ORGANOSILICON AND ORGANOTIN COMPOUNDS IN THE SYNTHESIS AND TRANSFORMATION OF β-LACTAMS

Grigory A.Veinberg and Edmunds Lukevics*

Latvian Institute of Organic Synthesis, 21, Aizkraukles, LV 1006, Riga, Latvia

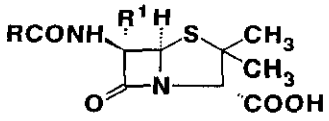
Abstract - The present review describes the general trends in the synthesis and structural modification of β-lactams based on the employment of organosilicon and organotin compounds.

Abbreviations:

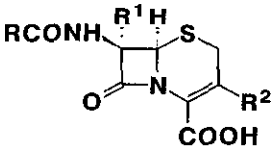
AIBN – azobisisobutyronitrile
Bn – benzyl
CSI – chlorosulfonylisocyanate
LDA—lithium diisopropylamide
Pht—phthalimido
PMB – para-methoxybenzyl
Tf – trifluoromethanesulfonyl
TMCS – trimethylchlorosilane
TMSOTf – trimethylsilyltriflate
Ts – tosyl

1. INTRODUCTION

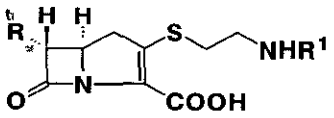
Intensive investigation of β-lactam antibiotics during the last decades resulted in the discovery of numerous natural and synthetic biologically active substances with common heterocyclic moiety used in their general name (Scheme 1).[1-3]



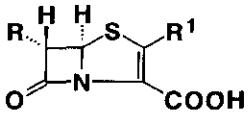
Penicillin



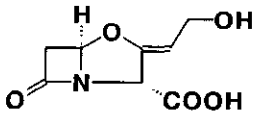
Cephalosporin



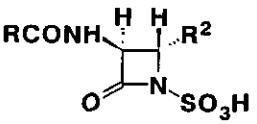
Carbapenem



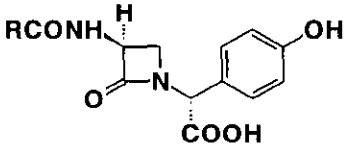
Penem



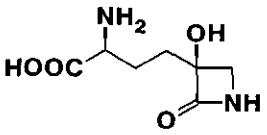
Clavulanic acid



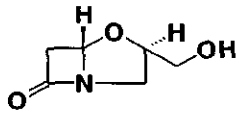
Monobactam



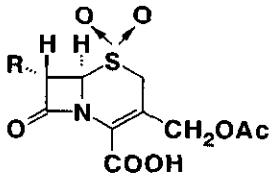
Nocardicin



Tabtoxin



Antifungal clavam



Elastase inhibitor

Scheme 1

Due to their practical importance β-lactams are objects of permanent chemical interest. There is a variety of synthetic and biosynthetic methods developed for their preparation and subsequent transformation into substances needed for medicine, veterinary, agriculture, biology, etc.

Complicated multi-step processes of their production and constant efforts to reduce expenses by technological modernization have favored elaboration and introduction of new synthetic approaches in the chemistry of β-lactams. The so-called silyl methods are playing among them a very important role. Their application for the modification of β-lactam started in 1964 by the preparation of 6-aminopenicillanic acid trimethylsilyl ester by Glombitza.[4]

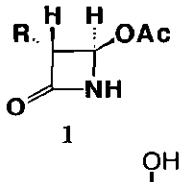
Since that date and especially in the last two decades methodology based on the use of organosilicon and organotin compounds has become an important part of bioorganic chemistry and it is widely employed in the synthesis and chemical transformation of all compounds presented in Scheme 1.

The available information on the problem could be classified in the following manner:

- synthesis of monocyclic β-lactams;
- stereocontrolled functionalization of β-lactams or β-lactam antibiotics;
- structural transformations of penicillins, cephalosporins, penems, carbapenems, etc. with the help of trialkylsilyl protecting groups;
- technological improvements in production and isolation of β-lactams;
- biological properties of β-lactams containing group IVB elements.

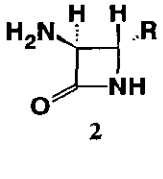
2. SILYL AND STANNYL METHODS IN THE SYNTHESIS OF MONOCYCLIC β-LACTAMS

Investigation of the alternative methods for the preparation of biologically active mono- and bicyclic β-lactams stimulated interest to the chemistry of azetidin-2-ones (**1–3**).



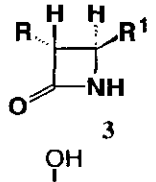
1

R = H, Alk, Me-CH(OH)



2

R = H, Alk, Ar



3

R = H, Alk, Me-CH(OH); R^1 = C≡CH, CH=CHPh, CO_2Me, SOPh, Me-CH(CO_2Me), etc.

First of all this study was aimed at the synthesis of **1–3** using organic substances commercially more available. Several approaches have been developed for the solution of this problem during the last decade, the most effective based on the utilization of organosilicon or organotin compounds are listed below:

a) aldimine – ester enolates or aldimine – acid chloride cyclocondensation;

b) cyclization of β-amino acid or β-hydroxy acid esters;

c) cycloaddition of chlorosulfonyl isocyanate to functionalized alkenes;

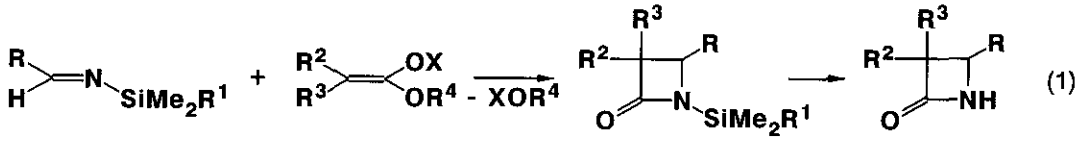
d) cyclization of β-amido sulfoxides.

2. 1. Preparation of Azetidin-2-one Derivatives by Cyclocondensation of Aldimines with Ester Enolates

Reformatsky type reaction between α-bromoacetates and *N*-arylidenaniline described by Gilman and Speeter[5] has become a prototype for the synthesis of azetidin-2-ones by aldimine and ester enolate cyclocondensation.

Birkofer and Schramm have successfully used *N*-trimethylsilyl substituted aldimines for this purpose.[6] It permited to obtain *N*-unsubstituted azetidin-2-ones being more suitable for the transformation into biologically active derivatives. It was the first application of silyl methodology in the synthesis of monocyclic β-lactams.

Hart, Colvin, Cainelli and other authors have introduced important improvements for this synthetic procedure.[7-10] It has been shown that *N*-trimethylsilyl protection of aldimines allows to avoid some important structural limitations of the reagent. It gives the possibility to use enolizable aldehydes as azomethine component in this reaction and, thus, to obtain β-lactams substituted with saturated and unsaturated alkyl substituents in 4 position.

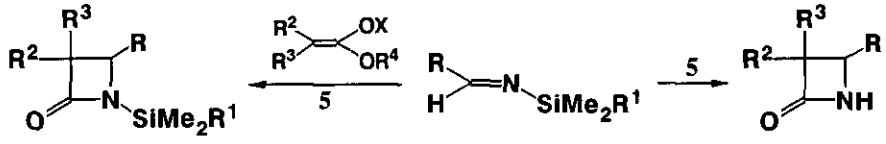


4 5 6 7 (1)

R = Alk, Ar, Het; R^1 = Me, *t*-Bu; R^2 = H, Alk, Ar; R^3 = H, Alk; R^4 = Me, Et, *t*-Bu, $SiMe_3$;
X = Li^+, $ZnCl^+$, $ZnEt^+$, $SiMe_3$

Various methods for the preparation of *N*-trialkylsilyl aldimines (**4**) and their condensation with ester enolates or ketene silyl acetals (**5**) are analyzed in the excellent Hart's review published in 1988.[7] However, since that time new experimental data (see the Table 1) on the successful usage of organosilicon and organotin compounds in these reactions became available allowing to compare the yields and stereochemical effectiveness for different chemical approaches.

Table 1. Trialkylsilyl Derivatives of Aldimines Used in Azetidin-2-ones Synthesis



6 4 7

R	R^1	Conditions[a]	R^2	R^3	X	R^4	Azetidin-2-one yield, %	Azetidin-2-one *cis : trans*	Ref.
Me	Me	B	Me	Me	Li	Et	(7) 94	-	8
Me	Me	A	Et	H	Li	t-Bu	(7) 46	78 : 22	9
Me	Me	A	Et	H	Li	Et	(7) 38	86 : 14	9
Me	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 40	90 : 10	9
Me	Me	A	$(PhCH_2)_2N$	H	Li	Et	(7) 36	95 : 5	9
Et	Me	A	Me	Me	Li	Et	(7) 40	-	9
Et	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 57	90 : 10	9
i-Pr	Me	A	Me	Me	Li	Et	(7) 60	-	9
i-Pr	Me	A	Et	H	Li	t-Bu	(7) 29	8 : 92	9
i-Pr	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 28	8 : 92	9
n-Pr	Me	A	Et	H	Li	Et	(7) 28	72 : 28	9
n-Pr	Me	C	Et	H	Li	Et	(7) 40	75 : 25	10
n-Bu	Me	B	Me	Me	Li	Et	(7) 98	-	8
n-Bu	Me	B	Et	H	Li	Et	(7) 93	91 : 9	8
n-Bu	Me	B	i-Pr	H	Li	Et	(7) 99	100 : 0	8
s-Bu	Me	B	Me	Me	Li	Et	(7) 60	-	8
s-Bu	Me	B	i-Pr	H	Li	Et	(7) 73	100 : 0	8
$n\text{-}C_5H_{11}$	t-Bu	G	Me	Me	Li	Et	(6) 20	-	11
$n\text{-}C_7H_{15}$	t-Bu	G	Me	Me	Li	Et	(6) 25	-	11
$n\text{-}C_9H_{19}$	Me	A	Et	H	Li	Et	(7) 44	92 : 8	9
$CH_2=CH$	Me	A	i-Pr	H	Li	Et	(7) 11	100 : 0	12
$CH_2=C(OMe)$	Me	B	Et	H	Li	Et	(7) 46	59 : 41	8
$Me_2C=CH$	Me	A	Me	Me	Li	Et	(7) 33	-	9
$Me_2C=CH$	Me	A	Et	H	Li	Et	(7) 20	77 : 23	9
$MeOCH_2$	Me	B	Me	Me	Li	Et	(7) 58	-	8
$COOC_2H_5$	t-Bu	H	Me	Me	SiMe3	Me	(6) 85	-	13
PhCH=CH	Me	A	Me	Me	Li	Et	(7) 69	-	14
PhCH=CH	Me	C	Me	Me	Li	Et	(7) 20	-	15
PhCH=CH	t-Bu	G	Me	Me	Li	Et	(6) 82	-	11
PhCH=CH	t-Bu	G	Me	MeO	Li	Et	(6) 62	64 : 36	11
PhCH=CH	Me	C	Et	H	Li	Et	(7) 24	86 : 14	15
PhCH=CH	t-Bu	G	Et	H	Li	Et	(6) 35	87 : 13	11
PhCH=CH[b]	Me	A		H	Li	Et	(7) 50	70 : 30	16
PhCH=CH	Me	A		Me	Li,ZnEt	Me	(7) 85	100 : 0	17
PhCH=CH[c]	CH_2SiMe_3		MeO	H		OH	(6) 48	100 : 0	18
PhCH=C(Me)[c]	CH_2SiMe_3		PhO	H		OH	(6) 62	100 : 0	18
PhCH=C(Me)[c]	CH_2SiMe_3		Pht	H		OH	(6) 70	100 : 0	19

Table 1. Trialkylsilyl Derivatives of Aldiminės Used in Azetidin-2-ones Synthesis (Continued).

