# Short Synthesis of (*R*)- and (*S*)-4-Amino-3-Hydroxybutyric Acid (GABOB)

Marcello Tiecco,* Lorenzo Testaferri, Andrea Temperini, Raffaella Terlizzi, Luana Bagnoli, Francesca Marini, Claudio Santi

Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, 06123 Perugia, Italy
Fax +39(075)5855116; E-mail: tiecco@unipg.it

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**Abstract:** A simple and stereospecific synthesis of both (*R*)- and (*S*)-GABOB has been developed. The synthetic approach involves the conversion, through organoselenium intermediates, of commercially available ethyl (*R*)- and (*S*)-4-chloro-3-hydroxybutyrate into a protected 1,2-amino alcohol with retention of the original configuration.

**Key words:** selenium oxidation, ring closure, amino acids, β-hydroxyselenides, 1,3-oxazolidin-2-ones

4-Amino-3-hydroxybutyric acid (GABOB) is a compound of great pharmacological importance due to its biological function as a neuromodulator in the mammalian central nervous system and due to its hypotensive and antiepileptic activity.[1] The (*R*)-(–)-isomer **1** (Figure 1) has been shown to have a greater biological activity than the (*S*)-(+) isomer. Furthermore, the trimethylamino analogue of GABOB, i.e. (*R*)-(–)-carnitine (**2**), plays a significant role in the human energy metabolism via the transport of long chain fatty acids into the mitochondria.[2] In recent years, a large number of reports and patents dealing with the synthesis of enantiomerically pure (*R*)-GABOB employing optical resolution of diastereoisomeric salts,[3] enzymatic or microbial technique,[4] and asymmetric synthesis,[5] have been published. Moreover, several syntheses which make use of chiral non-racemic starting materials have also appeared.[6] Following our recently proposed stereospecific transformation of β-hydroxyalkyl phenyl selenides into *N*-benzoyl-1,3-oxazolidin-2-ones[7] we now report a short synthesis of both (*R*)- and (*S*)-GABOB.

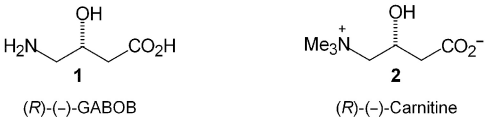
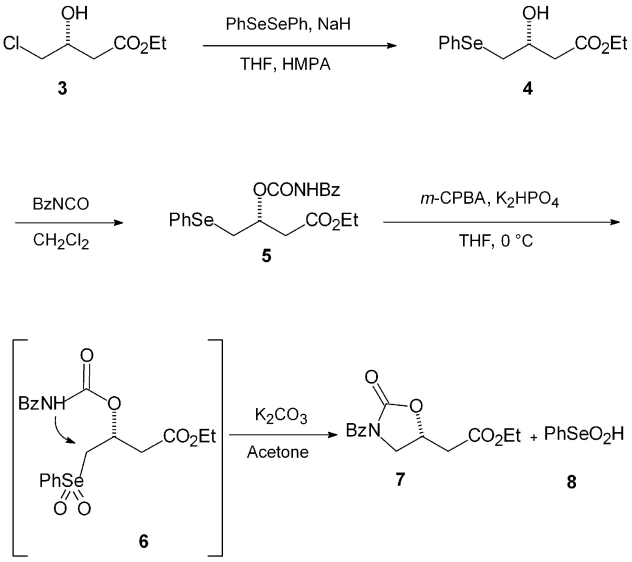



**Figure 1**

Thus, ethyl (*R*)-4-chloro-3-hydroxybutyrate (**3**) was reacted with phenylselenium anions to give the corresponding β-hydroxyalkyl phenyl selenide **4** in excellent yield (Scheme 1).




