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SELENIUM-CONTAINING BICYCLIC β-LACTAMS

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Abstract – The first β-lactam ring system was synthesized by H. Staudinger in 1907, but β-lactams as a class of compounds became attractive only after it was established that penicillin contained a β-lactam unit as the structural feature. Over the years, countless numbers of penicillin derivatives and a variety of new β-lactam ring systems have been prepared, tested, and introduced. As a class of β-lactam derivatives, selenium-containing bicyclic β-lactams have received only a limited attention. In this review the advances in the development of synthesis methods for selenium-containing bicyclic β-lactams are presented and discussed.

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1. INTRODUCTION

The first β-lactam ring system was synthesized by H. Staudinger in 1907,[1] but β-lactams as a class of compounds became attractive only after it was established that penicillin contained a β-lactam unit as the structural feature.[2] In early 1900's the discovery of penicillin began the antibiotic era. The β-lactam (2-azetidinone) skeleton becomes the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics[3] and counts for about half of all prescribed antibacterial drugs (cephalosporins: 30%; penicillins: 16%; penams: 5%; macrolides: 18%; quinolones: 19%; others: 12%).[4] β-Lactam derivatives with various functional groups are important compounds that attract research interests from both synthetic and pharmaceutical fields.[3,5] Interestingly, all known classes of β-lactam antibiotics (with the exception of the monocyclic and spirocyclic β-lactams) share a common structural feature in that the lactam nitrogen is at the ring fusion (Figure 1). The extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria[6] and efforts have been made to meet this challenge by exploring new β-lactam chemistry by the skeletal modification of naturally occurring β-lactam antibiotics (Figure 1).[7] The nuclear sulphur of penicillins and cephalosporins has been replaced by different atoms (O, N, C) and the chemophysical and microbiological effects of these substitutions have become object of investigation. Also, there is a considerable interest in the modification of the ring system of β-lactams by placing a heteroatom at the 2 or 3 position.

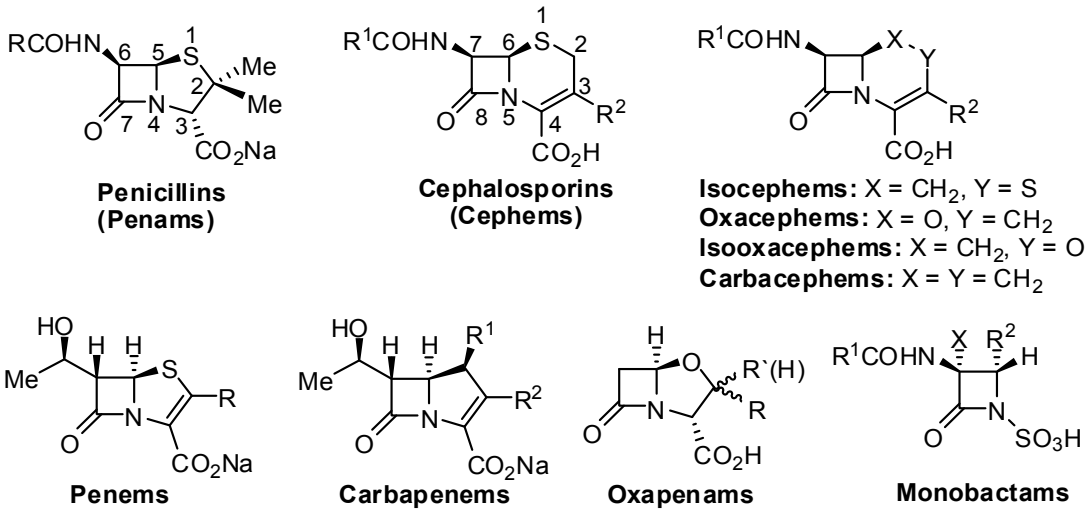
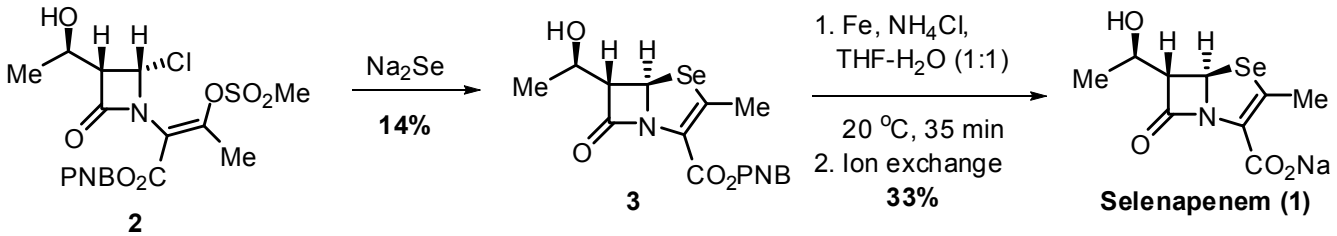


Figure 1. Structures of β-lactam ring systems

Selenium was discovered in 1817 by J. J. Berzelius[8] and the most progress in the area of the synthetic organic chemistry of selenium was accomplished more than 100 years later, in contrast to the chemistry of oxygen- and sulphur-containing organic molecules, which are much better developed. Although the chemistry of selenium-containing compounds is often similar to that of the corresponding sulphur analogues, some significant differences are also known, and because of the toxicity and instability of many selenium compounds, the synthesis of selenium-containing heterocycles is much less developed. In recent years, interest in synthesis of selenium-containing compounds has increased because of their interesting reactivities[9] and their potential biological activities. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their anticancer,[10] and for other medicinal applications,[11] as well as biologically active substances exhibiting antiviral,[12] antibacterial,[13] antihypertensive,[14] and fungicidal properties.[15] It was considered that substitution of the sulphur atom of azetidin-2-ones with selenium preserves its shape and electronic properties but may differ in reactivity and thus potency. Whereas, as a class of β-lactam derivatives, selenium-containing bicyclic β-lactams such as selenapenams and selenacephems have received only a limited attention. In this review the advances in the development of synthesis methods for selenium-containing bicyclic β-lactams are presented and discussed.

2. SYNTHESIS OF SELENAPENEM

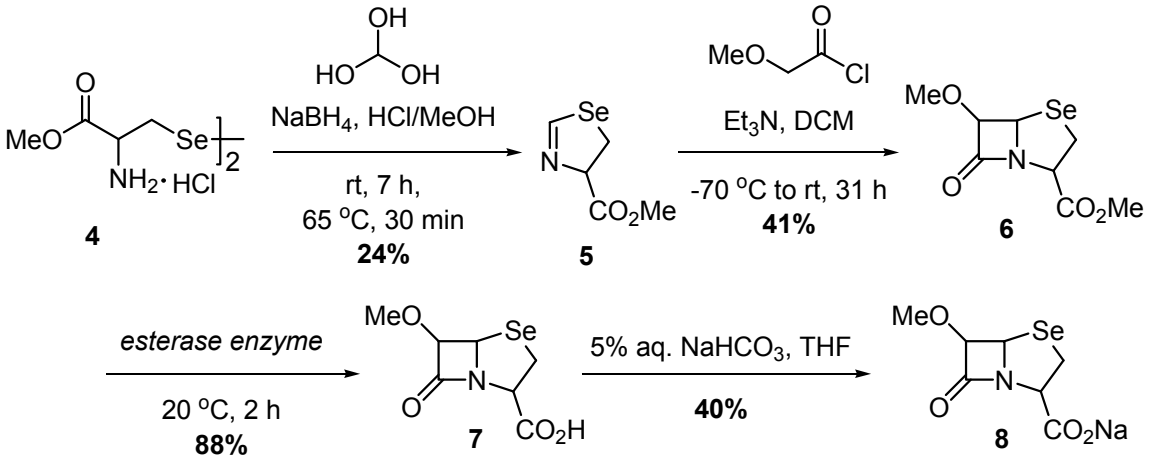
Pioneering research contributions in synthesis of selenium-containing bicyclic β-lactam i.e. selenapenems have been made by E. Perrone *et al*.[16] The first synthesis of selenapenem (**1**) was achieved in two steps from azetidinone **2**, and reported together with an evaluation of the antibacterial activity of this novel ring system, which resembled the corresponding penem (Scheme 1).[16] As shown in Scheme 1, the treatment of 3,4-*cis* azetidinone **2** with sodium selenide to afford the (5*R*)-selenapenem **3**, albeit in poor yield (14%). The removal of the PNB-group of **3** was achieved by reduction with iron powder in a buffer medium and the product required for microbiological evaluation was isolated as sodium salt **1** after ion exchange and reverse-phase chromatography. The selenapenem **1** was four-fold less active than the corresponding penem. The selenapenem **1** was prepared in total 8-steps reaction sequence with 0.7% overall yield.