$PhCH=C(Me)$[c]	CH_2SiMe_3		Pht	H			(6) 70	100 : 0	19
$PhCH_2OCH_2$	Me	B	Me	Me	Li	Et	(7) 58	-	8
$PhSCH=CH$	Me	A	i-Pr	H	Li	Et	(7) 76	91 : 7	20
$Me_3SiCH=CH$	Me	E	Me	Me	$SiMe_3$	Me	(7) 75	-	13
$PhC\equiv C$	Me	E	Me	Me	$SiMe_3$	Me	(7) 78	-	13
$PhC\equiv C$	Me	E	Me	H	$SiMe_3$	Me	(7) 82	25 : 75	13
									
$PhC\equiv C$	Me	A	Me	H	Li,ZnEt	Me	(7) 85	100 : 0	17
$PhC\equiv C$	Me	A	Et_2N	H	ZnCl	Et	(7) 98	0 : 100	21
$4\text{-}MeOC_6H_4C\equiv C$	Me	A	i-Pr	H	Li	Et	(7) 81	100 : 0	12
$Me_3SiC\equiv C$	Me	A	Me	Me	Li	Et	(7) 79	-	14
$Me_3SiC\equiv C$	Me	E	Me	H	$SiMe_3$	Me	(7) 62	38 : 62	13
$Me_3SiC\equiv C$	Me	E	Et	H	$SiMe_3$	Me	(7) 44	30 : 70	13
$Me_3SiC\equiv C$	Me	A	i-Pr	H	Li	Et	(7) 57	91 : 9	12
$Me_3SiC\equiv C$	Me	E	Ph	H	$SiMe_3$	Me	(7) 59	8 : 92	13
$Me_3SiC\equiv C$	Me	A	PhS	Me	Li	Et	(7) 76	29 : 71	14
$Me_3SiC\equiv C$	Me	A	Et_2N	H	ZnCl	Et	(7) 98	0 : 100	21
$Me_3SiC\equiv C$	Me	A	$(CH_2SiMe_2)_2N$	H	ZnCl	Et	(7) 93	3 : 97	22
									
$Me_3SiC\equiv C$	Me	A	Me	H	Li	Et	(7) 75	75 : 25	23
									
Me	Me	A	Et	H	Li	t-Bu	(7) 61	96 : 4	24
									
Me	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 85	98 : 2[k]	25
Ph	Me	E	H	H	$SiMe_3$	Me	(7) 27	-	13
Ph	Me	A	Me	Me	Li	Me	(7) 72	-	14
Ph	Me	B	Me	Me	Li	Me	(7) 86	-	8
Ph	Me	C	Me	Me	Li	Et	(7) 57	-	15
Ph	Me	A	Me	H	Li	Et	(7) 44	93 : 7[d]	12
Ph	Me	A	Et	H	Li	Et	(7) 72	100 : 0[d]	12
Ph	Me	E	Et	H	$SiMe_3$	Me	(7) 61	10 : 90	13
Ph	Me	A	i-Pr	H	Li	Et	(7) 81	99 : 1[d]	12
Ph	Me	E	i-Pr	H	$SiMe_3$	Me	(7) 68	17 : 83	13
Ph	Me	A	t-Bu	H	Li	Et	(7) 40	100 : 0	12
Ph	Me	A	$CH_2=CMe$	H	Li	Et	(7) 42	0 : 100	12
Ph	Me	A	H_2NCH_2	H	Li	Et	(7) 57	88 : 12	12
Ph	Me	A	Et_2N	H	ZnCl	Et	(7) 95	0 : 100	21
Ph	Me	A	$MeCH(SPh)CH_2$	H	Li	Et	(7) 61	100 : 0	12
Ph	Me	A	PhS	H	Li	Et	(7) 53	9 : 91	14
Ph	Me	A	PhS	Me	Li	Et	(7) 58	29 : 71	14
Ph	Me	A	PhS	Et	Li	Et	(7) 8	75 : 25	12
Ph	Me	A	$(Me_3Si)_2N$	H	ZnCl	Et	(7) 70	1 : 99	22
Ph	Me	A	$(CH_2SiMe_2)_2N$	H	ZnCl	Et	(7) 96	14 : 85	22

Table 1. Trialkylsilyl Derivatives of Aldimines Used in Azetidin-2-ones Synthesis (Continued).

			$SiMe_2Ph$						
Ph	Me	A	Me	H	Li	Et	(7) 63	100:0	26
4-$MeOC_6H_4$	Me	D	Et	H	Li	Et	(7) 68	89 : 11	10
PhSCH = CH	Me	A	i-Pr	H	Li	Et	(7) 76	93 : 7	12
2-furyl	Me	C	Me	Me	Li	Et	(7) 60	-	10
2-furyl	Me	E	Me	Me	$SiMe_3$	Me	(7) 76	-	13
2-furyl	t-Bu	G	Me	Me	Li	Et	(6) 65	-	11
2-furyl[e]		G	Me	Me	Li	Et	(6) 29	-	11
2-furyl[f]		A	Me	H	$SiMe_3$	Me	(7) 69	67 : 33	13
2-furyl	t-Bu	G	Me	Ph	Li	Et	(6) 42	68 : 32	11
2-furyl	Me	E	Et	H	$SiMe_3$	Me	(7) 66	33 67	13
2-furyl	Me	C	Et	H	Li	Et	(7) 56	70 : 30	10
2-furyl	t-Bu	G	Et	H	Li	Et	(6) 36	100 : 0	11
2-furyl	Me	A	i-Pr	H	Li	Et	(7) 85	99 : 1	12
2-furyl	Me	C	$CH_2 = C(Me)$	H	Li	Et	(7) 30	10 : 90	10
2-furyl	Me	C	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 43	95 : 5	10
2-furyl	Me	A	$(CH_2SiMe_2)_2N$	H	ZnCl	Et	(6) 92[g,h]	8 : 92	27
2-furyl	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 95[i]	97 : 3	27
2-furyl	Me	E	PhO	H	$SiMe_3$	Me	(7) 58	56 : 44	13
2-thienyl	Me	D	Me	Me	Li	Et	(7) 45	-	10
2-thienyl	Me	C	Et	H	Li	Et	(7) 50	50 : 50	15
2-thienyl	Me	D	Et	H	Li	Et	(7) 50	75 : 25	10
2-thienyl	Me	A	$(CH_2SiMe_2)_2N$	H	ZnCl	Et	(7) 87[h]	15 : 85	27
2-thienyl	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 99[i]	94 : 6	27
2-thienyl	Me	D	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 35	90 : 10	10
2-pyridyl	Me	A	$(CH_2SiMe_2)_2N$	H	ZnCl	Et	(7) 82	1 · 99	27
2-pyridyl	Me	A	$(CH_2SiMe_2)_2N$	H	Li	Et	(7) 92	91 : 9	27

[a] Conditions (preparation of 7), reagents, solvent, temperature: A = RCHO, $LiN(SiMe_3)_2$, THF (ether), -30 – -78°C ; B = RLi, $(Me_3Si)_2NCHO$, THF, -78°C; C = RCN, $LiAl(OEt)_3H$, Me_3SiCl, ether, 0°C(imino aluminates and ester enolates also form monocyclic β-lactams but with considerably lower yield in comparison with their *n*-trialkylsilyl analogs, see ref. 17); D = RCN, $LiAl(i\text{-}Bu)_2(n\text{-}Bu)H$, Me_3SiCl, toluene, hexane, 0°C; E = RCHO, $LiN(SiMe_3)_2$, Me_3SiCl, hexane, 0°C; G = RCHO, $N(SnMe_3)_3$, THF, ether, room temperature; H = $RNHSiMe_2t\text{-}Bu$, *t*-BuOCl, DBU, THF, ether, 0°C.

[b] *trans*-PhCH = CH is used in all experiments.

[c] N-CH_2SiMe_3 group is used in **4** instead of $SiMe_3$ group,condensation of aldimine with substituted acetic acid is performed in the presence of triethylamine and phenyl dichlorophosphate.

[d] Addition of the hexamethylphosphoramide solution to the reaction mixture of **4** and **5** affects cis:trans ratio of azetidin-2-ones (**7**) (see ref. 13).

[e] N-$SiPh_2t$-Bu group is used in **6** and **7**.

[f] Furfural *N,N,O*-tris(trimethylsilyl)amine acetal is used instead of *N*-trimethylsilyl-2-furfuraldimine.

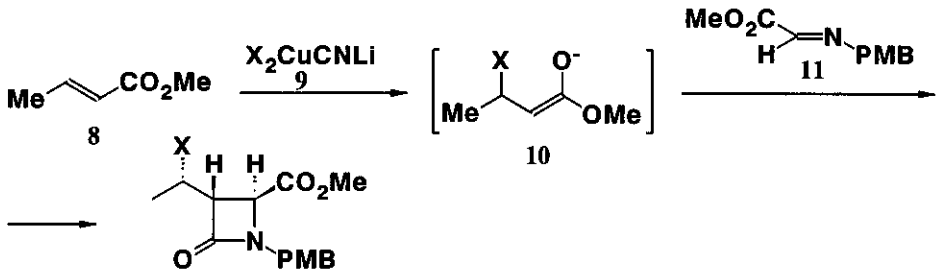
[g] The protecting trimethylsilyl group at 1 position is not removed even after aqueous workup.

[h] Zinc enolate activation of the ester (**5**).

[i] Lithiun enolate activation of the ester (**5**).

[k] Ratio of isolated (3S*, 4R*, 1'R*) and (3R*, 4S*, 1'R*)-3-(benzyloxycarbonylamino)-4-(1'-*t*-butyldimethylsiloxy)ethylazetidin-2-ones.

Palomo *et al.* have developed a new method for the preparation of 3-*trans*-1'-dimethylphenylsilyl-4-methoxycarbonyl and 3-(1'-tributylstannyl)-4-methoxycarbonyl substituted β-lactams (**12**) trapping organocopper enolates (**10**) obtained by the addition of silylcuprate or stannylcuprate reagents (**9**) to methyl crotonate (**8**) by methyl glyoxalate imine (**11**). [28,29]



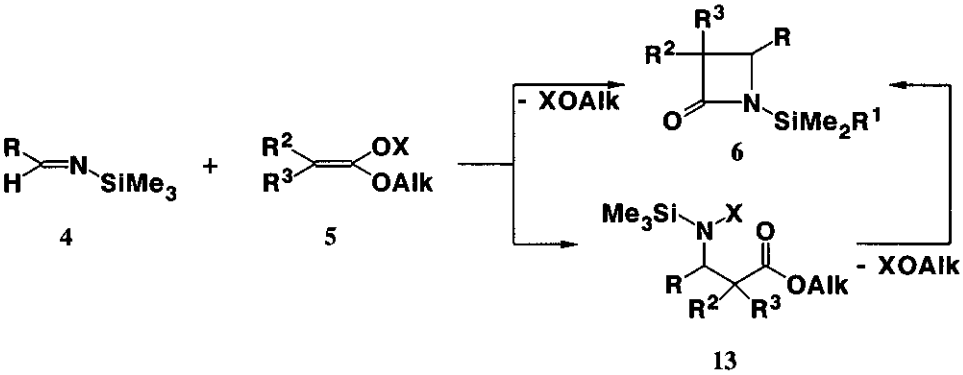
(2)

R	R^1	X	Yield of **12**, %	*trans:cis* ratio
H	Me	$PhMe_2Si$	80	100 : 0
H	Ph	$PhMe_2Si$	77	85 : 15
H	4-MeC_6H_4	$PhMe_2Si$	80	100 : 0
Me	Me	$PhMe_2Si$	85	100 : 0
H	Me	*n*-Bu_3Sn	65	60 · 40

Azetidin-2-ones could be prepared from **4** and **5** in two ways:

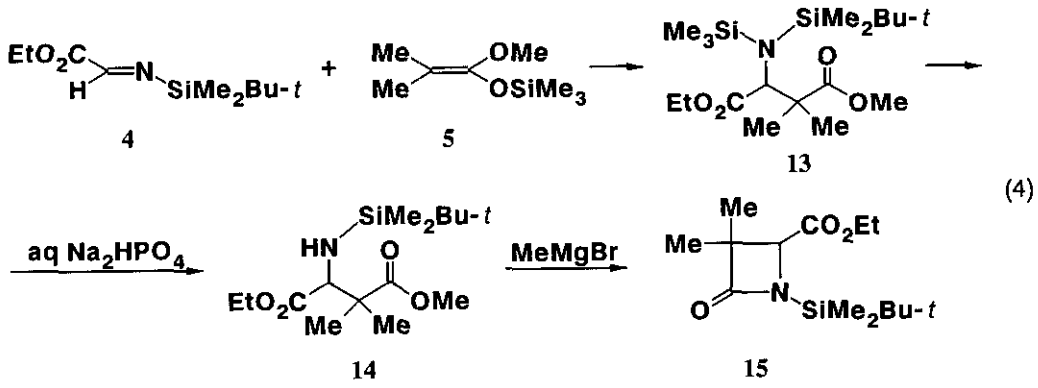
a) cyclocondensation and the formation of azetidin-2-ones (**6**);

b) generation of the intermediate β-amino esters (**13**) and their cyclization into **6** .[7]



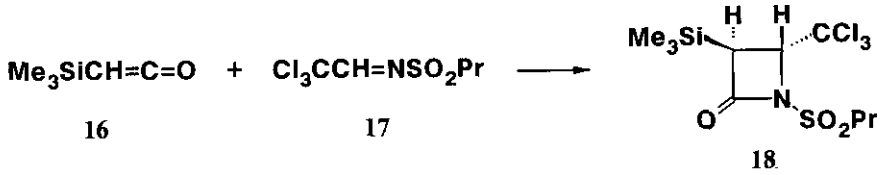
(3)

Colvin et al. proved the formation of β-amino esters as a cyclocondensation primary product using the selective mono-desilylation of **13** in aqueous Na_2HPO_4 and the following conversion of *N*-*t*-butyldimethylsilylamino ester (**14**) into β-lactam (**15**) by Grignard reagent in the overall yield of 60%. [13]



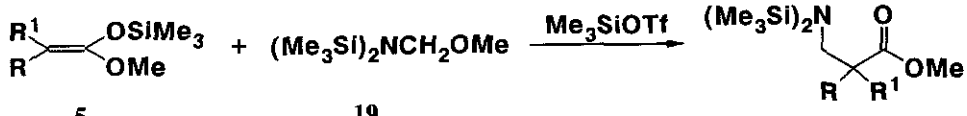
(4)

[2+2] Cycloaddition mechanism between ketene and imine has been vividly demonstrated in the reaction between trimethylsilyl ketene (**16**) and *N*-propylsulphonylimine (**17**) at room temperature with quantitative formation of *trans*-3,4-disubstituted azetidin-2-one (**18**). [30]



(5)

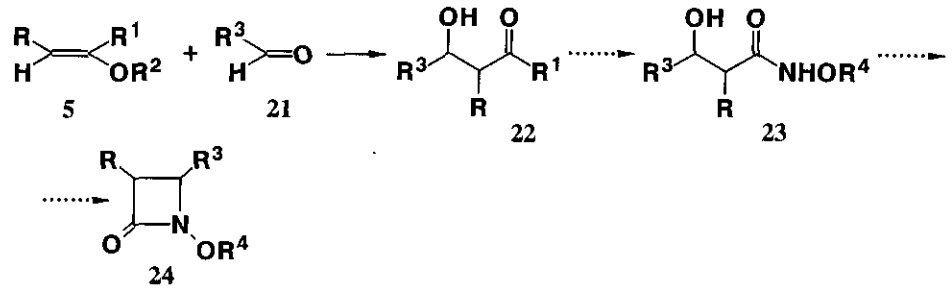
Cyclization of β-amino esters into azetidin-2-ones by Grignard reagent or LDA stimulated interest to their synthesis as intermediate products and accordingly elaboration of silyl methods for their preparation. For example, β-[*N*,*N*'-bis(trimethylsilyl)]amino esters (**20**) were obtained in high yields (78-93%) by the treatment of *O*-trimethylsilyl ketene acetals (**5**) with *N*,*N*'-bis(trimethylsilyl)methoxymethylamine (**19**) in the presence of trimethylsilyl triflate. [31]



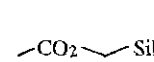
(6)

a) R = R^1 = Me; b) R = Me, R^1 = H; c) R = Ph, R^1 = H; d) R = R^1 = $(CH_2)_4$, $(CH_2)_5$;
e) R = $(CH_2SiMe_2)_2N$, R^1 = H

Biomimetic approach developed by Miller [32] involving the intramolecular cyclization of β-hydroxyhydroxamates (**23**) into β-lactams (**24**) stimulated interest to stereocontrolled synthesis of β-hydroxy esters (**22**) by aldol addition of ketene silyl acetals or ester enolate (**5**) to aldehydes (**21**).