**Scheme 1**

By reaction with benzoyl isocyanate in $CH_2Cl_2$ at room temperature, this compound was converted into its *N*-benzoyl-carbamate derivative **5**. Treatment of this β-carbamoyloxyalkyl phenyl selenide with an excess of *m*-chloroperoxybenzoic acid (*m*-CPBA) in THF,[8] in the presence of potassium hydrogenphosphate, afforded the corresponding selenone intermediate **6**. The *N*-benzoyl-1,3-oxazolidin-2-one **7** was then obtained as a result of the displacement of the selenonyl group by the nitrogen atom of the carbamate. This new cyclization reaction, which represents the crucial step of the entire process, is an intramolecular nucleophilic substitution, which occurs easily because of the great leaving ability of the selenonyl group. During this process no racemization occurred,[9] as demonstrated by HPLC analysis on chiral column. The phenylseleno moiety, introduced in the first step is eliminated as benzeneseleninic acid (**8**) in the oxidation/cyclization step. After addition of $K_2CO_3$ the water-soluble potassium benzeneseleninate could be separated. From this diphenyl diselenide was recovered[10] in good yield. An attempt to obtain (*R*)-GABOB by basic hydrolysis of **7** with NaOH in EtOH was unsuccessful because **7** undergoes a rapid β-elimination,[6e] giving the ethyl *N*-benzoyl-4-aminocrotonate as the sole reaction product. An optimization study revealed that the following two-steps sequence gave the best results (Scheme 2).

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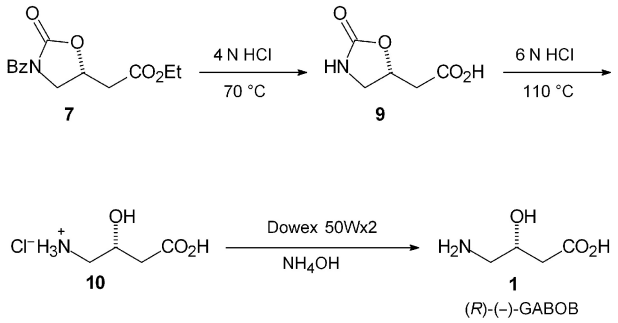


**Scheme 2**

The *N*-benzoyl-1,3-oxazolidin-2-one **7** was first hydrolyzed to the corresponding acid **9** by treatment with 4 N HCl at 70 °C. Treatment of **9** with refluxing 6 N HCl then afforded the (*R*)-GABOB hydrochloride (**10**). Purification of **10** by ion-exchange chromatography on a cation exchange resin afforded crude (*R*)-(–)-GABOB (**1**) in good yield and with spectral data in good agreement with those reported in the literature. The product was contaminated by the corresponding dehydrated derivative, as demonstrated by the $^1$H NMR spectrum. The enantiomeric purity was determined by chiral HPLC after conversion into the corresponding 4-hydroxy-2-pyrrolidinone as reported in the literature.[11] An enantiomeric ratio of 96:4 was thus determined. Following the same procedure, the ethyl (*S*)-4-chloro-3-hydroxybutyrate [*ent*-**3**] (97% ee) was transformed into (*S*)-(+)-GABOB [*ent*-**1**] with practically the same global yield. Chiral HPLC analysis was affected as described above for the (*R*)-enantiomer. The measured enantiomeric ratio was 96:4.

In summary, starting from commercially available chiral building blocks, optically active (*R*)- and (*S*)-GABOB were synthesized by simple chemical reactions promoted by the versatile organoselenium intermediates. The key step of our synthesis is the ring-closure reaction, which occurs by intramolecular nucleophilic substitution of the selenone group by the nitrogen atom of the carbamate.

$^1$H NMR spectra were recorded in $CDCl_3$ or $D_2O$ at 200 MHz on a Bruker Avance DR 200 spectrometer and TMS or HOD was used as internal reference. $^{13}$C NMR spectra were recorded at 50.3 MHz with a Bruker Avance DR 200 spectrometer in $CDCl_3$ or $D_2O$ using the resonance of $CDCl_3$ or dioxane ($\delta_C$ = 67.4 ppm), respectively, as internal reference. FT-IR spectra were recorded with a Jasco model 410 spectrometer equipped with a diffuse reflectance accessory. GC–MS analyses were performed on an HP-6890 gas chromatograph (dimethyl silicone column; 12.5 m) equipped with an HP-5973 mass selective detector at an ionizing voltage of 70 eV. HPLC analyses were performed on an HP 1100 instrument equipped with chiral columns and an UV detector. Melting points are uncorrected. Optical rotations were measured in a 50 mm cell with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. Commercial grade $Et_2O$, $CH_2Cl_2$, $CCl_4$ and THF were used without purification and were dried, if necessary. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Ethyl (*R*)-(+)-4-chloro-3-hydroxybutyrate (97% ee) and ethyl (*S*)-(–)-4-chloro-3-hydroxybutyrate (97% ee) were purchased from Sigma-Aldrich Chemical Co.

