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Synthesis of Novel 4-Halomethyl-1,3-oxaselenolane Substituted Spirocyclic Azetidin-2-ones from *cis*-3-Allyloxy-3-benzylselenoazetidin-2-ones

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A mild and efficient synthetic approach for the synthesis of novel 4-halomethyl-1,3-oxaselenolane substituted spirocyclic β-lactams *via* intraselenyl cyclization of *cis*-3-allyloxy-3-benzylselenoazetidin-2-one mediated by halogens (I_2, Br_2) is described. The mechanism involves step-wise electrophilic addition-dealkylation sequence generating spiroseleno-β-lactams stereospecifically. The novel synthesized β-lactams have been characterized by spectroscopic techniques *viz*. NMR (^1H, ^{13}C, ^{77}Se), FT-IR and elemental analysis. The *cis* configuration of the nucleophilic substituent at C-3 was assigned with respect to C4-H. Intraselenyl cyclization is a novel approach in the chemistry of β-lactam research.

Keywords: Spirocyclic, Azetidin-2-ones, Nucleophile, Intraselenyl Cyclization, 1,3-Oxaselenolane, Lewis acid.

INTRODUCTION

β-Lactams (azetidin-2-ones) have been considered as one of the most important aza-heterocyclic frameworks with broad applications in biology, medicine and chemistry. These mark their presence in innumerable antibiotics, representing an important class of modern pharmaceuticals [1,2]. Selenium, an essential trace element, is required for the proper functioning of the immune system, influences endocrine processes (thyroid hormone synthesis and metabolism) and delays aging [3]. The incorporation of selenium into azetidin-2-ones leading to selenopenams with β-lactamase inhibitory properties [4], antibacterial selenapenems and selenacephems [5] has been reported in the literature.

Over recent years, there has been a surge of attention towards synthesizing spirocyclic β-lactams in view of their inimitable biological properties such as antiviral [6], antibacterial [7], antimalarial (**A**,**B**) [8], antidiabetic [9], acyl-CoA cholesterol *O*-acyl transferase (ACAT) inhibitors (**C**) [10,11], β-turn mimetics [12] and β-lactamase inhibitors (**D**) [13]. The spiro-β-lactam (**E**) serves as a precursor for the synthesis of glutamine synthetase inhibitor [14] (Fig. 1).

A number of preparative methods for spirocyclic β-lactams are available in literature. Recently, Arndtsen and co-workers [15] have synthesized spiro-β-lactams with good yields and selectivity by a carbonylative method involving multicomponent reaction (MCR) of aryl halide *viz*. iodoaryl-substituted imines, imines, CO and a palladium catalyst, $Pd(P^tBu_3)$. Koketsu and co-workers [16] utilized the direct ketene-imine cycloaddition strategy for the synthesis of C-4 seleno-spiro-β-lactams from ketenes and α-selenium substituted exocyclic imines *viz*. 2-imino-1,3-thiaselenanes with Et_3N as a base.

Tremendous efforts have been directed toward the synthesis of stable organoselenium compounds [17] that could be used as antimicrobials, antivirals, antifungals, antioxidants, antitumor, antiinflammatory and antiinfective agents, thereby initiating and maintaining substantial interest in chemists for synthesizing novel biologically active selenium derivatives. In a report by Schinazi *et al*. [18] the synthesized purine and pyrimidine 1,3-oxaselenolane nucleosides were found to be antiviral in nature, wherein, particularly the racemic cytosine and 5-flourocytosine 1,3-oxaselenolane nucleoside analogues, Se-ddC and Se-FddC, exhibited potent anti-HIV and anti-HBV activities. Chiral HPLC separation of racemic α- and β-nucleosides of Se-ddC and Se-FddC into individual (+)-α/β- and (-)-α/β-enantiomers, followed by their biological evaluation studies suggested most of the antiHIV activity to reside within the (-)-β-Se-ddC (**F**) and (-)-β-Se-FddC (**G**) isomers (Fig. 1). At this point, we thought that the combination of structural motifs of β-lactam and 1,3-oxaselenolane in a single spiro-β-lactam could be interesting in generating biologically active molecules.

