Research Article

Journal of Physical Organic Chemistry

Received: 14 February 2010, Revised: 25 March 2010, Accepted: 6 April 2010, Published online in Wiley Online Library: 16 June 2010

(wileyonlinelibrary.com) DOI 10.1002/poc.1729

Reaction of selenium and tellurium halides with propargyl alcohols. The regio- and stereoselectivity of addition to the triple bond†

Samuel Braverman[a]*, Marina Cherkinsky[a], Ranjan Jana[a], Yuliya Kalendar[a] and Milon Sprecher[a]

A convenient method to incorporate selenium into an organic molecule is reported. Various aspects of the reaction of $SeCl_2$ with propargyl alcohols, i.e., identity of reacting functionality, regiospecificity, and stereospecificity, differ from expectations based on known reactions of these alcohols with SCl_2. Selenium dihalides undergo smooth 1,2-addition to the triple bond of various propargylic alcohols resulting in the formation of the corresponding functionalized divinyl selenides in high yields and with complete regio- and stereospecificity. Of special mechanistic interest is the *syn*-addition and anti-Markovnikov orientation observed in all cases. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: alkynes; divinyl selenides; electrophilic addition; regioselectivity; selenium dichloride; stereoselectivity

INTRODUCTION

The field of sigmatropic rearrangements of allylic and propargylic esters of sulfur acids at various oxidation states has proven to be a rich source of synthetically valuable and mechanistically intriguing reactions, often yielding novel and surprising products.[1–4] Some of the best and most productive examples are the reactions of propargylic alcohols with sulfur dichloride and sulfur monochloride. The former results in the formation of the appropriate sulfoxylates **1** followed by tandem double [2,3]sigmatropic rearrangement and cyclization of the generated diallenyl sulfone **2** via a diradical intermediate to thiophene dioxide derivatives **3** (Scheme 1).[5] This reaction was used by us as a model for the cycloaromatization of various π and heteroatom bridged diallenes.[6–9] More recently, this cyclization has also been used as a model for the design of a new class of DNA cleaving molecules, which could mimic the anti-tumor activity of the naturally occurring enediynes.[10,11] This activity is attributed to a cyclized diradical intermediate. The reactions of propargylic alcohols with sulfur monochloride result in the formation of dialkoxy disulfide esters.[12] The latter undergo facile multiple sigmatropic rearrangements and cyclization to yield novel products related to the naturally occurring zwiebelanes.[13]

Due to the distinct characteristic features of the organoselenium compounds in organic synthesis[14] as well as in biological systems[15] on the one hand, and our past work on the reaction of electrophilic sulfur reagents such as SCl_2 and S_2Cl_2 with hydroxyalkynes, on the other, we decided to examine the reactivity of the corresponding selenium halides with such substrates. We were surprised to discover that the various aspects of the reaction of $SeCl_2$ with propargyl alcohols, i.e., chemoselectivity, regiospecificity and stereospecificity, differ from expectations based on known reactions of these alcohols with SCl_2. Here we present the complete results of the continuing investigation, partly reported in a preliminary communication.[16]

EXPERIMENTAL

Materials and methods

The THF solution of selenium dichloride was prepared by the known procedure[17] and used immediately. All solvents and reagents were obtained from Aldrich or Fluka and used without further purification with the following exception: THF was distilled from sodium benzophenone dianion just before use and chloroform was distilled from P_2O_5. All reactions were carried out under dry argon atmosphere using oven-dried glassware. Reagents and solvents were handled by using standard syringe–septum cap techniques. Column chromatography was performed with Merck silica gel 60 (230–400 mesh), and TLC was run on precoated Merck silica gel plates 60 F_{254}. Preparative thin layer chromatography was carried out in glass sheets precoated with Merck silica gel 60 F_{254} (0.5 mm). All new compounds have satisfactory analytical and spectroscopic data.

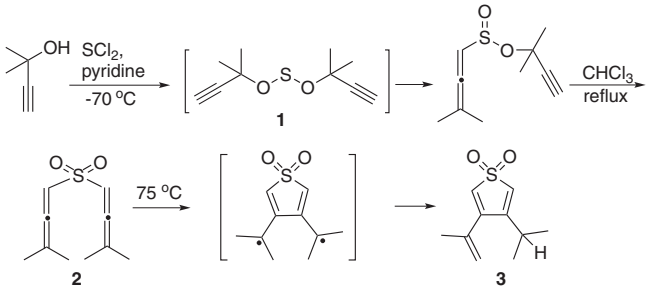
Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FTIR instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200, DPX-300 or DMX-600 spectrometers in either $CDCl_3$ or other deuterated solvents, using TMS as an internal standard. Chemical shifts are reported in δ units, and coupling constants in Hertz. COSY and NOSY experiments have been carried out in order to assign ^{1}H and ^{13}C spectra and confirmed the structures of new compounds. Mass spectra were

* *Correspondence to: S. Braverman, Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel.*
E-mail: bravers@mail.biu.ac.il

a *S. Braverman, M. Cherkinsky, R. Jana, Y. Kalendar, M. Sprecher*
Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel

† *This article is published in Journal of Physical Organic Chemistry as a special issue on Twelfth European Symposium on Organic Reactivity, edited by Amnon Stanger, Zvi Rappoport, and Marie-Françoise Ruasse.*

Journal of Physical Organic Chemistry



Scheme 1. Reaction of propargyl alcohols with SCl_2. Tandem sigmatropic rearrangements and cyclizations of dipropargylic sulfoxylates

obtained on Auto flex Tof/Tof Bruker (Germany) MALDI (matrix assisted laser desorbtion ionization) instrument with graphite matrix. High-resolution mass spectra were obtained on a VG-Fison Autospec instrument.

General procedure for the preparation of divinyl selenides (and diselenides) from selenium dichloride and propargyl alcohols

The THF solution of selenium dichloride (1 mmol) prepared by the known procedure[17] was added dropwise to a solution of the corresponding propargyl alcohol (2 mmol) in dry THF (2 ml) at 0 °C. Then the reaction mixture was stirred at room temperature for 0.5–2 h. After the completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (20 ml) and washed with water (5 ml) and brine (2 × 5 ml). The organic layer was dried over $MgSO_4$. After the evaporation of the solvent, the crude product was purified by column chromatography on silica gel with hexanes-EtOAc, 4:1 as eluent. Whenever possible, by-product diselenides were chromatographically separated from their selenide counterpart, collecting the fractions with larger Rf values.