(7)

R	R^1	R^2	R^3	β-Hydroxy ester (22)		R^4	Ref
				syn:anti ratio	yield, %		
Et	O-ephedrinyl	$SiMe_3$		100 : 0[a]	70	Me	33
H	OEt	$SiMe_3$		66 : 34[b]	96	Me	34
$SiMe_3$	OEt	$SiMe_3$		99 : 1[a]	95	Me	34
Et	SBu-*t*	$SiMe_2Bu$-*t*		99 : 1[a]	80	Me	33
H	SBu-*t*	$SiMe_2Bu$-*t*		50 : 50[b]	80	Me	35
H	OBu-*t*	$SiMe_2Bu$-*t*		3 : 97[b]	45	Me	35
$(CH_2SiMe_2)_2N$	OMe	Li	C≡CSiMe$_3$	50 : 50[a]	80		36

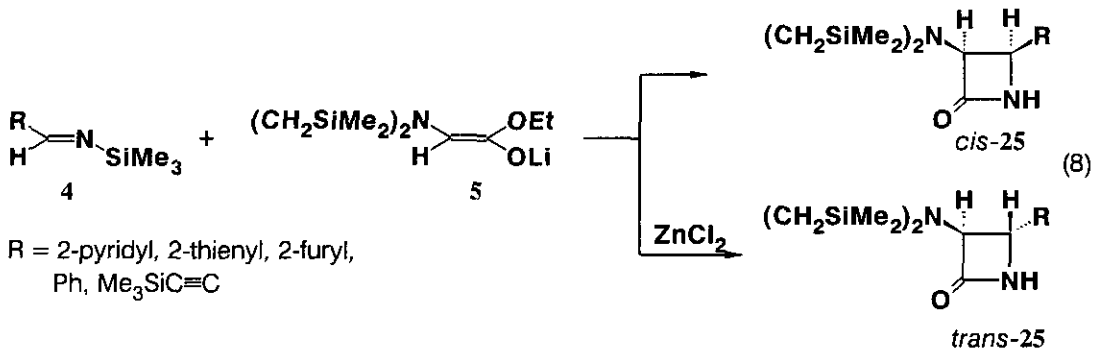
[a] configuration at C-2, C-3
[b] configuration at C-3, C-4

2.2. Catalysis in the Synthesis of β-Amino and β-Hydroxy Esters and Their Conversion into Azetidin-2-ones

The Lewis acids are preferable catalysts for the reaction of ester enolates or ketene silyl acetals with aldimines or aldehydes. They are usually used in the equimolar amount and help to improve both the yields and stereoselectivity of azetidin-2-ones or intermediate β-amino esters and β-hydroxy esters due to their ability to form chelated transition structures. The stereoselectivity of these reactions also depends on configuration of aldimines and ketene acetals, the structure of substituents and the nature of catalysts.[7,22,27,33]

Information available does not allow to trace special role of organosilicon or organotin reagents and catalysts on stereochemistry of the corresponding reactions. However, the high stereoselectivity achieved in some reactions could be directly associated with the usage of above mentioned organometallic compounds, for example:

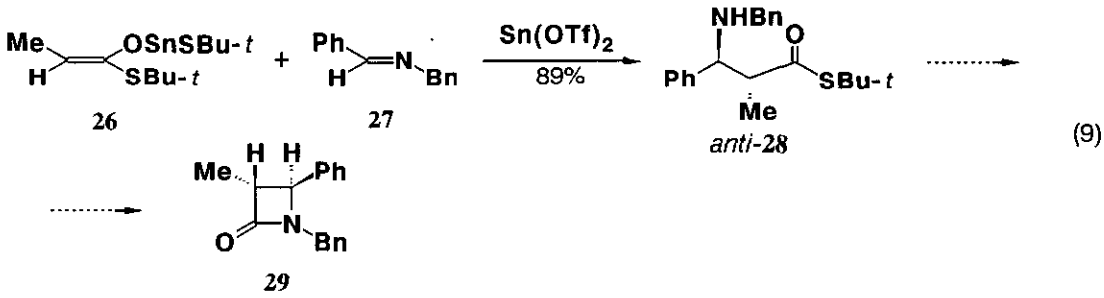
(a) formation in high yields (82-99%) of the predominant *trans*-azetidin-2-ones (**25**) during condensation of aldimine (**4**) with the enolate of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester (**5**) in the presence of $ZnCl_2$ and *cis*-isomers (**25**) in the absence of a catalyst.[27,37]



R = 2-pyridyl, 2-thienyl, 2-furyl, Ph, $Me_3SiC{\equiv}C$

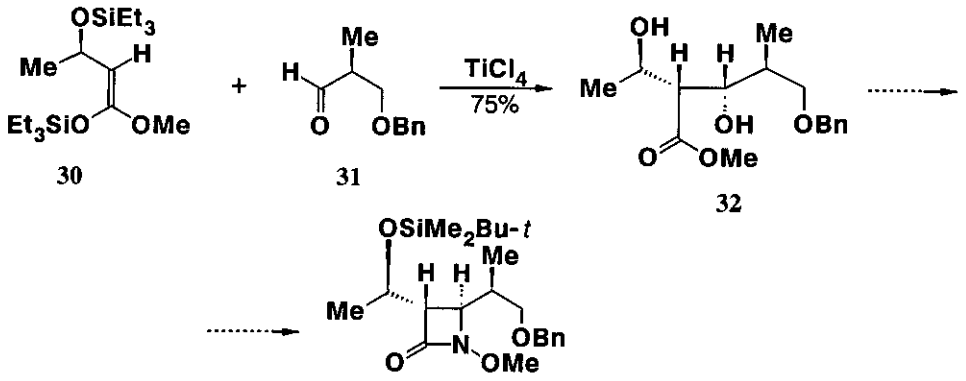
(8)

(b) prevalent *anti*-diastereoselectivity for *β*-amino esters (**28**) in the reactions of imines (**27**) with tin(II) carboxylic thioester enolates (**26**) catalyzed with stannous triflate which after cyclization provided *trans*-configuration for the corresponding azetidin-2-one (**29**).[38]



(9)

(c) high diastereomeric purity for *anti*-*β*-hydroxy ester (**32**) in the aldol process between ketene silyl acetal (**30**) and *β*-benzyloxy aldehyde (**30**) under Lewis acids conditions necessary for *trans*-configuration of substituents in the precursors of carbapenem antibiotic (**33**).[39]



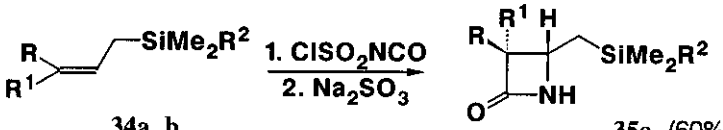
(10)

It was noted in Guanti's paper that TMSOTf differently from $TiCl_4$ and ZnI_2 influences the reaction in really catalytic amount.[40]

In Palomo's works it has been found that Reformatsky type reaction between ethyl bromoacetate and Schiff's base could be effectively catalyzed with zinc dust in combination with TMCS. [41]

2.3. Other Methods of Azetidin-2-ones Synthesis with Organosilicon and Organotin Compounds

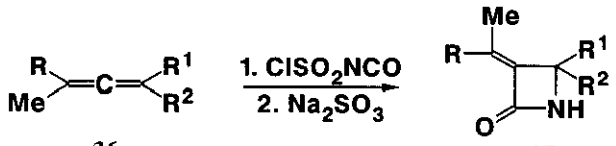
The reaction of CSI with alkene derivatives proved to be very popular in the preparation of monocyclic β-lactams for the purpose of their following transformation into biologically active substances. This method was used by Colvin for the synthesis of mono- and disilyl derivatives of azetidin-2-one (**35**) from allylsilanes (**34**).[42]



34a, b **35a** (60%) **35b** (50%) (11)

a) R = R^1 = R^2 = Me; b) R = H, R^1 = $SiMe_3$, R^2 = Ph

Addition of CSI to allenylsilanes (**36**) resulted in formation of 3-alkylidene-β-lactams (**37**) - potent β-lactamase inhibitors.

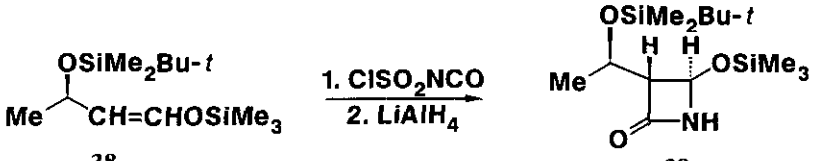


36 **37** (12)

a) R = H, Me; R^1 = CH_2SiMe_3, R^2 = H [42]

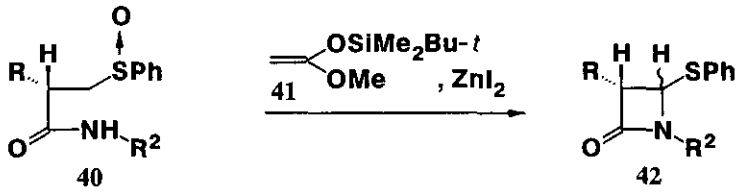
b) R = H, $SiMe_3$; R^1 = $SiMe_3$; R^2 = SC_6H_4Cl-4 [43]

In the same manner 1,3-bis(trialkylsiloxy)but-1-ene (**38**) was used for the formation of *O,O'*-bis(trialkylsilyl)-protected (3R*,4R*,5R*)-3-(1-hydroxyethyl)-4-hydroxyazetidin-2-one (**39**).[44]

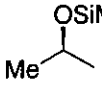


38 **39** (13)

Silicon-induced cyclization of variously substituted 3-phenylsulfinylpropionamides is new perspective approach to synthesis of monocyclic β-lactams. It was used for β-amido sulphoxides (**40**) conversion to azetidin-2-ones (**42**) by the treatment with TMSOTf or 1-dimethyl-*t*-butylsiloxy-1-methoxyethylene (**41**) and ZnI_2.[45,46]

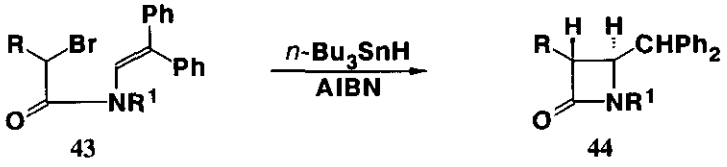


40 **42** (14)

R = H, Et, 

; R^2 = H, Bn, PMB, $SiMe_2Bu$-*t*

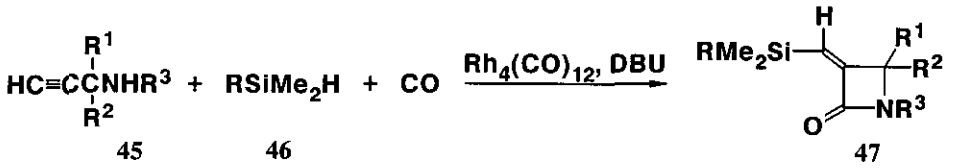
In the case of 2-substituted propionamides (**40**) this reaction gave the mixture of *cis/trans* β-lactams (**42**). Unprotected amides (**40**, R = H) were converted by **41** into *N*-*t*-butyldimethylsilylazetidin-2-ones (**42**). β-Lactam ring formation from appropriately functionalized enamides (**43**) α-brominated to carbonyl group was realized by free radical reduction in the presence of tributyltin hydride.[47]



43 **44** (15)

R = Me, Et; R^1 = Me, *t*-Bu, C_6H_{11}

A new method for creation of 3-alkylidenazetidin-2-ones (**47**) was developed by rhodium catalysed silylcarbonylation of propargylamine derivatives (**45**).[48]



45 46 47 (16)

R = *t*-Bu, Ph; $R^1 = R^2$ = H, Me; $R^1 = C_5H_{11}$, R^2 = H; R^1 and $R^2 = (CH_2)_5$;
R^3 = H, Ts, CO_2Me

3. DERIVATIZATION OF AZETIDIN-2-ONES WITH ORGANOSILICON AND ORGANOTIN COMPOUNDS

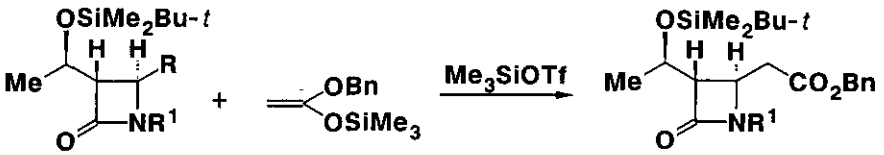
The known synthetic strategies for the transformation of monocyclic β-lactams into carbapenems, penems, oxapenems and other types of biologically active substances include special stages of stereocontrolled introduction of substituents in the azetidinone ring. In some cases this problem is solved during the construction of β-lactam ring. But usually special methods have been developed for this purpose. Some of them are based on the usage of organosilicon and organotin compounds for activation, protection and masking of various functional groups.

