

ENANTIOSELECTIVE SYNTHESSES OF CARBAPENEM ANTIBIOTICS

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**Dedicated to Professor Gilbert Stork on the occasion of his
65th birthday.**

Abstract — A family of carbapenem antibiotics, represented by thienamycin, exhibits strong and broad antibacterial activities. In this review, recent enantioselective syntheses of naturally occurring carbapenems are summarized as a main subject.

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[I] Introduction

Just a decade has passed since the discovery of a new β -lactam antibiotic, thienamycin (1),¹ from fermentation broths of the soil microorganism Streptomyces Cattleya by the Merck research group¹ in 1976. It was named thienamycin owing to its novel β -thioenamine chromophore.

Since the discovery of thienamycin (1), nearly forty compounds of this carbapenem family have been found by many research groups. They are summarized in Table 1.

Table 1

Numerous efforts have been made for the syntheses of the carbapenem family of compounds and its derivatives, because of their unique antibacterial activity and the low fermentation yields. In the synthesis of these compounds, the following two points are always the main problems;

- i) the control of their absolute stereochemistry.
- ii) the construction of a highly strained bicyclic ring system.

Here, we would like to summarize recent studies of the chiral synthesis of carbapenem antibiotics, published so far in journals,¹⁷ regarding the above two points, especially the chiral synthesis of the β -lactam ring.

Table I - (1)
Thienamycin and Epithienamycins

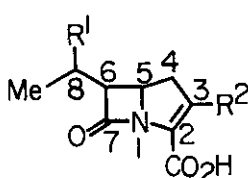
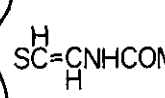
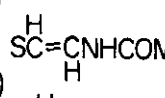
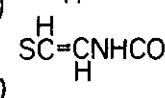
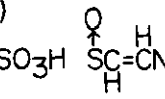
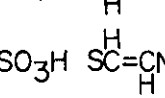
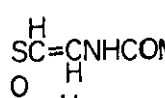
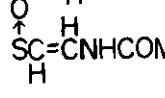
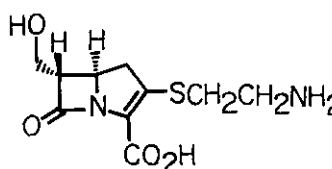
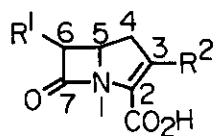
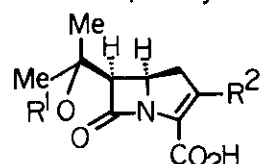
			Absolute configuration			
			5	6	8	5-H/6-H
(1) Thienamycin ¹	OH	SCH ₂ CH ₂ NH ₂	R	S	R	trans
(2) Epithienamycin A ² (Olivanic acid MM22380 ^{3c} 17927 A ₁ ⁴)	OH	SCH ₂ CH ₂ NHCOMe	R	R	S	cis
(3) Epithienamycin B ² (Olivanic acid MM22382 ^{3c} 17927 A ₂ ⁴)	OH		R	R	S	cis
(4) Epithienamycin C ² (Olivanic acid MM22381 ^{3c})	OH	SCH ₂ CH ₂ NHCOMe	R	S	S	trans
(5) Epithienamycin D ² (Olivanic acid MM22383 ^{3c})	OH		R	S	S	trans
(6) Epithienamycin E ² (Olivanic acid MM13902 ^{3b})	OSO ₃ H		R	R	S	cis
(7) Epithienamycin F ² (Olivanic acid MM17880 ^{3a})	OSO ₃ H	SCH ₂ CH ₂ NHCOMe	R	R	S	cis
(8) Olivanic acid MM4450 ^{3b} (MC 696-SY2-A ⁵)	OSO ₃ H		R	R	S	cis
(9) Olivanic acid MM27696 ^{5e}	OSO ₃ H		R	R	S	cis
(10) N-Acetylthienamycin ⁶	OH	SCH ₂ CH ₂ NHCOMe	R	S	R	trans
(11) N-Acetyl-11,12-dehydrothienamycin ⁷	OH		R	S	R	trans
(12) C-19393 E ₅ ⁸	OH		R	R	S	cis
(13) 9-Northienamycin ⁹						

Table 1 - (2)
PS-series Compounds

			Absolute configuration		
	R ¹	R ²	5	6	5-H/6-H
(14) PS-5 ¹ Oab	MeCH ₂ -	-SCH ₂ CH ₂ NHCOMe	R	S	trans
(15) PS-6 ¹ Oc	Me ₂ CH-	-SCH ₂ CH ₂ NHCOMe	R	S	trans
(16) PS-7 ¹ Oc	MeCH ₂ -	-SC(=H)CNHCOMe	R	S	trans
(17) PS-8 ¹ Od	Me ₂ CH-	-SC(=H)CNHCOMe	N.D.	N.D.	trans

N.D. Not Determined

Carpetimycins

			Absolute configuration		
	R ¹	R ²	5	6	5-H/6-H
(18) Carpetimycin A ¹ la (C-19393 H ₂ ¹ lb)	H	-SC(=H)CNHCOMe (R) O	R	R	cis
(19) Carpetimycin B ¹ la (C-19393 S ₂ ¹ lb)	-SO ₃ H	-SC(=H)CNHCOMe (R) O	R	R	cis
(20) Carpetimycin C ¹ lc	H	-SCH ₂ CH ₂ NHCOMe (R) O	R	R	cis
(21) Carpetimycin D ¹ lc	-SO ₃ H	-SCH ₂ CH ₂ NHCOMe (R) O	R	R	cis

Asparenomycins

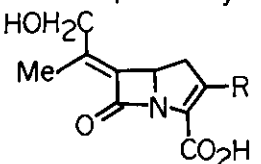
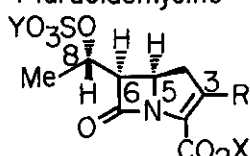
			Absolute configuration		
	R ¹	R ²	5	6	5-H/6-H
(22) Asparenomycin A ¹ 2a~d	R	-SC(=H)CNHCOMe (R) O	R	R	cis
(23) Asparenomycin B ¹ 2b~d	R	-SCH ₂ CH ₂ NHCOMe (R) O	R	R	cis
(24) Asparenomycin C ¹ 2b~d	R	-SC(=H)CNHCOMe H	R	R	cis
(25) 6643-X ¹ 2e	R	-SCH ₂ CH ₂ NHCOMe	R	R	cis

Table 1 - (3)

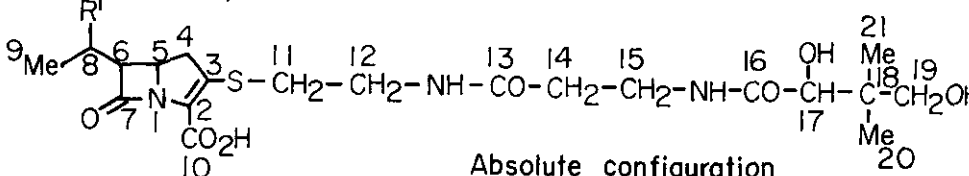
Pluracidomycins



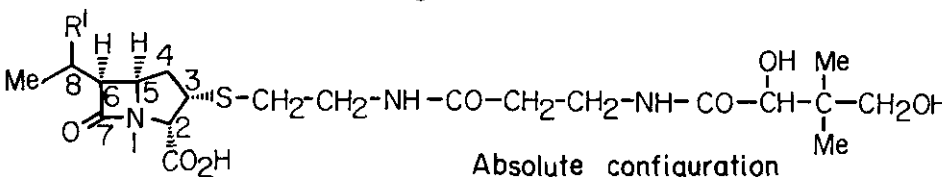
	X	Y	R	Absolute configuration			5-H/6-H
				5	6	8	
(26) Pluracidomycin A ^{13a}	Na	Na	-SO ₃ Na	R	R	S	cis
(27) Pluracidomycin B ^{13a}	Na	Na	(R)-CH ₂ CO ₂ Na	R	R	S	cis
(28) Pluracidomycin C ^{13a}	Na	Na	(R)-CH(OH) ₂	R	R	S	cis
(29) SF-2103 A ^{13b}	H	H	-SO ₃ H	N.D.	N.D.	N.D.	—

N.D. Not Determined

OA-6129 Compounds

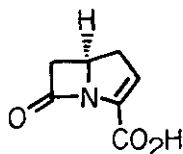


	R ¹	Absolute configuration			
		5	6	8	Pantoyl
(30) OA-6129 A ¹⁴	H	R	R	—	R
(31) OA-6129 B ¹⁴	OH	R	R	N.D.	R
(32) OA-6129 B ₂ ¹⁴	OH	R	S	S	R
(33) OA-6129 C ¹⁴	OSO ₃ H	R	R	N.D.	R



	R ¹	Absolute configuration				
		2	3	5	6	8
(34) OA-6129 D ¹⁵	H	S	S	R	R	N.D.
(35) OA-6129 E ¹⁵	Me	S	S	R	R	N.D.

N.D. Not Determined

(36) SQ-27860¹⁶

[II] Synthesis of Optically Active Carbapenems and Their Key Intermediates

II-1 Syntheses from Amino Acids

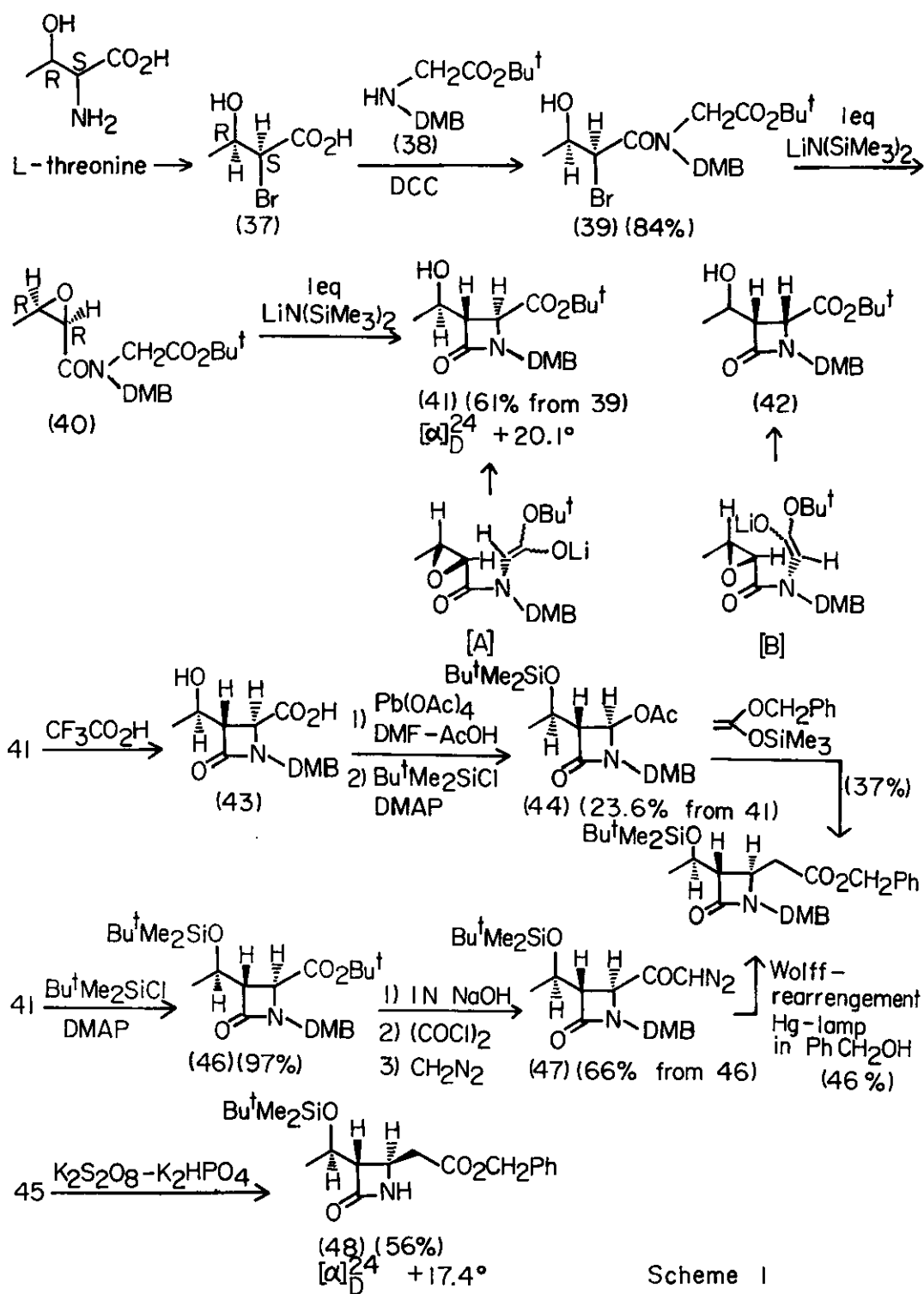
Amino acids are recognized to be one of the most important chiral sources. The Sankyo group prepared chiral precursors of thienamycin from L-threonine^{18,19,20} and D-allo-threonine.^{18,21,22} Chiral butyric acid (37),²³ derived easily from L-threonine, was coupled with glycinate (38) to give an amide (39). Azetidinone (41) was constructed from 39 through an epoxide intermediate (40) using two equivalents of lithium hexamethyldisilazide. When this reaction was carried out at -78 °C, a small amount of cis-isomer (42) (4.8%) was formed along with 41 (28%) and the epoxide (40) (50%). On the other hand, when the same reaction was run at 20-23 °C, no cis-isomer (42) was observed.²⁰ These results were explained by assuming that this reaction proceeded through the preferred conformational isomer (A) rather than B. Compound 41 could be converted into a key intermediate (48) for the synthesis of thienamycin by two alternative routes; one using the Wolff rearrangement and the other the Merck procedure,²⁴ as shown in Scheme 1.

Scheme 1

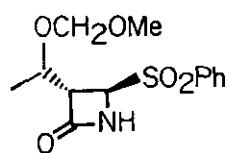
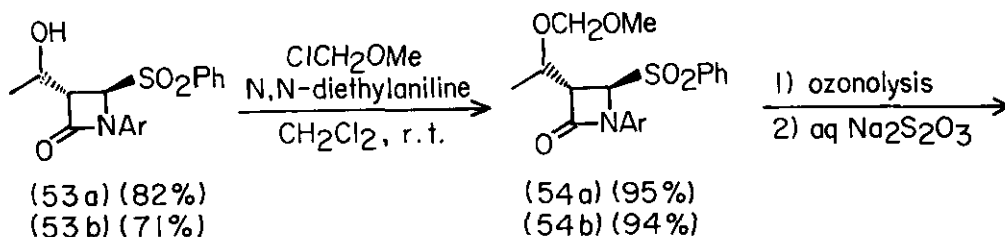
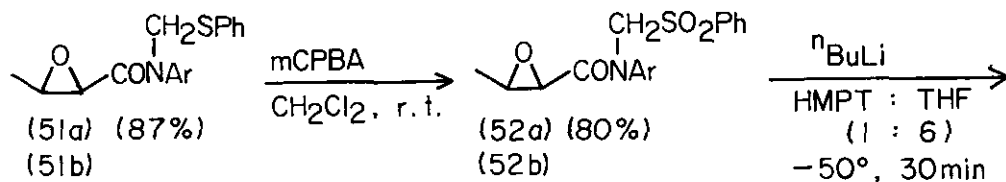
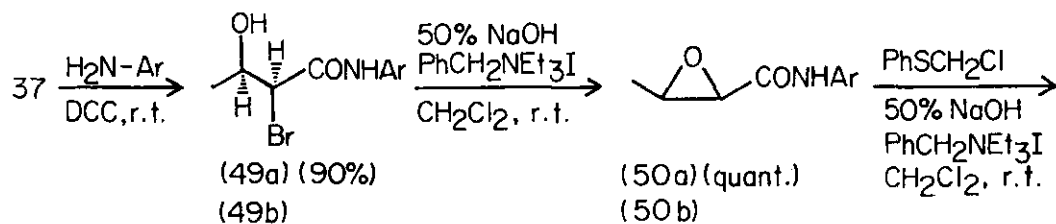
On the basis of the same strategy, a convenient 8-step synthesis of the key intermediate (55) of the carbapenem²⁵ and penem²⁶ antibiotics from L-threonine was reported by the same group.¹⁹

Scheme 2

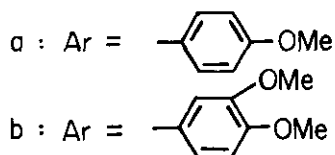
D-Allo-threonine could also be used as a chiral precursor.^{18,21,22} D-Allo-threonine was converted to (2R,3R)-butyryl chloride²⁷ (56) with retention of the configuration. After condensation of 56 with a 2,4-dimethoxybenzylamine derivative (57), the amide (58) was subjected to the key step by treatment with DBU and this azetidinone formation proceeded via a complete $\text{S}_{\text{N}}2$ mechanism to give azetidinone (59). Monosaponification of 59, followed by decarboxylation afforded the ester (60), whose hydrolysis with sodium hydroxide and subsequent treatment with hydrochloric acid gave a lactone (61) and trans carboxylic acid (43) in 62% and 14% yields, respectively. Lactone (61) and carboxylic acid (43) are transformed into useful intermediates (65), (70), (48) and (66) for the synthesis



Scheme 1



(55) (57% from 54a)
 (71% from 54b)



HMPT : hexamethylphosphoric triamide

Scheme 2

of penems²⁸ and carbapenems^{17c,2a} by several steps utilizing Baeyer-Villiger oxidation and Barrett's displacement method of 4-acetoxiazetidinone,³⁰ as key reactions.

Scheme 3

The first total synthesis of (+)-thienamycin (1)³¹ was accomplished from L-aspartic acid by the Merck group. They also reported a practical stereospecific synthesis of (+)-thienamycin (1) from the same starting material as described in Scheme 4. A lead tetraacetate oxidative decarboxylation of 76 and subsequent introduction of a four carbon diazo-containing unit into 4-acetoxy-2-azetidinone (72) afforded the diazo compound (78), which had been converted into (+)-thienamycin (1).³²

Scheme 4

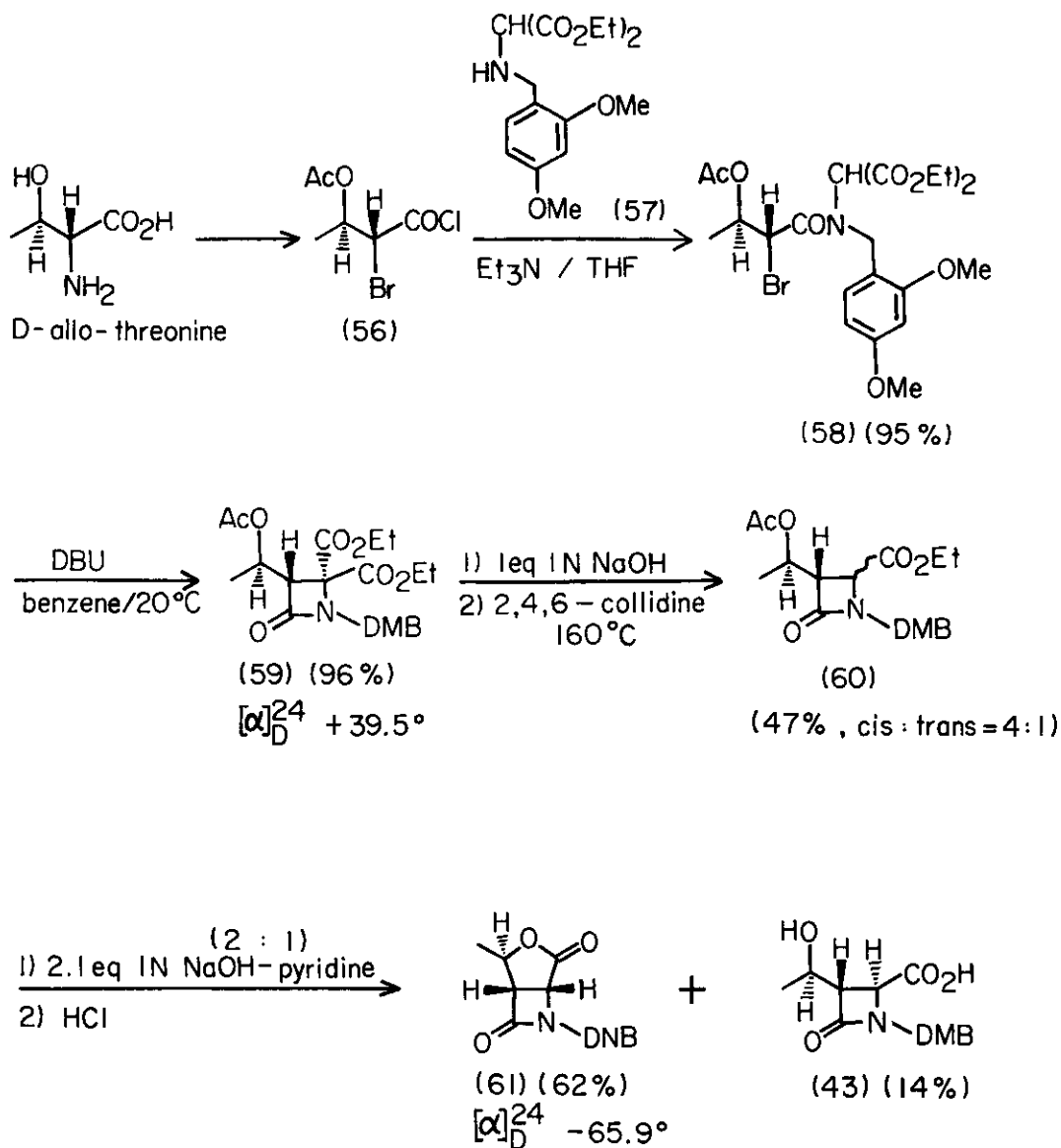
II-2 Synthesis from Chiral γ -Butyrolactone

Takano and his coworkers have published the synthesis of optically active β -keto ester (94),³³ which has been converted into the carbapenam³⁴ and carbapenem^{34b} ring systems, using the chiral lactone (79) as a starting material, and this procedure involved Ohno's method³⁵ for the preparation of the azetidinone ring.

