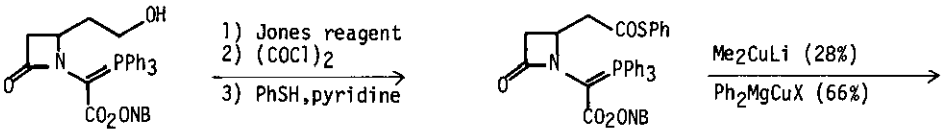
Scheme 20

5-3-2. Intramolecular Reaction between Ketone and Phosphorane

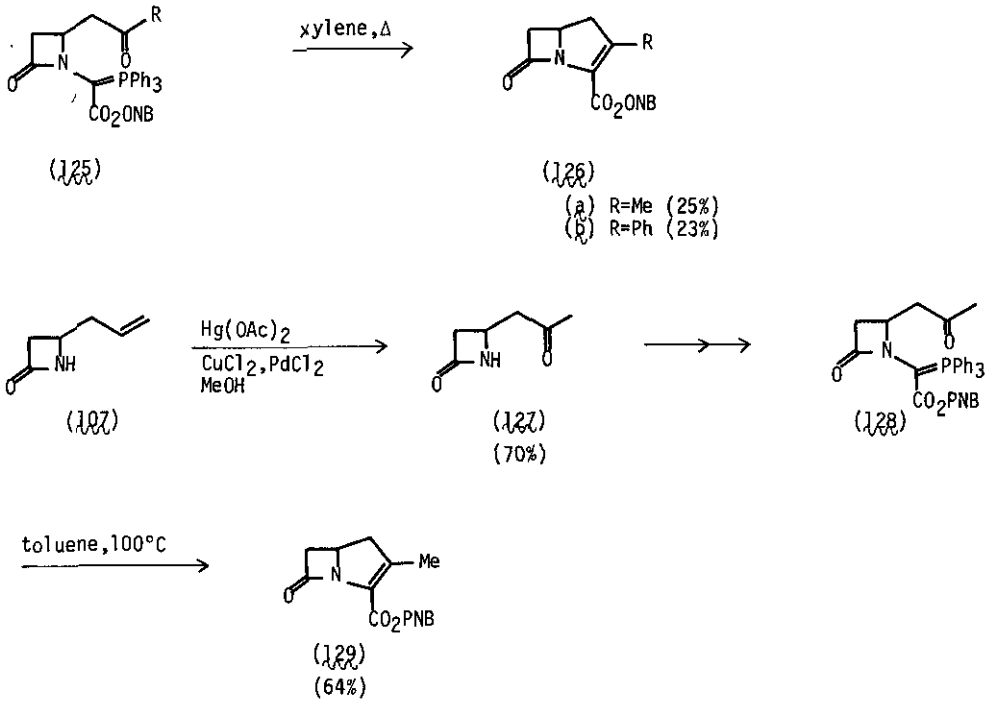
Intramolecular Wittig reaction of ketones, which were prepared by different routes, was investigated by several groups.[63,70,97] Reaction rate of the ketone was slower than that of the aldehyds as expected, and 2-alkyl-and 2-arylcarbapen-2-ems were prepared in moderate yields.

Oxidation of the phosphorane (123) with Jones reagent gave the corresponding acid which was converted into the thioester (124) via the acid chloride. The thioester (124) was a key intermediate which on reaction with a lithium alkyl or aryl cuprate or a magnesium alkyl or aryl cuprate, provided the corresponding alkyl or aryl ketones (125). Cyclization to carbapenems (126) was carried out by heating in xylene.[70] The carboxylic acids of 2-alkyl and aryl substituted derivatives showed good antibacterial activity.

Oxypalladation of the β-lactam (107) previously described yielded the ketone (127), which was converted into the phosphorane (128). Heating (128) in toluene at 100°C resulted in cyclization to the carbapenem (129).[63]



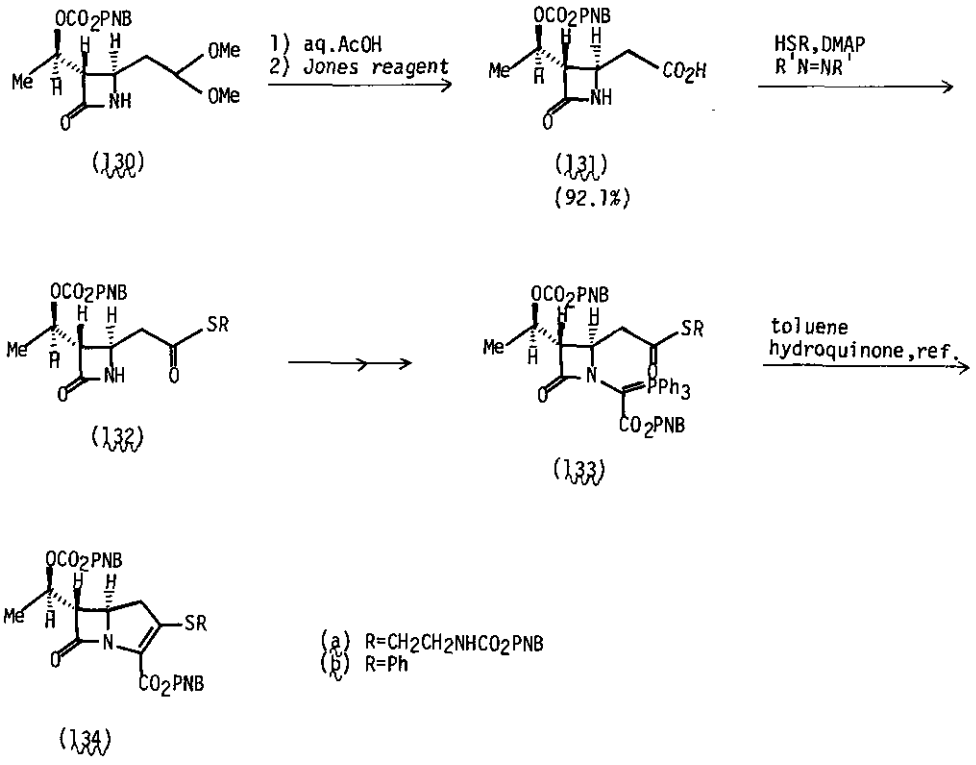
(123) (124) (66%)



Scheme 21

5-3-3. Intramolecular Reaction between Thioester and Phosphorane

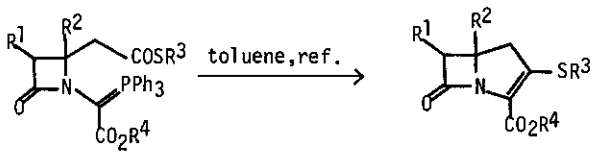
The ease of cyclization is influenced by both the thioester and phosphorane ester. Alkyl thioesters are not so reactive for the cyclization. For example, the phosphorane (133a) did not give a sufficient amount of the protected thienamycin derivative (134a) for purification, while heating phenyl thioester-phosphorane (133b) for 60 hr provided the 2-thiophenylcarbapenem (134b) in 36% yield based on the consumed starting material.[71] The thioesters (132a and b) were prepared by the reaction of the carboxylic acid (131), derived from the previously synthesized β-lactam (68)[49] via (130), with the corresponding thiol in the presence of DMAP and DCC or N,N-diisopropylcarbodiimide.[72]