3.1. Introduction of Substituents with the Formation of C-C Bond

Carbon-carbon bond formation at 4-position of azetidin-2-one could be efficiently realized by nucleophilic substitution of acetoxy, phenylsulfinyl groups or chlorine with *O*-silyl enols or ketene *O*-silyl acetals.

In contrast to the alternative methods utilising the strong bases or acids and low temperature for this kind of substitution resulting in the dramatic consequences for unstable β-lactam ring the silyl ones are carried out in the presence of mild Lewis catalyst at room temperature and characterized by good yields.

This type of stereochemical *trans*-functionalization at 4-position of β-lactam is demonstrated by the substitution of acetoxy or phenylsulfinyl group in **48** with ketene silyl acetal (**49**). Other examples of azetidin-2-ones alkylation are presented in the Table 2.

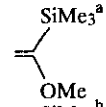
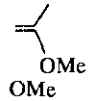
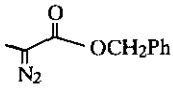
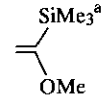
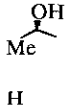
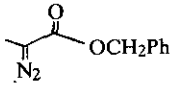
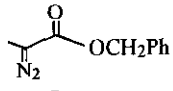
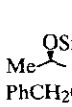
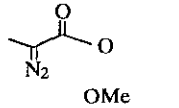
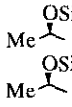


48a, b 49 50a (91%) 50b (75%) (17)

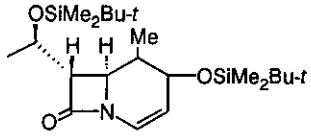
a) R = OAc; $R^1 = SiMe_3$ [49]
b) R = SOPh; R^1 = PMB [45]

Table 2. Alkylation of Azetidin-2-ones by O-Silyl(Stannyl) Enolates and Silyl Ketene Acetals.

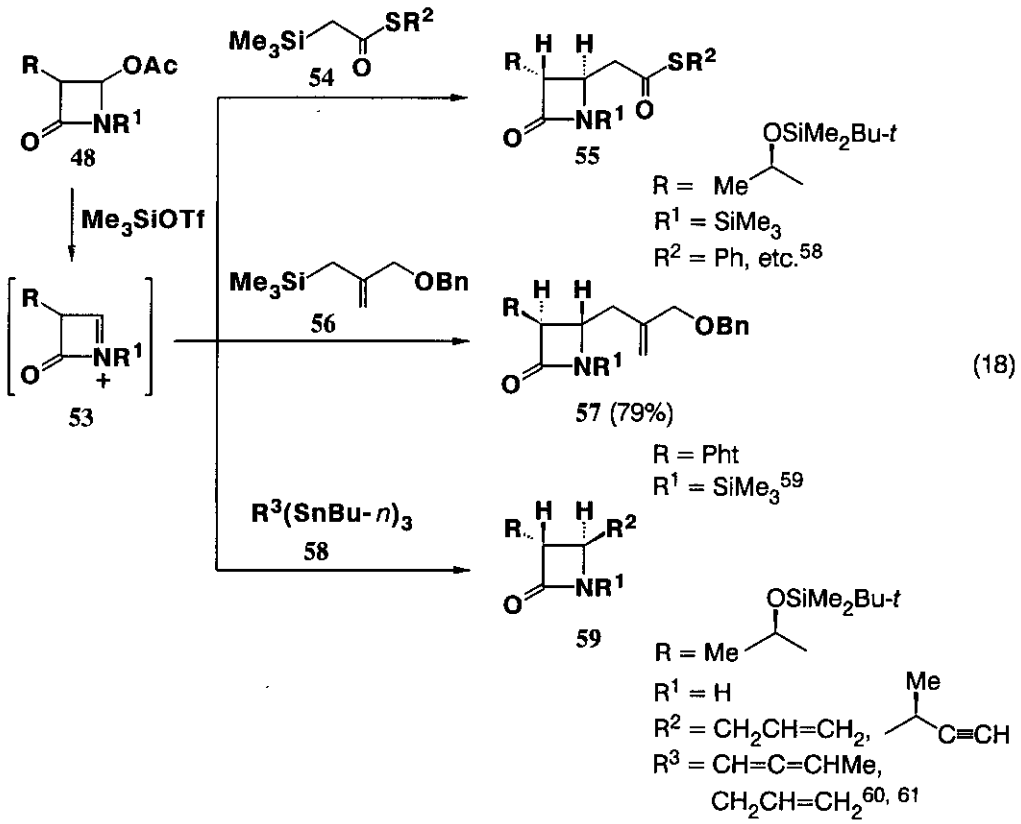
48 51 52

R	R^1	R^2	X	Y	Z	Yield, %	Config. at 3 and 4 positions of 52	Ref.
H	H	AcO	H	Ph	$SiMe_3$	89		50
H	H	AcO	H	4-ClC_6H_4	$SiMe_3$	81		50
H	H	AcO	H	4-MeC_6H_4	$SiMe_3$	75		50
H	H	AcO	Me	Ph	$SiMe_3$	71		50
H	H	AcO	H	SPh	$SiMe_3$	76		50
H	H	AcO	Me	OCH_2Ph	$SiMe_3$	58		50
H	H	AcO	Me	OEt	$SiMe_3$	95		50
H	$SiMe_3$	AcO	H		SiMe3	56		50
H	$SiMe_3$	AcO	H		SiMe3	30		50
H	H	AcO	CO_2Me	OMe	$SiMe_3$	53		51
H	H	AcO	H		$SiMe_3$	53		51
	H	AcO(Cl)	Me		$SiMe_3$	75	3S, 4R	52
	H	AcO	H		$SiMe_3$	81	3S, 4R	53
H	$SiMe_2Bu$-*t*	PhSO	H	OMe	$SiMe_2Bu$-*t*	86		54
Et	$SiMe_2Bu$-*t*	PhSO	H	OMe	$SiMe_2Bu$-*t*	95	3R, 4R	54
Et	$SiMe_2Bu$-*t*	PhSO	H		$SiMe_2Bu$-*t*	43	3R, 4R	54
	H	AcO	Me		SnBr	75[c]	3S, 4R	55
$PhCH_2CONH$	H	AcO	Me	OMe	$SiMe_3$	81[d]	3S, 4S	56
$PhCH_2CONH$	H	AcO	Me	OEt	$SiMe_3$	71[d]	3S, 4S	56
$PhCH_2CONH$	H	AcO	Me	OBu-*t*	$SiMe_3$	45[d]	3S, 4S	56
$PhCH_2CONH$	H	AcO	Me	OCH_2Ph	$SiMe_3$	74[d]	3S, 4S	56
	H	AcO	Me	$CH=CH_2$	$SiMe_2Bu$-*t*	50[e]	3S, 4R	57
	H	AcO	Me	$CH=CH_2$[f]	$SiMe_2Bu$-*t*	24[e]	3S, 4R	57

Notes to Table 2.
a $CH_2COCH_2CO_2Me$ structure of substituent at 4 position of **52**
b $CH(COMe)CO_2Me$ structure of substituent at 4 position of **52**
c preferable catalyst - $AgBF_4 + I_2$
d preferable catalyst - $Zn(OAc)_2$
e preferable catalyst - $ZnCl_2$
f structure **52**

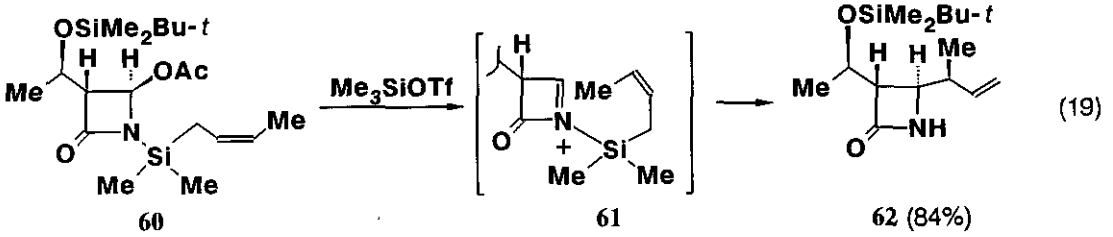


The treatment of 4-acetoxyazetidin-2-ones (**48**) with TMSOTf generated iminium intermediate (**53**)which was attacked in the 4-position by trimethylsilyl or tributylstannyl activated carbon chains (**54, 56, 58**) with the formation of C-C bond. Reaction occurred exclusively at the sterically less hindered face of **53** affording 3,4-disubstituted *trans*-azetidin-2-ones (**55, 57, 59**).



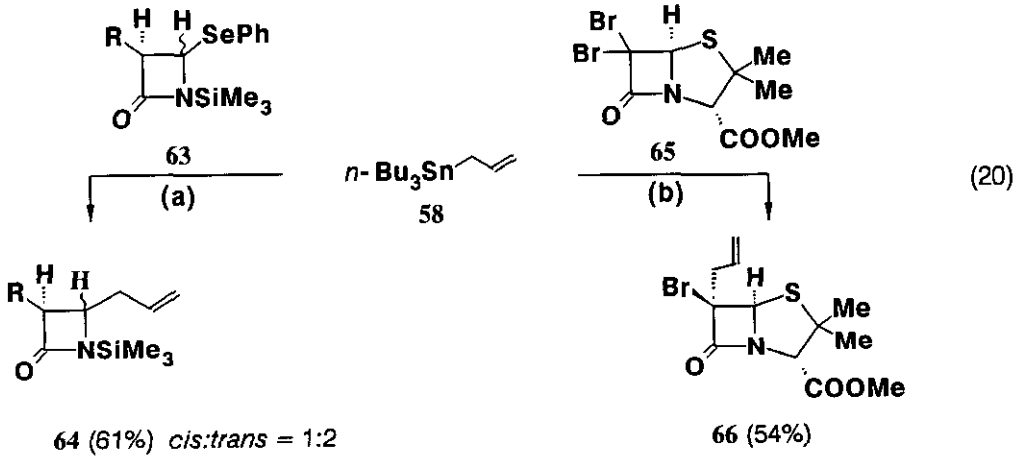
(18)

Original intramolecular stereoselective alkylation of 4-acetoxy-1-[dimethyl(2-butenyl)silyl]azetidin-2-one (**60**) in the presence of TMSOTf with the formation of (4R)-4-[(1S)-1-methylallyl]azetidin-2-one (**62**) could be attributed to the same mechanism.[62]



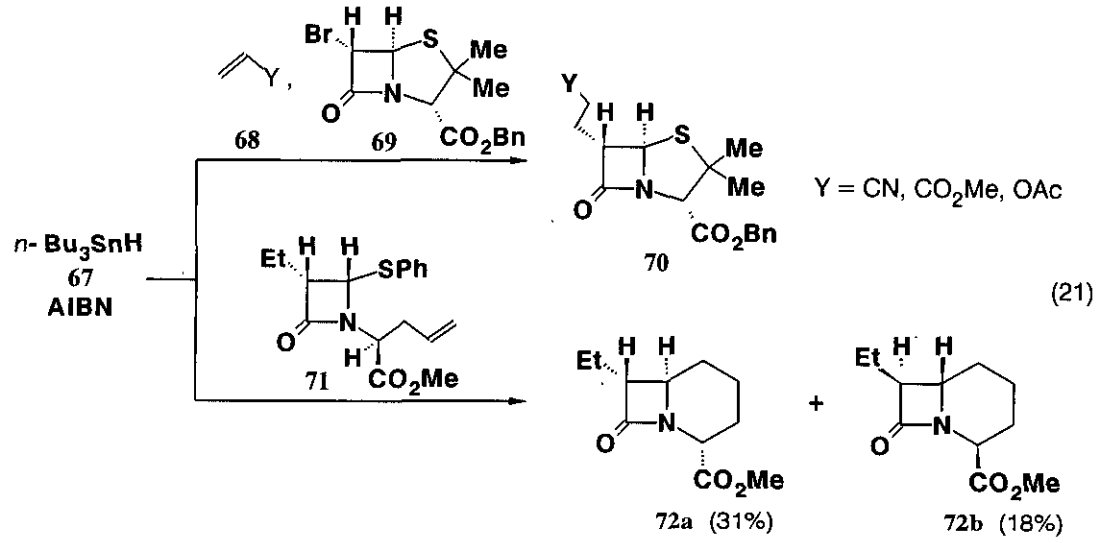
60 **61** **62** (84%) (19)

Application of organotin reagents for introduction of carbon chains into mono- and bicyclic β-lactams is based on two main methodological approaches. One of them is radical allylation of (4-phenylselenenyl)azetidin-2-ones (**63**) or 6,6-dibromopenicillanate (**65**) by allyltributyltin (**58**) in the presence of AIBN.[63,64]