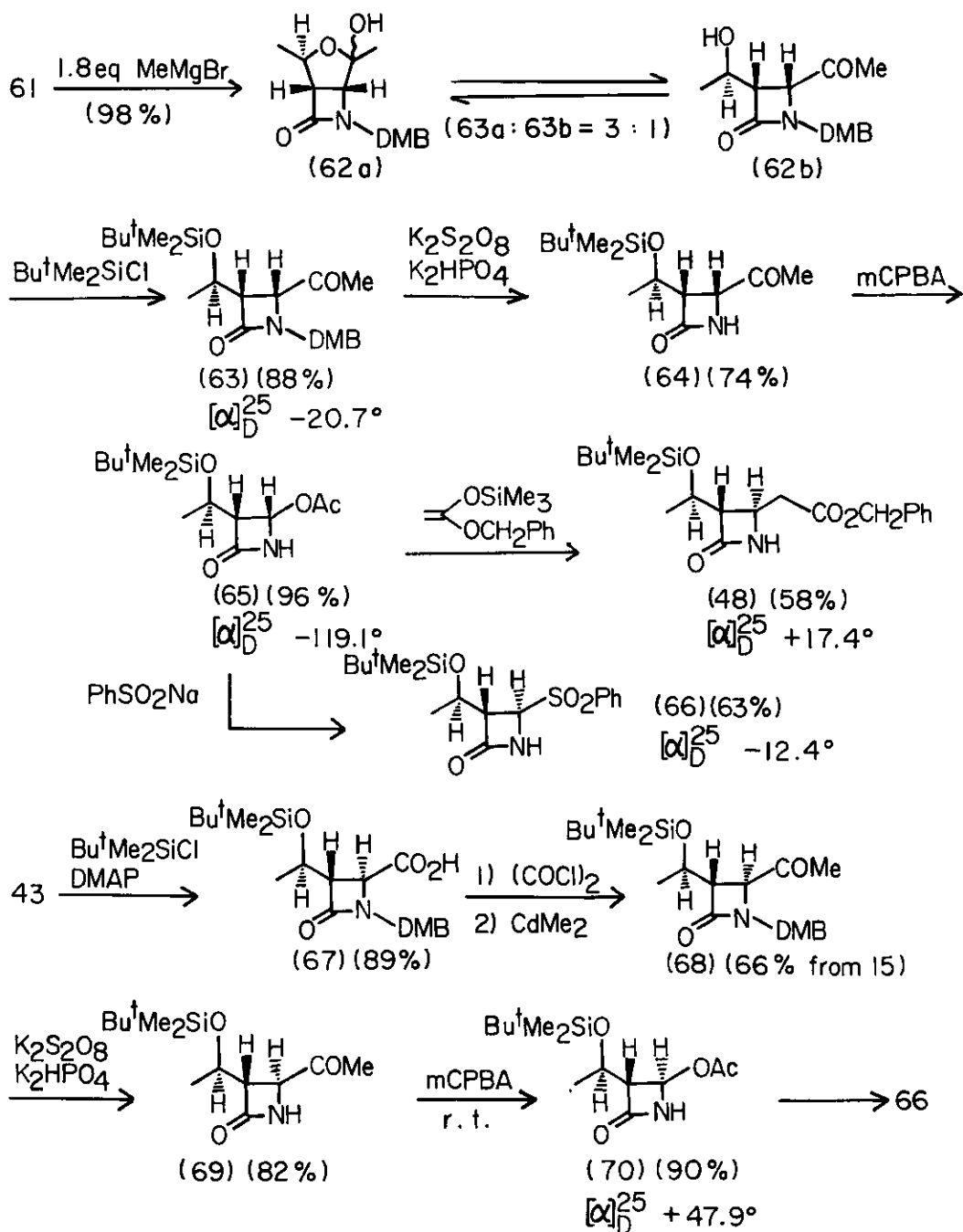
Scheme 5

II-3 Synthesis from D-Glucosamine

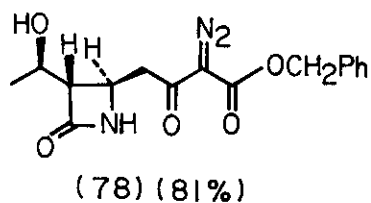
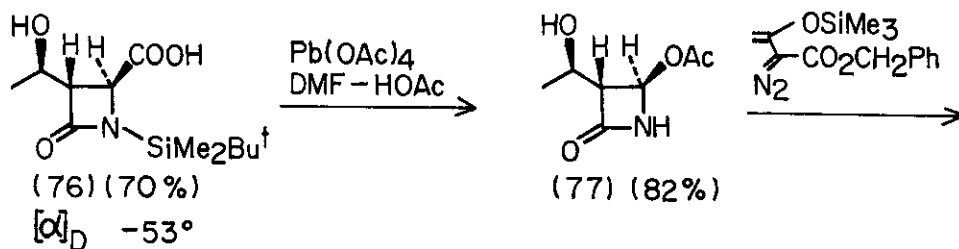
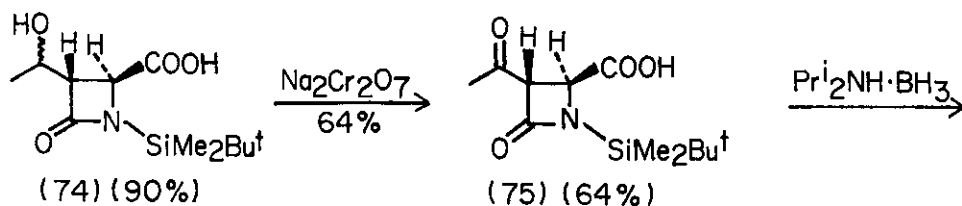
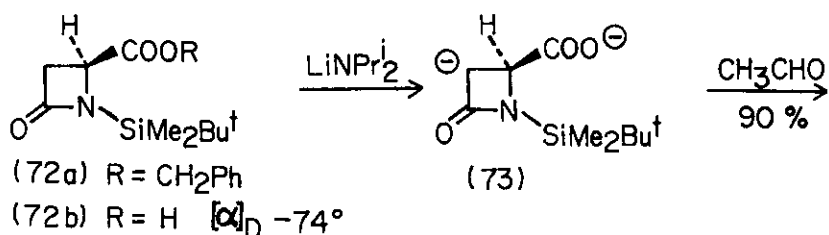
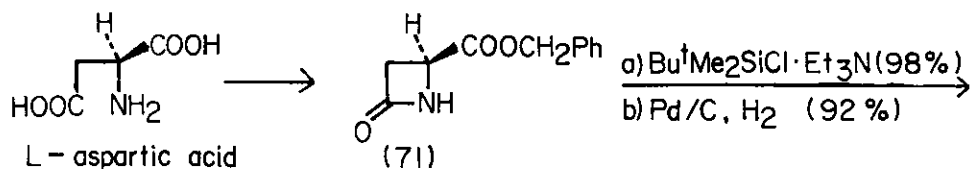
Yoshikoshi and his coworkers reported a synthesis of the precursor of (+)-thienamycin³⁶ from D-glucosamine. Hydroxyethylation, followed by silylation of 106, gave a separable desired diastereoisomer (6S,8R)-(108) via 107 with a 39% yield. The undesired diastereoisomers, (6S,8S)-, (6R,8R)-, and (6R,8S)-(108), could be recycled to (6S,8R)-107 by successive desilylation, Swern oxidation and K-selectride reduction. The selective oxidation of the primary hydroxy group of 10a was achieved by Pt-catalyzed autoxidation yielding a hydroxy acid (110), which was further esterified and then oxidized to afford the intermediate (111)³² for



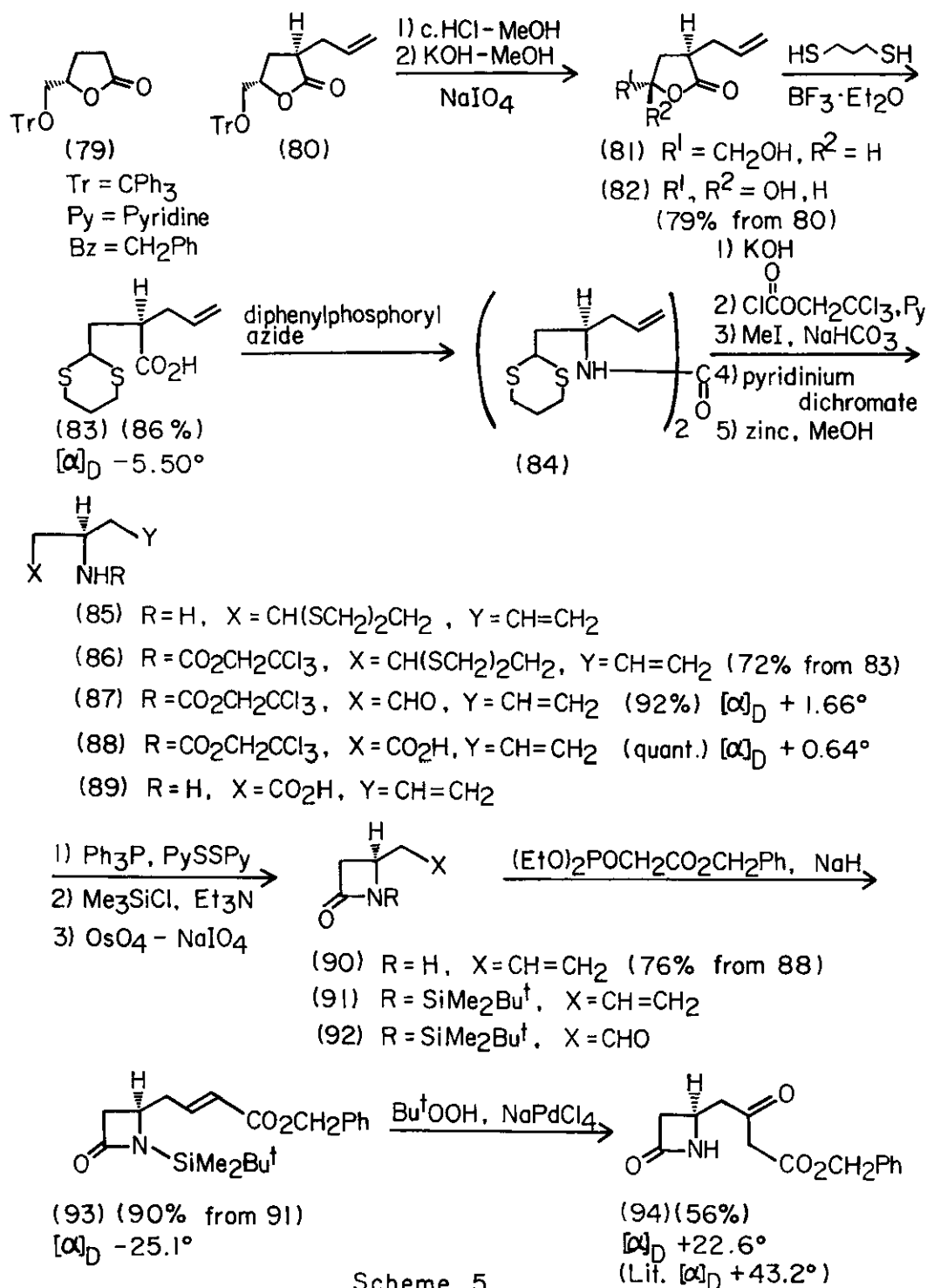
Scheme 3 - (1)



Scheme 3-(2)



Scheme 4



Scheme 5

(+)-thienamycin synthesis. The optical purity of (111) was determined by the transformation of 106 into the known 94.^{33,34a} On the basis of the obtained optical rotational value, the stereocontrolled transformation from D-glucosamine to the target molecule was performed throughout without loss of optical purity.

Scheme 6

The above β -amino acid (103) was converted into p-nitrobenzyl ester (119),³⁷ whose spectral data (i.r. and ¹H NMR) and optical rotation are identical with those of SQ-27860 p-nitrobenzyl ester.¹⁶ Thus, the absolute configuration of SQ-27860¹⁶ was confirmed to be 5-R by this synthesis.

Scheme 7

II-4 Syntheses from D-Glucose

D-Glucose is readily available and an inexpensive starting material as a chiral source in organic synthesis. Independently, three groups have published the preparation of the key intermediates for the synthesis of (+)-thienamycin, such as 125 (P.L. Durette - Scheme 8),³⁸ 135 (K. Koga - Scheme 9),³⁹ and 144 (S. Hanessian - Scheme 10),⁴⁰ with the desired stereochemistry, from D-glucose.

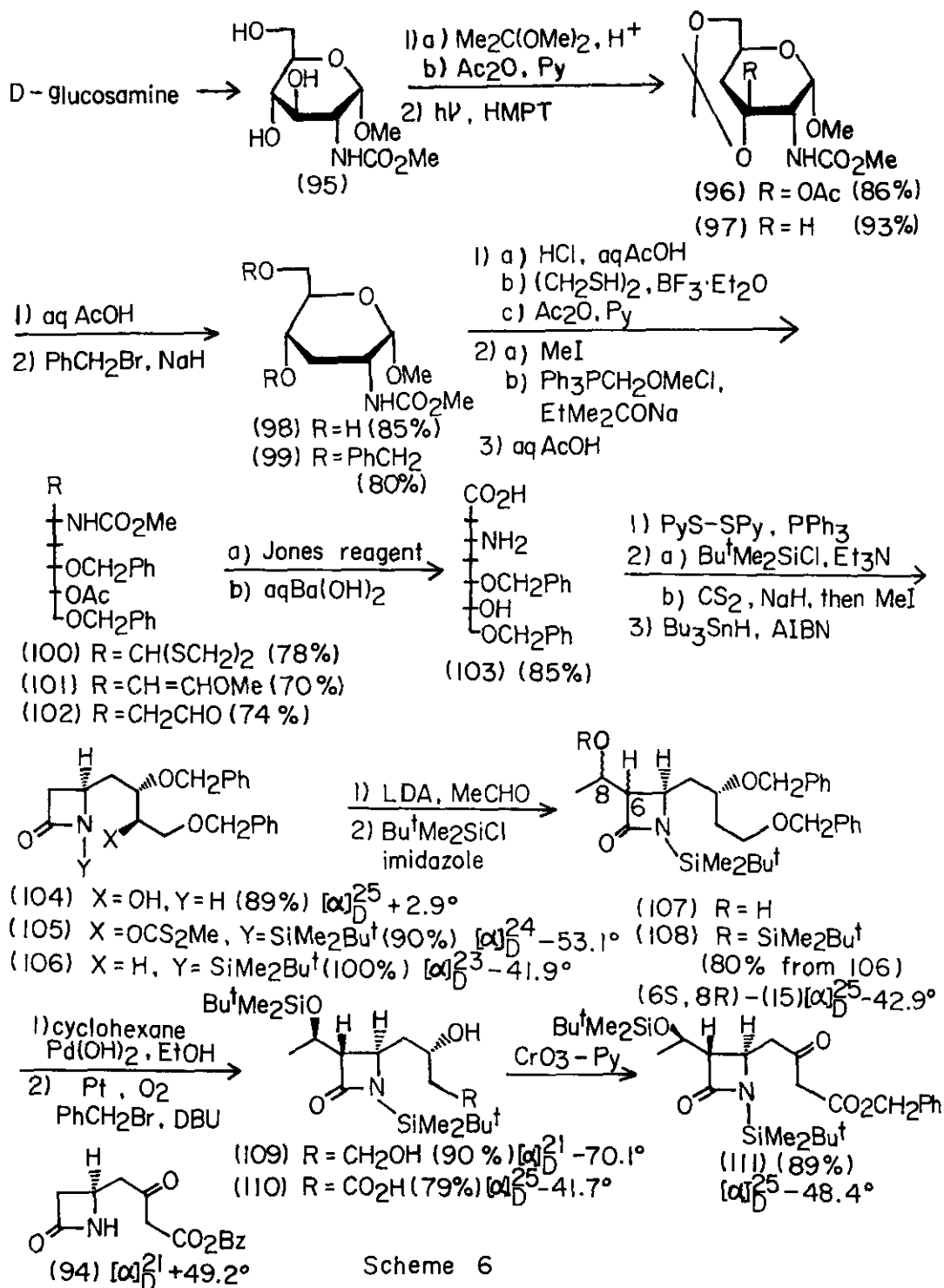
Scheme 8

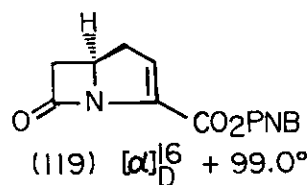
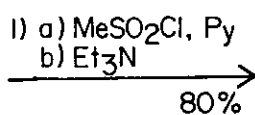
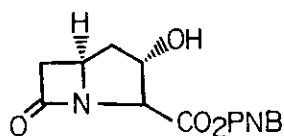
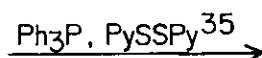
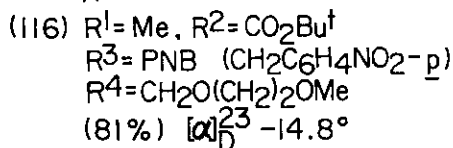
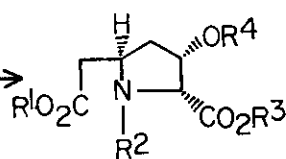
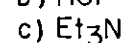
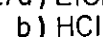
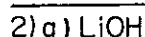
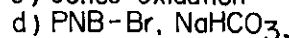
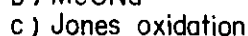
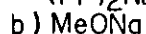
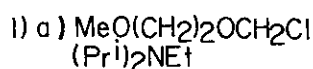
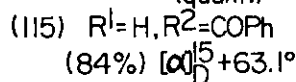
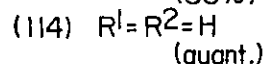
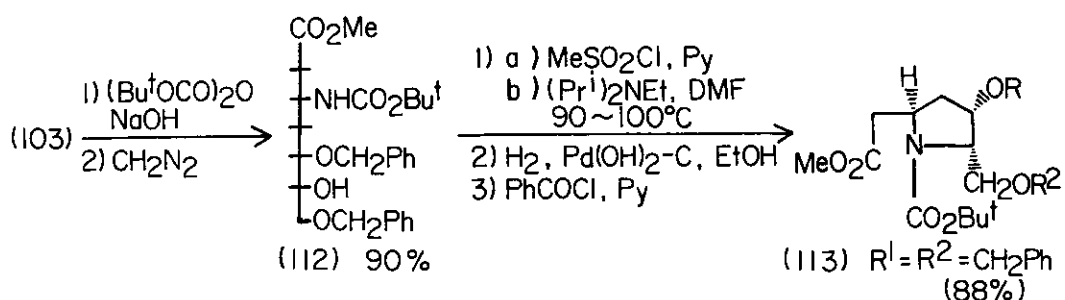
Scheme 9

Scheme 10

On the other hand, Vasella and Knierzinger prepared 6-epithienamycin (158) from D-glucose,⁴⁵ as shown in Scheme 11. The compound possessing a 5R-6R-8R configuration, like 158, had not been found in nature.

