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Factors Controlling the Selenium-Induced Cyclizations of Alkenyl Hydrazines to Pyridazine or Pyrrolidinamine Derivatives

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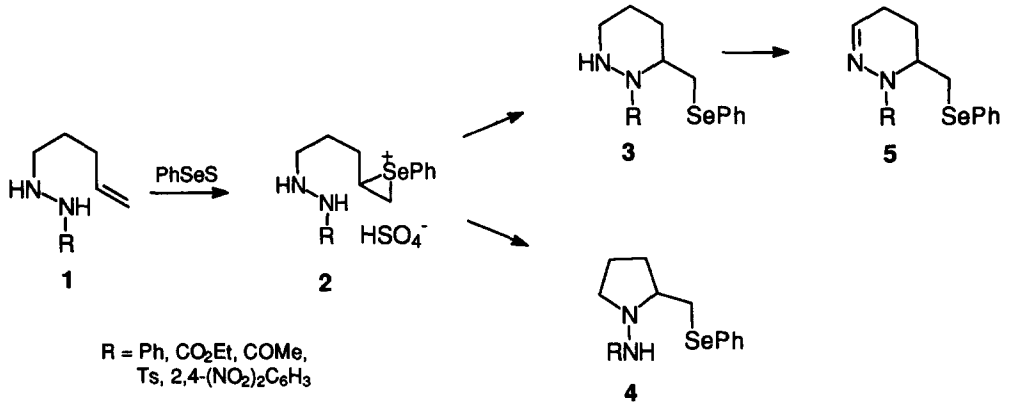
Abstract: 4-Pentenyl hydrazines, CH_2=$CHCH_2CH_2CH_2NHNHR$, react with phenylselenenyl sulfate, produced by diphenyl diselenide, ammonium persulfate and trifluoromethanesulfonic acid, to afford phenylseleno-substituted hexahydropyridazine or pyrrolidinamine derivatives depending on the nature of the substituent R. © 1997 Elsevier Science Ltd.

One of the most versatile methods to synthesize a variety of heterocyclic compounds is the cyclization reaction which occurs when an alkene containing a suitably positioned nucleophilic group is treated with electrophilic reagents.[1,2] Several interesting examples of this procedure have been reported in recent years.[3] Nitrogen heterocyclic compounds have been obtained from the selenium-induced cyclization of alkenes containing internal nitrogen nucleophiles.[4-10] Interesting competitive reactions leading to different heterocycles can be observed whenever the nitrogen atom is incorporated in a functional group containing other nucleophilic atoms. The course of these reactions is influenced by several factors. In some cases a change in the experimental conditions employed can give rise to different compounds as the result of kinetic or thermodynamic product control. Thus, alkenyl hydroxamic acids,[11] O-(2-butenyl) hydroxamic acids[12] and N-(2-butenyl) acethydrazides[13] give the N-hydroxy imidates, 1,4,2-dioxazines and 1,3,4-oxadiazines, respectively, as the kinetically controlled products and the N-hydroxy γ-lactams, N-acyl isoxazolidines and N-acetyl pyrazolidines, respectively, as the thermodynamically controlled products. The cyclization occurs through the formation of a carbon-oxygen bond in the first case and of a carbon-nitrogen bond in the second case. Since the addition of the electrophilic selenium reagent and of the internal nucleophile occurs with a Markovnikov orientation, the structure of the alkene is very important in determining the nature of the cyclization products. In fact, the reaction of O-(2-propenyl) hydroxamic acids[12] and of N-(2-propenyl) acethydrazides,[13] in which the carbon-carbon double bond is terminal, gave the 1,4,2-dioxazines and the 1,3,4-oxadiazines, respectively. On the contrary, the O-(3-phenyl-2-propenyl) hydroxamic acids[12] and the N-(3-phenyl-2-propenyl) acethydrazides[13] gave the N-acyl isoxazolidines and the N-acetyl pyrazolidines, respectively. In these cases the experimental conditions have no effect on the nature of the reaction products. Geometrical restrictions on the nucleophilic group can be important in directing the cyclization reactions. In the case of alkenyl oximes the reaction affords 1,2-oxazines or cyclic nitrones depending on the geometry of the starting substrates.[14,15] However, nitrones are always the major reaction products since the formation of 1,2-oxazines is a reversible process and the starting oximes equilibrate under the condition employed.[15] On the contrary, the recently reported cyclizations of alkenyl phenylhydrazones[16] selectively give either

pyrrolidinamine or tetrahydropyridazine derivatives depending on the geometrical structure of the hydrazones.

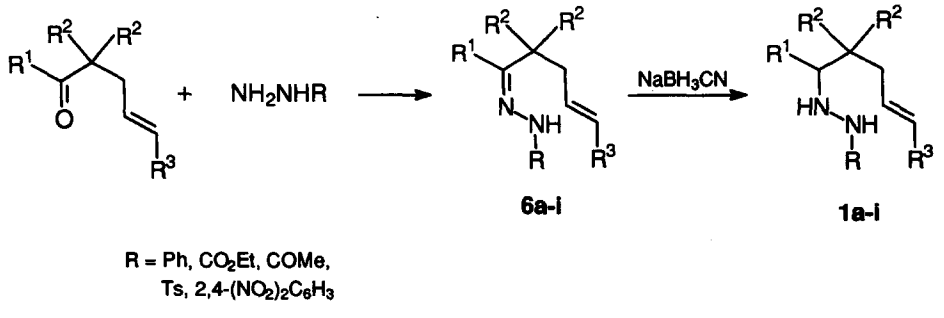
We report in this paper the results of an investigation concerning the selenium-induced cyclization of alkenyl hydrazines **1** (Scheme 1). It was expected that the cyclization reaction could easily occur with these substrates and that the substituent R could greatly influence the competition between the two nitrogen atoms in trapping the seleniranium intermediates **2**. According to Baldwin's rules the two favoured cyclization reactions should be the *5-exo-trig* and the *6-exo-trig*, respectively.[17] Indeed the reactions of hydrazines **1** with phenylselenenyl sulfate (PhSeS) selectively proceeded towards the formation of the hexahydropyridazine **3** or of the pyrrolidinamine derivatives **4** depending on the nature of the substituent R. During work-up compounds **3** were easily oxidized to the tetrahydro derivatives **5**.

