Tetrahedron Letters 51 (2010) 5395–5398

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective electrophilic cyclization of *o*-ethynylbenzyl phenyl selenides to (*Z*)-1-methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium salts ☆

Haruki Sashida [a,*], Shoko Nakabayashi [a], Hirokazu Suzuki [a], Mamoru Kaname [a], Mao Minoura [b]

[a] *Faculty of Pharmaceutical Sciences, Hokuriku University, Kanagawa-machi, Kanazawa 920-1181, Japan*
[b] *Department of Chemistry, School of Science, Kitasato University, 1-15-1 Kitasato, Minami-Ku, Sagamihara, Kanagawa 252-0373, Japan*

ARTICLE INFO

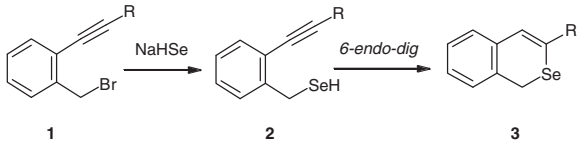
Article history:
Received 21 June 2010
Revised 23 July 2010
Accepted 29 July 2010
Available online 4 August 2010

ABSTRACT

o-Ethynylbenzyl phenyl selenides regioselectively reacted with trifluoromethanesulfonic acid to afford the (*Z*)-1-methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium salts as the major products during the *5-exo-dig* mode cyclization in good yields together with minor *E* isomers. The structure of the major (*Z*)-selenophenium salt was established by the single crystal X-ray crystallographic analysis using a *tert*-butyl derivative.

The electrophilic intramolecular cyclization of disubstituted acetylenic compounds has been extremely effective for the synthesis of a wide variety of five-membered nitrogen-,[2] oxygen-[3–5], or sulfur-containing[5–8] heterocycles, because of their common occurrence in nature and their significant biological activity including pharmaceutical use. Benzyl *o*-ethynylphenyl sulfides react with iodine to produce 3-iodobenzo[*b*]thiophenes[8a] during the *5-endo-dig* iodocyclization by removing a benzyl moiety. Larock and Yue[7] also reported the synthesis of benzo[*b*]thiophenes having an electrophilic substitution at the C-3 position by a related process involving the electrocyclization of the *o*-1-ethynylphenyl methyl sulfides. Similarly, the electrophilic intramolecular cyclization of the methyl phenyl selenides with an ethynyl group on the benzene ring has been reported; the 2,3-disubstituted benzo[*b*]selenophenes were obtained.[9] Kitamura and co-workers[5,6] have described that the intramolecular addition of *o*-1-ethynylphenyl phenyl sulfides with electrophiles such as perchloric acid, tetrafluoroboric acid, bromine, and benzenesulfenyl chloride produced the 1-phenyl-1-benzo[*b*]thiophenium salts. A variety of 3-substituted isocoumarins and α-pyrones, six-membered heterocycles, have been obtained via the iodocyclization of the carboxylic acid derivatives.[10]

On the other hand, we have previously succeeded in the preparations of the 1*H*-isoselenochromenes **3**, six-membered heterocycles with a bivalent selenium atom, by the successive *6-endo-dig* intramolecular cyclization of the *o*-ethynylbenzyl selenols **2**, which are easily prepared from the benzyl bromides **1** and NaHSe (Scheme 1).[11] The isoselenochromenes **3** were transformed into the 2-benzoselenopyrylium salts, six-membered aromatic heterocycles containing a selenium cation. As an extension of our ongoing



Scheme 1.

works[12,13] in which we succeeded in preparing the various types of the chalcogen-containing heterocycles based on the intramolecular ring-closure reaction of the chalcogenols into an acetylene moiety, we now report that the electrophilic cyclization using the *o*-ethynylbenzyl phenyl selenides, in which the hydrogen atom of the benzyl selenol is replaced by a phenyl group, and trifluoromethanesulfonic acid (TfOH) provides a highly regioselective *5-exo-dig* mode method for the preparation of the 1-methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]-selenophenium salts.