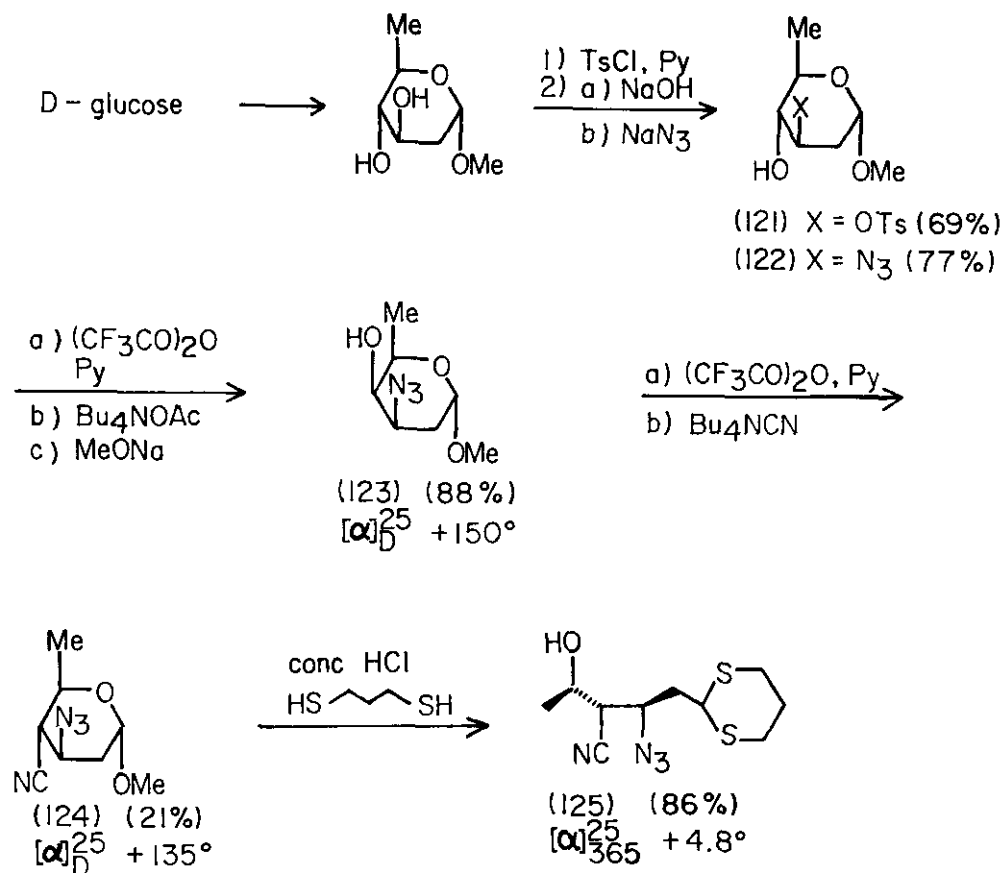
Scheme 11





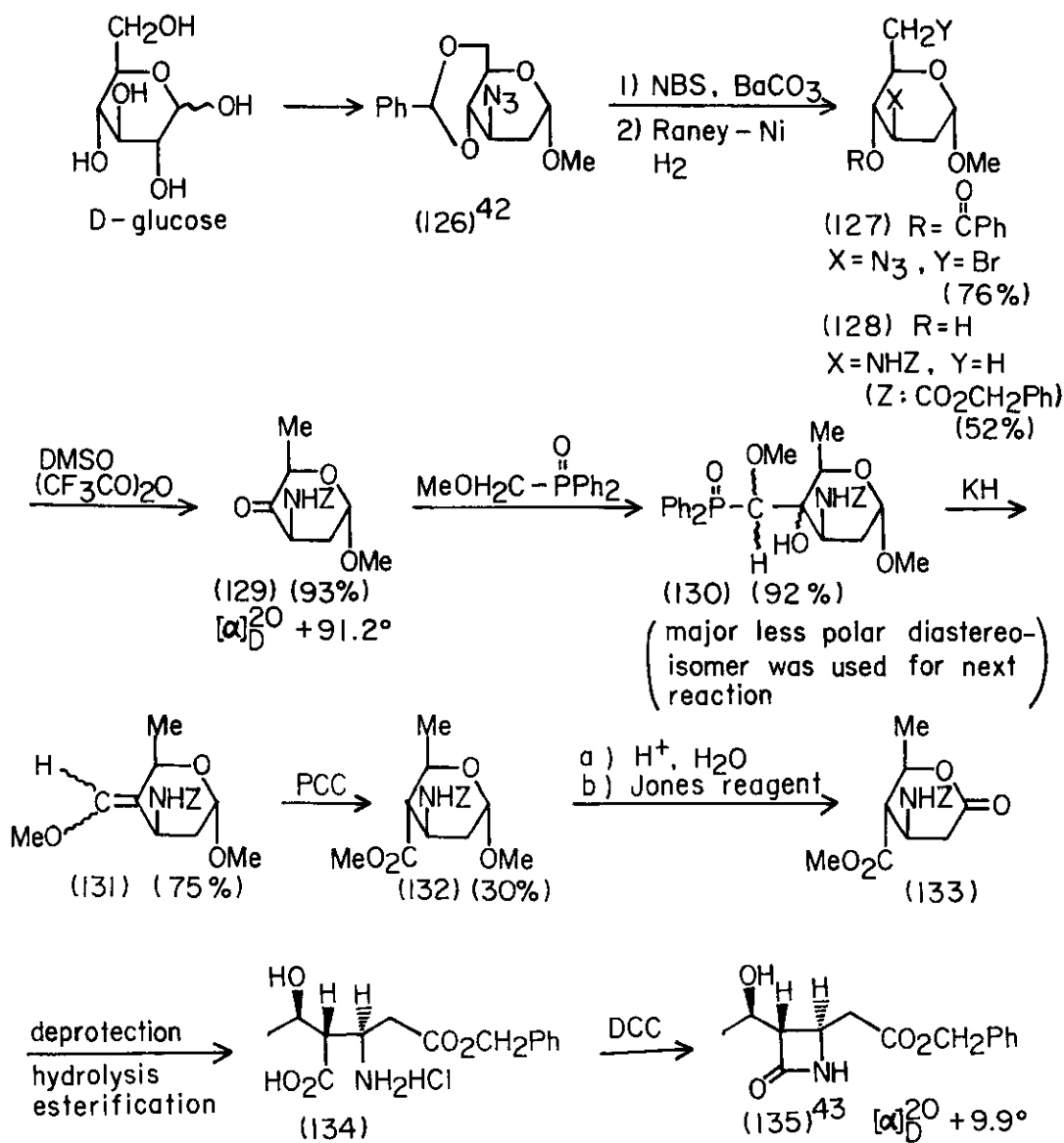
Scheme 7

i) P. L. Durette



Scheme 8

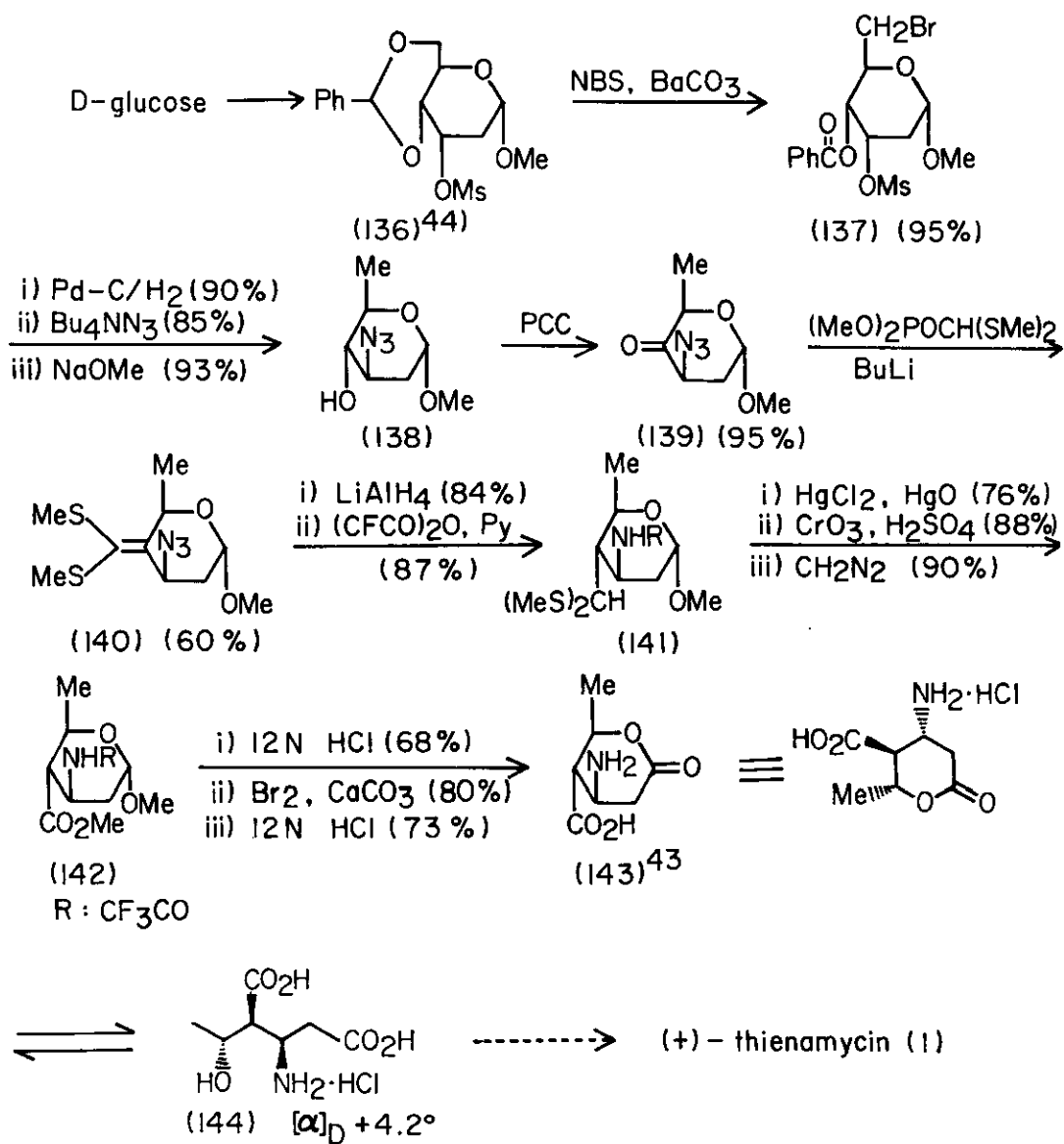
ii) K. Koqa



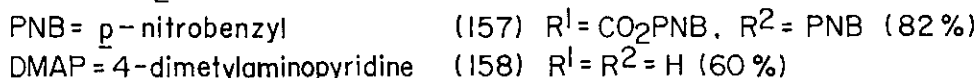
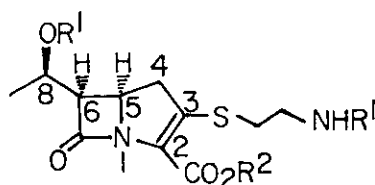
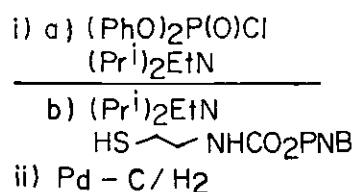
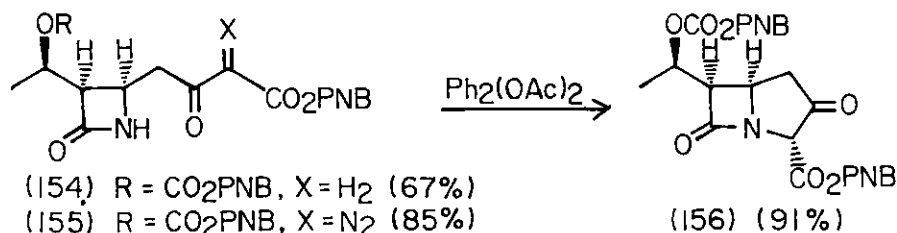
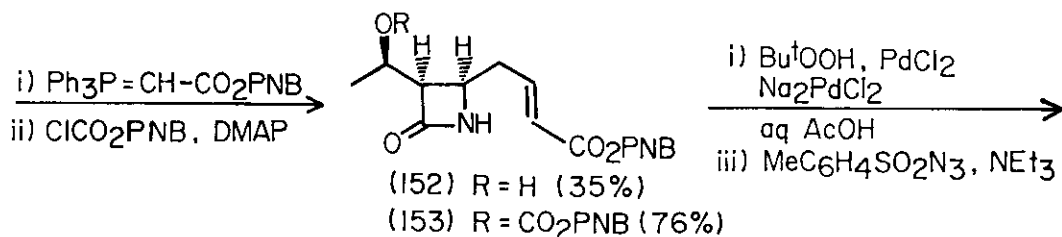
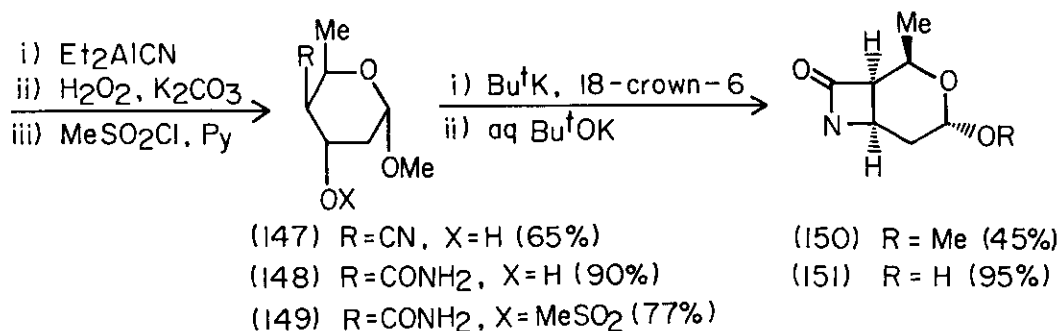
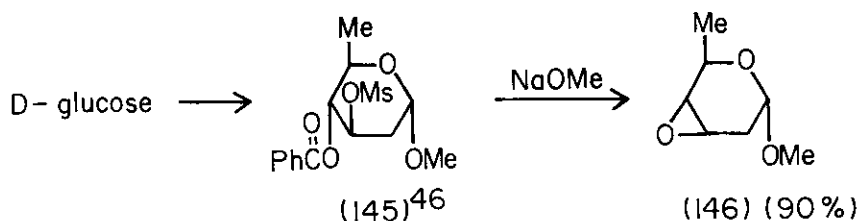
-----> (+)-thienamycin (1)

Scheme 9

iii) S. Hanessian



iv) A. Vasella



Scheme 11

II-5 Synthesis from D-Glyceraldehyde Acetonide

Yamada and his coworkers synthesized (4S)-azetidinone (169),⁴⁷ a synthetic intermediate for (+)-thienamycin (1), using the highly stereoselective 1,4-addition reaction as a key step. Addition of benzylamine to the chiral α,β -unsaturated ester (160a), prepared from D-glyceraldehyde acetonide (15a),⁴⁸ gave 161 stereoselectively. The product ratio of 161 and 162 in this addition reaction was not dependent on either the Z or E conformation of 160 but on the reaction temperature. The conversion of 161 into 169 is outlined in Scheme 12.

Scheme 12

II-6 Synthesis from Chiral Hydroxybutyric Acid

Retrosynthetic analysis of (+)-thienamycin (1) suggests the possibility of 3R-hydroxybutyric acid as a chiral precursor.

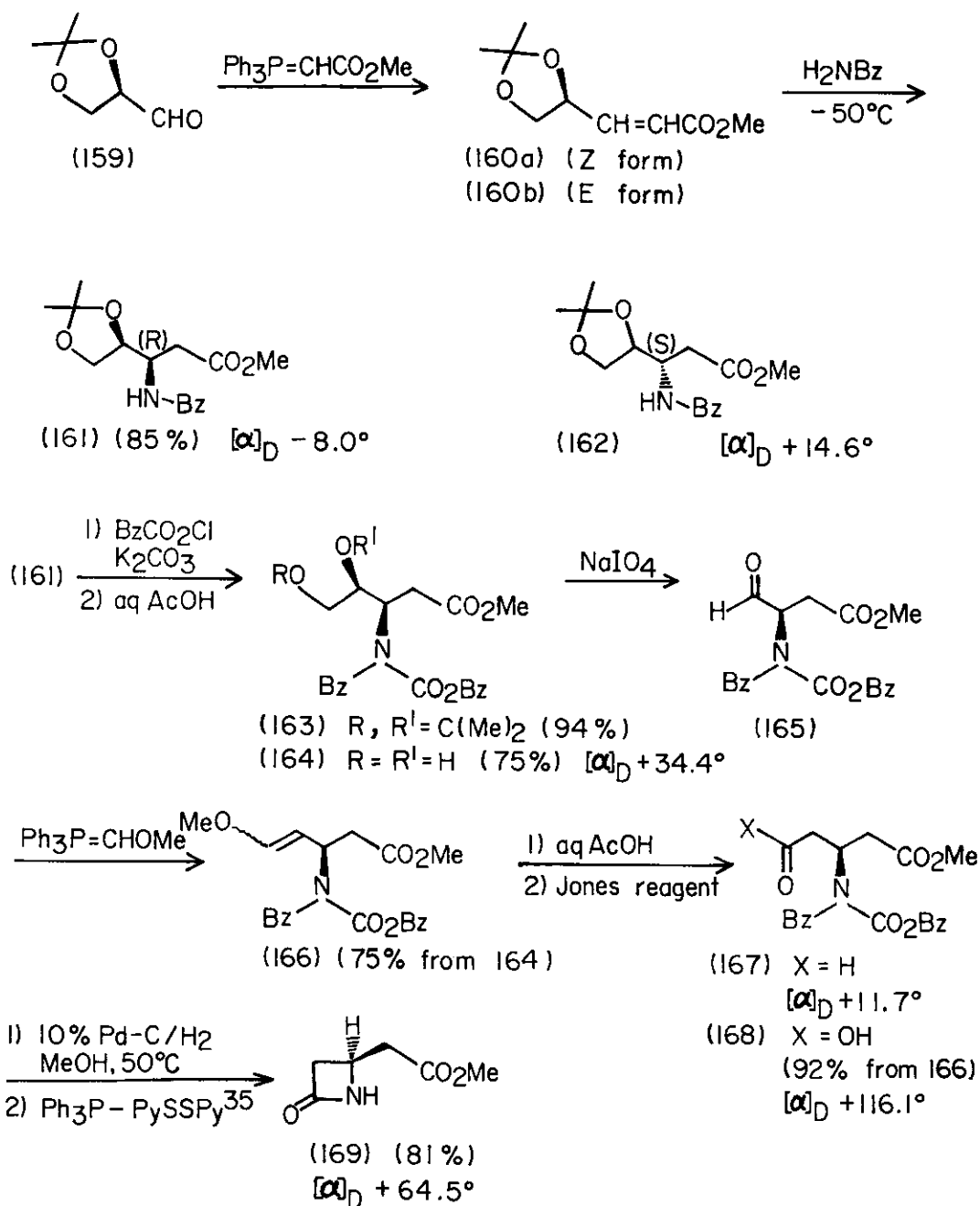
Azetidinone formation by the reaction of ester enolates and N-trimethylsilylimines was investigated by Hart and coworkers.⁴⁹ The stereochemical course of the enolate-imine condensation reaction depends on the ester enolate geometry. Usually, (E)-enolate gave mainly cis-azetidinone. The reaction of racemic 170 with imine (171) gave partially separable β -lactams (172)-(175), whose structures were confirmed by their conversion into known β -lactams. On the other hand, the ester (+)-170 and imine (176) afforded a mixture of β -lactams (177), which could be converted into separable forms by silylation.

Scheme 13

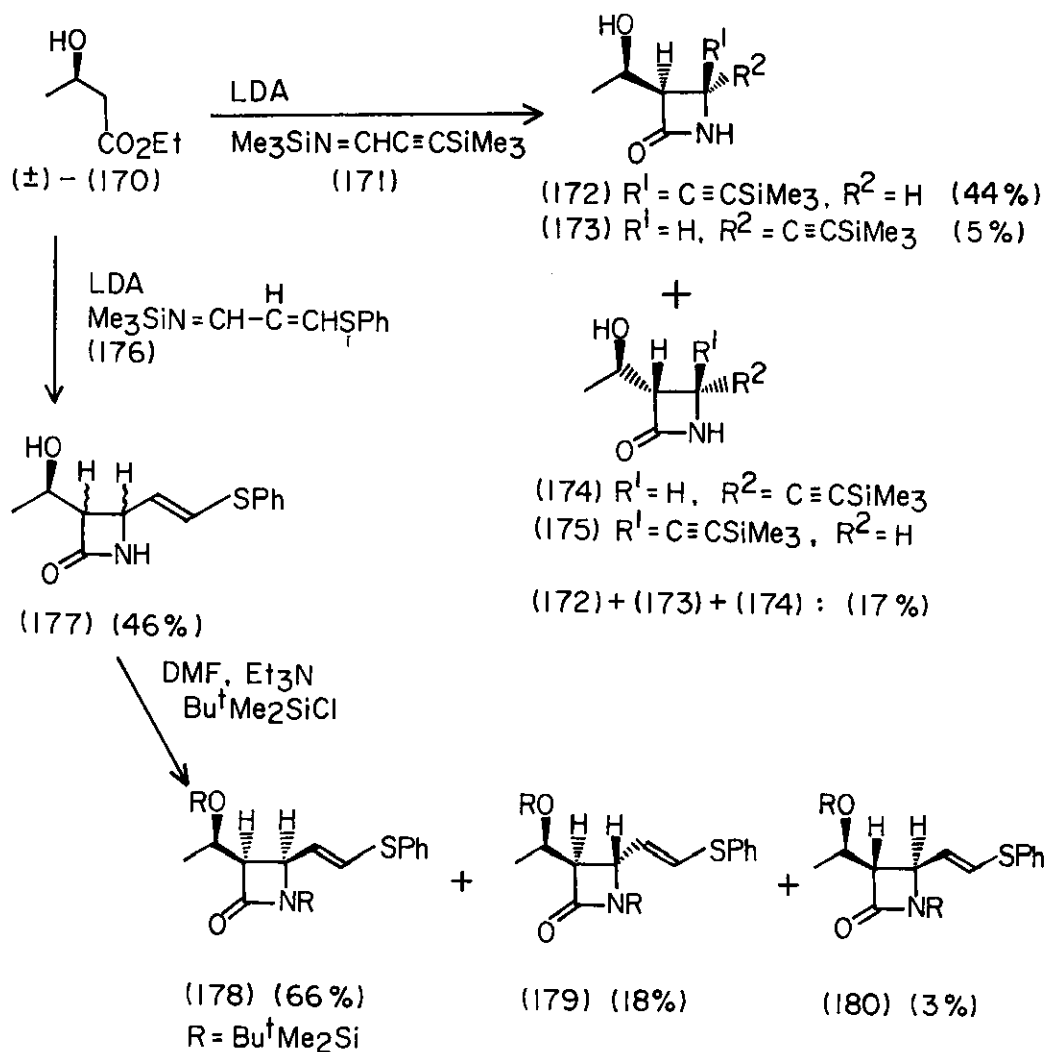
Syntheses of chiral intermediates for the preparation of (+)-thienamycin (1) using enolate-imine condensation methodology was reported by two groups, independently. Nakai and coworkers prepared the known (+)-70 from azetidinone (-)-(172),⁵⁰ easily derived from R-(-)-(181).⁵¹ The optical purity of the obtained (+)-(70) was deduced to be 69% by comparison with the highest literature $[\alpha]_D$ -value $[+50.0^\circ]$.⁵²

Scheme 14

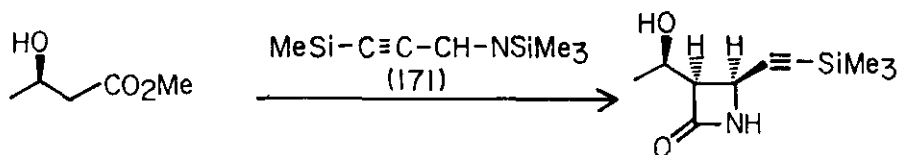
Shibasaki and coworker prepared the (+)-thienamycin (1) intermediate (135)⁵³



Scheme 12

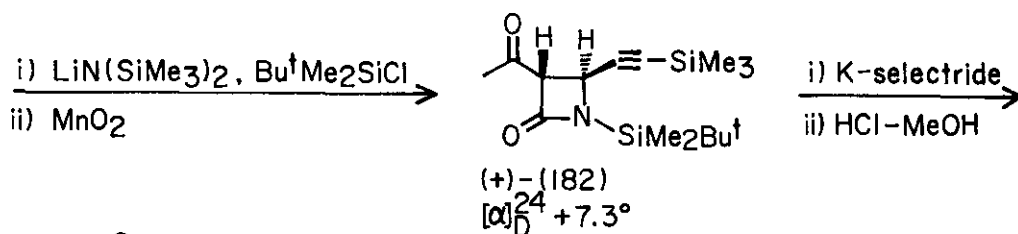


Scheme 13

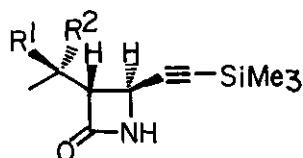


R-(-)-(181) (79% optical purity)

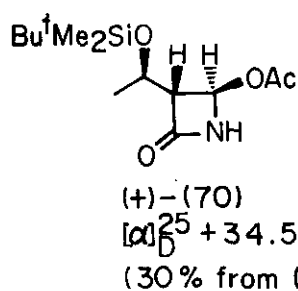
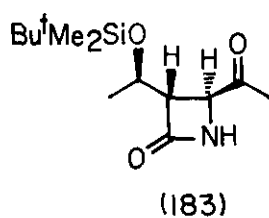
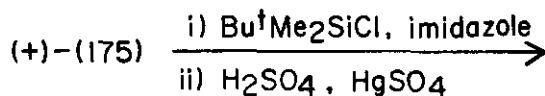
(-)-(172)
(major product)
 $[\alpha]_D^{16} - 11.8^\circ$



i) K-selectride
ii) HCl-MeOH



(+)-(175) $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$
 $[\alpha]_D^{25} + 47.2^\circ$, (62% from 6)
(-)-(173) $\text{R}^1 = \text{H}, \text{R}^2 = \text{OH}$



Scheme 14

utilizing the aldol-type condensation of the vinyloxyborane (185) with the enolizable imine (186). The reaction product, β -benzylamino thiol ester, (187) was assumed to have the configuration leading to the stereoisomer (190b). The authors anticipated that the epimerization required at C-3 to obtain the (+)-tienamycin intermediate (10) could be achieved during azetidinone formation. Indeed, the stereoisomer (190a) was stereoselectively obtained by the subsequent ring closure reaction and 190a was further transformed to the known compound (135).³⁹

Scheme 15

Georg investigated a highly diastereoselective method to synthesize 194 having the correct relative stereochemistry of thienamycin (1) from the racemic 3S*-hydroxybutyrate employing the chelation-controlled aldol-type reaction as a key step. Their study is shown in Scheme 16.

Scheme 16

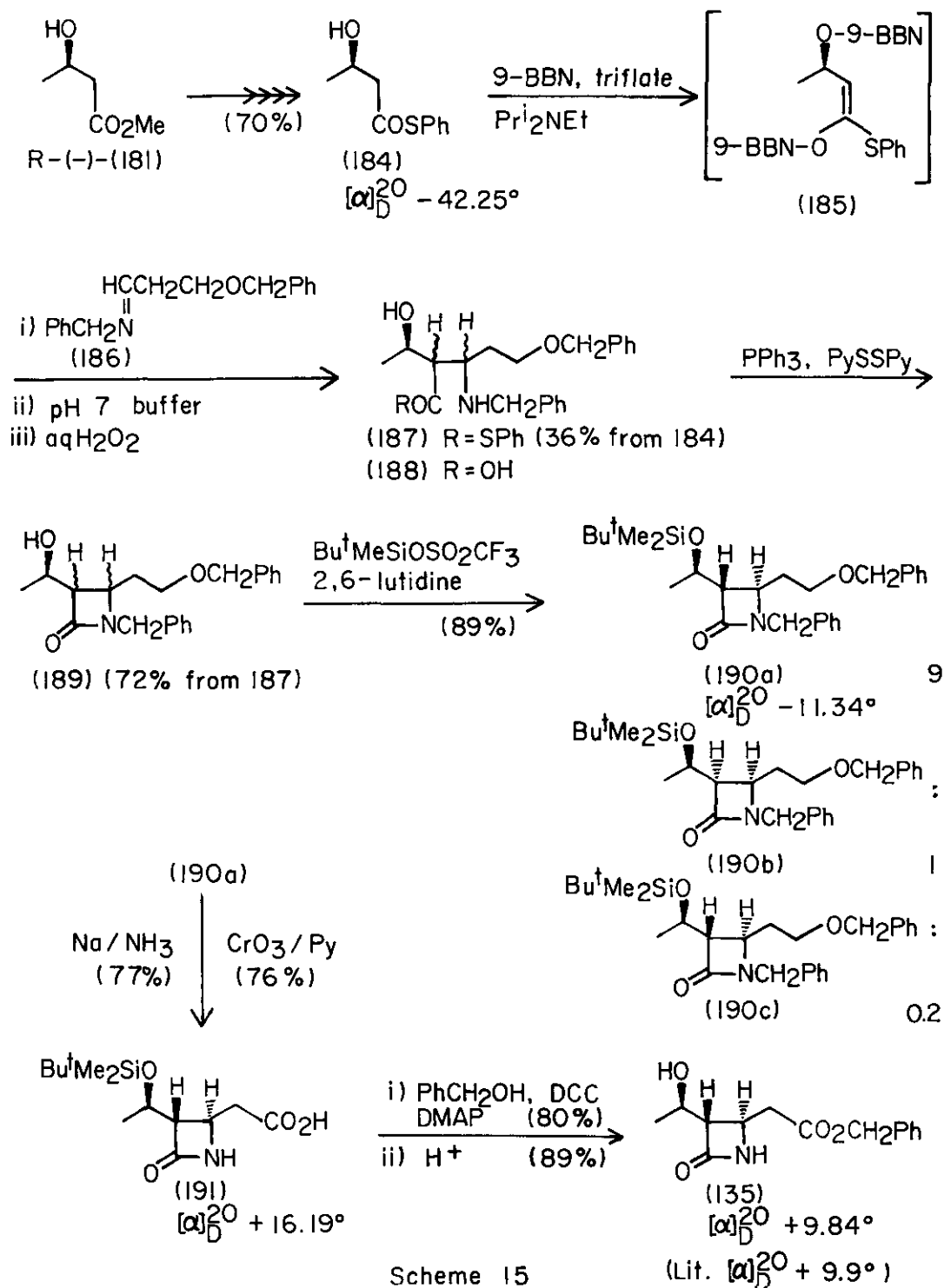
A similar enolate-imine condensation was applied to the reaction of S-(+)-(170) with 195 by Panunzio and coworkers.⁵⁵ The reaction product was a mixture of 4S and 4R diastereoisomers in a ratio of 7:3, respectively. This low stereoselectivity at the C-4 position was ignored because of the C-4 configuration in a later step. Inversion of the hydroxy group of 196 was achieved by applying the Mitsunobu procedure to give 198. Compound (198) was transformed into reported compound (201)⁵⁶ through two alternative routes, as described in Scheme 17.