Scheme 1. Synthesis of selenapenem **1**

3. SYNTHESIS OF SELENAPENAM USING STAUDINGER REACTION

The Staudinger reaction, involving the [2 + 2] cycloaddition reaction of imines and ketenes, is regarded as one of the most versatile procedures for the stereo-controlled synthesis of substituted 2-azetidinones (β-lactams).[17] The next report on the synthesis of selenium-containing bicyclic β-lactams i.e. selenapenam (but lacking a *C*(2) substituent) was appeared in a Japanese patent based on the use of Staudinger reaction (Scheme 2).[18] The synthetic method was started with the diselenide **4**, which on treatment with sodium borohydride afforded selenocystine methyl ester followed by *in situ* reaction with orthoformic acid in 1M HCl/methanol solution resulted in the formation of methyl 1,3-selenazoline-4-carboxylate **5** in 24% yield (Scheme 2). Further, [2+2] cycloaddition of **5** with methoxyacetyl chloride afforded selenapenam **6** in 41% yield, which was converted to free acid by treatment with esterase enzyme to afford selenapenam **7** in 88% yield. Finally, the sodium salt **8** was prepared by the treatment of **7** with 5% $NaHCO_3$/THF solution (Scheme 2).[18]

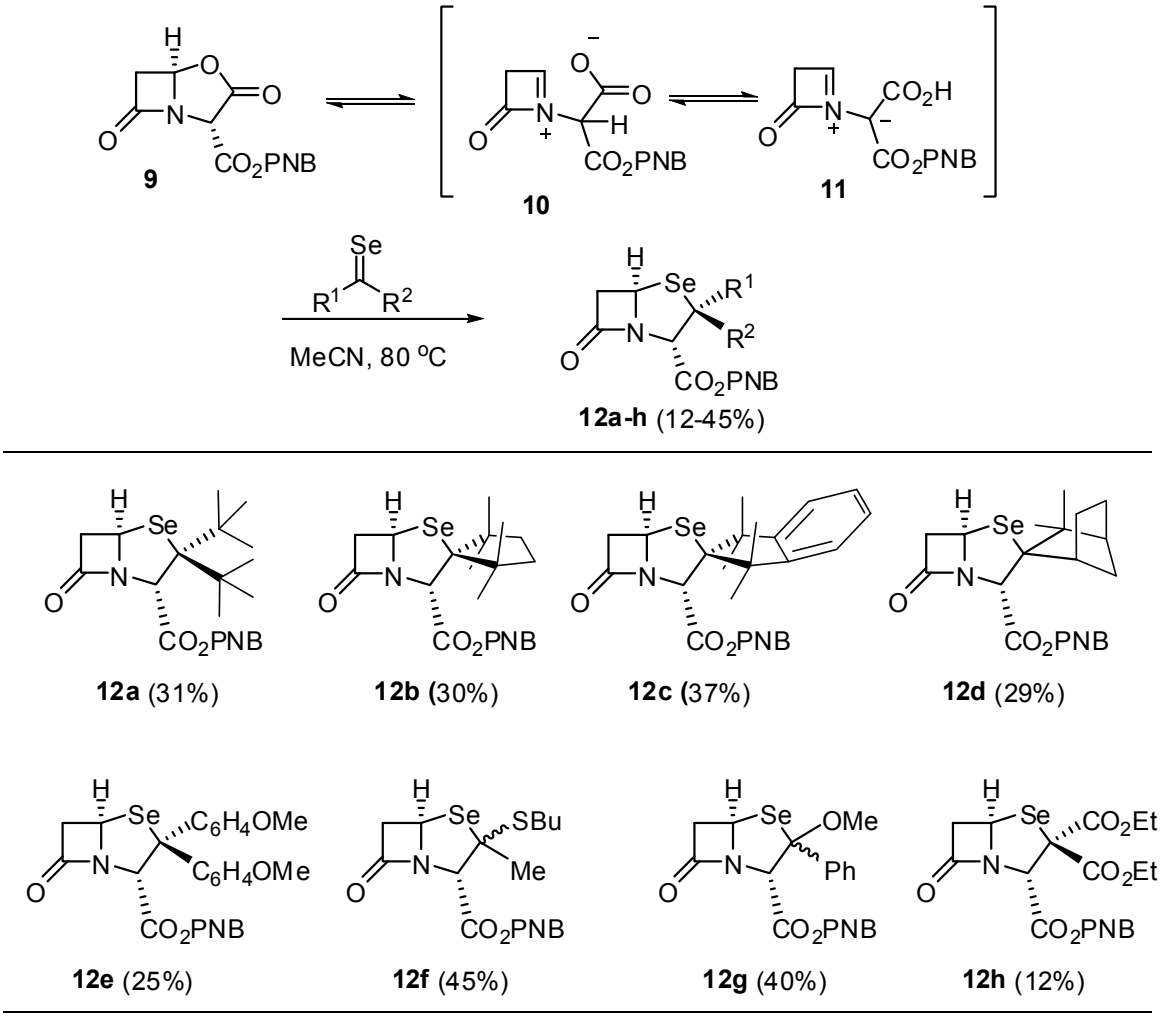


Scheme 2. Synthesis of selenapenam using Staudinger reaction

4. SYNTHESIS OF SELENAPENAMS USING AZOMETHINE YLIDE STRATEGY

Recently, T. Gallagher *et al*. described a novel synthetic strategy for the assembly of a variety of bicyclic β-lactam skeletons based on the generation and reactivity of azomethine ylides.[19] β-Lactam based *N*-acyloxazolidinones, such as **9**, are critical to this process and thermolysis of **9** in the presence of alkenes or thioketones provides direct access to carbapenams and penams, respectively.[19] To date, stable (isolable) 2π dipolarophiles have served as viable traps for **11** (Scheme 3). The equilibrium process shown in Scheme 3 makes it clear that the reactive azomethine ylide **11** is "always present" and, as a consequence, constantly available for the reaction. This unusual mechanistic property has been exploited by capturing a range of less conventional dipolarophiles. By this device, T. Gallagher *et al*. have extended the scope of β-lactam-containing cycloadducts available. In the similar fashion, the treatment of

oxazolidinone **9** with variety of 2π dipolarophiles such as selenoketones, selenothio ester and selenoesters in acetonitrile at reflux resulted in the formation of *C*(2) substituted selenapenams **12a**–**12h** in moderate yields (Scheme 3).[20]

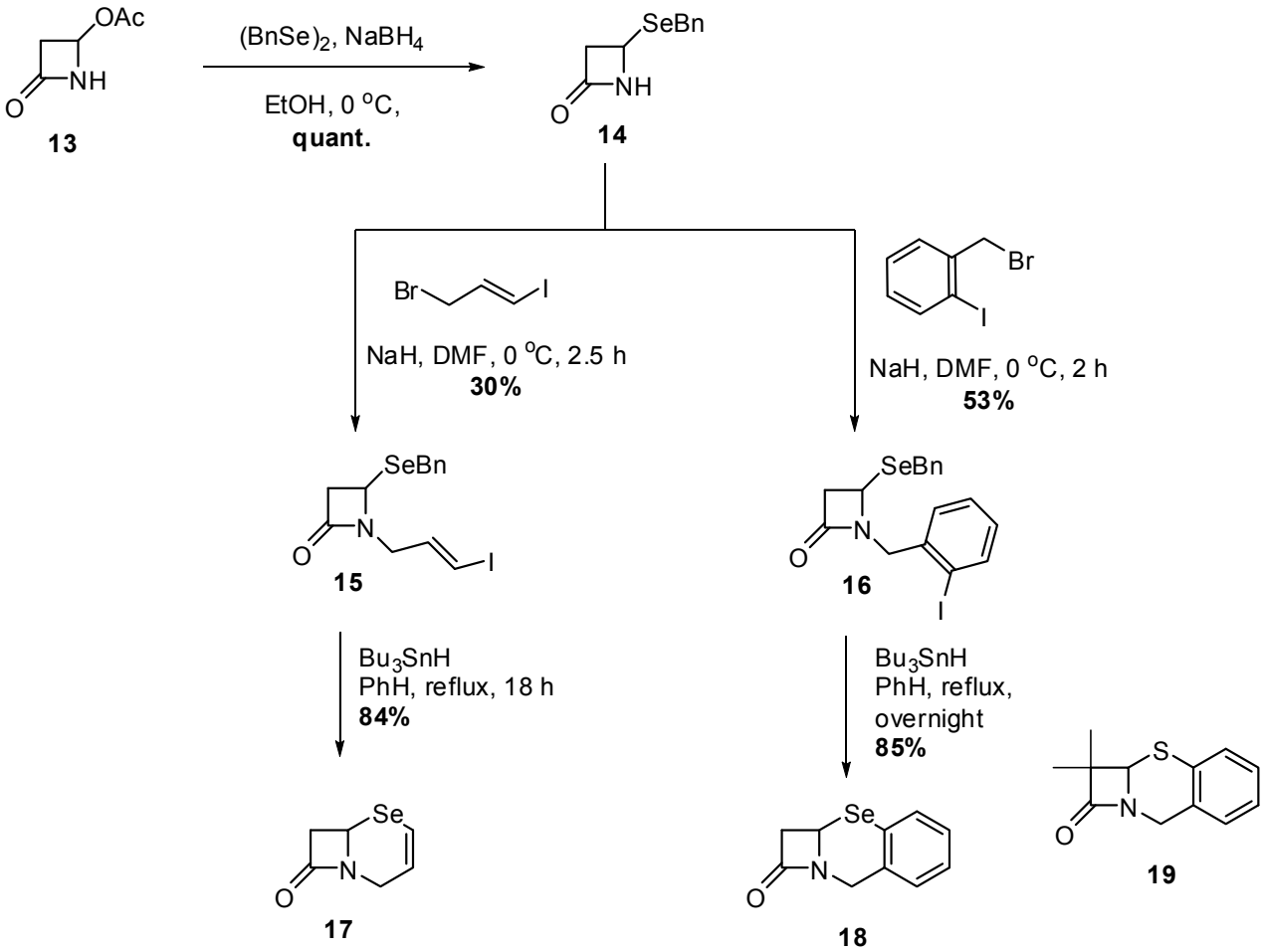


Scheme 3. Synthesis of selenapenams via azomethine ylide strategy

5. SYNTHESIS OF SELENAPENAMS AND SELENACEPHEMS USING FREE-RADICAL HOMOLYTIC SUBSTITUTION CHEMISTRY

Free-radical homolytic substitution chemistry is rapidly gaining acceptance as a versatile synthetic method.[21] Over the past few years, C. H. Schiesser *et al*. and his group have demonstrated the effectiveness of this chemistry for the preparation of selenium and tellurium-containing higher membered-ring heterocycles, also have established that the benzyl selenide moiety acts as a "masked" selenolate ion in intramolecular nucleophilic chemistry and this observation has been used to good effect to provide further methods for the construction of selenium-containing rings that include the benzoselenazine-2,4-dione system.[22] To that end, selenacephems **17** and **18** were efficiently prepared