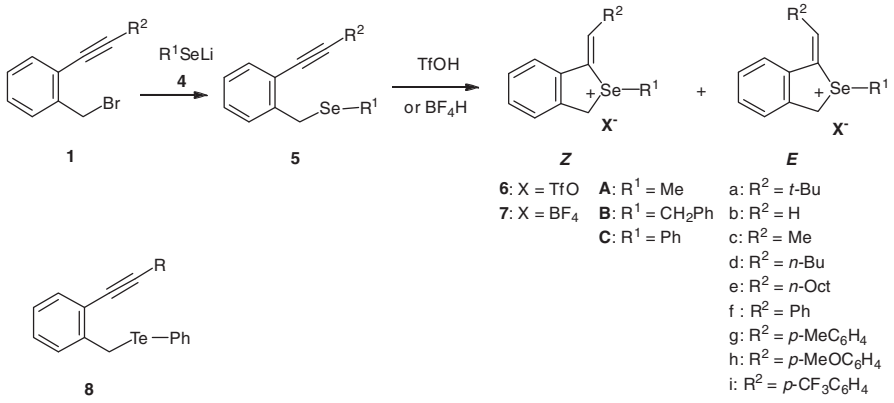
The key starting materials, the *o*-ethynylbenzyl methyl selenides **5A**, benzyl *o*-ethynylbenzyl selenides **5B,** and *o*-ethynylbenzyl phenyl selenides **5C**, were readily synthesized by the coupling reaction of the benzyl bromides **1**[11] with the corresponding lithium selenolate **4A–C**, which were freshly generated from elemental selenium and the alkyl or phenyllithium in dry THF in good yields, respectively.

The reaction of the methyl selenide **5Aa** with 1.2 equiv of TfOH in dry CH_2Cl_2 at 0 °C gave a complex mixture (Table 1, entry 1). No characterized products were also obtained by the reaction of the benzyl selenide **5Ba** with TfOH (entry 2). However, the treatment of the *o*-ethynylbenzyl phenyl selenides **5C** with 1.2 equiv of TfOH under the same conditions resulted in the regio- and stereoselective *5-exo-dig* mode cyclization to give the (*Z*)-1-methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium trifluoromethanesulfonates (triflates) (*Z*)-**6C** as major products, together with the *E*

☆ See Ref. 1.

* Corresponding author. Tel.: +81 76 229 6211; fax: +81 76 229 2781.
E-mail address: h-sashida@hokuriku-u.ac.jp (H. Sashida).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.07.160



Scheme 2.

Table 1
1-Methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium salts **6**, **7**

Entry	R^1	R^2	Acid	Product	Yield[a] (%)	Ratio *Z*/*E*[b]
1	Me	*t*-Bu	TfOH	**6Aa**	0[c]	—
2	CH_2Ph	*t*-Bu	TfOH	**6Ba**	0[c]	—
3	Ph	*t*-Bu	TfOH	**6Ca**	82	4:1
4	Ph	*t*-Bu	BF_4H	**7Ca**	76	5:3
5	Ph	H	TfOH	**6Cb**	77	—
6	Ph	Me	TfOH	**6Cc**	76	4:1
7	Ph	*n*-Bu	TfOH	**6Cd**	71	4:1
8	Ph	*n*-Oct	TfOH	**6Ce**	82	4:1
9	Ph	Ph	TfOH	**6Cf**	78	1:0
10	Ph	*p*-MeC_6H_4	TfOH	**6Cg**	92	1:0
11	Ph	*p*-$MeOC_6H_4$	TfOH	**6Ch**	78	1:0
12	Ph	*p*-$CF_3C_6H_4$	TfOH	**6Ci**	73	1:0

[a] Isolated yield.
[b] Determined by ^1H NMR spectra.
[c] Decomposed.