Scheme 17

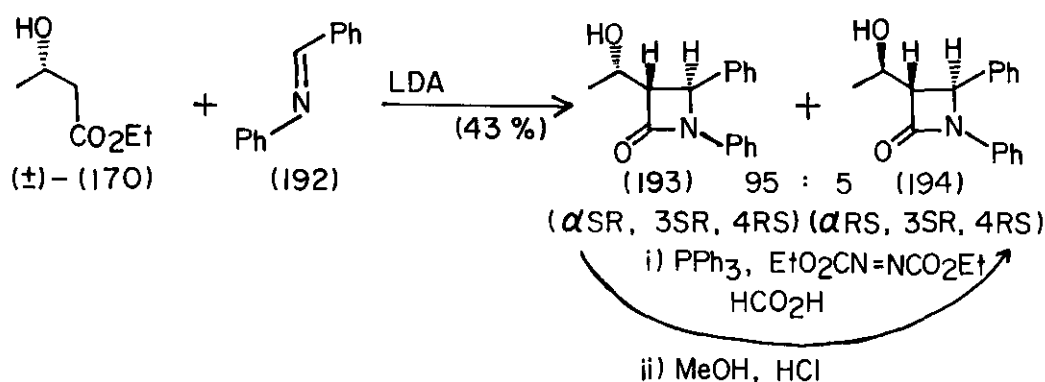
II-7 Synthesis from 6-Aminopenicillanic Acid

Although 6-aminopenicillanic acid (6-APA) is considered a readily available and inexpensive source of natural carbapenam compounds or its intermediates, it is necessary to convert C-5 thio and C-6 amino groups of penicillins into two properly functionalized alkyl groups with correct stereochemistry.

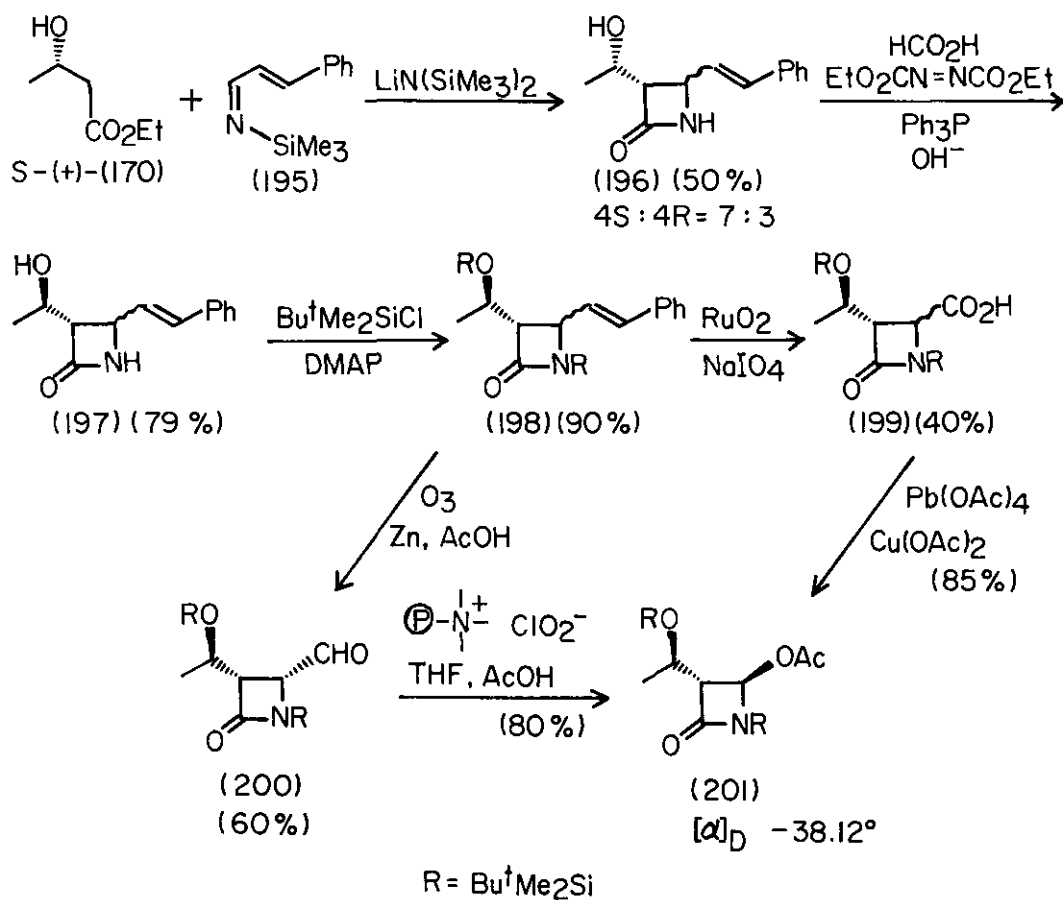
Karady and coworkers reported a stereospecific conversion of penicillin to



Scheme 15



Scheme 16



Scheme 17

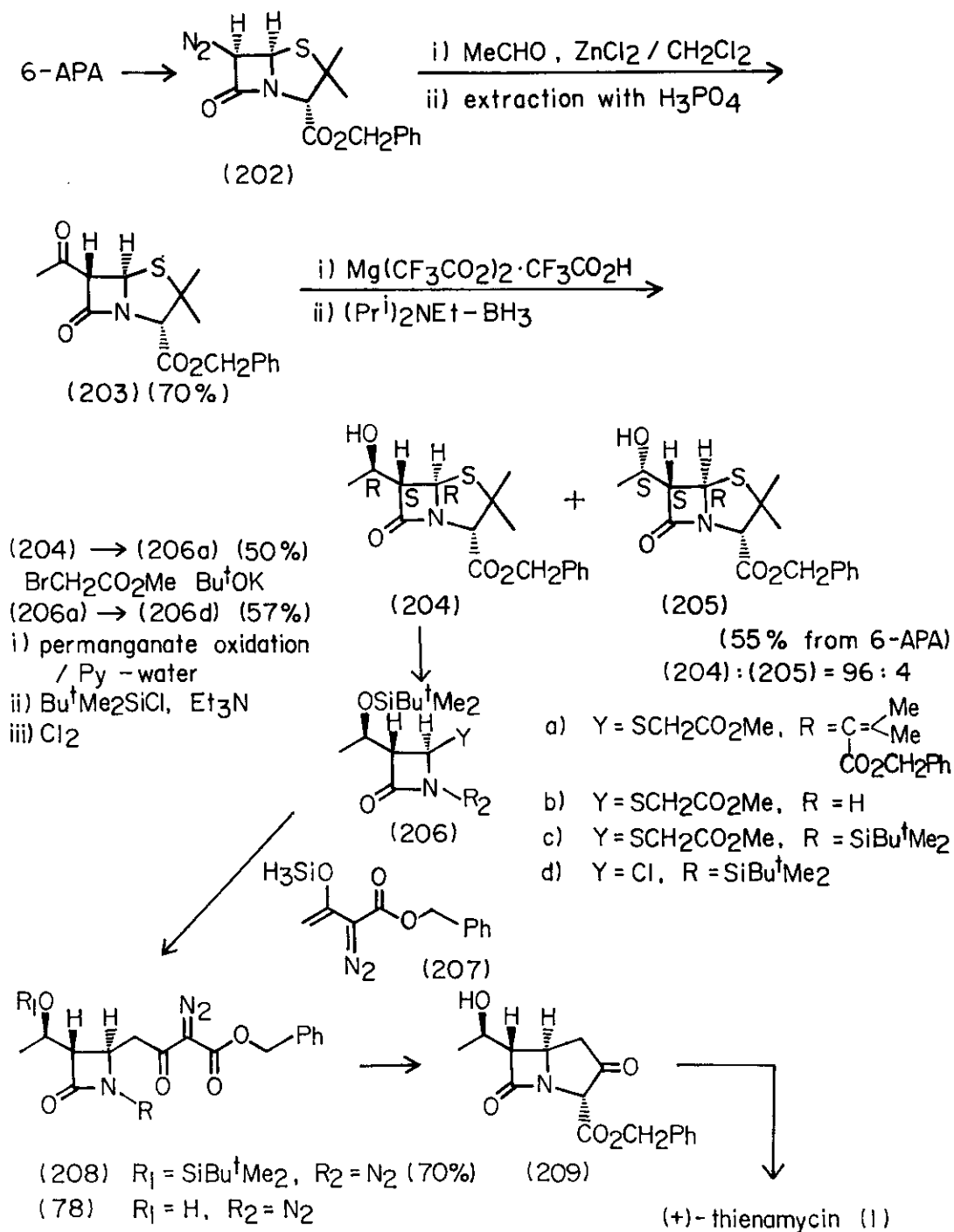
(+)-thienamycin.³² This synthesis involved two noteworthy features, which were the stereospecific amine-borane reduction of the acetyl group and the one-step introduction of an α -diazoacetoacetate unit required for the construction of the bicyclic system. Namely, the reaction of benzyl 6-diazopenicillanate⁵⁷ (202) with acetaldehyde afforded an unstable benzyl acetyl penicillanate⁵⁸ (203). Highly stereospecific reduction of the magnesium chelate of (203) with diisopropylamine-borane yielded the desired (R)(S)(R) and (S)(S)(R) alcohols (204) and (205) in a ratio of 96:4. The opening reaction of the thiazolidine ring of O-protected (204) with methyl bromoacetate and ^tBuOK gave 206a. Permanganate oxidation, successive protection of an amide nitrogen, and chlorinolysis at the C-4 position afforded 206d. The silver-mediated coupling reaction of a four carbon diazo-containing unit (207) with (206d) yielded 208. Ring closure of 78 (deprotected 208) to the bicyclic keto ester (209)⁵⁹ according to the carbenoid insertion method^{34b} accomplished the formal total synthesis of (+)-thienamycin (1).

Scheme 18

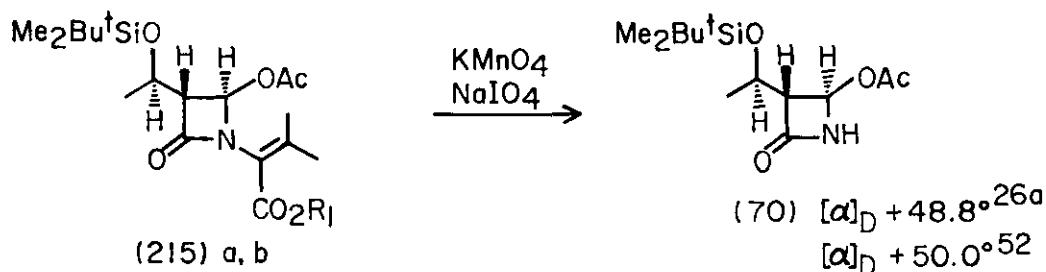
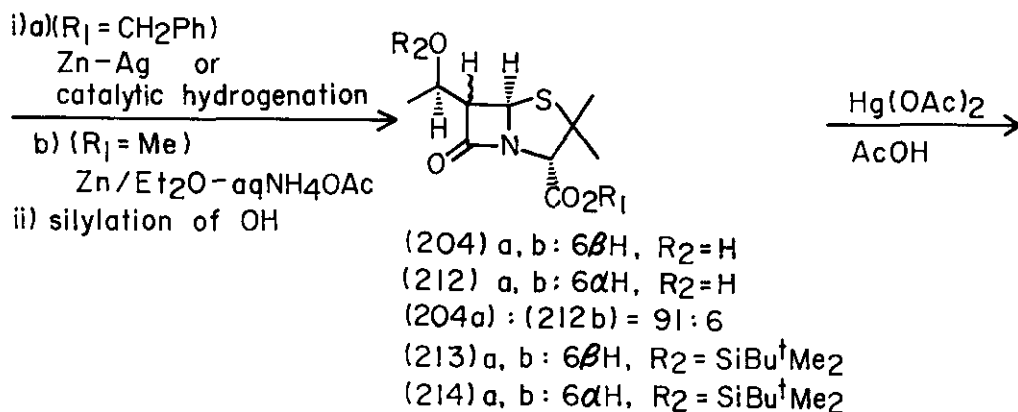
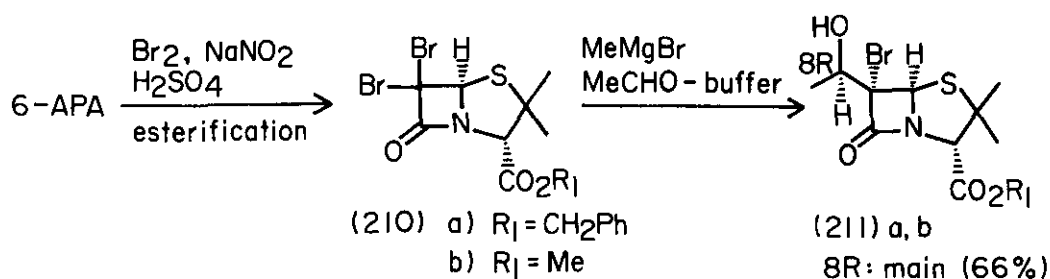
Preparation of 70 from 6-APA was also independently reported by three groups. Previously, DiNinno et al. reported that hydroxyethylation at the C-6 position of penicillanate enolate gave 211.⁶⁰ Reductive debromination of 211 was achieved by using three different methods; Zn-Ag couple,⁶⁰ catalytic hydrogenation⁶⁰ or Zn in a mixture of diethyl ether and aqueous ammonium acetate,⁵² to give stereoisomers (204) and (212). Oida and coworkers have published the conversion of protected 204 (213a) to 70 by two steps,^{26a} which involved treatment with mercuric acetate in acetic acid and permanganate oxidation. DiNinno also reported a synthesis of 70 from methyl ester (204b).⁶⁰ The synthesis of 70 by the Sankyo group was essentially the same as the above two groups.⁶¹

Scheme 19

Syntheses of versatile starting materials (222) and (60) for carbapenam type compounds were reported by the Sankyo group.⁶² Treatment of the diphenylseleno derivative (216)^{63,64} with methylmagnesium bromide, followed by reaction with an excess of acetaldehyde afforded 217 and 218 in a ratio of 30:1. When



Scheme 18



Scheme 19

n-butyllithium was used instead of methylmagnesium bromide, the ratio changed to 2:3. Tin hydride reduction of 217 removed the phenylselenenyl group to give 212. Silylation of 212, followed by oxidation with *m*-chloroperbenzoic acid gave sulfone (219). Epimerization at the C-6 position was achieved by treatment with a catalytic amount of diazabicyclo[4.3.0]nonene to afford 220. After the ring opening of its thiazolidine, the *N*-substituent of 221 was oxidatively removed to give 222. The compound (222) could be transformed into 66. These reactions were also applicable to 211b. Transformation of 222 or 66 to the known intermediate³¹ for the preparation of (+)-thienamycin is shown in Scheme 20.⁶⁵

Scheme 20

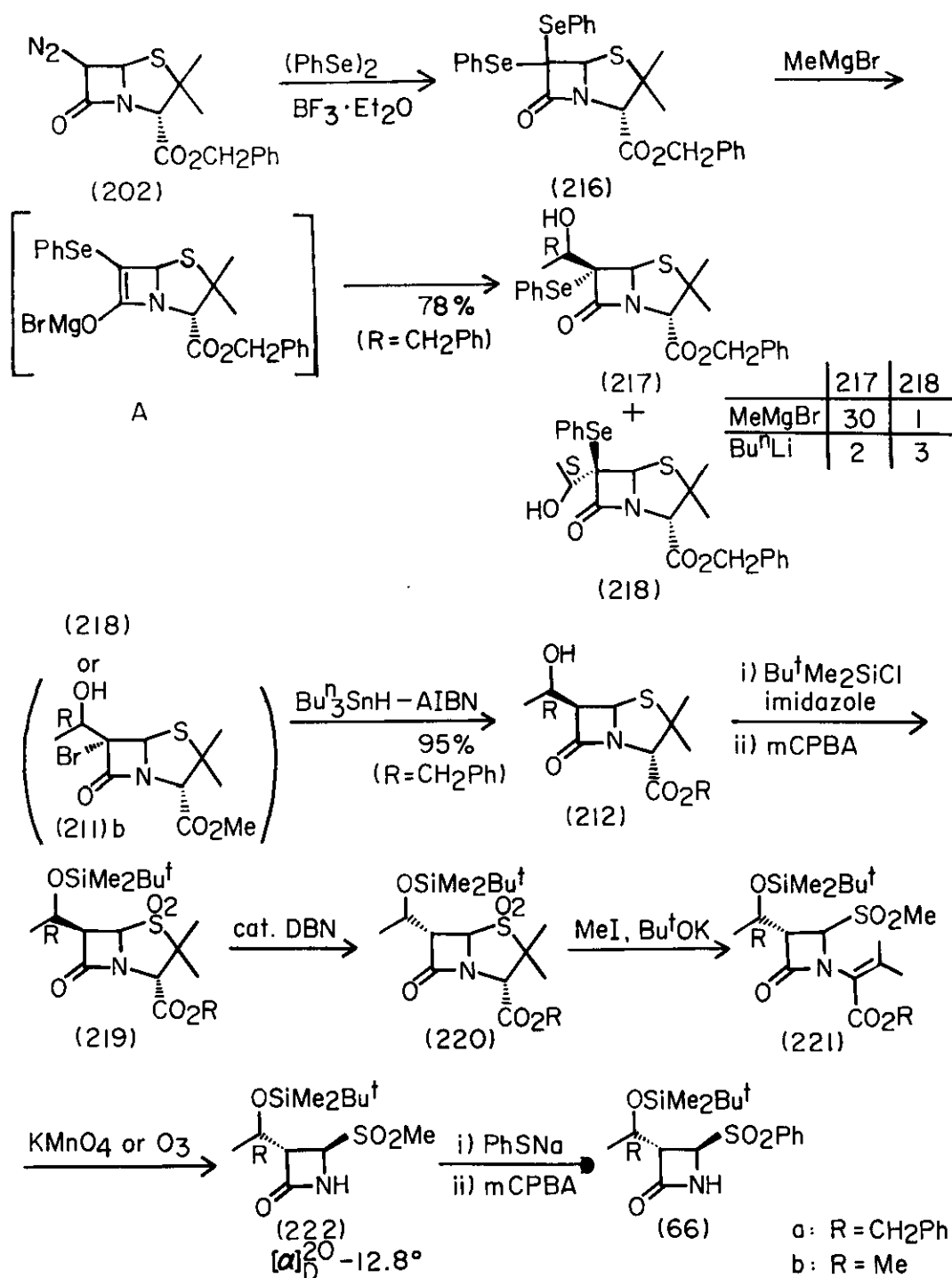
The above 4-iodomethylazetidinone (229)⁶² was further converted into an important precursor for the synthesis of carbapenam derivatives via the transiodopropenylation method.⁶⁶ Reaction of protected (229) ((230))⁶⁵ with the lithium salt of allylthiothiazoline gave 231. Rearrangement with methyl iodide, followed by Kornblum oxidation afforded aldehyde (233). The carboxylic acid (234) was obtained from 233 by the method of Smith and Holm.⁶⁷ After esterification of 234, palladium-catalyzed oxidation of the β -position of the α,β -unsaturated ester gave the β -keto ester (237). Cyclization of 237 using the Merck method afforded the known 238.³¹

Scheme 21

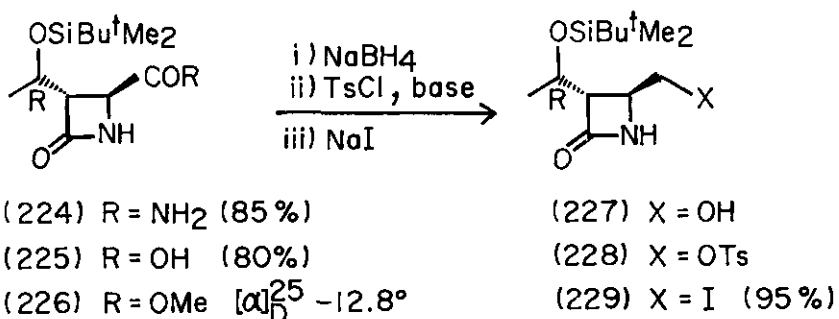
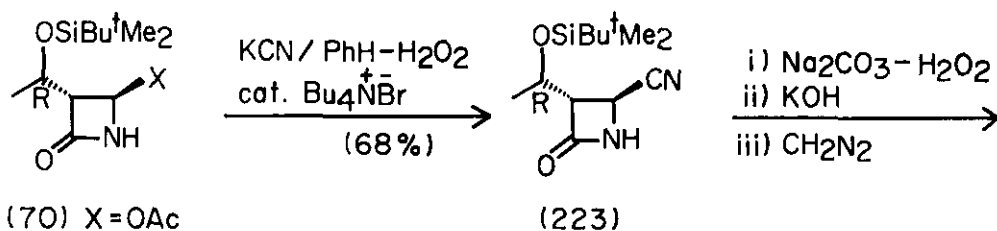
The Sankyo group developed a new allyl unit substitution reaction at the C-4 position of the 4-acetoxiazetidinone derivative⁶⁸ (70)⁶¹ with tetraallyltin (239) in the presence of 0.1 eq. of trifluoroborane etherate. The 4-allylazetidinone (240) obtained was converted to dethiathienamycin (250), which showed half of the antibacterial activity of (+)-thienamycin (1). The synthesis of 250 is outlined in Scheme 22.