Analytical and spectroscopic data for representative compounds:

(2Z,2′Z)-2,2′-selenobis(3-chloroprop-2-en-1-ol) (**4a**): Viscous liquid, IR (neat) 3453 (broad), 2972, 1571, 1368, 1169, 1129, 980 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.62 (bs, 2H, OH), 4.46 (d, 4H, J = 1.1 Hz), 6.55 (t, 2H, J = 1.1 Hz); ^{13}C NMR (150 MHz): δ 60.9 (CH_2), 122.2 (CH, $^2J_{C,Se}$ = 22.6 Hz), 132.8 (C, $^1J_{C,Se}$ = 112.6 Hz); HRMS: *m/z* calcd for $C_6H_8Cl_2O_2^{78}Se$: 259.9074; found: 259. 9058.

(2Z,2′Z)-2,2′-selenobis(3-chlorobut-2-en-1-ol) (**4b**): Solid, m.p. 56–58 °C; IR (KBr) 3324 (broad), 2976, 1606, 1455, 1015 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 2.40 (t, 6H, J = 0.9 Hz), 3.67 (bs, 2H), 4.41 (q, 4H, J = 0.9 Hz); ^{13}C NMR (150 MHz): δ 26.6 (CH_3), 63.5 (CH_2), 126.5 (=CCH_2, $^1J_{C,Se}$ = 112.3 Hz), 134.0 (=CCl, $^2J_{C,Se}$ = 15.9 Hz); HRMS: *m/z* calcd for $C_8H_{12}Cl_2O_2^{80}Se$: 289.9380; found: 289.9358.

(3Z,3′Z)-3,3′-diselanediylbis(4-chloro-2-methylbut-3-en-2-ol **(8a):** Yellowish solid, yield 6%, m. p. 88–89 °C; ^1H NMR (600 MHz, $CDCl_3$): δ 1.64 (s, 12H), 2.70 (bs, 2H), 6.17 (s, 2H); ^{13}C NMR (150 MHz): δ 28.22 (CH_3), 74.9 (C), 113.0 (CH), 139.5 (C=, $^1J_{C,Se}$ = 132.4 Hz); HRMS: *m/z* calcd for $C_{10}H_{16}^{37}Cl_2O_2^{78}Se_2$: ($M^+$), 397.8814; found: 397.8816; Anal. Calcd C, 30.25; H, 4.06; found C, 30.29; H, 3.88.

(3Z,3′Z)-3,3′-selenobis(4-chlorobut-3-en-1-ol) (**5**)

Colorless oil, yield 52.6%. IR (neat): 3437 (broad), 3066, 2961, 2915, 1722, 1605, 1416, 1293, 1037, 952, 779 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$), δ (ppm): 2.05 (2H, br), 2.76 (4H, td, J = 6.4, 0.9 Hz), 3.83 (4H, t, J = 6.4 Hz), 6.5 (2H, t, J = 0.9 Hz). ^{13}H NMR (175 MHz, $CDCl_3$), δ (ppm): 36.1 (C-2), 60.2 (C-1), 122.1 (CH=, $^2J_{C,Se}$ = 22.5 Hz), 129.2 (C=, $^1J_{C,Se}$ = 109.7 Hz). HRMS Calcd. for $C_8H_{12}Cl_2O_2^{80}Se$ 289.9380, found 289.9385.

4-chloro-3-(2-hydroxypropan-2-yl)-5,5-dimethyl-5H-1,2-oxaselenole 2-oxide (**6**)

White solid, mp 175–177 °C; yield 15%. IR (neat): 2981, 1653, 1360, 1170, 1035, 852, 676 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$), δ (ppm): 1.51 (3H, s), 1.62 (3H, s), 1.68 (3H, s), 1.75 (3H, s), 5.20 (1H, br). ^{13}H NMR (175 MHz, $CDCl_3$), δ (ppm): 28.1 (CH_3-C-5), 28.5 (CH_3-C-OH), 29.3 (CH_3-C-OH), 30.4 (CH_3-C-5), 72.5 (C-OH), 98.8 (C-5, $^2J_{C,Se}$ = 13.2 Hz), 141.8 (C-4), 152.7 (C-3, $^1J_{C,Se}$ = 119.2 Hz). HRMS Calcd. for $C_8H_{14}ClO_3^{80}Se$ (MH^+) 272.9797, found 272.9793.

General procedure for the preparation of divinyl selenides 4j-l from selenium dibromide and propargyl alcohols

The $CHCl_3$ solution of selenium dibromide (2 mmol) prepared from metallic selenium (0,158 g, 2 mmol) and molecular bromine (0.1 mL, 2 mmol)[18] was added dropwise to a solution of the corresponding propargyl alcohol (4 mmol) in dry $CHCl_3$ (5 ml) at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred at room temperature for 0.75–1.5 h. After the completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane (20 ml) and washed with water (5 ml) and brine (2 × 5 ml). The organic layer was dried over $MgSO_4$. After the evaporation of the solvent, the crude product was purified by column chromatography on silica gel (hexane-EtOAc, 4:1).

Analytical and spectroscopic data for representative compounds:

(3Z,3′Z)-3,3′-selenobis(4-bromo-2-methylbut-3-en-2-ol) (**4k**)

Colorless solid, yield 85%, mp 96 °C; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.62 (s, 12H), 2.71 (s, broad, 2H), 6.43 (s, 2H). ^{13}C NMR (75 MHz): δ 28.5 (CH_3), 75.1 (C), 103.2 (CH=), 144.3 (C). HRMS Calcd. for $C_{10}H_{16}Br_2O_2Se$ 405.8682, found 405.8675.