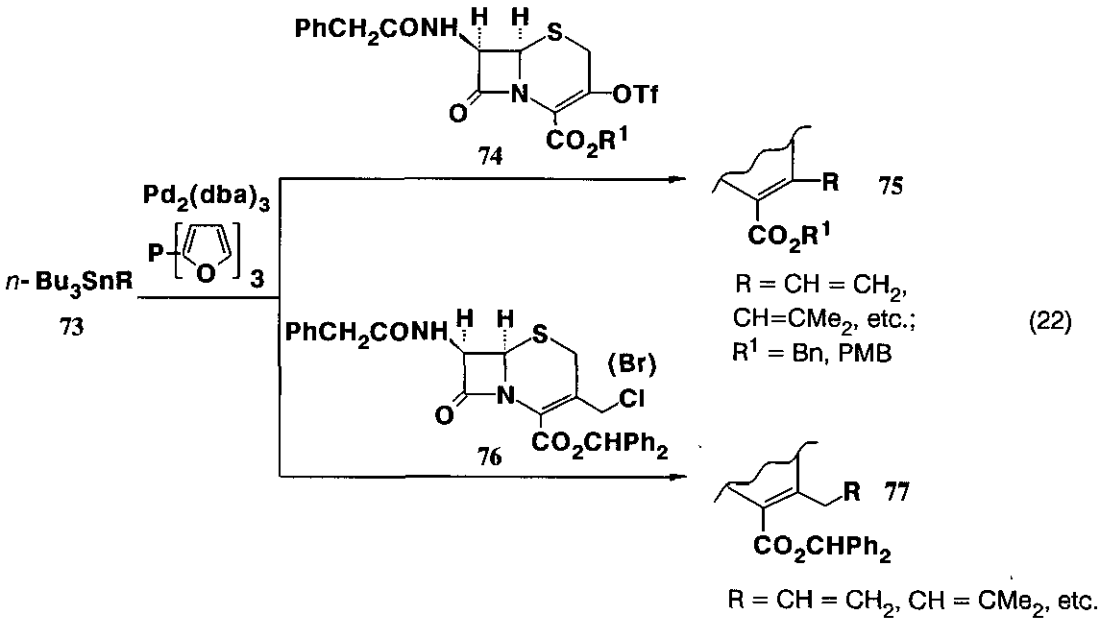
64 (61%) *cis:trans* = 1:2 **66** (54%) (20)

Predominant *trans*-configuration of allyl group towards the second substituent in the β-lactam ring is caused by sterical difficulties for bulk organotin reagent during its approach to molecule's active center. Modification of this methodology aimed at structural variation of substituents could be reached by usage of alkene and tributyltin hydride combination. This synthetic protocol is realized in radical substitution of bromine at 6-position of penicillanate (**69**) by vinyls (**68**)[65] and in the formation of carbacephams (**72a**) and (**72b**) by intramolecular cyclization of **71**.[66]



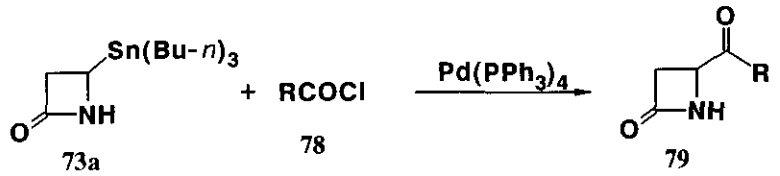
(21)

Another methodology of carbon-carbon bond formation is based on Pd(0) catalysed reaction between vinyl triflates and organostannanes, primarily described by Stille and Scott. [67] Farina and others from Bristol-Myers Squibb[68] adopted this reaction for derivatization at 3-position of cephalosporin. On the base of thorough investigation they developed very mild and effective conditions for triflate/chloride exchange in **74** and **76** by various saturated and unsaturated alkyl radicals from corresponding alkyltributylstannanes (**73**).[68,69]



(22)

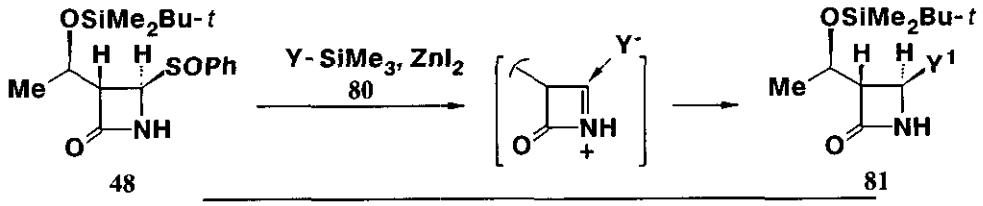
4-Tributylstannylazetidin-2-one (**73a**) was also successfully acylated with acyl chlorides (**78**) using palladium catalysed Stille coupling reaction.[70]



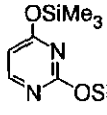
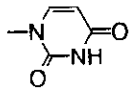
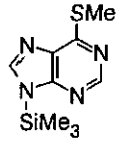
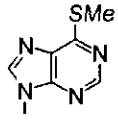
(23)

3.2. Introduction of Heteroatom Substituents

4-Phenylsulfinyl group in 3-(1-*t*-butyldimethylsiloxy)ethylazetidin-2-one (**48**) was successfully substituted with silylated *N-*, *S-*, *O-*, and *P*-nucleophiles in the presence of Lewis acids giving the corresponding 4-*trans*-heterofunction-substituted *β*-lactams (**81**).[71] This reaction occurs *via* acyliminium intermediate under nearly neutral conditions and provides high yields of various potentially biologically active 4-substituted azetidin-2-ones.

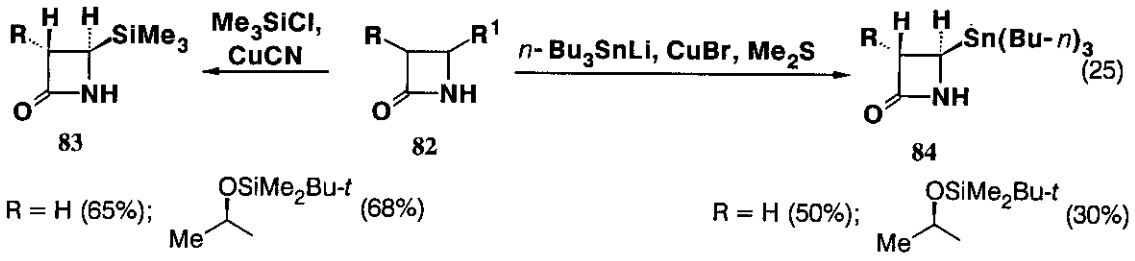


(24)

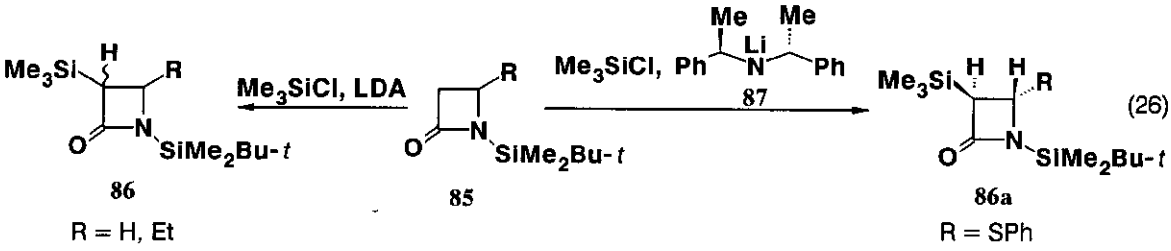
Y-SiMe$_3$	Y^1	Yield, %*
N_3-SiMe$_3$	N_3	87
$Me_3SiN{=}C(Me)OSiMe_3$	NHCOMe	67
Me_3SiSMe	SMe	98
$Me_3SiSCOCH_2CO_2Me$	$SCOCH_2CO_2Me$	73
$Me_3SiOCOMe$	OCOMe	52
$Me_3SiOCOCH_2CO_2Me$	$OCOCH_2CO_2Me$	66
		89
		57
$Me_3SiOP(OEt)_2$	$PO(OEt)_2$	77

* other examples cited in ref. 71

Silyl- and tin-functionalised β-lactams were prepared by nucleophilic acetoxy substitution in **82** by silylcuprate and tincuprate.[70]

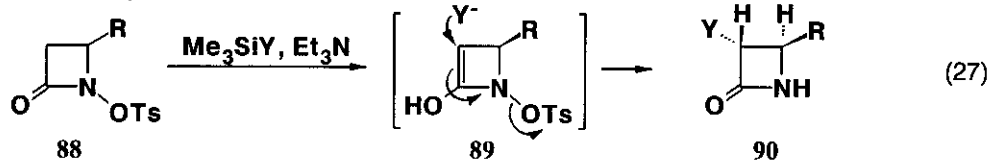


Deprotonation of 3-unsubstituted azetidin-2-one (**85**) with LDA and following treatment of intermediate carbanion with TMCS led to formation of racemic 3-trimethylsilylazetidin-2-one (**86**).[72]



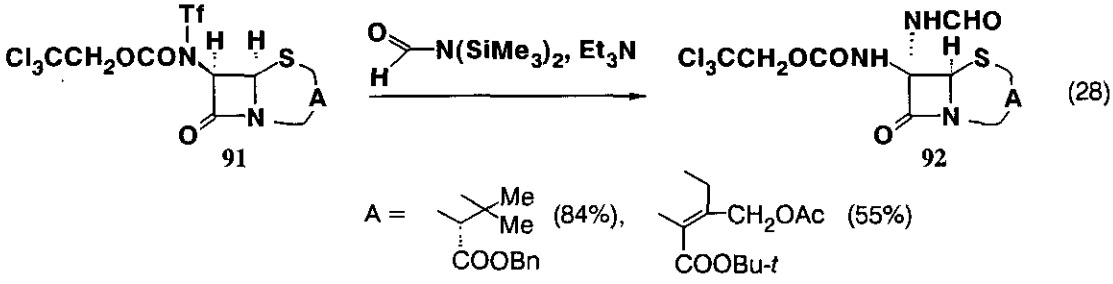
The usage of homochiral lithium amide base (**87**) for the enantioselective deprotonation of racemic β-lactam (**85**) gave (3R,4S)-azetidin-2-one (**86a**) in up to 72% enantiomeric excess.[73]

In Miller's investigation it was found that 1-tosyloxy-substituted azetidin- 2-ones (**88**) provided new variant of diastereoselective nucleophilic addition of heteroatoms at 3-position with halogenated trimethylsilanes and trimethylsilylazide in the presence of triethylamine.[74] This reaction presumed base-initiated enolization of **88** to **89** followed by S_N2' displacement of tosylate.



R = Me, $(CH_2)_2CO_2(CH_2)_2SiMe_3$; Y = Cl, Br, I, N_3

It is known that certain 6α(7α)-formamidopenicillins and cephalosporins are β-lactamase stable and highly active antibacterial agents. Modification of amino group in **91** with trichloroethoxycarbonyl and trifluoromethylsulphonyl functions facilitated direct incorporation of formamido substituent after treatment of **91** with *N,N*-bis(trimethylsilyl)formamide and triethylamine.[75]



3.3. Conversion of Azetidin-2-ones into α-Amino Acids or Amino Sugars

The development of the new strategies of azetidin-2-one synthesis and stereocontrolled functionalization is stimulated not only by the possibility of their conversion to β-lactam antibiotics but by the opening of azetidin-2-one cycle also to potentially biologically active products such as α-hydroxy-β-amino acids, amino sugars and other substances.[76]

Application of above mentioned organosilicon and organotin compounds in reactions of stereocontrolled synthesis of monocyclyc β-lactams, protection, masking and transformation of their substituents and even in the splitting of β-lactam ring helped to develop multistep protocols for the preparation of the derivatives of β-hydroxyalkylaspartic acid[29,78] , aminosugars (Daunosamine, Acosamine)[20] and α-hydroxy-β-amino acids (fragments of Taxol and Bestatine).[77,78]

4. ORGANOSILICON AND ORGANOTIN REAGENTS IN THE PROTECTION, MASKING AND TRANSFORMATION OF SUBSTITUENTS OF β-LACTAMS

The vast usage of trialkylsilyl protecting groups in the chemical transformations of β-lactam antibiotics and their derivatives could be explained by following reasons:

a) mild conditions and high or quantitative yields in silylation and desilylation processes;

b) stability of silyl protecting groups in reactions aimed at formation of C-C, C-S, C-N, C-O, C-Hal, C-H bonds;

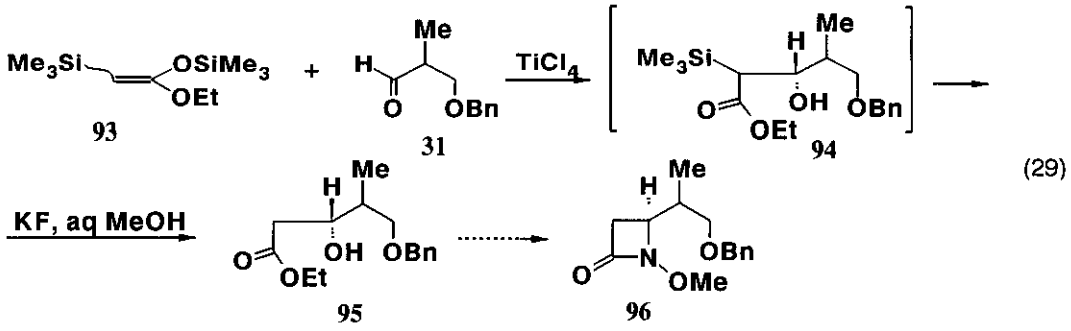
c) possibility of selective silyl protection and deprotection of two or more functional groups in one molecule.[76]

In many papers separation of reaction mixtures and positive solution of stereochemical problems are directly connected with bulky hydrophobic trialkylsilyl groups. That is why the trimethylsilyl and *t*-butyldi-

methylsilyl protection is employed in the majority reactions with participation of mono- and bicyclic β-lactams.