(130) (131) (92.1%) (132) (133) (134)

Scheme 22

Cyclizations of variable kinds of thioester-phosphoranes were investigated by Beecham group. The results by refluxing in toluene are shown in Table 1. It is made clear from the Table that electron-withdrawing thioester and electron-donating phosphorane ester accelerated the rate of cyclization. Particularly, 2-pyrimidinylthioesters provided the carbapenem derivatives in high yields (entries 13,14 and 16 in Table).[73] Even when the ester function contained the very bulky phthalidyl ester group, the cyclized product was obtained in a moderate yield (entry 15).



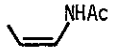
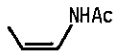
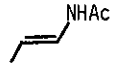
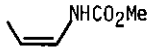
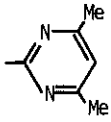
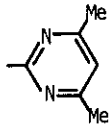
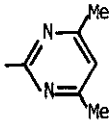
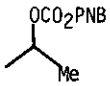
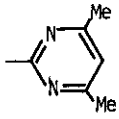
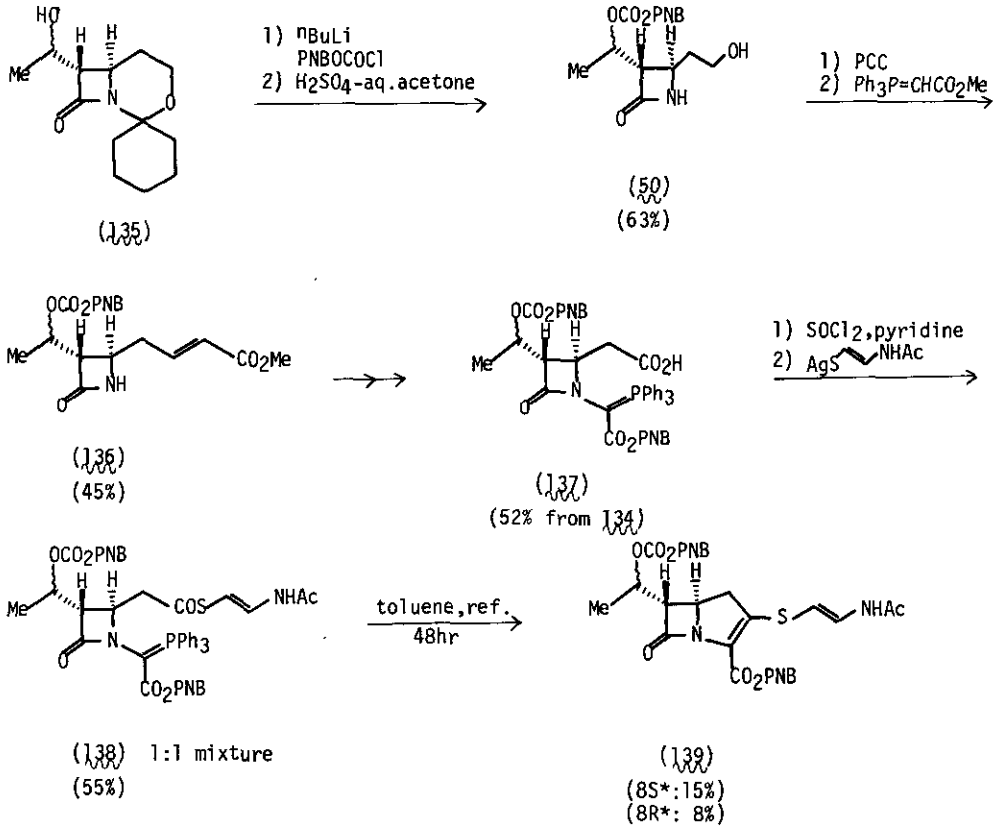
entry	R^1	R^2	R^3	R^4	reaction time	yield (%)	reference
1	H	Me	Ph	PNB	3days	53	66
2	H	H	Ph	PNB	24hr	18	66
3	H	H	Ph	^{t}Bu	6hr	39	66
4	H	Me	p-NO_2Ph	^{t}Bu	5hr	54	66
5	H	H	p-NO_2Ph	^{t}Bu	15min	7	66
6	H	Me	p-NO_2Ph	Bz	10hr	61	66
7	H	H	p-NO_2Ph	Bz	1.5hr	7	66
8	H	Me	Et	^{t}Bu	3days	32	66
9	H	H		Bz	9hr	32	67
10	H	H		PNB	48hr	25	67
11	H	H		PNB	8hr	21	67
12	H	H		Bz	9hr	20	67
13	H	H		Bz	3hr	80	73
14	H	H		PNB	3hr	70	73
15	H	H		phtalidyl	3.5hr	27	73
16		H		PNB	3hr	76	73

Table 1

By application of this method, olivanic acid, MM22383 (epithienamycin D) was totally synthesized as follows.[48] After protection of the 1 : 1 mixture of diastereoisomers of β-lactams (135)[47] with p-nitrobenzyloxycarbonate group, the acetonide was deprotected to the alcohol (50). Oxidation with PCC and trapping of the intermediate aldehyde using stabilized Wittig reagent yielded the ester (136). After conversion into the phosphorane (137), the corresponding acid chloride was treated with silver (E)-2-acetamidoethenethiolate[67] to give the thioester-phosphorane (138). Heating the 1 : 1 mixture of diastereoisomers (138) in toluene afforded the mixture of 8S*- and 8 R*-carbapenems (139) in the ratio of 15 : 8, which were separable by chromatography. Hydrogenolysis of the 8S*-isomer afforded (±)-olivanic acid, MM22383[(±)-epithienamycin D].[48]



(135)

(50)
(63%)

(136)
(45%)

(137)
(52% from 134)

(138) 1:1 mixture
(55%)

(139)
(8S*:15%)
(8R*: 8%)