Scheme 1



The alkenyl hydrazines **1a-i**, necessary for the present investigation, were obtained from the corresponding hydrazones **6a-i** (Scheme 2) by reduction with sodium cyanoborohydride. The hydrazones were prepared, under standard conditions, from the reactions of 2,2-dimethyl-4-pentenal, 5-hexen-2-one, 1-phenyl-4-penten-1-one or 6-phenyl-(*E*)-5-hexen-2-one with the phenyl-, ethoxycarbonyl-, acetyl-, tosyl- or 2,4-dinitrophenyl hydrazines.

Scheme 2

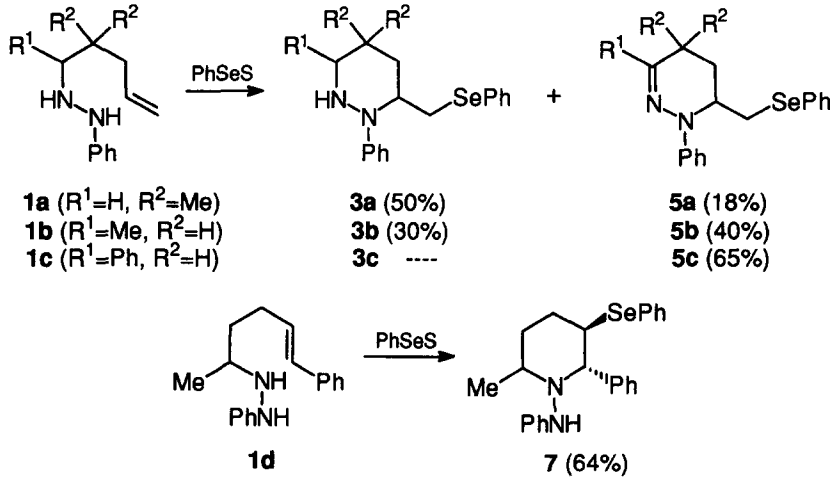


These hydrazines were not very stable and readily decomposed on standing or on attempted purification by column chromatography. As indicated by GC-MS, ^{1}H and ^{13}C NMR spectra, the crude products were sufficiently pure and they were therefore directly used for the cyclization reactions.

The cyclization reactions were carried out by adding the hydrazines **1a-i** to the solution of phenylselenenyl sulfate, prepared from diphenyl diselenide, ammonium persulfate and trifluoromethane sulfonic acid,[15] in acetonitrile at room temperature. The progress of the reaction was monitored by TLC. After 2-3 h the reaction mixtures were poured into 10% sodium carbonate solution and worked up in the usual way. The reaction products were obtained in a pure form by column chromatography on silica gel. In one case purification was effected by repeated washings of the crude product with acetone.

The first experiments were carried out with the phenylhydrazines **1a-c**. In every case the reactions proceeded selectively to afford the six-membered hexahydropyridazines **3a-c** from the trapping of the seleniranium intermediates **2** by the nitrogen atom linked to the phenyl group. During column chromatography coumponds **3a** and **3b** were partially converted into the corresponding tetrahydropyridazines **5a** and **5b**. In the case of **3c**, the conversion into **5c** was complete (Scheme 3). Yields of isolated products after column chromatography are indicated in parentheses. Complete conversion of **3a** and **3b** into **5a** and **5b** occurred on standing after two days and one day, respectively. Thus, the ease of oxidation of the hexahydropyridazines **3a-c** to the tetrahydropyridazines **5a-c** is a function of the substituent R_1 and follows the order Ph > Me > H. Compound **3b** was obtained as a single stereoisomer. Decoupling experiments allowed the vicinal coupling constants of the protons H_3 and H_6 with the protons in position 4 and 5, respectively, to be measured. These coupling constants indicate that both the Me and the $PhSeCH_2$ groups occupy an axial position.

Scheme 3



1a (R^1=H, R^2=Me) **3a** (50%) **5a** (18%)
1b (R^1=Me, R^2=H) **3b** (30%) **5b** (40%)
1c (R^1=Ph, R^2=H) **3c** ---- **5c** (65%)

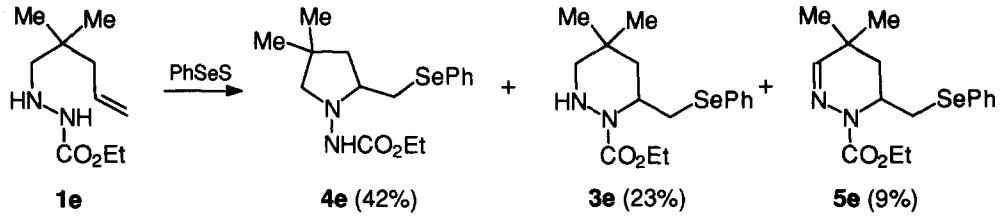
1d **7** (64%)

An experiment was then carried out starting from the phenylhydrazine **1d** (Scheme 3). In this case the ring-closure through the nitrogen atom linked to the phenyl group would give rise either to a seven-membered or to a six-membered ring depending on the Markovnikov or anti-Markovnikov addition to the carbon-carbon

double bond, respectively. These processes were not observed, the only product obtained being the piperidinamine **7** deriving from the trapping of the seleniranium intermediate by the nitrogen atom linked to the alkenyl chain. In this case therefore the regiochemistry of the addition and the preference for the formation of a six-membered rather than a seven-membered ring produce a change in the selectivity of the ring-closure reaction. Compound **7** was present as a 1:1 mixture of two stereoisomers which could not be separated. Since *anti* addition is generally observed in similar selenium-induced cyclizations,[2,3] it is proposed that the two observed stereoisomers have the structure indicated in Scheme 3 in which the methyl group can assume an axial or an equatorial position.

In the case of the alkenyl hydrazines with a terminal carbon-carbon double bond it can be expected that ring-closure reactions through the nitrogen linked to the alkenyl chain, leading to the formation of the pyrrolidinamine derivatives **4**, can be observed if the nucleophilic power of the other nitrogen atom is decreased by replacing the phenyl with an electron-withdrawing group. As a first example we investigated the reactivity of the ethoxycarbonyl hydrazine **1e**. Indeed from the reaction of this compound with phenylselenenyl sulfate the pyrrolidinamine **4e** was obtained as the major reaction product (Scheme 4). This product, however, was accompanied by considerable amounts of the hexahydropyridazine **3e** and of the tetrahydropyridazine **5e**. In this case therefore both the nitrogen atoms can trap the seleniranium intermediate.