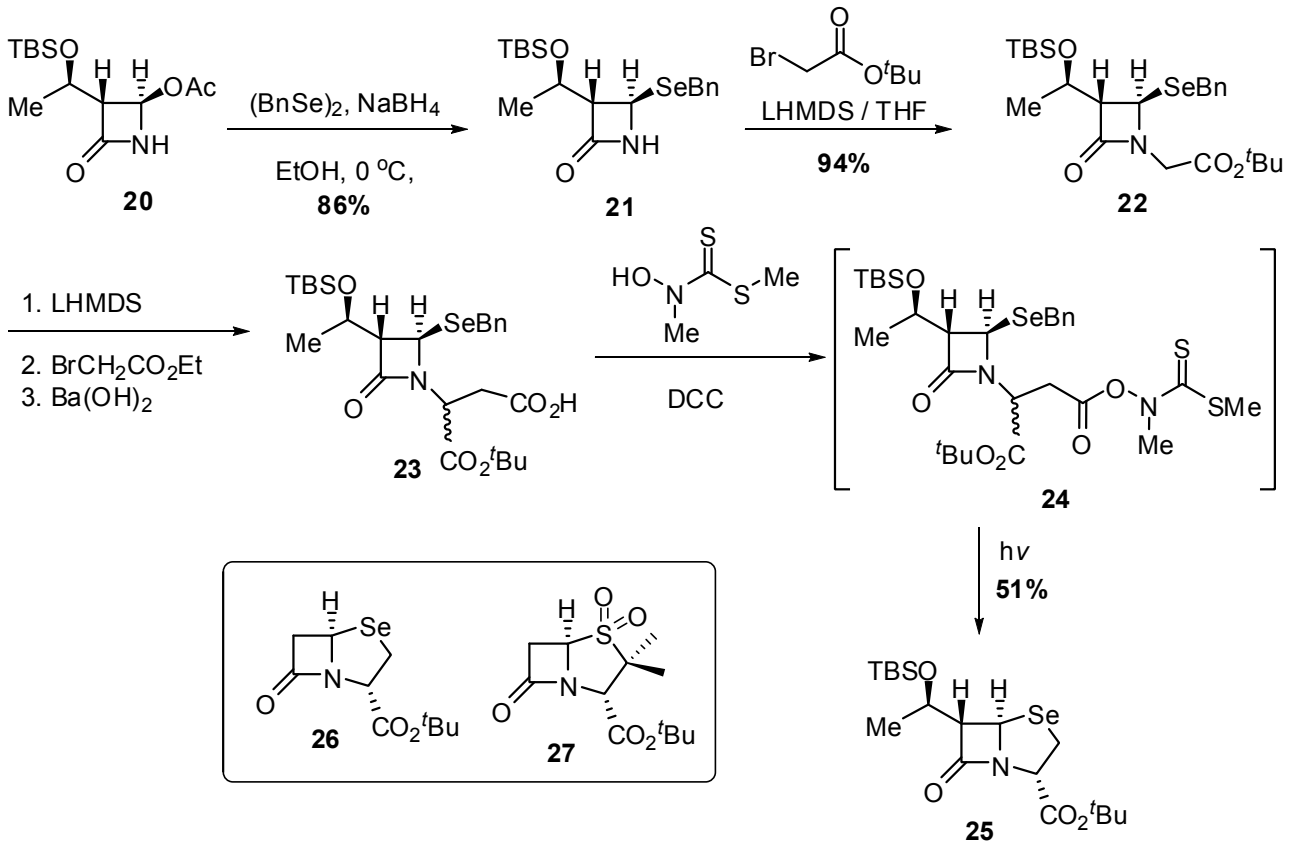
through homolytic substitution chemistry under standard conditions (Scheme 4).[23,24] As shown in Scheme 4, the synthetic route was started with commercially available 4-acetoxy-2-azetidinone **13** which was reacted with sodium benzylselenolate, prepared by treatment of dibenzyl diselenide with sodium borohydride, to give 4-(benzylseleno)-2-azetidinone **14** in quantitative yield. Subsequent treatment of **14** with sodium hydride in DMF at 0 °C followed by an activated electrophile afforded the *N*-alkylated products **15** or **16** in 30 or 53% yield, respectively (Scheme 4). Finally, the treatment of iodides **15** and **16** with tributyltin hydride in benzene reflux afforded selenacephems **17** and **18** in 84% and 85% yields, respectively (Scheme 4). The compounds **17** and **18** were formed by homolytic attack of the first-formed aryl and vinyl radicals respectively at the selenium moiety, with expulsion of the benzyl leaving group.[23,24] This chemistry is analogous to that reported by Beckwith and Boate for the preparation of penicillin analogue (**19**).[25]



Scheme 4. Synthesis of selenacephems

C. H. Schiesser *et al*. and his group expanded this chemistry to include the synthesis of the selenapenam **25** through the use of a Kim thiohydroxamate ester **24**[26] (Scheme 5).[24,27] The commercially available,

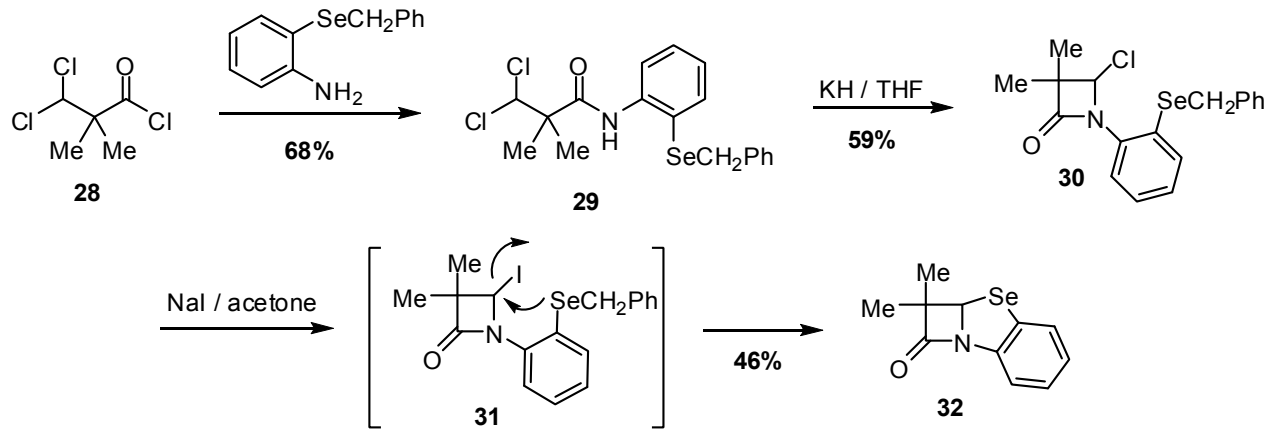
optically pure, (3*R*,4*R*)-4-acetoxy-3-[(*R*)-(*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (**20**) was reacted with sodium benzylselenolate, prepared by treatment of dibenzyl diselenide with sodium borohydride, to afford the benzylseleno derivative **21** with complete retention of configuration (de > 98%) (Scheme 5). The treatment of selenide **21** with *t*-butyl bromoacetate under basic conditions (LHMDS) afforded the ester **22** in 94% yield. Subsequent reaction with ethyl bromoacetate and LHMDS, followed by hydrolysis using barium hydroxide provided the acid **23** as a 7:1 mixture of diastereoisomers. Further conversion of **23** into the thiohydroximate ester **24**, which on photolysis afforded the required selenapenam **25** in 51% yield (based on **22**) (Scheme 5). In similar fashion, the selenium analogue **26** of the β-lactamase inhibitor, Sulbactam (**27**) was also prepared (Scheme 5).[24,27] Initially the diastereometric ration for the selenapenam **26** was observed to be 1:1, however, upon standing, epimerization to a single diastereoisomer (**26**) was observed within 72 hours (Scheme 5).[24]



Scheme 5. Synthesis of selenapenams using free-radical homolytic substitution chemistry

In an alternative approach by C. H. Schiesser *et al*. and his group to these classes of compounds, 3,3-dichloro-2,2-dimethylpropionyl chloride **28** was firstly converted into the corresponding amide **29** by reaction with 2-benzylselenoaniline and then into the chloroazetidinone **30** (Scheme 6). The treatment of chloride **30** with one equivalent of sodium iodide in acetone did not provide the iodide **31**, rather, the

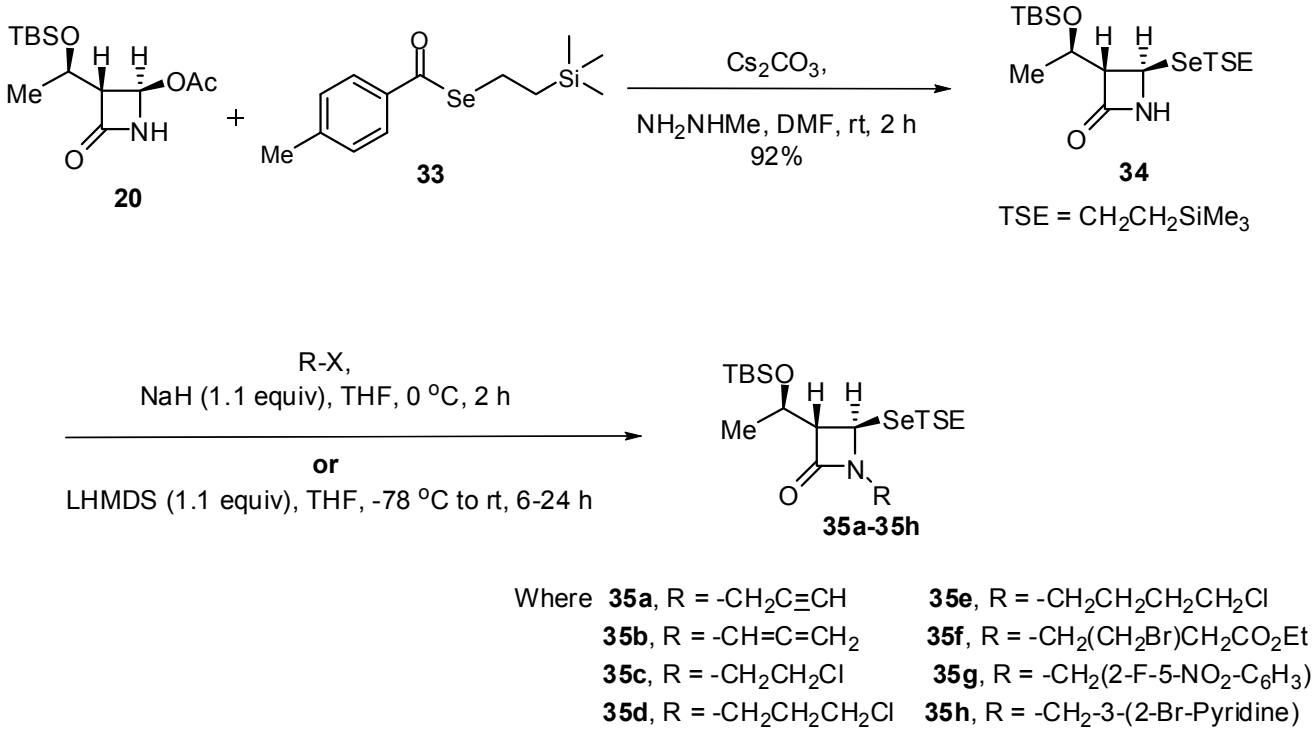
ring-closed selenapenem nucleus, 2,2a-dihydro-2,2-dimethyl-1*H*-azeto[2,1-*b*]benzo[1,3]selenazol-1-one **32** was obtained in 46% yields (Scheme 6).[23] Presumably the corresponding iodide **31** is formed *in situ*, but undergoes rapid intramolecular attack by the nucleophilic benzylseleno moiety to provide selenapenem **32** (Scheme 6).



