Chemistry of Heterocyclic Compounds, Vol. 34, No. 11, 1998

RECENT ADVANCES IN CARBAPENEM CHEMISTRY* (REVIEW)

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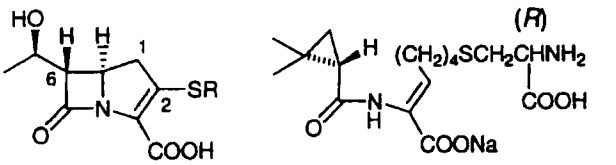
Recent synthetic works of carbapenems, focused on their efficiency and applicability to synthesize a variety of substituted carbapenem derivatives for the effective screening research of the new generation carbapenem antibiotics, are reviewed.

INTRODUCTION

Since the isolation of thienamycin (**1**), the first naturally occurring carbapenem, reported by the Merck research group [1], 22 years have passed. During the past 22 years the synthetic and medicinal chemistry of carbapenems have been investigated extensively. Efficient synthetic methodologies toward carbapenem derivatives were established and a variety of carbapenems were prepared. Their structure–activity relationships (SARs) (see review [2]) concerning not only the antibacterial activities, the metabolic degradation by renal dehydropeptidase-I (DHP-I) [3], and chemical stability but also the side effects such as nephrotoxicity [4] and neurotoxicity [5], have been widely studied to improve the advantages of **1** and to overcome its shortcomings such as physicochemical instability, metabolic instability versus DHP-I, nephrotoxicity, and neurotoxicity for clinical use. As a result, the first-generation carbapenem antibiotic, imipenem (**2**), was launched in the middle of the 1980s as a coadministered drug with cilastatin (**3**), which inhibits the degradation by DHP-I and decreases the nephrotoxicity. Panipenem (**4**), which had a similar profile to **3**, was also developed in Japan as a coadministered drug with an inhibitor against the organic anion transportation, betamipron (**5**). In the middle of the 1990s, the second-generation carbapenem (1β-methylcarbapenem [6]) meropenem (**6**) had arrived as a prominent drug, as it was the first drug which could be utilized as a single agent without any coadministered drugs.



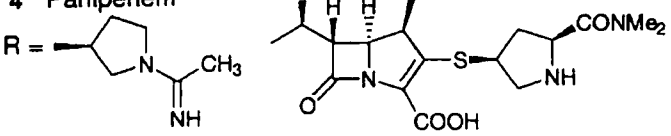
1 Thienamycin
R = $-CH_2CH_2NH_2$

2 Imipenem
R = $-CH_2CH_2NHCH{=}NH$

3 Cilastatin

5 Betamipron

4 Panipenem



6 Meropenem

*Part of this review was published in Japanese [Yuki Gosei Kagaku Kyokaishi, 54, 761 (1996); Chem. Abstr., 125, 221386 (1996)].

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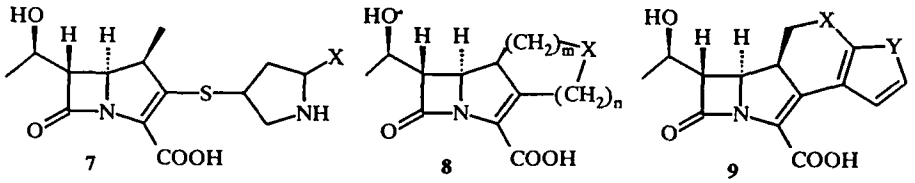
Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1475-1493, November, 1998. Original article: submitted July 29, 1998.

0009-3122/98/3411-1249$20.00

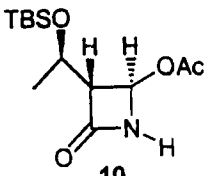
In the development of these carbapenem antibiotics, synthetic studies have played a very important role because the antibiotics could only be sufficiently supplied by total synthesis. The establishment of the effective synthetic methods enabled thorough screening using various derivatives and provided the antibiotics on a large scale for developmental purposes. After concentrating studies for more than two decades, some epoch-making work in the field has established practical methods to prepare this new family of totally synthetic β-lactam antibiotics. And now, much attention has been directed toward the development of next generation carbapenem antibiotics that possess further advantages such as potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [7], enhanced antipseudomonal activity [8], and so on [9]. In these studies, the SARs, relating to the substituents at $C_{(2)}$ position, are most widely investigated since excellent synthetic methods have been established in the relatively early examinations. By this popular approach, many interesting derivatives, for example over ten 2-(5'-substituted pyrrolidin-3'-ylthio)carbapenems (**7**) [7h, 10] which are related to **6**, have been synthesized in the last several years. As a new approach, there are synthetically novel polycyclic carbapenems **8**, **9** [11], for example tricyclic carbapenems (trinems), from the Glaxo Wellcome research group.



Though carbapenem chemistry started as the total synthesis of a natural product, it now has more practical aspects: the fast and effective lead-generation which is the object of ongoing pharmaceutical development and the practical preparation applicable to mass production. In spite of many excellent reviews already published [12], it is useful to pay attention to recent papers from the point of the laboratory-scaled synthetic procedures, in particular, the construction of the carbapenem skeleton and the newly-developed methods to introduce substituents in order to overview the synthetic chemistry of the forthcoming "next generation carbapenem antibiotics."

SYTHETIC STUDIES OF CARBAPENEM COMPOUNDS

During the 1980s, the aggressive studies on carbapenem chemistry have greatly improved practical synthetic methodologies. In particular, the synthetic studies of 6-(1'-hydroxyethyl)carbapenems, those possessing the same substituent at $C_{(6)}$ position as thienamycin, have been enthusiastically achieved. Due to the development of practical and efficient synthetic methods, 4-acetoxyazetidin-2-one (**10**), which was the key intermediate for the preparation of carbapenems, became commercially available [12f]. This inevitably propelled the progress of synthetic chemistry in this field.



