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# Synthesis of enantiomerically pure β-azidoselenides starting from natural terpenes

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**Abstract**—Several unsaturated natural terpenes have been easily converted, in good yields, into the corresponding enantiomerically pure β-azidoselenides by addition of the electrophilic selenium reagent PhSeOTf in the presence of sodium azide. These reactions are stereospecific *anti* additions, which occur with a Markovnikov orientation. Examples of the synthetic importance of these β-azidoselenides are also reported.


## 1. Introduction

Organic azides are valuable synthetic intermediates.[1] They can be used in cycloaddition reactions, in the synthesis of amine derivatives, and as precursors of nitrogen-containing heterocycles and of nitrenes.[2] The preparation of azido derivatives has been considerably improved by the use of organoselenium reagents to produce β-azidoselenides. These products have a greater synthetic importance since they combine the well known reactivity of the azido group with that of the selenium containing group.[3] β-Azidoselenides can be conveniently prepared from alkenes by reaction with an electrophilic organoselenium reagent, such as phenylselenenyl halide or triflate, in the presence of sodium azide. This addition reaction is regioselective (Markovnikov) and stereospecific (*anti*).[4] Radical azidoselenenylation of alkenes can also be effected. In this case the reactions are initiated by the azido radicals, produced by oxidation of azido anions with iodobenzene diacetate; the final products are then formed by trapping the so-formed carbon radical with diphenyl diselenide.[5] Obviously, in this case the reaction is not stereospecific and produces the *anti*-Markovnikov regioisomers. Asymmetric synthesis of azido derivatives is very rarely reported in the literature. They can involve diastereoselective reaction of a preformed chiral center,[6] or a desymmetrization reaction of *meso*-epoxides promoted by chiral auxiliaries.[7]

Very recently, we reported the first example of an asymmetric electrophilic azidoselenenylation of olefins, which occurs in good yields and with a very high level of facial selectivity. This process was made possible by the use of chiral nonracemic selenium reagents in the presence of sodium azide.[8] Electrophilic reagents produced from enantiomerically pure diselenides were previously employed also to effect asymmetric hydroxy[9] and methoxy selenenylations[10] as well as cyclofunctionalization reactions[11] with very high facial selectivity under very mild experimental conditions.

## 2. Results and discussion

A different approach for the synthesis of enantiomerically pure β-azidoselenides is now proposed starting from unsaturated natural terpenes. According to the 'chiral pool approach', terpenes can be considered as convenient starting materials in asymmetric synthesis because they are commercially available, not expensive, and generally easily accessible in both enantiomeric forms. Azidoselenenylation of unsaturated terpenes can be obtained by treatment with PhSeOTf **1** and $NaN_3$ in dry MeCN at 0 °C. In a typical experiment, silver triflate (1.1 mmol) was added to a solution of PhSeBr (1.0 mmol) in MeCN (2.5 mL) at 0 °C and after 15 min $NaN_3$ (1.0 mmol) was added. The reaction mixture was stirred for 30 min and then 1.0 mmol of terpenes **2a–f** were added. The mixture was allowed to gradually reach room temperature. The progress of the reaction was monitored by TLC and GC–MS. The final mixture was filtered through anhydrous $K_2CO_3$ and the filtrate was evaporated under vacuum. β-Azidoselenides were then purified by flash column chromatography. Reaction times, chemical yields, and diastereomeric ratios are reported in Table 1.

These results clearly indicate that the azidoselenenylation reaction is a stereospecific trans addition, which occurs

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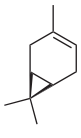
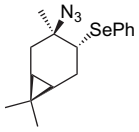
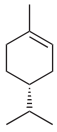
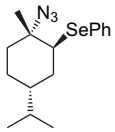
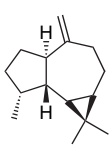
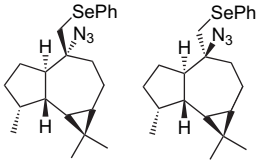
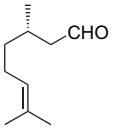
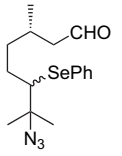
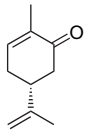
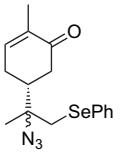
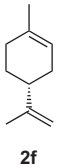
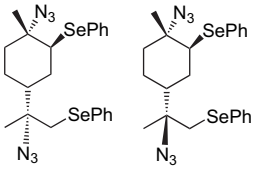
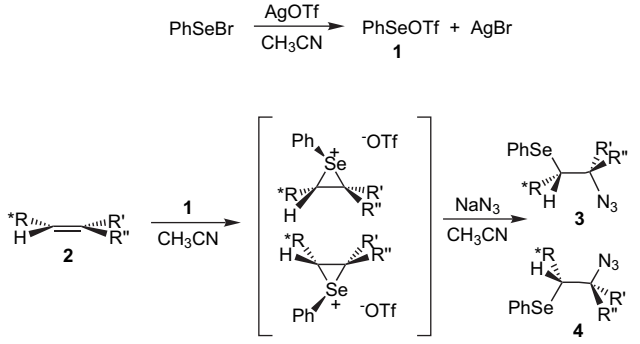
**Table 1**. β-Azidoselenides from the reaction of terpenes with PhSeOTf and $NaN_3$ in $CH_3CN$ at 0 °C