(3Z,3′Z)-3,3′-selenobis(4-bromo-2-phenylbut-3-en-2-ol) (**4l**)

Colorless solid, yield 73%, was obtained as an inseparable mixture of two diastereomers in the ratio 1: 1 (according ^1H NMR spectrum). IR (neat): 3454 (br), 3059, 2983, 1708, 1493, 1446, 1357, 1207, 1134, 1068, 910, 765, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm) (for both diastereomers): 1.939 & 1.944 (6H each, s), 6.66 & 6.666 (2H each, s), 3.24 & 3.27 (2H each, br), 7.29–7.48 (m). ^{13}C NMR (75 MHz) δ (ppm): 28.13 & 28.25 (CH_3), 78.46 & 78.49 (CCH_3), 106.43 & 106.51 (CH=), 124.93 (C-ipso), 125.73 & 125.77 (CH), 127.82 (CH), 128.39 & 128. 43 (CH), 143.14 & 144.99 (C=). HRMS Calcd. for $C_{20}H_{20}Br_2O_2Se$ 529.8995, found 529.8963.

3-Z-4-trichlorotelluro-3-chloro-2-methylbut-3-en-2-ol (**9a**).

White crystals, mp 81–83 °C (from Et_2O), yield 49%. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.57 (6H, s), 1.85 (1H, br), 7.75 (1H, s). ^1H NMR (75 MHz, $CDCl_3$), δ (ppm): 28.6 (CH_3), 95.3 (C-2), 131.7 (C-4, $^1J_{C,Te}$ = 281.5 Hz), 161.2 (C-3). MS MALDI (Graphite) *m/z* 353.14 ([M-H]$^-$, 2643).

(3Z,5Z)-3,5-bis(chloromethylene)-2,2,6,6-tetramethyl-1,4-oxaselenane (**10**)

The $CHCl_3$ solution of selenium dichloride (5.1 mmol), prepared from elemental Se (0.4 g) and SO_2Cl_2 (0.41 ml) in dry $CHCl_3$ (6 ml) at rt and stirring for 4 h, was added dropwise to a solution of the corresponding propargyl alcohol (0.5 ml, 5.1 mmol) in dry $CHCl_3$ (10 ml) at 0 °C. Then the reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction (TLC), the reaction mixture was evaporated and the crude product was purified by column chromatography on silica gel with hexanes-EtOAc, 7:1 as eluent.

Light-yellow solid, m. p. 49–59 °C; yield 28%. IR (neat): 3058, 3007, 2935, 1578, 1449, 1365, 1302, 1218, 1168, 1130, 1017, 985, 735 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$), δ (ppm): 1.64 (12H, s), 6.31 (2H, s). ^{13}C NMR (75 MHz) δ (ppm): 28. 4 (CH_3), 76.6 (C-2 & C-6), 111.2 (CH═, $^2J_{C\text{-}Se} = 39.0$ Hz), 140.5 (**C**-3, $^1J_{C,Se} = 97.5$ Hz)). MS (CI/CH_4): *m/z* 300 ($[M\text{-}H]^+$, 100%), 265 (M-Cl, 31%), 229 (M-2Cl, 26%), 207 (31%), 185 (29%). HRMS Calcd. for $C_{10}H_{14}^{37}Cl_2O^{78}Se$ 301.9536, found 301.99530.

(Z)-3-chloro-2-((1,2-dibromo-1-chloro-3-hydroxyprop-2-yl)selenanyl)prop-2-en-1-ol (**11**)

Colorless solid, yield 53%, was obtained as an inseparable mixture of two diastereomers in the ratio 2.3:1. IR (neat): 3425, 3070, 2926, 1658, 1592, 1444, 1129, 1059, 779, 522 cm^{-1}. Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.04 (1H, t, J = 1.4 Hz, CH═), 6.31 (1H, s, CHClBr), ABq system: 4.75 & 4.37 (1 H each, dd, J = 14, 1.4 Hz, CH_2C═), ABq system: 4.12 & 3.96 (1 H each, J = 12.5 Hz, CH_2CBr), 3.90 (2H, br). ^{13}C NMR (75MHz) δ (ppm): 62.0 (CH_2C═), 63.5 (CHBrCl), 67.3 (CH_2CBr), 76.4 (CBr), 129.6 (CH═), 131.3 (C═). Minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.02 (1H, t, J = 1.4 Hz, CH═), 6.32 (1H, s, CHClBr), ABq system: 4.71 & 4.38 (1 H each, dd, J = 14, 1.4 Hz, CH_2C═), ABq system: 4.10 and 3.99 (1 H each, J = 12.5 Hz, CH_2CBr), 3.90 (2H, br). ^{13}C NMR (75 MHz) δ (ppm): 62.0 (CH_2C═), 63.9 (CHBrCl), 69.1 (CH_2CBr), 77.5 (CBr), 129.7 (CH═), 131.2 (C═). HRMS Calcd. for $C_6H_8^{79}Br^{81}Br^{35}Cl_2O_2^{80}Se$ 421.7413, found 421.7421.

(3Z,3′Z)-3,3′-selenodibromide(bis(4-chloro-2-methylbut-3-en-2-o-methylbut-3-en-2-ol)) (**13**)

Viscous oil, yield 38%. IR (neat): 3414, 2983, 2935, 1689, 1604, 1463, 1368, 1238, 1178, 981, 940, 869, 793 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.52 (12 H, s), 1.94 (2H, br) 6.82 (2H, s). ^{13}C NMR (150 MHz) δ (ppm): 28.1 (CH_3), 74.8 (C-2), 118.1 (CH═), 139.4 (C-3). HRMS Calcd. for $C_{10}H_{15}BrCl_2O^{78}Se$ 395.8798; found 395.8831.