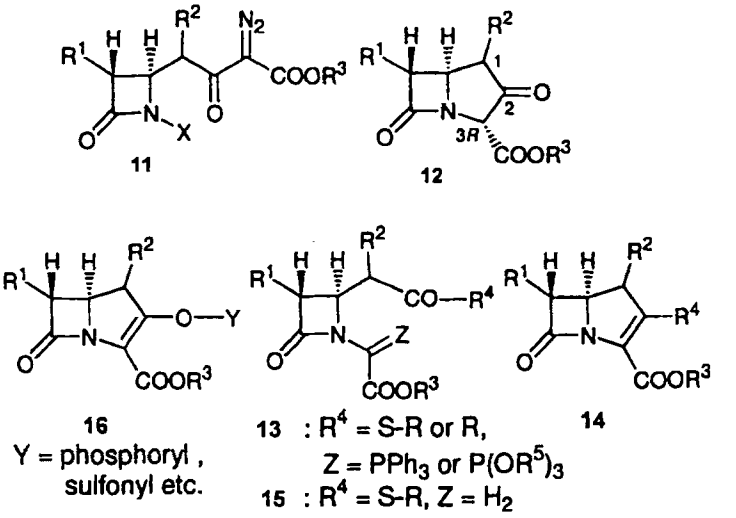
10

TBS = *t*-$BuMe_2Si$

1. CONSTRUCTION OF THE CARBAPENEM SKELETON

It is a generally useful strategy to construct the five-membered ring of the bicyclic system after preparing the appropriately functionalized β-lactam derivative. The most significant synthesis of this class was pioneered at Merck. They used the quite elegant carbenoid-mediated cyclization of a diazo azetidinone **11** (X = H) to form the targeted

carbapenem bicyclic nucleus **12** ($C_{(3)}$—$N_{(4)}$ bond formation) in an excellent yield [13]. Other methods were typical: the intramolecular Wittig-type cyclization of the precursor **13** to directly produce the carbapenem **14** ($C_{(2)}$—$C_{(3)}$ bond formation) [14] and the Dieckmann-type cyclization of the thiol ester **15** to give the keto ester **12** ($C_{(2)}$—$C_{(3)}$ bond formation) [15]. All three procedures were also applicable to preparation of 1β-methylcarbapenems [6, 16].



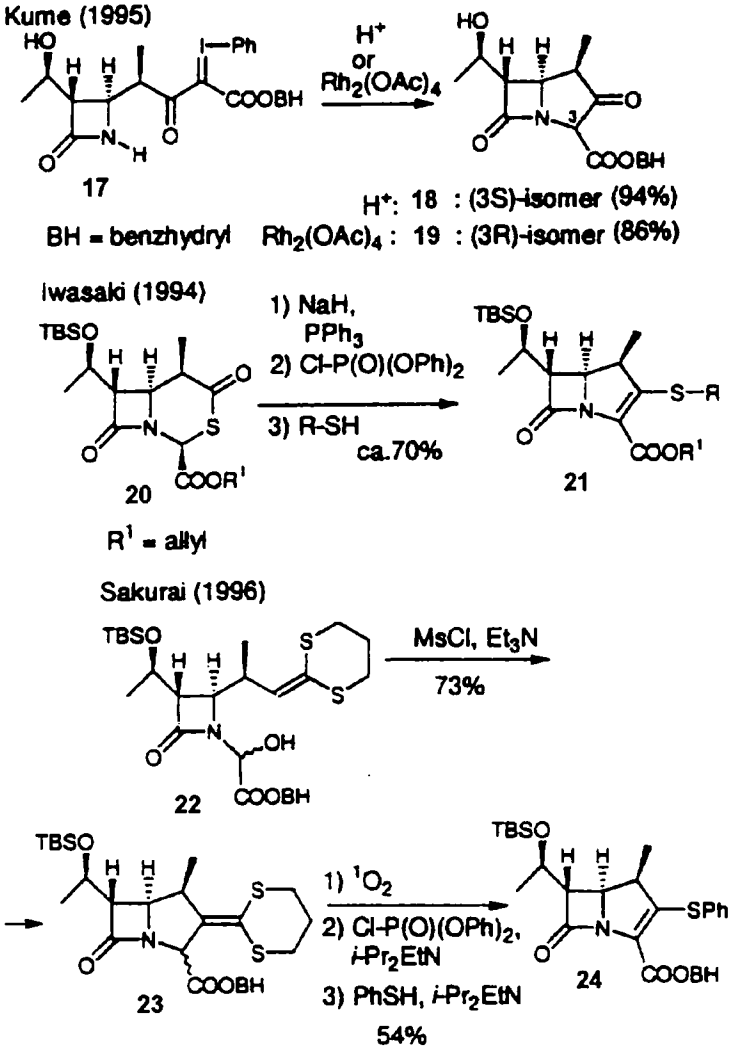
Concerning the introduction of the $C_{(2)}$-substituent via the sulfur atom, a highly effective method, utilizing a thiol addition–elimination reaction of the enol phosphate **16**, has been established. To obtain the nonnatural dethia-analogues, which have carbon–carbon bond at the $C_{(2)}$ position, it was found that the Wittig-type reaction was a very useful tool. Despite the presence of these reliable methods, more solutions have long been desired to create new series of carbapenems. In addition to the modification of the classical methods described above, several attractive new reactions have recently been developed. For example, Miller and co-workers reported that N-substituted diazo componds **11** (X = alkoxy) gave the cyclized products **12** in the presence of catalytic rhodium(II) acetate dimer [17a,b]. Kume et al. found that the iodonium ylide **17** also cyclized to produce the keto ester in the presence of either a rhodium or an acid catalyst. Interestingly, the 3*S*-isomer **18** was obtained stereoselectively under acidic conditions. However, rhodium-catalyzed conditions afforded the 3*R*-isomer **19** stereoselectively, as in the case of the classical Merck procedure (Scheme 1) [17c].

Iwasaki and co-workers reported a unique method involving the Eschenmoser sulfide contraction [18a,b] accompanied with a useful modified method of the Dieckmann-type cyclization reaction for transformation of compound **20** to carbapenem derivative **21** [18c,d]. Sakurai and Horikawa utilized an acyliminium ion-mediated cyclization to form $C_{(2)}$—$C_{(3)}$ bond in the sequence **22** → **23** → **24** [18e]. Some novel cyclization methods utilizing $C_{(3)}$—$N_{(4)}$ or $C_{(2)}$—$C_{(3)}$ bond formation reactions were investigated. As shown in Scheme 2, Feigelson reported that a keto ester **25** was converted to carbapenem **26**, having the $C_{(2)}$ substituents introduced *via* either carbon atom [17d] or sulfur atom [17e] by treatment with titanium(IV) chloride.

Iwasaki and co-workers by treatment of the enol ether **27** with N-bromosuccinimide (NBS) and successive reduction synthesized the 2-unsubstituted carbapenem **28** [17f]. Hannesian et al. prepared compound **12** by utilizing a unique intramolecular Michael addition reaction of the nitro olefin **29** for the $C_{(2)}$—$C_{(3)}$ bond formation and phenylselenylation to give compound **30** as the key steps [18f]. Genet and colleagues succeeded in the efficient preparation of compound (**32**) by applying a palladium mediated cross-coupling reaction to the $C_{(2)}$—$C_{(3)}$ bond formation, from compound (**31**) [18g].

