ORGANIC LETTERS

2008
Vol. 10, No. 15
3319−3322

Synthesis of 3-Selena-1-dethiacephems and Selenazepines via Iodocyclization

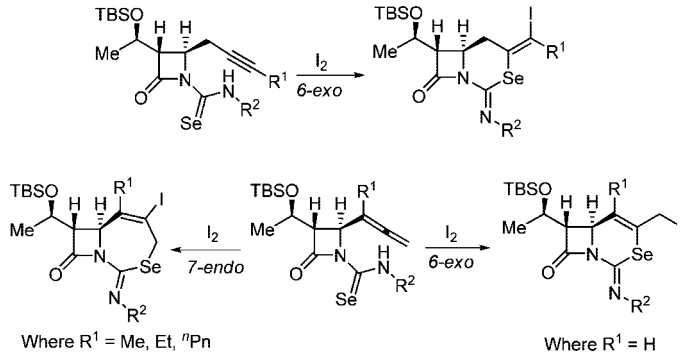
Dinesh R. Garud[†] and Mamoru Koketsu[‡,*]

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

Received May 23, 2008

ABSTRACT



A convenient approach to synthesize novel selenium-β-lactams, 3-selena-1-dethiacephems and selenazepines, was accomplished via the regioselective iodocyclization reaction. The substituent of allenyl moieties dramatically influenced the regiochemical outcome in the iodocyclization of allene-selenourea derivatives.

In recent years, interest in synthesis of selenium-containing compounds has increased because of their interesting reactivities[1] and their potential biological activities. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[2] The β-lactam (2-azetidinone) skeleton is the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[3] There is considerable interest in the modification of the ring system of β-lactams by placing a heteroatom at the 2 or 3 position. In this regard, several groups have published the synthesis of β-lactams differing from the penam and cephem systems.[4] However, it is surprising to note that only a few reports are available in the literature for the synthesis of selenium-

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

(1) (a) Krief, A. In *Comprehensive Organometallic Chemistry*; Abel, W. W., ; Stone, F. G. A., ; Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 11, p 515. (b) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University Press: U.K., 1999. (c) Wirth, T. *Angew. Chem.* **2000**, *112*, 342; *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3740. (d) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., ; Ramsden, C. A., ; Scriven, F. V., ; Taylor, J. K., Eds.; Elsevier: Oxford, 2008.

(2) (a) Mehta, S.; Andrews, J. S.; Johnson, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783. (b) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125. (c) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2003**, *125*, 13455. (d) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255. (e) Nishina, A.; Sekiguchi, A.; Fukumoto, R.; Koketsu, M.; Furukawa, S. *Biochem. Biophys. Res. Commun.* **2007**, *352*, 360.

(3) For some reviews on β-lactam antibiotics, see: (a) *Chemistry and 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 Microbial Products*; Luckacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2, pp 621. (c) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417.

(4) For papers and reviews, see:(a) Sakurai, O.; Ogiku, T.; Takahashi, M.; Hayashi, M.; Yamanaka, T.; Horikawa, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 7889. (b) Anada, M.; Watanabe, N. *Chem. Commun.* **1998**, 1517. (c) Hwu, J. R.; Tsay, S.-C.; Hakimelahi, S. *J. Med. Chem.* **1998**, *41*, 4681. (d) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921. (e) Brabandt, W. V.; Vanwalleghem, M.; D'hooghe, M.; Kimpe, N. D. *J. Org. Chem.* **2006**, *71*, 7083.

10.1021/ol801010y CCC: $40.75
Published on Web 07/04/2008

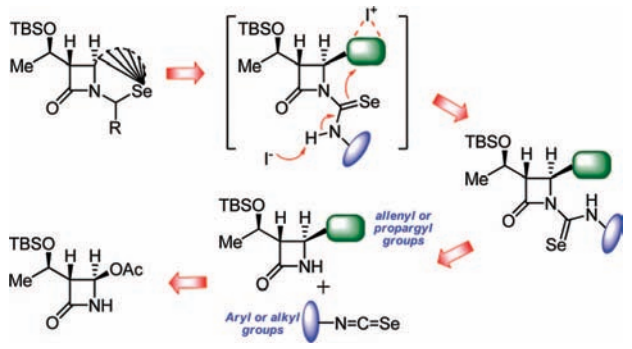


Figure 1. Retrosynthesis of selenium-β-lactam.