Due to our continuing interest in the design of methods for the synthesis of novel C-3 functionalized azetidin-2-ones [19], we present here the application of *cis*-3-chloro-3-benzyl-

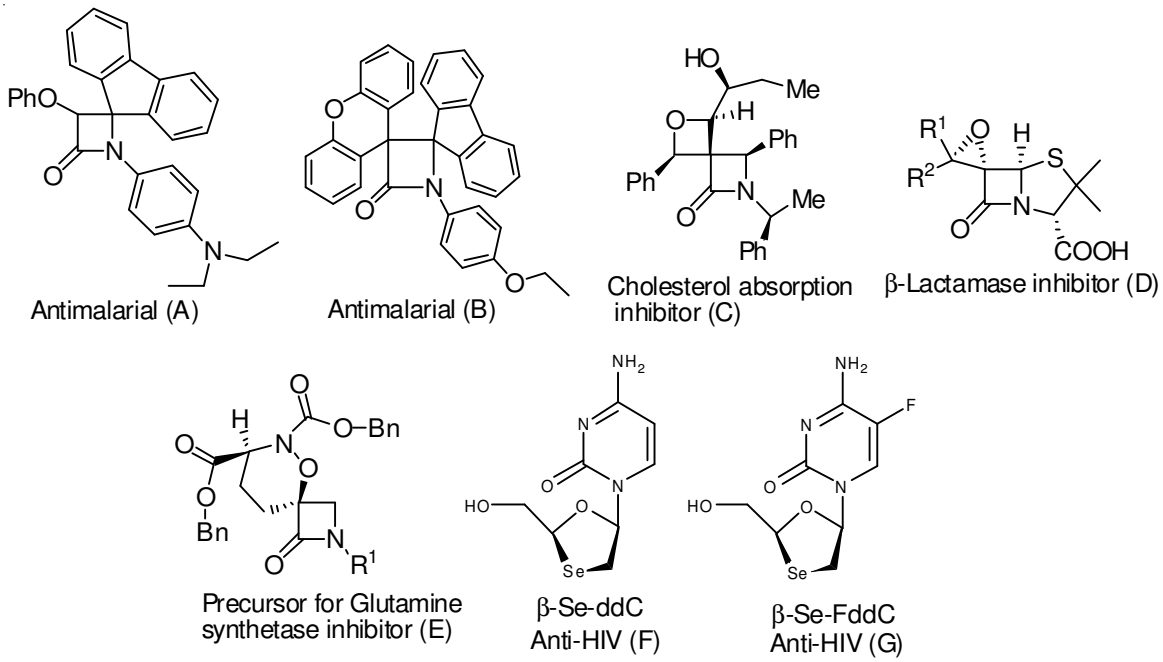


Fig. 1. Spiro-β-lactams (**A**-**E**) and 1,3-oxaselenolane nucleosides (**F**,**G**)

seleno-β-lactams for the synthesis of novel selenospiro-β-lactams. Studies of the chalcogen (selenium) in which its nucleophilic character has been utilized in the halogen-mediated (I_2, Br_2) intraselenyl cyclization reactions leading to 4-halomethyl-1,3-oxaselenolane substituted spiro-β-lactams from *cis*-3-allyloxy-3-benzylseleno-β-lactams is investigated.

EXPERIMENTAL

^{1}H NMR (300 MHz), ^{13}C NMR (100 MHz), ^{77}Se NMR (57 MHz) were recorded using BRUKER 400 MHz and JEOL 300 MHz NMR spectrometers. Chemical shift values were recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Fourier transform Infrared spectra were recorded on a Thermo scientific Nicolet iS50 (FT-IR) spectrophotometer (ν_{max} in cm^{-1}). The elemental analysis (C, H, N) was carried out using a PERKIN-ELMER 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (60-120 mesh) and eluted with ethyl acetate:hexane mixtures. Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapours. Melting points were determined with a Thomas-Hoover capillary melting point apparatus. The reactions were carried out under dry and deoxygenated nitrogen atmosphere. Allyl alcohol, bromine, iodine (CDH) and all other commercially available compounds/reagents/solvents were of reagent grade quality and used without any further purification. Dichloromethane and chloroform were dried and distilled over anhydrous phosphorus pentoxide (P_2O_5) immediately before use.

