New Reactions of Selenocarboxylates

Spencer Knapp* and Etzer Darout

Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey,
Piscataway, NJ 08854-8087

Supporting Information

Page

- S-1 to S-7 Experimental procedures for the synthesis of **2**, **8**, **11**, **13**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, and **30**
- S-8 to S-29 Copies of ^1H and ^{13}C NMR spectra of **8**, **11**, **13**, **16**, **18**, **20**, **22**, **24**, **26**, **28**, and **30**, and the FT-IR spectrum of **2**.

CAUTION: The organophosphorus and organoselenium compounds described herein should be treated as potentially toxic and should be handled in a good fume hood with gloves. Glassware was conveniently washed with a solution of dilute bleach. Except for dichlorophenylphosphine and pentaphenylcyclopentaphosphine, none of the organoselenium or organophosphorus reagents or residues was particularly malodorous.

Pentaphenylcyclopentaphosphine.¹ Dichlorophenylphosphine (8.95 g, 0.05 mol) was added dropwise to 1.22 g (0.05 mol) of magnesium turnings in 50 mL of THF (CAUTION: EXOTHERMIC). The reaction mixture was allowed to stir at room temperature until all the magnesium was consumed, about 24 h. The solution was poured into an extraction funnel and 60 mL of water was added. The organic layer was dried and concentrated under vacuum; crystallization from THF gave 3.92 g (73%) of pentaphenylcyclopentaphosphine as a white solid, mp 149–152 °C.

Woollins' Reagent (2).² A heterogeneous mixture of 2.70 g (4.99 mmol) of pentaphenylcyclopentaphosphine, 3.94 g (0.05 mol) of selenium powder, and 30 mL of toluene was heated at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and the red precipitate was collected by filtration to give 5.5 g (86%) of **2** as a red solid, mp 192–197

¹ DuPont, T. J.; Mills, J. L. *Inorg. Chem.* **1973**, *12*, 2487–2489.

² Fitzmaurice, J. C.; Williams, D. J.; Wood, P. T.; Woollins, J. D. *J. Chem. Soc., Chem. Commun.* **1988**, 741–743.

°C (lit³ 192–204 °C). Extensive ³¹P and ⁷⁷Se NMR studies of **2** have been previously reported,³ and we supply its FT-IR spectrum (KBr pellet) below. The reagent **2** was conveniently stored in a desiccator under air, and showed no signs of decomposition after six weeks.

Se-(3-Oxo-cyclohexyl) 2-Phenyl-selenolacetate (8). A heterogeneous mixture of 105 mg (0.774 mmol) of phenylacetic acid (**5**), 124 mg (0.233 mmol) of Woollins' reagent, and 2 mL of dry toluene was heated at reflux for 2 h. The resulting solution containing selenoacid **6** was cooled to 0 °C, and then cyclohexenone (**7**, 0.075 mL, 0.774 mmol, 1 equiv based on **5**) was added. The reaction mixture was stirred at 23 °C for 4 h, concentrated, and then chromatographed on silica with 2:3 CH₂Cl₂/hexanes as the eluant to give 194 mg (85%) of the adduct **8** as a colorless oil, *R_f* 0.4 in 40% CH₂Cl₂/hexanes: ¹H NMR (400 MHz, CDCl₃) 7.25–7.38 (m, 5 H), 3.75–3.84 (m, 3 H), 2.80 (ddt, *J* = 1.2, 4.4, 14.4 Hz, 1 H), 2.51 (ddd, *J* = 1.2, 10.0, 14.4 Hz 1 H), 2.16–2.42 (m, 3 H), 1.76–2.60 (m, 3 H); ¹³C (100 MHz, CDCl₃) 208.31, 199.69, 132.57, 130.04, 128.73, 127.82, 54.32, 48.27, 40.92, 39.96, 32.00, 25.56; ESI-MS 319 MNa⁺. In a separate experiment employing 3 equiv of **5** and 1 equiv of **7**, **8** was isolated in quantitative yield.