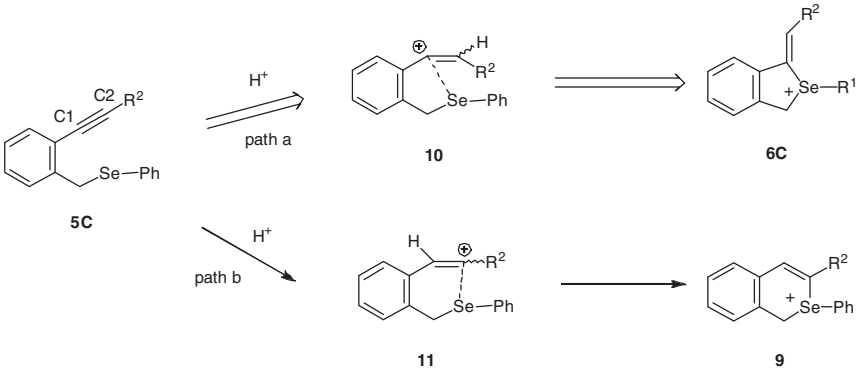
derivatives (*E*)-**6C**[14] as shown in Scheme 2. These results are summarized in Table 1. The reaction of *o*-(3,3-dimethylbutynyl)benzyl phenyl selenide **5Ca** with TfOH afforded the (*Z*)-1-(2,2-dimethylpropylidene)-2-phenyl-1,3-dihydro-1*H*-benzoselenophenium triflate (*Z*)-**6Ca** and *E* derivative (*E*)-**6Ca** in 82% yield as a mixture of diastereomers; the former is the major product (entry 3). When tetrafloroboric acid (HBF_4) was used instead of TfOH as the electrophile, the *5-exo-dig* mode cyclization reaction proceeded to give the corresponding (*Z*)-benzoselenophenium tetrafluoroborate (*Z*)-**7Ca** as the major product together with the *E* minor product (*E*)-**7Ca** in 76% yield (entry 4). The treatment of the unsubstituted substrate **5Cb** with TfOH furnished the 1-methylideneselenonium salt **6Cb** in 77% yield as the sole crystalline product (entry 5). The *o*-ethynylbenzyl pheny selenides **5Cc**–**e** having an alkyl group at the sp-carbon atom of the ethynyl moiety cyclized to produce the diastereomeric mixtures of the (*Z*)-1-methylidene-1*H*-benzoselenophenium salts (*Z*)-**6Cc**, (*Z*)-**6Cd**, and (*Z*)-**6Ce** and (*E*)-isomers (*E*)-**6Cc**, (*E*)-**6Cd**, and (*E*)-**6Ce** by the reaction with TfOH under the same conditions in 76%, 71%, and 82% yields, respectively; the formers were also the major products in these cases (entries 6–8). On the contrary, the phenyl *o*-(2-phenylethynyl)benzyl selenides **5Cf** regio- and stereoselectively reacted with TfOH to produce the single (*Z*)-1-benzylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium salt (*Z*)-**6Cf** in 78% yield; the *E* isomer (*E*)-**6Cf** was not obtained. Similarly, the reaction of the selenides **5Cg–i** having a functional group, such as methyl, methoxy, and trifluoromethyl, at the *p*-position of the phenyl group, also regio- and stereoselectively proceeded to afford only the (*Z*)-benzoselenophenium salts (*Z*)-**6Cg**, (*Z*)-**6Ch**, and (*Z*)-**6Ci** in 73–92% yields in spite of the nature of the impressive electronic effect on the benzene ring (entries 9–12). This distinction between an alkyl group and an aryl group at the ethynyl moiety with respect to the selectivity ratio of the geometry of the olefin is not totally understood. However, the significant differences of success or failure in these electrophilic cyclizations of the *o*-ethynylbenzyl selenides **5A**–**C** with TfOH according to whether or not the Se-substituent is a phenyl group may be explained by the difference of the Se-C bond energy dependent on the bond length. The Se–Csp^2 distance in the Se-phenyl group for **5C** is clearly shorter than that of the Se–Csp^3 in the Se-methyl and -benzyl groups for **5A** and **5B**, respectively. Thus, the expected Se-methyl **6A** and Se-benzyl products **6B** were probably decomposed because of their thermal instability under the reaction conditions. The Te–Csp^2 distance in the Te-phenyl group for **8** is also longer than that of the corresponding selenium compound.