containing β-lactams because of difficulties involved in their preparations.[5] Only one report is available in the literature for the preparation of isodethiaselenapenam and isodethiaselenacephems by Hakimelahi et al. with limited biological activity.[6] The prepared compounds possessed functionality that compromised their biological activity. To the best of our knowledge, the 3-selena-1-dethiacephem has never been described in the literature thus far. Recently, we have reported a TSE-protection approach for the synthesis of a variety of selenium-β-lactams.[7] In continuation of the above investigations, we recently decided to search for a new procedure that would allow us to synthesize selenium-containing β-lactams having a selenium atom at the 3 or 4 position. 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.[8] In contrast, only a few examples for the synthesis of selenium hererocycles via electrophilic cyclization have been reported in the literature,[9] and to the best of our knowledge, the electrophilic cyclization of alkyne-selenoureas or allene-selenoureas has never been described thus far. We describe herein, for the first time, an approach to place the selenium to the 3 or 4 position in the β-lactam ring system by a regioselective iodocyclization reaction of alkyne- and allene-selenoureas resulting in the synthesis of selenium-β-lactams.

(5) (a) Alpegiani, M.; Bedeschi, A.; Perrone, E.; Franceschi, G. *Tetrahedron Lett.* **1986**, *27*, 3041. (b) Brown, G. A.; Anderson, K. M.; Murray, M.; Gallagher, T.; Hales, N. J. *Tetrahedron* **2000**, *56*, 5579. (c) Brown, G. A.; Anderson, K. M.; Large, J. M.; Planchenault, D.; Urban, D.; Hales, N. J.; Gallagher, T. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1897. (d) Carland, M. W.; Martin, R. L.; Schiesser, C. H. *Tetrahedron Lett.* **2001**, *42*, 4737. (e) Carland, M. W.; Martin, R. L.; Schiesser, C. H. *Org. Biomol. Chem.* **2004**, *2*, 2612.

(6) Hwu, J. R.; Lai, L.-L.; Hakimelahi, G. H.; Davari, H. *Helv. Chim. Acta* **1994**, *77*, 1037.

(7) Garud, D. R.; Ando, H.; Kawai, Y.; Ishihara, H.; Koketsu, M. *Org. Lett.* **2007**, *9*, 4455.

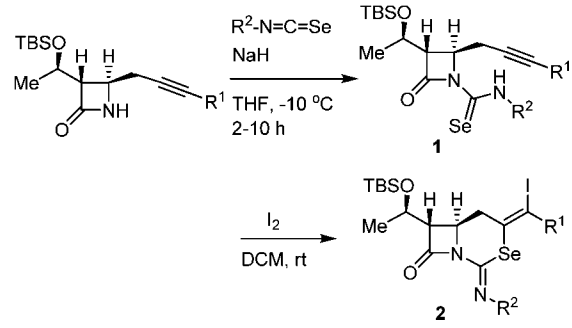
(8) For a two-part review of iodocyclization, see:(a) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Int.* **1997**, *2*, 33. (b) ibid, p 63. (c) Martins da Silva, F.; Jones, J., Jr.; de Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393.

(9) (a) Bui, C. T.; Flynn, B. L. *J. Comb. Chem.* **2006**, *8*, 163. (b) Koketsu, M.; Kiyokuni, T.; Sakai, T.; Ando, H.; Ishihara, H. *Chem. Lett.* **2006**, *35*, 626. (c) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307. (d) Alves, D.; Luchese, C.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2007**, *72*, 6726. (e) Garud, D. R.; Makimura, M.; Ando, H.; Ishihara, H.; Koketsu, M. *Tetrahedron Lett.* **2007**, *48*, 7764.

Our retrosynthetic disconnection approach (Figure 1) suggests that a variety of selenium-β-lactams can be easily prepared from allene- or alkyne-selenoureas via an iodocyclization reaction.

The key starting materials, alkyne-selenoureas **1**, for our approach were readily prepared by the *N*-alkylation reaction of the corresponding previously known propargyl-azetidinones[10] with a wide variety of isoselenocyanates[11] under basic conditions (Table 1, entries **1a**−**1h**).