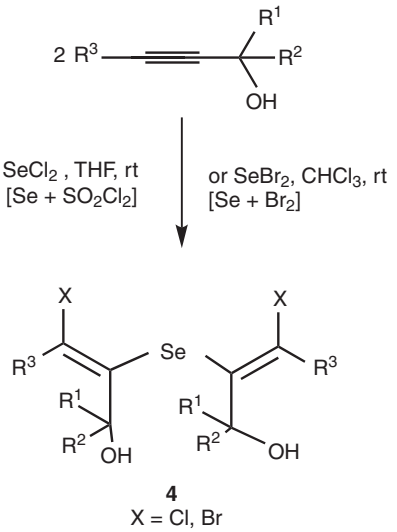
(S,4Z,11Z)-4,11-bis(chloromethylene)-1,8-dioxa-5,12-disele naspiro[6.6]tridecane (**15**)

Viscous oil, yield 36%. IR (neat): 1643, 1413, 1267, 1192, 1082, 1027, 967, 800, 756 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$), δ (ppm): 2.67 (2H, dddd, J = 16.0, 11.5, 4.0, 2.0 Hz, CH_2C═) and 3.17 (2H, dddd, J = 16.0, 4.0, 2.0, 1.0 Hz, CH_2C═), 3.01 & 3.03 (2H each, AA′XX′ system, $J_{AX} = 13.5$ Hz, CH_2Se), 3.77 (2H, dtd, J = 13.0, 4.0, 0.5 Hz, CH_2O), 3.96 (2H, ddd, J = 13.0, 11.5, 2.0 Hz, CH_2O), 6.53 (2H, dd, J = 2.0, 1.0 Hz, CH═). ^{13}C NMR (175 MHz) δ (ppm): 33.9 (C-6 & C-13, $^1J_{C,Se} = 68.8$ Hz), 35.8 (C-3 & C-10), 60.4 (C-2 & C-9), 105.2 (C-7), 118.6 (CH═, $^2J_{C,Se} = 36.3$ Hz), 130.0 (C-4 & C-11, $^1J_{C,Se} = 103.6$ Hz). HRMS Calcd. for $C_{11}H_{14}^{37}Cl_2O^{78}Se_2$ 407.8658; found 407.8624.

RESULTS AND DISCUSSION

Reaction of propargyl alcohols with selenium dihalides. Regio- and stereospecific synthesis of functionalized divinyl selenides

In sharp contrast to the above-mentioned findings with sulfur halides, we have found that *in situ* prepared selenium dichloride, readily obtained from elemental selenium and sulfuryl chloride,[17] in all cases with one exception (*vide infra*) undergoes smooth 1,2-addition to the triple bond of various propargylic alcohols resulting in the formation of functionalized divinyl selenides **4** (X = Cl) in high yields and with complete regio- and stereospecificity (the latter varying with substrate) (Scheme 2) and Table 1, compounds 4a–4i.[16] Similarly, 2-bromovinyl selenides **4** (X = Br) are prepared by the reaction of *in situ* prepared selenium dibromide, readily obtained from elemental selenium and bromine in chloroform (Table 1, compounds 4j–4l).



Scheme 2. Synthesis of functionalized divinyl selenides by electrophilic addition of selenium dihalides to propargylic alcohols

Although a number of methods have been developed for the synthesis of vinyl selenides,[19,20] the synthesis of divinyl selenides is much less investigated.[21–27] Furthermore, although the addition of electrophilic selenium species to olefinic systems has been the subject of many studies,[28–30] the additions to acetylenic systems have received much less attention.[18,19,31–36] Electrophilic addition of phenylselenenyl chloride to internal double bonds of acyclic allylic alcohols usually resulted in the formation of a mixture of regioisomers.[37] Allylic alcohols with terminal double bonds react with phenylselenenyl chloride under

Table 1. Preparation of divinyl selenides by electrophilic addition of selenium dihalides to propargyl alcohols

Compound	R^1	R^2	R^3	X	Yield (%)[a]
4a	H	H	H	Cl	87
4b	H	H	Me	Cl	91
4c	H	H	Et	Cl	89
4d	H	H	Ph	Cl	86
4e	Me	Me	H	Cl	82
4f	Me	Et	H	Cl	83
4g	Me	Ph	H	Cl	77[b]
4h	Ph	H	H	Cl	63
4i	Cy		H	Cl	72[b]
4j	H	H	H	Br	90
4k	Me	Me	H	Br	85
4l	Me	Ph	H	Br	73

[a] Yields are given for isolated products after column chromatography, except for compounds **4g** and **4i**.
[b] In these cases, we were unable to separate selenides **4g** and **4i** from the corresponding diselenides **8d** and **8e**, by column chromatography; yields refer to the mixture of two products.

Journal of Physical Organic Chemistry

kinetic conditions to provide anti-Markovnikov adducts and under thermodynamic conditions to produce Markovnikov adducts.[37] Treatment of unsymmetrical nonterminal alkynes with *in situ* generated phenylselenenyl fluoride afforded a 1: 1 mixture of the two regiomers.[35] It was also reported that the addition of electrophilic selenium reagents to alkynes produced preferably the corresponding *E*-adducts.[32,34]

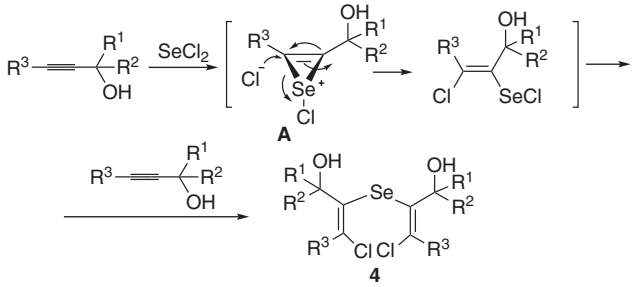
In contrast to the above, and of special mechanistic interest, is our finding of *syn*-addition and anti-Markovnikov orientation in the addition of the selenium halides to the triple bond of propargyl alcohols.[16] The structures of these products have been assigned on the basis of their NMR spectra. The Se-C coupling constants (measured from the ^{77}Se satellites in the ^{13}C NMR spectra) were of special diagnostic value in determining the regiochemistry of the obtained divinyl selenides. The stereochemistry of the newly generated double bond was assigned as *Z* by NOESY experiments.

It would seem that the observed regiospecific *syn*-addition of selenium dichloride to the triple bond of propargylic alcohols involves a directing effect by the hydroxyl group, since the acetate and tosylate esters of propargyl alcohols do not react even after a prolonged period of time, and alkynes such as phenyl acetylene and propargyl bromide react very sluggishly and lead to a mixture of possible isomers. When the reaction was run in the presence of triethylamine, the electrophilicity of the selenium was neutralized and neither 1,2-adducts nor seleninate ester were detected.