**Ethyl (3*R*)-3-Hydroxy-4-(phenylseleno)butanoate (4)**

To a solution of diphenyl diselenide (0.96 g, 3 mmol), in anhyd THF (30 mL), sodium hydride (0.14 g, 6 mmol) was added. The suspension was refluxed for 2 h and then allowed to cool to 40 °C. HMPA (6 mL) was then added. To the resulting orange-colored solution, ethyl (*R*)-(+)-4-chloro-3-hydroxybutyrate (**3**; 1.0 g, 6 mmol) was added. After 36 h the reaction was quenched with a 10% solution of $NH_4Cl$ (10 mL). The reaction mixture was extracted with $Et_2O$ (3 × 30 mL) and the combined organic layers were dried over $Na_2SO_4$ and evaporated. The reaction product was purified by column chromatography on a silica gel column using a mixture of $Et_2O$ and light petroleum (4:6) as eluent. Pure compound **4** was obtained as a pale yellow oil in 86% yield; $[\alpha]_D^{25}$ +2.58 (*c* = 2.23, $CHCl_3$).

FT-IR (KBr): 3472 (br), 2981, 1730, 1186, 1022 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 25 °C, TMS): δ = 7.58–7.47 (m, 2 H, ArH), 7.30–7.21 (m, 3 H, ArH), 4.14 (q, *J* = 7.2 Hz, 2 H, $OCH_2$), 4.24–4.08 (m, 1 H, OCH), 3.24 (d, *J* = 4.0 Hz, 1 H, OH), 3.17–2.95 (m, 2 H, $SeCH_2$), 2.74–2.48 (m, 2 H, $CH_2$), 1.25 (t, *J* = 7.2 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 25 °C): δ = 172.0 (CO), 132.8 (2 × CH), 129.2 (2 × CH), 127.2, 126.4, 67.1 (OCH), 60.8 ($OCH_2$), 40.4 ($CH_2$), 34.7 ($SeCH_2$), 14.1 ($CH_3$).

GC–MS: *m*/*z* (%) = 288 (100) [M$^+$], 270 (32), 183 (23), 157 (63), 131 (59), 103 (63), 91 (58), 77 (29).

Anal. Calcd for $C_{12}H_{16}O_3Se$ (287.2): C, 50.18; H, 5.61. Found: C, 50.42; H, 5.33.

**Ethyl (3*S*)-3-Hydroxy-4-(phenylseleno)butanoate (*ent*-4)**

This compound was prepared as **4**. Yield: 89%; pale yellow oil; $[\alpha]_D^{26}$ –2.63 (*c* = 4.59, $CHCl_3$).

Anal. Calcd for $C_{16}H_{16}O_3Se$ (287.2): C, 50.18; H, 5.11. Found: C, 50.04; H, 5.50.

**Ethyl (3*R*)-3-{[(Benzoylamino)carbonyl]oxy}-4-(phenylseleno)butanoate (5)**

Under an inert atmosphere, benzoyl isocyanate (0.83 g, 5.6 mmol) was added to a solution of the β-hydroxyalkyl phenyl selenide **4** (1.48 g, 5.1 mmol) in anhyd $CH_2Cl_2$ (30 mL) and the reaction was stirred at r.t. until TLC analysis showed that the starting alcohol was completely consumed (14–15 h). The solvent was evaporated and the crude benzoyl carbamate was purified by column chromatography on silica gel with $Et_2O$–light petroleum (6:4) as eluent. Compound **5** was obtained as an oil in 89% yield; $[\alpha]_D^{25}$ –24.70 (*c* = 1.65, $CHCl_3$).