Scheme 4

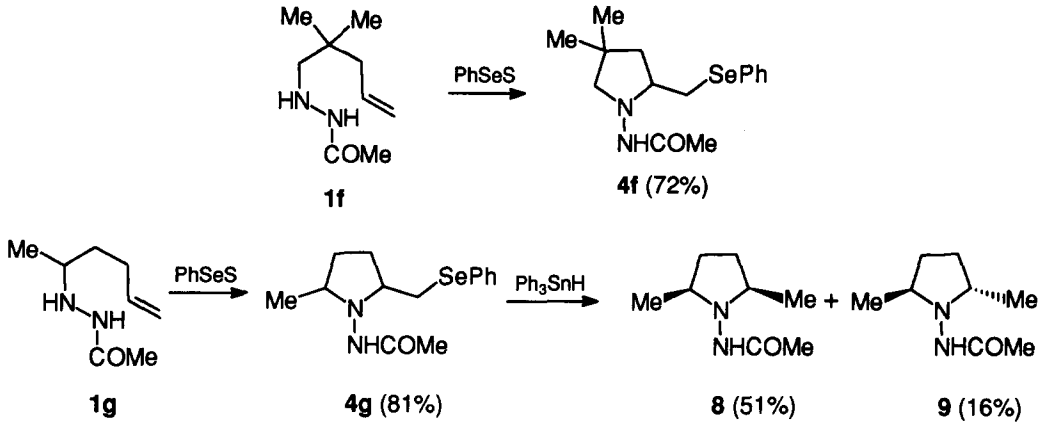


1e **4e** (42%) **3e** (23%) **5e** (9%)

The results obtained with **1e** suggested that, in order to obtain a process involving only the nitrogen atom linked to the alkenyl chain, it is necessary to introduce a more powerful electron-withdrawing group. Thus, the two acetyl hydrazines **1f** and **1g** were synthesized and allowed to react with phenylselenenyl sulfate (Scheme 5).

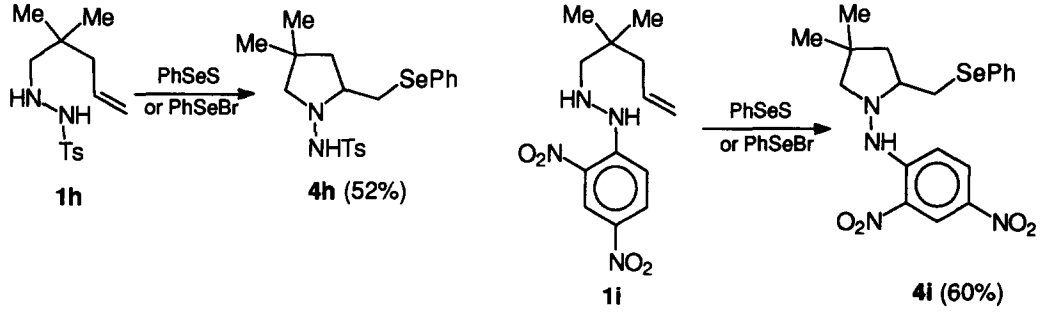
The reaction of **1f** afforded the pyrrolidinamine **4f** as the sole reaction product. From **1g** compound **4g** was obtained in good yield. GC-MS analysis demonstrated that this was a 3:1 mixture of two stereoisomers. After column chromatography only the major isomer was separated in pure form. The 3:1 mixture of the two isomers of **4g** was also deselenenylated with triphenyltin hydride and AIBN. Two stereoisomers were obtained from this reaction after medium pressure column chromatography. ^{1}H and ^{13}C NMR spectra indicated that these were the *cis* and *trans* pyrrolidinamines **8** and **9** indicated in Scheme 5. Structural attribution was made on the basis of the symmetrical structure of the *cis* isomer **8**. Thus the presence of the acetyl group produced the expected change in the reactivity of the hydrazines. In the cyclizations of the acetyl hydrazines the seleniranium intermediate is selectively trapped by the nitrogen atom linked to the alkenyl chain.

Scheme 5



Other electron-withdrawing groups can give similar results. Thus, as indicated in Scheme 6, the tosyl hydrazine **1h** gave the pyrrolidinamine **4h**. The same process can be observed even with phenylhydrazines, provided electron-withdrawing groups are linked to the benzene ring.

Scheme 6



Also reported in Scheme 6 is the example of the 2,4-dinitrophenylhydrazine **1i** which reacted with phenylselenenyl sulfate to afford the pyrrolidinamine **4i**. In the latter two cases cleaner reaction mixtures were obtained when the cyclization reactions were carried out with phenylselenenyl bromide. Column chromatography or crystallization caused extensive decomposition of compounds **4h** and **4i**. Crude **4h** was almost pure and was obtained in 85% yield. After column chromatography this compound was recovered in 52% yield. Compound **4i** was purified by multiple washings of the crude material with acetone. Decomposition of **4h** and **4i** also occurred on attempted GC-MS analysis.

In conclusion the presently described selenium-induced cyclization of alkenyl hydrazines represents a new process which can be conveniently used to synthesize pyridazine or pyrrolidinamine derivatives. The reactions can be directed towards the formation of one or the other of the two types of heterocyclic compounds by changing the nature of the group R. Pyridazines are obtained when R is a phenyl group and pyrrolidinamines are obtained when R is an acetyl or another electron-withdrawing group. The formation of pyridazines from the cyclizations of the alkenyl phenylhydrazines is interesting also in view of the fact that in most cases the recently reported cyclizations of the corresponding alkenyl phenylhydrazones[16] afforded pyrrolidinamine derivatives. Besides their synthetic interest the results now described bring a contribution to a better knowledge of the factors governing the course of the selenium-induced cyclization reactions.