General procedure: The synthesis of compound **1** and its spectroscopic data has been described previously [20].

Synthesis of *cis*-3-allyloxy-3-benzylseleno-β-lactam (3): A mixture of allyl alcohol (**2**) (4.35 mmol), molecular sieves (3-4) Å, silica gel (1.00 g, 100-200 mesh) and anhydrous zinc chloride (0.03 mmol) in anhydrous chloroform (10 mL) was stirred for 25-30 min under a positive pressure of nitrogen, followed by the addition of a solution of *cis*-3-chloro-3-benzyl-seleno-β-lactam (**1**) (0.09 mmol) in 1 mL of chloroform. The reaction mixture was refluxed with constant stirring until complete disappearance of the starting chloro-β-lactam (**1**) was observed by TLC analysis. The reactants were filtered, washed with water (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The residue after solvent evaporation *in vacuo*, was purified by silica gel column chromatography (10 % EtOAc/hexane) to yield compound **3**.

***cis*-3-Benzylseleno-1-(4'-methoxyphenyl)-4-phenyl-3-(prop-2-enyloxy)-azetidin-2-one (3):** Pale yellow-white fluffy solid (70 %); m.p.: 86-87 °C; IR (neat, cm^{-1}): 1732 (C=C) and 1746 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24-6.70 (14H, *m*, ArH), 5.93-5.80 (1H, *m*, H_2C=C*H*-), 5.35-5.28 (1H, *m*, CH_aH$_b$O), 5.20-5.15 (1H, *m*, CH$_a$*H*$_b$O), 5.06 (1H, *s*, C4-H), 4.39-4.32 (1H, *m*, *H*$_a$H$_b$C=CH-), 4.18-4.11 (1H, *m*, H$_a$*H*$_b$C=CH-), 4.08 (1H, *d*, *J* = 11.1 Hz, C*H*$_a$H$_b$Se), 3.84 (1H, *d*, *J* = 11.1 Hz, CH$_a$*H*$_b$Se), 3.67 (3H, *s*, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 156.4, 138.4, 133.2, 133.1, 130.3, 129.1, 129.1, 128.5, 128.5, 127.5, 126.8, 119.0, 118.0, 114.4, 95.7, 67.8, 67.6, 55.5, 26.0; Anal. calcd. (%) for $C_{26}H_{25}NO_3Se$; C, 65.27; H, 5.27; N, 2.93. Found: C, 65.21; H, 5.23; N, 2.89.

Synthesis of spirocyclic β-lactams 4a,b and 5a,b: To a stirred solution of *cis*-3-allyloxy-3-benzylseleno-β-lactam (**3**) (1 mmol) in 10 mL of dry methylene chloride was added iodine/bromine (1.2 mmol) at room temperature. The mixture was allowed to stir (5-6 h). The progress of the reaction was monitored by TLC. After the completion of reaction, aqueous 5 % $Na_2S_2O_3$ was added to the reaction mixture until colouration of iodine/bromine gets dissipated. The aqueous mixture was extracted with methylene chloride (3 × 10 mL) and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and crude

product was purified by silica gel column chromatography (7 % ethyl acetate/hexane).