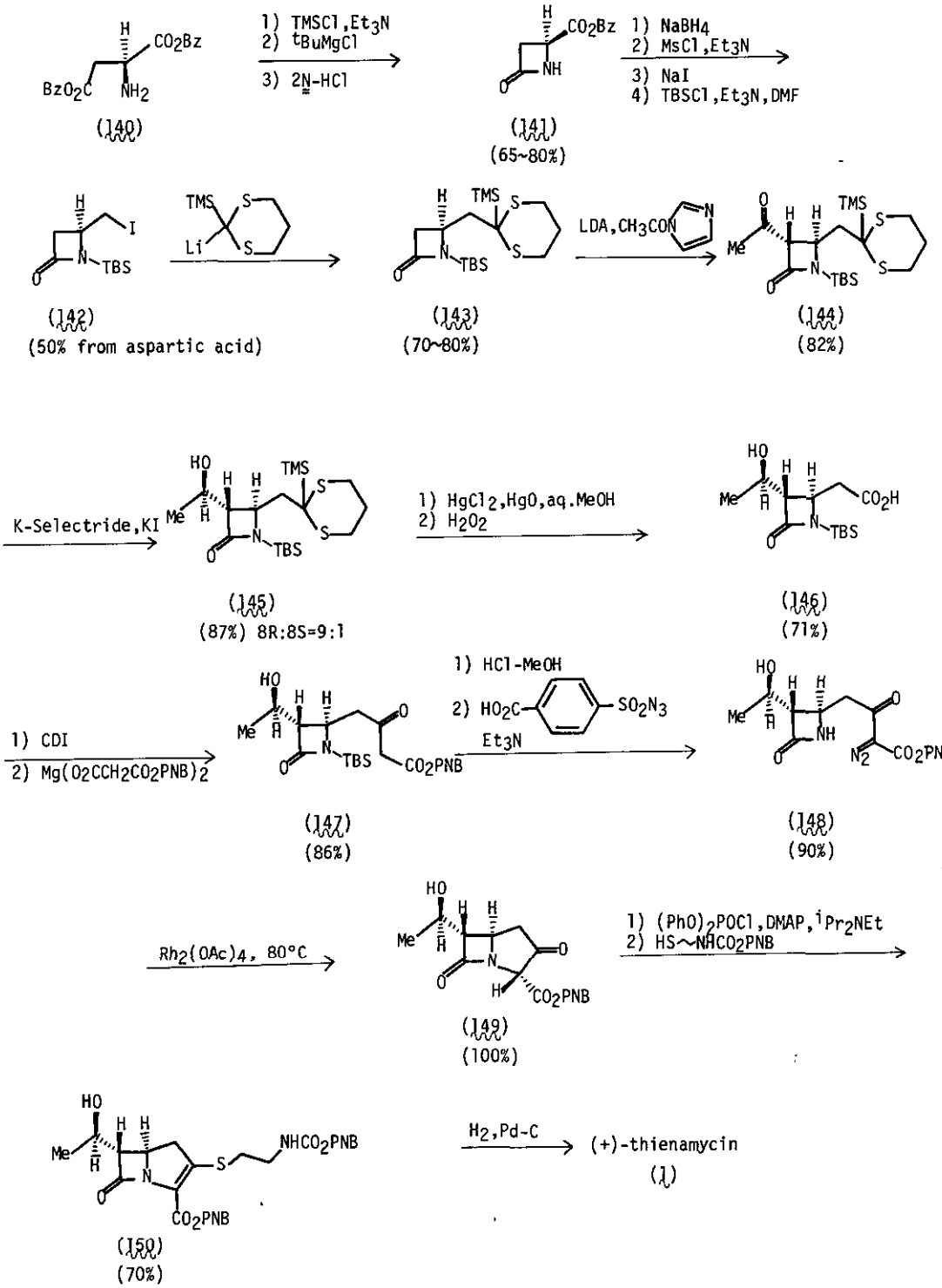
Scheme 23

6. C_3-C_4 Bond Formation

Merck research group developed very efficient method for construction of the bicyclic nucleus by carbene insertion reaction forming C_3-N_4 bond.[74] This methodology coupled with introduction of the cysteamine moiety by addition-elimination reaction[74,75] led the elegant total synthesis of (+)-thienamycin.[76]

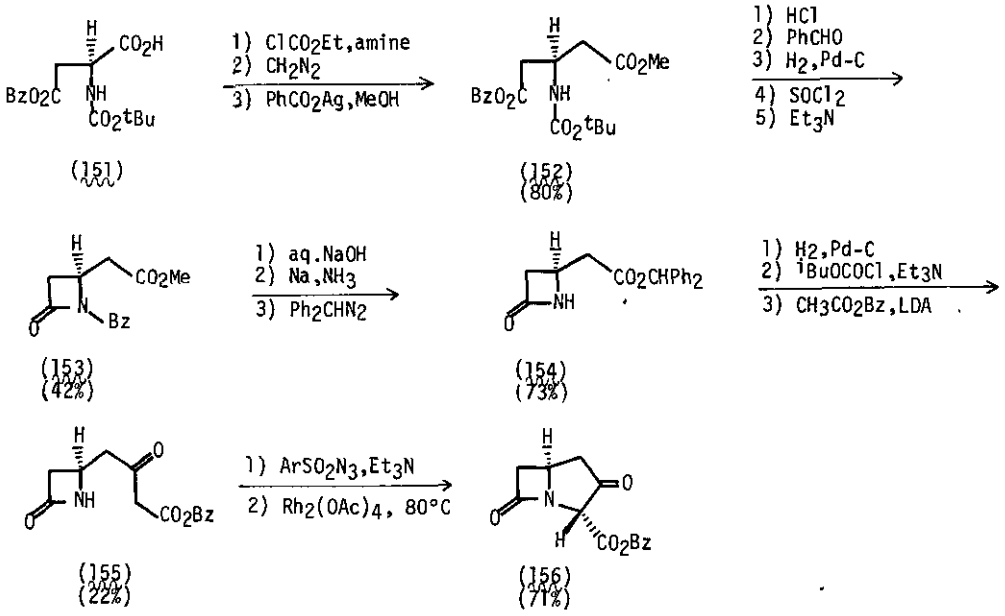
Namely, N-silylation of dibenzyl aspartate (140), followed by cyclization with Grignard reagent provided the β-lactam (141). Reduction of (141) with sodium borohydride, conversion of the alcohol into the iodide via the mesylate and then N-protection with TBS group furnished (142). Reaction of (142) with 2-lithio-2-(trimethylsilyl)-1,3-dithiane gave the substituted dithiane derivative (143) having only one acidic center. Direct acylation of (143) using N-acetylimidazole and LDA-followed by reduction with K-Selectride in the presence of potassium iodide as previously described,[46] produced predominantly the (8R)-hydroxyethyl compound (145). The acetyl compound (144) was prepared by an alternative route; aldol condensation of (143) with acetaldehyde and oxidation of the resultant mixture of epimeric alcohols containing mainly the (8S)-isomer with dimethyl sulfoxide and trifluoroacetic anhydride. Hydrolysis of (145), followed by oxidation of the resultant silyl ketone with hydrogen peroxide provided the carboxylic acid (146). The required keto ester chain was homologated by using a slight modification of Masamune's method.[77] Thus, the acid (146) was converted, on the treatment with N,N-carbonyldimidazole (CDI), into an imidazolide, which was reacted in situ with the magnesium salt of the mono ester of malonic acid to afford the keto ester (147). After deprotection of the silyl group, the carbene precursor (148) was prepared by diazo exchange. Thermolysis of (148) in the presence of catalytic amount of rhodium (II) acetate in hot benzene or toluene produced the bicyclic keto ester (149) in quantitative yield.