In addition to traditional $C_{(3)}$—$N_{(4)}$ and $C_{(2)}$—$C_{(3)}$ bond formations described above, some methods, including $C_{(1)}$—$C_{(2)}$ or $C_{(1)}$—$C_{(5)}$ bond formation as the key step, were reported (Scheme 3). Anaya et al. prepared the 2-unsubstituted carbapenem **35** by a radical $C_{(1)}$—$C_{(2)}$ bond formation (**33** → **34**) [18h]. Iwasaki and co-workers have succeeded in the synthesis of the key intermediate (**12**) from the carbapenam (**37**), which was obtained by the application of an Aza-Cope rearrangement reaction to β-lactam **36** [18i]. Martel and colleagues utilized a novel

Scheme 1

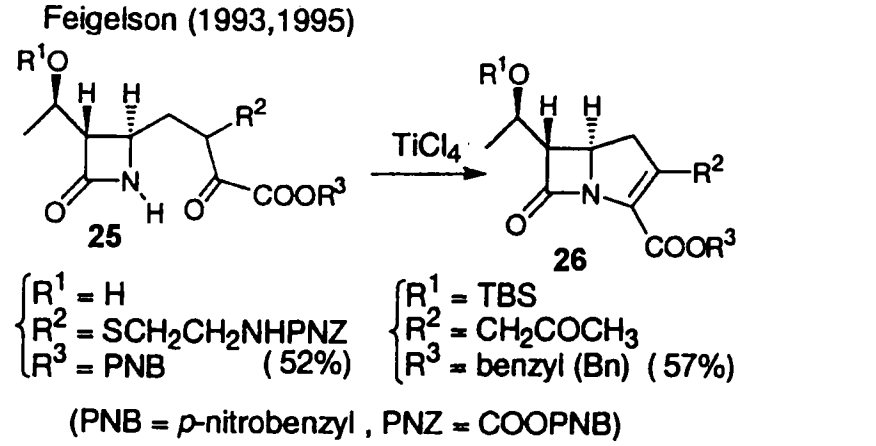


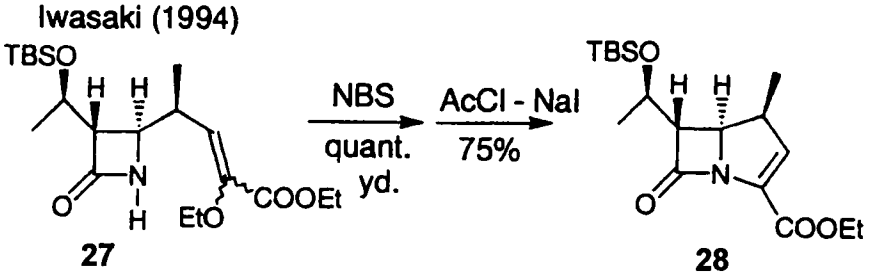
azomethine ylide to form the $C_{(1)}$—$C_{(5)}$ and $C_{(2)}$—$C_{(3)}$ bonds simultaneously in transformation of compound **38** to carbapenam derivative **39** that gave under the action of hydrogen peroxide carbapenem **40** [18j]. These new trends of reactions are quite a good prospect.

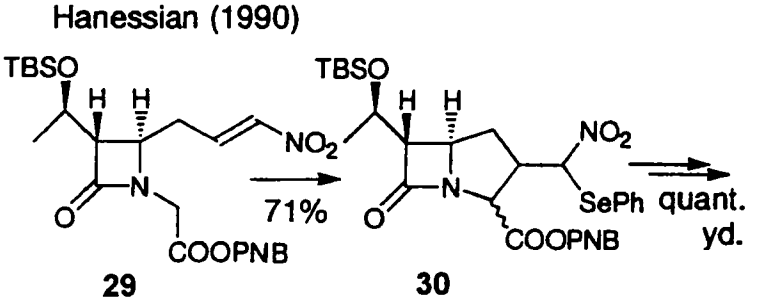
2. INTRODUCTION OF SUBSTITUENTS INTO THE CARBAPENEM NUCLEUS

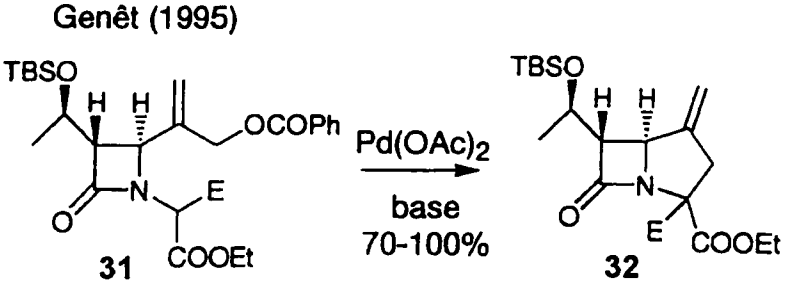
In general, the substituents at $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ positions greatly influence the biological properties of carbapenem antibiotics. Therefore, the studies on the structure–activity relationships relating to these functionalities were thoroughly investigated. Modification of the substituents could be achieved by three methods: before β-lactam ring formation, after β-lactam ring formation, and after the construction of the bicyclic system. Although the latter method is more favorable in regards to efficiency, the variety of possible reactions is limited because of chemical instability of carbapenems. Since the quite effective introduction of thiol chains to $C_{(2)}$ position was established in the early stage of the synthetic studies, the structure–activity relationships of the $C_{(2)}$-substituents were most widely and systematically studied. However, the chemical modification was difficult in the carbapenem derivatives and some mildly achievable reactions were only utilized. Recently, several useful procedures have been reported but more attractive methodologies are still desirable. In this section, some interesting work is reviewed.