FT-IR (KBr): 3271 (br), 2982, 1757, 1737, 1508, 1184 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 25 °C, TMS): δ = 8.15 (s, 1 H, NH), 7.91–7.80 (m, 2 H, ArH), 7.60–7.40 (m, 5 H, ArH), 7.32–7.10 (m, 3 H, ArH), 5.48–5.30 (m, 1 H, OCH), 4.11 (q, *J* = 7.2 Hz, 2 H, $OCH_2$), 3.35–3.15 (m, 2 H, $SeCH_2$), 2.88 (dd, *J* = 16.1, 5.5 Hz, 1 H, $CH_2$), 2.76 (dd, *J* = 16.1, 7.1 Hz, 1 H, $CH_2$), 1.24 (t, *J* = 7.2 Hz, 3 H, $CH_3$)

$^{13}$C NMR ($CDCl_3$, 25 °C, TMS): δ = 169.6 (CO), 164.8 (CO), 146.8 (CO), 132.7 (CH), 132.6 (CH), 132.5 (CH), 132.4 (CH), 129.0 (2 × CH), 128.4 (2 × CH), 127.5 (2 × CH), 127.0 (2 × CH), 71.7 (OCH), 60.6 ($OCH_2$), 38.0 ($CH_2$), 30.0 ($SeCH_2$), 13.8 ($CH_3$).

Anal. Calcd for $C_{20}H_{21}NO_5Se$ (434.3): C, 55.30; H, 4.87; N, 3.22. Found: C, 55.62; H, 5.13; N, 3.04.

**Ethyl (3*S*)-3-{[(Benzoylamino)carbonyl]oxy}-4-(phenylseleno)butanoate (*ent*-5)**

This compound was prepared as **5**. Yield: 88%; oil; $[\alpha]_D^{26}$ +19.74 (*c* = 1.70, $CHCl_3$).

Anal. Calcd for $C_{20}H_{21}NO_5Se$ (434.3): C, 55.30; H, 4.87; N, 3.22. Found: C, 55.07; H, 5.19; N, 3.11.

**Ethyl [(5*R*)-3-Benzoyl-2-oxo-1,3-oxazolidin-5-yl]acetate (7)**
To a solution of *N*-benzoyl carbamate **5** (1.96 g, 4.5 mmol) in THF (100 mL) at 0 °C powdered potassium hydrogenphosphate (3.81 g, 22.5 mmol) and *meta*-chloroperoxybenzoic acid (3.10 g, 18 mmol) were added. The reaction mixture was allowed to slowly reach r.t. and was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (4 h). The solvent was evaporated in vacuo and the residue was suspended in reagent grade acetone (160 mL). Powdered $K_2CO_3$ (3.10 g, 22.5 mmol) was then added at r.t. The consumption of the selenone was monitored by TLC (20 h). The mixture was then concentrated in vacuo, poured into water (100 mL) and extracted with $Et_2O$ (3 × 60 mL). The organic layer was dried over $Na_2SO_4$ and evaporated. The reaction product was purified by column chromatography on silica gel using a mixture of $Et_2O$ and light petroleum (6:4) as eluent. Yields, physical and spectral data of pure **7** and *ent*-**7** are reported below.

Yield: 90%; white solid; mp 81–82 °C; $[\alpha]_D^{24}$ –46.68 (*c* = 3.36, $CHCl_3$). Analytical HPLC: Chiracel OD-H column (250 × 4 mm, Daicel), eluent: *i*-PrOH–hexane (20:80), flow rate: 0.8 mL/min, UV detection at 240 nm; $t_R$ 50.8 min; er > 99:1.

FT-IR (KBr): 2982, 1788, 1736, 1682, 1328, 1205 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 25 °C, TMS): δ = 7.70–7.62 (m, 2 H, ArH), 7.55–7.30 (m, 3 H, ArH), 5.01 (dddd, *J* = 8.2, 7.2, 6.9, 6.0 Hz, 1 H, OCH), 4.32 (dd, *J* = 11.2, 8.2 Hz, 1 H, $NCH_2$), 4.18 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 3.90 (dd, *J* = 11.2, 7.2 Hz, 1 H, $NCH_2$), 2.89 (dd, *J* = 16.7, 6.0 Hz, 1 H, $CH_2$), 2.76 (dd, *J* = 16.7, 6.9 Hz, 1 H, $CH_2$), 1.28 (t, *J* = 7.1 Hz, 3 H, $CH_3$).