Scheme 22

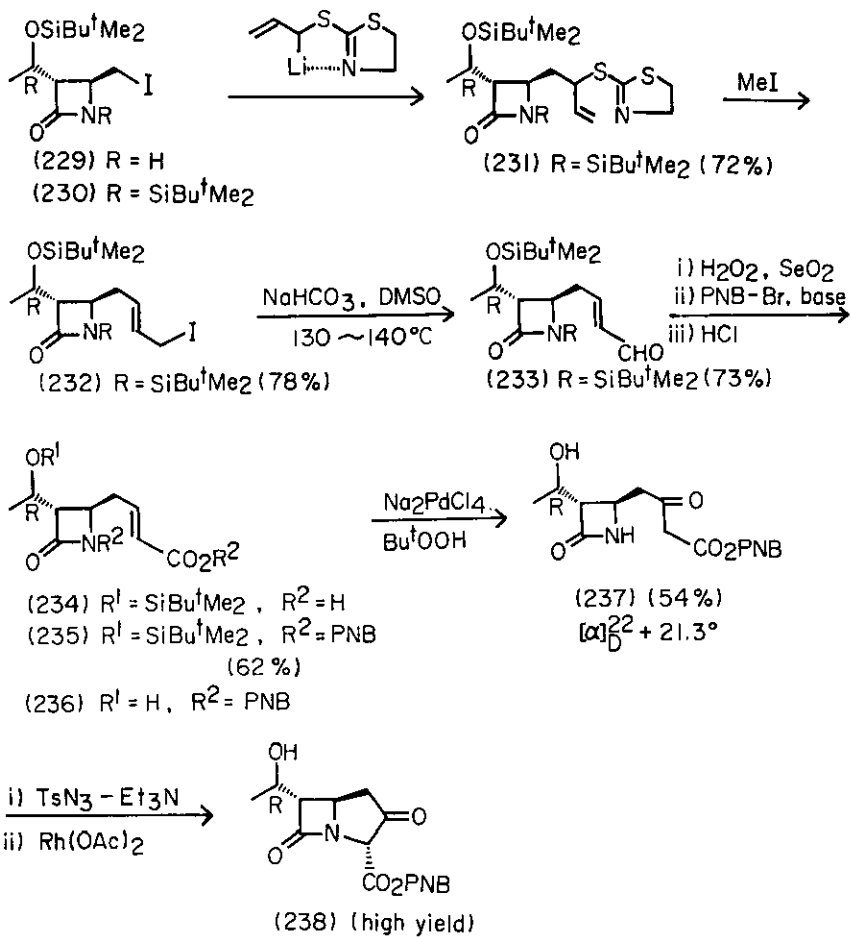
A mixture of the R- and S-carbonates (254) and (255), separable by silica gel chromatography, was obtained⁶⁹ by protection of the hydroxy group in an epimeric



Scheme 20 - (I)

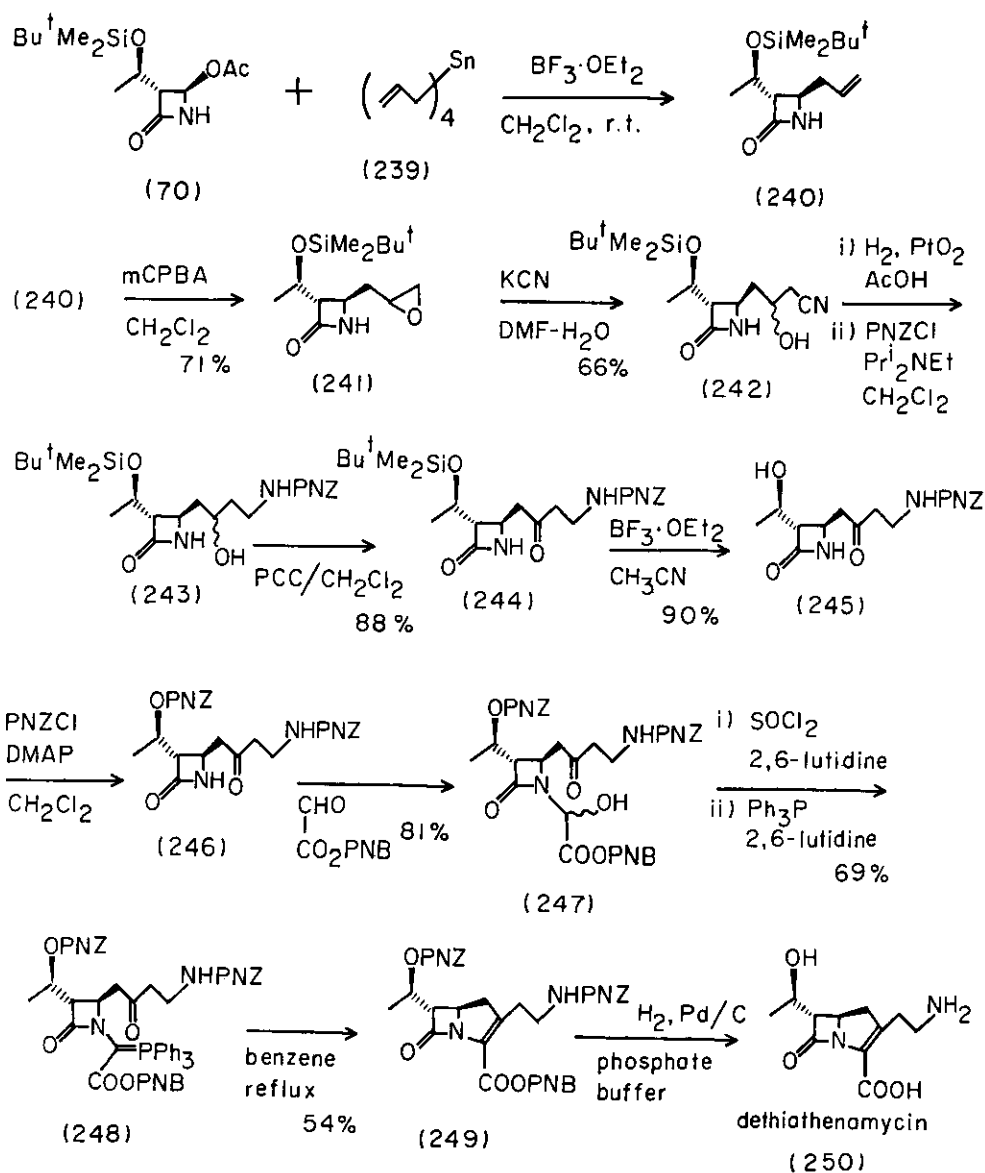


Scheme 20-(2)



PNB: p - nitrobenzyl

Scheme 21



Scheme 22

PNZ: p-nitrobenzyloxycarbonyl
 DMAP: 4-dimethylaminopyridine

mixture of (253),^{26a} prepared from (252)⁷⁰ by diethylaluminum chloride-zinc mediated hydroxyethylation with a *p*-nitrobenzyloxycarbonyl group. The Fujisawa group derived 261 and 262 from (254) and (255),⁶⁹ which could then be converted into natural carbapenam compounds. Chlorination of 254 gave an inseparable mixture of the C-4 epimeric chlorides 256 (*cis*:*trans*=9:11), while 255 afforded a separable mixture of the two C-4 epimers, *cis* 258 and its *trans* isomer. The silver-promoted coupling reaction of allylsilane (258) with 256 or 257 proceeded stereo- and regiospecifically to give 259 or 260, respectively. Oxidative removal of the N-substituents of 259 or 260 afforded 261 or 262, respectively.

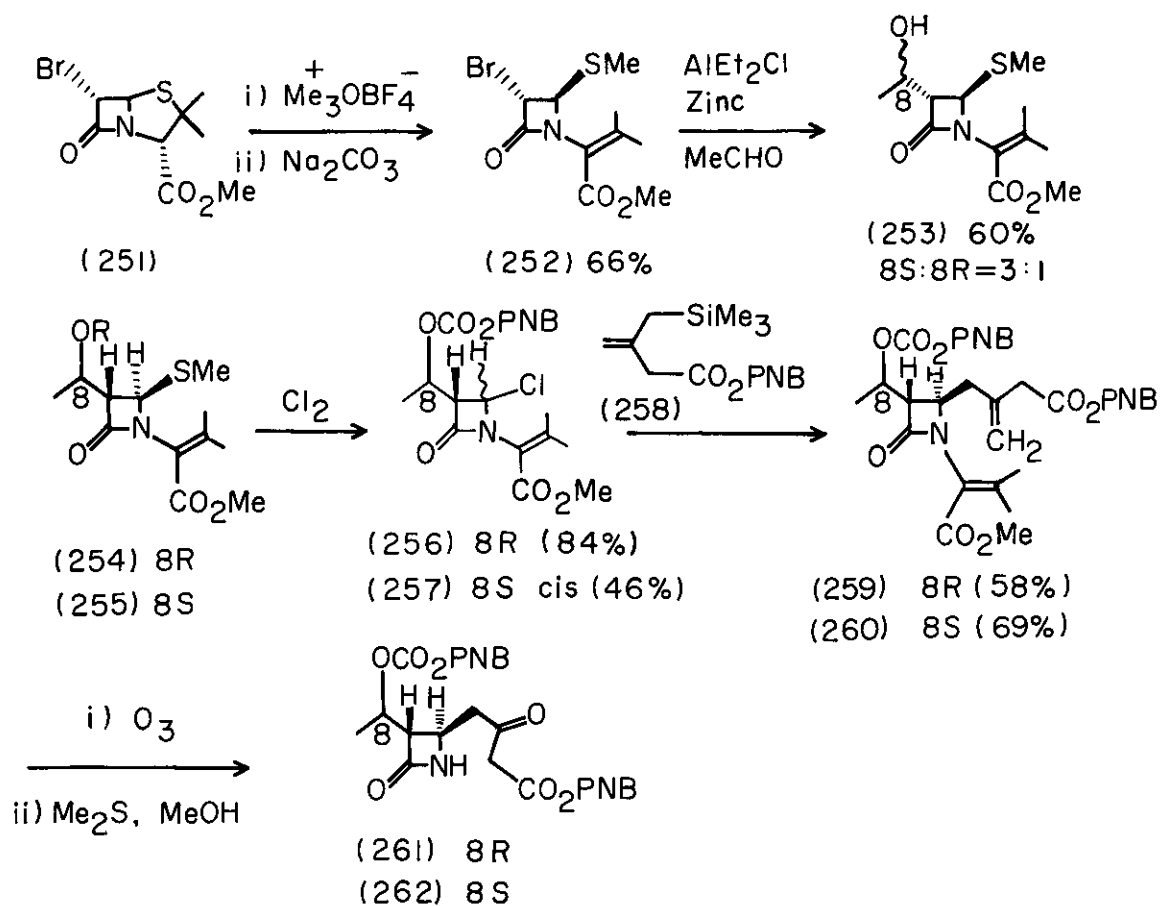
Scheme 23

The Fujisawa group synthesized optically active 6-epicarpetimycin and carpetimycin.^{71,72} Aldol type condensation of (263) ((264)) easily obtained from 6-APA in chiral form, with acetone, followed by treatment with triethylamine gave *trans*-azetidinone (267) and its *cis*-isomer (268). The *trans*-isomer (267) was converted into optically active 6-epicarpetimycins (275), (276), and (277) by employing the Merck method.⁷¹

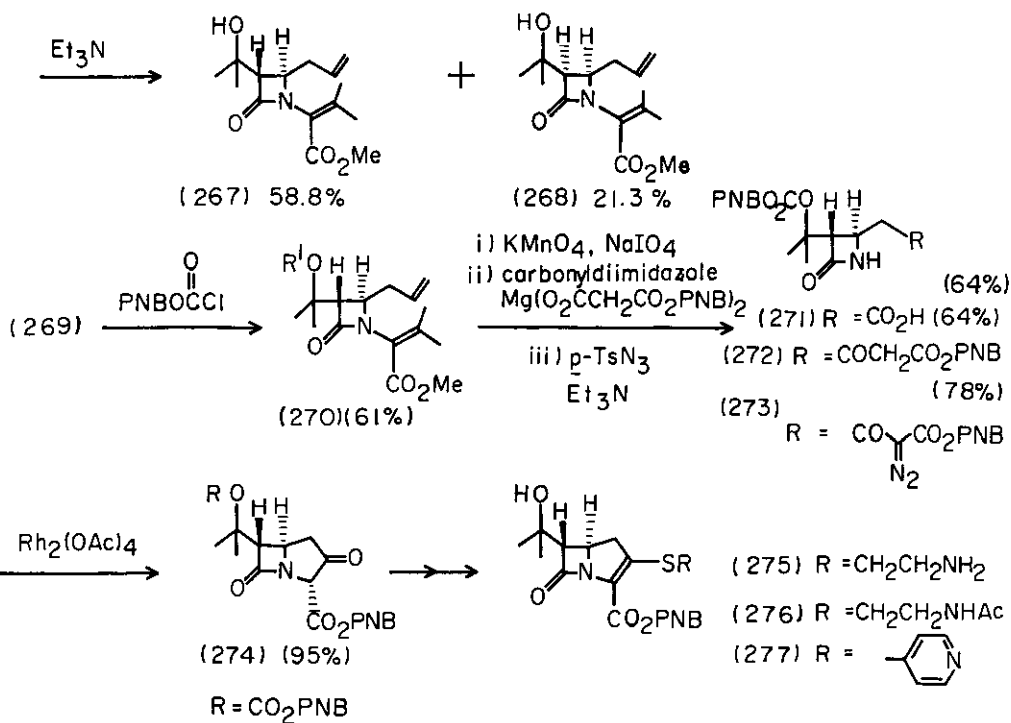
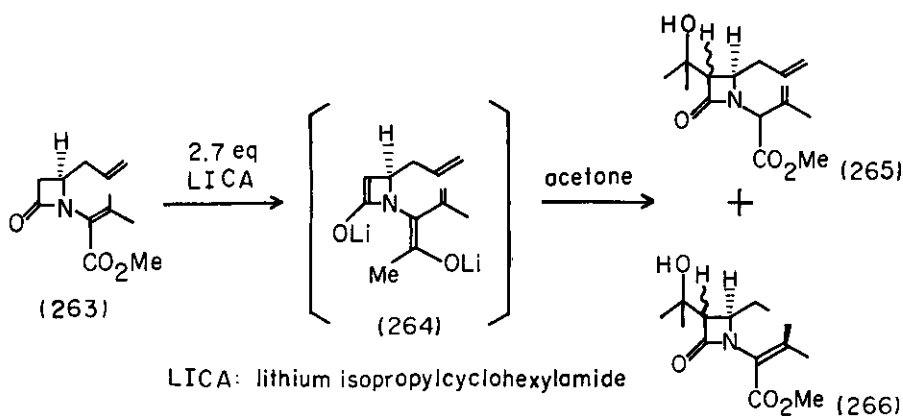
Scheme 24

On the other hand, an aldol reaction of 278⁷² with acetone was conducted to form a 5:1 mixture of 279 and 280. Radical reduction of 271 using tributyltin hydride in the presence of azobisisobutyronitrile afforded the *cis* compound 281 as a major product. The reduction of 282 also gave a similar result. The *cis*-selectivity was explained by the α -face attack of the hydride owing to a steric influence of the 6 β -substituents. Protection of the hydroxy group in 281, followed by removal of the acetonide group gave 283. Carboxylic acid 284 was transformed to carpetimycin derivatives⁷ (285), (286), and (287) by employing the Merck method.⁴³ The improved synthesis of 6,7-*cis*-azetidinone (281) was achieved via the aldol reaction of 288 with acetone followed by kinetic protonation with triphenyltinhydride as a soft proton source.⁷²

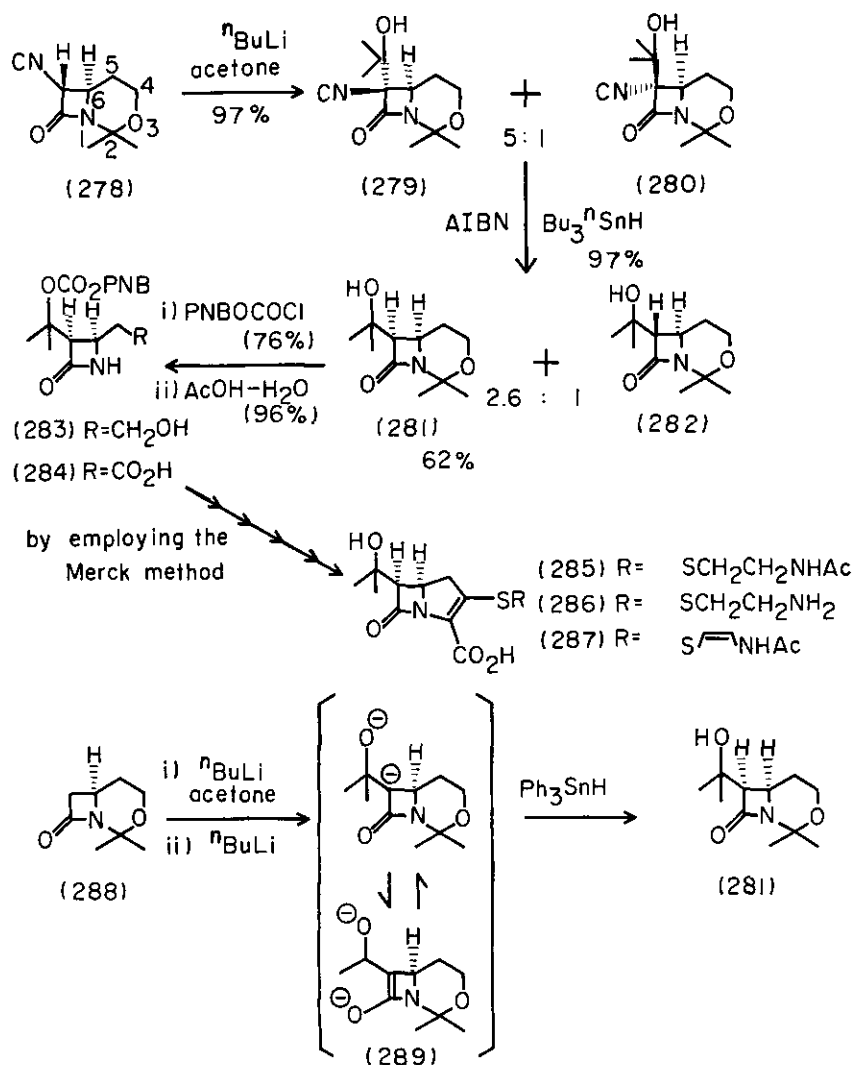
Scheme 25



Scheme 23



Scheme 24



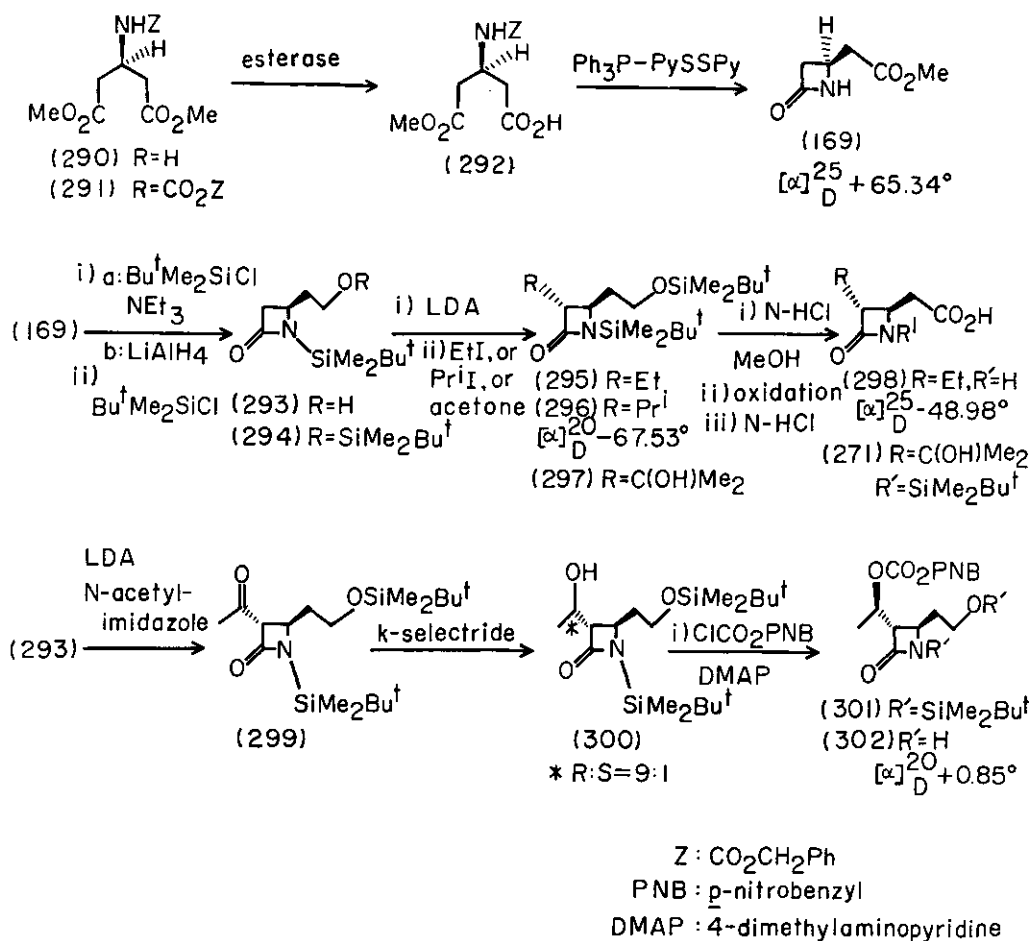
Scheme 25

II-8 Synthesis using Chemicoenzymatic Hydrolysis

Optically active 4-methoxycarbonylmethyl-2-azetidinone (169) had been obtained by selective cyclization of the prochiral β -aminoglutaric acid derivative (291) involving an enzymatic hydrolysis step.³⁵ The optically active compound (169) obtained was converted to the key intermediates (298), (296), (271), and (302)⁷³ for the synthesis of natural carbapenem antibiotics (+)-PS-5 (14),⁷⁴ (+)-PS-6 (15),⁷⁴ 6-epicarpetimycin homologue (276), and (+)-thienamycin (1), respectively. Ohno and coworker reported two stereocontrolled syntheses of natural carbapenem compounds, (-)-carpetimycin A (18)⁷⁵ and (-)-asparenomycin C⁷⁶ (24) using the compounds (292)³⁵ and (293)⁷³ as starting materials.

Scheme 26

Reduction of 292, followed by cyclization gave δ -lactone (303). Stereocontrolled hydroxyisopropylation of 303 was achieved by the reaction of the enolate anion of 303 with acetone to yield 304. The base-catalyzed reaction of δ -lactone (304) easily brought about a retroaldol type reaction by releasing the acetone moiety and did not afford the desired hydrolyzed product (305). On the other hand, the lactone (304) was opened by acid-catalyzed cleavage to afford an equilibrium mixture of 305 and 304 (about 3:1). The mixture of 305 and 304 was separated by column chromatography. Silylation of deprotected 305, followed by Grignard-mediated cyclization and selective removal of N- and O-(primary)silyl groups gave 307. The cis-carboxylic acid (308) was obtained by oxidation of the alcohol (307) using Sarett reagent. Applying Masamune's procedure,⁷⁷ followed by construction of the bicyclic ring system according to the Merck group,³¹ to carboxylic acid (308) afforded keto ester (309). Conversion of 309 to 310 was carried out through the vinyl phosphate,^{31,78} followed by treatment with m-chloroperbenzoic acid to give 311 and 312. Catalytic hydrogenation of 311 or 312 gave natural carpetimycin A (18) or 313, respectively. Reaction of 293 with trimethylsilyl chloride in the presence of lithium diisopropylamide and then with [(methylthio)methoxy]acetone gave E-ethylideneazetidinone 314 as a single product. The E-selectivity of this reaction was explained by assuming that the chelation-controlled aldol reaction occurred from the α -face and was followed by Peterson olefination or syn elimination of Me_3SiOLi . The chelation between the



Scheme 26

lithium cation and oxygens was considered to play a key role in controlling the stereochemistry via transition state A affording the intermediate B. The methylthiomethyl group was selectively cleaved by treatment with mercuric chloride and calcium carbonate; the resultant allyl alcohol (315) was reprotected with p-nitrobenzyl (PNB) chloroformate in the presence of 4-dimethylaminopyridine to give 316. Deprotection of the silyl group of 316 with hydrochloric acid afforded 317. The alcohol (317) was transformed to asparenomycin C (21) by the method similar to that of carpetimycin A (18).

Scheme 27

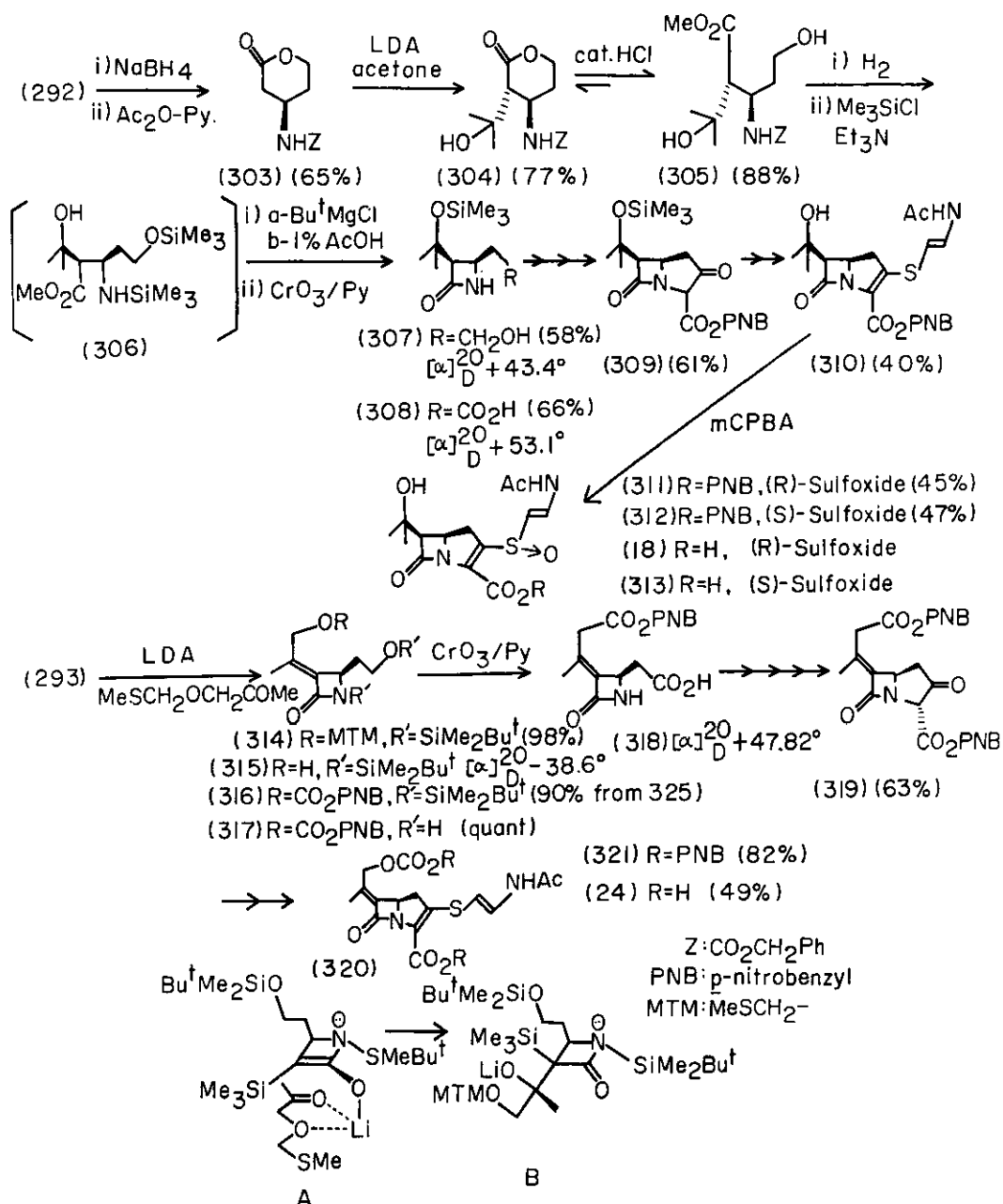
Shibasaki and coworkers reported a stereoselective synthesis of 307⁷⁵ by the use of direct aldol condensation of (322) with acetone via the titanium enolate.⁷⁹ The predominant formation of the cis- β -lactam (324) would be expected in the aldol condensation of (322) and acetone, because a metal cation would be coordinated by the neighboring methoxyethoxymethyl group, thus the metal cation is located on the β -face of the molecule, and the aldol condensation would proceed via the tightly coordinated 6-membered transition state as in the case of (323). Indeed, the predominant formation of (324) was observed in the aldol condensation as expected, although the stereoselectivity was not very satisfactory.