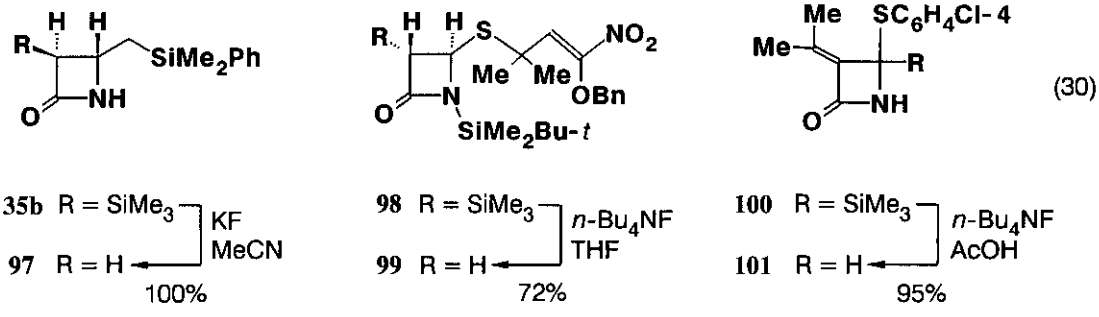
Attachment of trimethylsilyl or dimethylphenylsilyl groups to carbon chain creates synthetic possibilities of their substitution for hydrogen, hydroxyl or alkenyl group. This methodology allows to solve structural problems of β-lactams creation and modification in the presence of bulky and relatively inert silyl substituents in chemical conditions unfavorable for above mentioned masked functions.[26,60]

For example, introduction of trimethylsilyl group in ketene silyl acetal (**93**) followed by its elimination from intermediate (**94**) with hydrogen in methanol solution of KF provided stereoselective formation of *anti*-β-hydroxy ester (**95**) and its cylization in the precursor of Carbapenem (**96**) with R*-configuration of substituent at 4-C atom.[34]



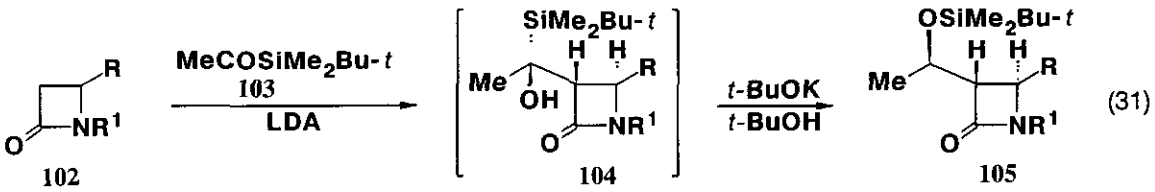
(29)

The same transformations in the similar conditions were realized with azetidin-2-ones (**35b, 98**) and (**100**) containing silyl masking group at 3- or 4-position.[42,43,79]



(30)

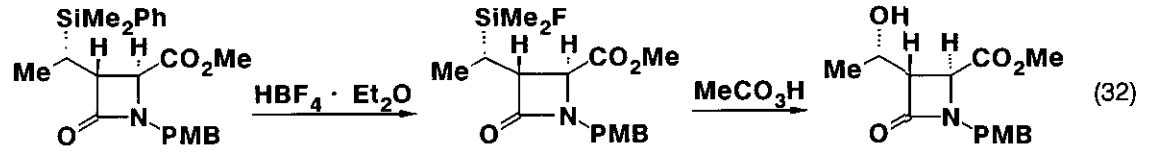
Analogous structural problem was solved by stereoselective aldol reaction of silylated ketone (**103**) to 3-unsubstituted azetidin-2-one (**102**) and following rearrangement of (1S*)-1-*t*-butyldimethylsilyl-1-hydroxyethyl group in **104** into (1R*)-1-(*t*-butyldimethylsiloxy)ethyl group.[80]



102 104 105 (31)

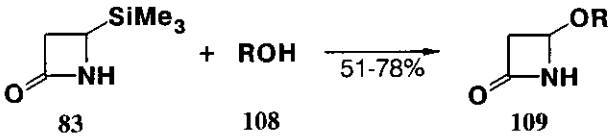
R = $SCPh_3$ (79%), COOH (77%), R^1 = $SiMe_2Bu$-*t*

The two-step sequence of the oxidative splitting of C-Si bond in the azetidin-2-one (**12**) after its stereocontrolled synthesis provided stereospecific generation of (1S*)-1-hydroxyethyl group at the 3-position of *β*-lactam (**107**) in 81% overall yield.[29]



12 106 107 (32)

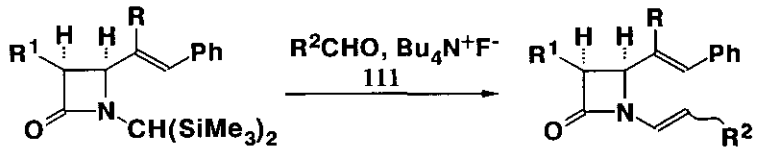
Anodic oxidation in the presence of alcohols also allowed to substitute the trimethylsilyl group at 4-position of azetidin-2-one (**83**) by hydroxyl or alkoxyls.[81]



83 108 109 (33)

R = H, *s*-Bu, $(CH_2)_2CH{=}CH_2$, Bn, $CH_2CH{=}CH_2$

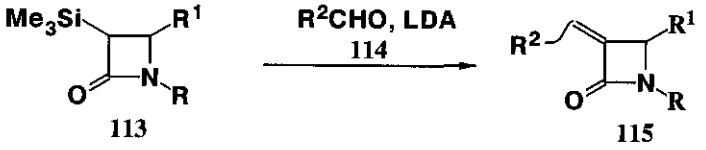
N-Vinyl derivatives of azetidin-2-ones (**112**) were obtained in high yields by means of a fluoride-induced catalytic Petersen alkenation of *N*-bis(trimethylsilyl)methyl-*β*-lactams (**110**).[18]



110 112 (34)

R = H, Me; R^1 = MeO, PhO; R^2 = Me, 4-ClC_6H_4

3-Alkylideneazetidin-2-ones (**115**) were generated from α-trimethylsilyl β-lactams (**113**) by treatment with aldehydes (**114**) and LDA.[72,82]



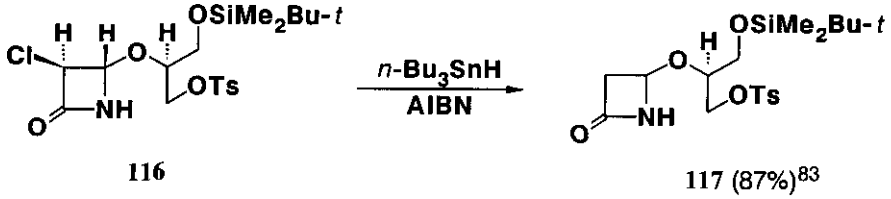
113 **115** (35)

R = H, Ph; R^1 = H, Ph; R^2 = Me, Et, Ph, etc.

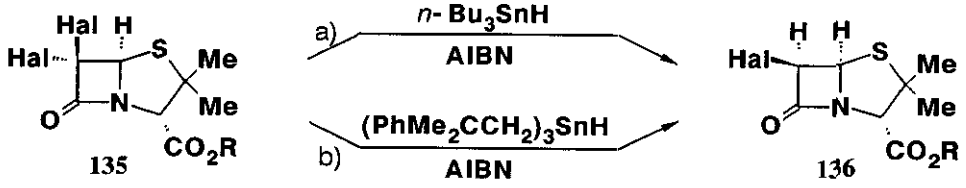
Widely used functionalization and derivatization of mono- and bicyclic β-lactams with organosilicon and organotin reagents were enlarged during the last decade by many new reactions.

Some of them based on the reductive properties of trialkyltin hydride in the presence of AIBN were utilized for the following transformations:

Dehalogenation

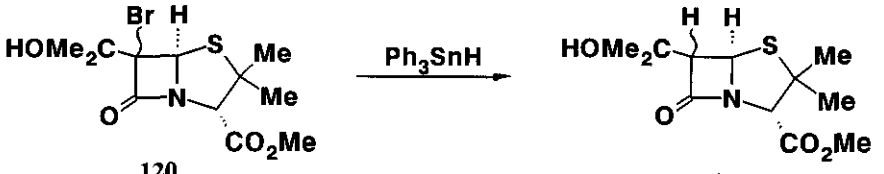


116 **117** (87%)[83] (36a)



135 **136** (36b)

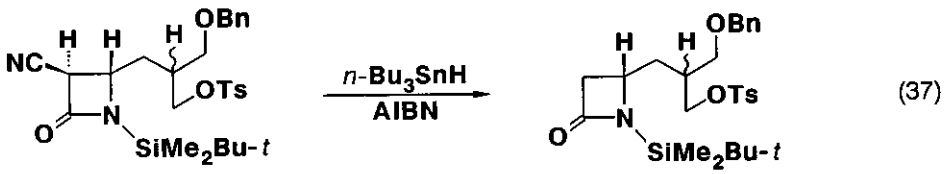
a) Hal = Br, R = Bn (73%)[65]; b) Hal = Br, I; R = $CH_2OCOBu\text{-}t$[84]



120 **121** (99%) (36c)

cis : *trans* = 9 : 1[85]

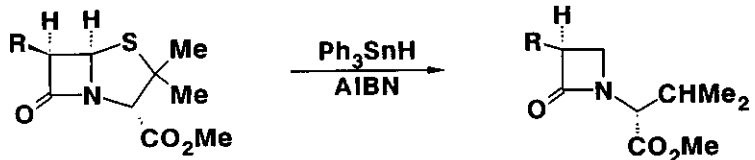
Decyanation[59]



(37)

122 123 (77%)

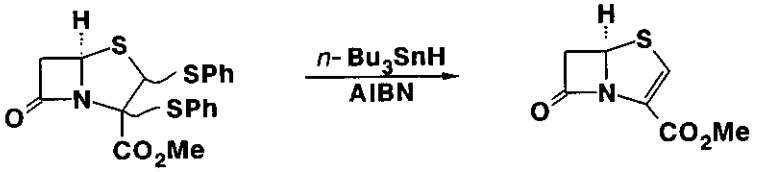
Desulphurization[86,87,88]



(38a)

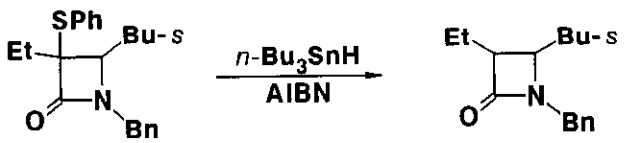
124 125

R = $PhOCH_2CONH$



(38b)

126 127 (78%)

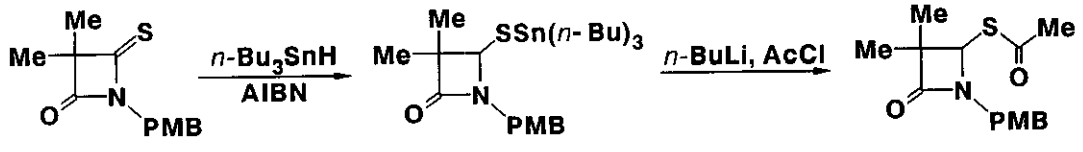


(38c)

128 129 (95%)

cis : *trans* = 1 : 7

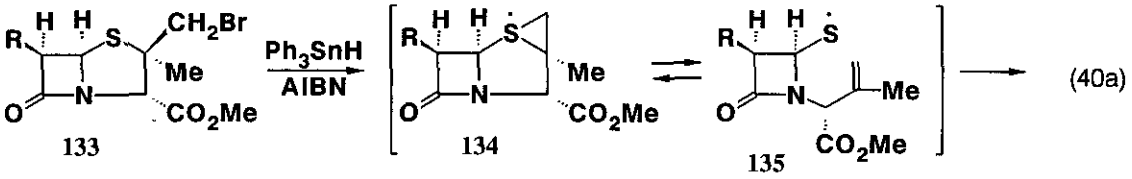
Conversion of thiocarbonyl group into sulphide group[89]

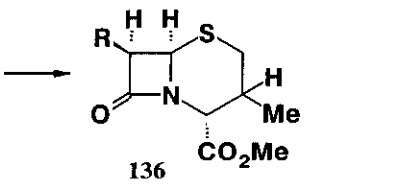


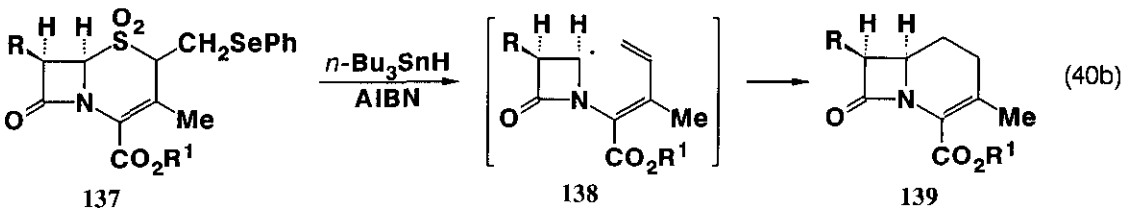
(39)

130 131 132

Reaction of 2-β-bromomethylpenam (**133**) or 2-phenylselenylmethylceph-3-em (**137**) with tributyltin hydride generated intermediate radicals (**134**) and (**138**) and the following cyclization gave the corresponding cepham (**136**) and carbaceph-3-em (**139**) systems.[90,91]