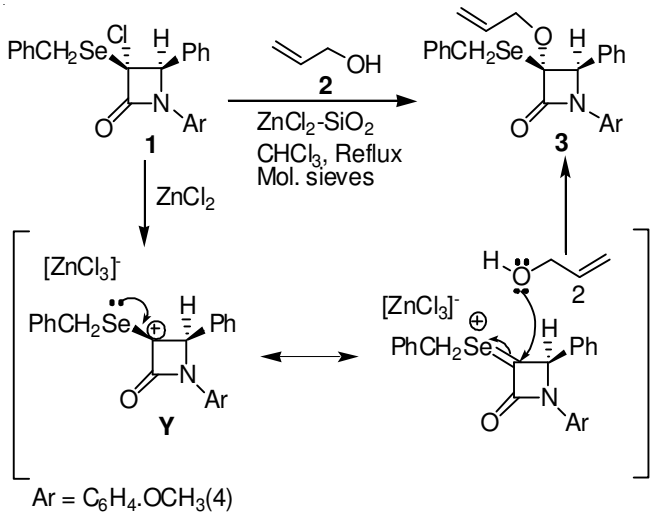
7-Iodomethyl-2-(4'-methoxyphenyl)-3-phenyl-5-oxa-8-seleno-2-aza-spiro[3.4]octan-1-one (both 7α-and 7β-isomers; 4a and 5a): White crystalline solid (68 %); m.p.: 158-159 °C; IR (neat, cm^{-1}): 1738 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, 7α-isomer) δ: 7.30-6.67 (9H, *m*, ArH), 5.06 (1H, *s*, C3-H), 4.53 (1H, *dd*, *J* = 1.5, 1.2 Hz, CH_aH_bO), 4.17-4.07 (1H, *m*, CH_aH_bO), 4.02-3.95 (1H, *m*, $CH_\beta Se$), 3.66 (3H, *s*, OCH_3), 3.47-3.43 (1H, *m*, ICH_aH_b), 3.28-3.21 (1H, *m*, ICH_aH_b); ^{1}H NMR (300 MHz, $CDCl_3$, 7β-isomer) δ: 7.30-6.67 (9H, *m*, ArH), 5.10 (1H, *s*, C3-H), 4.43 (1H, *dd*, *J* = 3.6, 3.6 Hz, CH_aH_bO), 4.39-4.35 (1H, *m*, CH_aH_bO) 4.17-4.07 (1H, *m*, $CH_\alpha Se$), 3.70-3.62 (1H, *m*, ICH_aH_b), 3.66 (3H, *s*, OCH_3), 3.28-3.21 (1H, *m*, ICH_aH_b); ^{13}C NMR (100 MHz, $CDCl_3$, both isomers) δ: 164.8, 164.3, 156.5, 136.2, 135.8, 130.2, 129.2, 129.1, 126.2, 126.1, 119.2, 119.1, 114.4, 102.5, 102.3, 78.4, 77.6, 70.0, 67.8, 55.4, 48.7, 47.5, 9.0, 8.3; ^{77}Se NMR (57 MHz, $CDCl_3$, Both isomers) δ: 449.2, 447.8; Anal. calcd. (%) for $C_{19}H_{18}NO_3ISe$; C, 44.38; H, 3.53; N, 2.72. Found: C, 44.35; H, 3.51; N, 2.69.

7-Bromomethyl-2-(4'-methoxyphenyl)-3-phenyl-5-oxa-8-seleno-2-aza-spiro[3.4]octan-1-one (both 7α-and 7β-isomers; 4b and 5b): Colourless crystalline solid (70 %); m.p.: 142-143 °C; IR (neat, cm^{-1}): 1740 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$, 7α-isomer) δ: 7.32-6.70 (9H, *m*, ArH), 5.11 (1H, *s*, C3-H), 4.53 (1H, *dd*, *J* = 1.5, 1.5 Hz, CH_aH_bO), 4.15-4.06 (1H, *m*, CH_aH_bO), 4.04-3.96 (1H, *m*, $CH_\beta Se$), 3.67 (3H, *s*, OCH_3), 3.48-3.43 (1H, *m*, $BrCH_aH_b$), 3.29-3.22 (1H, *m*, $BrCH_aH_b$); ^{1}H NMR (300 MHz, $CDCl_3$, 7β-isomer) δ: 7.32-6.70 (9H, *m*, ArH), 5.14 (1H, *s*, C3-H), 4.48 (1H, *dd*, *J* = 3.3, 3.3 Hz, CH_aH_bO), 4.41-4.35 (1H, *m*, CH_aH_bO) 4.15-4.06 (1H, *m*, $CH_\alpha Se$), 3.69-3.62 (1H, *m*, $BrCH_aH_b$), 3.67 (3H, *s*, OCH_3), 3.29-3.22 (1H, *m*, $BrCH_aH_b$); ^{13}C NMR (100 MHz, $CDCl_3$, Both isomers) δ: 164.3, 164.2, 156.6, 135.1, 134.5, 130.3, 130.1, 129.2, 129.1, 126.8, 126.6, 119.3, 119.1, 114.5, 114.4, 104.0, 103.5, 75.5, 74.9, 70.0, 68.2, 55.5, 55.2, 50.8, 49.6. 33.1, 32.9; Anal. calcd. (%) for $C_{19}H_{18}NO_3BrSe$; C, 48.84; H, 3.88; N, 3.00. Found: C, 48.80; H, 3.83; N, 2.98.

