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Synthesis of Novel Selenapenams, Selenacephems, and Selenazepines Using a 2-(Trimethylsilyl)ethyl Protection Approach

Dinesh R. Garud,[†] Hiromune Ando,[‡] Yumiko Kawai,[†] Hideharu Ishihara,*[,†] and Mamoru Koketsu*[,†]

Department of Chemistry, Faculty of Engineering, Gifu University, Gifu-501-1193, Japan, and Division of Instrumental Analysis, Life Science Research Center, Gifu University, Gifu-501-1193, Japan

koketsu@gifu-u.ac.jp

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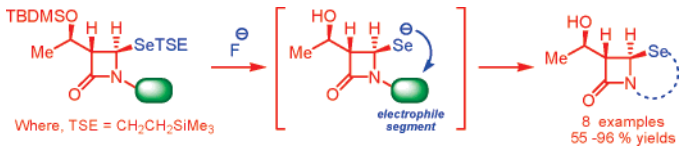
ABSTRACT



Selenapenams, selenacephems, and selenazepines were synthesized using a 2-(trimethylsilyl)ethyl (TSE) protection approach in an extremely simple way. TSE protection for selenium is used for the first time in the synthesis of selenium-containing β-lactam. Novel intramolecular cycloaddition reaction of selenium with alkynes and allenes is used in the present synthesis.

The β-lactam (2-azetidinone) skeleton is the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[1] The first β-lactam ring system was synthesized by H. Staudinger in 1907,[2] 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.[3] In recent years, interest in syntheses of compounds containing selenium has increased because of their interesting reactivities[4] and their potential biological activity. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[5] In this regard, very few reports are available in the literature for the synthesis of selenapenams or selenacephems due to difficulties involved in their preparations.[6] Previously developed radical and nucleophilic methodologies[6b−d] or an azomethine ylide strategy[6e,f] were used to synthesize the selenium analogue of β-lactam antibiotics. In each report, the yields of the target molecules were either poor or the prepared compounds possessed functionality that compromised their biological activity. Therefore, the development of a new and efficient

[†] Department of Chemistry.
[‡] Division of Instrumental Analysis.

(1) For some recent reviews on β-lactam antibiotics, see: (a) *Chemical Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.: Academic Press: New York, 1982; Vols. 1−3. (b) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbital Products*; Luckacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2, p 621. (c) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417.

(2) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *51*, 356.

(3) Clarke, H. T.; Johnson, J. R.; Robinson, R. *The Chemistry of Penicillin*; Princeton University Press: Princeton, NJ, 1949.

(4) (a) Ogawa, A.; Sonoda, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 461. (b) Ogawa, A.; Sonoda, N. *Rev. Heteroat. Chem.* **1994**, *10*, 43. (c) Guziec, F. S., Jr.; Guziec, L. J. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 6, p 587. (d) Dell, C. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon: Oxford, 1995; Vol. 5, p 565. (e) Krief, A. In *Comprehensive Organometallic Chemistry*; Abel, W. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11, p 515. (f) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999. (g) Wirth, T. *Angew. Chem.* **2000**, *112*, 342; *Angew. Chem., Int. Ed.* **2000**, *39*, 3740. (h) Schiesser, C. H. *Chem. Commun.* **2006**, 4055.

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reaction that combines several transformations in a single procedural step is an important objective. Our goal is to open efficient access to selenium-containing β-lactam antibiotics. Herein, we report our first step toward achieving this goal by demonstrating an elegant method for the synthesis of these compounds.