Scheme 2

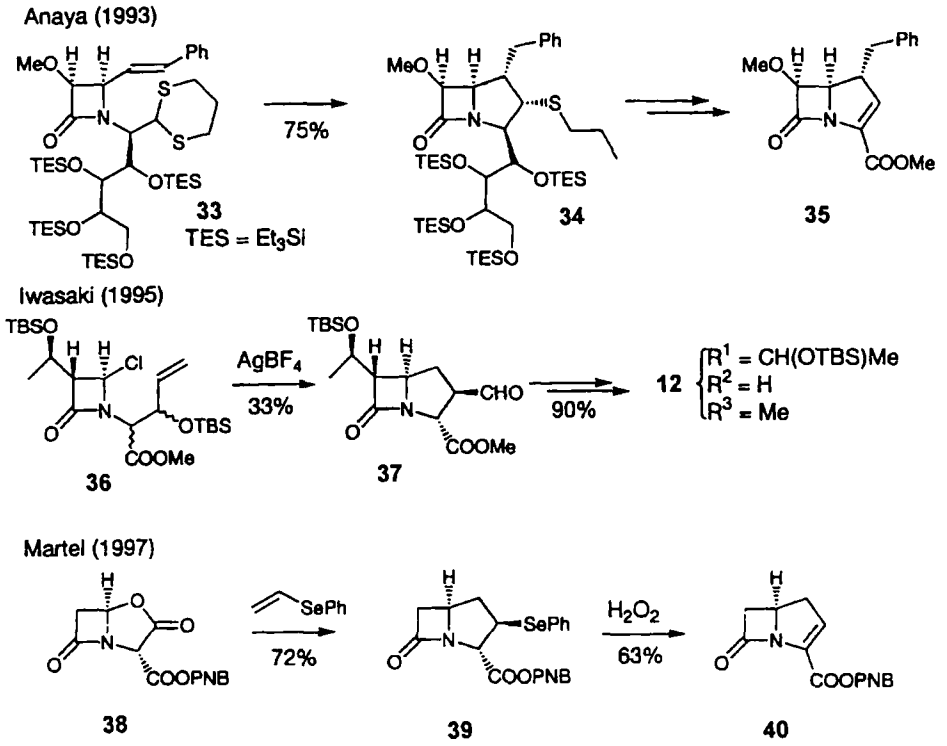

Feigelson (1993,1995)
TiCl4
25
26
R1 = H
R2 = SCH2CH2NHPNZ
R3 = PNB (52%)
R1 = TBS
R2 = CH2COCH3
R3 = benzyl (Bn) (57%)
(PNB = p-nitrobenzyl , PNZ = COOPNB)


Iwasaki (1994)
NBS
quant. yd.
AcCl - NaI
75%
27
28


Hanessian (1990)
71%
SePh
quant. yd.
29
30


Genêt (1995)
Pd(OAc)2
base
70-100%
31
32

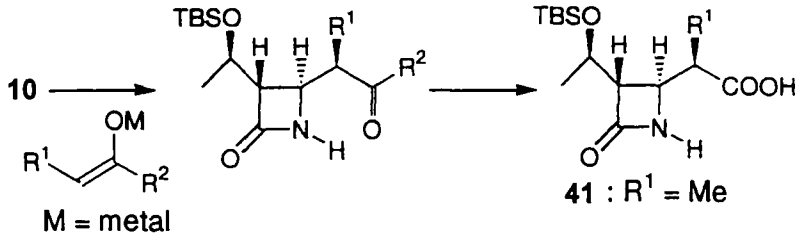
Scheme 3



2.1. Introduction of $C_{(1)}$-Substituents

Due to the competition among many research groups in the late 1980s, the stereoselective synthesis of 1β-methylcarbapenems greatly progressed and thereafter practical and efficient preparations of the key intermediate **41** were continuously developed. This has been excellently reviewed by A. H. Berks [12f] and recent additional work is referred here. The direct introduction of any substituents into $C_{(1)}$ position is difficult, and in all previous examples this was achieved before the construction of the carbapenem skeleton. The most popular approach has been the nucleophilic substitution reaction at $C_{(4)}$ of compound **10**, or its equivalents, to prepare compound **41** (Scheme 4).

Scheme 4

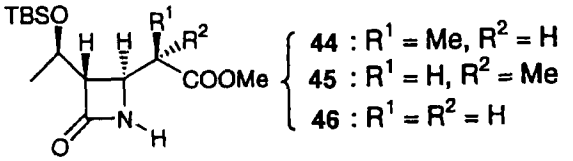


Other typical approaches, which do not utilize **10** as an intermediate, are the following: a) the conversion of an appropriately functionalized straight-chain type compounds, that had the desired stereochemistry, into the key intermediates such as **41-43**; b) introduction of the hydroxyethyl group into the β-lactam compound, which had been stereoselectively prepared. In the former approaches, Kang and Lee [19a], Yung and Vu [19b], Ishibashi et al. [19c,d] and Nakai et al. [19e] contributed new methodologies (Scheme 5).

As for the latter approaches, Rao et al., [19f] Tanner [19g] and Fujisawa et al. [19h] showed other possibilities (Scheme 6).

On the other hand, Shinkai and co-workers brushed up the first synthetic method [6] for the preparation of **41** because of its poor stereoselectivity. They achieved a practical and efficient isomerization of (**45**) and stereoselective methylation of (**46**), in the presence of triethylborane or triethylaluminum [19i].

Shinkai (1992)



Functionalities other than the methyl group could be introduced at the $C_{(1)}$ position by analogous methods, although modification may be necessary. The application of the $C_{(4)}$-alkylation in **10** was independently reported by Ueda et al. [20a] and Sakurai et al. [18d] for the introduction of the 1β-(2-hydroxyethyl) group, by Sendo et al. [20b] for a 1β-(substituted methyl) group such as hydroxymethyl etc., by Remuzon et al. [20c] for 1β-(2-aminoethyl) group, by Nagao et al. [21a] for a 1β-methoxy group, by Shah et al. [21b] for the 1,1-difluoro derivative, by Wildonger et al. [21c] for the 1-fluoro-1-methyl derivative, and by Fukumoto et al. [21d] for 1β-fluoro group. Especially Sakurai's, Remuzon's, and Nagao's methodologies were interesting due to their quite high stereoselectivities. On the other hand, a stereocontrolled synthesis was developed for the preparation of 1β-(functionalized alkyl)-carbapenem derivatives, taking advantage of the additional functional group. Menard et al. selected a rigid [4.2.0] bicyclic system **47** and **48** as intermediates and accomplished the stereoselective preparation of 1β-(functionalized methyl) and 1β-(functionalized ethyl) **49** derivatives substituted by use of thermodynamically-controlled isomerization (Scheme 7) [22].

The introduction of a 1α-hydroxy group by the stereoselective oxidation of 4-allylazetidin-2-one (Southgate et al. [23a]) and the synthesis of 1-hydroxycarbapenem **50** by the photochemical rearrangement of the 1-oxocarbapenem **51**, which was derived from the cephalosporin S-oxide **52** (Rosati et al. [23b]), were also of note (Scheme 8).