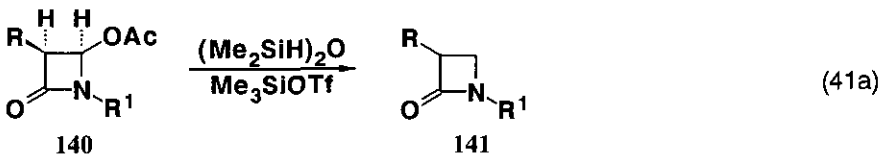




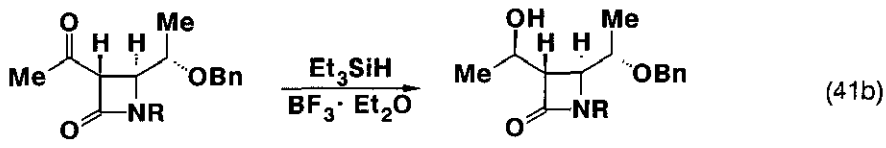


R = $PhOCH_2CONH$; R^1 = $CH_2CH{=}CH_2$

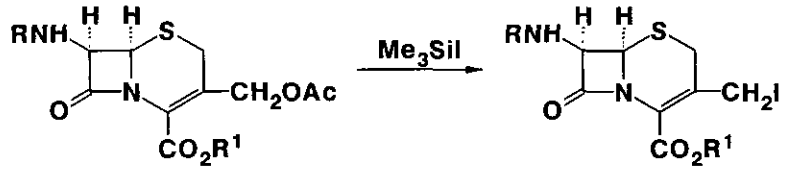
Catalytic hydrosilylation of 4-acetoxyazetidin-2-ones (**140**) and 3-acetylazetidin-2-one (**142**) resulted in reductive deacetoxylation[92] and highly stereoselective (1R*)-1-hydroxyethyl group formation at the 3-position of β-lactam (**143**).[93]



R = Pht, PhO, MeO; R^1 = CH_2CO_2Me, PMB



The nucleophilic properties of the iodotrimethylsilane were utilized in the substitution of acetoxy group in **144** and formation of 3-iodomethylcephalosporins (**145**) used as intermediates in the preparation of C-3 heterocycle-substituted ceph-3-ems.[94,95]

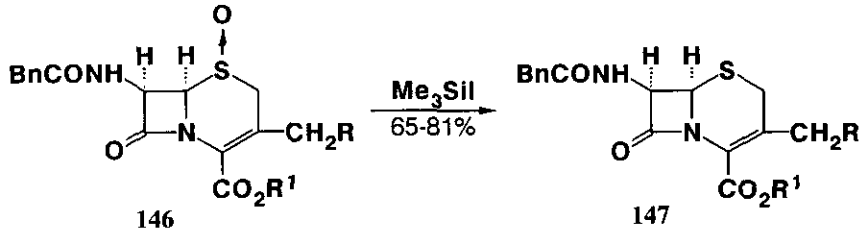


(42)

144 **145**

R = Me_3Si, BnCO; R^1 = $SiMe_3$, Bn

The iodotrimethylsilane also proved to be an efficient selective reagent for sulphoxide group reduction in **146** even in the presence of the acetoxy group sensitive to nucleophilic substitution (eq. 42).[96]

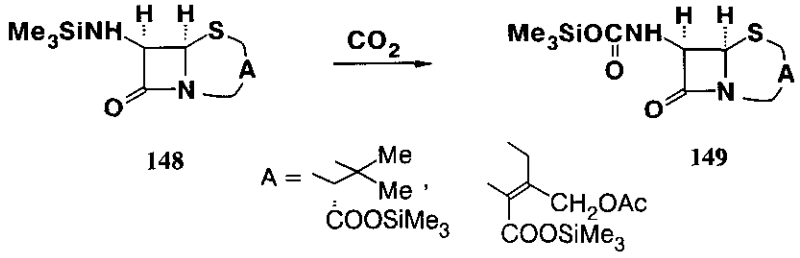


(43)

146 **147**

R = H, OAc; R^1 = Me, CH_2CCl_3, 4-$NO_2C_6H_4$

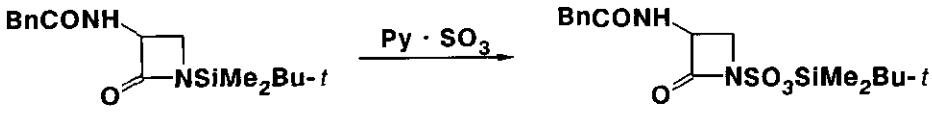
Gentle dry CO_2 introduction into the solution of *N*-trimethylsilyl-substituted β-lactams (**148**) led to the formation of *N*-trimethylsilyl carbamate protecting group in **149**.[91,97] Analogous N-Si bond cleavage by sulphur trioxide-pyridine complex allowed to convert **150** to the corresponding monobactam (**151**).[98]



(44a)

148 **149**

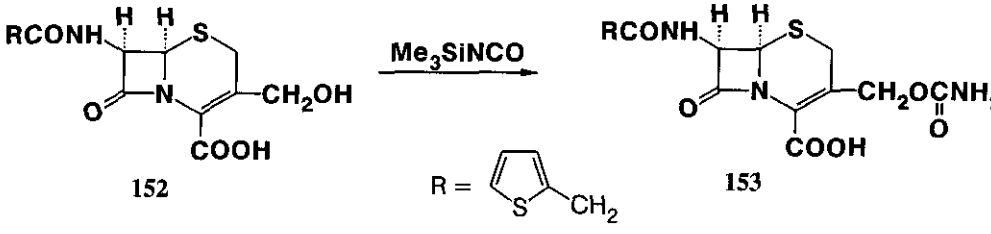
A =



(44b)

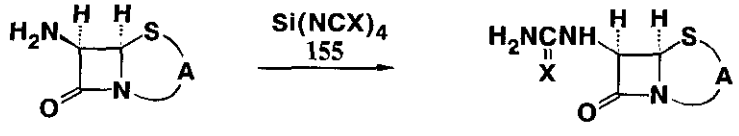
150 **151**

Trimethylsilyl isocyanate helped to transform hydroxyl at the 3-position of cephalosporin (**152**) into carbamoyl group.[99]

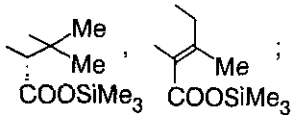


152 **153** (45)

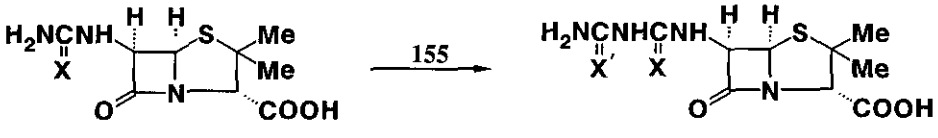
Tetraisocyanato- and tetraisothiocyanatosilanes (**155**) proved to be the mild and effective carbamoylation reagents of amino acids (**154**), 6-ureido or 6-thioureido penicillanic acids (**156**) and 6(α)-hydroxypenicillanic acid (**158**).[100,101]



154 **156** (46a)

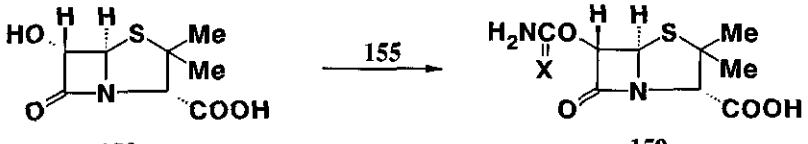
A* =  ; X = O,S

* upon hydrolysis $SiMe_3$ group in **156** replaced by proton



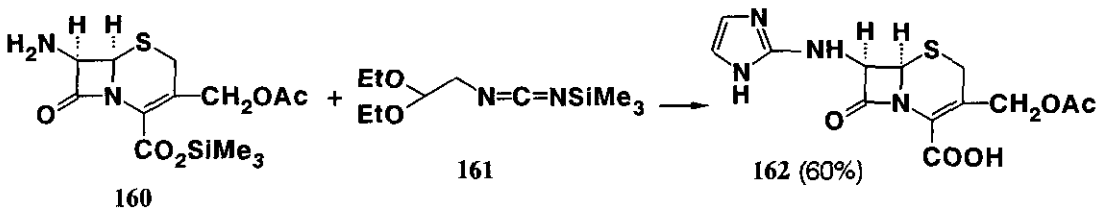
156 **157** (46b)

a) X = X′ = O; b) X = O, X′ = S; c) X = X′ = S



158 **159** (46c)

Specially synthesized silylated carbodiimide (**161**) helped to develop a new mild approach to aminoimidazole derivative of cephalosporin (**162**).[102]



(47)

5. APPLICATION OF ORGANOMETALLIC REAGENTS IN THE TECHNOLOGY OF β-LACTAM ANTIBIOTICS

The relatively easy adaptation to the large scale production is one of the benefits of organometallic methods. They are used in the following important modifications of β-lactams:

a) deacylation of the side chain in penicillin and cephalosporin;

b) acylation of amino group in β-lactams;

c) transformation of penicilline 1-oxide into deacetoxycephalosporin, etc.[103-105]

Silyl methods help to solve certain technological problems. For example, alcoholysis of ampicillin trimethylsilyl ester in non aqueous solvent is proposed for the preparation of anhydrous antibiotic. *N,O*-bis(trimethylsilyl)acetamide and *N,N*-bis(trimethylsilyl)urea act not only as effective silylating agents but also as acceptors of HCl in acylation of β-lactams by acid chlorides.[103]

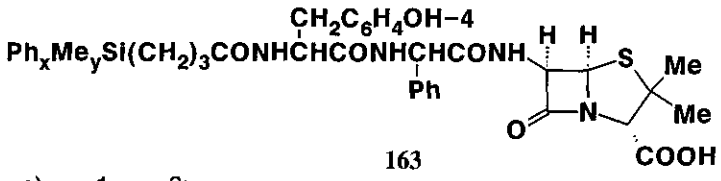
It seems to us that majority of such kind of data are not published because they belong to confidential "know how" information.

6. BIOLOGICALLY ACTIVE β-LACTAMS CONTAINING GROUP IVB ELEMENTS

Antibacterial activity of semi synthetic penicillins and cephalosporins containing trialkylsilyl group in the aliphatic side chain is restricted by gram positive microorganisms. Maximal activity was achieved in the case of introduction in antibiotics β-silyl propionyl and γ-silyl butyryl radicals. Structure-activity analysis for semisynthetic penicillins and cephalosporins containig in their side chain unsubstituted and trimethylsilyl substituted furan and quinoline heterocycles had not demonstrated any biological advantage for this type of modification.[106]

Homologous series of silicon-containing antibiotics were successfully used in the development of automated *TOPLOG system for the quantitative* estimation of structure-activity relationships for semisynthetic penicillins.[107]

Some silyl derivatives of penicillin (**163**) demonstrated good antiinflammatory properties *in vivo* in the treatment of oedema induced by carragenine. [108]



163

a) x = 1, y = 2;
b) x = 2, y = 1

7. CONCLUSIONS

It could be easily noticed that the development of organometallic methodology for the needs of β-lactam chemistry and the creation of new effective drugs representing the same class of antibiotics are connected. The structural variety of highly biologically active penicillins, cephalosporins, carbapenems, monobactams etc. stimulates the development of new approaches for the solution of arising chemical problems. The utilization of organosilicon and organotin compounds for these purposes is in many cases more effective in comparison with alternative methods. Due to this relationship synthesis and biological investigation of β-lactam antibiotics remains the most dynamic and promising field of medicinal chemistry during the last three decades.

REFERENCES

1. R.B.Morin and M.Gorman, 'Chemistry and Biology of β-Lactam Antibiotics,' Academic Press, New York, 1982, Vol. 1-3.
2. J.R.E.Hoover, Handbook of Experimental Pharmacology, Springer, Berlin, 1983, Vol. 67, part 2, pp. 119 - 245.
3. W.Durckheimer, J.Blumbach, R. Lattrell, and K.H.Scheunemann, *Angew. Chem. Int., Ed. Engl.*, 1985, 24, 180.
4. K.W.Glombitza, *Ann.*, 1964, **673**, 166.
5. H.Gilman and H.Speeter, *J. Am. Chem. Soc.*, 1943, **65**, 2250.
6. L.Birkofer and J.Schramm, *Liebigs Ann. Chem.*, 1977, 760.
7. D.J.Hart and D.-C.Ha, *Chem.Rev.*, 1989, **89**, 1447.
8. T.Uyehara, I.Suzuki, and Y.Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 4275.
9. G.Cainelli, D.Giacomini, M.Panunzio, G.Martelli, and G.Spunta, *Tetrahedron Lett.*, 1987, **28**, 5369.
10. P.Andreoli, G.Cainelli, M.Contento, D.Giacomini, G.Martelli, and M.Panunzio, *J. Chem. Soc., Perkin Trans. I*, 1988, 945.
11. S.Busato, G.Cainelli, M.Panunzio, E.Bandini, G.Martelli, and G.Spunta, *Synlett,* 1991, 243.
12. D.-C.Ha, D.J.Hart, and T.K.Yang, *J. Am. Chem. Soc.*, 1984, **106**, 4819.
13. E.W.Colvin, D.McGarry, and M.J.Nugent, *Tetrahedron*, 1988, **44**, 4157.
14. D.J.Hart, K.-i.Kanai, D.G.Thomas, and T.-K.Yang, *J.Org.Chem.*, 1983, **48**, 289.
15. P.Andreoli, G.Cainelli, M.Contento, D.Giacomini, G.Martelli, and M.Panunzio, *Tetrahedron Lett.*, 1986, **27**, 1695.
16. G.Cainelli, M.Contento, D.Giacomini, and M.Panunzio, *Tetrahedron Lett.*, 1985, **26**, 937.
17. N.Oguni and Y.Ohkawa, *J. Chem. Soc., Chem. Commun.*, 1988, 1376.
18. J.Lazarte, C.Palomo, J.P.Picard, J.Dunogues, and J.M.Aizpurua, *J. Chem. Soc., Chem. Commun.*, 1989, 72.
19. A.Arrieta, F.P.Cossio, J.M.Garcia, B.Lecea, and C.Palomo, *Tetrahedron Lett.*, 1988, **29**, 3129.
20. J.C.Gallucci, D.-C.Ha, and D.J.Hart, *Tetrahedron*, 1989, **45**, 1283.
21. J.T.B.H.Jastrzebski, F.H.van der Steen, and G.van Koten, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 516.
22. F.H.van der Steen, H.Kleijn, G.van Koten, and J.T.B.H.Jastrzebski, *J. Org. Chem.*, 1991, **56**, 5147.
23. T.Chiba, M.Nagatsuma, and T.Nakai, *Chem. Lett.*, 1984, 1927.
24. G.Cainelli, M.Panunzio, D.Giacomini, G.Martelli, and G.Spunta, *J. Am. Chem. Soc.*, 1988, **110**, 6879.
25. P.Andreoli, L.Billi, G.Cainelli, M.Panunzio, E.Bandini, G.Martelli, and G.Spunta, *Tetrahedron*, 1991, **47**, 9061.
26. D.A.Burnett, J.C.Gallucci, and D.J.Hart, *J. Org. Chem.*, 1985, **50**, 5120.