Se-[3,4,6-Tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranosyl] Selenolpropionate (11). A heterogeneous mixture of 0.202 mL (2.70 mmol) of propionic acid, 387 mg (0.729 mmol) of Woollins' reagent, and 2 mL of dry toluene was heated at reflux for 2 h. The solution containing the selenoacid **9** was cooled to -40 °C and then the neat glucal **10** (112 mg, 0.269 mmol) was added. The reaction mixture was allowed to stir at -5 °C for 16 h, and then was concentrated and chromatographed on silica with 1:5 ethyl acetate/hexanes as the eluant to give 105 mg (70%) of the selenoester **11** as a colorless oil, *R_f* 0.4 in 1:5 ethyl acetate/hexanes: ¹H NMR (400 MHz, CDCl₃) 7.15–7.35 (m, 15 H), 6.30 (dd, *J* = 1.2, 4.6 Hz, 1 H), 4.88 (d, *J* = 10.4 Hz, 1 H), 4.46–4.70 (m, 5 H), 3.79 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.59–3.74 (m, 4 H), 2.66 (q, *J* = 7.6 Hz, 2 H), 2.42 (m, 1 H), 2.29 (m, 1 H), 1.17 (t, *J* = 7.6 Hz, 3H); ¹³C (100 MHz, CDCl₃) 200.11, 138.23, 138.21, 138.00, 128.42, 128.33, 128.00, 127.92, 127.70, 127.63, 80.98, 79.66, 77.62, 76.92, 75.19, 73.46, 71.73, 68.47, 42.37, 38.36, 9.33; ESI-MS 575 MNa⁺.

³ Grossmann, G.; Ohms, G.; Krüger, K.; Karaghiosoff, K.; Eckstein, K.; Hahn, J.; Hopp, A.; Malkina, O.; Hrobarik, P. *Zeitschr. Anorg. Allgem. Chem.* **2001**, 627, 1269–1278.

***Se*-(2-phenyl-2-propyl) 2-Phenylselenolacetate (**13**).** A heterogeneous mixture of 100 mg (0.734 mmol) of phenylacetic acid (**5**), 117 mg (0.220 mmol) of Woollins' reagent, and 2 mL of dry toluene was heated at reflux for 2 h. The solution containing selenoacid **6** was cooled to 0 °C, and 0.025 mL (0.192 mmol) of α -methyl styrene **12** was added. The reaction mixture was stirred at room temperature for 2 h, and then was concentrated and chromatographed on silica with 1:4 dichloromethane/hexanes as the eluant to give 45 mg (74% yield) of **13**, R_f 0.6 in 1:1 dichloromethane/hexanes: ^1H NMR (400 MHz, CDCl_3) 7.22–7.60 (m, 10 H), 3.95 (s, 2 H), 1.82 (s, 6 H); ^{13}C (100 MHz, CDCl_3) $^{\text{TM}}$ 195.28, 144.42, 132.65, 129.87, 128.80, 128.29, 127.79, 127.32, 126.35, 51.57, 49.15, 30.11; ESI-MS 339 MNa^+ .

3',5'-Di-O-acetyl-2'-*Se*-acetyl-2'-selenouridine (16**).** A heterogeneous mixture of 0.507 mL (8.84 mmol) of acetic acid, 1.27 g (2.65 mmol) of Woollins' reagent, and 2 mL of dry toluene was heated at reflux for 2 h. The solution containing the selenoacid **14** was allowed to cool to room temperature and was transferred by cannula into a flask containing a solution of 100 mg (0.442 mmol) of cyclouridine diacetate **15** in 1 mL of DMF. The reaction was heated at 70 °C for 12 h. The solution was concentrated and chromatographed on silica with 1:4 ethyl acetate/dichloromethane as the eluant to give 118 mg (80%) of the 2'-seleno nucleoside **16** as a colorless oil, R_f 0.2 in 20% ethyl acetate/dichloromethane: ^1H NMR (400 MHz, CDCl_3) 9.09 (s, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 6.36 (d, J = 10.0 Hz, 1 H), 5.82 (d, J = 8.0 Hz, 1 H), 5.26 (d, J = 5.6 Hz, 1 H), 4.49 (dd, J = 4.4, 12.8 Hz, 1 H), 4.29 (dd, J = 2.0, 12.8 Hz, 1 H), 4.27 (s, 1 H), 4.08 (dd, J = 5.6, 10.0 Hz, 1 H), 2.40, 2.21, 2.13 (three s, 3 H each); ^{13}C (100 MHz, CDCl_3) 195.16, 170.12, 169.83, 162.65, 150.63, 138.76, 103.57, 87.29, 82.08, 75.22, 63.94, 44.32, 34.23, 20.78, 20.69; ESI-MS 455 MNa^+ .