2.2. Introduction of $C_{(2)}$-Substituents

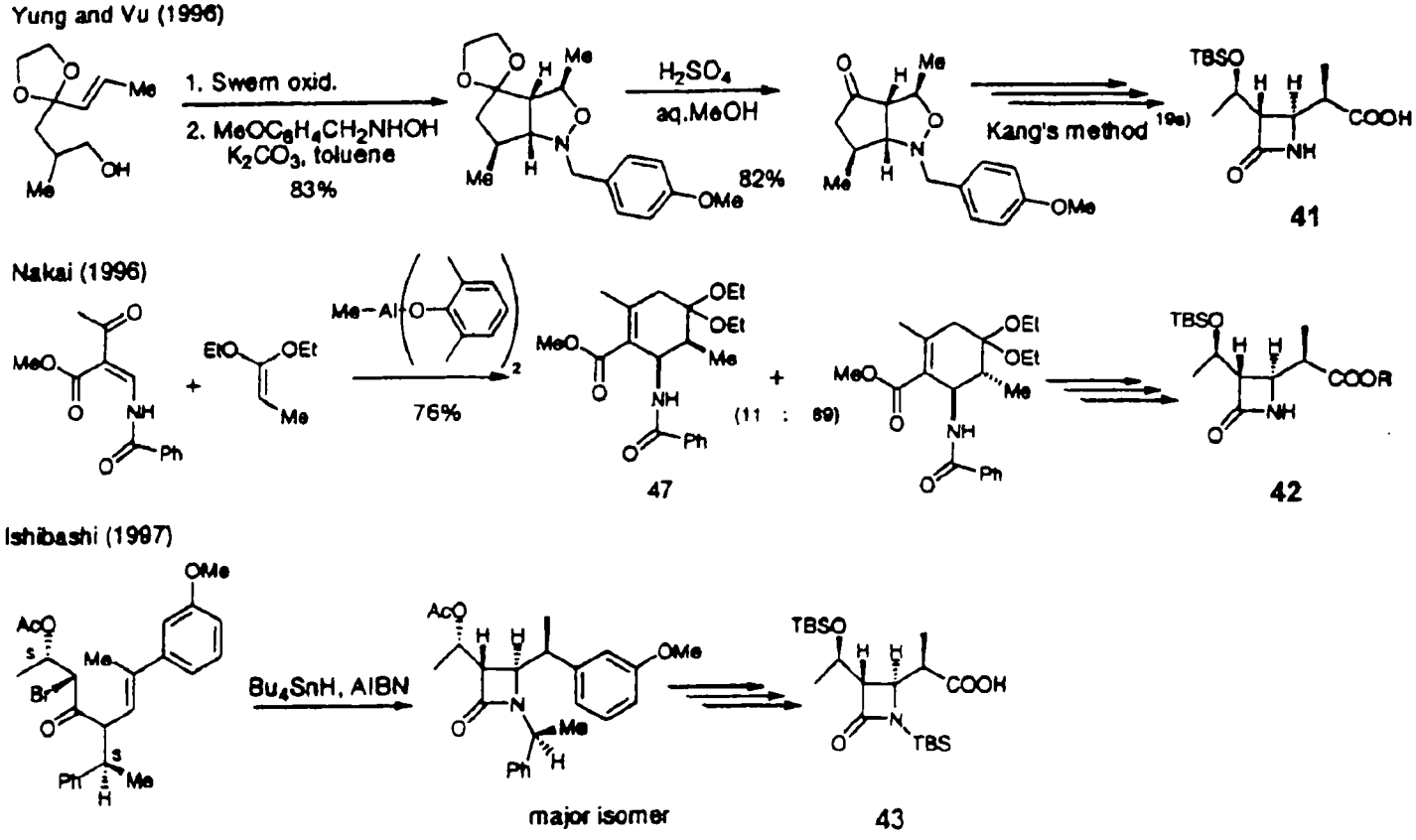
As for the introduction of substituents at the $C_{(2)}$ position, the Wittig-type cyclization and the thiol addition–elimination method have already been established. Additionally, Oda and Yoshida recently reported another type of the thiol addition–elimination procedure by utilizing the easily obtainable sulfone derivative **53** as the key intermediate, which was transformed to carbapenem of the type **21** [24] (Scheme 9).

Although the Wittig-type procedure is convenient for the introduction of the $C_{(2)}$-substituent with the formation of C—C as well as C—S bonds its efficiency for rapid screening studies is low, because functionalization is necessary in the early stage of the preparation, i.e. before the construction of the carbapenem skeleton. The latter addition–elimination type method is very effective, but the application to the C—C bond formation has not been sufficiently investigated. Recently several solutions were reported.

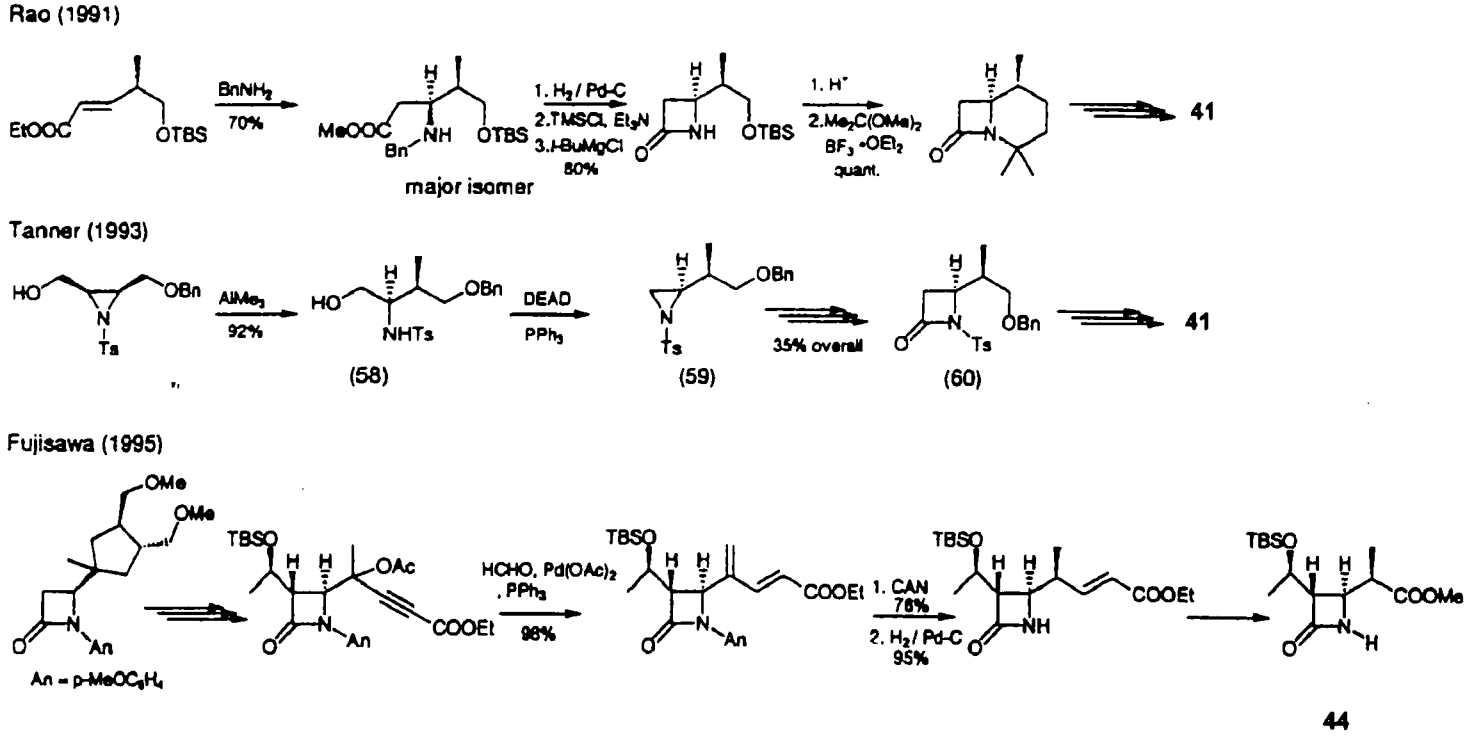
Rano and co-workers developed a synthetic method to prepare 2-aryl-substituted carbapenems **54** (R^4 = Ar) from the known intermediates **55** by application of a palladium-mediated cross-coupling reaction [25a]. Afterwards, the introduction of the aryl or alkenyl group by Yasuda et al. was reported [25b]. Independently, Onoue et al. established a general method to introduce alkyl [25c,d] or alkenyl [25e] groups at $C_{(2)}$ position. And recently, Dykstra and DiNinno reported the introduction of an alkynyl group by the Stille cross-coupling reaction [25f]. These methods enabled the systematic and efficient syntheses of these types of carbapenems (Scheme 10).