| Entry | Terpene | β-Azidoselenide | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  **2a** |  **3a** | 24 | 60 |
| 2 |  **2b** |  **3b** | 24 | 65 |
| 3 |  **2c** |  **3c** **4c** | 30 | 54 (**3c**)<br>16 (**4c**) |
| 4 |  **2d** |  **3d/4d** | 30 | 30 (**3d**)<br>30 (**4d**) |
| 5 |  **2e** |  **3e/4e** | 24 | 45 (**3e**)<br>45 (**4e**) |
| 6 |  **2f** |  **3f** **4f** | 26 | 41 (**3f**)<br>41 (**4f**) |

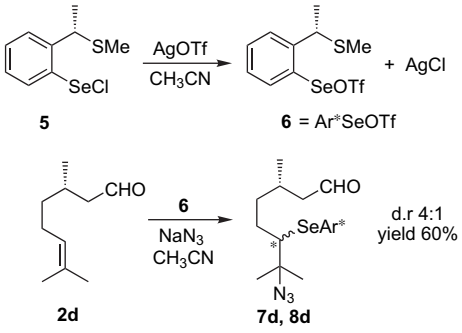
regioselectively with Markovnikov orientation. As indicated in Scheme 1, the reaction of terpenes **2** with phenyselenenyl triflate **1** proceeds through the formation of a seleniranium ion intermediate, which is then trapped by the azide anion to afford addition products **3** and **4**. With cyclohexene derivatives **2a** and **2b**, as well as with **2f** (entries 1, 2, and 6) the ring opening of the seleniranium ion intermediate occurs to give a trans diaxial addition product, a phenomenon, which has been named Furst–Plattner rule.[12] Thus, starting from (+)-3-carene **2a** (entry 1) and (+)-*p*-menth-1-ene **2b** (entry 2) the azidoselenenylation reaction leads to the stereospecific formation of compounds **3a** and **3b**, respectively, derived from the attack of the electrophilic selenium reagent from the less hindered face of the double bond. When the addition occurs in an exocyclic olefin, as in the case of (+)-aromadendrene (entry 3), a lower diastereoselectivity was observed and two isomers **3c** and **4c** were obtained in a ratio of 77:23.




**Scheme 1**. The azidoselenenylation reaction.

Starting from the linear (−)-citronellal **2d** (entry 4) an equimolar mixture of β-azidoselenides **3d** and **4d** has been observed. This is not surprising if one considers that in **2d** the olefinic double bond to be attacked by the electrophile is very far from the chiral center.

The reaction with **2d** was also performed using the enantiomerically pure sulfur-containing reagent **6**, generated in situ by treatment of Ar*SeCl **5** with silver triflate (Scheme 2).



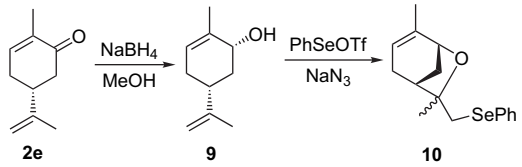

**Scheme 2**. Azidoselenenylation reaction promoted by Ar*SeOTf **6**.

From this reaction a mixture of compounds **7d** and **8d** was obtained in 60% yield and in a 4:1 diastereoisomeric ratio. In both cases the two diastereoisomers (**3d**, **4d** and **7d**, **8d**) could not be separated and the diastereomeric ratios were determined from the proton NMR spectra of the crude reaction mixtures and then confirmed after purification by column chromatography.

In order to investigate the competition between two carbon–carbon double bonds present in the molecule, azidoselenenylation reactions were then carried out on (*R*)-(−)-carvone **2e** and (*R*)-(+)-limonene **2f**. In the first case, as a consequence of the conjugation of the endocyclic double bond with the carbonyl group, the electrophilic reagent reacted only with the terminal double bond affording the two diastereoisomers **3e** and **4e** in a 1:1 ratio and in 90% yield.