EXPERIMENTAL

Unless otherwise specified, all new compounds were characterized by MS, ^1H and ^{13}C NMR spectroscopy. Melting points were determined on a capillary melting point apparatus and are uncorrected. GLC analyses and MS spectra were carried out with an HP 5890 gaschromatograph (dimethyl silicone column, 12.5 m) equipped with an HP 5971 Mass Selective Detector; for the ions containing selenium only the peak arising from the selenium-80 isotope is given. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC 200 instrument; $CDCl_3$ was used as solvent and TMS as standard. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer and were in good agreement with the calculated values.

Synthesis of Alkenyl Hydrazones. 2,2-Dimethyl-4-pentenal, 5-hexen-2-one, phenylhydrazine hydrochloride, ethyl carbazate, acetic hydrazide, p-toluenesulfonhydrazide and 2,4-dinitrophenylhydrazine were commercial products. 1-Phenyl-4-penten-1-one[18] and 6-phenyl-(*E*)-5-hexen-2-one[19] were prepared according to the procedures described in the literature. The alkenyl phenylhydrazones **6a-d** have already been described.[16] The other alkenyl hydrazones were obtained, as *E* isomers, by refluxing for 2-5 h a solution of equimolecular amounts of aldehyde or ketone and hydrazine derivative in benzene in the presence of molecular sieves. The crude products obtained after removal of the solvent were sufficiently pure and were directly used for the reduction reactions. Physical and spectral data are reported below.

2,2-Dimethyl-4-pentenal ethoxycarbonyl hydrazone (6e): mp 35-37 °C; ^1H NMR δ 7.85 (br s, 1 H), 7.10 (s, 1 H), 5.78 (ddt, 1 H, J = 7.5, 11.1, 15.7 Hz), 5.10-4.98 (m, 2 H), 4.24 (q, 2 H, J = 7.1 Hz), 2.18 (d, 2 H, J = 7.4 Hz), 1.30 (t, 3 H, J = 7.1 Hz), 1.10 (s, 6 H); ^{13}C NMR δ 154.6, 154.0, 133.9, 117.2, 60.8, 44.7, 37.1, 24.5 (2 carbons), 14.1. MS *m/z* (relative intensity) 198 (M^+, 10), 183 (12), 157 (100), 129 (32), 111 (33), 110 (22), 68 (24), 62 (41), 58 (25), 55 (30), 41 (52).

2,2-Dimethyl-4-pentenal acetyl hydrazone (6f): mp 75-76 °C; ^{1}H NMR δ 10.50 (br s, 1 H), 7.13 (s, 1 H), 5.77 (ddt, 1 H, *J* = 7.3, 11.0, 15.9 Hz), 5.10-4.95 (m, 2 H), 2.22 (s, 3 H), 2.19 (d, 2 H, *J* = 7.3 Hz), 1.07 (s, 6 H); ^{13}C NMR δ 171.3, 151.1, 131.7, 114.7, 42.1, 34.6, 22.0 (2 carbons), 17.1. MS *m/z* (relative intensity) 168 (M^+, 1), 127 (20), 85 (100), 68 (21), 60 (20), 58 (23), 43 (88), 41 (39).

5-Hexen-2-one acetyl hydrazone (6g): mp 52-54 °C; ^{1}H NMR δ 9.00 (br s, 1 H), 5.93-5.70 (m, 1 H), 5.15-4.90 (m, 2 H), 2.42-2.25 (m, 4 H), 2.25 (s, 3 H), 1.89 (s, 3 H); ^{13}C NMR δ 173.6, 151.2, 137.4, 116.1, 38.1, 30.1, 20.3, 15.2. MS *m/z* (relative intensity) 154 (M^+, 11), 139 (22), 111 (21), 99 (68), 97 (33), 96 (42), 94 (38), 81 (47), 80 (39), 71 (68), 57 (45), 54 (50), 43 (100).

2,2-Dimethyl-4-pentenal tosyl hydrazone (6h): viscous oil; ^{1}H NMR δ 8.45 (br s, 1 H), 7.80 (AA'BB' system, 2 H), 7.28 (AA'BB' system, 2 H), 7.10 (s, 1 H), 5.44 (ddt, 1 H, *J* = 7.4, 10.2, 17.3 Hz), 4.95-4.80 (m, 2 H), 2.40 (s, 3 H), 2.02 (d, 2 H, *J* = 7.4 Hz), 0.95 (s, 6 H); ^{13}C NMR δ 159.0, 143.7, 135.0, 133.8, 129.3, 127.9, 117.5, 44.5, 37.8, 24.6 (2 carbons), 21.4. MS *m/z* (relative intensity) 280 (M^+, 1), 265 (1), 239 (31), 155 (32), 139 (21), 125 (82), 91 (78), 55 (100), 41 (33).

2,2-Dimethyl-4-pentenal 2,4-dinitrophenyl hydrazone (6i): mp 113-115 °C; ^{1}H NMR δ 10.95 (br s, 1 H), 9.11 (d, 1 H, *J* = 2.5 Hz), 8.29 (dd, 1 H, *J* = 2.5, 9.6 Hz), 7.92 (d, 1 H, *J* = 9.6 Hz), 7.44 (s, 1 H), 5.91-5.65 (m, 1 H), 5.15-5.00 (m, 2 H), 2.28 (d, 2 H, *J* = 7.4 Hz), 1.20 (s, 6 H); ^{13}C NMR δ 158.9, 145.2, 137.7, 133.6, 129.8, 128.8, 123.3, 118.2, 116.5, 44.9, 38.4, 25.0 (2 carbons).

Synthesis of Alkenyl Hydrazines. The hydrazones **6a-i** were reduced, under argon, by treatment with sodium cyanoborohydride and hydrochloric acid in methanol.[20] After stirring at 25 °C for 1 h, the reaction mixture was poured into a 10% aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the crude hydrazines were directly used for the cyclization reactions. Physical and spectral data are reported below.

1-(2,2-Dimethyl-4-pentenyl)-2-phenyl hydrazine (1a): oil; ^{1}H NMR δ 7.23-7.10 (m, 2 H), 6.90-6.70 (m, 3 H), 5.80 (ddt, 1 H, *J* = 7.4, 9.1, 17.7 Hz), 5.13-4.90 (m, 2 H), 4.85 (br s, 1 H), 3.40 (br s, 1 H), 2.58 (s, 2 H), 2.04 (d, 2 H, *J* = 7.4 Hz) 0.95 (s, 6 H); ^{13}C NMR δ 149.3, 135.1, 129.0, 118.9, 117.1, 112.8, 61.9, 44.8, 33.9, 25.5 (2 carbons). MS *m/z* (relative intensity) 204 (M^+, 31), 121 (60), 93 (77), 92 (100), 77 (31), 55 (17), 41 (18).