Therefore, no desired electrophilic cyclization telluronium salts from **8** were obtained; the starting material was gradually decomposed. When other electrophiles such as $HClO_4$, Br_2, I_2, and PhSeCl instead of TfOH were allowed to react with the benzyl phenyl selenides **5C**, these cyclization reactions were unsuccessful, and the starting material was recovered.

In this electrophilic cyclization, there are two possible types of ring closure modes: *5-exo* mode (path a) and *6-endo* mode (path b), but no *6-endo* mode cyclization products **9**[13b] were actually obtained as shown in Scheme 3. In order to explain this remarkable result in the cyclization mode of the phenyl selenides **5C**, the HOMO coefficients of the C1 and C2 positions of the triple bond have been calculated by the frontier orbitals theory using the GAUSSIAN 03 (B3LYP/STO-3G) and are listed in Table 2. As can be seen from Table 2, the HOMO electron density values of the C2 position are higher than that of the C1 position for all substituents at the triple bond. It is evident that the protonation of the C2 position is favored than that of the C1 position generating the cationic intermediate **10**. Thus, the five-membered product **6C** was formed through the attack of the lone pair on the selenium atom (path a).

Furthermore, the calculated Se···C1 distance of 1.96 Å for the intermediate **10** is much shorter than that for **11** (2.97 Å); the former indicates the approximate value of the normal Se–Csp^3 bond (2.12 Å). The results of the experiments are in good agreement with the calculation values.

The structures of these benzoselenophenium salts **6**, **7** were elucidated from their ^1H and ^{13}C NMR spectra and elemental analyses and also from single crystal X-ray studies[15] in the case of the (*Z*)-1-(2,2-dimethyl-propylidene)-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]



Scheme 3.

Table 2

Compd	R^2	HOMO electron density	
		C1	C2
5Ca	*t*-Bu	0.0271	0.0405
5Cb	H	0.0169	0.0192
5Cc	Me	0.0248	0.0357
5Cd	*n*-Bu	0.0257	0.0427
5Ce	*n*-Oct	0.0231	0.0422
5Cf	Ph	0.0265	0.0413
5Cg	*p*-MeC_6H_4	0.0280	0.0422
5Ch	*p*-$MeOC_6H_4$	0.0506	0.0574
5Ci	*p*-$CF_3C_6H_4$	0.0229	0.0387