The reaction of **2e** with $NaBH_4$ in MeOH proceeded stereospecifically and afforded allylic alcohol **9**.[13] Under the experimental conditions described above, the

azidoselenenylation reaction did not afford the azidoselenenylation product but afforded the two diastereoisomeric cyclic ethers **10** arising from an intramolecular cyclofunctionalization reaction (Scheme 3).

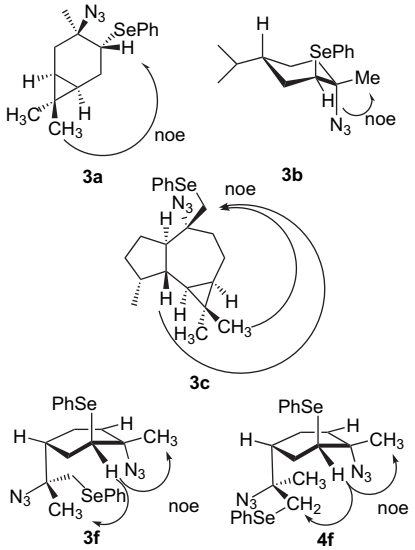



**Scheme 3**. The cyclization of allylic alcohol **9**.

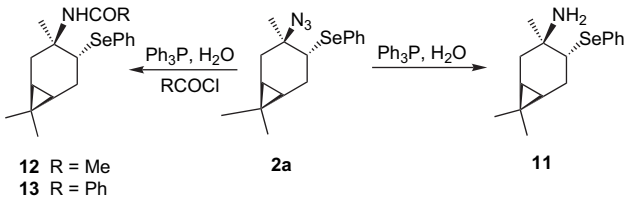
Finally, in the case of (*R*)-(+)-limonene **2f**, the reaction of 0.5 mmol of **1** with 0.5 mmol of terpene in the presence of $NaN_3$ produced a mixture of the mono- and the bis-addition derivatives in a ratio of 4:1 indicating that the attack of the electrophile on the two different double bonds proceeds with a similar rate. The reaction was therefore repeated using double the amount of selenenylating reagent. From this experiment the two diastereoisomers **3f** and **4f** were obtained in good yield and in a 1:1 ratio. As observed in the case of (+)-3-carene (entry 1) and (+)-*p*-menth-1-ene (entry 2) the azidoselenenylation of the endocyclic double bond is stereospecific and the isomers **3f** and **4f** are the results of a regiospecific but not stereospecific addition to the second double bond.

The absolute configurations of the chiral centers generated during the azidoselenenylation and reported in Table 1 were assigned by proton NMR spectroscopy on the basis of the values of the coupling constants, and were then confirmed by some NOE correlations. These are summarized in Scheme 4.

Examples of the possible synthetic uses of β-azidoselenides described above are illustrated in Scheme 5. Using classical procedures, compound **2a** was transformed into enantiomerically pure β-aminoselenide **11**, and into β-amidoselenides **12** and **13**. As previously reported for similar β-amidoselenide compounds, **12** and **13** can be employed




**Scheme 4**. Nuclear Overhauser effects.




**Scheme 5**. Examples of the elaboration of the azido group.

as good starting materials for the synthesis of enantiomerically pure oxazolines, thiazolines, and aziridines.[8] Further elaborations can be effected on the phenylseleno group.[3]

## 3. Conclusion

In conclusion, the results reported in this paper illustrate a convenient approach for the synthesis of enantiomerically pure β-azidoselenides, using as chiral substrates some natural olefins, which are easily accessible and which are able to produce a good stereocontrol on the addition of the electrophilic selenium reagents to the carbon–carbon double bond.

## 4. Experimental section

### 4.1. General

All new compounds were fully characterized by $^1H$ and $^{13}C$ NMR, mass, and IR spectroscopies. $^1H$ and $^{13}C$ NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker Avance-DRX 400 instrument. Unless otherwise specified, $CDCl_3$ was used as the solvent and TMS as internal standard. GC–MS analyses were carried out with an HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass-selective detector. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer using a multiple reflection horizontal ATR (HATR) accessory. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter.

### 4.2. Azidoselenenylation: general procedure

The azidoselenenylation experiments were carried out as follows: AgOTf (258 mg, 1.1 mmol) was added to a solution containing PhSeBr (236 mg, 1 mmol) in dry $CH_3CN$ (2.5 mL) at 0 °C. After 15 min, $NaN_3$ (65 mg, 1 mmol) was added and the reaction mixture was stirred at the same temperature for additional 30 min observing the progressive change of the mixture color from orange to pale yellow. Then, alkenes **2a–f** or **9** (1.0 mmol) was added and the mixture was allowed to gradually reach room temperature. The progress of the reaction was monitored by TLC and GC–MS. The reaction mixture was filtered through anhydrous $K_2CO_3$ and the filtrate was concentrated under vacuum. The reaction products were isolated by flash column chromatography on silica gel. The eluant employed and the physical and spectral data of products **3a–f** and **4c–f** are reported below.