On the basis of the retrosynthetic disconnection (Figure 1), we felt that selenium β-lactam can be easily prepared

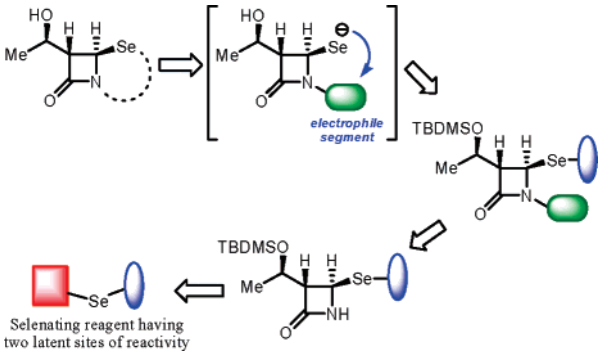
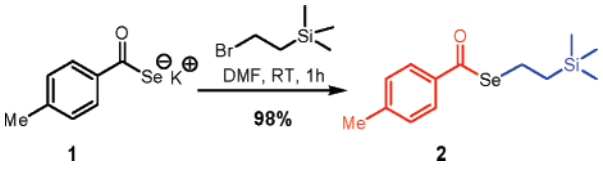


Figure 1. Retrosynthesis of selenium β-lactams.

from a selenating reagent which has two latent sites of reactivity. Recently, we reported a novel method for the seleno-glycosidation using *p*-methylselenobenzoate **1**.[7] The method features the in situ production of glycosyl selenolate anion from the corresponding *p*-toluylselenoglycoside resulting from the chemoselective cleavage of the C−Se bond by piperazine. The glycosyl selenolate anion can react with various electrophilic coupling partners in high yields, with complete retention of stereochemistry.

Inspired by the chemistry of this method, we have designed a novel selenating reagent **2** as depicted in Scheme 1. Treatment of potassium *p*-methylselenobenzoate with (2-

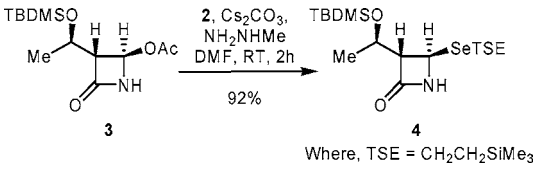
Scheme 1. Synthesis of New Selenating Reagent



bromoethyl)trimethylsilane afforded a new selenating reagent **2**. This reagent has two latent reactive sites, that is, carbonyl carbon and tetraalkylated silicon. The former should be susceptible to the nucleophilic attack by amine, thereby producing a 2-(trimethylsilyl)ethaneselenolate[8] 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. Further, we envisaged that the TSE moiety would be readily cleaved by the chemoselective attack of silicon by the fluorinate anion. The resultant selenolate could then annulate with the electrophilic moiety.

The reaction with commercially available, optically pure, 4-acetoxyazetidinone **3** was studied to find applications for the newly synthesized selenating reagent. The reaction of the selenating reagent with 4-acetoxyazetidinone **3** afforded the previously unknown key intermediate TSE-protected seleno derivative **4**, with complete retention of configuration in 92% yield (Scheme 2). The relative configuration of the

Scheme 2. Synthesis of Key Intermediate



key intermediate **4** was concluded based on coupling constant between the protons at C-3 and C-4 ($J_{H(C3)-H(C4)} = 2.3$ Hz). This is in agreement with those of similar compounds in the literature.[9]

We first examined propargyl bromide in the N-alkylation reaction (Table 1, **5a** and **5b**). The key intermediate **4** was reacted with propargyl bromide under alkaline conditions using LHMDS or NaH to afford the alkyne compound **5a** in 75 or 52% yields, respectively (entry 1). The sodium hydride reaction resulted in the formation of allenamide **5b** in 12% yield (entry 2), whereas with LHMDS reaction, the alkyne **5a** was the sole product. Having established a standard protocol, we examined the scope of this process. The key intermediate **4** was reacted under alkaline conditions (LH-