$^{13}$C NMR ($CDCl_3$, 25 °C, TMS): δ = 169.5 (CO), 168.7 (CO), 152.4 (CO), 132.9 (CH), 132.7 (CH), 129.0 (2 × CH), 127.8 (2 × CH), 70.0 (OCH), 61.2 ($OCH_2$), 48.4 ($NCH_2$), 38.6 ($CH_2$), 14.4 ($CH_3$).

Anal. Calcd for $C_{14}H_{15}NO_5$ (277.3): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.82; H, 5.60; N, 5.21.

**Ethyl [(5*S*)-3-Benzoyl-2-oxo-1,3-oxazolidin-5-yl]acetate (*ent*-7)**
This compound was prepared as **7**. Yield: 90%; white solid; mp 79–81 °C; $[\alpha]_D^{30}$ +43.74 (*c* = 1.83, $CHCl_3$). Analytical HPLC: Chiracel OD-H column (250 × 4 mm, Daicel), eluent: *i*-PrOH–hexane (20:80), flow rate: 0.8 mL/min, UV detection at 240 nm; $t_R$ 61.6 min; er > 99:1.

Anal. Calcd for $C_{14}H_{15}NO_5$ (277.3): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.87; H, 5.71; N, 5.22.

**[(5*R*)-2-Oxo-1,3-oxazolidin-5-yl]acetic Acid (9)**
The *N*-benzoyl-1,3-oxazolidin-2-one **7** (0.46 g, 1.6 mmol) was heated at 70 °C with 4 N HCl (6 mL) for 5 h. After cooling the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL) to remove benzoic acid and then evaporated to yield almost pure **9**. Yield 99%; colorless viscous oil; $[\alpha]_D^{21}$ +35.89 (*c* = 2.02, $H_2O$).

$^1$H NMR ($D_2O$, 25 °C): δ = 4.97 (ddt, *J* = 8.9, 6.6, 6.3 Hz, 1 H, OCH), 3.71 (dd, *J* = 9.3, 8.9 Hz, 1 H, $NCH_2$), 3.29 (dd, *J* = 9.3, 6.6 Hz, 1 H, $NCH_2$), 2.78 (d, *J* = 6.3 Hz, 2 H, $CH_2$).

[Lit.[6f] $^1$H NMR (90 MHz, $D_2O$): δ = 4.85 (m, 1 H, OCH), 3.85 (dd, *J* = 9.0 Hz, 1 H, $NCH_2$), 3.40 (dd, *J* = 9.0, 6.5 Hz, 1 H, $NCH_2$), 2.70 (d, *J* = 6.0 Hz, 2 H, $CH_2$)].

$^{13}$C NMR ($D_2O$, 25 °C): δ = 173.8 (CO), 161.3 (CO), 73.6 (OCH), 44.9 ($NCH_2$), 38.4 ($CH_2$).

Anal. Calcd for $C_5H_7NO_4$ (145.1): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.57; H, 5.01; N, 9.49.

**[(5*R*)-2-Oxo-1,3-oxazolidin-5-yl]acetic Acid (*ent*-9)**
This compound was prepared as **9**. Yield: 99%; colorless viscous oil; $[\alpha]_D^{27}$ –35.51 (*c* = 1.36, $H_2O$).

Anal. Calcd for $C_5H_7NO_4$ (145.1): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.49; H, 5.11; N, 9.77.

**(3*R*)-4-Amino-3-hydroxybutanoic Acid (1)**
The pure acid **9** (0.23 g, 1.6 mmol) was dissolved in 6 N HCl (3 mL) and then refluxed (110–120 °C) for 7 h. Evaporation of the acid gave (*R*)-GABOB hydrochloride (**10**) which was dissolved in distilled water (2 mL), and passed through a column containing Dowex 50WX2-100 mesh ($H^+$ form) cation exchange resin (4 g). The column was washed with distilled water (60 mL) until the pH of the elute was neutral. The column was eluted with 25% aq $NH_3$ (20 mL) and the ammoniacal elute was evaporated under vacuum to afford crude (*R*)-(–) GABOB (**1**).