**4.2.1. ((1*S*,3*R*,4*R*,6*R*)-4-Azido-4,7,7-trimethylbicyclo[4.1.0] heptan-3-yl)(phenyl)selane 3a.** It was purified

by flash column chromatography (1% $Et_2O$/petroleum ether) to give the title compound **3a** (200 mg, 60%) as colorless oil; $R_f$ (2% $Et_2O$/petroleum ether) 0.64; $[\alpha]_D^{26.0}$ −12.2 (*c* 1.25, $CHCl_3$); $\nu$ ($N_3$) (HATAR) 2092.87 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.55 (2H, m, Ar–*H*), 7.30–7.20 (3H, m, Ar–*H*), 3.20 (1H, dd, *J* 7.2, 12.1 Hz, C*H*Se), 2.25–2.18 (2H, m, C$H_2$), 2.15–2.10 (1H, m, CH*H*), 1.45 (3H, s, C$H_3$), 1.45–1.40 (1H, m, C*H*H), 1.00 (3H, s, C$H_3$), 0.95 (3H, s, C$H_3$), 0.85 (1H, dt, *J* 4.7, 9.5 Hz, C*H*C), 0.65 (1H, dd, *J* 8.0, 9.5 Hz, C*H*C); $\delta_C$ (100 MHz, $CDCl_3$) 135.0, 130.0, 129.4, 127.9, 64.2, 51.9, 33.2, 29.0, 28.7, 20.7, 19.3, 19.2, 18.4, 15.7. Anal. Calcd for $C_{16}H_{21}N_3Se$: C, 57.48; H, 6.33; N, 12.57. Found: C, 56.97; H, 6.29; N, 12.68.

**4.2.2. ((1*S*,2*S*,5*R*)-2-Azido-5-isopropyl-2-methylcyclohexyl) (phenyl)selane (3b).** It was purified by flash column chromatography (1% $Et_2O$/petroleum ether) to give the title compound **3b** (219 mg, 65%) as colorless oil; $R_f$ (2% $Et_2O$/petroleum ether) 0.50; $[\alpha]_D^{20.3}$ +69.5 (*c* 063, $CHCl_3$); $\nu$ ($N_3$) (HATAR) 2099.14 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.75–7.50 (2H, m, Ar–*H*), 7.50–7.30 (3H, m, Ar–*H*), 3.46 (1H, td, *J* 3.5, 2.5, 2.5 Hz, C*H*Se), 1.90–1.30 (8H, m, 3C$H_2$ and 2C*H*), 1.5 (3H, s, C$H_3$), 0.90 (3H, d, *J* 6.5 Hz, C$H_3$CH), 0.86 (3H, d, *J* 6.5 Hz, C$H_3$CH); $\delta_C$ (100 MHz, $CDCl_3$) 134.8, 130.9, 129.4, 128.1, 65.9, 53.1, 38.9, 33.6, 32.9, 32.4, 26.7, 25.2, 20.3, 20.2, 20.1; GC–MS *m*/*z* (relative intensity): 337 (10) [$M^{+\bullet}$], 309 (4), 266 (4), 228 (7), 157 (18), 125 (25), 110 (40), 95 (18), 81 (26), 69 (100), 55 (64).