The keto ester (149) was activated by conversion into the vinyl phosphate, which could be isolated from the reaction mixture. However it was more convenient to directly treat it in situ with the cysteamine derivative to give the protected thienamycin (150), which was converted into the natural product by hydrogenolysis.[76]


1) TMSCl, Et3N
2) tBuMgCl
3) 2N-HCl
1) NaBH4
2) MsCl, Et3N
3) NaI
4) TBSCl, Et3N, DMF
LDA, CH3CON
K-Selectride, KI
1) HgCl2, HgO, aq. MeOH
2) H2O2
1) CDI
2) Mg(O2CCH2CO2PNB)2
1) HCl-MeOH
2) HO2C SO2N3
Et3N
Rh2(OAc)4, 80°C
1) (PhO)2POCl, DMAP, iPr2NEt
2) HS~NHCO2PNB
H2, Pd-C
(+)-thienamycin
(1)

Scheme 24

Similarly, Koga and his coworkers started from an aspartic acid derivative for the preparation of optically active β-lactam, which was further converted into the bicyclic system (156) by the application of the above method. Thus the aspartic acid derivative (151) was transformed into (152) by the Arndt-Eistert reaction. The β-lactam (153) was prepared via the cyclization of an acid chloride and further transformed into the β-keto ester (155) as shown in Scheme 25.[78]



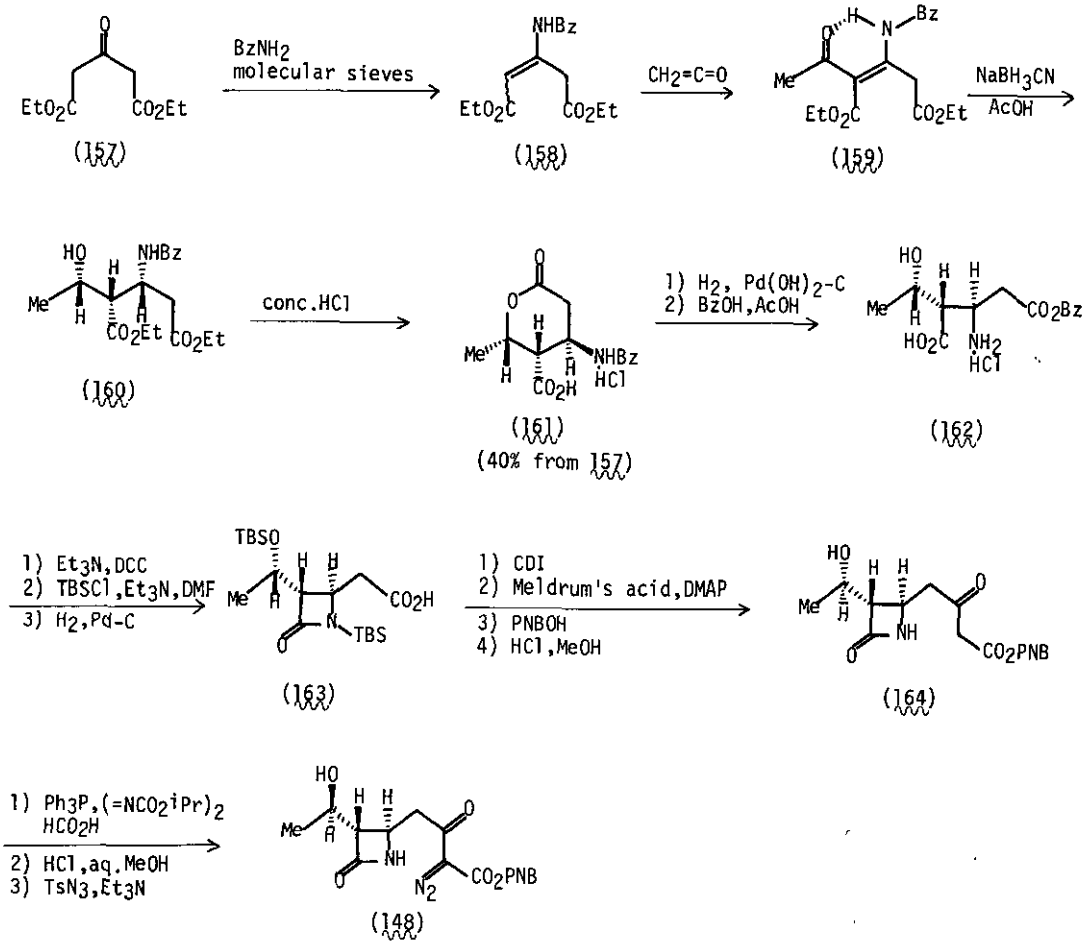
(151) (152) (80%) (153) (42%) (154) (73%) (155) (22%) (156) (71%)

Scheme 25

By application of this methodology, another group in the Merck laboratories developed a more practical route to (±)-thienamycin.[79,80] Namely, the symmetrical dicarboxylate (157) was converted into the keto enamine (159) via the enamine (158). After reduction using sodium cyanoborohydride, the crude reduction mixture (160) was subjected to an acid treatment to give the lactone (161) as a single stereoisomer having wrong stereochemistry at the methyl group.

After catalytic debenzylation of (161), the resultant lactone was solvolyzed in benzyl alcohol to give an equilibrium mixture of the acylic ester (162) and the starting lactone. On cyclization using DCC, followed by silylation and hydrogenolysis, the 4-caboxymethyl-β-lactam (163) was obtained in a good yield.