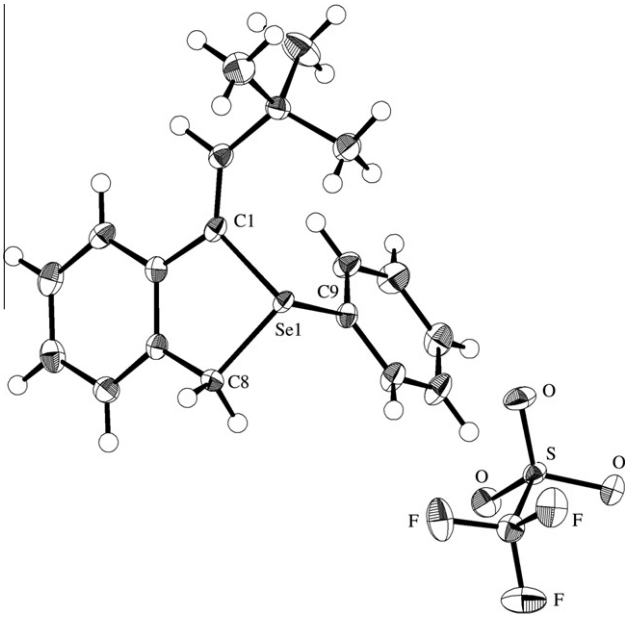


Figure 1. An ORTEP drawing of (*Z*)-**6Ca** with thermal ellipsoid plot (50% probability). Selected bond lengths (Å) and angles (°); Se1–C1 1.941(2), Se1–C9 1.953(2), Se1–C8 1.957(2), C1–Se1–C9 98.68(9), C1–Se1–C8 89.64(8), C9–Se1–C8 97.14(9).

selenophenium salt (*Z*)-**6Ca** (Fig. 1). In the crystal, the cationic selenium center of (*Z*)-**6Ca** is weakly coordinated by oxygen atoms of triflate anions, the distances from Se to O atoms are 2.967 and 3.047 Å, respectively.

In conclusion, we have shown that the employment of the *o*-ethynylbenzyl phenyl selenides in the *5-exo-dig* electrophilic cyclization reaction can provide the regioselective production of 1-methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]selenophenium salts at room temperature. Further reactions and applications are now in progress to extend the case of the methodology for the preparation of more complex system structures and sulfur analogs.

Acknowledgments

A part of this work was supported by a Grant-in-Aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 19590022). The authors wish to thank Miss Yohko Atoh (Hokuriku University) for her technical assistance.

References and notes

1. This Letter constitutes Part. 32 in the 'Studies on Tellurium-Containing Heterocycles', Part. 31: Sashida, H.; Chao, P.; Kaname, M.; Minoura, M. *Synthesis*, in press, doi:10.1055/s-0030-1258171. Art ID F07110SS.
2. Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409.
3. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432–1434.
4. Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409–2412.
5. Kitamura, T.; Takeuchi, T.; Kawasato, H.; Kobayashi, S.; Taniguchi, H. *Tetrahedron Lett.* **1989**, *30*, 7445–7446.
6. Kitamura, T.; Takeuchi, T.; Miyaji, M.; Kawasato, H.; Taniguchi, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1907–1911.
7. (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011–6013; (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905–1909.
8. (a) Flynn, B.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651–654; (b) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 572–576.
9. Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307–2312.
10. Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401–7404.
11. (a) Sashida, H.; Ohyanagi, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2123–2124; (b) Sashida, H.; Ohyanagi *Heterocycles* **1999**, *51*, 17–20; (c) Sashida, H.; Ohyanagi, K.; Minoura, M.; Akiba, K.-y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 606–612.
12. Reviews: (a) Sashida, H. *Rev. Heteroatom Chem.* **2000**, *22*, 59–78; (b) Sashida, H. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 355–362; (c) Sashida, H. *Mini-Rev. Org. Chem.* **2007**, *4*, 105–114; (d) Sashida, H.; Minoura, M. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 714–723.
13. Recent works: (a) Sashida, H.; Nakayama, A.; Kaname, M. *Synthesis* **2008**, 3229–3236; (b) Sashida, H.; Nakabayashi, S.; Kaname, M.; Minoura, M. *Heterocycles* **2010**, *80*, 1339–1352; (c) Sashida, H.; Satoh, H.; Ohyanagi, K.; Kaname, M. *Molecules* **2010**, *15*, 1466–1472; (d) Sashida, H.; Kaname, M.; Ohyanagi, K. *Heterocycles*, in press, doi:10.3987/COM-10-S(E)15.; (e) Sashida, H.; Kaname, M.; Nakayama, A.; Suzuki, H.; Minoura, M. *Tetrahedron* **2010**, *66*, 5149–5157.
14. A typical procedure for electrophilic cyclization of *o*-ethynylbenzyl phenyl selenide **5Ca** with TfOH is as follows: A mixture of *o*-ethynylbenzylphenylselenide **1** (328 mg, 1 mmol) and TfOH (180 mg, 1.2 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 12–15 h under argon atmosphere. Ether (50 mL) was added to the mixture, and then the resulting residual solid was triturated, collected by filtration, and washed with ether. The crude solid was recrystallized from chloroform–ether to give a mixture of diastereomers in 82% yield. The *Z* and *E* salts could be separated by recrystallization from $CHCl_3$–hexane and are stable under air at ambient temperature.