As reported by Arnould's group [26a], 2-hydroxymethyl carbapenem **56** was one of the key intermediates because the hydroxy group could be converted into various functionalities by using many different reactions, for example, the Mitsunobu reaction.

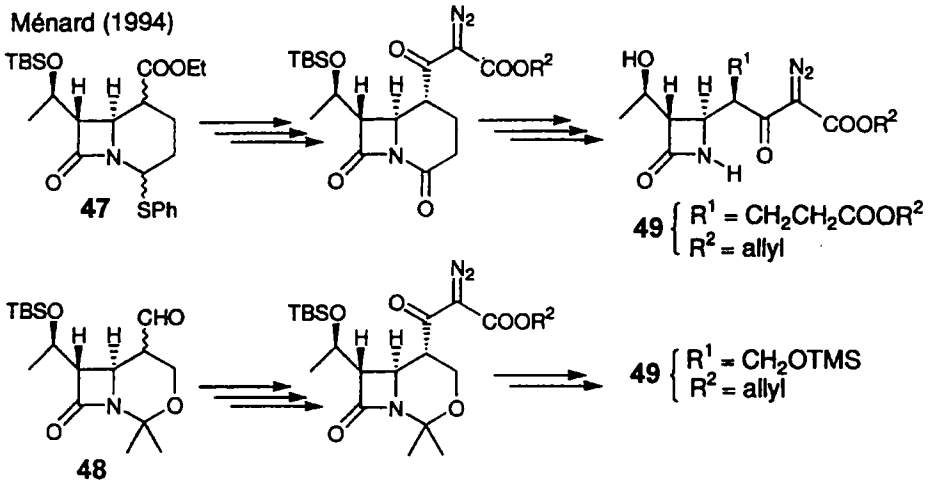
Scheme 5


Yung and Vu (1996)
1. Swern oxid.
2. MeOC6H4CH2NHOH
K2CO3, toluene
83%
H2SO4
aq.MeOH
82%
Kang's method [19a]
41
Nakai (1996)
76%
47
(11 : 89)
42
Ishibashi (1997)
Bu4SnH, AIBN
major isomer
43

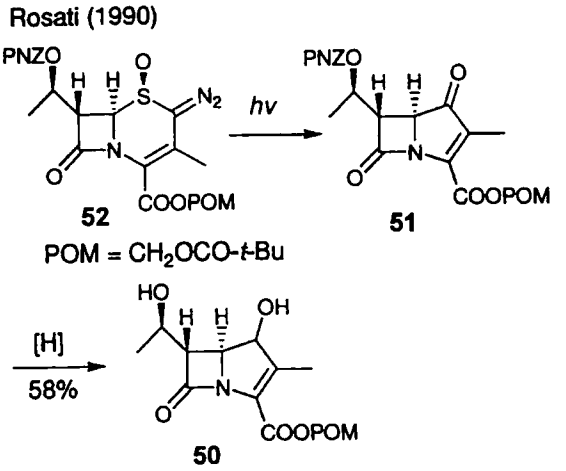
Scheme 6


Rao (1991)
EtOOC
OTBS
BnNH2
70%
MeOOC
Bn
NH
OTBS
major isomer
1. H2 / Pd-C
2.TMSCl, Et3N
3.i-BuMgCl
80%
NH
OTBS
1. H+
2.Me2C(OMe)2
BF3 ·OEt2
quant.
41
Tanner (1993)
HO
OBn
N
Ts
AlMe3
92%
NHTs
(58)
DEAD
PPh3
(59)
35% overall
(60)
41
Fujisawa (1995)
OMe
OMe
An
An = p-MeOC6H4
TBSO
OAc
COOEt
HCHO, Pd(OAc)2
, PPh3
98%
1. CAN
78%
2. H2 / Pd-C
95%
COOMe
44