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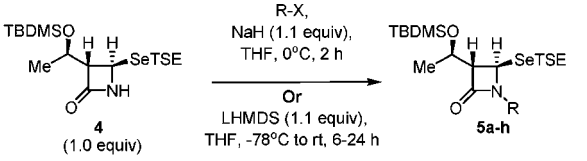
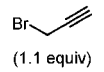
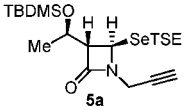
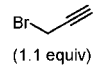
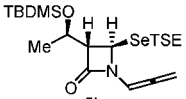
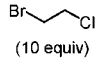
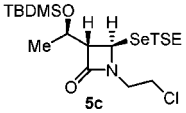
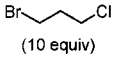
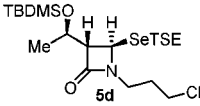
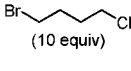
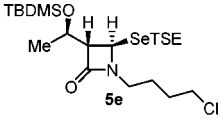
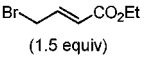
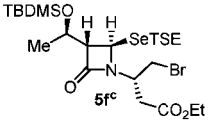
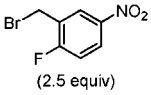
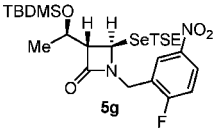
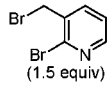
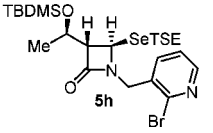
(7) (a) Kawai, Y.; Ando, H.; Ozeki, H.; Koketsu, M.; Ishihara, H. *Org. Lett.* **2005**, *7*, 4653. (b) Nanami, M.; Ando, H.; Kawai, Y.; Koketsu, M.; Ishihara, H. *Tetrahedron Lett.* **2007**, *48*, 1113.

(8) 2-(Trimethylsilyl)ethaneselenol was only once prepared from its diselenide and used for the preparation of ammonium aromatic diselenoates. See: Tani, K.; Murai, T.; Kato, S. *J. Am. Chem. Soc.* **2002**, *124*, 5960.

(9) (a) Linder, M. R.; Podlech, J. *Org. Lett.* **2001**, *3*, 1849. (b) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873. (c) Liang, Y.; Jiao, L.; Zhang, S.; Xu, J. *J. Org. Chem.* **2005**, *70*, 334.

Table 1. N-Alkylation Reaction of the Key Intermediate **4**[a]



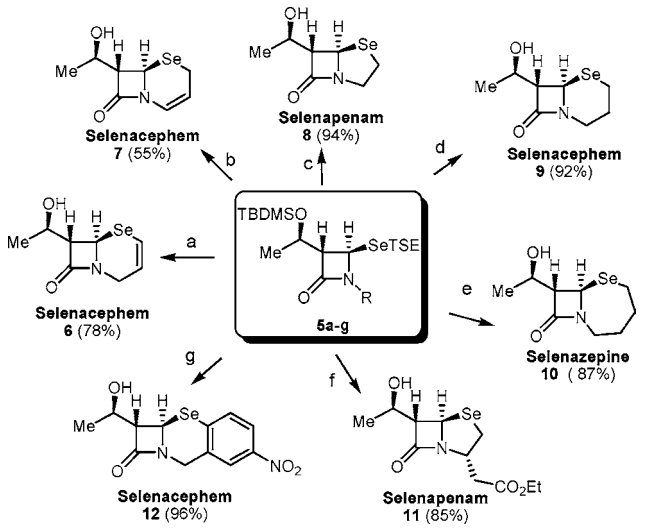
entry	R-X (equiv)	base	product	yield (%)
1	 (1.1 equiv)	LHMDS	 **5a**	75
2	 (1.1 equiv)	NaH	 **5b**	12[b]
3	 (10 equiv)	LHMDS	 **5c**	62
4	 (10 equiv)	LHMDS	 **5d**	72
5	 (10 equiv)	LHMDS	 **5e**	77
6	 (1.5 equiv)	NaH	 **5f**[c]	32
7	 (2.5 equiv)	LHMDS	 **5g**	82
8	 (1.5 equiv)	NaH	 **5h**	67

[a] All reactions except **5f** gave a single isomer as determined by ^{1}H NMR spectroscopic analysis. [b] **5a** was also formed in 52% yield. [c] Isolated as mixture of two diastereomers in a10:1 ratio. THF = tetrahydrofuran.