To confirm the directing effect by the hydroxyl group and to investigate the effect of the distance of the OH from the triple bond on the observed regio- and stereospecificity we performed the reaction of $SeCl_2$ with homopropargyl alcohol. In this case, substantial loss of stereo- and regioselectivity occurred. All possible isomers were observed in the NMR spectra of the crude reaction mixture and *Z*-anti-Markovnikov product **5** was chromatographically isolated as a major component (Scheme 3).

The reaction of selenium dihalogenides with the triple bond of propargyl alcohols rather than the other groups is in keeping with the Hard–Soft paradigm. Selenirenium ions have been postulated as principal intermediates in addition reactions of selenium-containing electrophiles to acetylenes.[35,38–40] Recently, the selenirenium ions, which were produced by the reaction of the electrophilic selenium reagents with acetylenes at −40 to −80 °C were detected by ^{77}Se NMR spectroscopy. The structures of 1-phenyl-2,3-di-*tert*-butyl-, 1-phenyl-2,3-diadamantyl-, and 1-methyl-2,3-di-*tert* butylselenirenium salts have been determined by single-crystal X-ray diffraction.[41]

Thus, although no reaction of the hydroxyl group with selenium dichloride to yield selenoxylate esters (R-O-Se-O-R) could be detected (with one exception, *vide infra*), the hydroxyl group still plays an important role, responsible for the surprising regio- and stereochemical results. These may be rationalized by the postulate that the stable conformation of **A** (Scheme 4) is one in which C–O bond is perpendicular to the plane of the



Scheme 4. Mechanism of electrophilic addition of $SeCl_2$ to the triple bond of propargylic alcohols

three-membered ring, permitting $\pi - \sigma^*$ (C–O) overlap. Nucleophilic attack of chloride ion in an Cl-addition–Se-elimination sequence is directed preferentially to the distal end of the π-bond because of the stabilization of the 'intermediate carbanion' by overlap with said σ^* (C–O) orbital.

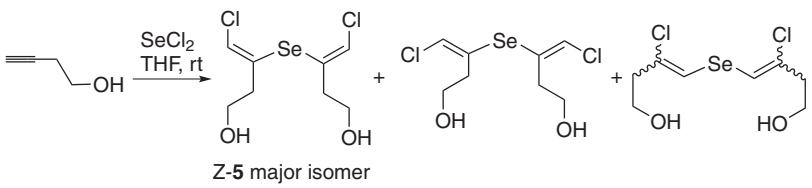
An interesting observation was made upon the reaction of $SeCl_2$ with 2,5-dimethyl-3-hexyne-2,5-diol. In this case, the reaction proceeded slowly and produced, instead of divinyl selenide, the seleninate ester **6** presumably via **7** (Scheme 5). Steric hindrance of the four methyl groups precluded addition to the triple bond.

The cyclic intermediate **7** is presumed to react with a second molecule of $SeCl_2$ followed by hydrolysis during aqueous work-up to give the observed product **6**. The presence of the seleninate moiety Se(=O)O is based on its NMR spectral data which reveal four non-equivalent methyl groups, as well as on IR data. 2,5-Dimethyl-3-hexyne-2,5-diol reacts with sulfur dichloride under the same reaction conditions in a similar manner.[42] Similar saturated γ-selentines have been prepared recently by Back,[43] by a procedure involving the [2,3]sigmatropic rearrangement of allylic selenoxide.[44,45] They were found to have significant biological activity related to oxidative stress.[46]

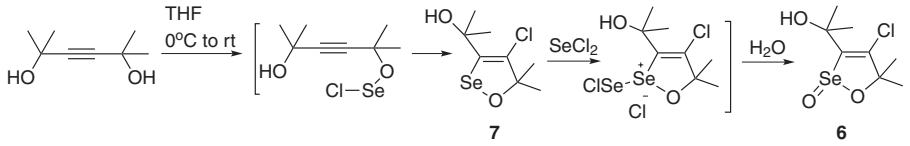
In some cases, synthesis of divinyl selenides **4** was accompanied by the formation of the corresponding divinyl diselenides **8** as minor products (Scheme 6). Diselenides **8a**, **8b**, and **8c** were separated from their selenide counterpart by column chromatography. However, we were unable to isolate diselenides **8d** and **8e** upon chromatography and their contents were determined by ^{1}H NMR analysis of crude reaction mixture. Diselenide formation can be explained by the formation of selenium monochloride Se_2Cl_2 via disproportionation of selenium dichloride.[47]

Reactions of propargyl alcohols with chalcogen tetrahalides

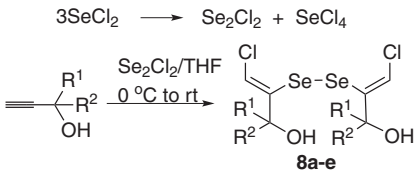
It was found that $SeCl_4$ also adds readily to propargyl alcohols in a completely regio- and stereospecific manner yielding the corresponding divinyl selenium dichlorides as unstable intermediates. The latter undergo either transposition of chlorine to



Scheme 3. Reaction of homopropargyl alcohol with $SeCl_2$



Scheme 5. Formation of cyclic seleninate ester **6**

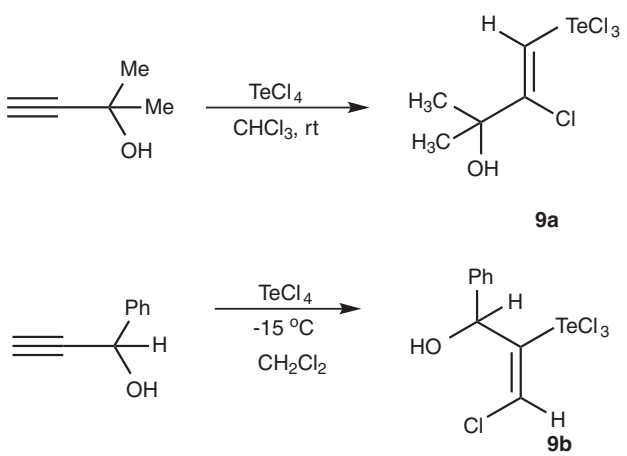


8a, R^1=R^2=Me, 6 %; **8b**, R^1=Me, R^2=Et, 10 %; **8c**, R^1=H, R^2=Ph, 12%; **8d**, R^1=Me, R^2=Ph, **8d/4g** 30:70; **8e**, R^1 – R^2=Cy, **8e/4i** 7:93

Scheme 6. Formation of divinyl diselenides.

the double bond, or hydrolysis to the corresponding divinyl selenoxides. In these reactions also *syn*-addition and anti-Markovnikov orientation are observed. The full description of these results will be published elsewhere.