***Se*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl) Selenolpropionate (18).** A mixture of 203 mg (0.617 mmol) of oxazoline triacetate **17**, 0.060 mL (0.802 mmol) of propionic acid, 128 mg (0.241 mmol) of Woollins' reagent, and 2 mL of dry toluene was heated at 80 °C for 3.5 h. The mixture was concentrated and then chromatographed on silica with 1:3 ethyl acetate/dichloromethane as the eluant to give 264 mg (92%) of the selenolester **18** as an off-white powder, mp 155–156 °C, R_f 0.50 in 40% ethyl acetate/dichloromethane: ^1H NMR (400 MHz, CDCl_3) 5.68 (d, J = 10.0 Hz, 1 H), 5.18 (d, J = 10.8, 1 H), 5.15 (t, J = 9.2 Hz, 1 H), 5.08 (t, J = 9.6 Hz, 1 H), 4.43 (q, J = 10.0 Hz, 1 H), 4.24 (dd, J = 4.4, 12.4 Hz, 1 H), 4.09 (dd, J = 2.0, 12.4 Hz, 1 H), 3.76 (ddd, J = 2.0, 4.4, 9.5 Hz), 2.66 (q, J = 7.6 Hz), 2.07, 2.03, 2.03, 1.89 (four s, 3 H each), 1.68 (t, J = 7.6 Hz); ^{13}C (100 MHz, CDCl_3) 201.54, 171.28, 170.68, 169.89, 169.18, 81.15, 77.51, 74.12, 67.77, 61.86, 53.28, 41.63, 23.14, 20.72, 20.65, 20.56, 9.16; ESI-MS 488 MNa^+ .

Methyl 2,3-Bis-*Se*,*O*-(phenylacetyl)-4,6-*O*-(phenylmethylene)-2-seleno- α -D-mannopyranoside (20). A heterogeneous mixture of 220 mg (1.84 mmol) of phenylacetic acid, 263.5 mg (0.495 mmol) of Woollins' reagent (0.3 equiv), and 2.5 mL of dry toluene was heated at reflux for 2 h. The reaction mixture containing **6** was cooled to -40 °C and then a solution of 136.9 mg (0.331 mmol) of the triflate **19**⁴ in 1 mL of DMF was added, followed by 0.432 mL (2.48 mmol) of diisopropylethylamine. The flask was removed from the dry ice/acetonitrile bath and allowed to warm to room temperature. After 2 h the reaction mixture was concentrated and then chromatographed on silica with 1:2 ether/hexanes as the eluant to give 150 mg (85%) of **20** as an off-white solid, mp 116–117 °C, R_f 0.3 in 30% ether/hexanes: ^1H NMR (400 MHz, CDCl_3) 7.15–7.40 (m, 15 H), 5.60 (dd, J = 5.0, 10.2 Hz, 1 H), 5.48 (s, 1 H), 4.80 (obsd d, J = 4.8 Hz, 1 H), 4.10–4.25 (m, 2 H), 3.94 (td, J = 5.0, 10.0 Hz, 1 H), 3.78 (dd, J = 15.6, 24.8 Hz, 2 H), 3.73 (t, J = 10.4 Hz, 1 H), 3.64 (t, J = 9.6 Hz, 1 H), 3.45 (dd, J = 15.2, 18.0 Hz, 2 H), 3.36 (s, 3 H); ^{13}C (100 MHz, CDCl_3) 197.91, 170.09, 137.01, 133.73, 132.25, 130.09, 129.29, 129.00, 128.80, 128.33, 128.17, 127.97, 126.84, 126.09, 102.85, 101.66, 78.97, 68.72, 68.22, 63.85, 55.17, 53.72, 47.26, 41.04; ESI-MS 603 MNa^+ .

⁴ Knapp, S.; Naughton, A. B. J.; Jaramillo, C.; Pipik, B. *J. Org. Chem.* **1992**, *57*, 7328–7334.