Table 1. Synthesis of 3-Selena-1-dethiacephem **2** via Iodocyclization[a]



entry	R^1	R^2	yield (%)	time (h)	yield (%)
1	H	*p*-ClC_6H_4	97 (**1a**)	6.5	92 (**2a**)
2	H	C_6H_5	96 (**1b**)	10	91 (**2b**)
3	H	*p*-$CH_3C_6H_4$	95 (**1c**)	11	88 (**2c**)
4	H	2-naphthyl	92 (**1d**)	8	93 (**2d**)
5	H	benzyl	93 (**1e**)	11	82 (**2e**)
6	H	*cyclo*-C_6H_{11}	85 (**1f**)	11.5	84 (**2f**)
7	C_6H_5	*p*-ClC_6H_4	98 (**1g**)	6.5	95 (**2g**)
8	C_6H_5	*p*-$CH_3C_6H_4$	99 (**1h**)	10	92 (**2h**)

[a] All iodocyclization reactions were conducted at room temperature with 1.25 equiv of I_2 in CH_2Cl_2.

First, we examined the reaction of β-alkyne-selenourea (**1a**) with 1.05 equiv of iodine or NIS in THF at room temperature. We found that the reaction was highly dependent on the type of electrophile used. With NIS, we obtained the desired 3-selena-1-dethiacephem **2a** along with 3-aza-4-selenoxo-1-dethiacephem **3a** and 3-aza-4-oxo-1-dethiacephem **4a** (Figure 2, R^1 = H, R^2 = *p*-ClC_6H_4). The 3-aza-

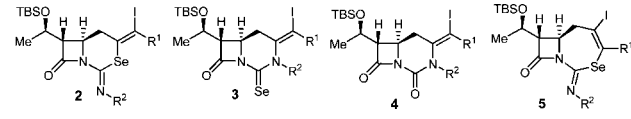


Figure 2. Iodocyclization reaction products of **1**.

4-oxo-1-dethiacephem **4a** was formed by the decomposition

(10) Propargyl- or allenyl-azetidinones were prepared according to the literature. See: Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840.

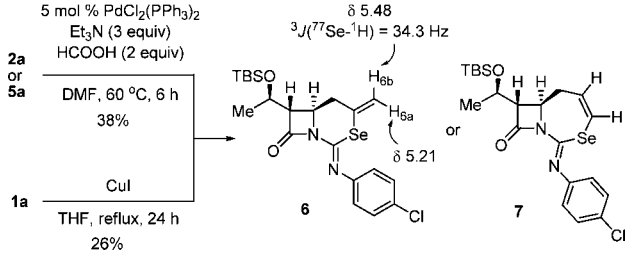
(11) See the review:Garud, D. R.; Koketsu, M.; Ishihara, H. *Molecules* **2007**, *12*, 504.

of **3a**. However, when the reaction was carried out using 1.05 equiv of iodine, the desired product **2a** was exclusively produced in good isolated yield (84%) with only a trace amount of byproduct **3a** (as indicated by TLC). To improve the yield of cyclization, different reaction conditions were then screened (see Supporting Information). CH_2Cl_2 was found to be the best solvent for the cyclization reaction. Furthermore, the reaction was heavily influenced by the amount of iodine added, and the best result was obtained when 1.25 equiv of iodine was used (92% yield). The structures of **2a**, **3a**, and **4a** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra. There was no seven-membered ring product **5a** detected in all cases (Figure 2).

On the basis of the above results, the iodocyclization of other alkyne-selenoureas **1** with 1.25 equiv of iodine was conducted in CH_2Cl_2 at room temperature, and the results are summarized in Table 1. A variety of 3-selena-1-dethiacephems **2** were obtained in good to excellent yields. The nature of the R^2 group on the selenourea had very little effect on the reaction rate or product yields. Aryl-substituted selenoureas (entries 1−4) gave slightly higher yield than alkyl-substituted selenoureas (entries 5 and 6). The aryl substitution at alkynes was also well accommodated and afforded the cyclized products **2g** and **2h** in excellent yields (entries 7 and 8).

The reaction shows high regioselectivity for six-membered ring selenacephems **2**. Seven-membered ring products **5** were never detected under these reaction conditions. The structures of **2** were confirmed by spectroscopic methods (see Supporting Information) and chemically. Thus, the palladium-catalyzed triethylammonium formate reduction of the iodide **2a**[12] provided only compound **6** but not compound **7**. The same product **6** can be alternatively obtained by the intramolecular cyclization of **1a** (Scheme 1).[13] It was relatively easy