RESULTS AND DISCUSSION

In the preparation of spirocyclic adducts for linking 1,3-oxaselenolane and β-lactam subunits *via* a spiro junction, initially it was necessary to convert the chloro group of *cis*-3-chloro-3-benzylseleno-β-lactams (**1**) into an allyloxy group. Thus, the synthesis began with the known starting materials *cis*-3-chloro-3-benzylseleno-β-lactams (**1**), which were prepared according to the reported literature procedure [20]. For the synthesis of *cis*-3-allyloxy-3-benzylseleno-β-lactams (**3**), the β-lactam carbocation equivalent **1** was treated with allyl alcohol (**2**) in the presence of Lewis acid $ZnCl_2$/silica gel (100-200 mesh) in dry chloroform, under nitrogen atmosphere, at reflux temperatures by the route outlined in **Scheme-I**.

Progress of the reaction was monitored by checking TLC at regular intervals of time, which did show the formation of more polar products. Entire consumption of 3-chloro-β-lactam (**1**) on TLC was considered as the completion of the reaction. Concentration of the reaction mixture followed by its column chromatographic purification furnished pure *cis*-3-(prop-2-enyloxy)-3-benzylselenoazetidin-2-ones (**3**) as a fluffy solid.



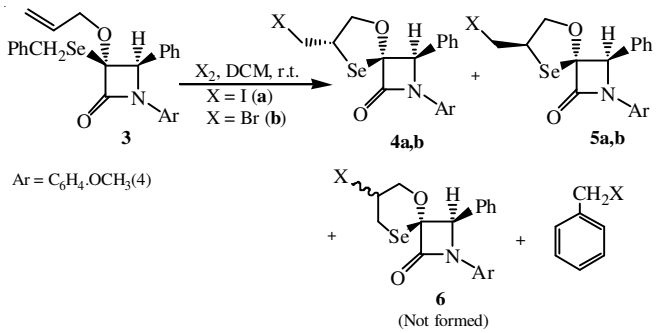
Scheme-I: Synthesis of *cis*-3-allyloxy-3-benzylseleno-β-lactams (**3**)

The results summarized above are consistent with the intervention of an intermediate carbocation **Y** formed *via* abstraction of chloro group of compound **1** by Lewis acid, $ZnCl_2$, also forming [$ZnCl_3^-$] anion (**Scheme-I**). The carbocation **Y** is well stabilized by the lone pair of electrons on selenium. Nucleophilic approach of-OH group of allyl alcohol to carbocation from the sterically less-hindered α-face results in the exclusive formation of *cis*-3-allyloxyazetidin-2-one (**3**) *via* SN^1 mechanism.

Spectral data (IR, ^{1}H and ^{13}C NMR) and elemental analysis of the product are consistent with the proposed structure. IR spectrum exhibited characteristic absorption of the β-lactam carbonyl at 1746 cm^{-1}. In the ^{1}H NMR spectrum of compound **3**, the C4-H, being slightly more upshielded, appeared as a singlet at 5.06 δ in comparison to singlet at 5.24 δ for C4-H of the starting 3-chloro-β-lactam (**1**), thereby confirming the transformation at C-3 of the azetidinone ring. ^{13}C NMR revealed a signal at 163.3 δ which could be assigned to the β-lactam carbonyl carbon. The assignment of α-stereochemistry at C-3 was tentatively assigned as *cis*, in view of single-crystal X-ray crystallographic studies of *cis*-3-benzylthio-3-methoxy-β-lactams [21].