**4.2.3. (((1a*S*,4*R*,4a*R*,7*R*,7a*S*,7b*R*)-4-Azido-1,1,7-trimethyldecahydro-1*H*-cyclopropa[*e*]azulen-4-yl)methyl)-(phenyl)selane (3c).** It was purified by flash column chromatography (cyclohexane) to give the title compound **3c** (218 mg, 54%) as colorless oil; $R_f$ (cyclohexane) 0.20; $[\alpha]_D^{26.0}$ −81.1 (*c* 2.40, $CHCl_3$); $\nu$ ($N_3$) (HATAR) 2096.24 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.55 (2H, m, Ar–*H*), 7.25–7.20 (3H, m, Ar–*H*), 3.17 (1H, dd, *J* 1.9, 12.4 Hz, C*H*HSe), 3.08 (1H, dd, *J* 12.4 Hz, CH*H*Se), 2.44 (1H, dd, *J* 6.9, 13.6 Hz, C*H*), 2.31 (1H, ddd, *J* 6.9, 8.3, 9.3 Hz, C*H*), 2.05 (1H, ddt, *J* 6.9, 13.6, 15.5 Hz, C*H*H), 1.88 (1H, ddt, *J* 6.2, 8.3, 12.7 Hz, C*H*H), 1.70–1.65 (1H, m, C*H*$CH_3$), 1.75–1.30 (5H, m, 3CH*H* and C$H_2$), 1.03 (3H, s, $CH_3CCH_3$), 0.96 (3H, d, *J* 7.1 Hz, C$H_3$), 0.95 (3H, s, C$H_3CCH_3$), 0.78 (1H, dt, *J* 11.2, 15.2 Hz, C*H*H), 065 (1H, dt, *J* 5.8, 9.1 Hz, C*H*), 0.59 (1H, dd, *J* 9.1, 10.5 Hz, C*H*); $\delta_C$ (100 MHz, $CDCl_3$) 147.0, 133.9, 129.5, 127.6, 69.3, 55.2, 39.8, 37.0, 36.9, 34.9, 32.2, 28.9, 28.7, 27.0, 26.9, 20.6, 19.9, 16.3, 16.2. Anal. Calcd for $C_{21}H_{29}N_3Se$: C, 62.67; H, 7.26; N, 10.44. Found: C, 63.17; H, 7.32; N, 10.38.

**4.2.4. (((1a*S*,4*S*,4a*R*,7*R*,7a*S*,7b*R*)-4-Azido-1,1,7-trimethyldecahydro-1*H*-cyclopropa[*e*]azulen-4-yl)methyl)-(phenyl)selane (4c).** It was purified by flash column chromatography (cyclohexane) to give the title compound **4c** (64 mg, 16%) as colorless oil; $R_f$ (cyclohexane) 0.30 $[\alpha]_D^{27.5}$ −18.8 (*c* 2.50, $CHCl_3$); $\nu$ ($N_3$) (HATAR) 2090.30 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.50 (2H, m, Ar–*H*), 7.30–7.20 (3H, m, Ar–*H*), 3.94 (1H, d, *J* 12.0 Hz, C*H*HSe), 3.22 (1H, d, *J* 12.0 Hz, CH*H*Se), 2.20–1.95 (3H, m, 3C*H*), 1.85–1.40 (8H, m, 4C$H_2$), 1.14 (3H, s, $CH_3CCH_3$), 1.05 (3H, s, C$H_3CCH_3$), 0.98 (3H, d, *J* 6.9 Hz, C$H_3$CH), 0.75–0.65 (2H, m, 2C*H*); $\delta_C$ 139.2, 129.3, 129.2, 125.7, 62.7, 52.9, 40.8, 36.5, 36.3, 35.0, 30.1, 29.7, 29.0, 28.9, 28.8, 27.2, 21.6, 16.6, 16.5. Anal. Calcd for $C_{21}H_{29}N_3Se$: C, 62.67; H, 7.26; N, 10.44. Found: C, 62.20; H, 7.23; N, 10.50.

**4.2.5. (*S*)-7-Azido-3,7-dimethyl-6-(phenylselenenyl)octanal (3d/4d).** They were purified by flash column chromatography (10% $Et_2O$/petroleum ether) to give a mixture of compounds **3d** and **4d** (212 mg, 60%) as colorless oil; $R_f$ (20% $Et_2O$/petroleum ether) 0.50 (**3d**) 0.49 (**4d**); some spectral data were assigned from enriched fractions of **3d** and **4d**.

Main signals for the enriched fraction of **3d**: $\nu$ ($N_3$) (HATAR) 2093.35 $cm^{-1}$; $\nu$ (CHO) 1723.09 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.76 (1H, t, *J* 2.3 Hz, C*H*O), 7.60–7.50 (2H, m, Ar–*H*), 7.30–7.20 (3H, m, Ar–*H*), 2.92 (1H, t, *J* 9.1 Hz, C*H*Se), 2.45–2.40 (1H, m, C*H*H–CHO), 2.25–2.20 (1H, m, CH*H*–CHO), 2.10–2.00 (1H, m, C*H*–$CH_3$), 2.00–1.90 (1H, m, C*H*H), 1.90–1.80 (1H, m, CH*H*), 1.65–1.40 (2H, m, C$H_2$), 1.45 (3H, s, C$H_3$), 1.39 (3H, s, C$H_3$), 0.98 (3H, d, *J* 6.3 Hz, CH–C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 203.0, 134.5, 131.6, 129.6, 127.9, 66.4, 59.3, 51.0, 36.4, 29.7, 28.5, 26.1, 24.1, 20.7; MS *m*/*z* (relative intensity): 353 (5) [$M^{+\bullet}$], 351 (2), 307 (3), 269 (3), 216 (7), 191 (37), 168 (100), 157 (53), 111 (32), 93 (50), 81 (26), 69 (41), 56 (68).