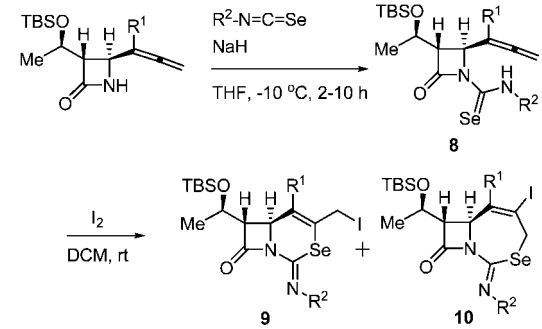
Scheme 1



to distinguish the isomers **6** and **7** by an NMR study. Recently, we found that selenium shows strong coupling with the *trans* proton of the exocyclic double bond, whereas similar coupling with the *cis* proton was not observed.[9e,14] We found the same observation in compound **6**; i.e., selenium shows coupling with the *trans* proton H_{6b}, $^3J(^{77}Se-^1H) = 34.3$ Hz exclusively (Scheme 1). Thus, this important spectral feature confirms our current findings. We anticipate that this spectral feature may become an important tool for confirming the structure of selenium-containing compounds.

Next, we turned our attention toward the iodocyclization of allene-selenoureas **8** (Table 2). Allenes are a versatile class

Table 2. Synthesis of 3-Selena-1-dethiacephems and Selenazepines via Iodocyclization[a]



entry	R^1	R^2	yield (%)	time (h)	yield (%)
1	H	C_6H_5	61% (**8a**)	3	67 (**9a**)
2	H	p-$CH_3C_6H_4$	61% (**8b**)	3.5	69 (**9b**)
3	H	p-ClC_6H_4	67% (**8c**)	4	65 (**9c**)
4	H	2-naphthyl	36% (**8d**)	4	69 (**9d**)
5	H	benzyl	45% (**8e**)	8	61 (**9e**)
6	CH_3	p-ClC_6H_4	85% (**8f**)	6	55 (**10f**) + 7[b]
7	CH_3	p-$CH_3C_6H_4$	83% (**8g**)	8	62 (**10g**) + 8[b]
8	C_2H_5	p-ClC_6H_4	93% (**8h**)	7	41 (**10h**) + 10[c]
9	C_2H_5	p-$CH_3C_6H_4$	96% (**8i**)	10	69 (**10i**)
10	n-C_5H_{11}	p-ClC_6H_4	92% (**8j**)	10	50 (**10j**)
11	n-C_5H_{11}	p-$CH_3C_6H_4$	96% (**8k**)	10	52 (**10k**)
12	1-naphthyl	p-ClC_6H_4	96% (**8l**)	2 days	complex mixture

[a] All iodocyclization reactions were conducted at room temperature with 1.25 equiv of I_2 in CH_2Cl_2. [b] Isodethiaselenapenam was isolated as an inseperable mixture. [c] Isodethiaselenapenam was isolated in 10% yields.

of organic compounds that feature numerous patterns of reactivities.[15] Allenamides are a subclass of allenes that have recently received much attention in the synthetic community.[16] The key intermediates, allene-selenoureas **8**, for the iodocyclization reaction were readily prepared by the reaction of previously known allenyl-azetidinones[10] with isoselenocyanates under basic conditions in good to excellent yields (Table 2, entries **8a**−**8l**).

We first examined the iodocyclization reaction of unsubstituted allene-selenoureas using iodine under standard conditions (Table 2). The iodine reaction resulted in the formation of 3-selena-1-dethiacephems **9** as the major product with traces of the five-membered product as confirmed by TLC (Table 2, entries 1−5).[17] Good yields were

(12) (a) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541. (b) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119.

(13) The reaction time can be shortened by the use of base such as DBU, but reaction gave the product in slightly lower yield.

(14) Koketsu, M.; Sakai, T.; Kiyokuni, T.; Garud, D. R.; Ando, H.; Ishihara, H. *Heterocycles* **2006**, *68*, 1607.

(15) Schuster, H. E.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984.

(16) For reviews on allenamides, see: (a) 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. (b) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.

(17) Iodocyclization reaction of **9c** using NIS resulted in the formation of multiple spots.