Finally, the reaction of $TeCl_4$ with propargyl alcohols was found to differ sharply from that of $SeCl_4$. The corresponding vinyl tellurium trichlorides **9** are obtained as a mixture of regio- and stereoisomers (Scheme 7). Unlike selenium halogenide additions, the reaction shows a surprising sensitivity to substitution on the propargylic moiety. Thus, 2-methylbut-3-yn-2-ol upon reaction in dry chloroform at room temperature affords as a major product (> 90% according to ^{1}H NMR spectrum of the crude reaction mixture) the *syn*-adduct with Markovnikov orientation (**9a**) (Scheme 7). The latter was isolated from the crude reaction mixture by recrystalization from Et_2O. The structure of this product has been assigned on the basis of its NMR spectra. The Te-C coupling constants (measured from the ^{125}Te satellites in the ^{13}C NMR spectra) were of special diagnostic value in determining the regiochemistry of the obtained vinyl tellurotrichlorides. The carbon atoms directly attached to tellurium were easily identified since $^1J_{C,Te} >> {}^2J_{T,Se}$. Thus, for compound **9a**, the one-bond coupling constant, $^1J_{C,Te} = 281.5$ Hz, was observed for the protonated olefinic carbon. The stereochemistry of the newly generated double bond was assigned as *Z* by NOESY experiments, which showed a strong interaction of the respective vinylic hydrogen with the methyl hydrogen atoms. Reaction of $TeCl_4$ with 1-phenyl-2-propyn-1-ol in dry CH_2Cl_2 at −15 °C produces an oil from which *anti*-adduct with anti-Markovnikov orientation **9b**[48] was isolated as a major product by recrystalization from dry Et_2O.



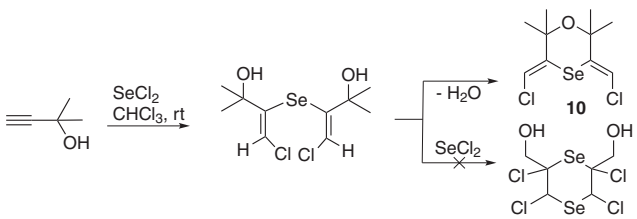
Scheme 7. Reaction of propargyl alcohols with $TeCl_4$

Reactivity of functionalized divinyl selenides

In contrast to the findings presented above, electrophilic addition of benzeneselenenyl chloride to internal double bonds of acyclic allylic alcohols usually resulted in the formation of a mixture of regioisomers.[37] In an attempt to explore the allylic alcohol functionality of the newly prepared selenides we have reacted selenium dichloride with one equivalent of α,α-dimethyl propargyl alcohol instead of two equivalents (refer to Scheme 2). However, instead of the formation of 1,4-diselenane derivatives, as possible $SeCl_2$ adduct to the original divinyl selenide, the 1,4-oxaselenane **10** shown in Scheme 8 was obtained. Formation of the latter via a simple intramolecular dehydration of the divinyl selenide diallylic diol is unlikely in view of the stability of the latter under acidic conditions. The alternative mechanism is being investigated.

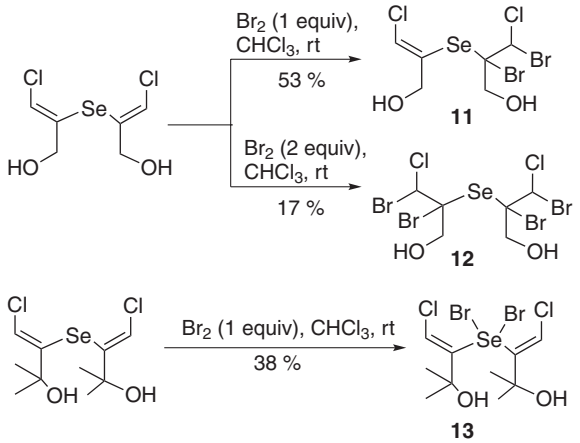
Interestingly, the reaction has shown a surprising sensitivity to the substitution of the allylic function. For example, using the unsubstituted propargyl alcohol afforded the corresponding 1,4-oxaselenane as a minor product. The major product appears to be formed via a subsequent intermolecular reaction of the appropriate divinyl selenide with $SeCl_2$.

Bromination of divinyl selenide also showed a surprising sensitivity to the substitution of the allylic function. Thus, using the unsubstituted propargyl alcohol, the products **11** and **12** of bromine addition to the double bond were obtained (Scheme 9). Bromination of divinyl selenide, derived from α,α-dimethylpropargyl alcohol, with one equivalent of Br_2 afforded selenium dibromide **13** (Scheme 10), whereas two equivalents of Br_2 produced a complex mixture of products, including bromination of double bond, formation of selenium dibromide and cyclization.

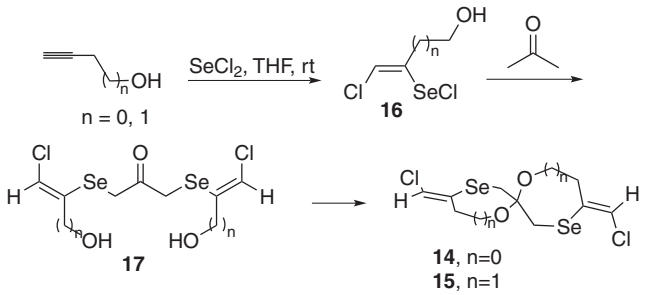


Scheme 8. Synthesis of 1,4-oxaselenanes

Journal of Physical Organic Chemistry



Scheme 9. Bromination of functionalized divinyl selenides



Scheme 10. Formation of novel selenium-containing spiroketals

Formation of selenium-containing spiroketals

When *in situ* prepared selenium dichloride was reacted with either propargylic or homopropargylic alcohols in the presence of acetone, then 1,2-addition to the triple bond was accompanied by selenylation at the α-position of the ketone[49] leading to the formation of novel selenium-containing spiroketals **14** and **15** (Scheme 10) presumably via the intermediate dihydroxyketone **17**.