Main signals for the enriched fraction of **4d**: $\nu$ ($N_3$) (HATAR) 2093.77 $cm^{-1}$; $\nu$ (CHO) 1722.89 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 9.70 (1H, t, *J* 2.2 Hz, C*H*O), 7.60–7.50 (2H, m, Ar–*H*), 7.30–7.20 (3H, m, Ar–*H*), 2.91 (1H, t, *J* 8.8 Hz, C*H*Se), 2.40–2.25 (2H, m, C$H_2$–CHO), 2.10–2.00 (1H, m, C*H*–$CH_3$), 1.80–1.70 (2H, m, C$H_2$), 1.65–1.40 (2H, m, C$H_2$), 1.45 (3H, s, C$H_3$), 1.40 (3H, s, C$H_3$), 0.96 (3H, d, *J* 6.3 Hz, CH–C$H_3$); $\delta_C$ (100 MHz, $CDCl_3$) 202.9, 134.5, 131.6, 129.4, 127.9, 66.4, 59.1, 51.6, 36.1, 29.5, 28.1, 26.1, 24.2, 19.7.

**4.2.6. (*R*)-5-(2-Azido-1-(phenylselenenyl)propan-2-yl)-2-methylcyclohex-2-enone (3e/4e).** They were purified by flash column chromatography (10% $Et_2O$/petroleum ether) to give a 1:1 mixture of compounds **3e** and **4e** (314 mg, 90%) as colorless oil; $R_f$ (20% $Et_2O$/petroleum ether) 0.36; $\nu$ ($N_3$) (HATAR) 2096.73 $cm^{-1}$; $\nu$ (CO) 1820.00 $cm^{-1}$; $\delta_H$ 7.70–7.60 (4H, m, Ar–H), 7.45–7.30 (6H, m, Ar–H), 6.80–6.75 (2H, m, 2CH═), 3.70 (1H, d, *J* 12.3 Hz, C*H*HSe), 3.66 (1H, d, *J* 12.1 Hz, C*H*HSe), 3.42 (1H, d, *J* 12.3 Hz, CH*H*Se), 3.41 (1H, d, *J* 12.1 Hz, CH*H*Se), 2.80–2.30 (10H, m), 1.78 (6H, s, 2$CH_3$), 1.80 (3H, s, $CH_3$), 1.30 (3H, s, $CH_3$); some $^{13}C$ NMR signals were assigned from enriched fraction of **3e** and **4e**: compound **3e** $\delta_C$ 199.5, 144.8, 139.1, 135.8, 129.8, 129.6, 125.8, 59.7, 52.7, 41.8, 40.9, 28.9, 23.8, 16.0; compound **4e** $\delta_C$ 199.4, 144.9, 139.1, 135.8, 129.8, 129.6, 125.8, 59.7, 52.7, 41.9, 40.6, 28.5, 23.4, 16.1. Anal. Calcd for $C_{16}H_{19}N_3OSe$: C, 55.17; H, 5.50; N, 12.06. Found: C, 55.56; H, 5.48; N, 12.16.

**4.2.7. (2-Azido-2-((1*R*,3*S*,4*S*)-4-azido-4-methyl-3-(phenylselenenyl)cyclohexyl)propyl)(phenyl)selane (3f/4f).** They were purified by flash column chromatography (5% $Et_2O$/petroleum ether) to give a 5.5:4.5 mixture of compounds **3f** and **4f** (438 mg, 82%) as colorless oil; $R_f$ (10% $Et_2O$/petroleum ether) 0.48; $\nu$ ($N_3$) (HATAR) 2102.5 $cm^{-1}$.

Some spectral data were assigned from enriched fraction of **3f** and **4f**.

Main signals for the enriched fraction of **3f**: $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.50 (4H, m, Ar–*H*), 7.30–7.20 (6H, m, Ar–*H*), 3.55 (1H, ddd, *J* 2.6, 5.9, 10.8 Hz, C*H*Se), 3.19 (1H, d, *J* 11.7 Hz, CH*H*Se), 3.15 (1H, d, *J* 11.7 Hz, C*H*HSe), 2.62 (1H, tdd, *J* 3.4, 11.0, 14.5 Hz, C*H*H), 2.25–2.05 (1H, m, C*H*H), 1.90–1.88 (1H, m, C*H*), 1.83–1.60 (4H, m, 1C*H*H and 3CH*H*), 1.36 (3H, s, $CH_3$), 1.12 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 133.9, 132.6, 131.0, 130.3, 129.0, 128.9, 127.2, 126.8, 76.5, 74.4, 45.3, 39.3, 33.7, 32.0, 27.9, 26.5, 26.3, 21.8.