With an objective of preparing spiroheterocycles of potential interest, we employed *cis*-3-allyloxy-3-benzylseleno-β-lactams (**3**) as substrates, which possess considerable potential for elaboration of the monocyclic β-lactam system to spirocyclic β-lactam by intramolecular cyclization reactions. Our initial studies involved the treatment of *cis*-3-allyloxy-β-lactam (**3**) with 1 eq. of I_2 in dichloromethane at room temperature under an inert atmosphere of nitrogen with continuous stirring (**Scheme-II**).

The progress of the reaction was monitored by TLC, which indicated appearance of close spots with slightly lower R_f value than the reactant. After complete consumption of compound **3** was indicated by TLC (after 5-6 h), the reaction mixture was quenched with 5 % $Na_2S_2O_3$ solution, extracted with dichloromethane and purified by means of column chromatography. The reaction resulted in the exclusive formation of a pair of diastereomeric five-membered ring spirocyclic β-lactams *viz.* 7α-iodomethyl-2-(4'-methoxyphenyl)-3-phenyl-5-oxa-8-



Scheme-II: Synthesis of spiro-β-lactams (**4a,b** and **5a,b)**

seleno-2-aza-spiro[3.4]octan-1-one (**4a**) and 7β-iodomethyl-2-(4'-methoxyphenyl)-3-phenyl-5-oxa-8-seleno-2-aza-spiro[3.4]octan-1-one (**5a**) in 68 % total yields respectively. The diastereomeric ratio *viz*. 1.1:1 of products **4a** and **5a** was determined on the basis of ^{1}H NMR analysis of the product mixture by evaluating integration at 5.06 δ and 5.10 δ for the methine proton of β-lactam ring at C-3. Compounds **4a** and **5a** have been drawn as diastereomers about 7th carbon atom in 1,3-oxaselenolane ring, respectively. However, all attempts to separate the diastereomers **4a**, **5a** were unsuccessful, both by column chromatographic purifications and subsequent crystallizations. *Albeit*, the spiro azetidinones obtained were crystalline compounds and stable. No six-membered ring spiro adducts of type compound **6** were detected in the intramolecular cyclization reaction.

The structural and stereochemical homogeneity of the diastereomers with molecular formula $C_{19}H_{18}NO_3ISe$ were confirmed by IR and NMR (^{1}H, ^{13}C, ^{57}Se) spectroscopic analysis. The amide bonds in the spiro-compounds showed carbonyl absorption at 1738 cm^{-1} thereby, indicating that β-lactam ring had remained intact after intraselenyl cyclization. In the ^{1}H NMR spectra, disappearance of a pair of doublets for the 3-benzylseleno group (PhC*H*$_2$Se-) and appearance of multiplets for-C*H*$_2$I and-C*H*Se groups confirmed the spiro products synthesis. Further, differences in the chemical shifts from 0.03 to 0.3 ppm were observable in the ^{1}H NMR spectra of the diastereomeric mixture (**4a** and **5a)**. ^{13}C decoupled NMR spectra revealed two signals at 164.3 δ and 164.8 δ, which could be assigned to the β-lactam carbonyls respectively. Further, the stereochemical assignment at the junctions (C-4 and C-7) of compounds **4a** and **5a** was made by correlating their NMR (^{1}H, ^{13}C) data with spiro-β-lactams synthesized from 3-allyloxy-3-benzylthio-β-lactams [22].

Attention was next directed to the preparation of the corresponding spiro adducts with bromine as the halogenating agent. The reaction of *cis*-3-allyloxy-3-benzylseleno-β-lactams (**3**) with bromine in dichloromethane (**Scheme-II**) led to the formation of both 7α- and 7β-epimers, **4b** and **5b**, as five-membered ring adducts exclusively, with similar diastereomeric ratio (1.1:1) as observed with iodine as halogenating agent.