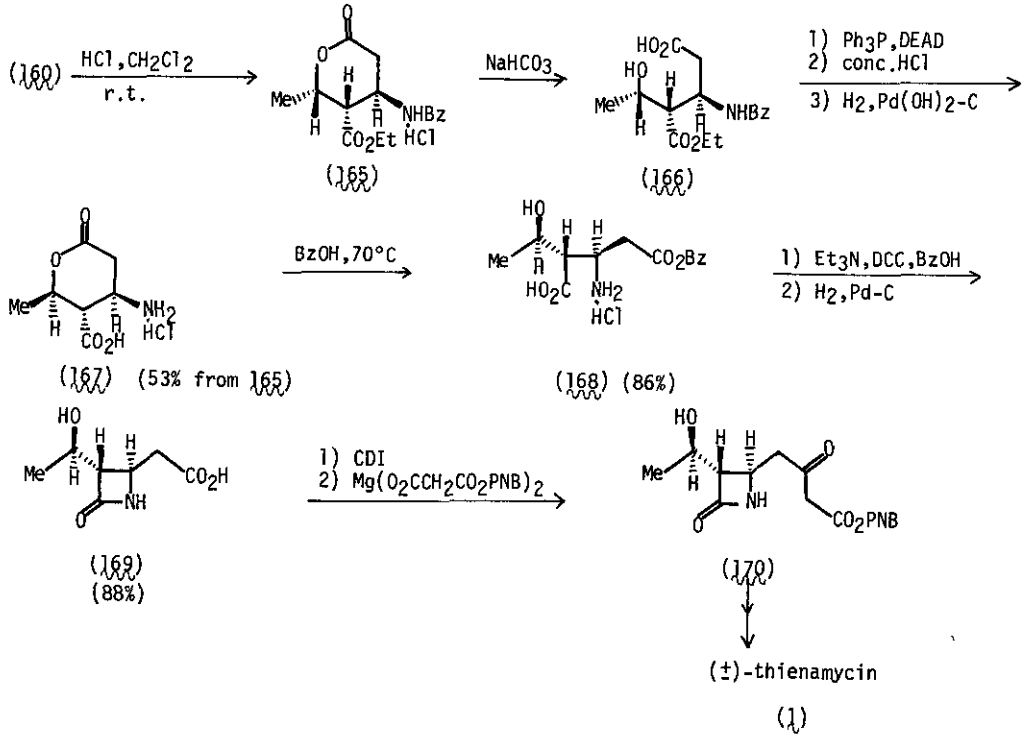
After chain-elongation and desilylation, the stereochemistry of the hydroxyethyl group of (164) was inverted by *Mitsunobu procedure*.[81] *The resulting inverted formate* was hydrolyzed to an alcohol, which was subjected to the diazo exchange to provide the diazo-ester (148). According to this procedure, (±)-thienamycin was synthesized in more than 10 % overall yield.[79]



(157) (158) (159) (160) (161) (40% from 157) (162) (163) (164) (148)

Scheme 26

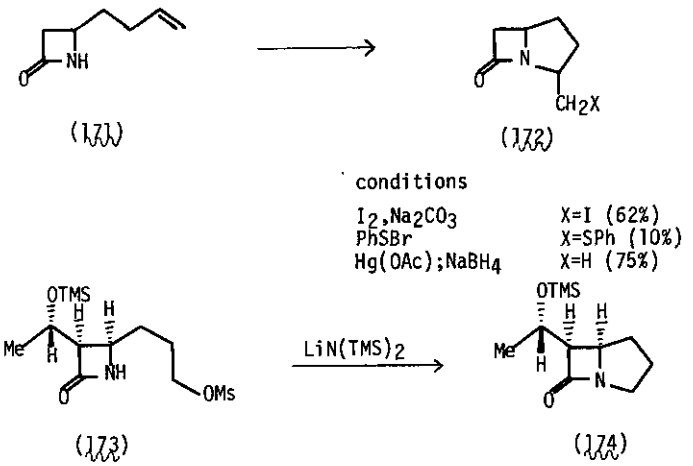
The inversion of the stereochemistry was performed intramolecularly prior to the β-lactam formation. Thus the lactonization of the above intermediate amino ester (160) was carried out under milder and anhydrous conditions to give the ester (165). After solvolysis, the resulting alcohol (166) was reacted with triphenylphosphine and diethyl azodicarboxylate (DEAD). The inverted lactone was similarly converted into the β-keto ester (170) as shown in scheme 27.[80] They also reported a facile synthesis of protected cysteamine derivatives.[82]



Scheme 27

Our β-lactam acetate (68)[49] having the same stereochemistry as that of thienamycin was effectively converted, by the application of the Merck method,[76] into (±)-thienamycin.[71,83] Furthermore the cis-β-lactam (69),[49] obtained as a major product from the isoxazoline methyl ester (64), was transformed into epithienamycins A (5) and B (6) (olivanic acids MM 22380 and MM 22382).[84] The proposed relative stereochemistry[4,5,8b] of these antibiotics was confirmed by this synthesis.

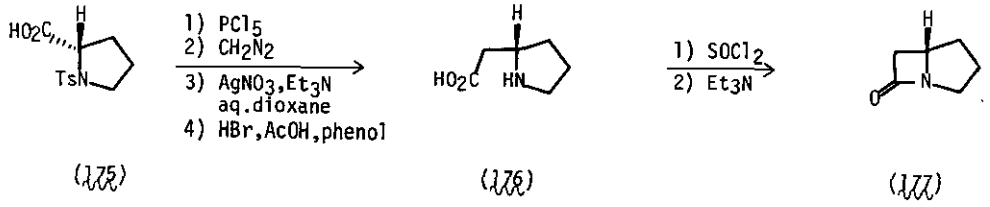
On the ring closure between C_3 and N_4, synthesis of carbapenams was further examined by the following two methods; cyclization of 4-(3'-butenyl)azetidinone (171) to (172) by electrophilic reagents[85] and intramolecular substitution of the mesylate (173) to (174).[86]



Scheme 28

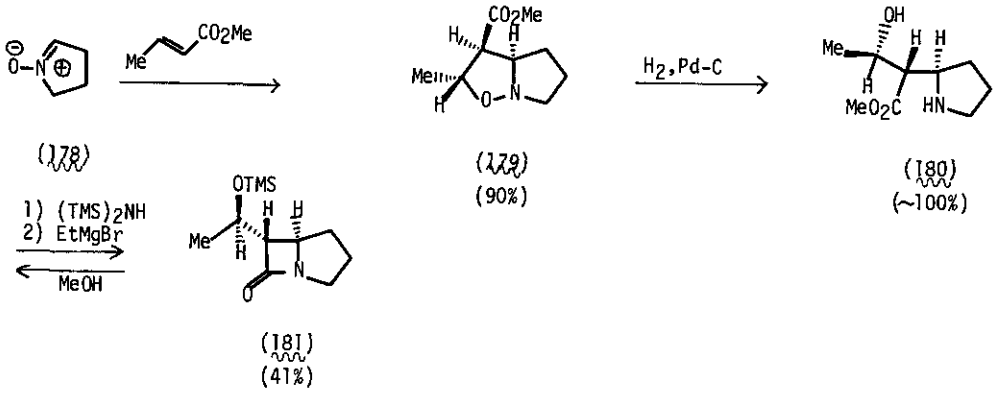
7. N_4-C_7 Bond Formation

The cyclization of 2-pyrrolidylacetic acid derivative would be the straightforward method for the synthesis of the bicyclic ring system. Chain-elongation of N-tosyl-L-proline (175) followed by detosylation provided homoproline (176), which was cyclized to (5S)-carbapenam (177).[87] The absolute configuration of (177) was reverse of natural product. The c.d. curve of (177) showed a negative Cotton effect at 231 nm, which was consistent with the predicted curve by calculation using semiempirical Extended Hückel and CNDO wavefunctions.[88]