Scheme 6. Synthesis of selenapenem

6. SYNTHESIS OF SELENAPENAMS AND SELENACEPHEMS USING TSE-PROTECTION APPROACH

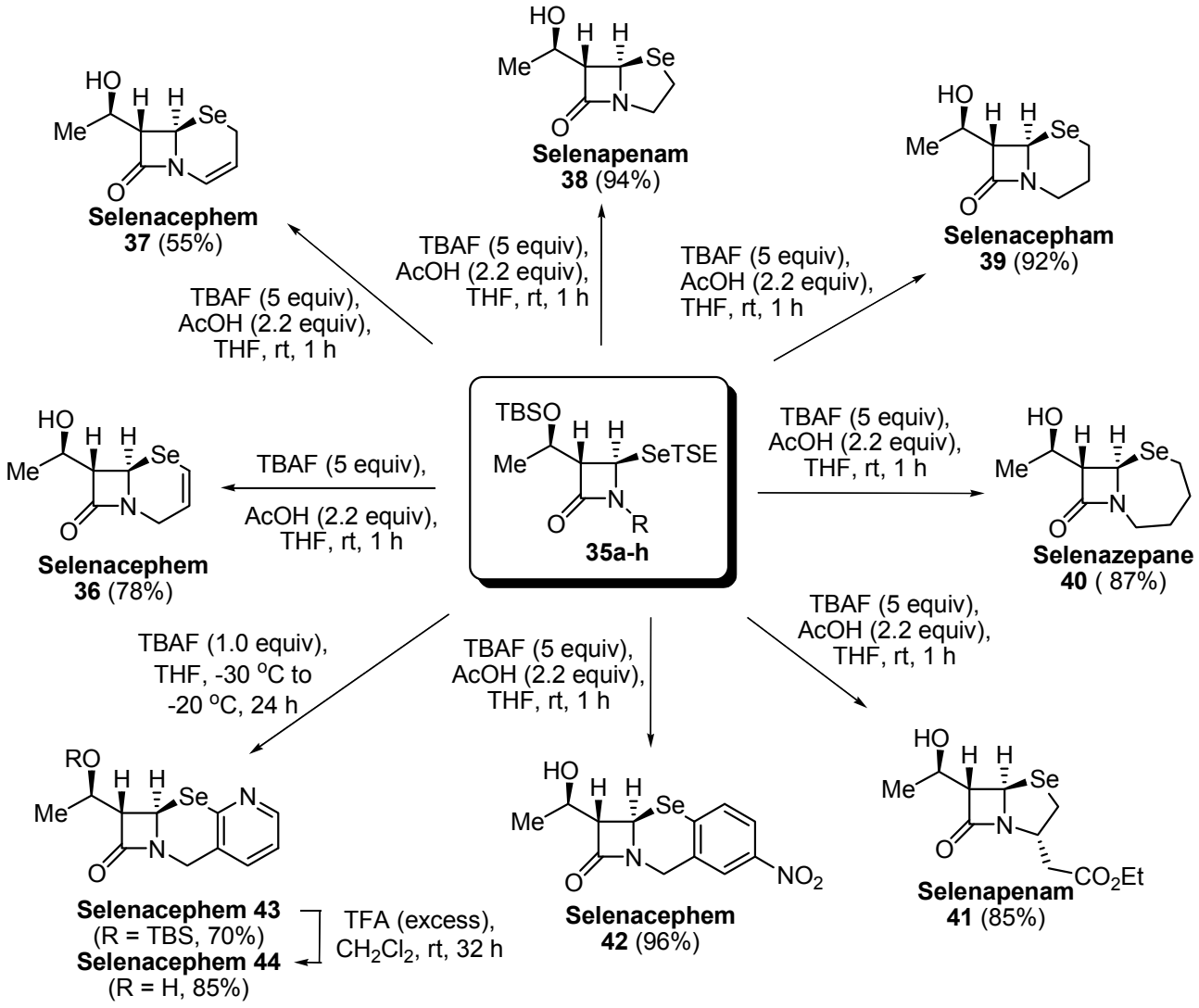
2-(Trimethylsilyl)ethyl (TSE) protection for alcohol[28] and thiol[29] is well known but the concept of TSE-protection in selenium chemistry was first introduced by T. Murai *et al*.[30] Further, the 2-(trimethylsilyl)ethyl (TSE) protection approach was used for the synthesis of the selenium-containing bicyclic β-lactams.[31] A novel selenating reagents, 2-(trimethylsilyl)ethyl *p*-methylselenobenzoate (**33**), prepared from potassium *p*-methylselenobenzoate,[32] was used for the incorporation of the TSE-protected seleno moiety onto β-lactam skeleton (Scheme 7). This selenating reagent, **33** has two latent reactive sites, that is, carbonyl carbon and tetraalkylated silicon. The former is susceptible to the nucleophilic attack by amine, thereby producing a 2-(trimethylsilyl)ethaneselenolate[30] anion. This anion is expected to react with electrophilic sites, allowing the incorporation of the 2-(trimethylsilyl)ethyl (TSE)-protected seleno moiety on to the β-lactam skeleton. As expected, the reaction of the selenating reagent with 4-acetoxyazetidinone **20** afforded the key intermediate TSE-protected seleno derivative **34**, with complete retention of configuration in 92% yield (Scheme 7). Subsequent treatment of **34** with either sodium hydride in THF at 0 °C or lithium hexamethyldisilazide (LHMDS) in THF at -78 °C followed by an activated electrophile afforded the corresponding compounds (**35a**–**h**) having electrophilic segments (Scheme 7).



Scheme 7. Synthesis of selenating reagent and key intermediates

The TSE-selenyl precursors were next applied to TBAF-initiated key annulation to deliver selenacephems, selenapenams, or selenazepane frames (Scheme 8).[31] Thus, the treatment of alkyne **35a** with excess of TBAF at rt led to formation of the selenium anion, and subsequent attack at the alkynyl carbon afforded the required selenacephem **36** by intramolecular cyclization reaction (Scheme 8). Allenes are a versatile class of organic compounds that feature numerous patterns of reactivity.[33] Allenamides are a subclass of allenes that have recently received much attention in the synthetic community.[34] The treatment of allenamide **35b** with excess of TBAF also resulted in the formation of corresponding selenacephem **37** by the intramolecular cyclization reaction. Further, the reactions of **35c** and **35d** with TBAF afforded the corresponding selenapenam **38** and selenacepham **39** in high yields, respectively. The treatment of **35e** with excess of TBAF resulted in the formation of seven-membered selenium-containing heterocycles i.e. selenazepane **40**. Further the TSE-deprotection of **35f** with excess of TBAF resulted in the formation of corresponding selenapenam **41** as a single diastereomer. With the aim of exploring other biologically important selenium heterocycles, a benzo-fused selenacephem **42** was obtained by the treatment of **35g** with TBAF. The nitro group in the selenacephem **42** is advantageous for the functionalization of selenacephem for structure-activity relationship studies. The selective TSE-deprotection of **35h** promoted by the minimized amount of TBAF (1.0 equiv) has yielded a TBS-protected pyridine fused ring system (i.e., selenacephem **43**). Further, the TBS-group within selenacephem **43** was cleaved by the action of

TFA to afford selenacephem **44** (Scheme 8). This chemoselectivity between silyl groups was first reported. The versatility in the TSE-protection approach was shown by the change in the size of the second ring of the bicyclic structure (5, 6, and 7 membered-rings) and the functional groups for further modifications (Scheme 8).



Scheme 8. Synthesis of selenium-containing bicyclic β-lactams using TSE-protection approach

7. SYNTHESIS OF SELENIUM-CONTAINING BICYCLIC β-LACTAMS *VIA* RCM AND RCEYM

Ring-closing metathesis (RCM)[35] and ring-closing enyne metathesis (RCEYM)[36] have recently emerged as a powerful tool for the formation of a variety of ring systems (Figure 2). The generation of β-lactam arrays by RCM and RCEYM has received considerable attention over the past few years. RCM[37] and RCEYM[38] approaches were first time used for the synthesis of higher ring selenium-containing bicyclic β-lactams.