Main signals for the enriched fraction of **4f**: $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.50 (4H, m, Ar–*H*), 7.30–7.20 (6H, m, Ar–*H*), 3.48 (1H, ddd, *J* 2.5, 5.6, 10.8 Hz, CHSe), 3.14 (2H, s, C$H_2$Se), 2.41 (1H, tdd, *J* 3.5, 11.1, 14.6 Hz, C*H*H), 2.25–2.05 (1H, m, C*H*H), 2.05–1.95 (1H, m, C*H*H), 1.90–1.88 (H, m, C*H*), 1.70–1.50 (3H, m, 3CH*H*), 1.38 (3H, s, $CH_3$), 1.13 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 133.9, 132.7, 131.0, 130.2, 129.0, 128.9, 127.2, 126.9, 76.5, 74.5, 45.3, 39.7, 33.5, 31.9, 27.6, 26.5, 25.9, 22.1. Anal. Calcd for $C_{22}H_{26}N_6Se_2$: C, 49.63; H, 4.92; N, 15.79. Found: C, 50.0; H, 4.89; N, 15.73.

**4.2.8. (1*S*,5*S*)-4,7-Dimethyl-7-(phenylselenenylmethyl)-6-oxabicyclo[3.2.1]oct-3-ene (10).** They were purified by flash column chromatography (15% $Et_2O$/petroleum ether) to give a 1:1 mixture of isomers **10** (154 mg, 50%) as colorless oil; $R_f$ (30% $Et_2O$/petroleum ether) 0.68; GC–MS *m*/*z* (relative intensity), first GC eluted isomer: 308 (30) [$M^{+\bullet}$], 306 (15), 215 (79), 213 (42), 197 (25), 195 (13), 171 (19), 158 (27), 137 (43), 93 (100), 77 (40); second GC eluted isomer: 308 (22) [$M^{+\bullet}$], 306 (11), 171 (12), 157 (10), 137 (100), 119 (9), 107 (15), 93 (88), 77 (21).

### 4.3. Reduction of the azido group: synthesis of 11

A solution of azide **3a** (1.0 mmol) and $Ph_3P$ (1.1 mmol) in THF (10 mL) was stirred at 40 °C overnight. Then, $H_2O$ (50.0 mmol) was added and stirring was maintained at 50 °C for additional 5 h. After this time, the reaction mixture was poured in $H_2O$ and extracted three times with $Et_2O$. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated under vacuum, and purified by flash chromatography.

**4.3.1. (1*R*,3*R*,4*R*,6*S*)-3,7,7-Trimethyl-4-(phenylselenenyl)bicyclo[4.1.0]heptan-3-amine (11).** It was purified by flash column chromatography (1% $CH_2Cl_2$/MeOH) to give the title compound **11** (186 mg, 60%) as colorless oil; $R_f$ (2% $CH_2Cl_2$/MeOH) 0.22; $\nu$ ($NH_2$) (HATAR) 3350.1 $cm^{-1}$; $[\alpha]_D^{21.2}$ −70.2 (*c* 0.80, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$)7.50–7.40 (2H, m, Ar–*H*), 7.30–7.20 (3H, m, Ar–*H*), 2.96 (1H, dd, *J* 7.2, 12.3 Hz, C*H*Se), 2.32 (1H, dd, *J* 7.2, 15.1 Hz, CH*H*), 2.20 (1H, ddd, *J* 7.8, 12.3, 15.1 Hz, C*H*H), 2.07 (1H, dd, *J* 9.7, 14.2 Hz, CH*H*), 1.25 (1H, dd, *J* 4.9, 14.2 Hz, C*H*H), 1.21 (3H, s, C$H_3$), 0.98 (6H, s, 2C$H_3$), 0.78 (1H, ddd, *J* 4.9, 9.5, 9.7 Hz, C*H*), 0.62 (1H, dd, *J* 7.8, 9.5 Hz, C*H*); $\delta_C$ (100 MHz, $CDCl_3$) 134.4, 131.0, 129.5, 127.6, 58.2, 52.5, 35.5, 29.9, 29.1, 23.5, 21.2, 20.1 18.0, 15.8; GC–MS *m*/*z* (relative intensity): 309 (22) [$M^{+\bullet}$], 307 (7), 213 (18), 152 (69), 138 (59), 124 (69), 110 (12), 107 (10), 91 (17), 70 (100).