1-(5-Hexen-2-yl)-2-phenyl hydrazine (1b): oil; ^{1}H NMR δ 7.28-7.10 (m, 2 H), 6.90-6.68 (m, 3 H), 5.82 (ddt, 1 H, *J* = 6.6, 10.1, 16.8 Hz), 5.10 (br s, 1 H), 5.10-4.87 (m, 2 H), 2.95 (sextet, 1 H, *J* = 6.3 Hz), 2.20-2.00 (m, 3 H), 1.72-1.33 (m, 2 H) 1.08 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 148.2, 138.6, 129.1, 118.7, 114.6, 112.6, 54.8, 34.21, 30.2, 18.6. MS *m/z* (relative intensity) 190 (M^+, 46), 175 (17), 135 (61), 108 (26), 107 (44), 105 (50), 93 (69), 92 (90), 77 (100), 65 (23), 55 (30), 41 (14).

1-(1-Phenyl-4-pentenyl)-2-phenyl hydrazine (1c): oil; ^{1}H NMR δ 7.45-7.10 (m, 7 H), 6.90-6.70 (m, 3 H), 5.78 (ddt, 1 H, *J* = 6.4, 10.1, 16.9 Hz), 5.10-4.82 (m, 3 H), 3.83 (t, 1 H, *J* = 6.7 Hz), 3.60 (br s, 1 H), 2.20-2.00 (m, 2 H), 2.00-1.60 (m, 2 H); ^{13}C NMR δ 149.0, 141.7, 138.1, 128.9, 128.6, 127.5, 127.2, 118.9, 114.7, 113.1, 63.5, 34.1, 30.5.

1-(6-Phenyl-(*E*)-5-hexen-2-yl)-2-phenyl hydrazine (1d): oil; ^{1}H NMR δ 7.35-7.10 (m, 7 H), 6.90-6.40 (m, 3 H), 6.38 (d, 1 H, *J* = 15.9 Hz), 6.17 (dt, 1 H, *J* = 6.5, 15.9 Hz), 5.10 (br s, 1 H), 3.40 (br s, 1 H), 2.95 (sextet, 1 H, *J* = 6.7 Hz), 2.37-2.20 (m, 2 H), 1.78-1.58 (m, 1 H), 1.58-1.35 (m, 1 H), 1.08 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 148.2, 137.5, 130.3, 130.2, 128.9, 128.4, 126.9, 125.9, 122.1, 117.2, 72.7, 34.8, 29.7, 18.9.

1-(2,2-Dimethyl-4-pentenyl)-2-ethoxycarbonyl hydrazine (1e): oil; ^{1}H NMR δ 6.82 (br s, 1 H), 5.83 (ddt, 1 H, *J* = 7.5, 11.6, 15.7 Hz), 5.08-4.97 (m, 2 H), 4.15 (q, 2 H, *J* = 7.1 Hz), 4.00 (br s, 1 H), 2.69 (s, 2 H), 2.02 (d, 2 H, *J* = 7.5 Hz), 1.26 (t, 3 H, *J* = 7.1 Hz), 0.91 (s, 6 H); ^{13}C NMR δ 157.6, 134.9, 117.0, 62.2, 61.0, 44.6, 33.8, 25.2 (2 carbons), 14.4. MS *m/z* (relative intensity) 200 (M^+, 3), 185 (4), 159 (3), 117 (100), 89 (95), 71 (89), 55 (25), 41 (25).

1-(2,2-Dimethyl-4-pentenyl)-2-acetyl hydrazine (1f): oil; ^{1}H NMR δ 7.90 (br s, 1 H), 5.92-5.70 (m, 1 H), 5.10-4.98 (m, 2 H), 4.60 (br s, 1 H), 2.63 (s, 2 H), 2.03 (d, 2 H, *J* = 7.4 Hz), 1.93 (s, 3 H), 0.90 (s, 6 H); ^{13}C NMR δ 169.4, 135.0, 117.0, 62.3, 44.7, 34.0, 25.3 (2 carbons), 20.9. MS *m/z* (relative intensity) 170 (M^+, 2), 155 (5), 112 (15), 87 (100), 55 (24), 45 (75), 43 (32), 41 (20).

1-(5-Hexen-2-yl)-2-acetyl hydrazine (1g): oil; ^{1}H NMR δ 7.60 (br s, 1 H), 5.80 (ddt, 1 H, *J* = 6.5, 10.1, 16.8 Hz), 5.10-4.90 (m, 2 H), 4.50 (br s, 1 H), 2.96 (sextet, 1 H, *J* = 6.3 Hz), 2.20-2.00 (m, 2 H), 1.99 (s, 3 H), 1.70-1.20 (m, 2 H), 1.03 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR δ 169.5, 138.3, 114.6, 55.2, 34.1, 30.0, 21.0, 18.3. MS *m/z* (relative intensity) 156 (M^+, 1), 141 (4), 101 (100), 98 (23), 59 (52), 55 (32), 43 (36), 41 (25).

1-(2,2-Dimethyl-4-pentenyl)-2-tosyl hydrazine (1h): mp 47-49 °C; ^{1}H NMR δ 7.82 (AA'BB' system, 2 H), 7.28 (AA'BB' system, 2 H), 6.70 (br s, 1 H), 5.64 (ddt, 1 H, *J* = 7.5, 10.6, 16.4 Hz), 5.00-4.82 (m, 2 H), 4.60 (br s, 1 H), 2.48 (s, 2 H), 2.42 (s, 3 H), 1.84 (d, 2 H, *J* = 7.5 Hz), 0.75 (s, 6 H); ^{13}C NMR δ 143.5, 135.4, 134.7, 129.2, 128.2, 116.9, 61.6, 44.3, 33.6, 25.0 (2 carbons), 21.3. MS *m/z* (relative intensity) 282 (M^+, 1), 278 (33), 155 (23), 139 (100), 123 (33), 91 (60), 65 (14).