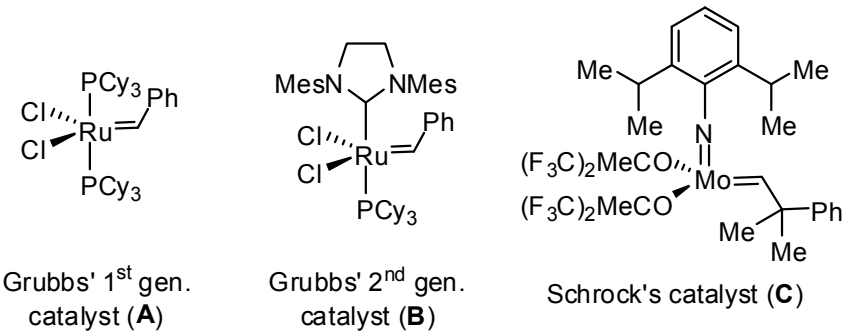
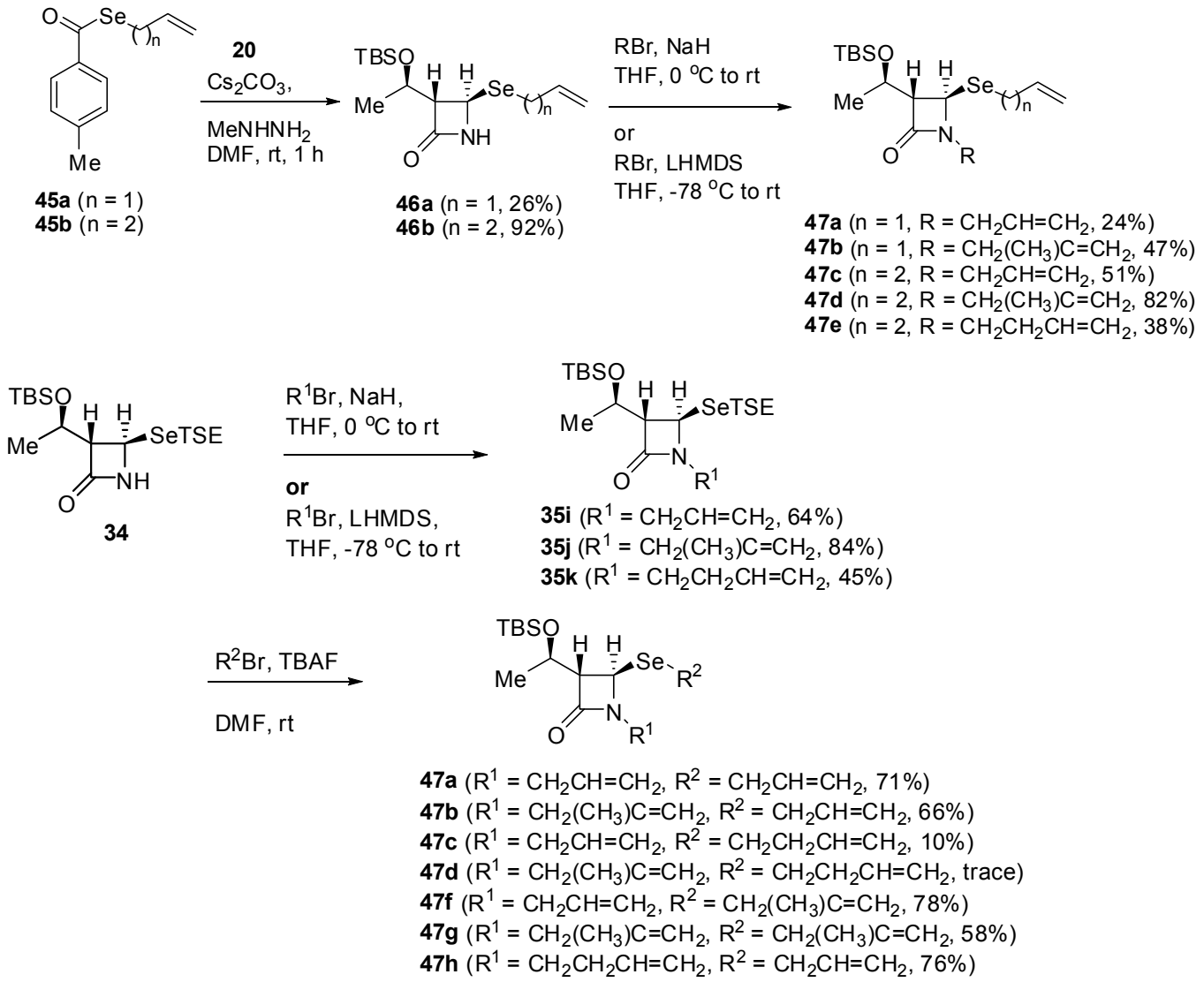


Figure 2. Common ruthenium and molybdenum carbene complexes used in ring-closure metathesis reactions

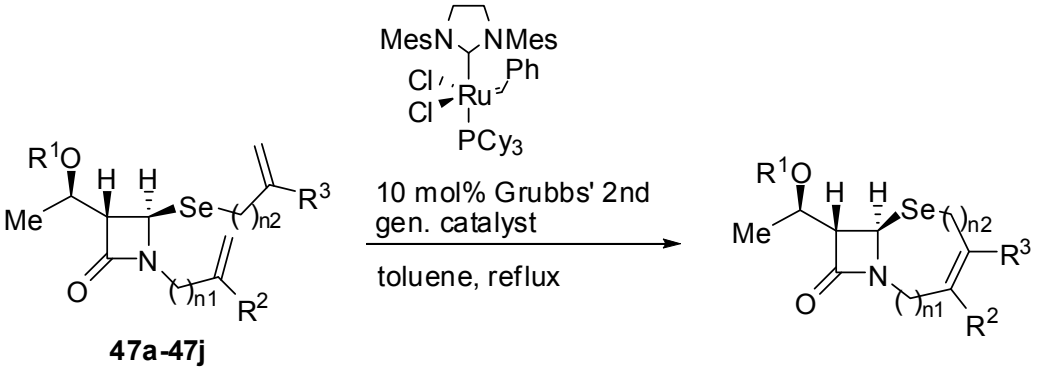


Scheme 9. Insertion of the alkene-seleno moieties at the *C*(4) position of the azetidinones

The difficult task in the synthesis of selenium-containing bicyclic β-lactams by ring-closing metathesis (RCM) was the insertion of the alkene-seleno moieties at the *C*(4) position of the azetidinones. For this,

new selenating reagents, *Se*-allyl *p*-methylselenobenzoate (**45a**) and *Se*-3-butenyl *p*-methylselenobenzoate (**45b**) were prepared. These reagents allowed the insertion of the allyl-seleno or butenyl-seleno moieties onto β-lactam skeleton i.e. compounds **46a**–**46b** under basic conditions (Scheme 9). Subsequent treatment of **46a** or **46b** with either sodium hydride in THF at 0 ºC or lithium hexamethyldisilazide (LHMDS) in THF at -78 ºC followed by an activated electrophile afforded the corresponding previously unknown key intermediates (**47a**–**47e**) in 24–82% yields, respectively (Scheme 9).[37]

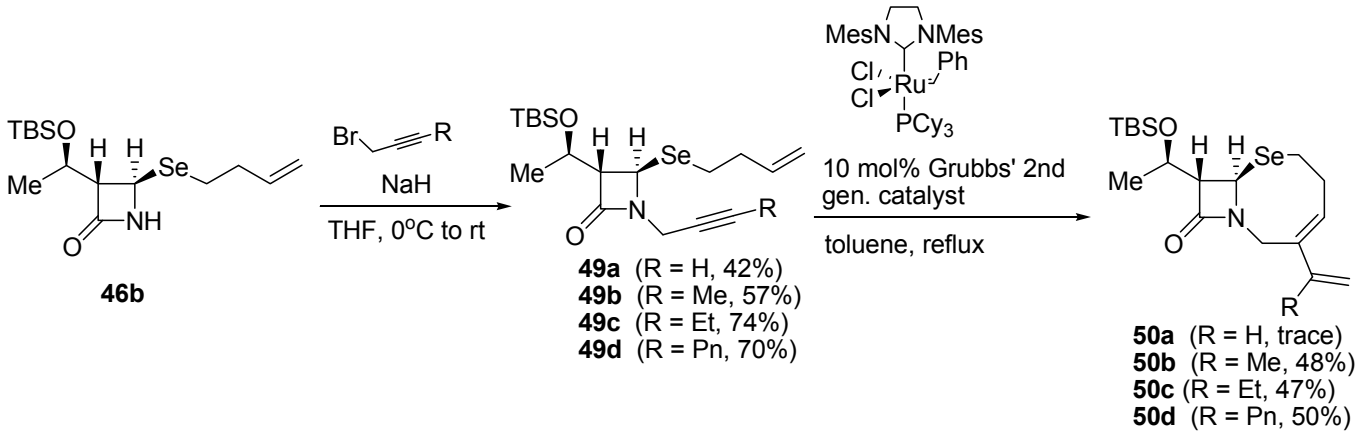
The TSE-protection approach was also used for the insertion of the allyl-seleno or butenyl-seleno moieties onto β-lactam skeleton. The treatment of **34** with either sodium hydride in THF at 0 ˚C or lithium hexamethyldisilazide (LHMDS) in THF at -78 ˚C followed by an activated electrophile afforded the corresponding compounds **35i**–**35k** (Scheme 9). The deprotection of the TSE-group of **35i**–**35k** by TBAF followed by *in situ* alkylation of the selenolate anion with alkyl bromide afforded the corresponding substrates (**47a**–**47d** and **47f**–**47h**) for the RCM reaction (Scheme 9).[37]



Where, **48a** (n1 = 1, n2 = 1, R^1 = TBS, R^2 = H, R^3 = H, 78%)
48b (n1 = 1, n2 = 1, R^1 = TBS, R^2 =Me, R^3 = H, 92%)
48c (n1 = 1, n2 = 1, R^1 = TBS, R^2 = H, R^3 = Me, 75%)
48d (n1 = 1, n2 = 1, R^1 = H, R^2 = Me, R^3 = H, 82%)
48e (n1 = 1, n2 = 1, R^1 = H, R^2 = H, R^3 = Me, 74%)
48f (n1 = 1, n2 = 1, R^1 = TBS, R^2 = Me, R^3 = Me, 0%)
48g (n1 = 1, n2 = 2, R^1 = TBS, R^2 = H, R^3 = H, 68%)
48h (n1 = 2, n2 = 1, R^1 = TBS, R^2 = H, R^3 = H, 74%)
48i (n1 = 1, n2 = 2, R^1 = TBS, R^2 = Me, R^3 = H, 91%)
48j (n1 = 2, n2 = 2, R^1 = TBS, R^2 = H, R^3 = H, 74%)