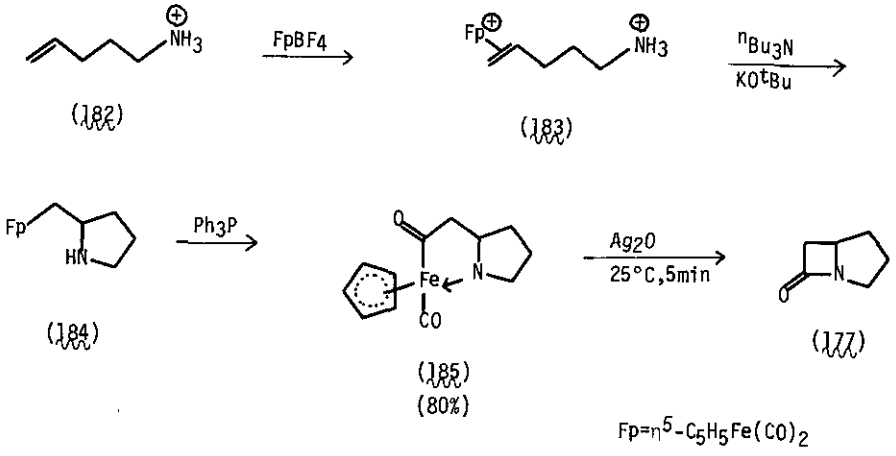
Scheme 29

Tufariello and coworkers[89] stereoselectively synthesized the amino alcohol (180) having the same relative configuration as that of thienamycin via the isoxazolidine (179) prepared by 1,3-dipolar cycloaddition of 1-pyrroline 1-oxide (178) and methyl crotonate. After blocking using hexamethyldisilazane, cyclization with Grignard reagent provided the carbapenam (181) which, on exposure to methanol, gave the starting amino alcohol (180).[89]



Scheme 30

Interestingly, Rosenblum and coworkers demonstrated the oxidative cyclization of the iron carbonyl complex (185).[90] Thus the exchange reaction involving 1-pentenyl-*ammonium* tetrafluoroborate (182) and Fp(isobutene) tetrafluoroborate produced the complex (183). Successive deprotonation with base gave the pyrrolidine complex (184), which was converted, on heating in the presence of triphenylphosphine, into the chelate (185). Treatment of (185) with silver(I) oxide resulted in the formation of the carbapenam (the racemate of 177).

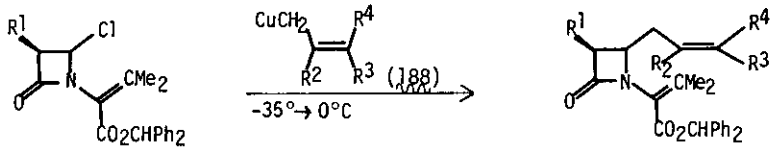


Scheme 31

8. Synthesis of 4-Alkylated β-Lactams

8-1. Substitution at the C_4 Position

Introduction of a properly functionalized alkyl group at the C_4 position of the readily available β-lactams would provide an efficient route to the synthesis of the carbapenems.[91] Shionogi group prepared allylazetidinone (189 and 190) by coupling of allylcoppers (188a~d) with chloroazetidinones (186 and 187) derived from penicillins. The coupling of either isomer of (187) (4β or 4α) with (188d) provided a mixture of (190d) with same isomer ratio (entries 5 and 6 in Table 2).[62] The allylazetidinones (189b and 190b) were converted into carbapenems using intramolecular Wittig reaction. Thus, epoxidation of (189b) followed by hydrolysis and subsequent acetonidation of the resulting glycol yielded (191), which was converted into the phosphorane (192). Deprotection of the acetonide group and glycol fission gave the aldehyde, which on neutralization resulted in the formation of the carbapenem (193).[62]



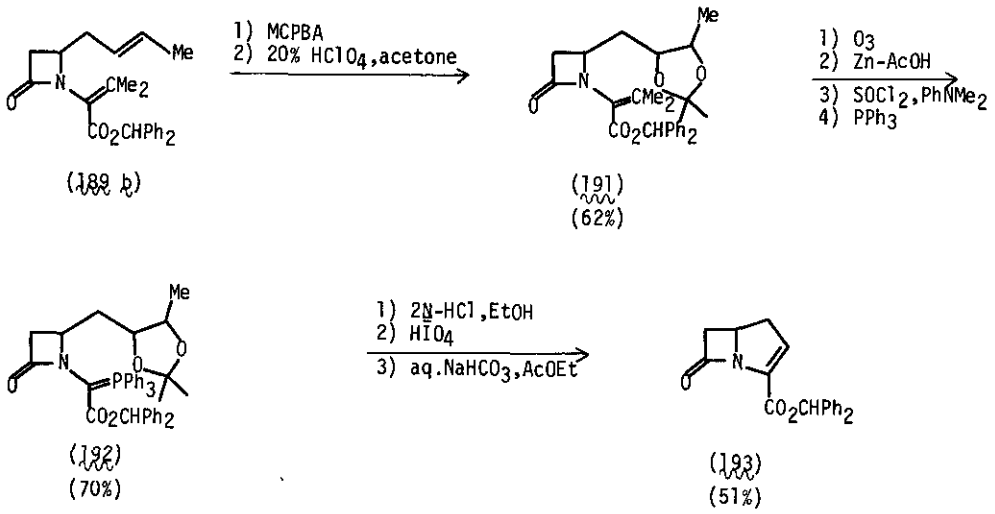
(186) R^1=H
(187) R^2=NHTr

(189)
(190)

	R^2	R^3	R^4
(a)	H	H	H
(b)	H	Me	H
(c)	H	Me	Me
(d)	Me	H	H

entry	chloride	allylcopper	product	yield(%)	ratio of 4β- to 4α-isomer
1	(186)	(188 b)	(189 b)	55.0	—
2	(4β-187)	(188 a)	(190 a)	12.4	33/67
3	(4β-187)	(188 b)	(190 b)	66.1	45/55
4	(4β-187)	(188 c)	(190 c)	64.0	55/45
5	(4β-187)	(188 d)	(190 d)	63.6	33/67
6	(4α-187)	(188 d)	(190 d)	48.2	33/67

Table 2



(189 b)

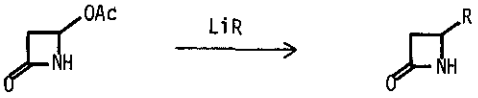
(191)
(62%)

(192)
(70%)

(193)
(51%)