MDS) with an excess of 1-bromo-2-chloroethane (10 equiv) to afford alkyl halide intermediate **5c** (entry 3). In this reaction, the use of excess 1-bromo-2-chloroethane was important to suppress the formation of a dimer as a byproduct. Similarly, the reaction of the intermediate **4** with excess of 1-bromo-3-chloropropane or 1-bromo-4-chlorobutane gave alkyl halide **5d** or **5e**, respectively (entries 4 and 5). Reaction of **4** with ethyl 4-bromocrotonate using NaH as a base afforded **5f** as a mixture of two diastereomers (10:1) (entry 6).[10] Regioselective alkylation of **4** with 2-fluoro-5-nitrobenzylbromide[11] or 2-bromo-3-bromomethylpyridine[12] was also successful, producing aryl intermediate **5g** in 82% yield or **5h** in 67% yield (entries 7 and 8).

The TSE-selenyl precursors, in hand, were next applied to TBAF-initiated key annulation to deliver selenacephems,

Scheme 3. Synthesis of Novel Selenacephems, Selenapenams, and Selenazepines[a]



[a] All reactions gave a single isomer as determined by ^{1}H NMR spectroscopic analysis. Reaction conditions: For **a**-**g**) TBAF (5 equiv), AcOH (2.2 equiv), **5a** to **5g** (1 equiv), THF, RT, 1h.

selenapenams, or selenazepine frames (Scheme 3). Thus, the treatment of alkyne **5a** with TBAF led to formation of the selenium anion, and subsequent attack at the alkynyl carbon afforded the required selenacephem **6** by intramolecular cycloaddition reaction. Allenes are a versatile class of organic compounds that feature numerous patterns of reactivity.[13] Allenamides are a subclass of allenes that have recently received much attention in the synthetic community.[14] To our delight, treatment of allenamide **5b** with TBAF also resulted in the formation of corresponding selenacephem **7**. This represents the first example for the intramolecular cycloaddition reaction of selenium with alkynes and allenes that results in the formation of a six-membered ring. Selenacephem **7** is unstable and easily decomposes even when stored in the freezer for 1 week.

Given the potential of this process to access the core ring systems of β-lactam targets containing six-membered rings, the reactions of **5c** and **5d** with TBAF were examined. Treatment of **5c** with TBAF afforded the required selenapenam **8**. The treatment of **5d** with TBAF afforded selenacephems **9**.

The synthesis of seven-membered selenium heterocycles has been found to be very difficult. To the best of our knowledge, there are only two reports on the preparation of seven-membered selenium-containing heterocycles, that is, 1,3-selenazepines.[15] Treatment of **5e** with TBAF resulted in

(10) The use of LHMDS as base was found to be less selective, giving a mixture of two diastereomers in a 1:1.5 ratio.

(11) Clement, E. C.; Carlier, P. R. *Tetrahedron Lett.* **2005**, *46*, 3633.
(12) Rebek, J., Jr.; Costello, T.; Wattley, R. *J. Am. Chem. Soc.* **1985**, *107*, 7481.
(13) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984.
(14) For reviews on allenamides, see: (a) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (b) Saalfrank, R. W.; Lurz, C. J. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; p 3093.

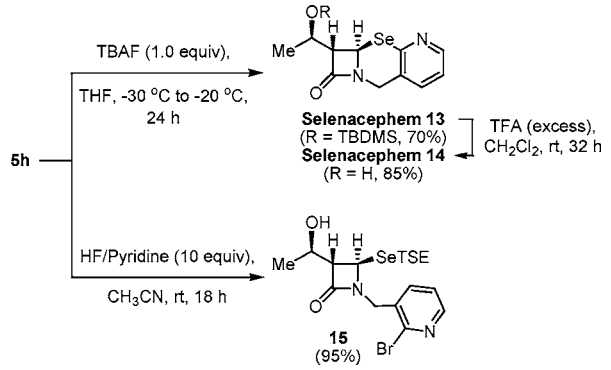
the formation of selenazepine **10**. Our method allows a new approach for the synthesis of seven-membered selenium-containing heterocycles.

Treatment of **5f** with TBAF afforded the required selenapenam **11** as a single diastereomer. This approach allows the synthesis of different substituted selenapenams.[16]

Finally, with the aim of exploring other biologically important selenium heterocycles, we considered the feasibility of preparing a benzo-fused system, and the treatment of **5g** with TBAF afforded selenacephem **12**. In this reaction, there is no need to add additional catalyst. The nitro group in the selenacephem **12** is advantageous for the functionalization of selenacephem for structure−activity relationship studies.