1-(2,2-Dimethyl-4-pentenyl)-2-(2,4-dinitro)phenyl hydrazine (1i): oil; ^{1}H NMR δ 9.35 (br s, 1 H), 9.04 (d, 1 H, *J* = 2.5 Hz), 8.25 (dd, 1 H, *J* = 2.5, 9.7 Hz), 7.79 (d, 1 H, *J* = 9.7 Hz), 5.97-5.72 (m, 1 H), 5.15-5.02 (m, 2 H), 4.00 (t, 1 H, *J* = 7.2 Hz), 2.78 (d, 2 H, *J* = 7.2 Hz), 2.13 (d, 2 H, *J* = 7.5 Hz), 1.01 (s, 6 H); ^{13}C NMR δ 149.5, 136.4, 134.3, 130.0, 128.8, 123.7, 117.8, 115.5, 62.0, 44.7, 34.0, 25.5 (2 carbons).

Cyclization of Alkenyl Hydrazines. General Procedure. To the solution of phenylselenenyl sulfate, prepared from diphenyl diselenide (0.6 mmol), ammonium persulfate (0.7 mmol) and

trifluoromethanesulfonic acid (1.4 mmol), in acetonitrile (10 mL) at room temperature or to the solution of phenylselenenyl bromide (1.05 mmol) in dichloromethane (10 mL) at 0 °C a solution of the hydrazine (1 mmol) in acetonitrile or in dichloromethane (10 mL) was added under argon. The mixture was stirred at room temperature for 2-3 h. The progress of the reaction was monitored by TLC. The reaction mixture was poured into a 10% aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed through a silica gel column using the eluants reported below. Compound **4h** was chromatographed through a florisil column and compound **4i** was purified by multiple washings with acetone. Compounds **5c** and **7** have already been described.[16] Physical and spectral data of the other reaction products are reported below.

4,4-Dimethyl-1-phenyl-6-[(phenylseleno)methyl]hexahydropyridazine (3a): petroleum ether/Et_2O (90/10); oil; ^1H NMR δ 7.55-7.42 (m, 2 H), 7.30-7.09 (m, 5 H), 6.94-6.84 (m, 2 H), 6.83-6.71 (m, 1 H), 3.71 (ddt, 1 H, *J* = 4.6, 5.7, 9.1 Hz), 3.50 (br s, 1 H), 3.11 (dd, 1 H, *J* = 4.6, 12.1 Hz), 2.96 (dd, 1 H, *J* = 9,1, 12.1 Hz), 2.71 (d, 1 H, *J* = 13.6 Hz), 2.61 (d, 1 H, *J* = 13.6 Hz), 1.75 (d, 2 H, *J* = 5.7 Hz), 1.02 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR δ 149.0, 133.4, 129.7, 128.9, 128.8, 127.2, 119.3, 115.2, 57.3, 54.0, 39.1, 30.5, 28.5, 28.2, 27.8. MS *m/z* (relative intensity) 360 (M^+, 4), 358 (6), 189 (64), 187 (100), 77 (23). Anal. Calcd for $C_{19}H_{24}N_2Se$: C, 63.51; H, 6.73; N, 7.80. Found: C, 63.44; H, 6.80; N, 7.69.

4,4-Dimethyl-1-phenyl-6-[(phenylseleno)methyl]-1,4,5,6-tetrahydropyridazine (5a): petroleum ether/Et_2O (90/10); oil; ^1H NMR δ 7.55-7.43 (m, 2 H), 7.30-7.08 (m, 5 H), 6.98-6.81 (m, 3 H), 6.60 (d, 1 H, *J* = 1.3 Hz), 3.91 (ddt, 1 H, *J* = 3.6, 5.0, 11.1 Hz), 3.12 (ddd, 1 H, *J* = 0.9, 3.6, 12.6 Hz), 2.93 (dd, 1 H, *J* = 11.1, 12.6 Hz), 2.27 (ddd, 1 H, *J* = 1.3, 5.0, 13.9 Hz), 1.96 (ddd, 1 H, *J* = 0.9, 5.0, 13.9 Hz), 1.18 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR δ 146.6, 146.2, 133.7, 133.4, 129.0, 128.9, 127.4, 120.8, 116.0, 50.5, 35.8, 29.5, 28.8, 28.2, 28.1. MS *m/z* (relative intensity) 358 (M^+, 4), 187 (100), 77 (15). Anal. Calcd for $C_{19}H_{22}N_2Se$: C, 63.87; H, 6.21; N, 7.84. Found: C, 63.94; H, 6.30; N, 7.79.

3-Methyl-1-phenyl-6-[(phenylseleno)methyl]hexahydropyridazine (3b): petroleum ether/Et_2O (95/5); oil; ^1H NMR δ 7.62-7.40 (m, 2 H), 7.30-7.05 (m, 5 H), 6.90-6.70 (m, 3 H), 3.69 (ddt, 1 H, *J* = 5.0, 5.2, 6.8 Hz), 3.18 (ddq, 1 H, *J* = 3.8, 5.1, 6.7 Hz), 3.15 (br s, 1 H), 2.99 (d, 2 H, *J* = 6.8 Hz), 2.20-2.02 (m, 1 H), 1.88-1.69 (m, 2 H), 1.35-1.15 (m, 1 H), 1.12 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 149.9, 133.4, 132.8, 129.0, 128.8, 127.2, 118.9, 115.0, 54.3, 50.4, 27.4, 27.3, 23.6, 18.4. MS *m/z* (relative intensity) 346 (M^+, 6), 344 (4), 175 (100), 173 (32), 77 (19). Anal. Calcd for $C_{18}H_{22}N_2Se$: C, 62.61; H, 6.42; N, 8.11. Found: C, 62.54; H, 6.50; N, 7.99.