The overall transformation of monocyclic unsaturated substrate **3** to the five-membered ring spiro-adducts (**4a,b** and **5a,b**; by 5-*exo-trig* cyclization) exclusively, rather to six-membered ring spiro-adducts (**6**; by 6-*endo-trig* cyclization) can be explained on the basis of the plausible mechanism discussed below (Fig. 2). An initial co-ordination of the halogen (I_2/Br_2) to olefinic bond generates the π-olefinic complex. This is followed by nucleophilic addition of selenide centre to the π-complex to form cyclic ion **L**, which is dealkylated by halide ion to produce spiro-β-lactams **4** and **5**. No six-membered spiro ring adducts **6** were isolated in these reactions, suggesting that the 5-*exo*-over 6-*endo*-regioselectivity of these alkenyl selenide ring closures is influenced by the large difference in the thermodynamic stabilities of the five-and six-membered cycloadducts, forcing the equilibrium in the direction of the more stable five-membered ring. Also, the larger size of selenium (in comparison to sulfur) makes its accommodation difficult in the bicyclic ring system of **M**, rendering it unstable and thereby, knocking out the possibility of the formation of **M** and the consecutive six-membered ring spiro adduct **6**. The plausible mechanism (Fig. 2) is in accordance with our studies for intrasulfenyl halocyclization [22] and well evident by Turos and co-workers [23].

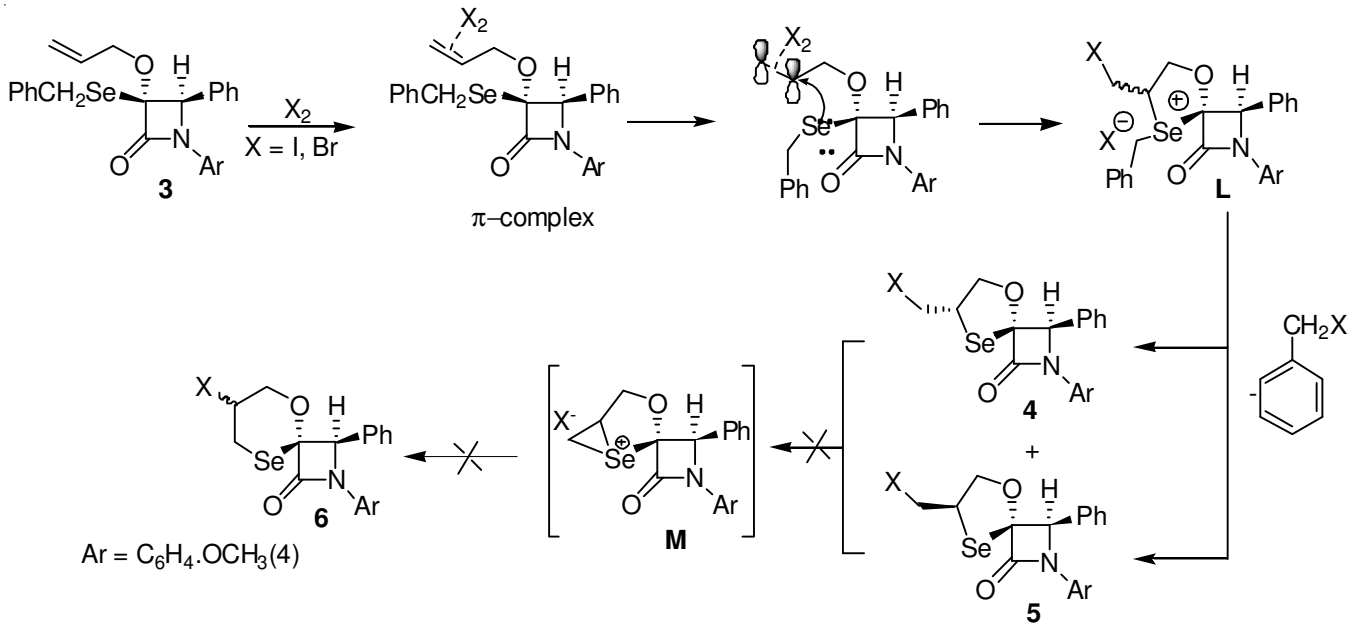


Fig. 2. Plausible mechanism for the formation of spiro-β-lactams (**4**, **5**)

Conclusion

A successful entry to novel class of spiroseleno-β-lactams has been achieved from *cis*-3-chloro-3-benzylseleno-β-lactams. The synthesis involves the exclusive formation of five-membered ring spiro adducts through intraselenyl 5-*exo-trig* cyclization. Further studies towards the biological evaluation and transformation of these to other heterospirocyclic scaffolds is under progress.

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