***Se*-(2,3,4,6-Tetra-*O*-acetyl- β -D-glucopyranosyl) 2-Phenyl-selenolacetate (**22**).** A solution of 2-phenyl-selenoacetic acid (**6**, prepared as before from 83 mg of phenylacetic acid and 1 mL of toluene) was transferred by cannula into a flask containing a solution of 50 mg (0.122 mmol) of acetobromoglucose (**21**) and 0.135 mL (1.03 mmol) of 2,6-lutidine in 2 mL of DMF. The solution was stirred at room temperature for 2 h. The reaction mixture was concentrated and chromatographed on silica with 3:7 ethyl acetate/hexanes as the eluant to give 62 mg (92%) of selenolester **22** as a white solid, mp 117–119 °C, R_f 0.40 in 30% ethyl acetate/hexanes: ^1H NMR (300 MHz, CDCl_3) 7.22–7.39 (m, 5 H), 5.05–5.27 (m, 4 H), 4.25 (dd, J = 4.5, 12.6 Hz, 1 H), 4.07 (dd, J = 2.0, 12.6 Hz, 1 H), 3.87 (s, 2 H), 3.78 (ddd, J = 2.1, 4.5, 9.9 Hz, 1 H), 2.05, 2.02, 1.98, 1.90 (four s, 3 H each); ^{13}C (75 MHz, CDCl_3) 197.06, 170.49, 169.90, 169.23, 169.12, 129.95, 128.79, 128.02, 79.80, 77.33, 73.95, 69.97, 67.91, 61.73, 54.08, 20.84, 20.70, 20.65; ESI-MS 551 MNa^+ .

***N*-tert-Butoxycarbonyl-*Se*-(phenylacetyl)-L-selenocysteine benzyl ester (**24**).** A solution of triphenylphosphine 308 mg (1.174 mmol) in 8 mL of THF was stirred at -30 °C. DIAD (0.233 mL, 1.174 mmol) was added dropwise, and the reaction mixture was maintained between -30 °C and -20 °C for 0.5 h. The reaction mixture was cooled to -78 °C, and then a solution of 173 mg (0.586 mmol) of L-serine benzyl ester (**23**) in 2 mL of THF was added dropwise by syringe, followed by 2 mL of a toluene solution of **6** (prepared from 2.2 mmol of phenylacetic acid) by cannula. The reaction was held at this temperature for 5 min, allowed to warm to 23 °C, and then stirred for 2 h. The solution was concentrated and chromatographed on silica with 1:4 dichloromethane/hexanes as the eluant to give 230 mg (83%) of the selenocysteine derivative **24** as a colorless oil, R_f 0.7 in 5% ethyl acetate/dichloromethane: ^1H NMR (400 MHz, CDCl_3) 7.24–7.38 (m, 10 H), 5.21 (d, J = 7.6 Hz, 1 H), 5.10 (dd, J = 12.0, 16.8 Hz, 2 H), 4.59–4.66 (m, 1 H), 3.82 (s, 2 H), 3.35 (dd, J = 4.8, 13.2 Hz, 1 H), 3.26 (dd, J = 6.0, 12.8 Hz, 1 H), 1.42 (s, 9 H); ^{13}C (100 MHz, CDCl_3) 199.14, 170.61, 135.08, 132.45, 129.96, 128.73, 128.54, 128.40, 127.82, 80.07, 67.44, 53.80, 53.35, 28.24; ESI-MS 498 MNa^+ .

***N*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl)-phenylacetamide (26).** A heterogeneous mixture of 23.2 mg (0.170 mmol) of phenylacetic acid, 27.2 mg (0.057 mmol) of Woollins' reagent (0.3 equiv), and 1 mL of dry toluene was heated at reflux for 2 h. The solution containing **6** was allowed to cool to room temperature and then was transferred by cannula to a flask containing 60 mg (0.161 mmol) of β -glucopyranosyl azide **25**, 0.033 mL (0.288 mmol) of 2,6-lutidine, and 2 mL of chloroform. Upon consumption of **25**, about 12 h according to TLC analysis, the mixture was concentrated and then chromatographed on silica with 1:3 ethyl acetate/hexanes to give 67 mg (90%) of the amide **26** as a white solid, mp 235–237 °C, R_f 0.30 in 2:7 ethyl acetate/toluene: ^1H NMR (400 MHz, CDCl_3) 7.22–7.35 (m, 5 H), 6.97 (d, $J = 8.4$ Hz, 1 H), 5.86 (d, $J = 8.4$ Hz, 1 H), 5.10 (t, $J = 9.6$ Hz, 1 H), 5.02 (dd, $J = 8, 10.4$ Hz, 1 H), 4.99 (t, $J = 9.2$ Hz, 1 H), 4.29 (dd, $J = 4.4, 12.8$ Hz, 1 H), 4.09 (dd, $J = 8.4, 10.0$ Hz, 1 H), 4.07 (dd, $J = 2.0, 12.4$ Hz, 1 H), 3.73 (ddd, $J = 2.4, 4.4, 10.0$ Hz, 1 H), 3.50 (dd, $J = 14.8, 34.8$ Hz, 2 H), 2.08, 2.04, 2.03, 1.76 (four s, 3 H each); ^{13}C (100 MHz, CDCl_3) 171.89, 171.66, 170.70, 169.21, 133.99, 129.23, 128.81, 127.27, 80.47, 73.56, 72.86, 67.58, 61.68, 53.13, 43.79, 22.85, 20.75, 20.67, 20.57; ESI-MS 487 MNa^+ .