3-Methyl-1-phenyl-6-[(phenylseleno)methyl]-1,4,5,6-tetrahydropyridazine (5b): petroleum ether/Et_2O (95/5); mp 81-82 °C; ^1H NMR δ 7.60-7.48 (m, 2 H), 7.35-7.21 (m, 3 H), 7.20-7.07 (m, 2 H), 6.95-6.86 (m, 2 H), 6.78-6.68 (m, 1 H), 4.02 (dddd, 1 H, *J* = 2.2, 3.2, 3.6, 11.7 Hz), 3.05 (ddd, 1 H, *J* = 1.6, 3.2, 12.7 Hz), 2.74 (dd, 1 H, *J* = 11.7, 12.7 Hz), 2.41 (ddt, 1 H, *J* = 2.2, 5.6, 12.6 Hz), 2.20-1.90 (m, 2 H), 1.98 (s, 3 H), 1.90-1.71 (m, 1 H); ^{13}C NMR δ 146.0, 142.9, 134.0, 129.1, 128.9, 128.6, 127.6, 118.7, 112.7, 49.2, 26.4,

24.1, 21.5, 19.4. MS *m/z* (relative intensity) 344 (M^+, 5), 342 (3), 173 (100), 77 (12). Anal. Calcd for $C_{18}H_{20}N_2Se$: C, 62.98; H, 5.87; N, 8.16. Found: C, 63.04; H, 5.80; N, 8.19.

1-Ethoxycarbonyl-4,4-dimethyl-6-[(phenylseleno)methyl]hexahydropyridazine (3e): petroleum ether/Et_2O (80/20); oil; ^1H NMR δ 7.55-7.45 (m, 2 H), 7.35-7.15 (m, 3 H), 4.50 (br s, 1 H), 4.29 (ddt, 1 H, *J* = 4.3, 6.4, 7.0 Hz), 4.13 (q, 2 H, *J* = 7.2 Hz), 3.39 (dd, 1 H, *J* = 7.0, 12.5 Hz), 3.16 (dd, 1 H, *J* = 7.0, 12.5 Hz), 2.62 (d, 1 H, *J* = 12.3 Hz), 2.53 (d, 1 H, *J* = 12.3 Hz), 1.67 (dd, 1 H, *J* = 4.3, 14.0 Hz), 1.54 (dd, 1 H, *J* = 6.4, 14.0 Hz), 1.22 (t, 3 H, *J* = 7.2 Hz), 1.10 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR δ 155.4, 132.5, 130.0, 128.9, 126.8, 61.6, 58.3, 51.7, 39.1, 31.1, 29.6, 29.0, 27.5, 14.5. MS *m/z* (relative intensity) 356 (M^+, 12), 185 (100), 113 (26), 112 (13), 91 (11), 84 (12). Anal. Calcd for $C_{16}H_{24}N_2O_2Se$: C, 54.09; H, 6.81; N, 7.88. Found: C, 53.94; H, 6.80; N, 7.79.

1-Ethoxycarbonyl-4,4-dimethyl-6-[(phenylseleno)methyl]-1,4,5,6-tetrahydropyridazine (5e): petroleum ether/Et_2O (80/20); oil; ^1H NMR δ 7.60-7.50 (m, 2 H), 7.35-7.20 (m, 3 H), 6.80 (d, 1 H, *J* = 1.6 Hz), 4.48-4.32 (m, 1 H), 4.28 (q, 2 H, *J* = 7.2 Hz), 3.37 (dd, 1 H, *J* = 4.8, 12.6 Hz), 3.02 (dd, 1 H, *J* = 11.2, 12.6 Hz), 2.34 (ddd, 1 H, *J* = 1.6, 3.0, 14.3 Hz), 1.80 (dd, 1 H, *J* = 6.2, 14.3 Hz), 1.32 (t, 3 H, *J* = 7.2 Hz), 1.18 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR δ 154.0, 152.5, 132.3, 132.2, 129.1, 126.9, 62.4, 49.1, 34.2, 29.6, 28.8, 28.3, 27.5, 14.5. MS *m/z* (relative intensity) 354 (M^+, 9), 197 (44), 183 (92), 169 (18), 139 (12), 111 (100), 91 (11), 69 (18), 55 (10), 41 (10). Anal. Calcd for $C_{16}H_{22}N_2O_2Se$: C, 54.40; H, 6.28; N, 7.93. Found: C, 54.54; H, 6.18; N, 7.90.

***N*-Ethoxycarbonyl-(4,4-dimethyl-2-[(phenylseleno)methyl]-1-pyrrolidin)amine (4e):** petroleum ether/Et_2O (80/20); oil; ^1H NMR δ 7.50-7.40 (m, 2 H), 7.30-7.15 (m, 3 H), 5.85 (br s, 1 H), 4.12 (q, 2 H, *J* = 7.1 Hz), 3.40-3.20 (m, 1 H), 3.18 (dd, 1 H, *J* = 3.7, 11.8 Hz), 3.03 (d, 1 H, *J* = 8.6 Hz), 2.98 (dd, 1 H, *J* = 8.4, 11.8 Hz), 2.68 (d, 1 H, *J* = 8.6 Hz), 1.81 (dd, 1 H, *J* = 7.4, 12.6 Hz), 1.47 (dd, 1 H, *J* = 8.8, 12.6 Hz), 1.23 (t, 3 H, *J* = 7.1 Hz), 1.12 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR δ 155.8, 132.0, 130.6, 128.8, 126.4, 68.4, 64.5, 60.7, 44.6, 34.3, 31.5, 29.8, 29,0, 14.4. MS *m/z* (relative intensity) 356 (M^+, 4), 186 (25), 185 (100), 157 (19), 139 (23), 55 (14). Anal. Calcd for $C_{16}H_{24}N_2O_2Se$: C, 54.09; H, 6.81; N, 7.88. Found: C, 54.14; H, 6.89; N, 7.79.

***N*-Acetyl-(4,4-dimethyl-2-[(phenylseleno)methyl]-1-pyrrolidin)amine (4f):** CH_2Cl_2/CH_3OH (98/2); mp 80-82 °C; ^1H NMR δ 7.48-7.30 (m, 2 H), 7.25-7.18 (m, 3 H), 6.80 (br s, 1 H), 3.20-2.90 (m, 4 H), 2.45 (dd, 1 H, *J* = 8.9 Hz), 2.15 (s, 3 H), 1.92-1.78 (m, 1 H), 1.60-1.45 (m, 1 H), 1.15 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR δ 175.1, 132.3, 130.3, 129.0, 126.8, 70.6, 68.3, 44.2, 34.2, 31.1, 30.1, 28.6, 19.9. MS *m/z* (relative intensity) 326 (M^+, 1), 267 (1), 169 (29), 156 (26), 155 (100), 113 (18), 96 (30), 55 (22), 43 (22), 41 (17). Anal. Calcd for $C_{15}H_{22}N_2OSe$: C, 55.39; H, 6.82; N, 8.61. Found: C, 55.44; H, 6.78; N, 8.69.