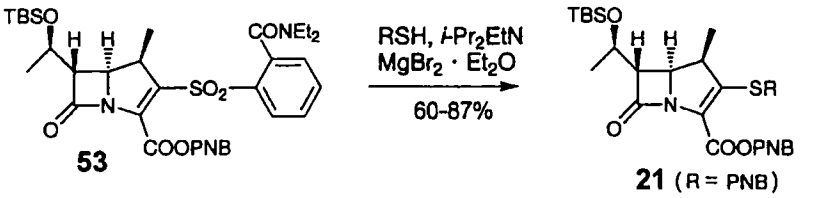
Scheme 7



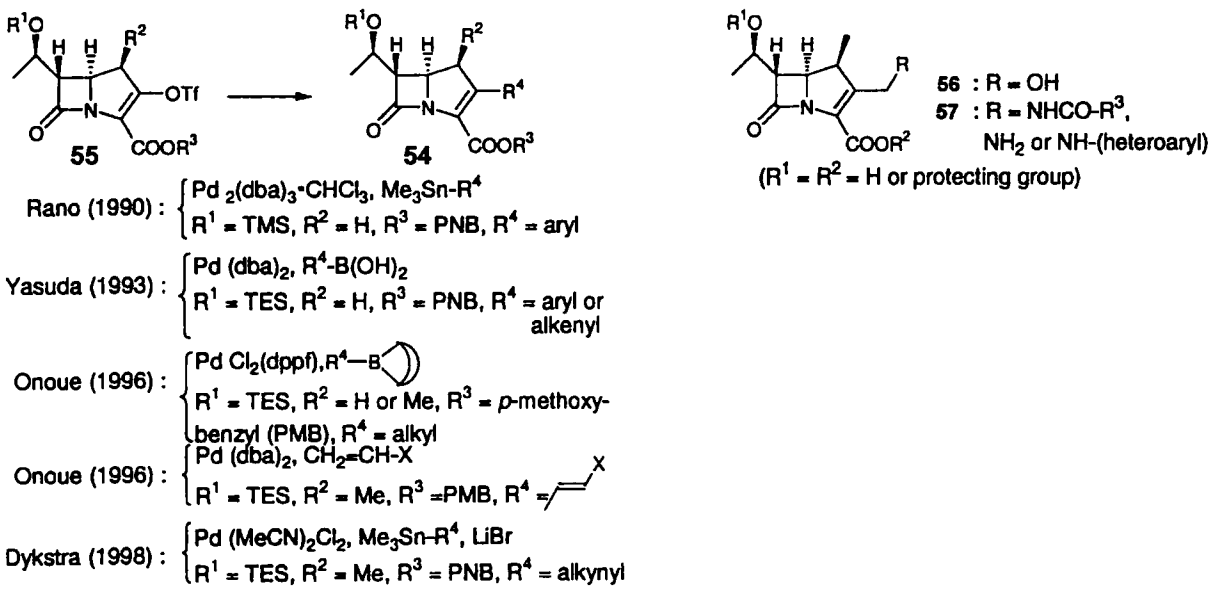
Scheme 8



Scheme 9



Scheme 10

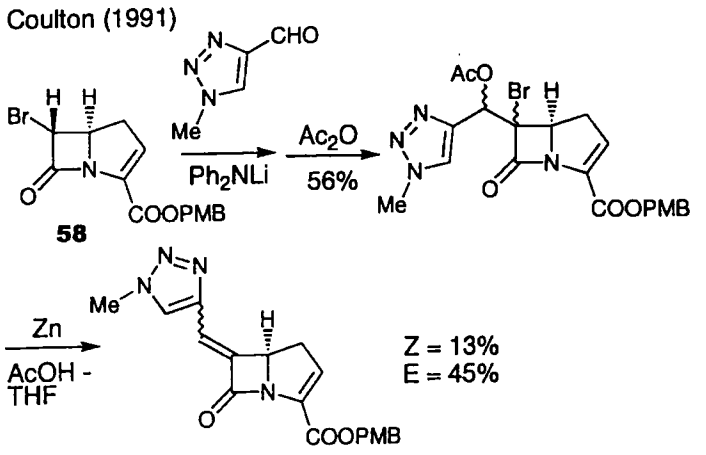


Therefore, new preparative methods for compound **56** have been investigated: for example, the synthesis by Imuta and colleagues [26b] or the procedure developed by Ueo et al. [26c]. The latter has applied the stereoselective $C_{(4)}$-alkylation reaction of **10** as the key step. Recently, Hu and Demuth reported the short and effective preparation of **56** from **41** [26d]. Independently, Yang and Yasuda developed another direct and practical procedure to obtain **57** from **41** [26e].

2.3. Introduction of $C_{(6)}$-Substituents

In view of the synthesis of natural products, the methods of introducing various groups, including the 1-hydroxyethyl moiety, at the $C_{(6)}$ position have been widely studied. They were all accomplished before the construction of the bicyclic system, that is, at the stage of the chain-type precursor or the monocyclic β-lactam derivative. The latter, which utilized

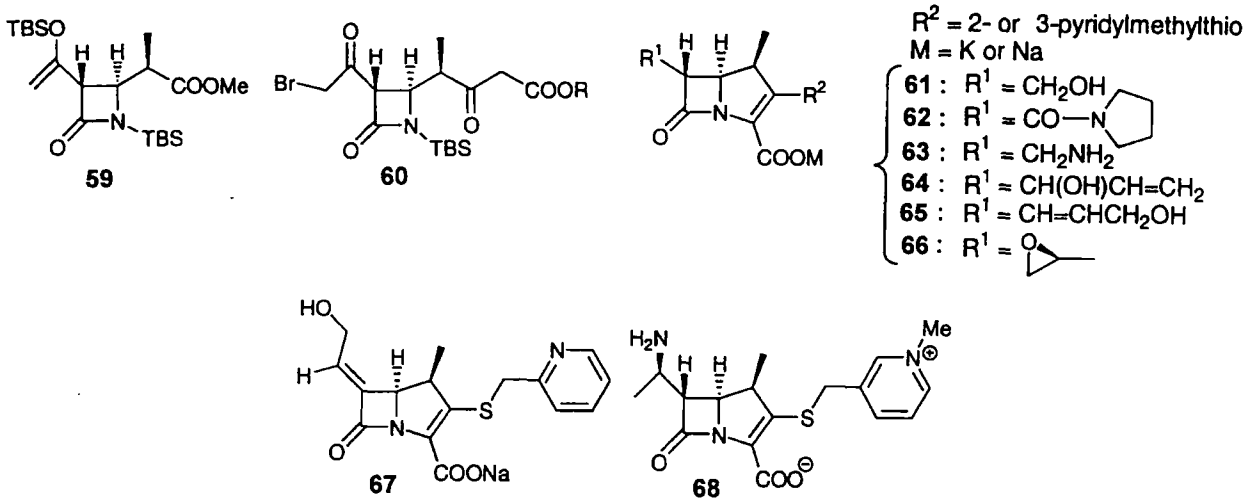
Scheme 11



the reactivity of α-anion in the β-lactam ring, was more favorable for effective screening studies. Nagao et al. revealed that this method was effective for introduction of various groups such as the methylthio group [27a].

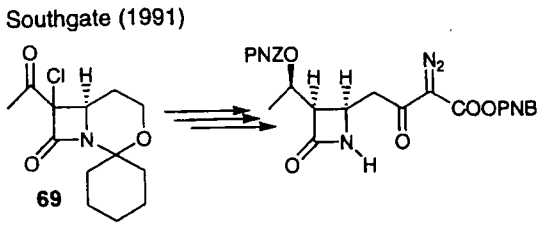
Although difficult to develop, the direct introduction of functionalities in the bicyclic system is interesting and useful from the point of fast screening. Coulton et al. reported that the aldol condensation of 6-bromocarbapenem **58** could proceed smoothly (Scheme 11) [27b]. The application of the systematic chemical modification at the $C_{(6)}$ position could be achieved in the near future.

The effective conversions of the 1-hydroxyethyl substituent in the key intermediate **10**, which has become rather easily achievable, into various functionalities were reported by Ruediger and Menard et al. The silyl enol **59** and α-bromoketone **60**, which were easily obtained from the 1-hydroxyethyl derivative, could be converted into a variety of 6-substituted carbapenems **61-68** [28].