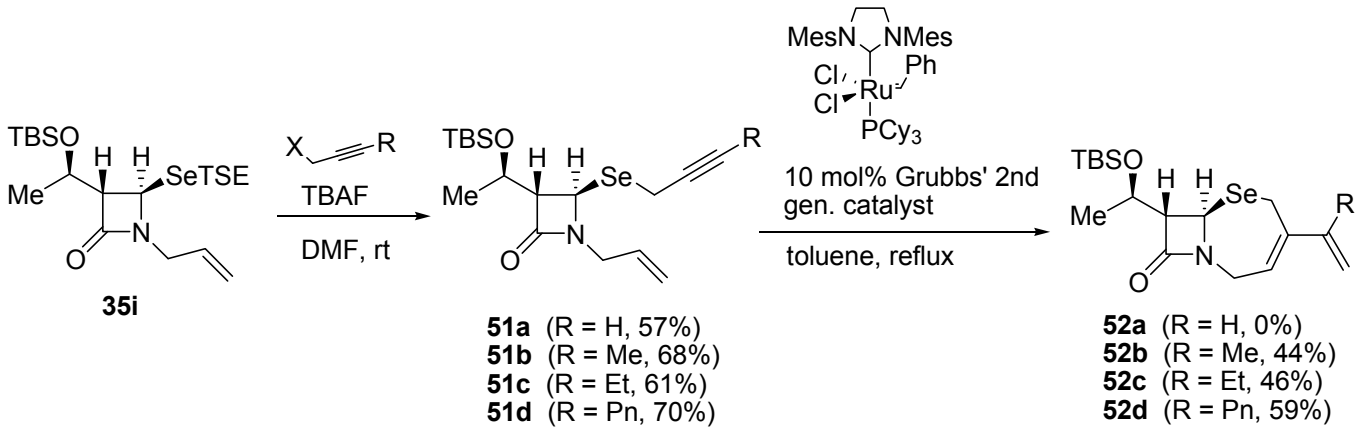
Scheme 10. Ring-closing metathesis (RCM) of alkene-seleno derivatives

Among the catalysts screened for the ring-closing metathesis (Figure 2), Grubbs 2nd generation catalyst was found to be most effective for the synthesis of selenium-containing bicyclic β-lactams **48a**–**48j** (Scheme 10).[37] This approach is useful for the synthesis of 7-, 8-, or 9-membered selenium-containing bicyclic β-lactams.



Scheme 11. Selenium-containing bicyclic β-lactams by RCEYM

For the synthesis of selenium-containing bicyclic β-lactams through RCEYM reactions, the compound **46b** having 3-butenyl-seleno moiety at the *C*(4) position in the azetidinones was treated with sodium hydride in THF at 0 °C and subsequent addition of substituted propargyl bromides afforded the corresponding key intermediates **49a**–**49d** for the RCEYM reaction in 42–74% yields (Scheme 11). Further the RCEYM of 3-butenyl-seleno compounds **49a**–**49d** using 10 mol% of Grubbs 2nd gen. catalyst resulted in the formation of 8-membered selenium-containing bicyclic β-lactams **50b**–**50d** in moderate yields (Scheme 11).[38]



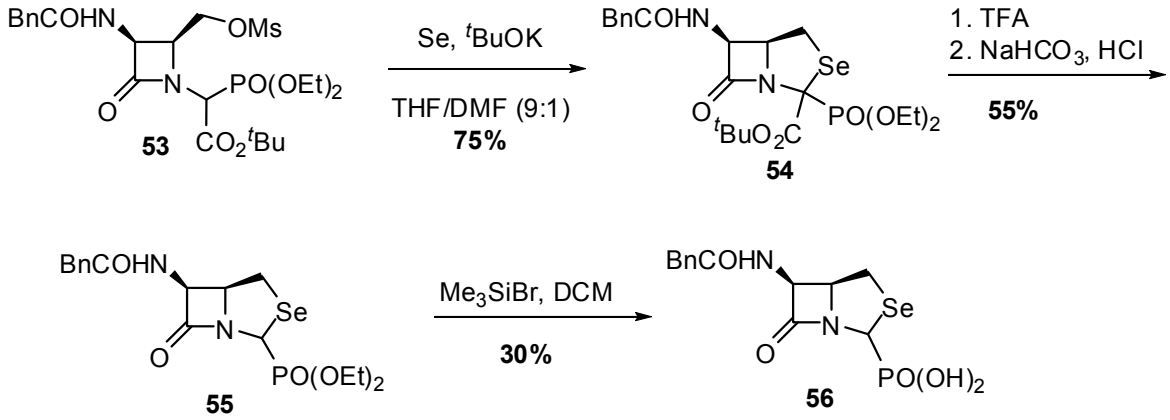
Scheme 12. Selenium-containing bicyclic β-lactams by RCEYM

Next, as shown in Scheme 12, the selective removal of the TSE-group of **35i** and subsequent *in situ* alkylation of the selenolate anion afforded the compounds **51a**–**51d** having propargyl-seleno moieties at their *C*(4) positions in the azetidinones (Scheme 12).[38] Further, the treatment of the intermediates **51b**–**51d** with Grubbs 2nd gen. catalyst (10 mol%) afforded the corresponding 1,3-selenazepine

compounds **52b**–**52d**, respectively, in good yields, however, an attempt to bring about the cyclization of **51a** in the presence of the Grubbs 2nd gen. catalyst (10 mol%) was failed (Scheme 12).[38] This RCEYM approach allows the synthesis of previously inaccessible selenium-containing bicyclic β-lactams.

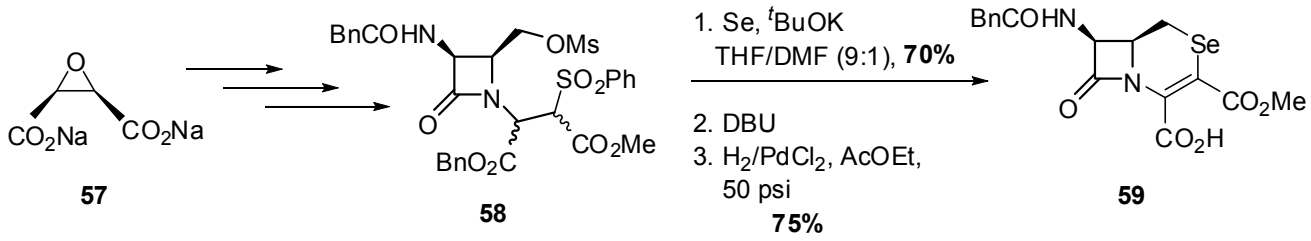
8. SYNTHESIS OF ISODETHIASELENAPENAM AND ISODETHIASELENACEPHEM

The synthesis of selenium-containing bicyclic β-lactams having selenium atom at the 2 or 3 position i.e. isodethiaselenapenam **56** and isodethiaselenacephem **59** were reported by G. H. Hakimelahi *et al*. with their biological activity.[39] The synthetic approach for isodethiaselenapenam **56** was started with the mesyl derivative **53** (Scheme 13). The treatment of **53** with ^{t}BuOK and selenium powder in THF:DMF (9:1) afforded the *cis*-substituted bicyclic β-lactam **54** as a mixture of two diastereomers in 75% overall yield (Scheme 13). Removal of the ^{t}Bu group of **54** with TFA followed by decarboxylation by use of $NaHCO_3$ gave phosphonate **55** (55%) upon acidic work up. Treatment of phosphonate **55** with Me_3SiBr in DCM produced isodethiaselenapenam **56** in 30% yield (Scheme 13).[39]



Scheme 13. Synthesis of isodethiaselenapenam

Further, the synthetic approach for isodethiaselenacephem **59** was started with the sodium salt **57** of the *cis*-epoxysuccinic acid (Scheme 14). After several reaction sequences, the sodium salt **57** was converted into a mesyl derivative **58**, which on treatment with ^{t}BuOK and selenium powder in THF:DMF (9:1) subsequent treatment of the corresponding isodethiaselenacepham intermediate with DBU *in situ* at reflux temperature gave racemic bicyclic β-lactam which on hydrogenolysis in the presence of $PdCl_2$ in AcOEt at 50 psi H_2 afforded the *cis*-substituted bicyclic β-lactam isodethiaselenacephem **59** (Scheme 14).[39] Next, the biological activity of the isodethiaselenapenam **56** and isodethiaselenacephem **59** was investigated. The isodethiaselenapenam **56** and isodethiaselenacephem **59** were exhibited antimicrobial activity.



Scheme 14. Synthesis of isodethiaselenacephem

9. SYNTHESIS OF 3-SELENA-1-DETHIACEPHAMS AND SELENAZEPINES *VIA* IODOCYCLIZATION

Iodocyclization of an unsaturated C-C bond with a wide variety of nucleophiles, including N, O, and S nucleophiles, has been extensively studied and has become a powerful tool for the construction of various heterocycles.[40] In contrast, only a few examples for the synthesis of selenium heterocycles *via* electrophilic cyclization have been reported in the literature.[41] The retrosynthetic disconnection approach as shown in Figure 3 suggests that a variety of selenium-containing β-lactams having selenium other than at C4-position can be easily prepared from the allene- or alkyne-selenoureas *via* an iodocyclization reaction.[42] Further, the key intermediates alkyne-selenoureas **60** (Scheme 15) or allene-selenoureas **64** (Scheme 17) for the iodocyclization reaction can be readily prepared by the *N*-alkylation reaction of previously known propargyl-azetidinones[43] or allenyl-azetidinones,[43] prepared from **20** *via* indium chemistry, with a wide variety of isoselenocyanates[44] under basic conditions in good to excellent yields, respectively (Figure 3).