***N*-Acetyl-(2-methyl-5-[(phenylseleno)methyl]-1-pyrrolidin)amine (4g):** CH_2Cl_2/Et_2O (70/30); oil; major isomer: ^1H NMR δ 7.52-7.40 (m, 2 H), 7.33-7.18 (m, 3 H), 6.85 (br s, 1 H), 3.20-2.81 (m, 3 H), 2.80-2.60 (m, 1 H), 2.12 (s, 3 H), 2.12-1.75 (m, 2 H), 1.75-1.30 (m, 2 H), 1.09 (d, 3 H, *J* = 6.1 Hz); ^{13}C NMR δ 175.6, 132.4, 130.2, 129.0, 126.8, 66.8, 63.6, 31.5, 28.6, 26.8, 20.2, 18.3. MS *m/z* (relative intensity) 312 (M^+, 1), 253 (3), 155 (31), 142 (17), 141 (100), 99 (13), 82 (24), 55 (16), 43 (18), 41 (13); minor isomer: MS *m/z*

(relative intensity) 312 (M^+, 1), 253 (1), 155 (12), 142 (9), 141 (100), 99 (6), 82 (11), 55 (6), 43 (7), 41 (5). Anal. Calcd for $C_{14}H_{20}N_2OSe$: C, 54.03; H, 6.48; N, 9.00. Found: C, 54.14; H, 6.38; N, 8.96.

***N*-Acetyl-((2*RS*,5*SR*)-2,5-dimethyl-1-pyrrolidin)amine (8):** Et_2O; mp 96-98 °C; ^1H NMR δ 6.50 (br s, 1 H), 2.70-2.50 (m, 2 H), 2.08 (s, 3 H), 2.00-1.80 (m, 2 H), 1.55-1.30 (m, 2 H), 1.10 (d, 6 H, J = 6.1 Hz); ^{13}C NMR δ 175.8, 62.9 (2 carbons), 28.5 (2 carbons) 20.2, 18.6 (2 carbons). MS *m/z* (relative intensity) 156 (M^+, 1), 141 (13), 113 (100), 99 (30), 98 (99), 97 (41), 82 (20), 56 (33), 55 (38), 43 (30). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.47; H, 10.38; N, 17.99.

***N*-Acetyl-((2*SR*,5*SR*)-2,5-dimethyl-1-pyrrolidin)amine (9):** Et_2O; mp 78-80 °C; ^1H NMR δ 6.50 (br s, 1 H), 3.42 (tq, 1 H, J = 2.6, 6.5 Hz), 2.89 (sext, 1 H, J = 6.7 Hz), 2.10-1.80 (m, 2 H), 1.98 (s, 3 H), 1.50-1.30 (m, 2 H), 1.08 (d, 3 H, J = 6.5 Hz), 0.99 (d, 3 H, J = 6.7 Hz); ^{13}C NMR δ 175.7, 57.8 (2 carbons), 28.9 (2 carbons), 19.1, 16.5, 13.8. MS *m/z* (relative intensity) 156 (M^+, 1), 141 (13), 113 (100), 99 (28), 98 (87), 97 (30), 82 (17), 56 (22), 55 (33), 43 (28). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.54; H, 10.28; N, 17.86.

***N*-Tosyl-(4,4-dimethyl-2-[(phenylseleno)methyl]-1-pyrrolidin)amine (4h):** CH_2Cl_2/petroleum ether (90/10); oil; ^1H NMR δ 7.85 (AA'BB' system, 2 H), 7.45-7.10 (m, 7 H), 5.45 (br s, 1 H), 3.14 (dd, 1 H, J = 3.0, 11.9 Hz), 3.05-2.85 (m, 1 H), 2.64 (dd, 1 H, J = 9.5, 11.9 Hz), 2.50 (d, 1 H, J = 8.5 Hz), 2.45 (s, 3 H), 2.16 (d, 1 H, J = 8.5 Hz), 1.75 (dd, 1 H, J = 8.1, 12.9 Hz), 1.31 (dd, 1 H, J = 8.6, 12.9 Hz), 0.95 (s, 3 H), 0.91 (s, 3 H);^{13}C NMR δ 143.7, 135.4, 131.7, 130.6, 129.3, 128.9, 128.8, 126.4, 69.8, 66.6, 43.9, 34.5, 30.9, 29.8, 28.5, 21.6. Anal. Calcd for $C_{20}H_{26}N_2O_2SSe$: C, 54.92; H, 5.99; N, 6.40. Found: C, 54.84; H, 6.05; N, 6.29.

***N*-(2,4-Dinitro)phenyl-(4,4-dimethyl-2-[(phenylseleno)methyl]-1-pyrrolidin)amine (4i):** mp 155-157 °C; ^1H NMR δ 9.07 (d, 1 H, J = 2.5 Hz), 8.80 (br s, 1 H), 8.24 (dd, 1 H, J = 2.5, 9.6 Hz), 7.73 (d, 1 H, J = 9.6 Hz), 7.45-7.32 (m, 2 H), 7.30-7.18 (m, 3 H), 3.40-3.18 (m, 1 H), 3.11 (d, 1 H, J = 8.7 Hz), 3.02 (dd, 1 H, J = 9.7, 12.0 Hz), 2.97 (dd, 1 H, J = 6.9, 12.0 Hz), 2.56 (d, 1 H, J = 8.7 Hz), 1.99 (dd, 1 H, J = 8.3, 13.0 Hz), 1.66 (dd, 1 H, J = 8.6, 13.0 Hz), 1.27 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR δ 149.2, 136.9, 132.2, 130.1, 129.4, 129.1, 127.6, 127.0, 123.6, 116.0, 69.8, 67.1, 44.2, 34.8, 30.9, 30.3, 28.8. Anal. Calcd for $C_{19}H_{22}N_4O_4Se$: C, 50.79; H, 4.94; N, 12.47. Found: C, 50.84; H, 4.80; N, 12.49.

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