Scheme 28

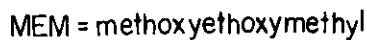
II-9 Synthesis from (2R,3R)-2,3-Epoxybutyric Acid

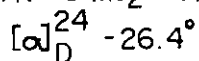
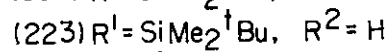
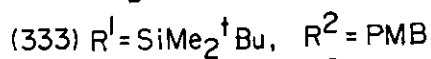
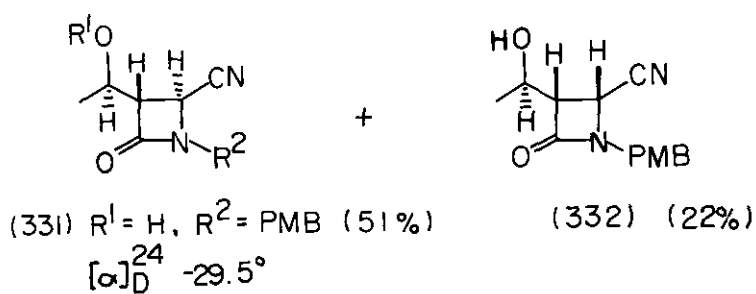
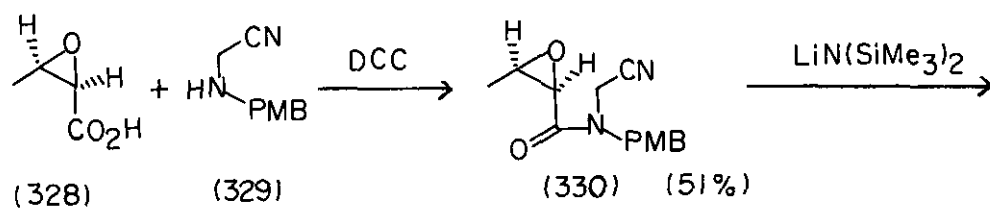
The Sankyo group reported an alternative short step synthesis⁸⁰ of the compound (223) which had already been prepared from penicillin by the same group.⁶⁵ Condensation of (2R,3R)-2,3-epoxybutyric acid (328)⁸¹ with p-methoxybenzyl-aminoacetonitrile (329)⁸¹ gave epoxyamide (330), whose azetidinone formation with lithium hexamethyldisilazide afforded the azetidinones (331) and (332) in 51% and 22% yields respectively. Protection of the hydroxy group, and then deprotection of the methoxybenzyl group of (333) gave the desired compound (223).

Scheme 29



Scheme 27





PMB = p-methoxybenzyl

Scheme 29

II-10 Asymmetric Synthesis

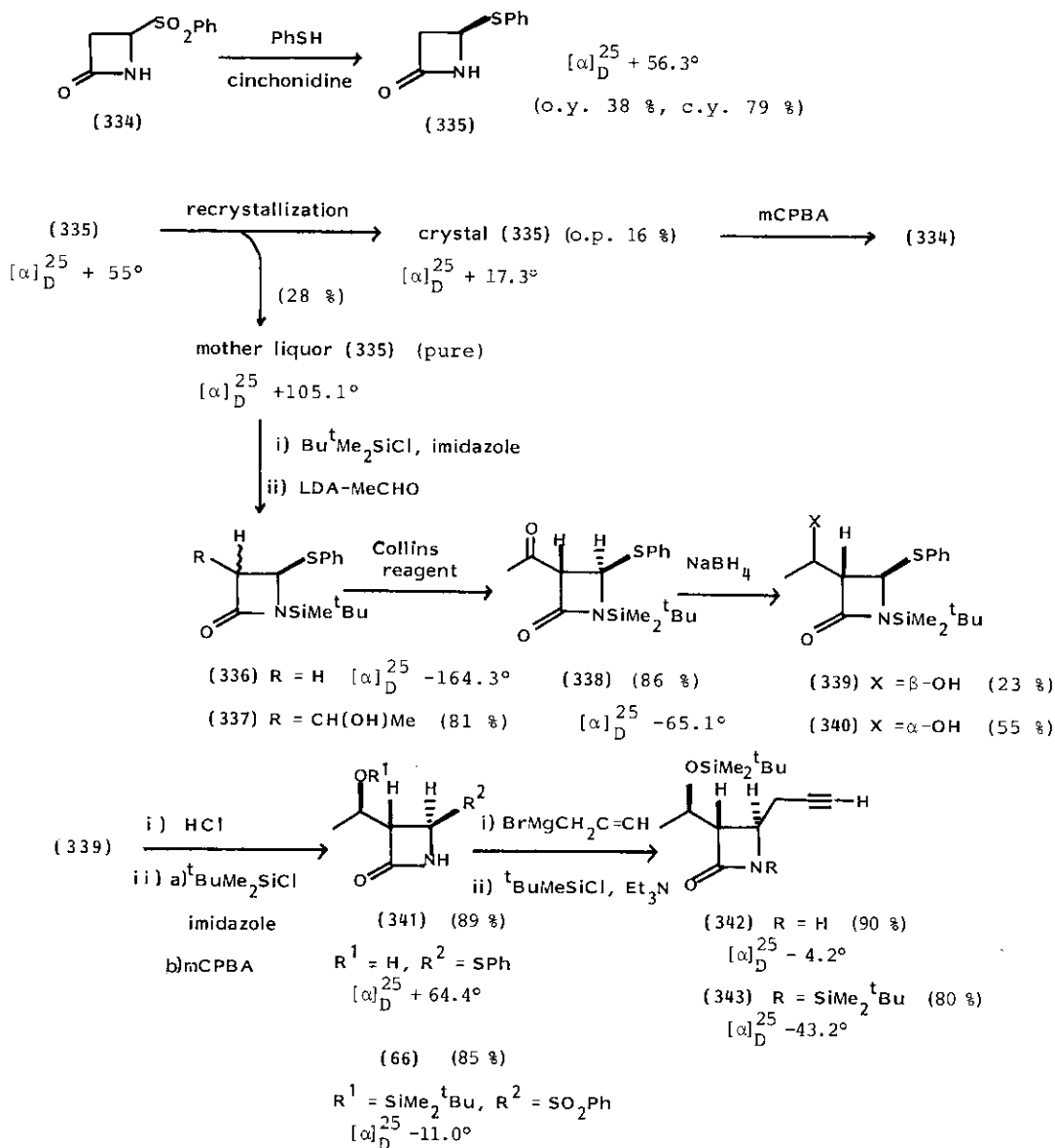
Treatment of 334⁸² with 5 equivalents of thiophenol in benzene containing 1.2 equivalents of cinchonidine at 35 °C for 62.5 h provided optically active 4-phenylthioazetidinone (+)-335,⁸³ whose recrystallization afforded crystalline (+)-335 with low optical purity which could be recycled to (+)-335 by successive oxidation and treatment under the same conditions as described above. Optically pure (+)-335 was obtained from the mother liquor of the above recrystallization and was transformed into the known key intermediate (343)⁸⁴ for thienamycin (1) synthesis. The undesired alcohol (340) could be converted into 341 using the modified Mitsunobu reaction.

Scheme 30

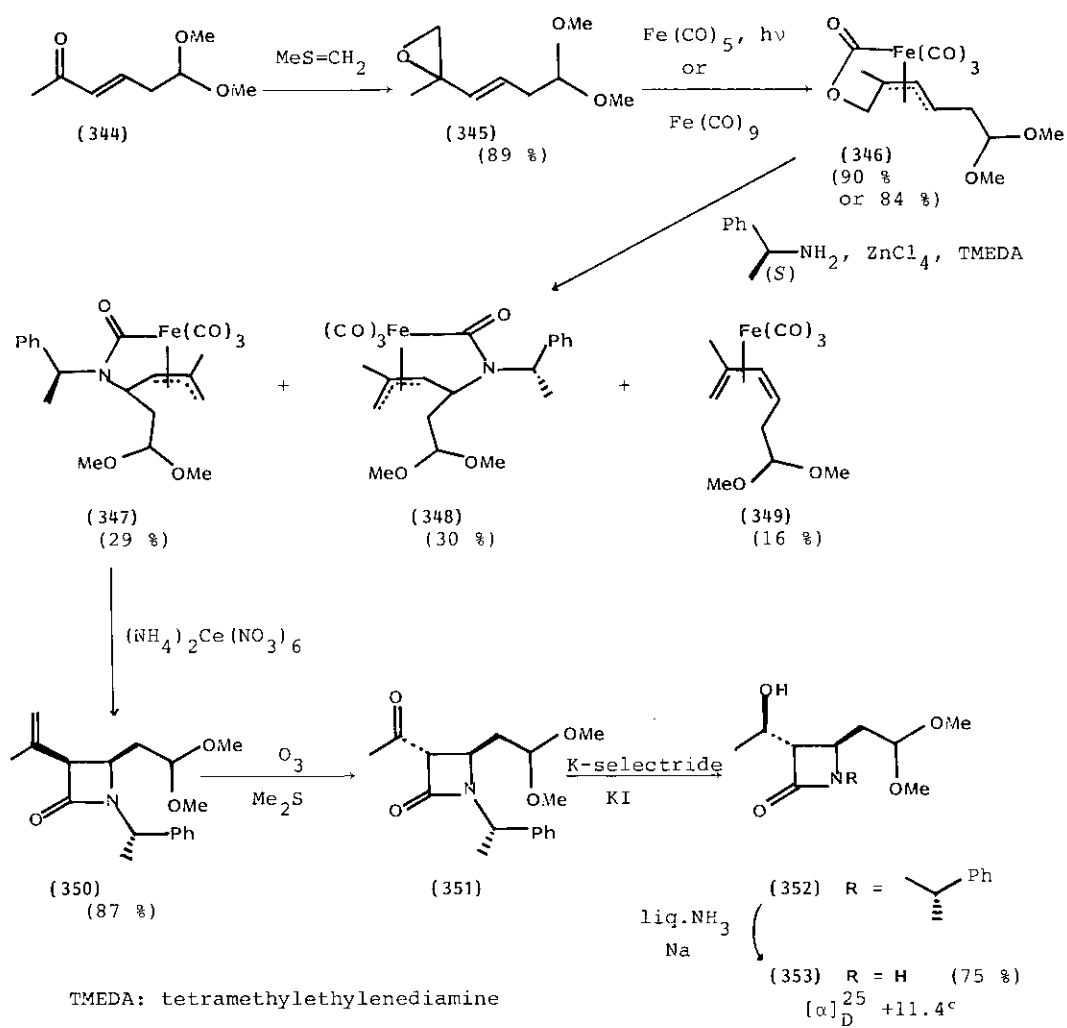
Ley and coworkers reported a synthesis of optically pure 353 through the π -allyltricarboxyliron lactone complexes.⁸⁵ Reaction of epoxide (345) with pentacarboxyliron [$\text{Fe}(\text{CO})_5$] and ultraviolet irradiation gave the stable π -allyltricarboxyliron lactone complex (346). Insertion of (-)-(1S)- α -methylbenzylamine into 346 afforded the desired (347) along with 348 and 349. Cerium (IV) ammonium nitrate oxidation of 347 provided cis-azetidinone (350). Ozonolysis of 350, followed by reduction with K-selectride-KI yielded the (1'R)-hydroxyazetidinone (352) and its (1'S)-epimer in the ratio of 9:1. Reductive removal of the N- α -methylbenzyl group of 352 gave the acetal 353, which had been converted into thienamycin.⁸⁶ The absolute configuration of 353 and its optical purity were determined by the conversion of 353 into its diastereomeric (R)- and (S)- α -methoxy- α -(trifluoromethyl)- α -phenylacetyl (MTPA) ester according to Mosher's NMR configuration-correlation method.

Scheme 31

Smale modified their tetrahydro-1,3-oxazine route to provide (5R)-thienamycin analogues.⁸⁷ Their key concept was replacement of the cyclohexane, used in the original synthesis,⁸⁸ by chiral ketone. 3-Amino-1-propanol was reacted with (R)-3-methylcyclohexanone to form a tetrahydro-1,3-oxazine, which was then acylated with diketene to produce the β -ketoamide (354). Diazo transfer reaction of 354



Scheme 30



Scheme 31

with methanesulfonylazide in the presence of triethylamine gave 355. The carbenoid insertion reaction was accomplished by the treatment of 355 with rhodium (II) acetate to give a 3:2 mixture of 356 and 357. Reduction of 356 with potassium tri-sec.-butylborohydride³¹ gave (R)-358 along with the (S)-isomer. Protected 358 (359) was hydrolyzed to the versatile intermediate (302),⁷³ bearing the three asymmetric centers with correct stereochemistry.

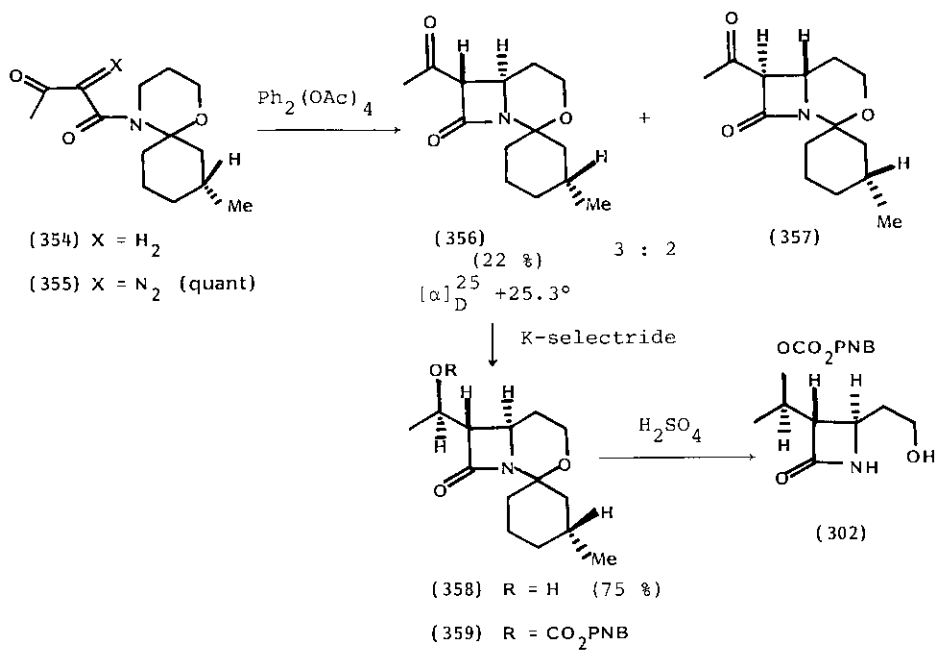
Scheme 32

Previously, we reported a synthesis of (+)-thienamycin analogue (373) bearing the hydroxyethyl function at the 6-position with the desired stereochemistry using 1,3-dipolar cycloaddition of the nitron (363) with benzyl crotonate (365).^{89a} The (+)-azetidinone (369) was also synthesized by Stevens and Albizzati independently on the basis of the same achiral route.⁹⁰ As a continuation of our work, the enantioselective [3+2]cycloaddition of a chiral nitron, prepared from the condensation of the aldehyde (360) and (S)-(-)-N-(α -phenylethyl)hydroxylamine (362), with benzyl crotonate (365) was examined.^{89b} The 1,3-dipolar cycloaddition of 364 with benzyl crotonate furnished the desired adduct (367), which is homogeneous on TLC and HPLC, with its stereoisomer (368). Catalytic hydrogenation of the isoxazolidine (367), followed by cyclization with dicyclohexylcarbodiimide gave the (+)-azetidinone (369). The formal total synthesis was accomplished by the transformation of 369 into the known key intermediate (273) for the synthesis of (+)-thienamycin (1).³¹ From the obtained $[\alpha]_D$ value of 237, none of the diastereoisomers of the desired products were detected in any step of the conversion of 367 into 237. Therefore we deduced that the enantioselectivity of the 1,3-dipolar cycloaddition reaction was greater than 98%. Moreover, (-)-237 was also synthesized using (R)-(+)-(α -phenylethyl)hydroxylamine by adopting the same procedure.

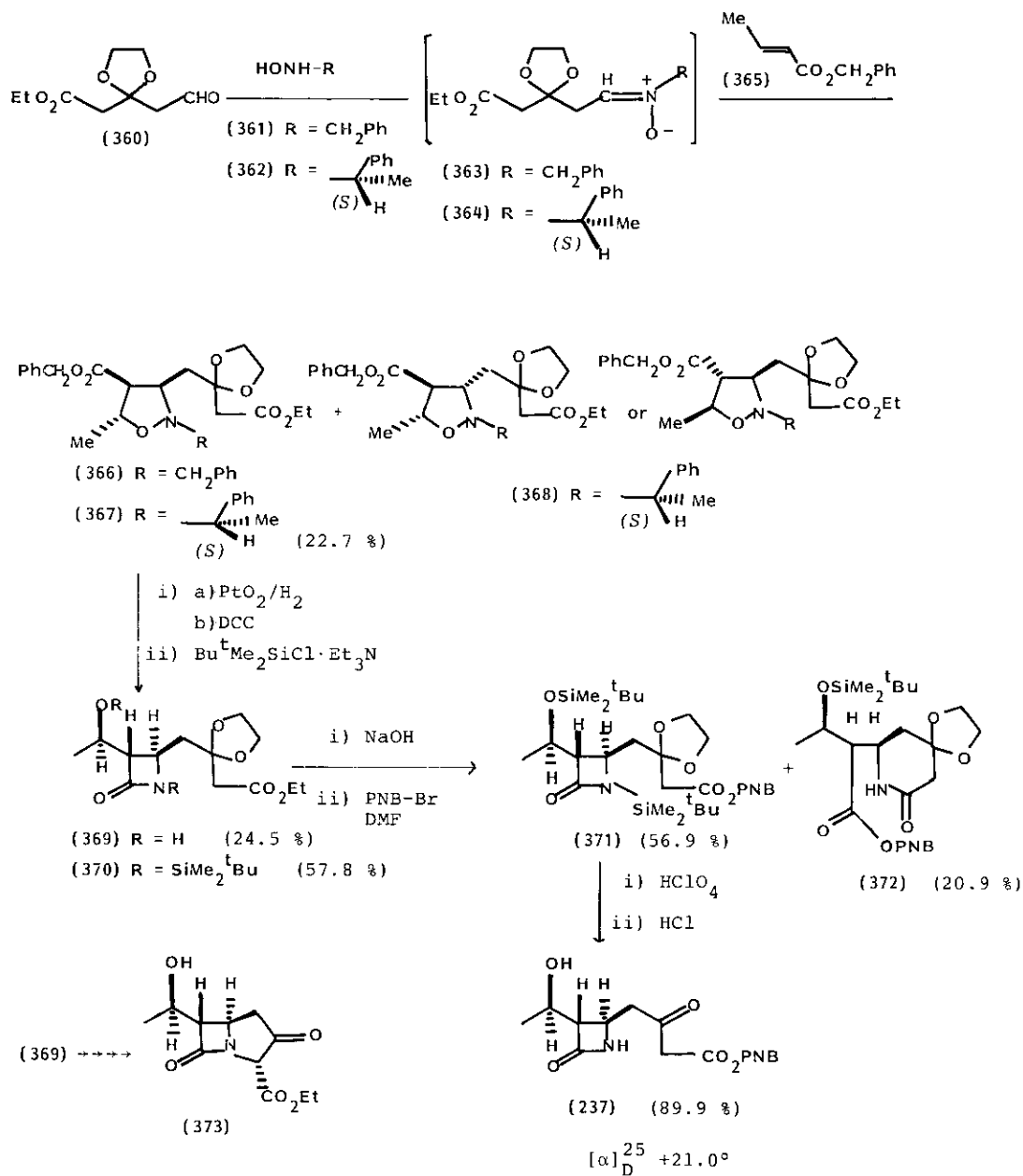
Scheme 33

II-11 Synthesis from Malic Acid

Optically pure (4S)(3S)-azetidinone (379)-(SS) was enantioselectively synthesized



Scheme 32



Scheme 33

from diethyl D-malate by Miller and coworkers.⁹¹ On the other hand, (4S)(3R)-azetidinone (379)-(SR), having adequate substituents with correct stereochemistry of PS-5 (14), was obtained from diethyl L-malate (374)-(S) via the inversion of the stereochemistry at the hydroxy carbon through the intramolecular formation of β -lactone (380)-(RR).⁹¹ The synthetic route is shown in Scheme 34. Furthermore, two other stereoisomers, (379)-(RR) and (379)-(RS), could be obtained.