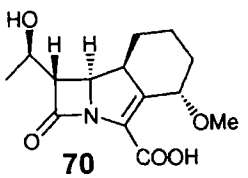
Among these syntheses, the functionalization into the aminomethyl moiety from the hydroxymethyl group and 1-aminoethyl group from 1-hydroxyethyl group at the $C_{(6)}$ position in the carbapenems, and preparation of the asparenomycin-type derivative **67** from the epoxide **66** were achieved on the carbapenem derivatives. Additionally, Southgate and coworkers reported the isomerization at the $C_{(6)}$ position via the chloride **69** (Scheme 12) [29].

Scheme 12

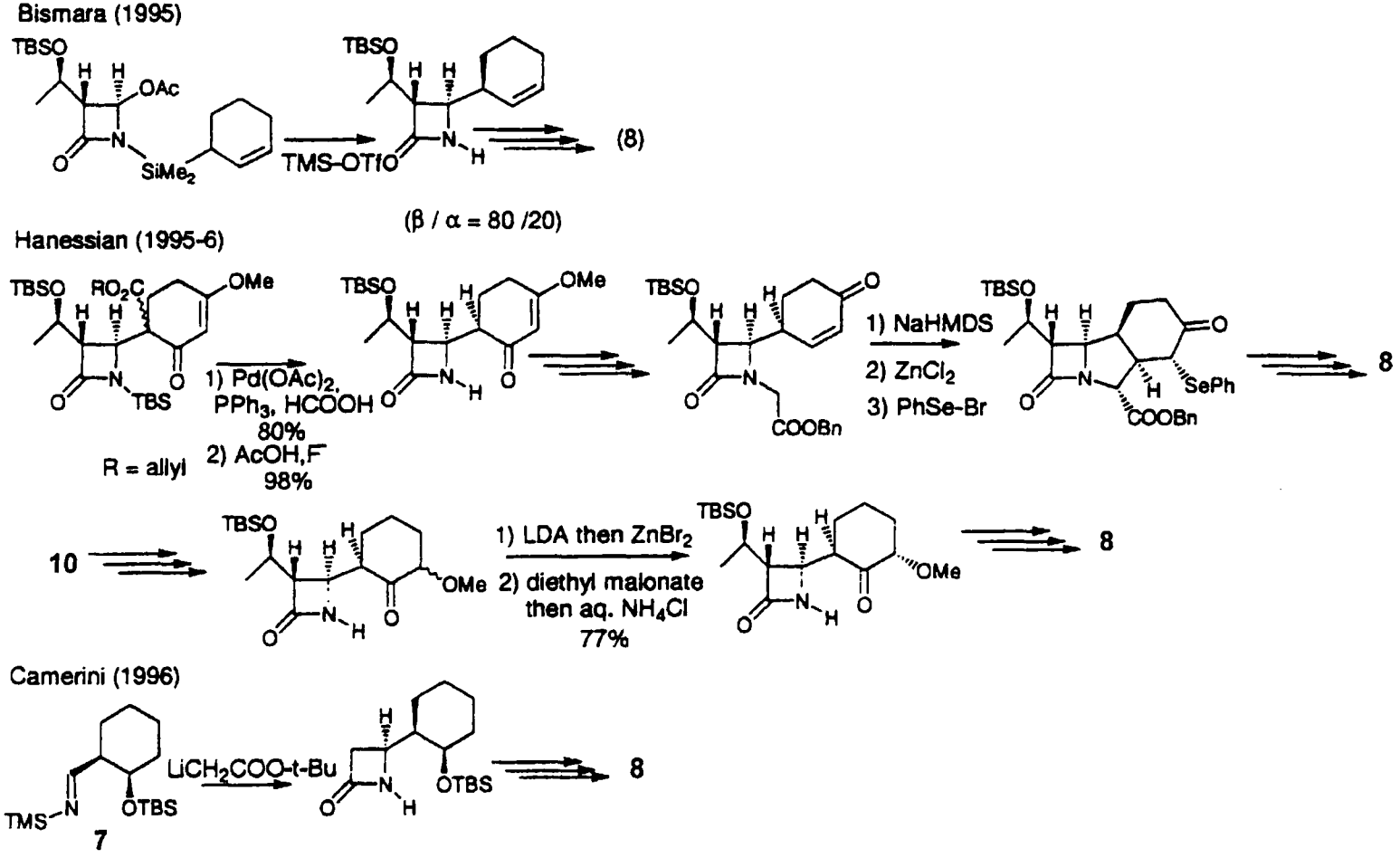


3. THE SYNTHESIS OF POLYCYCLIC CARBAPENEMS

The derivatives that were produced by fusing the carbapenem skeleton with other cyclic systems were investigated since the early study [30] and they were included in the category of modification at the $C_{(1)}$ and $C_{(2)}$ positions. Therefore, the synthetic procedures were almost the same as those discussed above. A typical method was the preparation of tri- and tetracyclic compounds **8** and **9** by Wittig-type cyclization, after the introductlon of the cycloaliphatic substituent [11].



Scheme 13


Bismara (1995)
TBSO
OAc
SiMe2
TMS-OTf
(8)
(β / α = 80 /20)
Hanessian (1995-6)
RO2C
OMe
TBS
1) Pd(OAc)2, PPh3, HCOOH 80%
2) AcOH,F 98%
R = allyl
COOBn
1) NaHMDS
2) ZnCl2
3) PhSe-Br
SePh
8
10
1) LDA then ZnBr2
2) diethyl malonate then aq. NH4Cl 77%
Camerini (1996)
LiCH2COO-t-Bu
OTBS
TMS
7

Since 1992, the chemists at Glaxo Wellcome have aggressively studied these types of synthetic carbapenems to find sanfetrinem (**70**) and its derivatives as clinical candidates. Bismara and colleagues reported the stereoselective synthesis of a tricyclic carbapenem **8** [11e] by the application of the $C_{(4)}$-alkylation developed by Ueo et al. [31]. Hanessian's group found a novel preparation of the tricyclic derivatives by the combination of stereocontrolled decarboxylation and cyclization, utilizing the intramolecular Michael reaction [11f], and afterwards established a highly stereoselective and practical synthetic route to prepare **8** by utilizing diastereoselective protonation as a key step [11n]. Camerini et al. reported an approach to construct the β-lactam ring from the functionalized cyclohexane **71** [11i]. This indicated that the knowledge about cyclohexane chemistry could be effectively applied to this series of carbapenems (Scheme 13).

As reviewed above, some efficient and practical preparative methods were developed for the screening studies. However, there were some points to be solved; for example, the systematic and effective substitution at $C_{(6)}$ position. The progress of the chemistry on the rather unstable bicyclic system is highly desirable now and the development of methodology to apply the efficient mass production is also required. Hopefully this review has put the recent literature on the carbapenem chemistry into perspective to create the next generation carbapenem antibiotics.

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