Spiroketals are molecular frameworks found in a variety of complex natural products that possess a wide range of biological activities.[50–57] Promising pharmacological effects (such as phosphatase inhibition, modulation of the tubulin cytoskeleton of breast cancer cells, and cytotoxic against tumor cell lines) have been discovered in the course of screening of simple spiroketals.[58–67] Since selenium is a required trace element for animals and its biochemical role in mammals has been established,[15,68–70] the design and synthesis of novel organoselenium compounds with useful biological activity currently constitute an engaging problem. Consequently, the introduction of selenium into the spiroketal framework is of obvious interest. While dehydrative cyclization of an oxodiol, or precursor, in acidic media is one of the most widely employed approaches to spiroketal synthesis,[53] the preparation of such spiroketal precursors is a more challenging task. Our approach allows a one-pot preparation of such synthetically and biologically interesting molecules. The scope, limitations, and stereochemical characteristics of the reactions presented above are now under investigation and detailed results will be published elsewhere.

CONCLUSION

In summary, we have shown that various aspects of the reaction of $SeCl_2$ with propargyl alcohols, i.e., identity of reacting functionality, regiospecificity and stereospecificity, differ from expectations based on known reactions of these alcohols with SCl_2. Selenium dihalides undergo smooth 1,2-addition to the triple bond of various propargylic alcohols under mild reaction conditions resulting in the formation of the corresponding functionalized divinyl selenides in high yields and with complete regio- and stereospecificity. The *syn*-addition and anti-Markovnikov orientation observed in all cases are of special mechanistic interest. This is a convenient method to incorporate selenium into an organic molecule, and novel highly functionalized divinyl selenides of synthetic and biological interests are accessible by this simple procedure.

Acknowledgements

This work has been supported by a grant from the Israel Science Foundation (Grant No.919-05).

REFERENCES

[1] S. Braverman, in: *The Chemistry of Sulfones and Sulfoxides (Chapter 13)* (Eds. S. Patai, Z. Rappoport, C. J. M. Stirling), Wiley, New York, **1988**.
[2] S. Braverman, in: *The Chemistry of Sulfenic Acids and their Derivatives (Chapter 8)* (Ed.: S. Patai), Wiley, New York, **1990**.
[3] S. Braverman, in: *The Chemistry of Sulfinic Acids, Esters and their Derivatives (Chapter 11)* (Ed.: S. Patai), Wiley, New York, **1990**.
[4] S. Braverman, M. Cherkinsky, in: *Topics in Current Chemistry*, Vol. 275 (Ed.: E. Schaumann), Springer, Berlin/Heidelberg, **2007**, pp. 67–101.
[5] S. Braverman, D. Segev, *J. Am. Chem. Soc.* **1974**, *96*, 1245–1247.
[6] S. Braverman, Y. Duar, *Tetrahedron Lett.* **1978**, 1493–1496.
[7] S. Braverman, Y. Duar, *J. Am. Chem. Soc.* **1990**, *112*, 5830–5837.
[8] S. Braverman, Y. Duar, M. Freund, *Isr. J. Chem.* **1985**, *26*, 108–114.
[9] S. Braverman, Y. Duar, D. Segev, *Tetrahedron Lett.* **1976**, 3181–3184.
[10] K. C. Nicolaou, G. Skokotas, P. Maligres, G. Zuccarello, E. J. Schweiger, K. Toshima, S. Wendeborn, *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1272.
[11] K. C. Nicolaou, A. L. Smith, in: *Modern Acetylene Chemistry* (Eds. P. J. Stang, F. Diedrich), VCH, Weinheim, **1995**, pp. 203–283.
[12] S. Braverman, T. Pechenick, H. E. Gottlieb, M. Sprecher, *J. Am. Chem. Soc.* **2003**, *125*, 14290–14291.
[13] E. Block, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1135–1178.
[14] T. Wirth, *Organoselenium Chemistry: Modern Developments in Organic Synthesis (Topics in Current Chemistry)*, Vol. 208, Springer, Berlin, **2000**.
[15] G. Mugesh, W.-W. du Mont, H. Sies, *Chem. Rev.* **2001**, *101*, 2125–2179.
[16] S. Braverman, R. Jana, M. Cherkinsky, H. E. Gottlieb, M. Sprecher, *Synlett* **2007**, 2663–2666.
[17] A. Maaninen, T. Chivers, M. Parvez, J. Pietikaeinen, R. S. Laitinen, *Inorg. Chem.* **1999**, *38*, 4093–4097.
[18] S. V. Amosova, A. V. Martynov, N. A. Mahaeva, O. V. Belozerova, M. V. Penzik, A. I. Albanov, O. G. Yarosh, M. G. Voronkov, *J. Organomet. Chem.* **2007**, *692*, 946–952.
[19] J. V. Comasseto, L. W. Ling, N. Petragnani, H. A. Stefani, *Synthesis* **1997**, 373–403.
[20] G. M. Gavrilova, S. V. Amosova, *Heteroatom Chem.* **2006**, *17*, 491–498.
[21] J. V. Comasseto, N. Petragnani, *J. Organomet. Chem.* **1978**, *152*, 295–304.
[22] T. Murai, T. Kondo, S. Kato, *Heteroatom Chem.* **2004**, *15*, 187–192.
[23] T. Murai, H. Takada, T. Kanda, S. Kato, *Tetrahedron Lett.* **1994**, *35*, 8817–8820.
[24] C. C. Silveira, P. C. S. Santos, A. L. Braga, *Tetrahedron Lett.* **2002**, *43*, 7517–7520.
[25] L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, *Tetrahedron* **1986**, *42*, 4577–4584.
[26] L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, *Tetrahedron* **1986**, *42*, 63–69.