Major product: (*Z*)-1-Methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*] selenophenium triflate (*Z*)-**6Ca**, colorless prisms, mp 155–156 °C. ^{1}H NMR ($CDCl_3$) δ: 1.26 (9H, s, *t*-Bu), 4.74 and 5.54 (each 1H, d, J = 16.0 Hz, 3-H_2), 7.09 (1H, s, 1′-H), 7.39–7.72 (9H, m, Ph-H). ^{13}C NMR ($CDCl_3$) δ: 29.8 (q), 36.1 (s), 51.8 (t), 120.7 (q_F), 122.9 (d), 127.3 (d), 128.9 (s), 129.2 (s), 129.2 (d), 129.4 (d), 130.9 (d), 131.3 (d), 133.1 (d), 134.2 (s), 137.7 (s), 148.4 (d). IR (KBr) (cm^{-1}): 1259, 1222, 1169 (SO_3). Anal. Calcd for $C_{20}H_{21}O_3F_3SSe$: C, 50.32; H, 4.43. Found: C, 50.29; H, 4.42.

Minor product: (*E*)-1-Methylidene-2-phenyl-1,3-dihydro-1*H*-benzo[*c*]-selenophenium triflate (*E*)-**6Ca**, colorless prisms, mp 142–143 °C. ^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s, *t*-Bu), 4.68 and 5.53 (each 1H, d, J = 15.8 Hz, 3-H_2), 6.84 (1H, s, 1′-H), 7.34–7.89 (9H, m, Ph-H). ^{13}C NMR ($CDCl_3$) δ: 29.7 (q), 36.1 (s), 49.1 (t), 120.7 (q_F), 128.1 (s), 128.2 (d), 128.6 (d), 128.8 (d), 129.0 (d), 130.7 (d), 130.9 (d), 132.7 (d), 134.36 (s), 134.43 (s), 139.2 (s), 155.7 (d).
IR (KBr) (cm^{-1}): 1281, 1275, 1155 (SO_3). Anal. Calcd for $C_{20}H_{21}O_3F_3SSe$: C, 50.32; H, 4.43. Found: C, 50.26; H, 4.46.

15. Single crystals of (*Z*)-**6Ca** were obtained from solutions of *n*-hexane/dichloromethane after slow evaporation of the solvent at room temperature. Diffraction data were collected on a Bruker Apex-II CCD diffractometer equipped with a graphite monochromated MoKa radiation source (l = 0.71073 Å). The structures were solved by direct methods (SHELXS-97),[16] and refined by full-matrix least-square methods on *F*2 for all reflections (SHELXL-97)[17] with all non-hydrogen atoms anisotropic and all hydrogen atoms isotropic. For (*Z*)-**6Ca**, the structure analysis is based on 4628 observed reflections with $I > 2.00\,s(I)$ and 260 variable parameters; colorless prisms, 196 K, monoclinic, space group $P2_1/n$, a = 12.386(12) Å, b = 8.570(5) Å, c = 19.326(13) Å, b = 98.560(3)°, V = 2029(3) Å^3, Z = 4, R = 0.0292, R_w = 0.0698, *GOF* = 1.040. CCDC-(*Z*)-**6Ca** for (*Z*)-**6Ca** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.
16. Sheldrick, G. M. SHELXS-97, Program for Crystal Structure Solution, Universität Göttingen, 1997.
17. Sheldrick, G. M. SHELXL-97, Program for Crystal Structure Refinement, Universität Göttingen, 1997.