Yield of the crude product 73%; white solid; mp 208–210 °C (Lit,[6f] mp 213–214 °C); $[\alpha]_D^{21}$ –17.51 (*c* = 0.96, $H_2O$). The value reported in the literature[6f] is $[\alpha]_D^{25}$ = –20.5 (*c* = 1.75 in $H_2O$), after recrystallization from aq EtOH. Analytical HPLC of the 4-hydroxy-2-pyrrolidinone derivative: Chirapak AD-H column (250 × 4 mm, Daicel), eluent: EtOH–hexane (5:95), flow rate: 1.0 mL/min, UV detection at 210 nm; $t_R$ 75.97 min; er = 96:4.

$^1$H NMR ($D_2O$, 25 °C): δ = 3.99 (ddt, *J* = 9.6, 8.9, 3.2 Hz, 1 H, OCH), 2.96 (dd, *J* = 13.1, 3.2 Hz, 1 H, $NCH_2$), 2.73 (dd, *J* = 13.1, 9.6 Hz, 1 H, $NCH_2$), 2.23 (d, *J* = 8.9 Hz, 2 H, $CH_2$).

[Lit.[5d] $^1$H NMR (250 MHz, $D_2O$): δ = 4.13–4.00 (m, 1 H, OCH), 3.03 (dd, *J* = 13.1, 3.3 Hz, 1 H, $NCH_2$), 2.81 (dd, *J* = 13.1, 9.4 Hz, 1 H, $NCH_2$), 2.29 (d, *J* = 6.6 Hz, 2 H, $CH_2$)].

$^{13}$C NMR ($D_2O$, 25 °C): δ = 178.1 (CO), 65.3 (OCH), 44.0 ($NCH_2$), 41.9 ($CH_2$).

[Lit.[5d] $^{13}$C NMR (100 MHz, $D_2O$): δ = 179.5 (CO), 66.4 (OCH), 45.0 ($NCH_2$), 43.2 ($CH_2$)].

Anal. Calcd for $C_4H_9NO_3$ (119.1): C, 40.33; H, 7.62; N, 11.76. Found: C, 40.98; H, 7.38; N, 12.14.

**(3*S*)-4-Amino-3-hydroxybutanoic Acid (*ent*-1)**
This compound was prepared as **1**. Yield of the crude product: 78%; mp 198–201 °C; $[\alpha]_D^{17}$ +16.7 (*c* = 0.41 in $H_2O$) {Lit.[6g] $[\alpha]_D^{22}$ +20.1 (*c* = 1.7 in $H_2O$)}. Analytical HPLC of the 4-hydroxy-2-pyrrolidinone derivative: Chirapak AD-H column (250 × 4 mm, Daicel), eluent: EtOH–hexane (5:95), flow rate: 1.0 mL/min, UV detection at 210 nm; $t_R$ 85.1 min; er = 96:4.

Anal. Calcd for $C_4H_9NO_3$ (119.1): C, 40.33; H, 7.62; N, 11.76. Found: C, 41.03; H, 7.30; N, 12.17.

**Recovery of Diphenyl Diselenide**
The alkaline aqueous extract from the oxidation/cyclization procedure (containing the benzeneseleninate anion) was neutralized with concd HCl and then acidified by further addition of the acid. The resulting suspension was evaporated and the residue was suspended in MeOH (50 mL). Hydrazine monohydrate (14.5 mmol, 0.65 mL) was added gradually to the suspension. Stirring was continued until diphenyl diselenide was formed, as indicated by the yellow color. The mixture was then concentrated in vacuo, poured into water (60 mL) and extracted with $Et_2O$ (3 × 30 mL). The organic layer was dried over $Na_2SO_4$ and evaporated. Diphenyl diselenide was recovered as a pure compound in 62% yield.

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