27. F.H.van der Steen, H.Kleijn, A.L.Spek, and G.van Koten, *J. Org. Chem.*, 1991, **56**, 5868.
28. C.Palomo, J.M.Aizpurua, and R.Urchegui, *J. Chem. Soc., Chem. Commun.*, 1990, 1390.
29. C.Palomo, J.M.Aizpurua, R.Urchegui, and M.Iturburu, *J. Org. Chem.*, 1992, **57**, 1571.
30. O.P.Novikova, L.I.Livantsova, and G.S.Zaitseva, *Zh. Obshch. Khim.*, 1989, **59**, 2630.
31. K.Okano, T.Morimoto, and M.Sekiya, *J. Chem. Soc., Chem. Commun.*, 1984, 883.
32. M.J.Miller, P.G.Mattingly, M.A.Morrison, and J.F.Kerwin, *J. Am. Chem. Soc.*, 1980, **102**, 7026.
33. C.Gennari and P.G.Cozzi, *J. Org. Chem.*, 1988, **53**, 4015.
34. F.Shirai and T.Nakai, *Chem. Lett.*, 1989, 445.
35. C.Gennari and P.G.Cozzi, *Tetrahedron*, 1988, **44**, 5965.
36. G.Guanti, E.Baldaro, L.Banfi, A.Guaragna, E.Narisano, and U.Valcavi, *Tetrahedron*, 1988, **44**, 3685.
37. F.H.van der Steen, J.T.B.H.Jastrzebski, and G.van Koten, *Tetrahedron Lett.*, 1988, **29**, 2467.
38. N.Yamasaki, M.Murakami, and T.Mukaiyama, *Chem. Lett.*, 1986, 1013.
39. F.Shirai and T.Nakai, *Tetrahedron Lett.*, 1988, **29**, 6461.
40. G.Guanti, E.Narisano, and L.Banfi, *Tetrahedron Lett.*, 1987, **28**, 4335.
41. C.Palomo, F.P.Cossio, A.Arrieta, J.M.Odriozola, M.Oiarbide, and J.M.Ontoria, *J. Org. Chem.*, 1989, **54**, 5736.
42. E.W.Colwin and M.Monteith, *J. Chem. Soc., Chem. Commun.*, 1990, 1230.
43. J.D.Buynak, M.N.Rao, R.Y.Chandrasekaran, and E.Haley, *Tetrahedron Lett.*, 1985, **26**, 5001.
44. T.Oohashi, K.Suga, I.Sada, A.Myama, and K.Watanabe, *Japan Patent* 89 131,188 (*Chem. Abstr.*, 1990, **112**, 35555t).
45. Y.Kita, N.Shibata, T.Miki, Y.Takemura, and O.Tamura, *Chem. Pharm. Bull.*, 1992, **40**, 12.
46. Y.Kita, O.Tamura, N.Shibata, and T.Miki, *J. Chem. Soc., Perkin Trans.I*, 1989, 1862.
47. S.L.Fremont, J.L.Belletire, and D.M.Ho, *Tetrahedron Lett.*, 1991, **32**, 2335.
48. I.Matsuda, J.Sakakibara, and H.Nagashima, *Tetrahedron Lett.*, 1991, **32**, 7431.
49. A.Yoshida, Y.Tajima, N.Takeda, and S.Oida, *Tetrahedron Lett.*, 1984, **25**, 2793.
50. R.P.Attrill, A.G.M.Barrett, P.Quayle, J.v.d.Westhuizen, and M.J.Betts, *J. Org. Chem.*, 1984, **49**, 1679.
51. P.J.Reider, R.Rayford, and E.J.J.Grabowski, *Tetrahedron Lett.*, 1982, **23**, 379.
52. M.Endo and R.Droghini, *Can. J. Chem.*, 1988, **66**, 1400.
53. P.J.Reider and E.J.J.Grabowski, *Tetrahedron Lett.*, 1982, **23**, 2293.
54. Y.Kita, N.Shibata, O.Tamura, and T.Miki, *Chem. Pharm. Bull.*, 1991, **39**, 2225.
55. R.Deziel, and M.Endo, *Tetrahedron Lett.*, 1988, **29**, 61.
56. J.C.Arnould, P.Boutron, and M.J.Pasquet, *Eur. J. Med. Chem.*, 1992, **27**, 131.
57. T.J.Sowin and A.I.Meyers, *J. Org. Chem.*, 1988, **53**, 4154.
58. Y.Tajima, A.Yoshida, N.Takeda, and S.Oida, *Tetrahedron Lett.*, 1985, **26**, 673.

59. T.Konosu, Y.Furukawa, T.Hata, and S.Oida, *Chem. Pharm. Bull.*, 1991, **39**, 2813.
60. J.Haruta, K.Nishi, K.Kikuchi, S.Matsuda, Y.Tamura, and Y.Kita, *Chem. Pharm. Bull.*, 1989, **37**, 2338.
61. H.Fliri and C.-P.Mak, *J. Org. Chem.*, 1985, **50**, 3438.
62. S.Uyeo and H.Itani, *Tetrahedron Lett.*, 1991, **32**, 2143.
63. L.C.Blaszczak, H.K.Armour, and N.G.Halligan, *Tetrahedron Lett.*, 1990, **31**, 5693.
64. S.Hanessian and M.Alpegiani, *Tetrahedron Lett.*, 1986, **27**, 4857.
65. G.Sacripante and G.Just, *J. Org. Chem.*, 1987, **52**, 3659.
66. T.Kametani, S.-D.Chu, A.Itoh, S.Maeda, and T.Honda, *J. Org. Chem.*, 1988, **53**, 2683.
67. W.J.Scott and J.K.Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033.
68. V.Farina, S.R.Baker, D.A.Benigni, S.I.Hauck, and C.Sapino, *J. Org. Chem.*, 1990, **55**, 5833.
69. S.R.Baker, G.P.Roth, and C.Sapino, *Synth. Commun.*, 1990, **20**, 2185.
70. C.Nativi, A.Ricci, and M.Taddei, *Tetrahedron Lett.*, 1990, **31**, 2637.
71. Y.Kita, N.Shibata, N.Yoshida, and T.Tohjo, *Chem. Pharm. Bull.*, 1992, **40**, 1733.
72. W.W.Ogilvie and T.Durst, *Can. J. Chem.*, 1988, **66**, 304.
73. P.Coggins and N.S.Simpkins, *Synlett*, 1992, 313.
74. M.Teng and M.J.Miller, *J. Am. Chem. Soc.*, 1993, **115**, 548.
75. C.L.Branch, M.J.Pearson, and T.C.Smale, *J. Chem. Soc., Perkin Trans. I*, 1988, 2865.
76. M.S.Manhas, D.R.Wagle, J.Chiang, and A.K.Bose, *Heterocycles*, 1988, **27**, 1755.
77. I.Ojima, Y.H.Park, C.M.Sun, T.Brigaud, and M.Zhao, *Tetrahedron Lett.*, 1992, **33**, 5737.
78. C.Palomo, A.Arrieta, F.P.Cossio, J.M.Aizpurua, A.Hielgo, and N.Aurrekoetkea, *Tetrahedron Lett.*, 1990, **31**, 6429.
79. A.G.M.Barret, M.-C.Cheng, S.Sakdarat, C.D.Spilling, and S.J.Taylor, *Tetrahedron Lett.*, 1989, **30**, 2349.
80. F.A.Bouffard and T.N.Salzmann, *Tetrahedron Lett.*, 1985, **26**, 6285.
81. K.Suda, K.Hotoda, J.-i.Watanabe, K.Siozawa, and T.Takanami, *J. Chem. Soc., Perkin Trans. I*, 1992, 1283.
82. S.Guertler and H.H.Otto, *Arch. Pharm.*, 1989, **322**, 3.
83. T.Konosu and S.Oida, *Chem. Pharm. Bull.*, 1991, 39, 2212.
84. E.G.Mata, O.A.Mascaretti, A.E.Zuniga, A.B.Chopa, and J.C.Podesta, *Tetrahedron Lett.*, 1989, **30**, 3905.
85. H.Tanaka, H.Suga, H.Ogawa, H.A.K.M.Abdul, S.Toriji, A.Jutand, and C.Amatore, *Tetrahedron Lett.*, 1992, **33**, 6495.
86. J.E.Baldwin, R.M.Aldington, T.W.Kang, L.G.King, and V.K.Patel, *Heterocycles*, 1989, **28**, 759.
87. T.Kametani, S.-D.Chu, A.Itoh, T.-C.Wang, A.Nakayama, and T.Honda, *J. Chem. Soc., Chem. Commun.*, 1988, 544.
88. Y.Sugano and S.Naruto, *Chem. Lett.*, 1989, 1331.
89. G.Cainelli, D.Giacomini, M.Panunzio, G.Martelli, and G.Spunta, *Tetrahedron Lett.*, 1987, **28**, 3593.

90. J.E.Baldwin, R.M.Aldington, T.W.Kang, E.Lee, and C.J.Schofield, *Tetrahedron*, 1988, **44**, 5953.

91. L.C.Blaszczak, *European Patent* 359,540 (*Chem. Abstr.*, 1990, **113**, 131868p.)

92. F.P.Cossio, B.Lecea, and C.Palomo, *J. Chem. Soc., Chem. Commun.*, 1987, 1743.

93. Y.Kobayashi, Y.Ito, and S.Terashima, *Bull. Chem. Soc. Japan*, 1989, **62**, 3041.

94. R.Bonjouklian and M.L.Phillips, *Tetrahedron Lett.*, 1981, **22**, 3915.

95. D.G.Walker, P.R.Brodfuehrer, S.P.Brundidge, K.M.Shih, and C.Sapino, *J. Org. Chem.*, 1988, **53**, 983.

96. J.Pitlik and F.Sztaricskai, *Synth. Commun.*, 1991, **21**, 1769.

97. D.A.Johnson, C.Sapino, H.H.Silvestri and D.Walker, *US Patent* 4,240,960 (*Chem. Abstr.*, 1981, **94**, 156921c).

98. T.Matsuo, H.Masuya, N.Noguchi, and M.Ochiai, *European Patent* 53, 387 (*Chem. Abstr.*, 1983, **98**, 16500x).

99. F.E.Roberts, *U.S.S.R. Patent* 608,477, (*Chem. Abstr.*, 1978, **89**, 109540q).

100. L.N.Petrulanis G.A.Veinberg, L.I.Kononov, I.Dipan, and E.Lukevics, *Khim. Heterotsikl. Soedin.*, 1983, 786.

101. L.N.Petrulanis G.A.Veinberg, L.I.Kononov, I.Dreibante, and E.Lukevics, *Khim. Heterotsikl. Soedin.*, 1985, 339.

102. F.Jung, A.Olivier, D.Boucherot, and F.Loftus, *Tetrahedron Lett.*, 1989, **30**, 2379.

103. G.A.Veinberg, L.N.Petrulanis, and E.Lukevics, *Khim. Heterotsikl. Soedin.*, 1982, 147.

104. R.C.Treadgold, *Process Biochemistry*, 1983, **18**, 30.

105. J.Verweij and E.de Vroom, *Recl. Trav. Chim. Pays-Bas*, 1993, **112**, 66.

106. G.A.Veinberg, A.M.Katcs, and I.E.Dalberga, *Abstracts of VI Conference on Chemistry and Application of Organosilicon Compounds,* Riga, 22-24th April 1986, p. 334.

107. G.A.Veinberg, A.M.Kats, L.N.Petrulanis L.I.Kononov, L.S.Gitlina, V.E.Golender, A.B.Rozenblit, and E.Lukevics, *Khim. Heterotsikl. Soedin.*, 1989, 683.

108. G.A.Veinberg, A.M.Kofman, and E.Lukevics, *Khim.Heterotsikl.Soed.*, 1992, 555.

Received, 30th September, 1993