Scheme 32

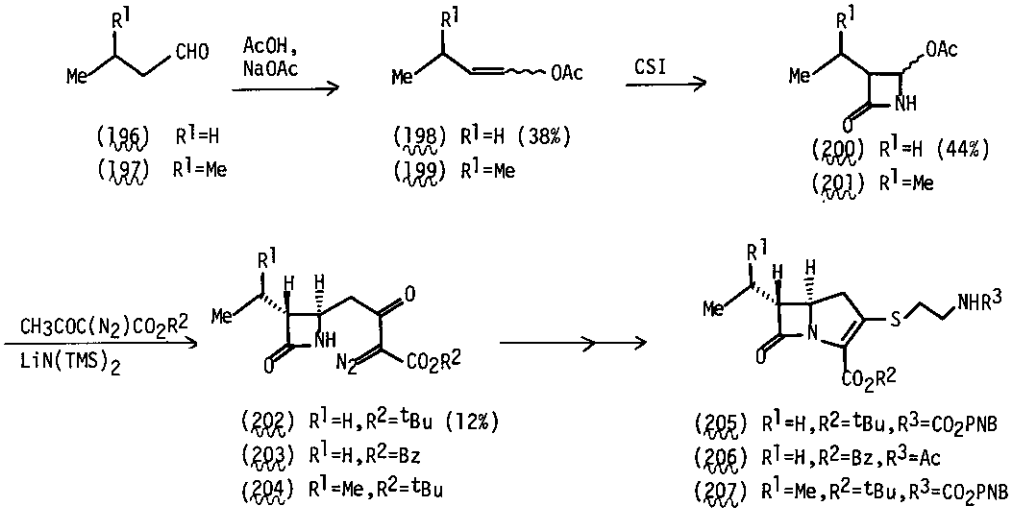
Since it was known[92] that 4-acetoxyazetidinones were readily displaced by sulfur, nitrogen, and oxygen functions, we investigated the analogous displacement reaction.[93] Reaction of 4-acetoxyl derivatives with several lithium salts produced the corresponding carbon displaced compounds although yields were not so high.[93] Thus the carbene precursors (e.g. 195d) could be obtained in one step from the 4-acetoxyazetidinones which are readily available by the cycloaddition of the enol acetates and CSI. The diazo esters (202 ~ 204), prepared in short steps, were transformed into the PS-5 and PS-6 derivatives (205 ~ 207).[94]



(194)

(195)

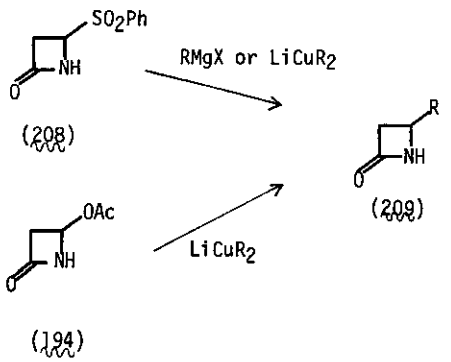
(a) R=^{n}Bu (12%)
(b) R=CH(CO$_2$Me)$_2$ (20%)
(c) R=CH$_2$CO$_2$Et (15%)
(d) R=CH$_2$COC(N$_2$)CO$_2$Et (11%)



(196) R^1=H
(197) R^1=Me
(198) R^1=H (38%)
(199) R^1=Me
(200) R^1=H (44%)
(201) R^1=Me
(202) R^1=H, R^2=tBu (12%)
(203) R^1=H, R^2=Bz
(204) R^1=Me, R^2=tBu
(205) R^1=H, R^2=tBu, R^3=CO_2PNB
(206) R^1=H, R^2=Bz, R^3=Ac
(207) R^1=Me, R^2=tBu, R^3=CO_2PNB

Scheme 33

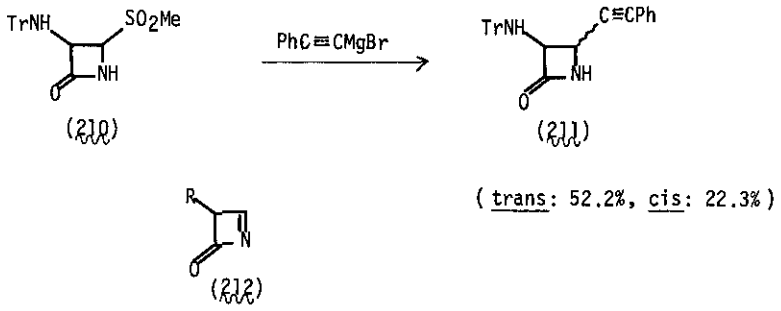
Independently, Sankyo group elucidated on carbon-extension reactions at the C_4 position of azetidinones. Treatment of 4-phenylsulfonylazetidinone (208) with either lithium organocuprates or Grignard reagents produced 4-alkyl, allyl, vinyl or ethynyl-azetidinones (209a ~ f) in good yields. Reaction of 4-acetoxyazetidinone (194) with lithium organocuprates gave the similar results but reaction using Grignard reagents resulted in low yields. (Table 3). When the starting azetidinone (210) had a substituent at the C_3 position the treatment with phenylethynylmagnesium bromide formed a mixture of trans-and cis-isomers (211).[95] 1,4-Addition of the organometallic reagents to the intermediate azetinone (212) was proposed.



(208)
(209)
(194)

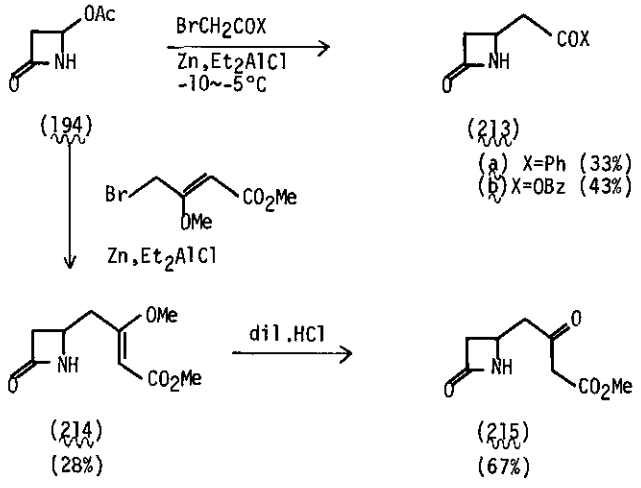
	R=	Reagent	Yield from (208)	Yield from (194)
(a)	^{n}Bu	$LiCu(^nBu)_2$	94.0	89.0
(b)	Et	EtMgBr	74.2	12.4
(c)	CH=CH_2	CH_2=CHMgBr	65.5	3.5
(d)	$CH_2CH=CH_2$	$LiCu(CH_2CH=CH_2)_2$	100.0	–
(d)	$CH_2CH=CH_2$	$CH_2=CHCH_2MgCl$	54.9	–
(e)	C≡COEt	EtOC≡CMgBr	95.4	–
(f)	C≡CSPh	PhSC≡CMgBr	68.9	–