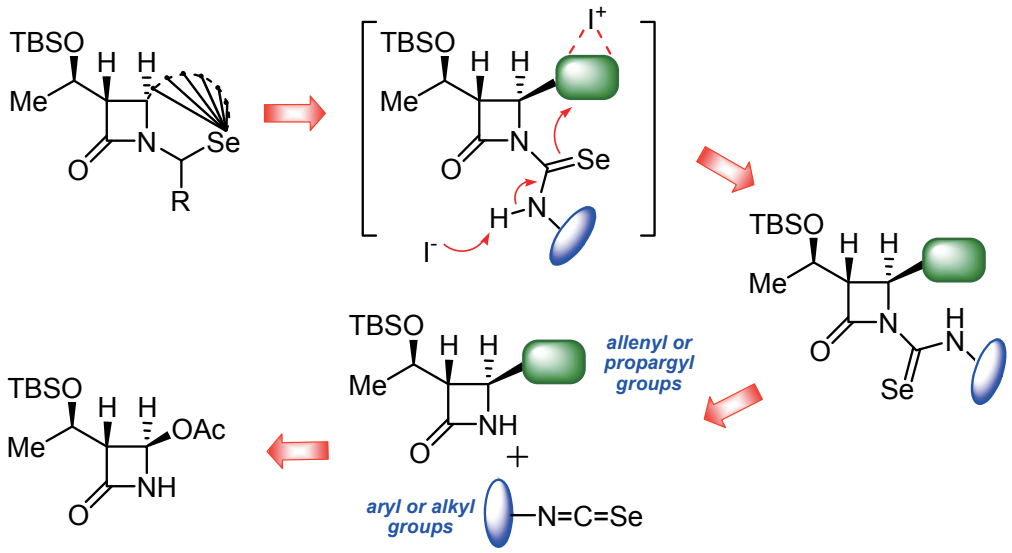
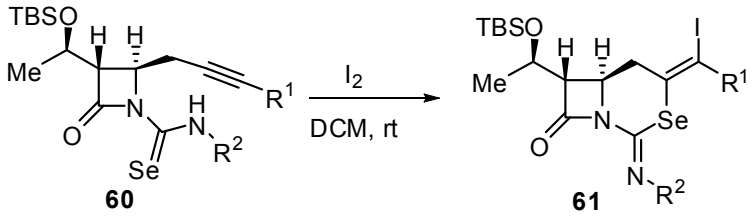


Figure 3. Retrosynthesis of selenium-containing β-lactams

After screening several reaction conditions it was found that, the iodocyclization reaction of β-alkyne-selenourea **60** using 1.25 equiv. of iodine in dichloromethane at rt resulted in the formation of

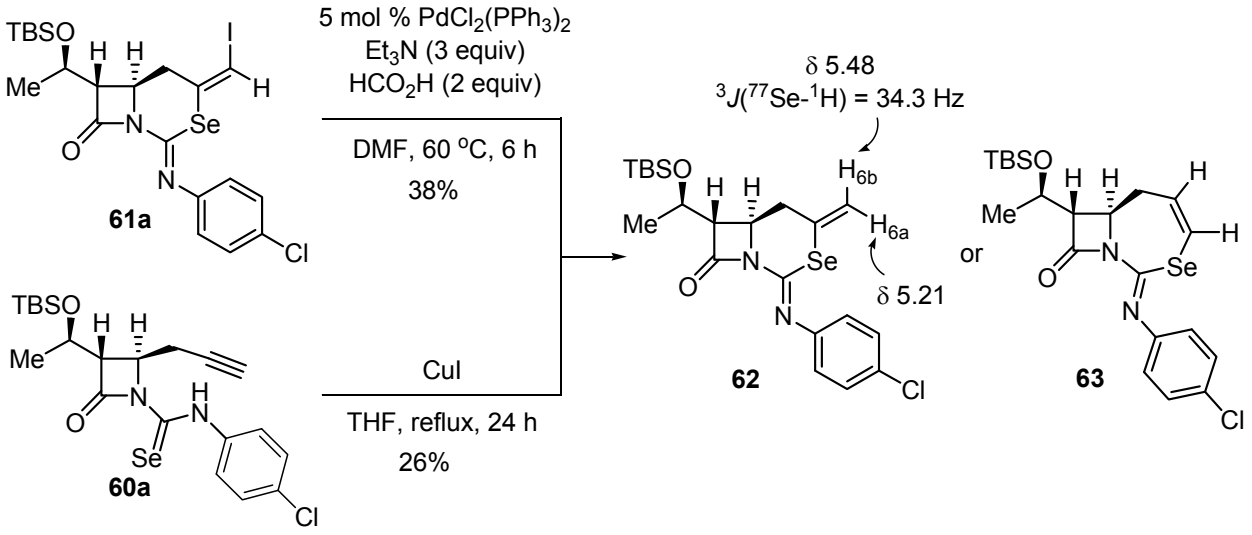
corresponding 3-selena-1-dethiacepham **61a**–**61h** in excellent yields (Scheme 15).[42] The nature of the R^2 group on the selenourea had very little effect on the reaction rate or product yields. Aryl-substituted selenoureas (**60a**–**60d**) gave slightly higher yield than alkyl-substituted selenoureas (**60e**–**60f**). The aryl-substitution at alkynes (i.e. $R^1 = C_6H_5$) were also well accommodated and afforded the cyclized products **61g** and **61h** in excellent yields (Scheme 15). The reaction shows high regioselectivity for six-membered ring 3-selena-1-dethiacephams **61**. Seven-membered ring products were never detected under these reaction conditions.[42]



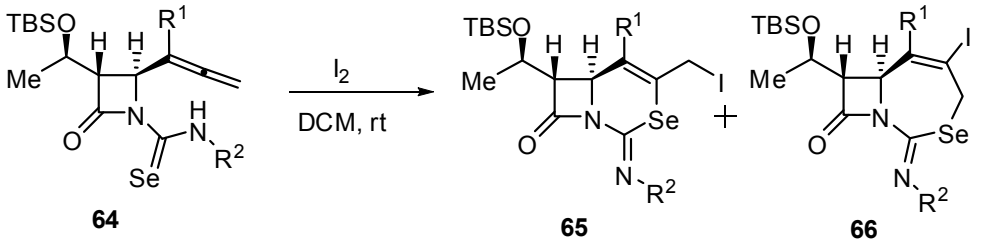
R^1	R^2	Yield (%)
H	*p*-ClC_6H_4	92 (**61a**)
H	C_6H_5	91 (**61b**)
H	*p*-MeC_6H_4	88 (**61c**)
H	2-naphthyl	93 (**61d**)
H	benzyl	82 (**61e**)
H	*cyclo*-C_6H_{11}	84 (**61f**)
C_6H_5	*p*-ClC_6H_4	95 (**61g**)
C_6H_5	*p*-MeC_6H_4	92 (**61h**)

Scheme 15. Synthesis of 3-selena-1-dethiacephams *via* iodocyclization reaction

The structure of the 3-selena-1-dethiacephams **61a** was also confirmed by chemically. Thus the palladium-catalysed triethylammonium formate reduction of the iodide **61a**[45] provided only compound **62** but not compound **63** (Scheme 16).[42] It was relatively easy to distinguish the isomers **62** and **63** by NMR study. Recently, M. Koketsu *et al.* and the group have reported that selenium shows strong coupling with *trans* proton of exocyclic double bond, whereas similar coupling with *cis* proton was not observed.[46] The same observation was found in the compound **62** i.e. selenium shows coupling with *trans* proton H_{6b} $^3J(^{77}Se\text{-}^1H) = 34.3$ Hz exclusively (Scheme 16). Thus, this spectral feature may become an important tool for confirming the structure of selenium-containing compounds. The 3-selena-1-dethiacepham **62** was alternatively obtained by direct CuI mediated intramolecular cyclization of **60a** (Scheme 16) in 26% yield.[42] Further, the synthesized compounds were screened for their biological activity. The compounds, 3-selena-1-dethiacepham **61e** and 3-selena-1-dethiacepham **61f**, are capable of attenuating oxidative stress and inhibiting cell growth in hormone-sensitive prostate cancer LNCaP cells.[47] Thus, these compounds possess the potential as pharmacological agents for chemoprevention of prostate cancer.



Scheme 16. Structural confirmation of 3-selena-1-dethiacepham by spectroscopic and chemical method



R^1	R^2	Yield (%)
H	C_6H_5	67 (**65a**)
H	*p*-MeC_6H_4	69 (**65b**)
H	*p*-ClC_6H_4	65 (**65c**)
H	2-naphthyl	69 (**65d**)
H	benzyl	61 (**65e**)
Me	*p*-ClC_6H_4	55 (**66f**)
Me	*p*-MeC_6H_4	62 (**66g**)
Et	*p*-ClC_6H_4	41 (**66h**)
Et	*p*-MeC_6H_4	69 (**66i**)
n-C_5H_{11}	*p*-ClC_6H_4	50 (**66j**)
n-C_5H_{11}	*p*-MeC_6H_4	52 (**66k**)

Scheme 17. Synthesis of 3-selena-1-dethiacephems **65** and selenazepines **66** *via* iodocyclization

Next, the iodocyclization reaction of unsubstituted β-allene-selenoureas **64** using 1.25 equiv. of iodine resulted in the formation of 3-selena-1-dethiacephems **65a**–**65e** as the major product with traces of the corresponding five-membered product isodethiaselenapenams (Scheme 17).[42] Good yields were obtained in all cases, irrespective of the nature of substituent present on the selenourea group (**65a**–**65e**). Seven-membered ring products, i.e. selenazepines **66**, were not detected. Thus, these reaction conditions show high regioselectivity towards six-membered ring products, 3-selena-1-dethiacephem **65**. Next, the iodocyclization reaction of β-allene-selenourea bearing alkyl or aryl groups at the allenyl position was examined with iodine (Scheme 17). It was found that the regiochemistry in the iodocyclization reaction is affected by the nature of the R^1 group at the allenyl position. The reaction of alkyl-substituted β-allene-selenoureas **64f**–**64k** with 1.25 equiv. of iodine afforded selenazepines **66f**–**66k**, respectively. The traces of five-membered isodethiaselenapenam were observed as side products.