Scheme 34

II-12 Synthesis from Chiral 1,3-Glycol

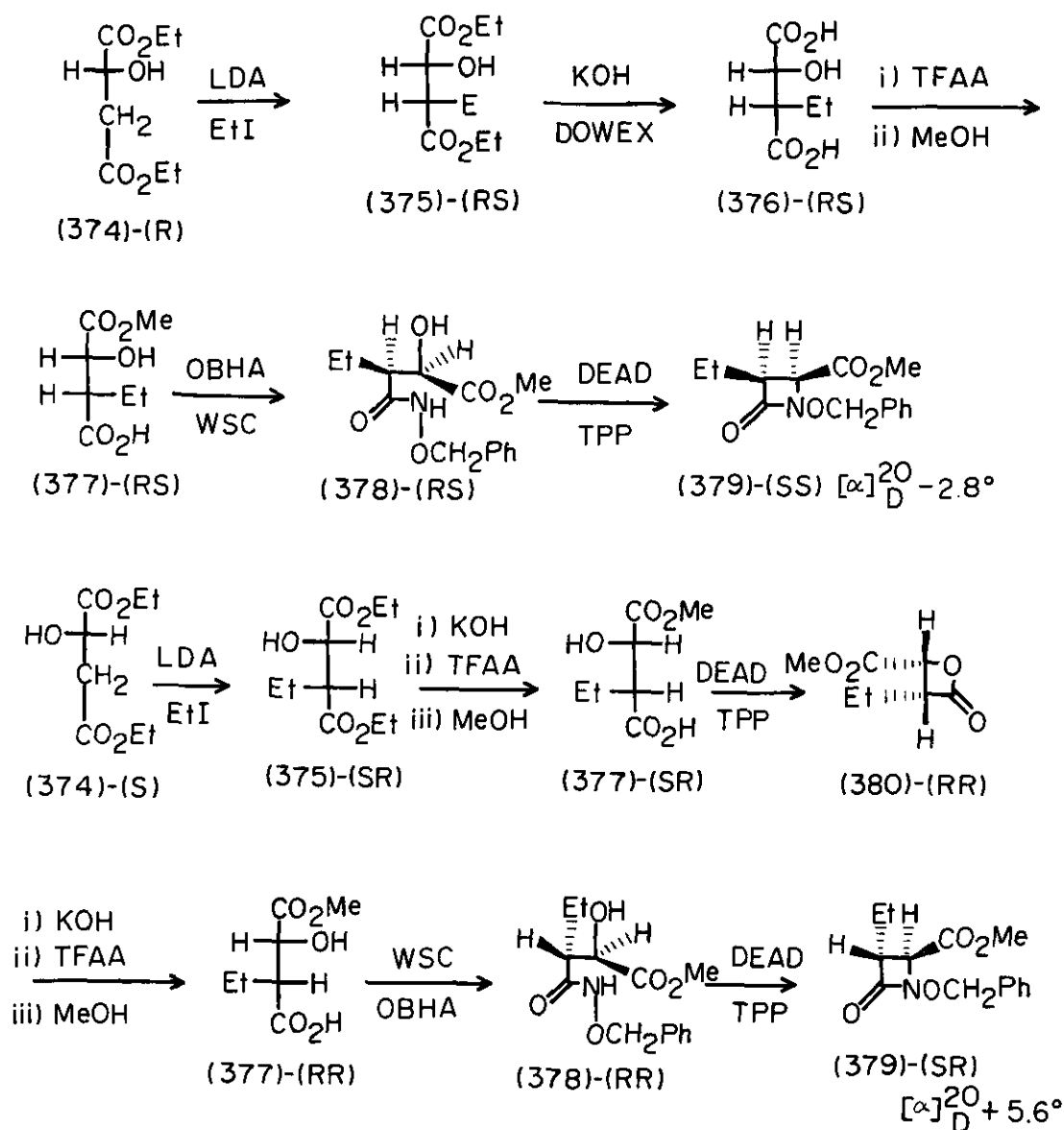
Takano and coworkers developed a 1,2-glycol chirality inversion method, and they applied this method to the synthesis of the key intermediate of the carbapenam antibiotics.⁹² Both 382-E and 382-Z were obtained from the corresponding E-381 and Z-381 by the Sharpless method.⁹³ Reduction of E-382 or Z-382 gave R-1,3-glycol (R-383) or S-1,3-glycol (S-383). Each enantiomer was convertible into each other. Mesylation of 383, followed by treatment with potassium acetate in boiling acetic anhydride gave diacetate (386). Methanolysis of the diacetate (386) regenerated the 1,3-glycol 383 having the opposite optical rotation of the original one (383). Conversion of R-383 into the imide (389) was achieved using Mitsunobu's conditions.⁹⁴ The imide (389) was oxidized to the acid (390). Hydrazinolysis followed by cyclization gave the azetidinone (392), which was estimated to 90% ee by ¹H-NMR spectroscopy using a shift reagent. Hydrogenolysis of 392 furnished the known compound (393).

Scheme 35

II-13 Synthesis using Optical Resolution

Favara and coworkers prepared optically active carboxylic acid (+)-(298)⁹⁵ by the optical resolution of ($\pm$)-298 using α -1,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol.⁹⁶ The (+)-(298) obtained was converted into PS-5 (14).⁹⁵

Scheme 36

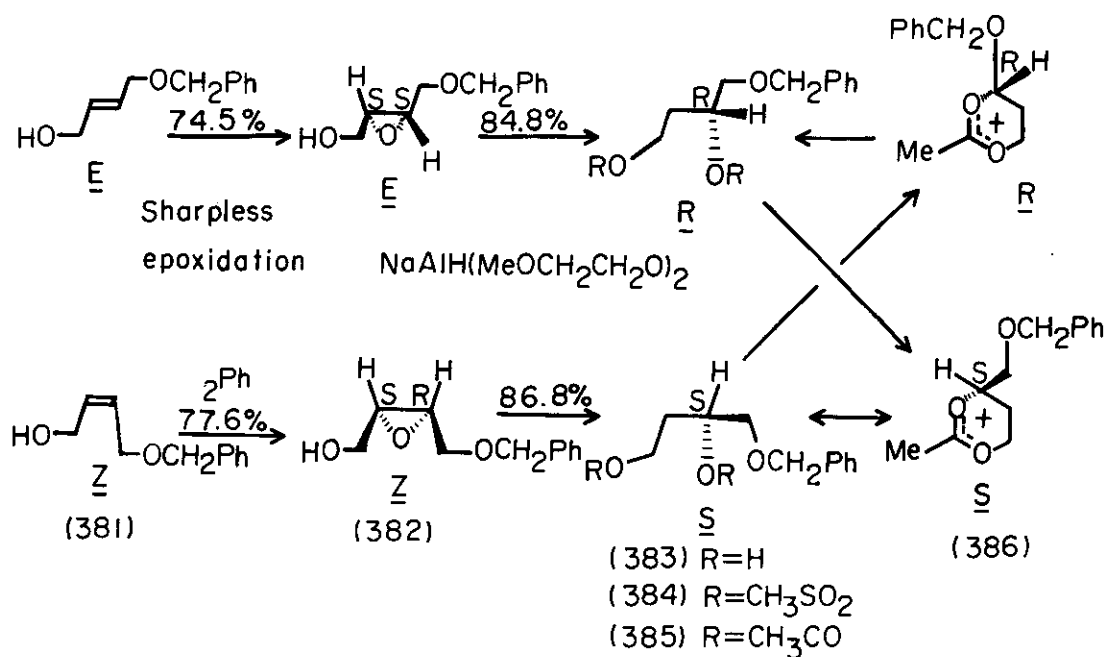


TFAA: $(\text{CF}_3\text{CO})_2\text{O}$ DEAD: $\text{EtO}_2\text{CN}=\text{NCO}_2\text{Et}$ WSC: (water-soluble carbodiimide)

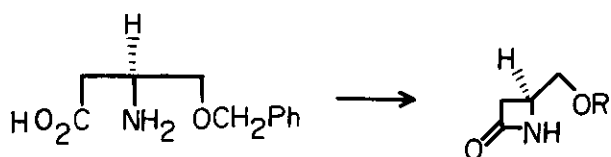
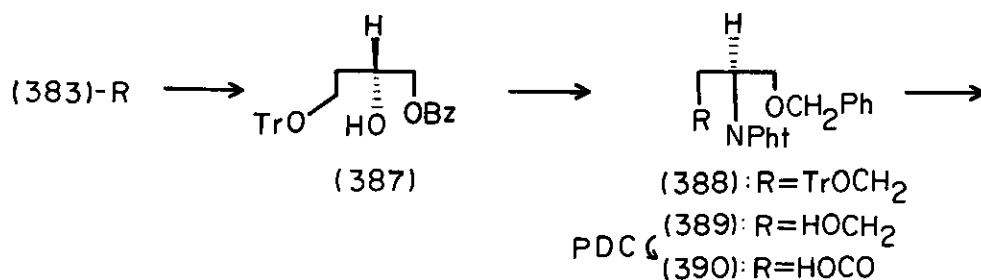
OBHA: $\text{NH}_2\text{OCH}_2\text{Ph}$ TPR: PPh_3

$\text{Et} = \text{C}=\text{N}(\text{CH}_2)_3\text{N}\cdot\text{Me}_2$

Scheme 34



(383)S $\rightarrow$ (384)S $\rightarrow$ (385)S $\rightarrow$ (383)R (60% overall)



(392) R=CH₂Ph $[\alpha]_D^{23} + 41.7^\circ$

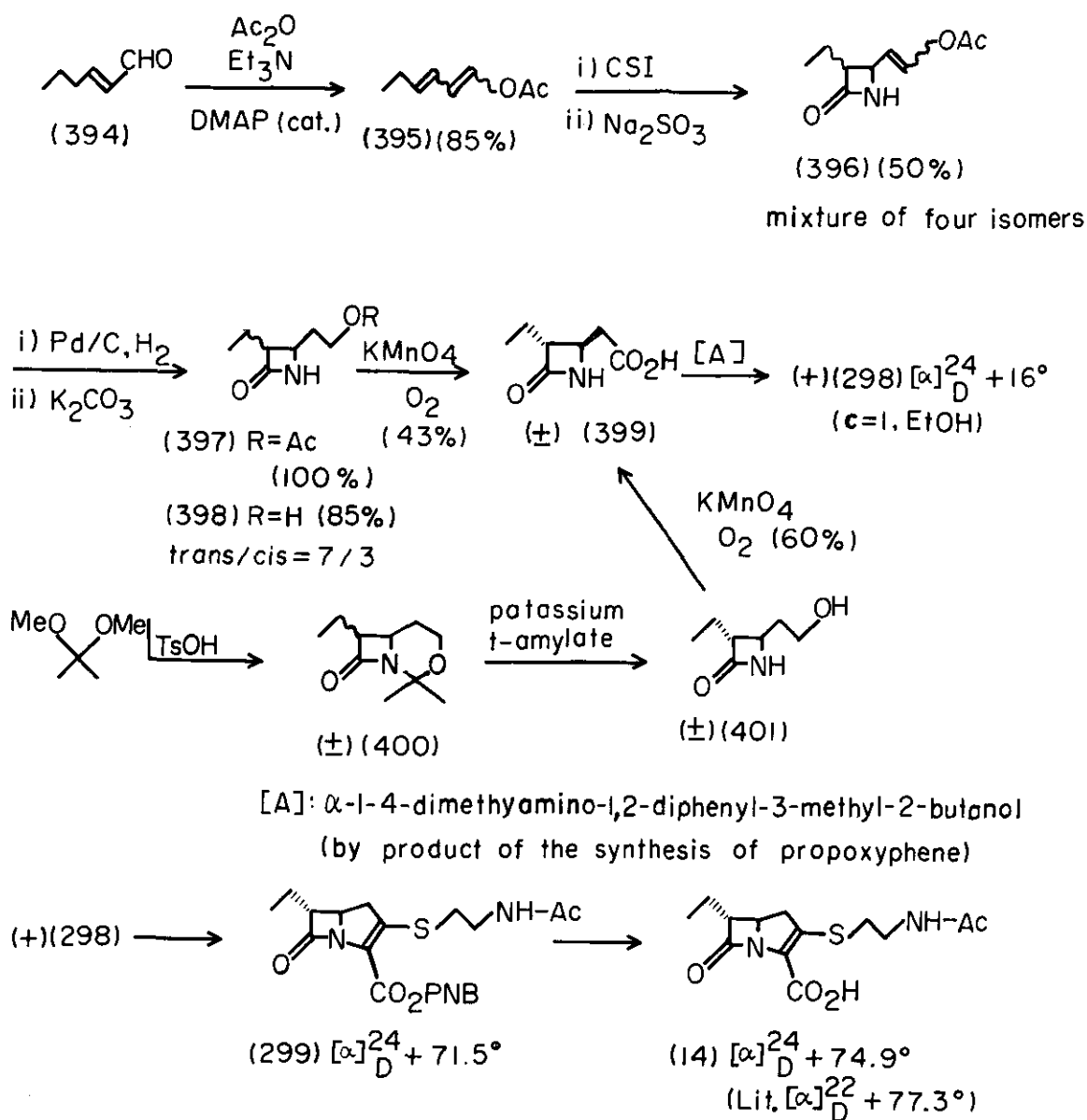
(393) R=H $[\alpha]_D^{21} + 27.8^\circ$

(37% from (383)-R)

Pht: phthaloyl

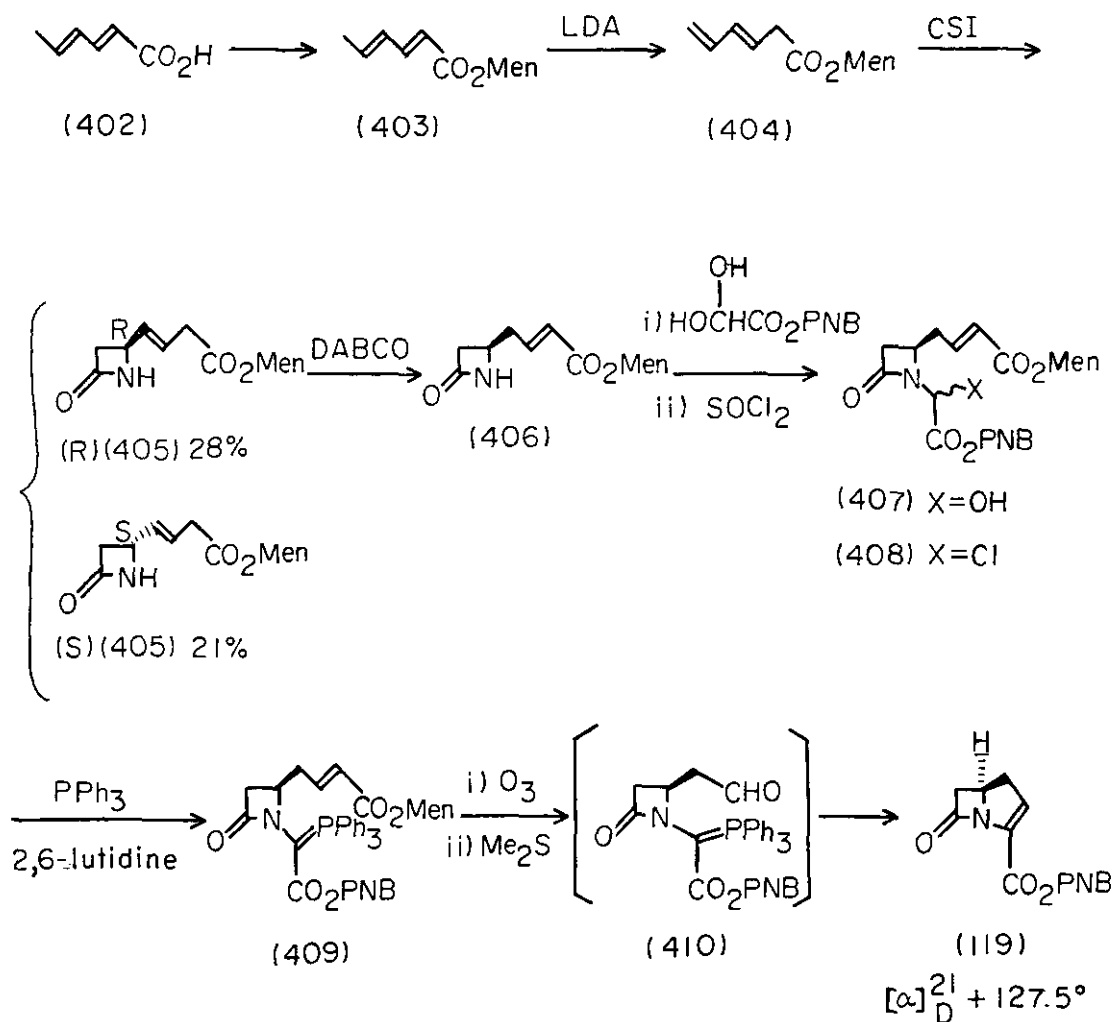
PDC: pyridinium dichromate

Scheme 35



Scheme 36

The Bristol group reported a synthesis of the *p*-nitrobenzyl ester of a natural product, SQ-27860 (36).⁹⁷ Optical resolution of the methyl ester (405) was achieved by recrystallization. The compound R-405 obtained was transformed into (+)-119 via the intramolecular Wittig reaction, as shown in Scheme 37.



Scheme 37

[III] Methods for Construction of the Bicyclic Ring System

III-1 Construction by Photochemical Transformation of Cephalosporins

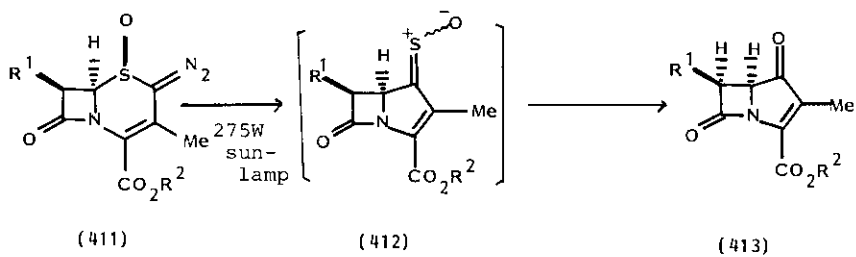
The Pfizer group reported a synthesis of oxocarbapenem ring system (413), using the photochemical transformation of a cephalosporin derivative (411).⁹⁸ Photolysis of 411a-c gave keto-carbapenems (413a-c) through intermediates (412a-c), respectively. The reduction of 413b with tetrabutylammonium borohydride, followed by acetylation afforded the stable acetate 415. The formation of sulfines 412 was anticipated as mechanistically analogous to the formation of ketenes during the Wolff rearrangement of α -diazo ketones.

Scheme 38

III-2 Construction using Dieckmann-type Cyclization

Shibuya and coworkers prepared trans-carbapenems (431)⁹⁹ by a Dieckmann-type condensation reaction and an efficient deprotection method.¹⁰⁰ Namely, the reaction of N-protected azetidinone (417) with lithium diisopropylamide followed by treatment with excess acetaldehyde gave a mixture of 418, 419, and 420. Separated derivatives 418 and 419 were deprotected to yield 421 and 422, which could be obtained by the reaction of the dilithiated 416 and acetaldehyde, alternatively. Condensation of 421 and 422 with bromoacetate followed by protection of the hydroxyl group, ozonolysis and Jones oxidation gave the carboxylic acid (425). Treatment of 425 with oxalyl chloride followed by cyclization to a bicyclic ring system with lithium hexamethyldisilazide via a Dieckmann-type reaction provided 2-oxocarbapenems (426). Reduction of 426 gave carbinols (427) stereoselectively. The relative stereochemistry at C-2, C-3 and C-5 of 427 was substantiated by the NMR nuclear overhauser effect. Mesylation of 427 with methanesulfonic anhydride followed by dehydromesylation of 428 by use of 3,3,6,9,9-pentamethyl-2,10diazabicyclo[4.4.0]-1-decene (PDBD) gave the carbapenems (429). Deprotection of 429 was efficiently achieved by hydrogenation in the presence of 1 equivalent of PDBD to afford PDBD salts (430). Treatment of 430 with 1 equivalent of potassium 2-ethylhexanone gave the corresponding potassium salts (431).⁹⁹

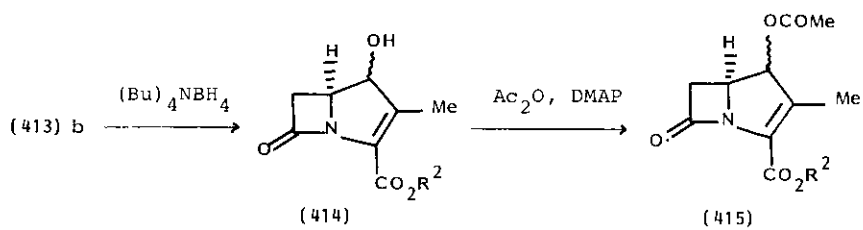
Scheme 39



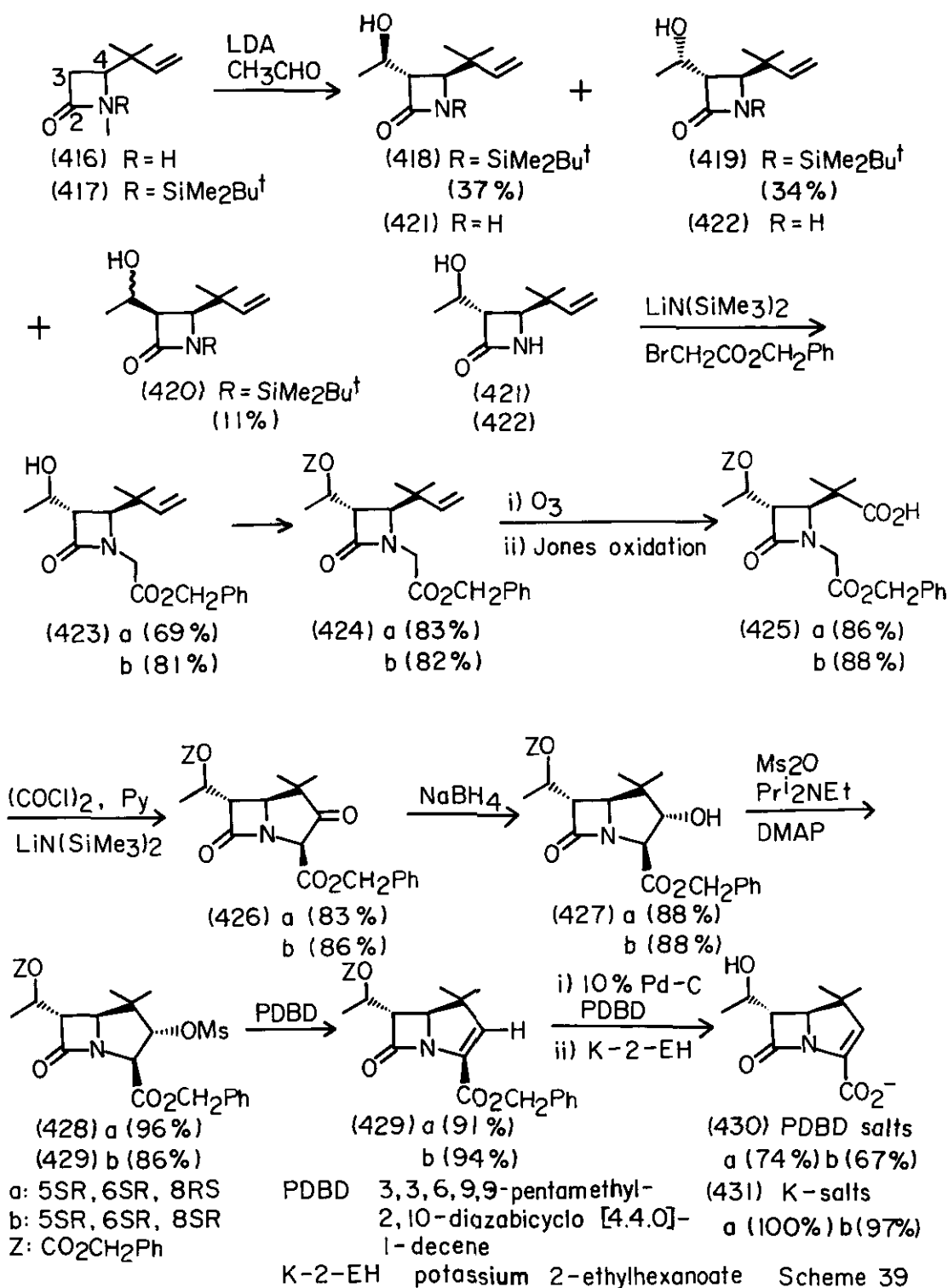
a: $R^1 = H$, $R^2 = CHPh_2$

b: $R^1 = H$, $R^2 = CH_2OCOCMe_3$

c: $R^1 = PhOCH_2CONH$, $R^2 = CHPh_2$



Scheme 38



Scheme 39

Hatanaka and coworkers synthesized (±)-PS-5 (14) and its 6-epi analogue¹⁰² by applying their regioselective Dieckmann-type reaction for constructing a 2-oxocarbapenem ring system.¹⁰¹ Reductive amination of 432 and successive hydrolysis gave a mixture of amino acids (433) and (434). N-Protected amino acids (435) and (436) could be separated. Each compound was transformed into monobenzyl esters (437) and (438) by hydrogenolysis of the N-benzyloxycarbonyl group followed by selective esterification. Four component condensation of (437) or (438) with formaldehyde and p-nitrobenzyl isocyanide gave 439a or 440a, respectively. These two azetidinones were converted into 439d and 440d, respectively, by successive cleavage of the benzyl ester, condensation with thiophenol, and transformation of the p-nitrobenzyl amide into the p-nitrobenzyl ester. Cyclization of 439d and 440d was achieved by a modified Dieckmann reaction to yield 441 and 442, respectively. The 2-oxocarbapenems 441 and 442 were converted into PS-5 (14) and its 6-epi derivative (444) using the Merck procedure⁴³ and successive hydrogenolysis.