During the formation of pyridine-fused ring systems, we have also attempted to retain the TBDMS group on the side chain to facilitate the chromatographic purification of the cyclized outcome (Scheme 4). According to our expectation,

Scheme 4. Synthesis of Selenacephem by Chemoselective Deprotection[a]



[a] All reactions gave a single isomer as determined by ^{1}H NMR spectroscopic analysis.

the annulation of **5h** promoted by the minimized amount of TBAF (1.0 equiv) has yielded a TBDMS-protected pyridine-fused ring system (i.e., selenacephem **13**).[17] TBDMS group within selenacephem **13** was able to cleave by the action of TFA to afford selenacephem **14**. Additionally, the exposure of **5h** to HF/pyridine in CH_3CN did not cleave TSE on selenium but TBDMS on oxygen, yielding **15** in 95% yield. This chemoselectivity between silyl groups is first observed in our study.

(15) (a) Sommen, G. L.; Linden, A.; Heimgartner, H. *Tetrahedron Lett.* **2005**, *46*, 6723. (b) Nurbaev, K. I.; Zakhidov, K. A.; Oripov, E. O.; Smiev, R. A.; Shakhidoyatov, K. M. *Uzb. Khim. Zh.* **1996**, *1*−*2*, 96; *Chem. Abstr.* **1996**, *126*, 47303.

(16) Recently, Buynak et al. found that the homologue of sulbactam has 10-fold better activity against a class C β-lactamase than does sulbactam itself. See: Buynak, J. D.; Ghadachanda, V. R.; Vogeti, L.; Zhang, H.; Chen, H. *J. Org. Chem.* **2005**, *70*, 4510.

(17) The reaction time can be shortened by the use of a base such as DIEA, but reaction gave slightly lower yield.

Next, we focused our attention on spectroscopic methods for the determination of structure of these products. ^{1}H, ^{13}C, and ^{77}Se NMR, COSY, HMQC, HMBC, MS, HRMS, and IR spectroscopy allowed us to assign the correct structure. Furthermore, the X-ray diffraction analysis of selenacephems **6** and **9** and selenapenam **8** provided the correct stereochemistry (i.e., *R*, *S*, *R*) and structure of the final products (Figure 2).[18]

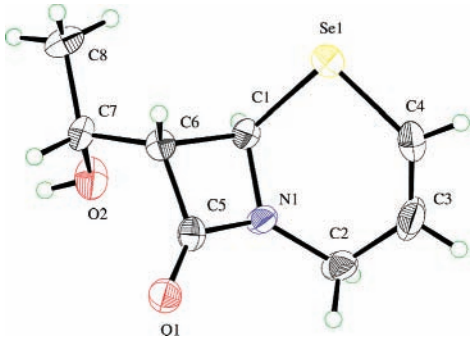


Figure 2. ORTEP diagram (50% thermal ellipsoids) of selenacephem **6**. Selected bond lengths (Å) and angles (°): Se(1)−C(4) 1.881(10), Se(1)−C(1) 1.943(7), C(1)−N(1) 1.425(9), N(1)−C(5) 1.341(9), C(1)−C(6) 1.553(9), C(5)−C(6) 1.526(11), C(5)−O(1) 1.223(9); C(1)−Se(1)−C(4) 97.0(4), N(1)−C(1)−Se(1) 113.3(5), N(1)−C(1)−C(6) 88.2(5), C(6)−C(1)−Se(1) 117.6(5), C(5)−N(1)−C(1) 95.7(6).

In conclusion, we have developed a pivotal approach to the variety of selenium-containing β-lactams, featuring 2-(trimethylsilyl)ethyl selenating reagent **2**. The compounds prepared during this study are expected to exhibit interesting biological properties. Further expansion of current strategies is in progress.

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Supporting Information Available: Experimental details for the synthesis and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Crystallographic data for selenacephem **6**, selenapenam **8**, and selenacephem **9** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-619550 (**6**), CCDC-619551 (**8**), and CCDC-619552 (**9**)). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.