### 4.4. Synthesis of amido derivatives 12 and 13

A solution of azide **3a** (1.0 mmol) and $Ph_3P$ (1.1 mmol) in THF (10 mL) was stirred at 40 °C overnight. Then, $H_2O$ (50.0 mmol) was added and stirring was maintained at 50 °C for additional 5 h. After this time, the reaction mixture was poured in $C_6H_6$ and the azeotropic mixture was completely evaporated under vacuum. The crude product was dissolved in THF (10 mL) and $Et_3N$ (2.0 mmol), and then 1.1 mmol of $CH_3COCl$ (for the synthesis of **12**) or PhCOCl (for the synthesis of **13**) was added at 0 °C stirring for 3 h. After this time, the reaction mixture was poured in $H_2O$ and extracted three times with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated under vacuum, and purified by flash chromatography. Physical and spectral data for **12** and **13** are reported below.

**4.4.1. *N*-((1*R*,3*R*,4*R*,6*S*)-3,7,7-Trimethyl-4-(phenylselenenyl)bicyclo[4.1.0]heptan-3-yl)acetamide (12).** It was purified by flash column chromatography (40% $Et_2O$/petroleum ether) to give the title compound **12** (225 mg, 64%) as colorless oil; $R_f$ (80% $Et_2O$/petroleum ether) 0.59; $[\alpha]_D^{20.0}$ −46.5 (*c* 0.40, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.50 (2H, m, Ar–H), 7.30–7.20 (3H, m, Ar–*H*), 5.50 (1H, s, N*H*), 3.75 (1H, dd, *J* 7.2, 12.3 Hz, C*H*Se), 2.49 (1H, dd, *J* 10.1, 14.6 Hz, CH*H*), 2.30 (1H, dd, *J* 7.2, 4.6 Hz, CH*H*), 2.19 (1H, ddd, *J* 7.8, 12.3, 14.6 Hz, C*H*H), 1.96 (1H, dd, *J* 4.0, 14.6 Hz, C*H*H), 1.66 (3H, s, C$H_3$CO), 1.27 (3H, s, C$H_3$), 1.06 (3H, s, C$H_3$), 0.98 (3H, s, C$H_3$), 0.78 (1H, ddd, *J* 4.0, 9.0, 10.1 Hz, C*H*), 0.60 (1H, dd, *J* 7.8, 9.0 Hz, C*H*); $\delta_C$ (100 MHz, $CDCl_3$) 169.9, 134.7, 130.1, 129.6, 127.9, 56.8, 51.1, 30.7, 29.1, 28.3, 24.7, 20.8, 20.5, 19.4, 15.9; GC–MS *m*/*z* (relative intensity): 351 (22) [$M^{+\bullet}$], 349 (11), 292 (87), 290 (41), 270 (13), 194 (34), 135 (76), 119 (42), 107 (25), 73 (100), 70 (44).

**4.4.2. *N*-((1*R*,3*R*,4*R*,6*S*)-3,7,7-Trimethyl-4-(phenylselenenyl)bicyclo[4.1.0]heptan-3-yl)benzamide (13).** It was purified by flash column chromatography (10% $Et_2O$/petroleum ether) to give the title compound **13** (264 mg, 64%) as colorless oil; $R_f$ (20% $Et_2O$/petroleum ether) 0.45; $[\alpha]_D^{23.4}$ −17.5 (*c* 0.85, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 7.60–7.30 (10H, m, Ar–*H*), 6.40 (1H, s, N), 3.77 (1H, dd, *J* 7.3, 12.1 Hz, C*H*Se), 2.83 (1H, dd, *J* 10.1, 14.7 Hz, CH*H*), 2.38 (1H, ddd, *J* 1.0, 7.3, 15.1 Hz, CH*H*), 2.31 (1H, ddd, *J* 7.6, 12.1, 15.1 Hz, C*H*H), 1.94 (1H, dd, *J* 4.8, 14.7 Hz, C*H*H), 1.51 (3H, s, $CH_3$), 1.10 (3H, s, C$H_3$), 1.02 (3H, s, C$H_3$), 0.85 (1H, ddd, *J* 4.8, 9.3, 10.1 Hz, C*H*), 0.67 (1H, ddd, *J* 1.0, 7.6, 9.3 Hz, C*H*); $\delta_C$ (100 MHz, $CDCl_3$) 167.0, 136.0, 135.0, 134.5, 131.4, 129.7, 128.7, 127.9, 127.1, 57.1, 52.3, 30.9, 30.1, 29.1, 28.7, 21.0, 20.2, 19.4, 18.1, 16.0. Anal. Calcd for $C_{23}H_{27}NOSe$: C, 66.98; H, 6.60; N, 3.40. Found: C, 66.71; H, 6.65; N, 3.42.

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