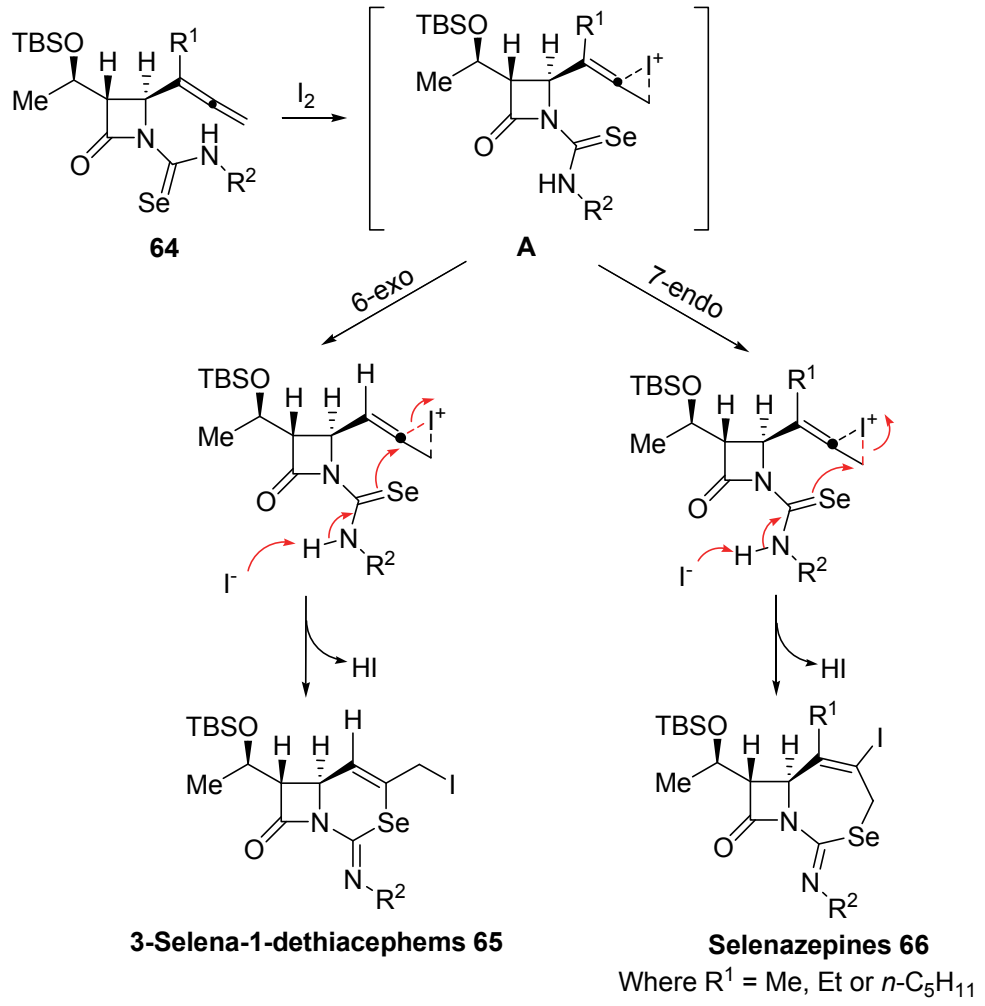
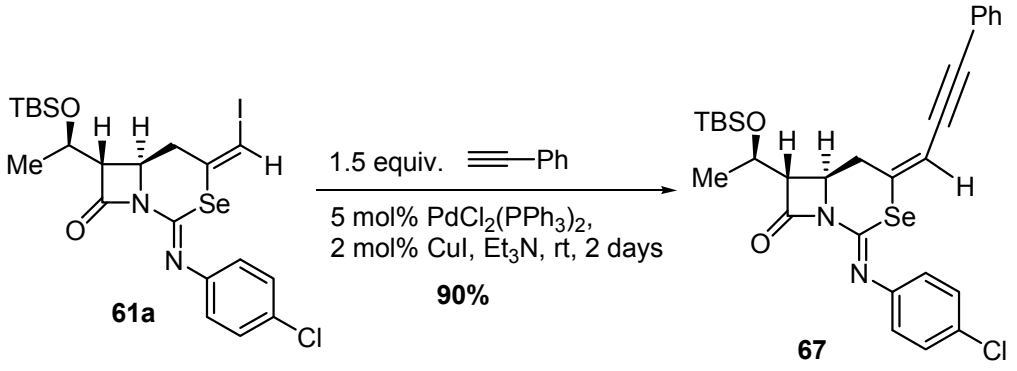


Figure 4. Mechanism for the iodocyclization reaction of β-allene-selenoureas

A plausible mechanism was proposed for the formation of **65** and **66** as shown in Figure 4. The reaction of **64** with iodine gave iodonium **A** and released an iodine anion at the same time. With the assistance of iodine anion, intramolecular nucleophilic attack of selenium in the selenourea group on the center carbon of allene (when R^1 = H) in the favored 6-*exo* mode affords the corresponding cyclization product 3-selena-1-dethiacephem **65**, whereas attack of selenium in selenourea group on the terminal carbon of allene (when R^1 = Me, Et, or *n*-C_5H_{11}) in the favored 7-*endo* mode affords the corresponding cyclization product, selenazepine **66**, accompanied by the simultaneous elimination of hydrogen iodide. The iodocyclization reaction is highly regioselective.



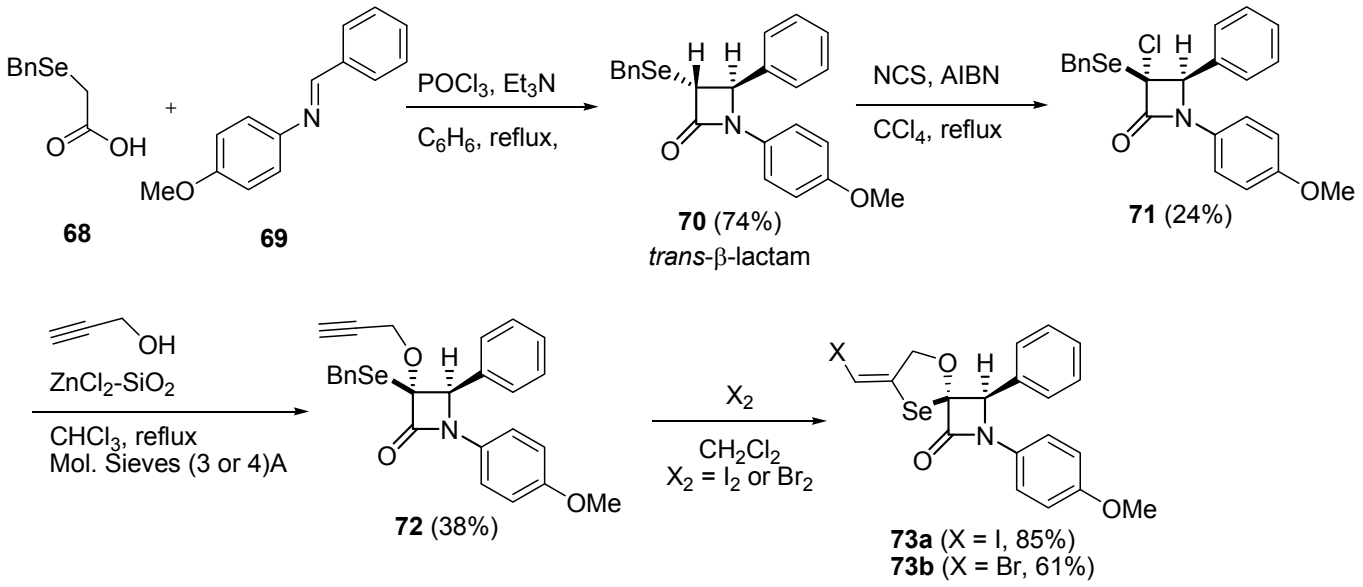
Scheme 18. Sonogashira coupling reaction of **61a** with phenylacetylene

Further, the presence of iodine in the 3-selena-1-dethiacepham **61a** allowed the further structural elaboration, most notably using palladium-catalyzed coupling reaction (Scheme 18).[42] When compound **61a** was exposed to Sonogashira coupling conditions[48] with phenylacetylene, the corresponding coupling product **67** was isolated in excellent yield (Scheme 18).[42] The imine group in the 3-selena-1-dethiacepham **67** is advantageous for further functionalization.

10. SYNTHESIS OF SPIROCYCLIC SELENIUM-CONTAINING β-LACTAMS

The ever-increasing applications of azetidin-2-ones have triggered a renewed interest in the spiro-β-lactams, as they behave as β-turn mimetics[49] and β-turn nucleators.[50] In this regard, S. S. Bari *et al*. reported the first synthesis of spirocyclic seleno-β-lactams.[51] The synthetic approach was started with 2-benzylselenoethanoic acid (**68**). Benzyl-selenoazetidin-2-one (**70**) was synthesized in good yield by treating 2-benzylselenoethanoic acid (**68**) with the Schiff's base **69** in the presence of triethylamine as the base and phosphorus oxychloride ($POCl_3$) as the condensing reagent in refluxing benzene (Scheme 19). This cycloaddition reaction resulted in an exclusive formation of *trans*-β-lactam **70**. The β-lactam carbocation equivalent **71** was prepared by chlorination of azetidin-2-one **70**, using *N*-chlorosuccinimide (NCS) with catalytic amount of AIBN in carbon tetrachloride (Scheme 19). The reaction is highly

stereoselective. The chlorination at benzylic carbon atom was not observed. Further, the treatment of **71** with propargyl alcohol in silica gel mediated by Lewis acid such as $ZnCl_2$ in refluxing chloroform afforded *cis*-3-alkoxy-3-benzylseleno-β-lactam **72** in 38% yield (Scheme 19). Finally, the synthesis of spiro seleno-β-lactams by halogen mediated intraselenyl cyclization of **72** was carried out. The treatment of compound **72** with 1 equiv of iodine in dry dichloromethane at room temperature afforded spiro seleno-β- lactam **73a** in 85% yield (Scheme 19). Furthermore, when the reaction was carried out with bromine as the halogenating reagent, spiro seleno-β-lactam **73b** was obtained but with comparatively lower yields (Scheme 19). The halocyclization reactions resulted in the exclusive formation of five-membered ring spiro seleno-β-lactams *via* a 5-*exo* closure process, instead of 6-*endo* closure (Scheme 19).



Scheme 19. Synthesis of spiro selenium-containing β-lactams

11. CONCLUSION

In summary, this review provides advances in the development of synthesis methods for selenium-containing bicyclic β-lactams. However, the synthesis of selenium-containing bicyclic β-lactams will surely have a magnificent future and we have no doubt that many further applications will appear in the future.

12. ACKNOWLEDGEMENTS

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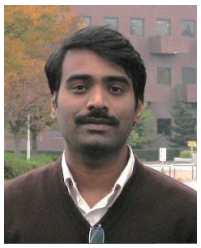

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