***N*-(2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl- β -D-glucopyranosyl)- N_α -(carbobenzyloxy)glycinamide (28).** Diisopropylethylamine (0.246 mL, 1.41 mmol) was added to a solution of 196 mg (0.940 mmol) of *N*-Cbz-glycine (**27**) in 2 mL of toluene and 0.500 mL of acetonitrile. The solution was stirred for 0.5 h, concentrated under vacuum and then further azeotropically dried with toluene (3x2 mL). Woollins' reagent (**2**, 200 mg, 0.376 mmol) was added, followed by 2 mL of dry toluene. The heterogeneous mixture was heated at reflux for 4 h, then cooled to 0 °C. Glycosyl azide **25** (70 mg, 0.188 mmol), 0.164 mL (1.41 mmol) of diisopropylethylamine, and 2 mL of chloroform was added, and the resulting reaction mixture was heated at 70 °C for 14 h. The solution was filtered to remove selenium, concentrated under vacuum, and then chromatographed with 7:2 ethyl acetate/chloroform as the eluant to give 72 mg (71%) of **28** as an off-white solid, mp 189–192 °C, R_f 0.1 in 7:2 ethyl acetate/chloroform: ^1H NMR (400 MHz, CDCl_3 , 45 °C) 7.52 (d, $J = 8.0$ Hz, 1 H), 7.27–7.40 (m, 5 H), 6.18 (d, $J = 8.4$ Hz, 1 H), 5.40 (t, $J = 5.2$ Hz, 1 H), 5.13 (s, 2 H), 5.05–5.12 (m, 3 H), 4.27 (dd, $J = 4.4, 12.4$ Hz, 1 H), 4.11–4.19 (m, 1 H), 4.07 (dd, $J = 2.0, 12.4$ Hz, 1 H), 3.74–3.90 (m, 3 H), 2.07, 2.05, 2.03 (three s, 3 H each), 1.93 (br s, 3 H); ^{13}C (100 MHz, CDCl_3) 172.28, 171.75, 170.69, 170.27, 169.25, 156.41, 136.06, 128.53, 128.25, 128.08, 80.28, 73.48, 72.71, 67.78, 67.31, 61.72, 53.14, 44.47, 23.02, 20.73, 20.68, 20.59; ESI-MS 560 MNa^+ .

(2*R, 3*R**, 4*R**)-1-*N*-(Benzyloxycarbonyl)-2-acetamido-3-hydroxy-4-(*tert*-butyldimethylsilyloxy)-piperidine (30).** A mixture of 0.101 mL (1.939 mmol) of acetic acid, 277 mg (0.521 mmol) of Woollins' reagent and 1 mL of dry toluene was heated at reflux for 2 h. The reaction mixture containing selenoacid **14** was cooled to room temperature and was transferred by cannula to a flask containing a solution of 78.2 mg (0.192 mmol) of azidopiperidine **29**, 0.448 mL (3.85 mmol) of 2,6-lutidine, and 1 mL of chloroform. The reaction was heated at reflux for 12 h. The solution was concentrated and then chromatographed on silica with 2:3 ethyl acetate/dichloromethane as the eluant to give 61 mg (75%) of acetamidopiperidine **30** as a foam, R_f 0.2 in 40% ethyl acetate/dichloromethane: ^1H NMR (300 MHz, CDCl_3) 7.25–7.42 (m, 5 H), 6.26 (d, $J = 8.7$ Hz, 1 H), 5.12 (s, 1 H), 4.02 (d, $J = 2.1$ Hz, 1 H), 3.93 (d, $J = 11.1$ Hz, 1 H), 3.76 (s, 1 H), 3.22 (t, $J = 12.0$ Hz, 1 H), 2.05–2.16 (m, 1 H), 1.90 (s, 3 H), 1.44 (d, $J = 13.8$ Hz, 1 H), 0.93 (s, 9 H), 0.12 (s, 6 H); ^{13}C (75 MHz, CDCl_3) 169.14, 155.69, 136.78, 128.39, 127.76, 127.64, 69.44, 68.77, 67.34, 61.26, 33.81, 27.35, 25.81, 23.38, 17.97, -4.99, -5.06; ESI-MS 445 MNa^+ .