Scheme 40

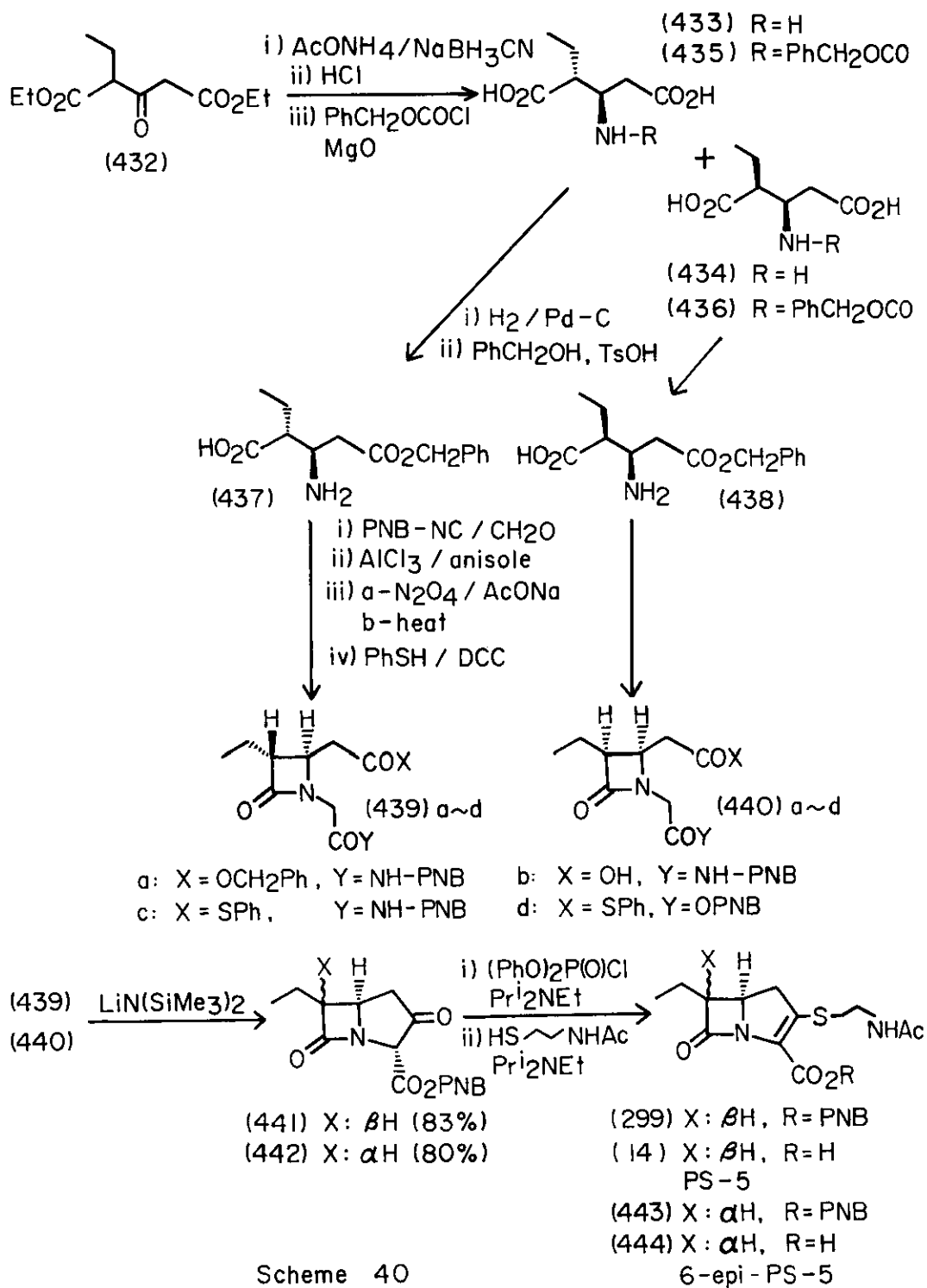
III-3 Construction using Reductive Cyclization

Two groups independently reported a new method for construction of a carbapenem ring system by an intramolecular Wittig reaction.

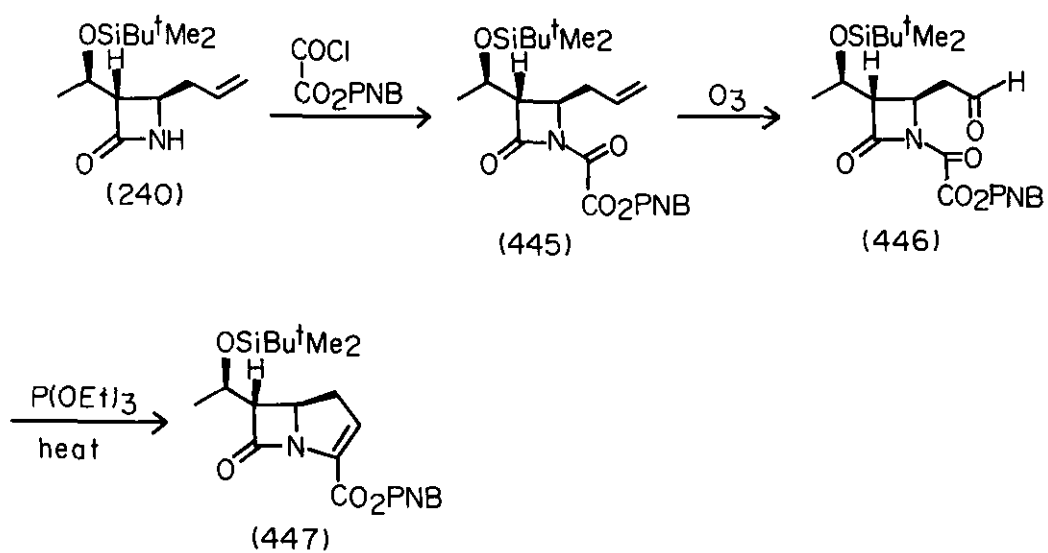
The Farmitalia Calro Erba group applied the carboxyl-carbonyl ring closure reaction, which had been developed for the formation of the penem framework, to the synthesis of a carbapenam bicyclic ring system.¹⁰³ After the N-acylation of 240, the oxalimide derivative 445 obtained was ozonized, providing crude 446. Cyclization of the crude 446 was achieved by refluxing in toluene with triethyl phosphite.

Scheme 41

The carbapenem cyclization reaction reported by the Sankyo group was based on an intramolecular Wittig reaction of trialkoxyphosphorane-thioesters which can be applied to non-activated thioesters.¹⁰⁴ N-Silylated compound (448) was treated with 1-benzyloxy-1-(trimethylsilyloxy)ethylene in the presence of trimethylsilyl



Scheme 40



Scheme 41

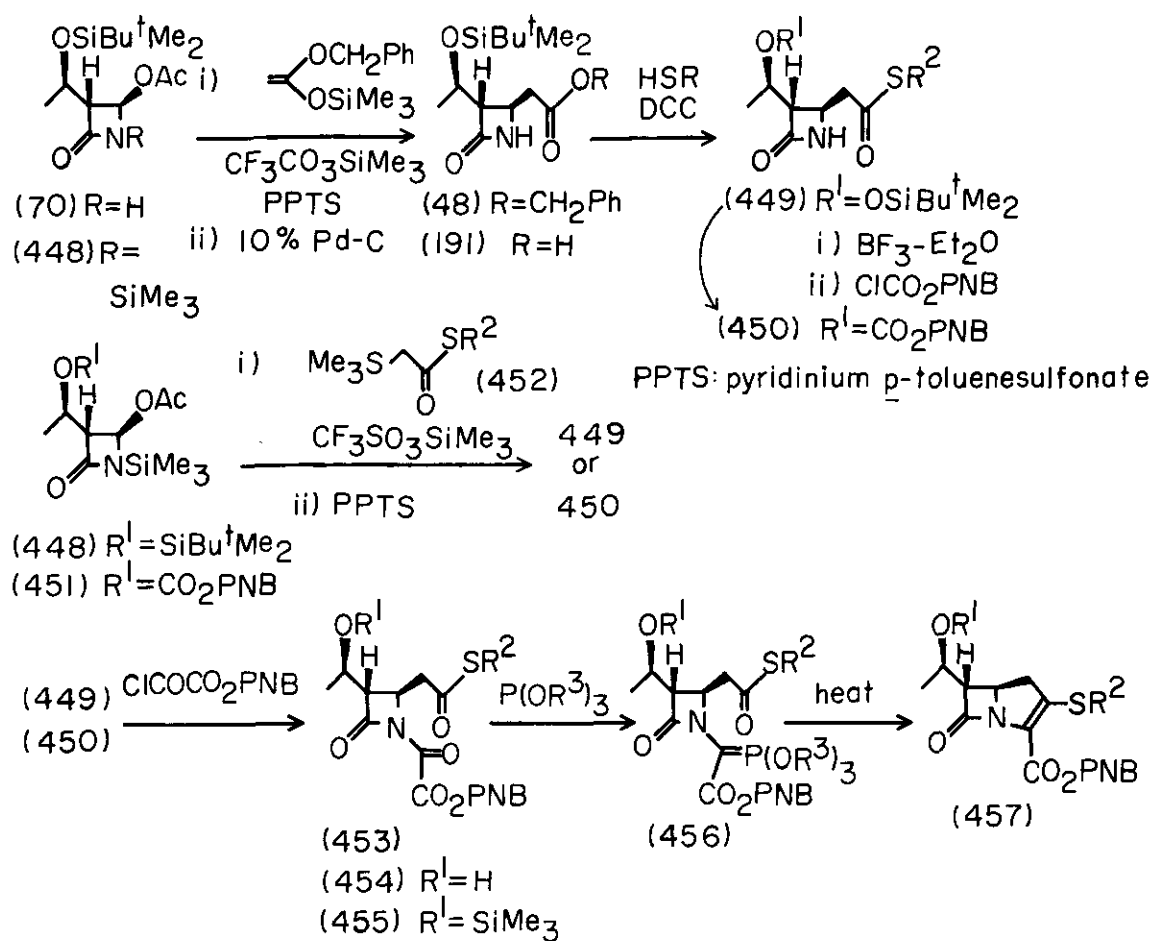
trifluoromethanesulfonate³⁰ to afford 48. After N-desilylation and debenzoylation of the ester, the acid (191) was transformed into various thioesters (449). Phenyl thioester could be obtained directly by the reaction of 448 with 1-phenylthio-1-(trimethylsilyloxy)ethylene. The hydroxy-protecting group in some of the thioesters (449) was changed to a p-nitrobenzyloxycarbonyl group (450). An alternative preparation of thioesters (449) and (450) was accomplished by the reaction of acetoxazetidinones (448) and (451) with trimethylsilylacetyl thioesters (452).¹⁰⁵ The thioesters (449) and (450) were treated with p-nitrobenzyloxalyl chloride to give the corresponding oxalimides (453). Conversion of the oxalimides (453) into the trialkoxyphosphoranes (456) were effected by heating 453 with excess triethyl or triisopropyl phosphite in benzene or toluene. The crude phosphoranes were heated in toluene or xylene in the presence of hydroquinone to afford the carbapenamams (457). When the hydroxy group was not protected as in the case of 454, cyclization with trialkyl phosphite did not occur.

Scheme 42

Table II

III-4 Construction by Sulfeno-cycloamination

The azetidinone (459), which had already been converted into (±)-epithienamycins A (2) and B (3),¹⁰⁶ was transformed into the unsaturated ester (460) via acetal (459) using the Wittig reaction. Treatment of 460, obtained as the E form, with phenylsulfenyl chloride, gave N-sulfenyl compound (461) as a major product together with a small amount of 462. On treatment with sodium borohydride, compound 461 was converted into 462. Cyclization of 462 by refluxing with triethylamine and potassium carbonate in the presence of sodium iodide afforded the carbapenam (465), whose structure was determined by direct comparison with the sample prepared by the alternative route, involving the established method.^{107,108,109} Thus, a new construction method for the synthesis of a 1-carbapenam ring system,¹¹⁰ which had a possibility of being converted to carbapenam derivatives by employing Beechams¹⁰⁹ and Sanraku-Ohcian¹¹¹ methods, was established, although the above yield of 465 was not satisfactory.



Scheme 42

Table II. Cyclization Reaction of Trialkoxyphosphoranes 456 to Carbapenem Ester 457

Compd.	R ¹	R ²	R ³	Reaction conditions			Yield of <u>457</u> (%)
				Solvent	Temp (°C)	Time (h)	
<u>456</u>	a	TBDMS	<i>i</i> -Pr	xylene	120	70	51
	b	TBDMS	Et	toluene	95	18	68
	d	PNZ	Et	toluene	100	44	40
	e	TMS	Et	toluene	100	24	48
	f	TBDMS	Et	toluene	95	70	83
	h	PNZ	Et	xylene	120	18	61
	i	TBDMS	Et	toluene	100	80	57
	k	TMS	Et	toluene	95	24	75
	l	TBDMS	Et	toluene	105	50	63
			Et	toluene	100	18	88
			<i>i</i> -Pr	toluene	100	18	77
	n	PNZ	<i>i</i> -Pr	toluene	105	48	67

Scheme 43

III-5 Construction by a New Type of (3+2) Cyclization

The Sankyo group prepared carbapenam derivatives (468), (469), and (470) using a new type of cyclization.¹¹² Namely, the reaction of 4-iodomethyl-2-azetidinone (229) and 466 (R=Ph) using potassium hydride in the presence of one equivalent of 18-crown-6 gave the desired compounds 468, and 479 (R=Ph). On the other hand, the compounds 468 and 469 (R=Me) were also obtained by the reaction of 229 and 466 (R=Me) using diphenylmethane carbanion in the presence of one equivalent of 18-crown-6. The compound 468 (R=Me) was hydrolyzed with sodium hydroxide to disodium salt (470).

Scheme 44

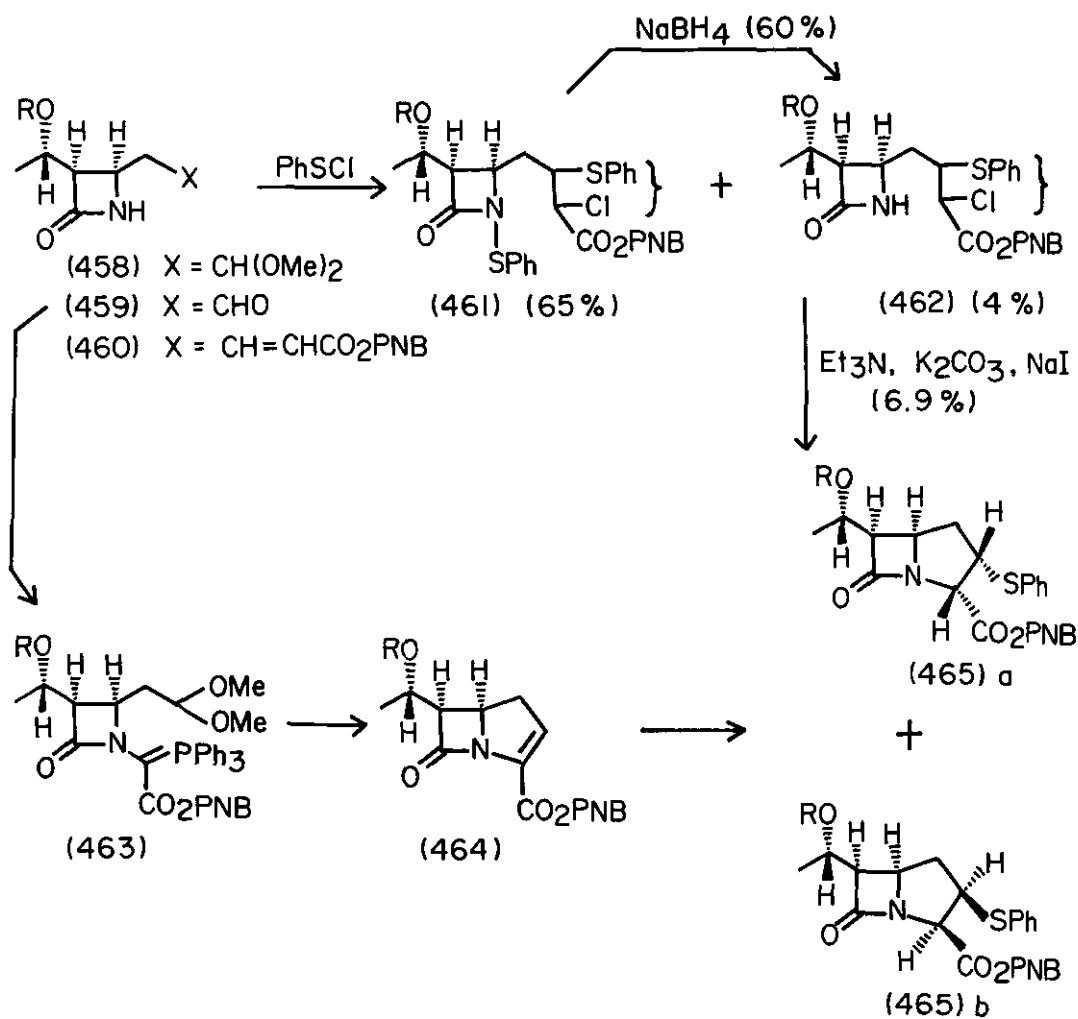
III-6 Construction using Intramolecular Cyclization of a Tricarbonyl Derivative

Wasserman and Han reported a formal total synthesis of (±)-PS-5¹¹³ using the intramolecular cyclization of a tricarbonyl residue,¹¹⁴ through 3,4-bond formation. 4-Allylazetidinone was converted into β-keto ester (475) in 4 steps. The active methylene group in 475 was converted to an enamino function (476). Photooxidative cleavage with the singlet oxygen of 475 gave a diketo ester (477). After treatment of 477 with HF-pyridine, the desilylated and hydrated tricarbonyl derivative underwent cyclization in the presence of molecular sieves to 478. The carbinol 478 was directly reduced by trimethylsilyl iodide to afford (±)-carbapenam (479). Chiral 479 had already been converted to (+)-PS-5 (14) by Favara.⁹⁵

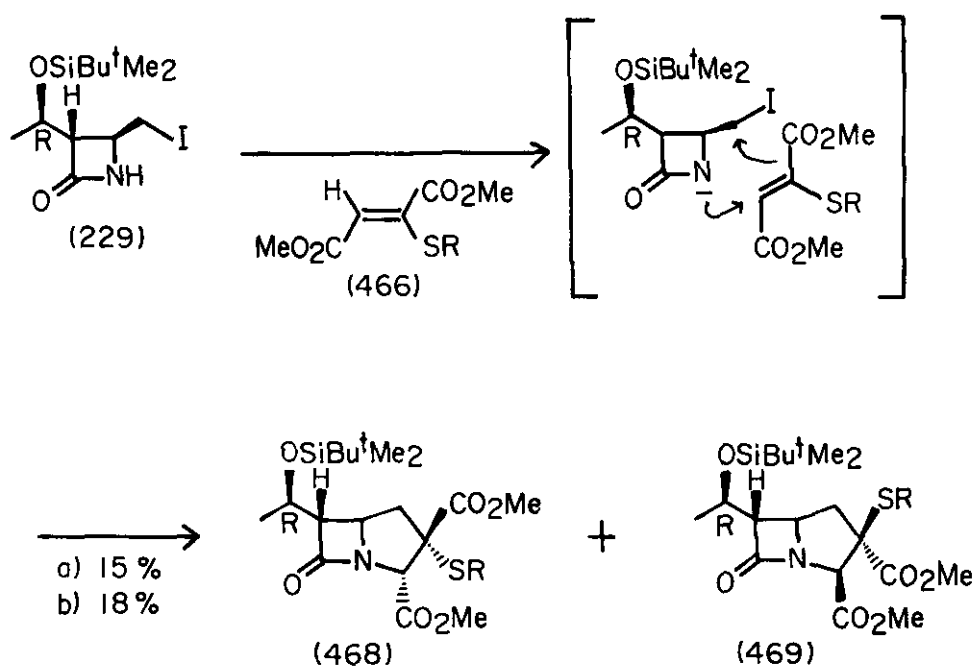
Scheme 45

IV Conclusion

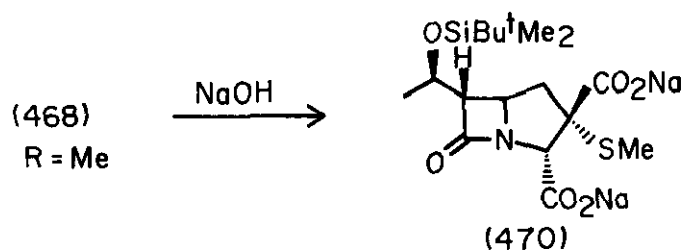
From the view point of antibacterial activity, the synthesis of carbapenems in an



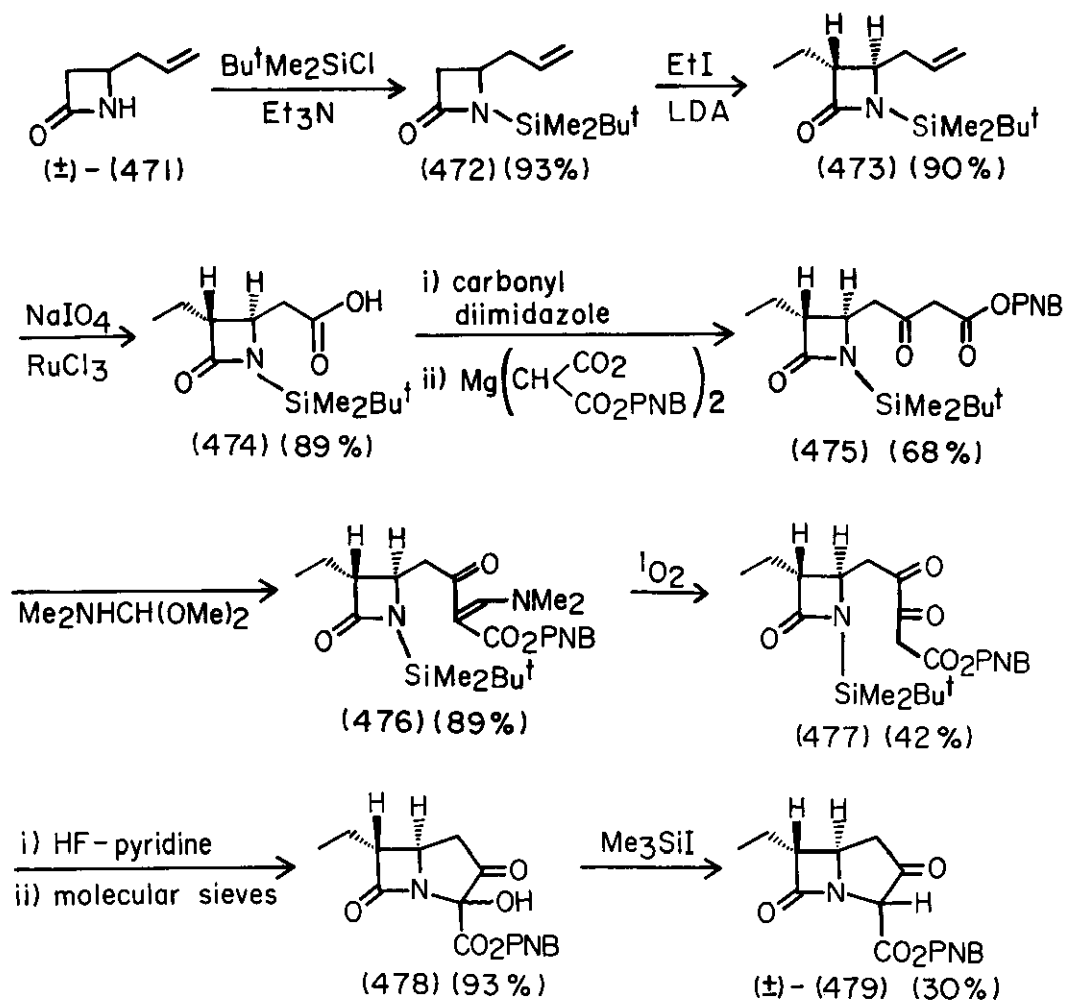
Scheme 43



- a) $\text{R} = \text{Ph}$, KH , 18-Crown-6
 b) $\text{R} = \text{Me}$, Ph_2CHK , 18-Crown-6



Scheme 44



Scheme 45

optically active form was in great demand. Although stereocontrolled syntheses using chiral precursors such as penicillin, D-glucose, amino acid, and so on were practical, these syntheses usually require multiple steps. On the other hand, in the case of chemical asymmetric induction, the optical yield is always the main problem.

Only a few new methods for construction of the bicyclic ring system were reported in the past four years because of the difficulty of this reaction. For the industrial production of synthetic carbapenem compounds, further development of the effective synthesis of chiral azetidinone and an efficient method for construction of the bicyclic ring system are desired.

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