[27] B. A. Trofimov, S. V. Amosova, N. K. Gusarova, G. K. Musorin, *Tetrahedron* **1982**, *38*, 713–718.
[28] P. L. Beaulieu, R. Deziel, in: *Organoselenium Chemistry* (Eds. G. Back Thomas), Oxford University Press, Oxford, UK, **1999**, pp. 35–66.
[29] D. M. Browne, T. Wirth, *Curr. Org. Chem.* **2006**, *10*, 1893–1903 .
[30] M. Tiecco, in: *Organoselenium Chemistry. Modern Developments in Organic Synthesis (Topics in Current Chemistry)*, Vol. 208 (Ed.: T. Wirth), Springer-Verlag, Berlin, **2000**, pp. 7–54.
[31] J. V. Comasseto, *J. Organomet. Chem.* **1983**, *253*, 131–181.
[32] C. N. Filer, D. Ahern, R. Fazio, E. J. Shelton, *J. Org. Chem.* **1980**, *45*, 1313–1315.
[33] J. Gerard, L. Hevesi, *Tetrahedron* **2001**, *57*, 9109–9121.
[34] G. H. Schmid, D. G. Garratt, *Tetrahedron Lett.* **1975**, 3991–3994.
[35] Y. Usuki, M. Iwaoka, S. Tomoda, *Chem. Lett.* **1992**, 1507–1510.
[36] T. G. Back, in: *Organoselenium Chemistry* (Ed.: D. Liotta), Wiley, New York, **1987**, pp. 1–125.
[37] D. Liotta, G. Zima, M. Saindane, *J. Org. Chem.* **1982**, *47*, 1258–1267.
[38] T. Brunetti, M. Diddoro, M. L. Di Vona, B. Floris, P. Galloni, S. Licoccia, *Eur. J. Org. Chem.* **2004**, 521–526.
[39] C. Saluzzo, G. Alvernhe, D. Anker, G. Haufe, *Tetrahedron Lett.* **1990**, *31*, 2127–2130.
[40] G. H. Schmid, D. G. Garratt, *Chem. Scr.* **1976**, *10*, 76–81.
[41] H. Poleschner, K. Seppelt, *Angew. Chem., Int. Ed.* **2008**, *47*, 6461–6464.
[42] Y. Ono, Y. Sugihara, A. Ishii, J. Nakayama, *Bull. Chem. Soc. Jpn* **2003**, *76*, 613–617.
[43] T. G. Back, Z. Moussa, *J. Am. Chem. Soc.* **2002**, *124*, 12104–12105.
[44] H. J. Reich, K. E. Yelm, S. Wollowitz, *J. Am. Chem. Soc.* **1983**, *105*, 2503–2504.
[45] H. J. Reich, I. L. Reich, S. Wollowitz, *J. Am. Chem. Soc.* **1978**, *100*, 5981–5982.
[46] T. G. Back, D. Kuzma, N. Berkowitz, Glutathione peroxidase mimetics and uses thereof, WO 2007044641, **2007**.
[47] J. Milne, *Polyhedron* **1985**, *4*, 65–68.
[48] R. L. O. R. Cunha, J. Zukerman-Schpector, I. Caracelli, J. V. Comasseto, *J. Organomet. Chem.* **2006**, *691*, 4807–4815.
[49] K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139.
[50] J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406–4440.
[51] M. Brasholz, S. Soergel, C. Azap, H.-U. Reissig, *Eur. J. Org. Chem.* **2007**, 3801–3814.
[52] J. Hassfeld, M. Kalesse, T. Stellfeld, M. Christmann, *Adv. Biochem. Eng./Biotechnol.* **2005**, *97*, 133–203.
[53] S. V. Ley, L. G. Milroy, R. M. Myers, *Science of Synthesis*, Vol. 29, Thieme, Stuttgart, **2007**, pp. 613–689.
[54] B. R. Moser, *J. Nat. Prod.* **2008**, *71*, 487–491.
[55] F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617–1661.
[56] B. R. Raju, A. K. Saikia, *Molecules* **2008**, *13*, 1942–2038.
[57] V. Vaillancourt, N. E. Pratt, F. Perron, K. F. Albizati, *Total Synthesis of Natural Products*, Vol. 8, John Wiley & Sons Ltd, New York, **1992**, pp. 533–691.
[58] R. Ballini, M. Petrini, G. Rosini, *Molecules* **2008**, *13*, 319–330.
[59] M. L. Gullino, P. Leroux, C. M. Smith, *Crop Prot.* **2000**, *19*, 1–11.
[60] K. Kikuchi, H. Shima, S. Mitsuhashi, M. Suzuki, H. Oikawa, *Drugs Future* **2000**, *25*, 501–507.
[61] T. K. Lindhorst, *Glycoscience* **2001**, *3*, 2393–2439.
[62] K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227–256.
[63] H. Oikawa, *Curr. Med. Chem.* **2002**, *9*, 2033–2054.
[64] F. M. Uckun, *Curr. Pharm. Des.* **2001**, *7*, 1627–1639.
[65] F. M. Uckun, C. Mao, S. T. Jan, H. Huang, A. O. Vassilev, C. S. Navara, R. K. Narla, *Curr. Pharm. Des.* **2001**, *7*, 1291–1296.
[66] F. M. Uckun, C. Mao, S.-T. Jan, H. Huang, A. O. Vassilev, E. A. Sudbeck, C. S. Navara, R. K. Narla, *Curr. Opin. Investig. Drugs (PharmaPress Ltd.)* **2000**, *1*, 252–256.
[67] F. M. Uckun, E. A. Sudbeck, C. Mao, S. Ghosh, X. P. Liu, A. O. Vassilev, C. S. Navara, R. K. Narla, *Curr. Cancer Drug Targets* **2001**, *1*, 59–71.
[68] C. Narajji, M. D. Karvekar, A. K. Das, *Indian J. Pharm. Sci.* **2007**, *69*, 344–351.
[69] K. Soda, H. Tanaka, N. Esaki, in: *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2 (Ed.: S. Patai), Wiley, New York, **1987**, pp. 349–365.
[70] M. Soriano-Garcia, *Curr. Med. Chem.* **2004**, *11*, 1657–1669.