Table 3



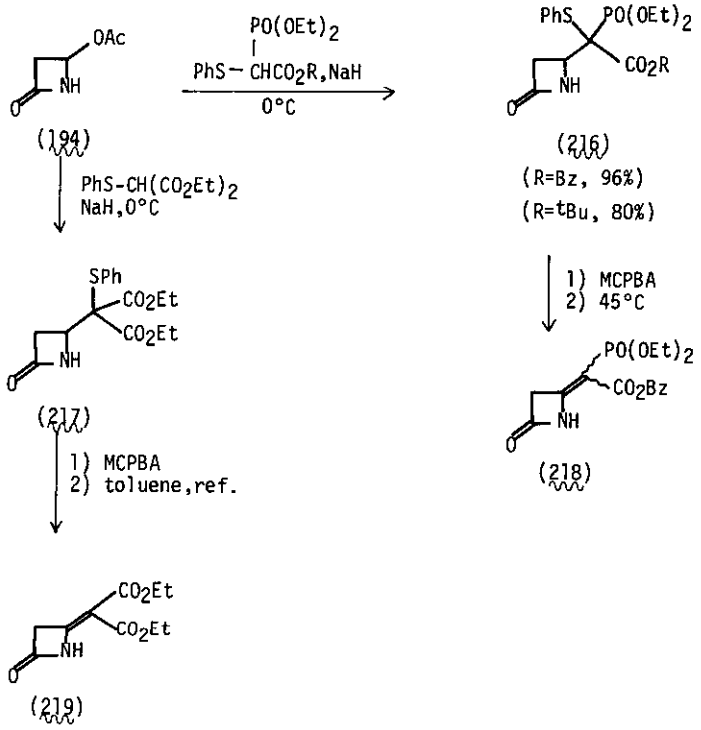
Scheme 34

Direct introduction of carbonyl substituents could not be achieved by the above reactions using Grignard reagents and organocuprates. On treatment of (194) with aluminium enolate, the desired 4-alkylazetidinones were synthesized in moderate yields.[96] Namely, condensation of (194) with halo-ketone or esters in the presence of zinc and diethylaluminum chloride[97] produced the 4-alkylazetidinones (213a and b), which were converted into carbapenems, respectively, using intramolecular Wittig reaction. On the other hand, reaction of (194) with γ-bromo-β-methoxycrotonate under the same reaction conditions produced the γ-substituted butyric ester (214) as a major product along with the α-substituted esters. After hydrolysis of (214), the resulting β-keto ester (215) was converted into the corresponding carbapenam by the carbene insertion reaction.[96]



Scheme 35

When the displacement reaction of (194) was carried out using stabilized tertiary carbanions, the carbon-substituted azetidinones were easily obtained.[98] Oxidative desulfurization of the azetidinones (216 and 217) produced the 4-alkylideneazetidinones (218 and 219)[98]. Furthermore 4-alkylideneazetidinones were alternatively prepared from 4-thioxoazetidinones.[99]

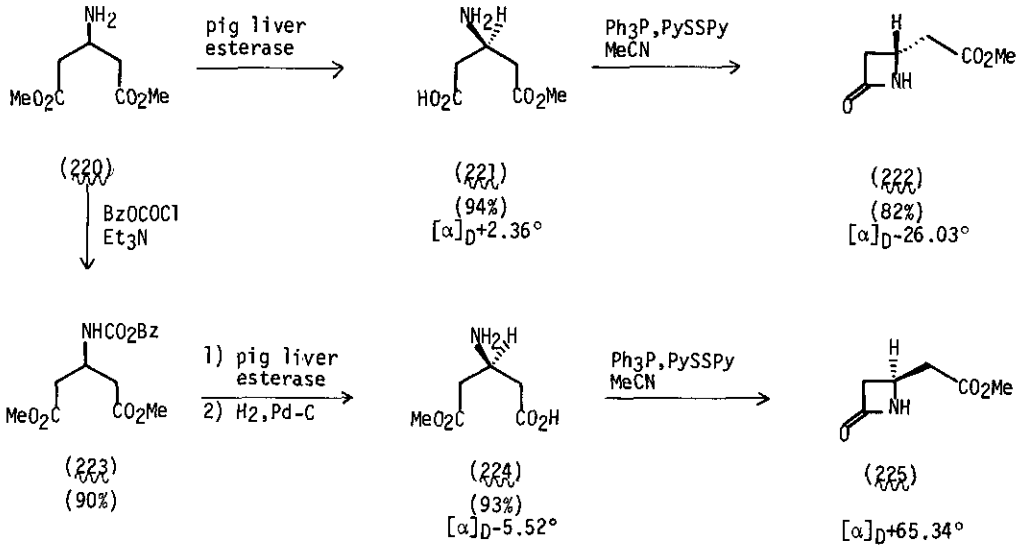


Scheme 36

8-2. Asymmetric Synthesis of 4-Substituted Azetidinone

Optically active 4-methoxycarbonylmethyl-2-azetidinone (225) could be obtained by selective cyclization of the prochiral β-aminoglutaric acid derivative. On hydrolysis of dimethyl β-aminoglutarate (220) with pig liver esterase, (3R)-half ester (221) was formed in low optical yield, because non-enzymatic self hydrolysis significantly occurred.[100] On the other hand, the N-protected derivative (223) gave the (3S)-half ester in high optical yield on incubation with the pig liver

esterase. After deprotection, the resultant β-amino acid (224) was cyclized by novel method using triphenylphosphine and 2,2'-dipyridyl disulfide in acetonitrile[101,102] giving the (4R)-β-lactam (225), $[\alpha]_D^{25}$ + 65.34° ($CHCl_3$). Cyclization of the above (3R)-half ester (221) under the same conditions gave the (4S)-isomer (222) in low optical purity, $[\alpha]_D^{25}$ - 26.03° ($CHCl_3$).[100]



Scheme 37

Summary

Synthetic methods for construction of the bicyclic ring system have explosively progressed since the discovery of thienamycin in 1976. However total syntheses of carbapenem antibiotics have been accomplished by only a few methods; ring closure between C_2 and C_3 position by substitution reaction or intramolecular Wittig reaction and the C_3-N_4 bond formation by carbene insertion reaction. Further development of effective synthesis and structural manipulation of the antibiotics for the chemical as well as biochemical stabilization are strongly desired.

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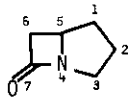
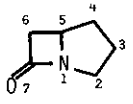
27. The numbering (a) of the ring system adopted throughout this review is based on assignment of the terms carbapenam, which is analogous to penam and cephem nomenclature. The structure is further designated as 1-azabicyclo[3.2.0]heptan-7-one with numbering as shown in (b).



(a)



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ADDENDUM

After the submission of this review, the following related papers have been published.

1. "A novel photochemical route to functionalised β-lactams", J. Brennan, J. C. S. Chem. Comm., 1981, 880.
2. "A facile synthesis of benzyl 3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. A potential precursor of thienamycin and clavulanic acid analogs", Tetrahedron Letters, 1981, 22, 3557.
3. "Synthesis of 1,1-dimethylcarba-2-penem derivatives via a Dieckmann-type cyclization", M. Shibuya and S. Kubota, Tetrahedrn Letters, 1981, 22, 3611.
4. "A novel synthesis of the carbapen-2-em derivatives", M. Hatanaka, Y. Yamamoto, H. Nitta, and T. Ishimaru, Tetrahedrn Letters, 1981, 22, 3883.

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