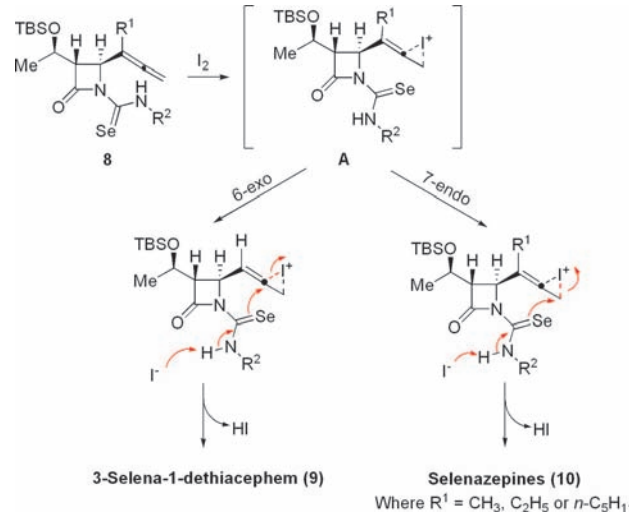
obtained in all cases, irrespective of the nature of the substituent present on the selenourea group (entries 1−5). Seven-membered ring products were not detected under these reaction conditions. Thus, these reaction conditions show high regioselectivity toward six-membered rings.

To further test the scope of the cyclization, alleneselenoureas bearing alkyl or aryl groups at the allenyl position are examined with iodine (Table 2, entries 6−12). We are pleased to find that regiochemistry in the iodocyclization reaction is affected by the nature of the R^1 group at the allenyl position. The reaction of methyl-substituted alleneselenoureas **8f** and **8g** with 1.25 equiv of iodine afforded selenazepines **10f** and **10g** along with corresponding five-membered isodethiaselenapenams as inseperable mixtures (entries 6 and 7). The reaction of ethyl-substituted alleneselenourea **8h** gave **10h** in 41% yield and the corresponding isodethiaselenapem in 10% yield (entry 8). The reaction of the alleneselenoureas **8i**−**8k** afforded the selenazepines **10i**−**10k** as the major product with trace amounts of five-membered product as confirmed by TLC (entries 9−11),[18] whereas the cyclization reaction of 1-naphthyl-substituted alleneselenourea **8l** gave a complex mixture (entry 12). The synthesis of seven-membered selenium heterocycles has been found to be very difficult. To the best of our knowledge, there are only three reports[7,19] on the preparation of seven-membered selenium-containing heterocycles, that is, 1,3-selenazepines. Our iodocyclization method provides a novel approach for the synthesis of seven-membered selenium-containing heterocycles.

A plausible mechanism is proposed for the formation of **9** and **10** as illustrated in Scheme 2. The reaction of **8** with iodine gave iodonium **A** and released an iodine anion at the same time. With the assistance of the iodine anion, intramolecular nucleophilic attack of selenium in the selenourea group on the center carbon of allene (when $R^1 = H$) in the favored *exo* mode affords the corresponding cyclization product **9**, whereas attack of selenium in the selenourea group on the terminal carbon of allene (when $R^1 = CH_3$, C_2H_5, or *n*-C_5H_{11}) in the favored *endo* mode affords the corresponding cyclization product **10** accompanied by the simultaneous elimination of hydrogen iodide.

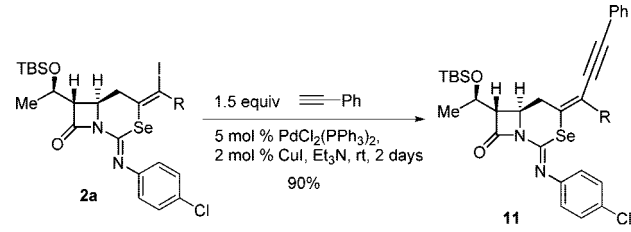
The presence of iodine in the 3-selena-1-dethiacephem **2a** allows further structural elaboration, most notably using palladium-catalyzed coupling reactions. For example, when compound **2a** was exposed to Sonogashira coupling conditions[20] with phenylacetylene, the corresponding coupling

Scheme 2



product **11** was isolated in excellent yield (Scheme 3). The imine group in the 3-selena-1-dethiacephem **2**, **6**, and **9** and selenazepine **10** is advantageous for further functionalization.

Scheme 3



In conclusion, we have developed a pivotal approach to prepare a variety of selenium-containing β-lactams, using an iodocyclization reaction with high regioselectivity. The regiochemical outcome of the iodocyclization of alleneselenourea was found to depend on the nature of the substituent on allenyl moieties. Further expansion of current strategies is in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Science Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 20590005) to which we are grateful.

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

OL801010Y

(18) The reaction of ethyl-substituted alleneselenourea **8i** using 2.0 equiv of NIS afforded two different products of six-membered 3-selena-1-dethiacephems (see Supporting Information).

(19) (a) 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. (b) Sommen, G. L.; Linden, A.; Heimgartner, H. *Tetrahedron Lett.* **2005**, *46*, 6723.

(20) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *23*, 4467. (b) Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., ; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 521.